

**DEPARTMENT OF VETERANS AFFAIRS
COOPERATIVE STUDIES PROGRAM (CSP)
#424**

C.O.U.R.A.G.E.

Clinical Outcomes Utilizing Revascularization
And Aggressive DruG Evaluation



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HUMAN RIGHTS CONSIDERATIONS

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EXECUTIVE SUMMARY/ABSTRACT

The principal objective of the **C**linical **O**utcomes **U**tilizing **R**evascularization and **A**ggressive **D**rug **E**valuation (COURAGE) Trial is to assess prospectively both “hard” endpoint outcomes (death, nonfatal myocardial infarction [MI], refractory angina/ischemia necessitating coronary artery bypass graft [CABG] surgery) and other health care outcomes (resource use, quality of life measures, cost-effectiveness and cost-utility measures) during long-term (3-6 year) follow-up in *all but the very highest-risk* coronary heart disease (CHD) patients (all but persistent Canadian Cardiovascular Society [CCS] Class IV angina, $\geq 50\%$ angiographic left main coronary artery disease [CAD], or ejection fraction [EF] $<30\%$, or severe three vessel CAD with $\geq 70\%$ stenosis of the proximal left anterior descending [LAD] and $EF \leq 35\%$) who meet one or more ACC/AHA Joint Task Force Class I (Definite) or II indications for PCI.

The two therapeutic strategies to be randomly compared in COURAGE are:

- 1) a strategy of “PCI” in addition to intensive medical therapy, and
- 2) a strategy of intensive medical therapy alone.

Intensive medical therapy, as proposed in this study, will conform to the recent AHA Treatment Guidelines¹, so that patients enrolled in COURAGE are in full compliance with contemporary pharmacological management and lifestyle guidelines. This therapy is “aggressive” and multifaceted. It targets both the stabilization (or regression) of atherosclerotic plaques and a reduction in clinical events. Patients in both treatment arms will receive:

- 1) aspirin (enteric-coated) 80-325 mg/day (clopidogrel 75 mg/daily for patients unable to take aspirin);
- 2) an HMG co-enzyme A reductase inhibitor (simvastatin) with a goal of reducing low-density lipoprotein (LDL)-cholesterol to 60-85 mg/dL (1.56-2.21 mmol/L). To date, no clinical trial in PCI-eligible CHD patients has ever attempted such vigorous lipid altering in both treatment arms. In trial patients whose LDL-cholesterol cannot be lowered below 85 mg/dL (2.21 mmol/L) with maximal simvastatin monotherapy (80 mg/day), a bile acid sequestrant will be added to achieve this desirable LDL target;
- 3) for patients with hypertension, as primary therapy, a choice of an angiotensin-converting enzyme (ACE) inhibitor (lisinopril), a long acting calcium antagonist (amlodipine) and/or an angiotensin receptor blocker (losartan):
- 4a) *for post-MI patients randomized to the medical therapy arm:* routine beta-blocker administration (usually begun in the hospital but may be started up to 1 year when patient is first seen at that time) will be utilized as standard secondary prevention for patients with Q-wave MI, whereas diltiazem or a beta-blocker will be administered as secondary prevention for patients with non-Q-wave MI; an ACE inhibitor (lisinopril) will be started in all patients with reduced LVEF and for many patients with normal LVEF especially those with an anterior MI or diabetes;
- 4b) *for CHD patients WITHOUT MI randomized to the medical therapy arm:* anti-ischemic

therapy will consist of administration of a beta-blocker when tolerated; and/or a long-acting dihydropyridine (amlodipine). In patients with mildly depressed LVEF, amlodipine may be added to or substituted for a beta blocker.

- 4c) *for CHD patients randomized to the “PCI” arm:* patients assigned to the PCI arm will receive similar anti-ischemic therapy as outlined in 4a and 4b, but, except for secondary prevention post-MI, an attempt will be made to discontinue routine anti-ischemic medical therapy in otherwise asymptomatic patients who have been successfully revascularized, 3-6 months after the performance of PCI.
- 5) for patients with unstable angina who are at moderate or high-risk as indicated in the protocol, initial therapy will include aspirin, nitrates, amlodipine, beta blockers, unfractionated heparin, and a glycoprotein IIb/IIIa inhibitor (tirofiban) and patients responding to therapy will be eligible for randomization. Following randomization they will be treated with anti-ischemic and antiplatelet drugs according to the algorithm included in the protocol.

Patients randomized to catheterization-based coronary interventions and those presenting with unstable angina will be continued on unfractionated heparin and IIb/IIIa inhibitors for at least 48 hours and for a minimum of 12 hours after coronary angioplasty. Patients randomized to conservative therapy after catheterization will receive unfractionated heparin and IIb/IIIa inhibitors for 48 hours and subsequently undergo stress testing on maintenance anti-ischemic therapy. Those patients with a high-risk stress test result or recurrent episodes of chest pain at rest with ECG changes will be candidates for subsequent PCI or surgical therapy.

The “PCI” to be used in this study is whichever catheter-based coronary revascularization technique the cardiologist/operator feels would be optimal for that patient. This could include balloon angioplasty, intracoronary stents, rotoblator, and directional coronary atherectomy.

The COURAGE Trial is the first large-scale, multicenter, randomized controlled trial comparing PCI and medical therapy that is powered for a combined primary endpoint of all-cause mortality and nonfatal myocardial infarction. Patients eligible for inclusion in COURAGE will comprise *all but very high-risk* subjects. These will include CHD patients with chronic angina pectoris (Canadian Cardiovascular Society [CCS] Class I-III), uncomplicated post-MI patients, patients with unstable angina who have responded to medical therapy, and asymptomatic (or “silent”) myocardial ischemia. They may have single- or multi-vessel coronary artery disease.

All patients must meet standard, clinically accepted inclusion criteria for CHD and have objective evidence of myocardial ischemia. If antecedent cardiac catheterization has not been done within the last 30 days, eligible patients will be informed and consented before diagnostic coronary angiography is undertaken. If, upon cardiac catheterization, the patient’s coronary anatomy is suitable for catheter-based revascularization, then he/she will be randomized and treated as assigned. Alternatively, if cardiac catheterization has been done recently, trial-eligible patients with suitable coronary anatomy will be consented, randomized, and treated as assigned.

It is important to emphasize that, as many types of CHD patients as possible—reflecting the

spectrum of patients encountered in contemporary clinical practice—will be enrolled in COURAGE. For instance, patients with left ventricular EF as low as 30%, patients with coronary angiographic narrowing of any severity (except >50% stenosis of left main CAD, or 3 vessel CAD including \geq 70% stenosis of the proximal LAD, and an EF of \leq 35%), and patients who have undergone CABG or PCI more than 6 months prior to randomization will be included. CCS Class IV patients not responding to medical therapy will be excluded.

The primary hypothesis for the study is that PCI (optimal catheter-based coronary revascularization) + intensive medical therapy is superior to intensive medical therapy alone using the combined endpoint of all-cause mortality or nonfatal MI. We project cumulative 3-year cardiac event rates of 11% and 14%, respectively, which yields an absolute difference of 3% or relative difference of 21%. Assuming a minimum duration of follow-up of 3 years and using a two-sided test of significance at the 0.05 level, these rates indicate that a sample size of 2,964 will be needed to test the hypothesis with 85% power. If a cumulative loss to follow-up rate of 10% is factored in, then 3,260 patients must be enrolled in order to obtain the required number of endpoints.

With a sample size of 3,260 patients and an average 3 year event rate of 12.5%, we anticipate that 217 first events will occur in the patients randomized in the first year, 177 events in the patients randomized in the second year, and 136 events in the patients randomized in the third year for a total of 530 events.

Thirty-six enrolling sites (12 V.A., 12 U.S. non-VA, 12 Canadian) will be needed to accrue 3,260 patients. Each site will be expected to enroll at least 90 patients during 3.0 years of intake (30 patients per year, or 2.5 per month).

Major trial secondary endpoints include quality of life assessments, health economic assessments, and resource use. Follow-up visits are scheduled for 1, 2, 3, and 6 months, and then every 6 months for the duration of the trial. Throughout the follow-up period, all patients are to be regularly counseled about diet, smoking cessation, exercise, diabetes control, and hypertension management.

The trial funding will be tripartite: the Department of Veterans Affairs (V.A.) Cooperative Studies Program will provide funding for the 12 V.A. sites, The Canadian government Medical Research Council plus unrestricted research grants from several pharmaceutical and industrial sources.

SUMMARY OF THE CHANGES TO THE PROTOCOL FOR CSP 424

The Human Rights Committee approved the protocol for CSP 424 in July 1996 and the Cooperative Studies Evaluation Committee approved it in October 1996. At that time the title of the study was “Specialized Medication And Revascularization Therapy (SMART). Since October 1996, the Co-Chairmen of the study have been working to secure some non-VA funding for the study. This has finally been achieved, with funding from several industry sources as well as the Canadian government.

In October 1998 the protocol was revised. The name was changed to COURAGE “Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation”. In addition to the name change there were some other modifications. Earlier in 1998 the drug tirofiban (a glycoprotein IIb/IIIa inhibitor) was approved by the FDA for the treatment of unstable angina and use in percutaneous coronary intervention (PCI) procedures in these unstable patients. Guidelines for the use of this drug were included in the October protocol along with updated definitions for unstable angina. The PCI procedure guidelines were also modified to accommodate the current practice of frequent use of stents. In addition, several drugs being donated by industry were named.

In December 1998 the analytic plans for the health economic section were updated and additional QOL administrations were added - 1 month, 3 months, and 2 years. Some donated drugs were included. The lipid-lowering algorithm was specified. An attempt was made to correct all of the small inconsistencies in the protocol.

The January 1999 protocol is a modification of the December protocol.

- 1) More donated drugs are identified.
- 2) Corrections were made to the algorithms for use of the donated drugs so that the specifications match the labeling more precisely.
- 3) A qualifier was added to the vessel size for the entry criteria.
- 4) A statement that the specified drugs are not mandated was added.
- 5) Small details in the protocol were corrected – i.e. making sure that they were consistent throughout the document, e.g. criteria for diabetes $HbA_{1C} < 7.5\%$ everywhere.

The February 1999 protocol reflects decisions made at the kickoff meeting.

- 1) The qualifier for the vessel size was replaced by more detailed distributional criteria intended to exclude patients with only small amounts of myocardium at risk.
- 2) The exclusion criteria for diabetics of creatinine > 1.4 was deleted.
- 3) The definition for a periprocedural MI was changed to use 3 X upper limit of normal (ULN) CK in presence of a clinical or procedural indication. And for CABG 5 X ULN with at least 5% MB. A new Q-wave at any time defines an MI.
- 4) The algorithm for lipid lowering was slightly modified.
- 5) A stronger recommendation was made for the use of ETT with gated technetium sestimibi and SPECT imaging for all ischemia documentation both at baseline and during follow-up.
- 6) SI units included everywhere.
- 7) Adverse event reporting was more clearly specified.

STUDY PROTOCOL

I. HYPOTHESIS

That clinically-meaningful long-term outcomes (all-cause mortality, nonfatal myocardial infarction (MI), resource utilization, and quality of life (QOL) comparisons) in *all but the very highest-risk* coronary heart disease (CHD) patients (those with persistent unstable angina despite maximal medical therapy, >50% left main coronary artery disease (CAD) stenosis, a left ventricular ejection fraction (LVEF) <30%, or severe 3 vessel CAD with $\geq 70\%$ LAD proximal stenosis and LVEF $\leq 35\%$) will be superior in patients randomized to a strategy of optimal catheter-based coronary revascularization (PCI) **and** intensive medical therapy compared to those who are randomized to a strategy of intensive medical therapy **alone** during a minimum 3 year follow-up, when outcomes are compared using the intention-to-treat principle.

II. BASIC STUDY DESIGN

Multicenter, prospective, randomized, parallel-design (but unblinded) clinical trial.

III. PREVIOUS WORK DONE BY OTHERS

A) Introduction

Despite the sustained, significant decline in cumulative death rate owing to coronary heart disease (CHD) during the last 3 decades, CHD remains the single-most important cause of morbidity and mortality in the Western World. Given the high prevalence of CHD in North America and Western Europe, physicians have sought to identify the most effective clinical strategies to reduce (or

eliminate) symptoms of angina pectoris, improve exercise performance and quality of life, and to improve survival.

Since the early 1970s, numerous large clinical trials have established convincingly the importance of medical therapy in the management of CHD and in post-myocardial infarction (MI) secondary prevention, while prospective trials have established the respective roles of coronary artery bypass graft surgery (CABG) versus medical therapy in patients with CHD, most notably those patients with medically-refractory angina, left main coronary artery disease, or 3-vessel coronary artery disease with depressed LV systolic function.

Following Grüntzig's initial report in 1979 that percutaneous transluminal coronary angioplasty (PTCA) could be used safely and effectively to dilate obstructed coronary arteries, angioplasty has emerged as a widely-used (and widely-available) technique in the cardiologist's therapeutic armamentarium.² Initially, PTCA was used predominantly in selected CHD patients with proximal stenoses of a single epicardial coronary artery whose symptoms of angina pectoris were unresponsive to maximal medical therapy, or for whom single-vessel CABG was considered therapeutically ill-advised.

Within a very few years, however, indications for PTCA became generalized to more challenging CHD patient subsets. As interventional cardiologists became more skilled and equipment and catheter systems became ever more sophisticated, the indications for routine angioplasty have broadened in scope to include patients with mild-moderate angina, to *asymptomatic* patients with demonstrable ischemia, and even to patients with coronary *angiographic* multivessel CAD but without objective evidence of myocardial ischemia.

Accordingly, the evolution of PCI has culminated in an exponential growth in the number of

angioplasties done in the U.S. over the past 15 years. Importantly, this has occurred *without* the guidance afforded by randomized controlled trials or prospective observational comparisons. It is, therefore, not surprising that, during the 15 years, a more than tenfold increase in PTCA procedures has occurred; in 1983, 30,000 procedures were performed, and in 1997, more than 500,000 procedures were performed at an estimated cost greater than \$10 billion, which represents over 1% of the entire U.S. annual gross expenditure on health care.

It is unlikely that a rising incidence of accelerating, or unstable angina—or angina unresponsive to medical therapy—accounts for a greater than 10-fold increase in procedure rate over one decade. On the contrary, as medical therapy has become more refined and sophisticated, one might expect that the need for undertaking PCI would have declined or at least remained constant, rather than having increased geometrically. It is thus abundantly clear that some other factor, or factors, must account for the rapid and sustained growth in PCI over the past decade.

Most likely is the fact that PCI is being performed increasingly in patients with Canadian Cardiovascular Society (CCS) Class I CHD disease. In fact, the current (1993) American College of Cardiology/American Heart Association (ACC/AHA) Joint Task Force Guidelines for PCI (Revision Pending) recommends that such asymptomatic or mildly symptomatic CHD patients with single-vessel or multi-vessel coronary artery disease undergo, or be considered for, PCI.³ These indications are:

- a) single-vessel coronary artery disease patients who are **asymptomatic to severely symptomatic** and who have a “large area” of ischemic myocardium subtending a significant ($\geq 50\%$ diameter reduction) coronary stenosis (ACC/AHA “Class I” Definition] Indication for PCI) (Revision pending) or a “moderate area” of ischemia (an ACC/AHA “Class II” for those with only asymptomatic or mildly symptomatic

ischemia [Probable but Uncertain] Indication);

- b) multi-vessel coronary artery disease patients who are **asymptomatic or mildly symptomatic** who have a “large ischemic area” or “moderate ischemic area” (ACC/AHA “Class II” for asymptomatic or minimally symptomatic patients).

Clearly, many of these CHD patients (asymptomatic and mildly symptomatic) without moderate to severe ischemia are routinely undergoing PCI in the United States.

B) Observational and Registry Data: Impact of Myocardial Revascularization on CHD Health Care Outcomes

While contemporary (1990s) "natural history" data on PTCA outcomes in CHD patients are not readily available, there are data in a report from the British Columbia Office of Health Technology Assessment on PTCA outcomes which show that outcomes in single-vessel disease in the 1980s⁴ are similar to outcomes in the 1970s.⁴ In addition, one case series assessed long-term outcome for 217 patients who underwent PTCA between 1978-1981--87% of whom had single-vessel disease.⁵ The actuarial survival rate for the whole cohort was 92% at 10 years (< 1%/year mortality), with 76% free from death, MI, CABG surgery, and 84% free of angina (1.5%/year).⁵ The lack of a medically-treated control group, however, made it impossible to decide whether PTCA was superior to medical therapy. Other studies show that long-term outcome for single-vessel disease patients treated medically is excellent, with 3% and 5% mortality at 5 and 10 years, respectively.^{6,7} Patients with single-vessel disease, however, are a heterogeneous group, and certain patients with left ventricular dysfunction or with a greater degree of stenosis may be at increased risk.⁶ Multi-vessel PCI has the potential for worse, intermediate, and long-term outcome.³ A greater amount of myocardium may be at risk for each stenosis dilated, and

"complete revascularization" may be impossible to achieve. "Incomplete revascularization" is associated with poorer long-term outcome following CABG surgery.⁸ In post-PTCA patients, it is associated with a higher incidence of subsequent CABG surgery^{9,10} and with lower event-free survival,¹¹ but overall survival is not affected once adjustment for baseline variables is made.^{9,12} In the 1985-1986 NHLBI registry, immediate outcomes for three-vessel PTCA versus single-vessel PTCA was: clinical success 77.7% versus 86.8%, mortality 2.8% versus 0.2%, nonfatal MI 5.1% versus 3.5%, emergency CABG 4.3% versus 2.9%, and elective (same hospitalization) CABG 3.3% versus 1.7%.¹³ In another uncontrolled study of PTCA in multi-vessel disease,¹⁴ the actuarial 5-year survival was 88%, and event-free rate was 74%. Most recently, a large-scale, prospective observational treatment comparison of CABG, PTCA and medicine from the Duke Cardiovascular Disease Databank has provided some insight into understanding treatment outcomes following the use of these therapies in CHD patients with differing baseline characteristics and variable degrees of CAD. Results from follow-up of 9,263 patients with CAD treated at the Duke Heart Center between 1984-1990 confirmed previously reported survival advantages for CABG over medical therapy for 3-vessel CAD and severe 2-vessel CAD (including a critical lesion of the proximal left anterior descending [LAD] coronary artery).¹⁵ For less severe 2-vessel CAD and single-vessel CAD, there was no clear-cut advantage of bypass surgery over medical therapy.

For PTCA compared to medical therapy, the data from this study suggests a *trend* in favor of mortality reduction in CHD patients with 1-vessel and less-severe forms of 2-vessel CAD with angioplasty (although confidence limits for the relative risk include 1.0 indicating the possibility of no difference); in severe 2-vessel CAD (with 95% proximal LAD involvement) and all forms of 3-vessel disease, the results indicate that clinical outcomes between PTCA and medical therapy groups are

equivalent.¹⁵

These observational comparisons require a statistical "leveling of the playing field" due to the differing baseline characteristics among the treatment groups, and must, therefore, be interpreted with caution. For example, only 10% of PTCA patients had three-vessel and 61% had single vessel CAD while the percentages were 22% and 48% respectively in the medical group; medical patients had the worst and PTCA patients the best LV function, judged in terms of the ejection fraction.¹⁵

The limitations inherent in registry studies or prospective observational comparisons are self-evident. First, despite extensive efforts to control for treatment selection bias by use of both standard cohort adjustments and covariate adjustment with treatment propensity scores, the presence of selection bias could easily account for some of the observed treatment differences. Second, covariate adjustment can correct only for observed imbalances; unobserved or unmeasured factors affecting both treatment selection and outcome could influence reported results. Third, such data are usually obtained on a highly-selected cohort of patients referred for myocardial revascularization to a tertiary medical center, and thus may not be generalizable to more broad-based, unselected populations. Accordingly, the results of these published studies must be regarded as non-definitive and hypothesis generating.

C) Randomized, Controlled Trials of CABG, PTCA and Medical Therapy: Impact of Myocardial Revascularization on CHD Health Care Outcomes

1) CABG Surgery versus Medical Therapy:

Three large, prospective, clinical trials and a number of smaller studies randomizing patients to CABG versus medical therapy have been reported. From January 1972 to December 1974, the final phase of the Veterans Administration Cooperative Study of Coronary Artery Bypass

Surgery for Stable Angina randomized 686 males.¹⁶ Patients with stable angina, electrocardiographic (ECG) evidence of previous myocardial infarction (MI), or changes consistent with ischemia at rest or with exercise, and at least one major coronary artery with a 50% or greater stenosis were eligible. Exclusion criteria included patients with unstable angina and uncompensated congestive heart failure. The trial primary endpoint was all-cause mortality.

A small but statistically significant decrease in mortality with CABG was identified at 7 years (77% versus 70%, P=0.043). This difference no longer existed at 11 years secondary to an accelerated mortality rate in the surgical group after the seventh year.^{17,18} Patients with high angiographic risk (3-vessel disease and impaired LV function) or high clinical risk (New York Heart Association Class III or IV heart failure, history of hypertension, previous MI, and ST depression on resting ECG) demonstrated significant benefit with CABG up to 11 years.¹⁹ In a small subgroup (91 patients) with significant left main stenosis, results with CABG were better throughout the period of follow-up; however, the difference was statistically significant only up to 7 years.^{17,20,21}

The European Coronary Surgery Study randomized 767 men with mild to moderate angina and at least 2-vessel CAD to CABG versus medical management between September 1973 and March 1976.²² Exclusion criteria included severe angina not controlled with medications, age greater than 65 years, and ejection fraction (EF) less than 50%. The trial primary endpoint was all-cause mortality.

Follow-up at 5 years showed a significant mortality benefit with CABG (P=0.001). The gap between the two therapies decreased gradually after 5-7 years secondary to a more rapid decrease in survival in the surgical group compared with the medically treated group, but was still

nominally significant at 12 years ($P=0.04$).^{23,24} The results suggested that patients at high risk, identified by advanced age, an abnormal resting ECG, a markedly positive exercise test, peripheral arterial disease, and proximal disease of the LAD coronary artery, tended to benefit most from early surgery.

The Coronary Artery Surgery Study (CASS) was designed to test the hypothesis that coronary bypass surgery significantly reduces the rate of mortality and MI in patients with mild angina and in patients who are asymptomatic after infarction.^{25,26} Between August 1975 and June 1979, 780 patients (≤ 65) with Canadian Cardiovascular Society Class I or II angina or a well-documented MI more than 3 weeks before randomization were randomized to medical management versus CABG surgery, angiographic inclusion criteria included 70% or greater stenosis in one of the major coronary arteries or a 50% to 70% luminal narrowing of the left main coronary artery. Patients with unstable or progressive angina, NYHA functional class III or IV heart failure, EF less than 35%, prior CABG surgery, or left main coronary artery stenosis greater than 70% were excluded from randomization. The trial primary endpoint was all-cause mortality and nonfatal Q-wave MI.

Follow-up during the first 6 years demonstrated that, for the study population as a whole, the probability of remaining alive and free of MI was not significantly different in the medical versus surgical groups.^{25,26} These results were confirmed at 10 years of follow-up.²⁷ Although the number of patients was small, a nonsignificant trend toward increased survival in favor of CABG surgery was observed in patients with 3-vessel CAD and an EF less than 50%.²⁵⁻²⁷ Seven-year survival data in these patients (160 patients with EF $< 50\%$) demonstrated a significantly better cumulative survival in the group randomized to CABG.²⁸ This difference was observed almost exclusively in patients with 3-vessel CAD. It was shown further that, in the registry of patients evaluated for CASS but not

randomized, the survival benefit from surgery was most apparent for patients with EF values below 26%, despite increased operative mortality.²⁹

Although the patient populations differed, all three trials reported that surgery was most beneficial in improving the survival of high-risk patients. An overview of these trials, combined with information from four smaller trials, also reported that benefits from CABG surgery are greater for subgroups of patients with more extensive CAD (left main artery disease, 3-vessel disease, or proximal LAD disease).³⁰ Interestingly, in this meta-analysis, the relative reduction in risk of death was similar for patients with normal or abnormal LV function at 5 years and showed no significant difference at 10 years. Bypass grafting did not reduce the incidence of MI, improve LV function, or increase the likelihood of return to gainful employment.

Significant limitations exist within these trials. First, these trials do not reflect improvements in surgical or medical management achieved in the past 15 to 20 years. Increasing use of internal mammary artery grafts for CABG and more routine use of beta blockers, antiplatelet agents, angiotensin-converting enzyme (ACE) inhibitors, and lipid lowering agents are expected to improve outcomes with bypass surgery and medical therapy, respectively. Second, these trials enrolled very few women and excluded elderly patients (age >65), as well as patients with more severe angina and those with evidence of severe LV dysfunction. Thus, the patients randomized were not necessarily representative of the population of patients presenting routinely for management of CAD.

2) *CABG versus PTCA Trials:*

Six prospective, randomized trials evaluating the effects of CABG versus PTCA on single or multivessel CAD have reported results. Two trials with more modern technology are on-going. Patients were included in these studies if they were documented to have stable or unstable angina or

objective signs of ischemia such as a positive exercise test. In 1996, the largest of these trials, the multicenter Bypass Angioplasty Revascularization Investigation (BARI), reported its results in 1,829 patients with multivessel coronary artery disease.³¹ This trial described 5-year survival in patients randomized to either an initial strategy of coronary angioplasty or initial revascularization with coronary artery surgery, and the results show no significant differences in death or MI between the two modalities of myocardial revascularization. Diabetic patients with 3 vessel CAD had a significantly better survival with CABG surgery in a post hoc analysis (see below).

Four other major trials are (RITA,³² GABI,³³ EAST³⁴, and CABRI³⁵). In each of these trials there was no difference between the groups for the hard endpoints, follow-up data on "hard" endpoints (death; MI) and need for repeat myocardial revascularization can be established for the PTCA cohorts under study.

In RITA,³² the incidence of death or MI during a median 2.5 year follow-up in 510 CHD patients with multi-vessel disease who underwent PTCA was **10%**. An additional 37% of patients underwent subsequent CABG surgery (19%) or PTCA (18%). Life-table analysis shows that, within 2 years of randomization, an estimated **38%** of PTCA patients experienced at least one of the following: further PTCA, CABG, MI or death. Of note, the risk of subsequent procedure or clinical event was **not** significantly related to the number of treatment vessels at randomization (36% in single-vessel, 41% in multi-vessel patients, $p = 0.27$).³²

In GABI,³³ which was restricted to symptomatic CHD patients with 2-or 3-vessel coronary artery disease, a total of 155 patients randomly assigned to PTCA were followed for 1 year. The cumulative 1-year incidence of death or MI was **7%**. By the end of the first year of follow-up, 21% of the PTCA patients had undergone subsequent CABG surgery, and 26% had undergone repeat PTCA in

at least one vessel; since 3% of patients underwent both procedures, the complete rate of further interventions in the PTCA cohort was **44%**.

In EAST,³⁴ a total of 198 CHD patients with multi-vessel coronary artery disease were randomly assigned to PTCA, and followed for an average of 3 years. A total of 43 patients (14 deaths; 29 Q-wave MIs) occurred during the follow-up period, an incidence of **22%**. Subsequent revascularization with either PTCA or CABG surgery was done in **54%** of the patients initially randomized to PTCA during the 3-year follow-up period.³⁴

In Europe, the Coronary Artery Bypass Revascularization Investigation (CABRI) has reported 1-year follow-up on 1,054 patients with multivessel disease randomized to PTCA versus CABG.³⁵ There were no significant differences in death (2.7% versus 3.9%, p=0.3) or non fatal MI (3.5% versus 4.9%, p=0.23) between the groups treated with CABG surgery or PTCA.

Finally, a report of 1 year outcomes from the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease Study, which randomized 127 patients, did report a significant advantage of CABG compared to PTCA in reducing the occurrence of the composite trial primary endpoint of death, MI, repeat revascularization, and angina.³⁶ This was secondary to the recurrence of angina and need for repeat revascularization after reocclusion of a successfully dilated coronary artery in the PTCA group. No significant difference in mortality or freedom from MI was reported after 1 year of follow-up.

Thus, in the four of the these clinical trials for which detailed data have been reviewed,³²⁻³⁵ the cumulative occurrence of "hard" endpoints (death or MI) in patients randomized initially to PTCA ranged from **7%** at 1 year to **22%** at 3 years of follow-up; the rate of subsequent myocardial revascularization (CABG; PTCA) ranged from **38% to 54%** during 1-3 years of follow-up.

3) *PTCA versus Medical Therapy:*

The first randomized, prospective trial evaluating PTCA versus medical management was the **Angioplasty Compared to medicine (ACME)** Study which randomized 212 patients with either stable angina or a recent MI (within 3 months), angiographic evidence of 70% to 99% stenosis of one major coronary artery, and a positive exercise-tolerance test.³⁷ Exclusion criteria included previous CABG or PTCA, or ongoing unstable angina. The primary endpoints in this study were changes in exercise tolerance between baseline and follow-up exercise tests, frequency of angina attacks, and use of nitroglycerin between baseline and the final month of the study. By 6 months, each group demonstrated significant improvement in exercise capacity, although the PTCA group had more improvement than the medical group (P=0.01). In addition, more PTCA patients were free of angina (61 of 96 versus 47 of 104, P=0.01) at 6 months. There was, however, a much higher incidence of bypass surgery in the PTCA group (7 versus 0).³⁷

ACME also randomized a small number of patients with two-vessel coronary artery disease (n=101) using the same protocol. This pilot study suggested that the symptom and exercise performance advantages of PTCA over medical therapy may be relatively diminished for patients with double-vessel disease compared to patients with single-vessel disease.³⁸ Possible explanations are the reduced likelihood of complete revascularization and the increased likelihood of restenosis in patients with multiple treatment targets.

ACME was the first randomized trial to investigate PTCA. It was not designed, however, to address the endpoint of death or nonfatal MI. Since the incidence of death or MI in CHD patients with stable single-vessel CAD is so low and the sample size was so small, ACME was simply underpowered to investigate "hard" clinical endpoints.

The second trial comparing angioplasty to medicine was the recently completed RITA-2 (Randomized Intervention Treatment of Angina) trial which was conducted in the United Kingdom and Ireland.^{38a} A total of 1018 patients at 20 centers, 40% with multivessel disease, were followed for a median of 2.7 years. Patients in the medical arm were treated with anti-anginal medications, but there was not a thorough protocol for medical management. In particular, lipid management was at the discretion of the physicians caring for the patient. In the PTCA arm, 93% of the patients had their procedures within 5 weeks of randomization. The primary endpoint was the composite of death and “definite” myocardial infarction, an endpoint in 6.3% of the PTCA group and 3.3% of the medical group (p=0.02), with 2.2% and 1.4% death in these groups respectively (p=0.32). The definition of myocardial infarction in RITA-2 included CPK rises over 2 times the upper limit of normal, and there were 1.4% periprocedural myocardial infarctions. In the PTCA group 7.9% underwent coronary surgery, 1.8% instead of PTCA and 1.4% after failed angioplasty. An additional 11.1% of the angioplasty patients required an additional angioplasty. In the medical arm, 5.9% underwent coronary surgery and 19.7% coronary angioplasty, mostly for continuing symptoms of angina. There was an improvement in angina in both groups, but the improvement was greater in the angioplasty arm, even though there was greater use of anti-anginal medication in the medical arm.

4) *PTCA versus Medical Management versus CABG*

A single randomized three-arm trial [The Medicine, Angioplasty, or Surgery Study (MASS)] compared PTCA, medical treatment, and CABG (LITA-LAD) for the treatment of isolated severe proximal LAD stenosis in patients with lesions ideal for treatment with PTCA.³⁹ With 214 patients randomized and followed for 3 years there was no difference in mortality or MI rate among the 3 groups. Both revascularization strategies resulted in more asymptomatic patients (CABG, 98%),

(PTCA, 82%) when compared to medical treatment (32%) ($P < 0.01$), but no patient in any treatment group had severe angina at follow-up. Patients assigned to PTCA and medicine had more revascularization procedures during the follow-up period than did the patients assigned to surgery. The primary endpoint of the study was the combined incidence of cardiac death, MI, or refractory angina requiring revascularization. The combined endpoint occurred more often for patients assigned to PTCA (24%) and medical therapy (17%) than it did for patients assigned to bypass surgery (3%, $p < 0.006$).

5) *Summary and Limitations:*

These clinical trials offer important insight into outcomes following PTCA. As illustrated by the fact that the GABI and EAST enrolled only 4% and 8% of all screened patients, respectively, the results, therefore, may apply to only a small proportion of the population with CAD. Angiographic exclusion criteria in many of these trials included chronic total coronary occlusion and greater than 30% left main stenosis. Also, even in the short time since these trials have been enrolling patients, advances in angioplasty technique and FDA approval of coronary artery stents have changed clinical practice. These advances, along with the results of recent trials involving adjunctive therapies such as glycoprotein IIb/IIIa platelet inhibitors will likely result in improved PCI clinical decision-making later in this decade. In addition, although PCI has been compared to CABG for long-term clinical outcomes, there are no long-term data on clinical outcomes available from a randomized comparison of PCI and contemporary medical therapy.

As noted above, only the previously-published V.A. Cooperative Study (ACME) demonstrated benefit in patients with single-vessel coronary artery disease, and this trial showed only that patients randomized to PCI experienced a reduction in angina pectoris and improved treadmill exercise

performance (so-called "soft" endpoints)³⁷ and, in patients with two-vessel disease, this salutary effect was diminished.³⁸

Despite the dearth of evidence-based data which support the adoption of PCI for reasons *other than* symptom control and functional performance, it is troubling to view the impact that ACME has had in the management of CHD patients with multi-vessel CAD. Indeed, it appears that the results of the ACME trial³⁷ are being extrapolated to various CHD patient subsets in a manner that was never intended originally, namely, to patients with 2-3 vessel CHD and to those who do not have "medically refractory" angina.

Increasingly, it also appears that PCI is being performed in patients based solely on angiographic documentation of a coronary stenosis. The premise for undertaking this "prophylactic" PCI must be that such revascularization will improve clinical outcomes (event-free survival). This, however, has not yet been tested (much less proven) prospectively. The absence of scientifically sound outcomes research thus remains a major impediment to the optimal management of CHD patients.

Topol et al's study confirms that PCI is being performed on the basis of coronary anatomic findings alone, irrespective of anginal symptoms or the objective presence of myocardial ischemia.⁴⁰ Among 2,101 medically-insured CHD patients who had undergone PCI, **only 29%** had first undergone exercise testing to document objectively the presence of myocardial ischemia. In the subgroup of patients who underwent PCI after thrombolytic therapy for evolving MI, only 9% had first undergone an exercise test prior to this procedure--despite abundant published data from multiple trials indicating that PCI be reserved for patients with documented myocardial ischemia or angina refractory to medical therapy.

Since evidence-based medical practice will likely command greater attention in the years to

come, both in terms of identifying appropriate risk strata of CHD patients who may benefit most from an interventional strategy and in terms of guiding reimbursement practices of third party payers, it is essential that carefully-conducted scientific trials using a prospective, randomized, controlled study design, be undertaken to address the long-term role of catheter-based coronary revascularization and modern aggressive medical therapy on a variety of health care outcomes.

D) Limitations of Balloon PTCA

With current techniques and equipment, stand alone balloon PTCA is successful in greater than 90% of cases in immediately improving coronary artery luminal diameter and is generally associated with acceptably low rates of morbidity and mortality.^{13,41} However, several limitations exist with this approach. First and foremost, PTCA has a high rate of restenosis (30%-50%) during the first 6 months, that may detract from its long-term efficacy.⁴²⁻⁴⁴ Numerous dietary and pharmacologic interventions have failed to significantly reduce this rate.^{44,45} Second, abrupt closure rate remains at 2%-5%, although the use of newer techniques such as intracoronary stents may restore vessel patency in most of these cases.⁴⁶⁻⁵⁰ Third, while PCI may reduce the percent stenosis and hence may increase the caliber of a given diseased coronary artery, these procedures have not been shown to reduce the subsequent risk of plaque rupture and the development of acute MI.

Over the last decade, a large effort in clinical research aimed at improving the results of percutaneous coronary intervention has led to a paradigm shift, wherein interventions other than stand alone balloon angioplasty are now more frequently performed and the now widespread use of stents has greatly improved the safety of the procedure.

E) Evolution of Catheter-Based Coronary Revascularization Techniques

As noted in the preceding section many catheter-based coronary techniques have become

widely used in the management of CHD patients. None, however, has attracted as much attention and enthusiasm as has coronary stenting. Many new devices (including a variety of stents, atherectomy catheters and ablative lasers) are undergoing clinical evaluation. Currently, the Palmaz-Schatz (P-S), Multilink, ORII, UIR and Crocan stents have been shown to impact the rate of restenosis and have received Food and Drug Administration (FDA) approval. In addition, FDA approval for the clinical use of the Gianturco-Rubin (G-R) coronary stent has been obtained to reverse acute vessel closure ("bailout").

Six recently published, randomized trials have studied the effects of coronary stents on the rate of subsequent restenosis. The Belgium-Netherlands **STENT (BENESTENT-I)** Trial studied the effects of the P-S coronary stent on restenosis compared with standard balloon PTCA in 520 patients and demonstrated an initially superior angiographic result with a mean diameter stenosis of 22% in the stent group (n = 259) versus 33% in those treated with PTCA (n = 257); $p < 0.001$).⁵¹

In the **STent REStenosis Study (STRESS-I)**,⁵² 407 patients were treated at 20 centers in the U.S. and Europe, with 205 patients randomized to the P-S coronary stent and 202 patients treated with PTCA alone. The initial angiographic success rate was superior in the group randomized to stenting (mean diameter stenosis post-procedure 19% versus 35%, respectively; $p < 0.001$).⁵¹ Although the rate of bleeding complications was greater in the stent group (7.3% versus 4%; $p = 0.014$), the incidence of angiographic restenosis at 6 months was modestly lower with stenting (32% versus 42%; $p = 0.046$). Clinical restenosis, defined as the requirement for target lesion revascularization, was reduced marginally in the stent group (10.2% versus 15.4%; $p = 0.06$), and there was a nonsignificant trend toward a higher 6 month event-free rate in the stent group (81% versus 76%).⁵¹

Ongoing research efforts designed to optimize stent placement and minimize bleeding and

thrombosis complications are underway at present. Some of these activities center on delivering materials locally at the site of stent placement (biodegradable stent in which dissolution of a biomaterial matrix releases antithrombotic agents; binding of antithrombotic agents to stent struts; coating the stent with autologous endothelial cells that release t-PA). Heparin-coated P-S coronary stents were placed in a number of patients as part of the **BENESTENT-II** Trial without the subsequent need for a complicated anticoagulation regimen (warfarin not used).⁵³ In addition the results of **START**, **REST**, and **EPISTENT** have provided further evidence of the effectiveness of intracoronary stents.¹⁹⁶⁻¹⁹⁸

Currently because of the documented decrease in restenosis associated with the change of stents, 50-70% of patients undergoing coronary angiography have one or more stents placed. In addition the use of glycoprotein IIb/IIIa inhibitors especially in high-risk patients has greatly improved the outcomes of PCI.⁹⁷⁻¹⁰³

It is clear that the appropriate use and selection of the intracoronary devices will be an important part of a prospective, randomized clinical trial whose intent is to test the "optimal" catheter-based coronary revascularization procedure with adjunctive, intensive medical therapy versus the "optimal" intensive medical therapy alone.^{54,55}

F) Importance of Contemporary Intensive Medical Therapy

To underscore the importance of undertaking a prospective, randomized, controlled trial comparing optimal catheter-based coronary revascularization with optimal medical therapy, recent evidence has shown that intensive pharmacotherapy, which includes aspirin as well as lipid lowering, can decrease dramatically the progression of coronary artery disease **and** clinical events in CHD patients with hyperlipidemia and coexisting CAD.⁵¹⁻⁶³ In addition, recent studies have shown that severity of coronary stenoses--frequently the target of myocardial revascularization procedures--is a

poor predictor of future coronary events.^{64,65} Despite these data, PCI is generally advised for patients with severe, and especially proximal, coronary narrowing, as current ACC/AHA Treatment Guidelines attest.³

Concurrent with the rapid evolution and expansion of PCI and CABG surgery, there has been an equally dramatic revolution in the medical therapeutics of CHD. Aspirin has been proven to be of benefit in both primary prevention of coronary events and in secondary prevention of recurrent coronary events in patients with CHD.⁶³ Clopidogrel has been shown to be effective in the secondary prevention of recurrent coronary events and is now recommended as a substitute therapy for aspirin in patients who cannot take the latter because of hypersensitivity or gastrointestinal effects.^{66,67} Beta-blockers have been shown to prolong life after myocardial infarctions.⁶⁸ ACE inhibition has proven to prolong life in patients with LV dysfunction recovering from acute MI, and may promote additional "vascular protection" via modulations of the renin-angiotensin system by inhibition of vascular smooth muscle cell growth.^{69,70}

Most of the recent advances in medical therapy, however, have centered around the pivotal role of lipid lowering. The importance of elevated blood cholesterol as a risk factor for CHD has been established through multiple epidemiologic studies.⁷¹ In particular, the risk of elevated blood cholesterol in the CHD patients with diabetes is especially noteworthy, Mattock and co-workers have reported previously that elevated total cholesterol in type II diabetics is associated with a 4-fold increase in mortality, compared to diabetics with CHD who have no significant elevation in blood cholesterol.⁷²

In this regard a disturbing report from the recently concluded BARI trial describes the potential risk of performing PTCA procedures in CHD patients with diabetes mellitus.^{31,59} These data suggest that mortality and non-fatal infarction may occur in a higher percentage of diabetic patients who

undergo PTCA, compared to CABG surgery. This was, however, a post hoc analysis and, as such, the findings should not be regarded as definitive, but rather as hypothesis generating. Clearly this is an important subset of CHD patients who warrant additional study, particularly since BARI did not employ aggressive medical therapy in these patients.

Moreover, the importance of LDL cholesterol in the formation of atherosclerotic plaque is clearly established. Lipid lowering for CHD patients has decreased dramatically the cumulative occurrence of coronary events in both primary and secondary prevention trials.⁸⁵⁻⁸⁶ In addition, angiographic trials have demonstrated that lipid lowering can decrease progression of CAD and inhibit new lesion formation, along with some slight evidence of CAD regression.^{58,60-62} Experimental and clinical data suggest that lipid lowering can attenuate the abnormal vasoconstrictive response to acetylcholine that is seen with atherosclerosis.^{73,74} This may play an important role in preventing the development and progression of CAD.

These data suggest strongly that correction of abnormal serum lipids needs to be a cornerstone of modern therapy for patients with CHD. There are also recent epidemiologic data to suggest that treatment with antioxidants such as vitamin E can decrease coronary events.^{75,76,76a} These data are in accord with basic scientific data which stress the important role of oxidized LDL in the development of atherosclerosis.

A major advance has been the development of more potent and effective lipid lowering drugs, primarily the HMG-CoA reductase inhibitors, and their proven efficacy in the treatment of patients with CHD. A large number of coronary angiographic studies have shown that lipid lowering will slow CAD progression and prevent cardiovascular events.⁷⁸⁻⁸⁰ Furthermore, progression of CAD has been clearly linked to the development of coronary events.^{58,81-83}

However, these trials were plagued universally by small sample size, and cardiovascular events were variably defined. Furthermore, until very recently, there was no conclusive proof that lipid lowering decreased *all-cause* mortality. Older lipid lowering studies actually suggested that non-cardiac death was increased on active lipid lowering drug.^{56,84}

These uncertainties have been answered in definitive fashion by two recently-completed trials: the Scandinavian Simvastatin Survival Study (4S),⁸⁵ and the West of Scotland Coronary Prevention Study (WOSCOPS).⁸⁶ In the 5-year 4S trial of 4,444 patients with proven CHD and elevated blood cholesterol (range: 5.5-8.0 mmol/L or 213-310 mg/dL), LDL cholesterol was decreased by 35% and HDL increased by 8% in the simvastatin-treated group. All-cause mortality was decreased by over 30%, from 12% in the control group to 8% in the treated group, and cardiac mortality by 42% in the treated group. There was a significant decrease in cumulative occurrence of nonfatal MI and the need for myocardial revascularization procedures, and equally importantly, no evidence of increased non-cardiac mortality in simvastatin-treated patients.⁸⁵

In the 5-year WOSCOPS trial of 6,595 CHD patients with elevated total cholesterol (mean = 272 mg/dL 7.03 mol/L) and LDL-cholesterol (mean = 192 mg/dL 4.97 mmol/L), pravastatin therapy was associated with a 31% reduction in non-fatal MI or CHD death ($p < 0.001$), a 31% reduction in non-fatal MI ($p < 0.001$), a 32% reduction in all cardiovascular deaths ($p = 0.033$), and a 22% reduction in total (all-cause) mortality ($p = 0.051$).⁸⁶

Thus, in the late 1990s, medical therapy and myocardial revascularization should be considered *complementary* forms of treatment, and should not be viewed as being mutually exclusive. On the contrary, recent data suggest strongly that patients treated aggressively with intensive medical therapy (aspirin; anti-ischemic therapy with beta-blockers or calcium antagonists; lipid lowering therapy; ACE

inhibitors) may experience not only an amelioration of angina symptoms, but also more importantly, a decrease in mortality and nonfatal infarction. Such therapeutic developments, in the context of parallel advances in catheter-based coronary revascularization procedures, offer hope that the addition of catheter-based revascularization to proven secondary prevention interventions may optimize the management of CHD patients.

Accordingly, there is a clear need to investigate the "best" coronary interventions coupled with the "best" intensive medical therapy compared to the "best" intensive medical therapy alone.

G) Health Care Economics Implications

The major therapeutic dilemma in CHD therapeutics remains the uncertainty over the indications for, and appropriate selection of, candidates for myocardial revascularization versus medical therapy. There are many asymptomatic or mild-to-moderately symptomatic CHD patients who meet ACC/AHA PCI guidelines³ and who are referred for revascularization based primarily on the *anatomic* distribution of CAD, despite the absence of evidence-based scientific data.

The problem regarding the rational use of myocardial revascularization in the asymptomatic or mildly symptomatic CHD patient has been emphasized by the high cost of these procedures, the requirements for repeat procedures in 40%-50% of patients, and the attendant public concern among health care planners and providers regarding the high cost of such medical care. If we were to assume that the average cost of PCI is \$15,000 per procedure and 400,000 procedures are performed annually, then the direct cost is \$6.0 billion. Changes in medical care that would decrease PCI by one-third, simply by identifying a subset of patients whose clinical outcome with intensive medical therapy was similar to those receiving myocardial revascularization, could save **\$2.0 billion** annually. Conversely, identifying subsets of patients whose long-term clinical outcomes are enhanced by optimal catheter-

based coronary intervention could result in refined management strategies which are targeted most appropriately for individuals in need of myocardial revascularization and health care providers would be more willing to fund this care.

IV. RELEVANCE/IMPORTANCE OF PROPOSED RESEARCH PROJECT TO THE DEPARTMENT OF VETERANS AFFAIRS

Within the Department of Veterans Affairs (DVA), CHD remains the single largest cause of morbidity and mortality in the predominantly male veteran population. A significant percentage of DVA health care resources are devoted to the diagnosis and treatment of CHD patients, particularly those with less-than-debilitating, chronic (CCS Class I-III) angina pectoris.

Cardiac catheterization and PCI, while available at many V.A. medical centers, is not universally accessible within the DVA health care system. CHD patients in DVA facilities without a cardiac catheterization laboratory or PCI capability are often referred to those (generally larger) centers who possess invasive/interventional resources--often at a significant cost to the referring DVA station, and at an inconvenience to veterans and their families who, in some instances, may have to travel hundreds of miles to access such cardiology care.

The possible finding in the proposed **CLINICAL OUTCOMES UTILIZING REVASCULARIZATION AND AGGRESSIVE DRUG EVALUATION (COURAGE) Trial** that "hard" outcomes could be equivalent in *all but the very highest-risk* CHD patients randomized to PCI plus medical therapy versus medical therapy alone could have far-reaching clinical and cost implications within the DVA, and may result in a more cost-effective approach to managing stable CHD patients in a health care system in which cardiovascular interventional resources are finite. On the

other hand, if CS #424 were to demonstrate that PCI + intensive medical therapy was superior to intensive medical therapy alone--even in prespecified patient subsets--such prospectively-acquired data would likewise have profound implications to health care practice within the V.A..

Finally, the DVA Cooperative Studies Program has a distinguished history and track record in clinical trial management of patients with CHD. Beginning with the V.A. Cooperative Coronary Surgery Study almost 25 years ago, which antedated the similar NHBLI-funded CASS trial, there have been scores of scientifically important clinical trials published to date. Thus, the Cooperative Studies Program and the DVA are uniquely qualified and ideally positioned to undertake and initiate the proposed clinical trial.

V PLANNING COMMITTEE FOR C.O.U.R.A.G.E TRIAL

Co-Principal Investigator:

William E. Boden, MD, Professor of Medicine, Chief of Medicine, Syracuse NY

Co-Principal Investigator:

Robert A. O'Rourke, MD, Charles Conrad Brown Distinguished Professor of Medicine
San Antonio, TX

Study Statistician:

Pamela M. Hartigan, PhD, Associate Professor, CSPCC, West Haven, CT

Health Care Economics/Resource Utilization:

William S. Weintraub, MD Professor of Medicine, Emory, Atlanta, GA

Study Pharmacist:

Nancy Morgan, RPH, CSPCRPCC, Albuquerque, NM

Additional Committee Members:

Alvin S. Blaustein, MD, Associate Professor of Medicine Baylor, Director, Non-Invasive Cardiology
Houston, TX

Michael H. Crawford, MD, Robert S. Flinn Professor of Medicine, Director, Division of Cardiology
Albuquerque, NM

Katherine M. Detre, MD, Dr.PH, Professor of Biostatistics, Pittsburgh, PA

Michael D. Ezekowitz, MB, ChB, Professor of Medicine at Yale, Chief, Cardiology
West Haven, CT

Alice Jacobs, MD, Associate Professor of Medicine, Boston MA

Merril Knudtson, MD, Professor of Medicine, Director, Cardiac Catheterization Laboratory
Calgary, Alberta, Canada

Koon Teo, MB, PhD, Associate Professor of Medicine, University of Alberta, Edmonton, Alberta
Canada

Salim Yusuf, MB, DPhil, Professor of Medicine, Hamilton General Hospital, Hamilton, Ontario
Canada

David J. Maron, MD, Assistant Professor of Medicine Vanderbilt, Director, Preventive Cardiology
Nashville, TN

Alfred F. Parisi, MD, Professor of Medicine Brown, Chief, Cardiology, Providence, RI

Joseph A. Vita, MD, Associate Professor of Medicine, Boston, MA

David O. Williams, MD, Professor of Medicine Brown, Director Cardiac Catheterization Laboratory
Providence, RI

VI. METHODS AND DESIGN OF PROPOSED TRIAL

A) Aims

Coronary artery disease (CAD) is a chronic, complicated disease process in which there can be recurring symptoms and ischemic events spanning decades. Included within the spectrum of this disease are cardiac events (death; nonfatal MI; refractory or unstable angina; need for subsequent myocardial revascularization), CAD effects on physical and social functioning, and economic consequences (direct and indirect costs) associated with CAD treatment. The complicated pathophysiology, variable clinical course and numerous approaches to management of the disease with its long time span has made the assessment of comparative therapies relatively difficult.

The classic manner in which a new form of therapy is evaluated generally involves, at some point, the selection of a clinically compelling endpoint followed by the design of a suitably powered randomized, controlled, clinical trial. Despite the widespread adoption of PCI and escalating use of newer catheter-based coronary interventions over the last 15+ years, there has not been, to date, a prospective, randomized comparison of angioplasty to medical therapy suitably powered for hard endpoints. As valuable as randomized trials have been, however, the classic trial design utilizing all-cause mortality as a singular primary endpoint may be unfeasible if the occurrence of death is

relatively infrequent.

Another potential limitation of the randomized, controlled trial is limited external generalizability, particularly when inclusion/exclusion criteria are stringent, and randomized patients represent a small percentage of the larger population of eligible CHD patients. Ongoing technical evolution may pose certain difficulties in study design, since it is imperative that state-of-the-art procedures and medical treatments be compared prospectively in a "real world" context that can be extrapolated to contemporary clinical practice.

However, other prognostically-important clinical outcomes (nonfatal MI; refractory angina/ischemia necessitating myocardial revascularization, stroke) and various health care outcomes (quality of life; cost-effectiveness; resource utilization) are important surrogate endpoints which are worthy of study, because many CHD patients will experience one or more events that may have significant effects on their quality of life and/or economic outcomes.

The intent of CSP #424 (COURAGE Trial) is to incorporate a study design which is both inclusive and representative of CHD clinical practice, permits investigator/operator decision-making in the choice of "optimal" catheter-based coronary revascularization procedures, uses standard published treatment guidelines adopted by national organizations, and entails sufficient sample size and power to assess the comparative effect of two randomized treatment strategies on the cumulative occurrence of a trial primary endpoint of all-cause mortality + nonfatal MI in CHD patients with documented myocardial ischemia.

B) Objectives

The principal objectives of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial are to assess prospectively both "hard" endpoint outcomes

(death; nonfatal MI; refractory angina necessitating CABG surgery, stroke) and other health care outcomes (resource utilization; quality of life measures; cost-effectiveness and cost-utility measures) during long-term (3-6 year) follow-up after randomization to PCI + intensive medical therapy versus intensive medical therapy alone in *all but the very highest-risk* CHD patients who meet one or more ACC/AHA Joint Task Force Class I (Definite) or II Indications for PCI.

C) Design Overview

The **COURAGE** Trial will be the first large-scale, multicenter, randomized controlled trial that is powered for a combined trial primary endpoint of all-cause mortality and nonfatal MI in CHD patients. Patients eligible for inclusion in **COURAGE** would comprise those with chronic angina pectoris (Canadian Cardiovascular Society [CCS] Class I-III), stable post-MI patients, and asymptomatic (or "silent") myocardial ischemia who have either single-vessel or multi-vessel CAD. The only major exclusions to patient enrollment will be persistent CCS Class IV angina status on medical therapy, angiographic left main stenosis $\geq 50\%$, left ventricular ejection fraction $< 30\%$, or severe three vessel CAD with proximal LAD disease $\geq 70\%$ and with an LVEF $\leq 35\%$.

All patients must meet standard, clinically accepted inclusion criteria for CHD **and** must exhibit objective evidence of myocardial ischemia. If antecedent cardiac catheterization has not been performed recently, eligible patients will be informed and consented prior to diagnostic coronary angiography. Cardiac catheterization will then be performed and, if coronary anatomy is suitable for myocardial revascularization, potential study patients will be randomized and treated as assigned. Alternatively, if cardiac catheterization has been performed within the last 30 days, trial-eligible patients with suitable coronary anatomy will be randomized and treated as assigned.

The two therapeutic strategies which will be compared randomly are "PCI" (whichever

catheter-based coronary revascularization technique the operator feels would be optimal for that patient; this could include standard balloon PTCA, directional coronary atherectomy, rotoblator, and intracoronary stents--alone or in combination) *in addition to* intensive medical therapy, versus a strategy of intensive medical therapy alone.

Intensive medical therapy will conform to recent, updated AHA Treatment Guidelines¹ so that patients enrolled in COURAGE will be in full compliance with contemporary pharmacologic management. All randomized patients will be counseled about diet, smoking cessation, exercise and hypertension management. Intensive medical therapy, as utilized in the COURAGE Trial, will be "aggressive" and multifaceted. It is configured to target both the stabilization or regression of atherosclerotic plaque and a reduction in clinical events. Patients in both treatment arms will receive:

- 1) aspirin (enteric-coated) 80-325 mg/day (clopidogrel 75 mg/day in patients unable to take aspirin);
- 2) an HMG co-enzyme A reductase inhibitor (simvastatin) with a goal of reducing low-density lipoprotein (LDL)-cholesterol to 60-85 mg/dL (1.56-2.21 mmol/L). To date, no prospective, clinical trial of PCI-eligible patients has ever attempted such vigorous lipid altering in both treatment arms. In trial patients whose LDL-cholesterol cannot be lowered below 85 mg/dL (2.21 mmol/L) with maximal dose simvastatin monotherapy (80 mg/day), a bile-acid sequestrant will be added to achieve the desirable LDL target. It is estimated that combination therapy will be required in no more than 10% of patients;
- 3) for patients with hypertension, as primary therapy, a choice of an angiotensin-converting enzyme (ACE) inhibitor (lisinopril), a long acting calcium antagonist (amlodipine) and/or an angiotensin receptor blocker (losartan).

4a) *for post-MI patients randomized to the medical therapy arm:*

routine beta-blocker administration usually begun in the hospital, or started when patient is first seen during first year of follow-up, will be utilized as standard secondary prevention for patients with Q-wave MI, whereas diltiazem or a beta-blocker will be administered as secondary prevention for patients with non-Q-wave MI; diltiazem or amlodipine will be used for all patients post-MI who have a contraindication or sensitivity to beta-blockers; ACE inhibitors will usually be prescribed for patients with depressed LVEF and for many patients with normal LVEF, especially patients with anterior MI or those with diabetes.

4b) *for CHD patients WITHOUT MI randomized to the medical therapy arm:*

anti-ischemic therapy will consist of a beta-blocker (as tolerated), long acting nitrates, and/or a long acting calcium antagonist (diltiazem or amlodipine); amlodipine may be substituted for a beta-blocker when the LV function is mildly depressed;

4c) *for CHD patients randomized to the "PCI" arm:*

patients assigned to the PCI arm will receive similar anti-ischemic therapy as outlined in 4a and 4b but, except for standard secondary prevention post-MI, an attempt will be made to discontinue *routine* anti-ischemic medical therapy, if possible, within 3-6 months after randomization to PCI in otherwise asymptomatic patients who have been successfully revascularized.

5) unstable angina patients at moderate to high risk who have responded to initial medical therapy with a glycoprotein IIb/IIIa inhibitor (tirofiban) and unfractionated heparin, beta-blockers, and nitrates will also be considered for randomization.

It is important to emphasize that, by trial design, the target population under study in COURAGE will **not** be low-risk. As many types of CHD patients as possible--reflecting the spectrum of CHD patients encountered in contemporary clinical practice--will be enrolled in COURAGE, including patients with LVEF as low as 30%, patients with coronary angiographic narrowing of any severity (except $\geq 50\%$ stenosis of left mainstem CAD or combined severe three vessel CAD with $\geq 70\%$ stenosis of proximal LAD and EF $< 35\%$), and patients who have undergone CABG or PCI more than 6 months prior to randomization. Persistent CCS Class IV patients despite maximal medication will not be included.

D) Inclusion Criteria

Male and female CHD patients will be eligible for enrollment in CS #424 if they meet each of the following *inclusion criteria*:

- 1) CCS Class I-III CHD patients, including patients with prior PCI or CABG, who have **objective evidence of myocardial ischemia** (see # 3 following) at the time of randomization, and who *can be managed medically* (or are candidates for medical therapy); eligible patient subsets might include:
 - a) chronic stable angina
 - b) stable post-MI course without recurrent rest or minimal-exertion angina (*not* CCS Class IV), severe LV dysfunction, or arrhythmia (see below);
 - c) acute coronary syndrome patients who have been stabilized on intravenous and/or oral medications, and who have not experienced recurrent rest angina/ischemia for at least 48 hours after discontinuation of intravenous medications (e.g., heparin, nitroglycerin, etc.);

- d) asymptomatic ("silent") myocardial ischemia, as detected by exercise or perfusion scintigraphy, or 24-hour ambulatory ECG monitoring;
- 2) Meets an existing ACC/AHA Joint Task Force Class I or II Indication for PCI,³

These indications are:

- a) single-vessel coronary artery disease patients who are **asymptomatic to severely symptomatic** and who have a “large area” of ischemic myocardium subtending a significant ($\geq 50\%$ diameter reduction) coronary stenosis (ACC/AHA “Class I” Definition] Indication for PCI) (Revision pending) or a “moderate area” of ischemia (an ACC/AHA “Class II” for those with only asymptomatic or mildly symptomatic ischemia [Probable but Uncertain] Indication);
 - b) multi-vessel coronary artery disease patients who are **asymptomatic or mildly symptomatic** who have a “large ischemic area” or “moderate ischemic area” (ACC/AHA “Class II” for asymptomatic or minimally symptomatic patients).
- 3) Has as least one vessel for angioplasty meeting on of the following criteria
- a) RCA: Proximal to the PDA in a right dominant vessel
 - b) LCX: Proximal to 2 or more OM branches or proximal to the PDA + PL branches in a left dominant vessel
 - c) LAD: Proximal or mid-vessel
 - d) SVG or IMA: Graft must supply same regions as outlined above,
or
 - e) In the opinion of the interventionalist the coronary stenosis subtends a “major” mass of myocardium.

- 4) Has objective evidence of myocardial ischemia, which **must include one of the following (a OR b):**
- a) spontaneous, transient ST-T changes on resting ECG; patients must display new (or changed, compared to previous ECG tracing(s)) repolarization, defined as *either* ≥ 1.0 mm ST-segment deviation from baseline (80 msec after the J point) *or* ≥ 2.0 mm T wave inversion (or "pseudonormalization", if T waves were previously inverted) in a minimum of 2 contiguous leads within 1 of 3 ECG lead groups (anterior = V₁-V₄; inferior = II, III, aVF; lateral = I, aVL, V₅-V₆);
 - b) objective evidence of stress-induced myocardial ischemia as detected by; standard 12 lead ECG exercise treadmill test; exercise or pharmacologic stress (adenosine or dipyridamole) coupled with perfusion scintigraphy (technetium sestimibi or thallium based-based isotopes); exercise or pharmacologic stress (dobutamine) coupled with 2-D echocardiography; or exercise radionuclide ventriculography, **based on one of the following criteria:**
 - i. ≥ 1.0 mm ST-segment deviation from baseline on standard treadmill exercise using 12 lead ECG; OR
 - ii. 1 or more scintigraphic perfusion defects (reversible or partially reversible) during exercise technetium sestimibi or thallium-based isotope imaging; OR
 - iii. 1 or more scintigraphic perfusion defects (reversible or partially reversible) with pharmacologic stress (dipyridamole, adenosine) during technetium sestamibi or thallium imaging; OR

- iv. 1 or more wall motion abnormalities during exercise radionuclide ventriculography or 2-dimensional echocardiography (exercise or dobutamine).

NOTE: The preferred method of establishing ischemia will be with technetium sestimibi SPECT perfusion imaging.

E) Exclusion Criteria

One or more of the following criteria will *exclude* a CHD patient from enrollment in CSP #424; these include:

- 1) CHD associated with unstable angina or symptoms refractory to maximum oral or intravenous medical therapy (persistent CCS Class IV);
- 2) Post-MI course complicated by persistent post-infarction angina/ischemia at rest, shock, persistent CHF, etc. for which the need or likelihood of urgent myocardial revascularization is high;
- 3) Coronary angiographic exclusions:
 - a) in patients with no prior CABG, left mainstem coronary stenosis $\geq 50\%$;
 - b) coronary anatomy technically unsuitable or hazardous for PCI;
 - c) patients with nonsignificant coronary artery disease in whom PCI would not be considered appropriate or indicated;
- 4) Ejection fraction $< 30\%$, except $\leq 35\%$ if patient has severe 3-vessel disease including $\geq 70\%$ LAD proximal stenosis;
- 5) Cardiogenic shock;
- 6) Pulmonary edema or CHF unresponsive to standard medical therapy;

- 7) CABG surgery or PCI within 6 months of randomization;
- 8) Concomitant valvular disease likely to require surgery or affect prognosis during follow-up period;
- 9) Congenital or primary cardiac muscle disease likely to affect prognosis during follow-up;
- 10) Resuscitated out-of-hospital sudden death, or symptomatic sustained or non-sustained ventricular tachycardia;
- 11) Significant persistent systemic hypertension (BP>200/100 mm Hg) despite treatment;
- 12) Lipid exclusion criteria: fasting TG >400 mg/dl (10.39 mmol/L), LDL >250 mg/dl (6.49 mmol/L) (LDL >200 mg/dl [5.19 mmol/L] in subjects already on statin therapy)
- 13) Pregnant, or likely to become pregnant, women
- 14) Other significant co-morbidity likely to cause death during the 3-6-year follow-up;
- 15) Patients with a significant active history of substance abuse;
- 16) Patients unwilling to give informed consent or follow study protocol;
- 17) Refusal of patient's physician to allow participation in the study
- 18) Participation in another long-term randomized clinical trial.

F) Pre-Randomization Testing and Stratification

Patients at clinical sites who are to undergo coronary angiography will be pre-screened prior to catheterization for possible trial entry. The tool to screen patients is the screening form (see Volume 2, Part B). If a patient is eligible, and his or her physician agrees, he or she will be

approached about participating in the trial. If antecedent diagnostic cardiac catheterization has not been performed, informed written consent will be obtained prior to the coronary angiography (preferred). If the diagnostic catheterization has already been performed, it should have been no longer than 30 days prior to study entry, with no intercurrent events.

Patients who are protocol-eligible based on the clinical inclusion/exclusion criteria will first undergo noninvasive diagnostic testing:

- 1) Assessment of LV ejection fraction (EF), utilizing radionuclide ventriculography, 2-D quantitative echocardiography, or left ventricular contrast angiography (EF < 30% excludes patient);
- 2) Stress test (standard ECG treadmill exercise; pharmacologic or exercise myocardial perfusion scintigraphy; exercise or pharmacologic wall motion analysis [radionuclide ventriculography; 2-D echocardiography]) to verify or quantify objective evidence of inducible myocardial ischemia or regional wall motion abnormality. Exercise myocardial perfusion scintigraphy using technetium sestamibi with SPECT imaging will be the *preferred* method in patients who are able to exercise. Thallium with planar or SPECT imaging in patients who are able to exercise is also acceptable. Standard treadmill exercise without perfusion scintigraphy can be used, if the baseline ECG-ST segment is not rendered uninterpretable (e.g. digoxin effect, left ventricular hypertrophy, left bundle branch block, pacemaker, etc.). In patients who are *unable to exercise* (or unable to achieve at least 5 METS of exercise) or have left bundle branch on ECG, pharmacologic stress (dipyridamole or adenosine [adenosine preferred]) will be used in conjunction with perfusion scintigraphy (technetium sestamibi is preferred,

but thallium is acceptable) to detect reversible defects. Alternatively, dobutamine 2-D echocardiography or exercise radionuclide ventriculography can be used to detect ischemia-induced regional wall motion abnormalities in patients unable to exercise;

- 3) Resting ECG documentation of ischemia (ST-T wave changes in 2 or more contiguous leads within a lead group). Ambulatory ECG, ST-segment depression of >60 seconds duration.

If the patient is still eligible, the catheterization (with a possibility of PCI) will be scheduled as soon as possible. Coronary angiograms will be obtained using a standardized protocol and, if coronary anatomy is suitable for catheter-based myocardial revascularization, the patient is a candidate for randomization. Of note, CHD patients with diabetes who undergo cardiac catheterization will receive non-ionic contrast media to minimize the risk of subsequent renal failure. Within each medical center, patients will be stratified into two strata based on the history of prior CABG surgery.

If the coronary angiogram is not available prior to the patient being consented, the clinical coordinator will call the West Haven Cooperative Studies Program Coordinating Center (CSPCC) to review the check list confirming the patient's eligibility, to discuss the stratum, and to alert the Coordinating Center that a randomization is imminent. For these cases, when the patient will be randomized while in the cardiac catheterization laboratory, a computer-generated envelope system will be used for treatment assignment.

If the angiogram is already available when the clinical coordinator calls the Coordinating Center to confirm the patient's eligibility, the treatment assignment will be given on the telephone. A "backup" envelope system will be available but, if it is used, the Coordinating Center must be informed as soon as possible after the randomization.

Patients will be stratified by medical center and history of antecedent CABG surgery. The randomization scheme will be constructed using a permuted block design within strata. The length of the blocks will be randomly determined between 2, 4, and 6.

In patients who are randomized to the "PCI + intensive medical therapy arm," PCI should be performed within 45 days of the diagnostic catheterization. Procedure and catheterization films will be forwarded to the Angiography Core Laboratory for assessment and coding. (See Operations manual for guidelines as to views and procedures for cinefilms).

G) Risk Factor Intervention for All Study Patients

The COURAGE clinical coordinator will perform a comprehensive risk factor assessment, including fasting blood tests. The coordinator will discuss an individualized risk intervention program with each patient. The intervention and goals are based largely on AHA guidelines and are summarized in Table 1.

1) Smoking Cessation:

Every subject will be asked at every visit about tobacco use. All smokers will be strongly encouraged to stop smoking. Smokers willing to make a quit attempt will be identified. Smoking cessation clinical practice guidelines from the AHCPR will be used to assist the subject in quitting (JAMA 1996;275:1270-1280). Individual counseling, nicotine replacement, bupropion, and formal cessation programs will be recommended as appropriate to current smokers. Each center will use their existing local smoking cessation programs on an as needed basis.

Table 1: Risk Factor Goals													
Variable	Goal												
Smoking	Cessation												
Total Dietary Fat	<30% calories (66g men, 45g women)												
Saturated Fat	<7% calories												
Dietary Cholesterol	<200 mg/day												
LDL cholesterol (primary goal)	60-85 mg/dL (1.56-2.21 mmol/L)												
HDL cholesterol (secondary goal)	>35 mg/dL (0.91 mmol/L)												
Triglycerides (TG) (secondary goal)	<200 mg/dL (5.19 mmol/L)												
Physical Activity	30-45 minutes of moderate intensity activity 5 days per week (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, using stairs, gardening, household work)												
Body Weight (<u>Weight Category</u>) By Body Mass index (BMI)	<table border="0"> <tr> <td></td> <td>Initial BMI</td> <td><u>Weight Loss Goal</u></td> </tr> <tr> <td>Desirable <25</td> <td>25-27.5</td> <td>BMI <25</td> </tr> <tr> <td>Overweight 25.0-29.9</td> <td>>27.5</td> <td>10% relative weight loss</td> </tr> <tr> <td>Obese ≥30.0</td> <td></td> <td></td> </tr> </table>		Initial BMI	<u>Weight Loss Goal</u>	Desirable <25	25-27.5	BMI <25	Overweight 25.0-29.9	>27.5	10% relative weight loss	Obese ≥30.0		
	Initial BMI	<u>Weight Loss Goal</u>											
Desirable <25	25-27.5	BMI <25											
Overweight 25.0-29.9	>27.5	10% relative weight loss											
Obese ≥30.0													
Blood Pressure	<130/85 mmHg												
Diabetes	HbA _{1c} <7.5%												

2) *Nutrition:*

If the volunteer is randomized into the study, a simple baseline dietary evaluation will be

obtained by the clinical coordinator using MEDFICTS (see appendix). At the first visit, subjects will be instructed by the nurse or dietitian to achieve and maintain an AHA Step II diet. Drug therapy will be initiated according to the COURAGE lipid management algorithm.(see Lipid-Altering Drug Therapy, Section H, part 4).

3) *Lipid Management:*

A fasting lipoprotein profile will be obtained prior to randomization. This will be the “baseline” value. The lipid lowering drug therapy will be begun immediately. A simple baseline dietary evaluation will be obtained by the case manager to assist in the development of individualized recommendations for each study subject. Subjects will be instructed by a dietitian in a low-fat, low-cholesterol, high complex carbohydrate diet with a goal of achieving $\leq 30\%$ of energy intake from fat, $< 7\%$ from saturated fat, and $\leq 200\text{mg}$ cholesterol per day. Fat intake may be liberalized, if hypertriglyceridemia results from the low fat/high carbohydrate study diet. (See Lipid Lowering Drug Therapy, Section H, part 4).

4) *Physical Activity:*

After randomization, the subject’s current level of physical activity will be assessed. Based on the subject’s activity level, readiness to change, and treadmill performance a specific endurance-training program will be prescribed by the coordinator. Moderate intensity activities (e.g., walking, jogging, and cycling) 5 times a week will be prescribed (minimum: 3 times/week; 30 minutes per session). In addition, an increase in daily activities such as walking breaks at work, using stairs whenever possible, gardening, and doing household work will be recommended.

5) *Weight Management:*

The AHA definition for obesity will be adopted for COURAGE. Body Mass Index (BMI,

kg/m²) <25 is desirable, 25-30 is overweight, and ≥30 is obese. If the initial BMI is 25-27.5, the goal is to achieve a BMI <25. If the initial BMI is >27.5, a 10% relative weight loss is the target. Calories will be restricted and physical activity increased as needed to achieve weight goals.

6) *Management of Diabetes Mellitus:*

Non-insulin-dependent diabetes mellitus (NIDDM) increases considerably the risk for all manifestations of atherosclerotic vascular disease; CHD, cerebro-vascular disease, and peripheral vascular disease.⁸⁷ While the recently published report from the Diabetes Control and Complications Trial (DDCT) showed that the risks for retinopathy, nephropathy, and neuropathy were substantially reduced in the intensively treated group of insulin-dependent diabetes mellitus (IDDM) patients with good glycemic control compared with the conventionally treated group, the association between glycemic control and the risk for developing CHD complications in NIDDM is less certain.⁸⁸

Two recent, prospective, population-based studies from Finland give evidence for the linear association of glycemic control (fasting blood glucose and glycated hemoglobin A_{1C} levels) with the risk of CHD in middle-aged and elderly patients with NIDDM.⁸⁹ In these studies, 10-year cardiovascular mortality was significantly and linearly associated with glycemic control (fasting blood glucose and glycated hemoglobin A_{1C} levels) independently of the mode of treatment. In addition, glycated hemoglobin A_{1C} was the most important single risk factor associated with CHD death and all CHD events. Accordingly, the goal for diabetes mellitus management in the COURAGE trial will be to maintain levels of fasting blood glucose 80-140 mg/dL (4.44-7.77 mmol/L) and HbA_{1C} <7.5% in diabetic patients enrolled in the trial. These guidelines are in accord with published recommendations of the American Diabetes Association⁹⁰ and the DDCT Consensus Report.⁸⁸ If the fasting plasma glucose is <80 or >140 mg/dl (<4.44 or >7.77 mmol/L), or HbA_{1C}

>7.5%, consultation with or referral to the primary care physician is recommended.

H) Intensive Medical Therapy: Guidelines and Management

Medical therapy for this study will conform to current, updated AHA Treatment Guidelines¹. It is aggressive and multifaceted. It is targeted for the dual purpose of achieving atherosclerotic plaque stabilization (or regression), and reducing prognostically important clinical events. The following guidelines (Table 2, 3, & 3a) are provided to ensure a consistent therapeutic approach with the understanding that a **particular drug may be administered for more than one purpose** (e.g. metoprolol for secondary prevention and angina or amlodipine for hypertension and angina). It is also understood that these are guidelines and no drug is mandated.

- 1) *All Patients will receive Anti-thrombotic Therapy*
 - a) aspirin (enteric-coated) 80-325 mg/day;
 - b) in patients who have an allergy or hypersensitivity to aspirin, clopidogrel will be administered in a dose of 75 mg daily.
- 2) *Anti-ischemic Therapy:*
 - a) *Chronic Coronary Syndromes:*

The post randomization anti-ischemic therapy guidelines are outlined in Table 2. Our goals for this therapy are to keep COURAGE Trial patients as symptom free as possible within their individual tolerances for medication, and to configure prophylactic therapy targeted to abolish (or diminish) myocardial ischemia.

Table 2: Specific Anti-ischemic therapy with or without LV dysfunction			
		LVEF > 40%	LVEF ≤ 40%
Recommendations	Secondary prevention (post MI; LV dysfunction)	<u>Q-wave MI:</u> <ul style="list-style-type: none"> • long acting metoprolol <u>Non-Q wave MI:</u> <ul style="list-style-type: none"> • diltiazem or long acting metoprolol • ± ACE I (lisinopril) 	<ul style="list-style-type: none"> • ACE I inhibitor (lisinopril) • long acting metoprolol (if tolerated)
Guidelines	Symptomatic Ischemia	<i>*Maximize existing drug therapy</i> <ul style="list-style-type: none"> • amlodipine • long acting metoprolol (if tolerated) • isosorbide 5-mononitrate 	<i>*Maximize existing drug therapy</i> <ul style="list-style-type: none"> • amlodipine • isosorbide 5-mononitrate • long acting metoprolol (if tolerated)
	Silent Ischemia only	<ul style="list-style-type: none"> • amlodipine • long acting metoprolol • isosorbide 5-mononitrate 	<ul style="list-style-type: none"> • amlodipine • long acting metoprolol (if tolerated) • isosorbide 5-mononitrate

*maximize drug therapy implies the use of optimal doses within classes

b) Unstable angina:

Patients with unstable angina will be characterized as low to high risk by the criteria indicated in Table 3a and therapy will be initiated according to Table 3b. Recent data support the use of either low molecular weight heparin or certain antiplatelet IIB/IIIa glycoprotein inhibitors (tirofiban, eptifibatide) plus unfractionated heparin in the treatment of intermediate to high risk unstable angina with additional benefit over aspirin and beta-blockers with unfractionated heparin alone.⁹¹⁻⁹⁵

Patients whose chest pain responds to the therapy outlined in Table 3b should be catheterized and if they are eligible for the study, randomized to PCI plus aggressive medical therapy or aggressive medical therapy alone.

Table 3a : Short-Term Risk of Death or Nonfatal Myocardial Infarction in Patients with Unstable Angina			
Patient Characteristics	Risk Level		
	High Risk	Intermediate Risk	Low Risk
Angina	Rest angina with <u>at least one</u> of the following criteria:	Current or recent rest angina <u>without</u> high-risk criteria but with at least one of the following:	No CCSC III or IV angina, but angina with at least one of the following
Other Criteria	<ul style="list-style-type: none"> A. Prolonged ongoing course (>20 min) B. ST-segment depression >1.0 mm during pain in multiple leads C. Elevated serum levels of cardiac markers of ischemic injury (troponin I or Troponin T) D. Clinical or laboratory evidence of moderate to severe left ventricular dysfunction 	<ul style="list-style-type: none"> A. Deep T-wave inversions (> 3 mm) in multiple leads B. Age ≥65 years C. Diabetes mellitus D. New Canadian Cardiovascular Society Class Grade III or IV angina within past two weeks E. Prior myocardial infarction by history or ECG evidence 	<ul style="list-style-type: none"> A. Increased angina frequency, severity, or duration with activity B. Angina provoked at a lower threshold C. New onset angina within two weeks to two months of presentation, D. A – C plus normal or unchanged electrocardiogram

Table 3b: Therapy According to Risk Stratification for Patients with Unstable Angina		
High Risk	Intermediate Risk	Low Risk
Aspirin, beta-blockers, nitrates, and IIb/IIIa inhibitors + unfractionated heparin	Aspirin, beta-blockers, nitrates, and IIb/IIIa inhibitors + unfractionated heparin	Aspirin, beta-blockers, amlodipine, and nitrates, as needed

If the patient is randomized to PCI plus aggressive medical therapy, unfractionated heparin and IIb/IIIa inhibitors should be continued for a minimum of 12 hours post-PCI with a

total duration of therapy of at least 48 hours. If the patient is randomized to aggressive medical therapy alone, unfractionated heparin plus GP IIb/IIIa inhibitors should be continued for a total of 48 hours. The patient will then undergo noninvasive stress testing to assess the severity of the residual ischemia, if any. Myocardial revascularization should be considered for those patients with severe residual ischemia.

INDICATIONS AND USAGE OF TIROFIBAN

Tirofiban in combination with heparin, is indicated for the treatment of **acute coronary syndrome**, including patients who are to be managed medically and those undergoing PTCA or atherectomy. In this setting, tirofiban has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure.

CONTRAINDICATIONS TO TIROFIBAN

1. Known hypersensitivity to any component of the product.
2. Active internal bleeding or history of bleeding diathesis within the previous 30 days
3. History of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm
4. History of thrombocytopenia following prior exposure to tirofiban
5. History of stroke within 30 days or any history of hemorrhagic stroke
6. Major surgical procedure or severe physical trauma within the previous month
7. History, symptoms, or findings suggestive of aortic dissection
8. Severe hypertension (systolic blood pressure > 180mmHg and/or diastolic blood pressure >110 mmHg).
9. Concomitant use of another parenteral GP IIb/IIIa inhibitor

10. Acute pericarditis

RECOMMENDED DOSAGE OF TIROFIBAN

In clinical trials establishing efficacy and in currently recommended use, tirofiban is given to patients with unstable angina or non-Q wave myocardial infarction as a two-staged intravenous infusion regimen of a loading infusion of 0.4 µg/kg/min for 30 minutes followed by a maintenance infusion of 0.1 µg/kg/min. This dose produces approximately 90% inhibition of the ex-vivo ADP-induced platelet aggregation with a 2.9 fold prolongation of bleeding time during the loading infusion. Inhibition persists over the duration of the maintenance infusion.

U.S. Investigators: For further information please refer to the CLINICAL STUDIES and DOSAGE AND ADMINISTRATION sections of the product circular included in the Pharmacy Handbook.

Canadian Investigators: Aggrastat is not a marketed product in Canada. For further information please refer to the Confidential Investigators Brochure provided you by Merck Frost.

3) Anti-Hypertensive Therapy:

All patients whose blood pressure consistently exceeds 130/85 mmHg should be prescribed anti-hypertensive therapy. In keeping with published therapeutic guidelines, the goal will be to reach and maintain the target of blood pressure below 130/85 mmHg. It is expected that most patients will be on beta-blockers and/or a long acting calcium antagonist. Established therapeutic regimens should be maximized to reach the target. If additional therapy is needed, the following drug choices are suggested:

- an ACE inhibitor (lisinopril) or amlodipine
- an angiotensin II inhibitor (losartan) often with a diuretic in addition, except in patients with an EF≤39% or those who had an MI in the previous 6 months
- a heart rate-lowering calcium antagonist
- a beta-blocker without ISA

- a diuretic

Within each treatment class, an attempt will be made to maximize the dosage, as tolerated clinically, in order to achieve a desired therapeutic effect; if blood pressure remains elevated, a second medication from a different class may be added to achieve an anti-hypertension effect.

4) *Lipid-Altering Therapy:*

Primary Goal: LDL 60-85 mg/dL (1.56-2.21mmol/L)

Secondary Goals: HDL >35 mg/dL (0.91 mmol/L);

TG <200 mg/dl (5.14mmol/L)

Lipid Exclusion Criteria: Fasting TG>400mg/dl (10.39 mmol/L), LDL>250 mg/dl (6.49 mmol/L) (LDL >200 mg/dl [5.19 mmol/L] in subjects already on statin therapy at baseline.

a) *Rationale for Target:*

To achieve a mean LDL <100 mg/dl (2.60 mmol/L) it will be necessary to have a target below that level. This was demonstrated in the SCRIP and post-CABG trials. In SCRIP the LDL goal (designed in the early 1980s before the NCEP was established) was 110 mg/dl (2.86mmol/L). The mean LDL achieved was 121 mg/dl (3.14 mmol/L). In the post CABG trial, the LDL goal was 60-85 mg/dl (1.56-2.21 mmol/L) and the mean LDL achieved ranged from 93-97 mg/dl (2.42-2.52 mmol/L). Based on this experience it appears that a stated goal at least 10 mg/dl (0.26mmol/L) below the desired goal is necessary. The reason for focusing on LDL is that this was the primary intervention in the 4S and CARE trials. In 4S, CARE, and post CABG Trial patients with low HDL at baseline benefited from LDL lowering.

b) *Lipid Measurements:*

Fasting lipid panels will be analyzed at the Core Lab at baseline, 6 months, and annually

thereafter until the termination of the trial. Fasting lipid panels will also be measured by laboratories at the local sites on each of these occasions and at other times as indicated clinically to achieve and maintain the LDL goal. A fasting lipoprotein profile will be obtained at the time of the initial clinical screening. This will be the “baseline” value even though the subject may not be in a stable metabolic state and may already be on lipid lowering drug therapy.

c) *Rationale for Lipid Exclusion Criteria:*

Excluding patients with TG >400 mg/dl (10.39 mmol/L) simplifies the algorithm making simvastatin the first line of therapy for all subjects and making the estimation of LDL simple using the Friedewald equation. The number of patients excluded from the protocol on the basis of high triglycerides should be sufficiently small that what is gained in simplicity exceeds what is lost in generalizability. Excluding patients with LDL >250 mg/dl (6.49 mmol/L) (LDL >200 mg/dl [5.19 mmol/L] in subjects already on statin therapy) will simplify the protocol as these patients will require more aggressive and individualized therapy, and will be very uncommon. It is anticipated that the average baseline LDL will be \leq 160 mg/dl (4.16 mmol/L) which should permit the majority of subjects to achieve the LDL goal with simvastatin monotherapy. If additional LDL lowering is required on maximum dose simvastatin, a bile-acid sequestrate will be added if there are no contraindications.

TABLE 4

LIPID ALGORITHM FOR COURAGE

Primary Goal:	LDL 60-85 mg/dl (1.56-2.21 mmol/L)	Secondary Goals:	HDL > 35 mg/dl (0.91mmol/L); TG < 200 mg/dl (5.19 mmol/L)
Baseline Fasting Lipid Profile (obtained in hospital). Discontinue lipid lowering medication unless it is simvastatin			
STEP 1: INITIATING THERAPY			
a. For subjects on statin other than simvastatin at baseline:			
<u>LDL (mg/dl) (mmol/L)</u>	<u>Initial Rx (mg)</u>		
If < 50 <1.30	Back-titrate to simvastatin at equivalent ½ dose		
If ≤ 50-85 ≤1.30-2.21	Simvastatin at equivalent dose		
If > 85 >2.21	Simvastatin dose at one step higher than current equivalent		
b. For subjects not on any lipid medication at baseline:			
<u>LDL (mg/dl) (mmol/L)</u>	<u>Initial Rx (mg)</u>		
<100 <2.60	Simvastatin 10 qhs		
100-129 2.60-3.37	Simvastatin 20 qhs		
>130 >3.38	Simvastatin 40 qhs		
c. For subjects on simvastatin at baseline: <u>GO TO STEP 2.</u>			
STEP 2: TITRATING THERAPY			
A	If LDL is > 85 mg/dl (2.21 mmol/L) at the next visit after starting simvastatin (or at baseline in subjects already on simvastatin), double simvastatin dose each 4-6 weeks until LDL ≤ 85 mg/dl (2.21 mmol/L) or dose = 80 mg qhs.		
B	If LDL < 50 mg/dl at any time during titration, back-titrate to previous step		
C	If LDL is > 85 mg/dl (2.21 mmol/L) on simvastatin 80 mg, keep simvastatin at 80 mg, add bile acid binding resin and titrate, as necessary		

D	If LDL \leq 85 mg/dl (2.21 mmol/L) on simvastatin 80 mg qhs + bile acid binding resin, continue therapy
E	If LDL is $>$ 85 mg/dl (2.21 mmol/L) on simvastatin 80 mg qhs + maximum tolerated dose of bile acid binding resin call lipid consultant

FOR SECONDARY GOALS

If LDL $<$ 85 mg/dl (2.21 mmol/L) on simvastatin 10 mg qhs

AND TG $>$ 200 mg/dl (5.19 mmol/L)

OR HDL $<$ 35 mg/dl (0.91 mmol/L)



ADD Niaspan or regular niacin (See instructions in Operations Manual for Rx)

THE DOSE OF SIMVASTATIN SHOULD GENERALLY NOT EXCEED 10 MG IN PATIENTS TAKING CONCOMITANT NIACIN.

5) Glycemic Control in Diabetics:

The goal for diabetes mellitus management in COURAGE patients is to **maintain** levels of HbA_{1c} $<$ 7.5% in both IDDM patients treated with insulin and in NIDDM patients treated with oral hypoglycemics.

6) New Treatment and Risk Reduction Therapies:

As new therapies become available during the course of the trial, they may be incorporated as part of the therapeutic and the risk intervention program, if their safety and efficacy are demonstrated and there is consensus among experts that routine use for therapy or secondary prevention is warranted. Examples might include specific hypolipidemics,

antioxidants, antithrombotics, or any other class of medication that may be shown to have anti-atherosclerotic, anti-ischemic, or anti-thrombotic properties.

I) Percutaneous Coronary Revascularization ("PCI")

1) Procedural Guidelines:

Every effort will be made to have the percutaneous revascularization procedure reflect current clinical practice. As such, the operator will be free to choose any primary or adjunctive catheter based technique he/she feels would most safely and effectively accomplish myocardial revascularization. In clinically eligible patients, left ventricular and coronary cineangiograms will be reviewed by the on-site interventionalist to determine suitability for percutaneous revascularization. Once a patient is assigned to percutaneous revascularization, the procedure will be performed within 45 days of the diagnostic catheterization. Prior to the procedure the investigator will specify the extent and severity of coronary disease and which lesions are intended for revascularization. Investigators will indicate in advance if the procedure is to be staged. In the event of staging, the second procedure will be completed within 2 weeks of the first.

In patients who are randomized to "PCI + Medical Therapy", the intent will be to perform as complete a myocardial revascularization as possible, in the judgement of the site clinical investigator/operator, while minimizing the risk of procedure-related untoward events. In all patients, revascularization of the "culprit" stenosis will be undertaken, as guided by the previously obtained noninvasive testing. In patients with multivessel disease, complete revascularization will not be mandated by protocol if, in the judgement of the operator, this poses

undue risk to the patient. Complete revascularization will also not be undertaken if incomplete revascularization is thought to be adequate, based upon regional left ventricular function, collateral flow to a chronic total occlusion, etc. In each patient, the procedural strategy will be predetermined. Most often, revascularization of the lesion, which is thought to be most likely responsible for the patient's ischemia, will be undertaken first. In some situations, however, initial revascularization of the "nonculprit" lesion may enhance the safety of the subsequent revascularization attempt.

For each target lesion, angiographic success will be defined as a reduction in the stenosis to less than 30% with normal TIMI (grade 3) flow. When an intracoronary stent is placed, angiographic success will be defined as a residual stenosis of less than 10% and normal TIMI flow. Clinical success will be defined as angiographic success plus the absence of in-hospital myocardial infarction, emergency coronary bypass surgery and death.

2) *Angiographic Inclusion Criteria*

Patients will be included in this study if percutaneous revascularization of all of the intended lesions is associated with a high (>90%) probability of success and low (<5%) probability of abrupt vessel closure. Specific inclusions:

- a) the stenosis represents $\geq 50\%$ diameter reduction,
- b) there is at least one vessel planned for angioplasty meeting one of the following criteria
 - i) RCA: Proximal to the PDA in a right dominant vessel
 - ii) LCX: Proximal to 2 or more OM branches or proximal to the PDA
+ PL branches in a left dominant vessel

- iii) LAD: Proximal or mid-vessel
 - iv) SVG or IMA: Graft must supply same region(s) as outlined above
- Or
- v) In the opinion of the interventionalist the coronary stenosis subtends a “major” mass of myocardium

3) *Angiographic Exclusion Criteria:*

Patients will be excluded from the study if the coronary anatomy suggests that the revascularization procedure would be excessively high risk or would not likely be successful. Specific exclusions include: excessive tortuosity of vessels proximal to a lesion, excessive angulation within a lesion, excessive lesion length, total chronic occlusion, inability to dilate because of excessive calcification and the lesion is not amenable to rotoblator, or a major side branch cannot be adequately protected. Patients will also be excluded if abrupt closure is likely to or would result in cardiogenic shock. Nonsignificant lesions, lesions located distally in small arteries, and lesions that supply areas of infarction will not be dilated.

4) *Protocol for the PCI Procedure:*

Prior to the procedure, patients will receive aspirin in a dose of ≥ 160 mg per day for at least 1 day and at least one dose of a calcium channel blocker. The patient will be brought to the catheterization laboratory in a fasting state. Heparin will be administered as a bolus of 50-70 U/kg and additional heparin will be given to maintain the activated clotting time 250-350 seconds, or according to local practice, during the procedure and depending on whether a glycoprotein IIb/IIIa receptor inhibitor is to be used. If a glycoprotein IIb/IIIa receptor inhibitor is not anticipated, ticlopidine or clopidogrel should be considered.

For high-risk angioplasty patients, specifically those with unstable angina, an intravenous platelet glycoprotein IIb/IIIa receptor inhibitor (tirofiban) can be given during the procedure together with unfractionated heparin with the IIb/IIIa inhibitor and heparin continued for a minimum of 12 hours after the procedure.^{97-102.}

The periprocedure drug therapy and postprocedure therapy will also be modified in patients undergoing placement of one or more coronary artery stents.¹⁰³ At the discretion of the investigator, the access sheaths will be removed as soon after the procedure as appropriate, with attention paid to the adoption of a uniform protocol at each site. Before and within 24 hours after the procedure, a 12-lead electrocardiogram will be obtained. Creatine kinase levels with myocardial isoenzymes will be measured at 8 hours and 16 hours or before discharge. Following the procedure a calcium channel blocker will be continued for at least 1 month and aspirin (325mg per day) will be continued indefinitely as per protocol. Patients having stent placement are usually treated with ticlopidine or clopidogrel, in addition, for two to four weeks.

At the beginning and end of the procedure, a coronary angiogram of the target vessel will be obtained in two orthogonal views with a 6, 7 or 8 French catheter after the administration of 100-200mcg of intracoronary nitroglycerin. Although multiple views of each lesion will be evaluated, only end-diastolic frames of the most severe view of the stenosis without foreshortening will be selected for analysis.

5) *Medical Therapy:*

Medical therapy as described in the preceding section, Section H, will be initiated as soon as possible after randomization. Except for beta-blocker or calcium channel blocker secondary prevention post-MI, an attempt will be made to discontinue *routine* anti-ischemic medical

therapy within 3-6 months after randomization to PCI in patients who remain asymptomatic after a successful PCI procedure. If symptoms of angina persist (or recur following discontinuation of medical therapy [see Section VI.J.3.b.]), medical therapy will be maintained (or re-initiated), respectively.

J) Post-Randomization Management Guidelines

1) Risk Factor Management

Shortly after randomization and prior to discharge, patients will be counseled briefly by the clinical coordinator regarding risk factor intervention including diet, weight loss (if appropriate), smoking cessation/relapse prevention, and the role of regular aerobic exercise. Intensive risk factor management will begin at the first clinic visit. The goals and strategies for the various risk factors are outlined in Section G. Lipid management will be according to the guidelines in Table 4. Some recommendations for promoting risk factor reduction compliance are contained in Volume 2. The process measures are outlined in Section 6.

2) Blood Pressure Management:

If blood pressure remains elevated despite maximally tolerated dosages of a given class of agent, the patient may switch to a different class, or a second medication from a different class may be added to achieve an appropriate anti-hypertensive effect. As noted in the previous section the goal will be to achieve and maintain blood pressure below 130/85 mmHg.

3) Recurrent Anginal Symptoms after Randomization:

a) Patients randomized to the "Medical Therapy Only " arm:

If a patient develops worsening or persistent angina after randomization, the following

management guidelines will be used:

- i) for all but CCS Class IV patients, intensify medical therapy (increase doses of anti-ischemic drugs, and/or add additional agents as needed clinically); if the patient subsequently stabilizes to CCS Class I-II, continue medical therapy indefinitely;
- ii) if symptoms do not stabilize, or worsen to CCS Class III after 6-8 weeks of **maximum** medical therapy, the patient should undergo stress testing preferably a 1 or 2 day protocol with ECG gated sestimibi SPECT imaging and if there is a high risk result (EF<35% or severe reversible ischemia) the patient should undergo re-catheterization and possible revascularization, as indicated clinically.

b) Patients randomized to the "PCI + Medical Therapy" arm:

Except for secondary prevention post-MI, an attempt will be made to discontinue routine anti-ischemic medical therapy, if possible, within 3 months after PCI, in otherwise asymptomatic patients who have undergone successful catheter-based coronary revascularization. However, if patients "destabilize" clinically after randomization, the following guidelines will be recommended:

- i) if the patient is in CCS Class I-II, and there is **no** evidence of spontaneous ischemic ECG changes at rest, a repeat stress test (exercise or pharmacologic, preferably with ECG gated technetium sestimibi imaging) will be obtained, and if this is positive for severe inducible ischemia or EF< 35% , the patient should be considered for re-catheterization;

- ii) if the patient is in CCS Class III-IV **after maximizing medical therapy**, repeat cardiac catheterization and/or PCI should be performed.

4) *Ischemia-Based Cardiac Catheterization:*

Cardiac catheterization will be performed only in patients who exhibit a **strongly positive** non-invasive test as indicated by:

- a) ECG exercise test showing >2 mm further ST-depression in multiple leads at low level exercise and/or a decrease in blood pressure with exercise
- b) Severe exercise left ventricular dysfunction (exercise LVEF <35%)
- c) Stress-induced large perfusion defect (particularly if anterior)
- d) Stress-induced multiple perfusion defects of moderate size
- e) Large, fixed perfusion defect with LV dilatation
- f) Stress-induced moderate perfusion defect with LV dilatation
- g) Echocardiographic wall motion abnormality (involving greater than two segments) developing at low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (<120 beats/min)
- h) Stress echocardiographic evidence of extensive ischemia.

5) *Role of the Clinical Coordinator:*

The clinical coordinator will provide risk factor goals to patients with instructions for their individualized risk reduction program. In addition to regular clinic visits, progress will be monitored by the clinical coordinator using telephone and mail. Patients will return frequently

during the first 6 months to have their progress evaluated and to receive additional assistance in meeting the risk factor goals. During these visits, lipids and lipoproteins, body weight, and blood pressure will be measured. In addition, diet, exercise, and (if applicable) smoking cessation counseling will be provided. These visits will also provide an opportunity to evaluate and optimize the medical therapy (anti-hypertensive, anti-ischemic and lipid therapy) as needed. Once risk factor goals have been achieved, the frequency of visits will decrease to every 6 months until the end of the trial, utilizing telephone and mail contact in between visits.

6) *Process Measures*

Risk factor	Goal	Measurement
LDL	<100 mg/dl (2.60 mmol/L)	Central Lab
Smoking	Cessation	Self (PACE score)
Blood Pressure	130/85 mmHg	Measured at each visit
HbA _{1C}	<7.5%	Measured
Obesity/Weight goals (BMI)	If BMI <27.5 goal is <25 If BMI >27.5 goal is 10% weight loss	Weight at each visit, (height at baseline)
Exercise	Minimum of 30 minutes of moderate exercise 3 times per week	PACE score
Diet	Step II	MEDFICTS score
Compliance with Medication	>80%	Score from Morisky

K) Follow-up Procedures

1) Regular Protocol-Mandated Assessments or Procedures:

- a) clinic visits at 1, 2, 3, 6, and 12 months, and 6 month intervals thereafter, until trial termination;
- b) ECG at 3 months, 6 months, 12 months, and annually thereafter until trial termination;
- b) stress test (modified symptom-limited exercise with gated sestimibi SPECT imaging preferred; pharmacologic stress in patients unable to exercise) at 1 year and 3 years;
- c) complete quality of life assessments at 6 months, 1, 2, and 3 years, and a limited assessment at 1 and 3 months;
- d) blood specimen sent to Lipid core laboratory at 6 months and then annually.

More frequent clinical visits may be necessary for some patients if risk factor goals are not met. Table 5 is a schematic representation of the scheduled protocol evaluations, with an indication of the form on which the information is to be collected and the timing of the evaluation.

Table 5: Schedule of Evaluations and Forms		Time - months after randomization											
		Before	Entry	1	2	3	6	12	18	24	30	36	q6m
Clinical screen	1	X											
Eligibility/Randomization	2	X											
Consent		X											
Patient Information	3		X										
Baseline History/status	4		X										
ECG ¹	5		X			X	X	X		X		X	X
Stress test (ETT preferred) ²	6	X						X				X	*
Stress imaging ²	7	X						X				X	*
Laboratory values	8		X	X	X	X	X	X	X	X	X	X	X
Cardiovascular Medications	9		X	X	X	X	X	X	X	X	X	X	X
PCI Procedure	10		X*	PRN									
Hospitalization	11		PRN	PRN									
Cardio /cerebro vascular tests	12		PRN	PRN									
Follow-up Visit	13		X	X	X	X	X	X	X	X	X	X	X
PACE exercise/smoking review	14		X	X	X	X	X	X	X	X	X	X	X
Diet review (MEDFICTS)	15		X	X	X	X	X	X	X	X	X	X	X
Missed visit notification	16		PRN										
Non routine termination	17												
Adverse Events	18												
Report of death	19												
Patient economic Questionnaire	20		X			X	X	X		X		X	
Social Support Index	21		X										
Seattle Angina Questionnaire	22		X	X		X	X	X		X		X	
Symptom Distress	23		X			X	X	X		X		X	
SF-36/Mood	24/25		X	X		X	X	X		X		X	
Standard Gamble (Trader)			X	X		X	X	X		X		X	
Self Management Demands	27					X	X	X		X		X	

1 As scheduled and also after PCI and for documentation of events

2 As scheduled and also if required clinically to demonstrate ischemia

2) *Follow-up Data Collection Procedures:*

The forms for CS #424 will be completed by personnel dedicated to the trial (clinical coordinator; institutional investigator). Preliminary forms are included in Volume 2, Part B. Follow-up forms will include compliance with medications and lifestyle recommendations, as well as cardiovascular events (fatal and nonfatal). Each form will be labeled with the patient's study number, as will the outside of the case report file. There will be a place on the bottom of each form for the coordinator to sign, with space for initials on multipage forms.

All patients will be seen by their primary physician and by the clinical coordinator at the prespecified intervals. There will be a window for completing follow-up visits (± 14 days for first 3 visits, ± 30 days for later visits). In the event of inability to complete a scheduled clinic visit due to hospitalization, intercurrent illness, or logistical constraints, the patient or family will be contacted by phone. When necessary, the patient's primary care physician will be contacted to provide necessary clinical information. The West Haven CSPCC will provide reporting of missing forms by site, as well as an accounting of those forms which contain incomplete information, to the sites and the appropriate committees.

Follow-up data will be screened for the presence and date of death (cardiac or non-cardiac; sudden or not sudden), nonfatal Q-wave and non-Q-wave MI, hospitalization for unstable angina, interval cardiac catheterization, revascularization procedures, and cardiac symptomatic status. All cardiac medications will be recorded. There will be a brief diet and physical activity review. All deaths or cardiac events requiring hospitalization will be reviewed by a panel of cardiologists (the independent Endpoints Committee--see Section IX, which will be

blinded as to the treatment allocation of the patients.

Follow-up data will be collected at 1, 2, 3, and 6 months during the first post-randomization year, and at 6 month intervals thereafter until trial termination. Follow-up visits that are outside the window or missing will be considered protocol violations. Clinical coordinators will follow each randomized patient at their study center. The clinical coordinators will contact each patient by telephone to confirm an office visit.

All follow-up hospitalizations will be recorded, including the cause of the hospitalization and dates. If the patient returns for additional procedures, including cardiac catheterization, PCI or CABG surgery, these data will be captured on the hospitalization form. The records for all interventional procedures, whether performed at a study site or at another institution, will be obtained for detailed review and appropriate forms completion. A copy of the discharge summary for each hospitalization will be attached.

3) *Lost to Follow-up:*

It is expected that some patients will move, change their mind about participation in the study, become incapacitated, or otherwise become lost to follow-up. If local attempts using locator information obtained at the time of randomization and throughout follow-up fail, an effort will be made to locate VA patients using the automated databases in the V.A. system. All lost to follow-up patients will be checked against the VA Beneficiary Information Locator Retrieval System (BIRLS), Equifax, and the National Death Index to determine vital status.

4) *Adverse Events:*

Adverse events will be monitored throughout the study. Any serious adverse event (SAE) that is reasonably thought to be related to any of the drugs being distributed by the Pharmacy

Coordinating Center (PCC), or to Cardiolite, will be recorded on the Adverse Event Form (FORM 18). An SAE should be filed even if it is unclear which agent is responsible for the event. Specific instructions for completing Form 18 will be found in the Operations Manual. The definition of an SAE as well as the time frame for form completion and directions for submission will be found in the PCC Handbook. Should a patient experience a serious unexpected event thought to be related to a drug that he/she is receiving in the study that was not distributed by the PCC, PCC should be contacted for instructions on reporting these events to the appropriate regulatory body.

L) Endpoints

1) Endpoints and Subgroups for Analysis

- *Primary:* All-cause mortality or nonfatal MI
- *Secondary:*
 - Quality of Life Measures
 - Resource Utilization, cost, cost-effectiveness analysis
 - Hospitalization for unstable angina
- *Tertiary:*
 - Death
 - MI
 - Stroke
 - Cardiac mortality
 - Myocardial revascularization (PCI or CABG)
 - Death, MI, or hospitalization for unstable angina
 - Hospitalization for CHF
 - Hospitalization for other cardiac event
 - Repeat cardiac catheterization
 - Angina status (Canadian Cardiovascular Society Class)
 - ETT duration
- *Subgroups of particular interest--in addition to the predefined stratum of prior CABG*
 - Extent of disease (single vessel disease versus multivessel disease)
 - Prior MI (yes/no)
 - Diabetes (yes/no)
 - LV function (EF>50% versus EF 30-50%)

- Non-cardiac surgery within 90 days
- Demographic variables: gender, race, age
- Risk category
- V.A. versus U.S. non-V.A. versus Canada, and U.S. versus Canada (implicit in medical center stratification)

2) *Endpoint Assessments:*

The primary and some of the other endpoints will be adjudicated by the endpoints committee. The primary data for these events, however, will be collected at regular intervals, and as needed, by the local study team.

a) *Deaths*

If a patient dies an attempt will be made to ascertain the circumstances of the death. As appropriate, the following will be obtained: a narrative of the circumstances of the death, a copy of the discharge summary, a copy of the death certificate, a copy of the autopsy report.

b) *Myocardial Infarction*

The diagnosis of MI will be made on the basis of clinical information available from hospitalization (discharge summary; laboratory data) and will require an EITHER

- 1) **appropriate clinical history consistent** with acute myocardial infarction along with biochemical confirmation of myocardial necrosis, based on creatine kinase (CK),

- i) at least 150% above the upper normal limit of the hospital laboratory value spontaneously,

- ii) 3x upper limit of normal in patients undergoing PCI,

iii) 5x upper limit of normal in patients undergoing bypass surgery and elevated myocardial-specific CK isoenzymes (MBCK), > 5% of the total CK sample by electrophoresis, or > 15 units by quantitative immunoassay,

OR

2) new Q-waves at any time during follow-up.

- c) *Hospitalizations:* Admitting and discharge diagnoses, and a copy of the discharge summary. Patients will be required to sign a release form for retrieval of information if the hospitalization is at a non-study site.
- d) *Revascularization procedures:* Discharge summary and procedure notes, either CABG or PCI, will be obtained.
- e) *Stroke:* Information will be obtained as per hospitalizations, including relevant diagnostic testing reports and discharge summaries.
- f) *CHF:* Information will be obtained as per hospitalizations

VII. STATISTICAL METHODOLOGY

A) Sample Size Estimate and Power Calculation

The primary hypothesis for CS #424 compares PCI (optimal catheter-based coronary revascularization) + intensive medical therapy to intensive medical therapy alone using the combined endpoint of all-cause mortality or nonfatal MI. As many types of CHD patients as possible will be enrolled in COURAGE, including patients with LVEF as low as 30%, patients with multivessel disease, and patients who have undergone CABG or PCI more than 6 months prior to randomization.

Table 6: Event rates in medically treated patients

Study (reference)	Years of Entry	Study Type	Patient Population	Length of follow-up	Death rate	Combined/other endpoint	Rate for comb.	Est. 3 yr comb. dth/MI rate	Estimated # patients
1.Hlatky ⁷	1984	Case series	110 SVD	5 years	3%	Death, MI	15%	10%	11
2.Murphy ¹⁶	1972-74	RCT	354	7 yrs	30%	Death, MI		see 5.	see 5.
3. Varnauskas ²⁴	1973-76	RCT	373 MVD	3 yrs	10%	MI, cardiac death	16%	18% see 5	see 5.
4. CASS ²⁶	1975-79	RCT	780 MVD	6 yrs				see 5	see 5.
5. Yusuf ³⁰	1972-79	Meta Analysis	1,325 MVD	5 yrs	12%	death, MI	30.7%	18.4%	244
6.Parisi ³⁷	1986-90	RCT	107 SVD	6 mths	1%	MI	3%	see 9	see 9.
7.Folland ³⁸	1986-90	RCT	50 DVD	5 yrs	20%	MI	12%	15%	8
8. Hueb ⁷⁹	1988-91	RCT	72 SVD	3.5 yrs	0%	death,MI	4%	4%	3
9.Giacomini ⁸⁰	1986-90	RCT	107 SVD	3 yrs	7%	MI	7%	13%	14
Total for RCTs			1,554						269

SVD=single vessel disease
MVD=multivessel disease
RCT=randomized clinical trial

Table 7: Event rates in PCI treated patients

Study (reference)	Years of Study entry	Study Type	Patient Population	Length of follow-up	Death rate	Combine d/other endpoint	Rate for comb.	Est 3 yr rate comb. dth/MI	Estimated # patients
1.Detre ¹³	1985-86	Registry	963 MVD	1 yr	4.6%	death,MI	8.8%	24%	231
2.Detre ¹³	1985-86	Registry	852 SVD	1 yr	1.8%	death,MI	5.4%	15%	128
3.Hampton ³²	1988-93	RCT	231SVD+ 273 MVD	2.5yrs	3%	death,MI	10%	11%	55
4.Hamm ³³	1986-91	RCT	155 MVD	1 yr	2%	death,MI	7%	21%	31
5.King ³⁴	1987-90	RCT	198 MVD	3 yrs	7%	death,MI	22%	22%	44
6.Rodrigues ³⁶	1988-90	RCT	63 MVD	1 yr	3.2%	death,MI, angina	35%	16%	10
7.Parisi ³⁷	1986-90	RCT	105 SVD	6 mths	0%	MI	5%	see 10.	see 10.
8.Folland ³⁸	1986-90	RCT	51 DVD	5 yrs	18%	MI	12%	22%	11
9.Hueb ⁷⁹	1988-91	RCT	72 SVD	3.5 yrs	1.4%	death,MI	4%	4%	3
10.Giacomini ⁸⁰	1986-90	RCT	105 SVD	3 yrs	5%	MI	10%	12%	13
Total for RCTs			1,148						167

SVD=single vessel disease
MVD=multivessel disease
RCT=randomized clinical trial

Event rates obtained from the literature are shown in Tables 6 (Medically treated patients) and 7 (PCI treated patients). These tables indicate when the study was performed, statistical design, type of patient studied, and choice of endpoints and observed event rate. In each case, a death rate is given and, if possible, a 3-year event rate for a combined endpoint was estimated from the information provided by the study and which is shown in the tables. Only event rates from randomized clinical trials are computed because they use intent to treat analyses and therefore include the diluting effect of dropins and dropouts.

In these tables, the 3-year rate for the combined endpoint of death and non-fatal MI among the medically treated patients varies from 4% to 18.4%, and among the PCI treated patients, it varies from 4% to 22%. Combining the calculated number of events at 3 years in the randomized trials, an estimated rate for each therapy would be 17.3% (269/1554) for medicine and 14.5% (167/1148) for PCI. The studies from which the medical therapy rates were derived, however, generally antedated the more recent PCI studies, and differences in medical therapy among non-contemporaneous studies is a potential confounding factor. In addition, the patient selection criteria were likely very different as no patients in the former group could have failed medical therapy. Actual event rate data obtained on CHD patients who underwent PCI in the V.A. during FY 92 are summarized subsequently (see Section VII. E).

Because many of the studies cited in Tables 5 and 6 were conducted as long as 20+ years ago, **none** were undertaken in the setting of the aggressive, multifaceted therapy that we propose to administer to **all** COURAGE Trial patients. In prescribing both comprehensive medical therapies together with risk factor modification for all CS# 424 patients, we project a lower overall event rate in our study patients compared to those who were enrolled in the former

studies. However, we expect that approximately 30% of the patients whom we enroll in CS #424 will have been previously revascularized. The event rate in these patients is expected to be higher than that reported in the literature therefore the inclusion of such patients in our trial will counterbalance the effect toward event rate reduction owing to advances in medical therapy.

The following table (Table 8) shows the sample size, which would be needed for a range of powers and rates in the two therapeutic arms. All of the sample size and power calculations have been done according to the method proposed by Lachin¹⁰⁴ which allows for staggered entry and assumes that the event rate follows an exponential distribution. To do the calculations the following assumptions were also made:

- randomization takes place over 3.0 years
- patients are followed for a minimum of 3.0 years.
- tests are two-sided tests done at the 0.05 level
- there is equal allocation to each treatment arm.

Table 8: Sample size for a range of rates, differences, and powers						
Rate for Treatment A	Rate for Treatment B	Relative* Difference	Absolute difference	Sample size required for power		
				80%	85%	90%
16%	14%	13%	2%	7123	8122	9537
16%	13%	19%	3%	3006	3428	4025
16%	12%	25%	4%	1643	1873	2200
16%	11%	31%	5%	1019	1162	1364
15%	13%	13%	2%	6326	7214	8470
15%	12%	20%	3%	2759	3146	3694
15%	11%	27%	4%	1509	1721	2021

Table 8: Sample size for a range of rates, differences, and powers						
Rate for Treatment A	Rate for Treatment B	Relative* Difference	Absolute difference	Sample size required for power		
				80%	85%	90%
15%	10%	33%	5%	951	1084	1273
14%	12%	14%	2%	6001	6843	8035
14%	11%	21%	3%	2590	2964	3469
14%	10%	29%	4%	1436	1637	1922

* Relative to Treatment A

Thus, projecting a cumulative 3-year event rate of 14% in the treatment A arm and 11% in the treatment B arm (absolute difference of 3%; relative difference of 21%), a sample of **2,964** patients will be needed to test the hypotheses with a power of 85%.

If we project a sample of size 2,964 and other rates actually apply, Table 8 indicates the power we would have to detect these differences at the 0.05 level using two-sided tests and assuming 3 years each for accrual and follow-up. Table 9 clearly shows that the factor which contributes most importantly to the power is the difference between the two rates.

Table 9: Power to detect differences between various rates with sample of size 2,964			
Treatment A 3 yr rate	Treatment B 3 yr rate	Absolute difference	Power
16%	13%	3%	80%
16%	12%	4%	97%
15%	13%	2%	48%
15%	12%	3%	83%
15%	11%	4%	98%
14%	12%	2%	50%
14%	10%	4%	98%
13%	10%	3%	87%

If the difference between the two rates is 4%, we would have > 95% power, if the difference is 3% we would have 80-87% power, and if the difference is 2%, we would have at most 50% power, regardless of the base rates.

B) Duration of Patient Intake and Follow-up

If we assume that the event rates are 14% in one treatment arm and 11% in the other, then Table 10 shows the impact of varying the intake duration and the follow-up period on the required sample size. In this table it has been assumed that two-sided tests were done at the 0.05 level and that the power was 85%. For example, if the study duration is 5 years, divided into 3 years of accrual and 2 years of follow-up then 3,732 patients would be needed. If, however, the division is 1.5 years and 3.5 years, respectively, then 3,113 patients would be needed.

Table 10: Sample size for various intake and duration periods, assuming rates of 14% and 11%				
Intake Period	Follow-up Period			
	2 years	2.5 years	3 years	3.5 years
1.5 years	4657	3983	3490	3113
2 years	4296	3722	3292	2958
2.5 years	3992	3497	3118	2820
3 years	3732	3299	2964	2696

(Note: shaded boxes on the diagonal represent equal study durations i.e. 4, 5 or 6 yrs respectively.)

The consensus of the planning committee was that it is both prudent and realistic to anticipate a trial duration of 6 years, with accrual taking place over a 3-year period, and follow-up after the last patient is randomized of 3 years. If this is the case, for the specified event rates of 14% and 11% and using previously described type I and type II probabilities, we have projected a sample size estimate of 2,964 patients.

C) Adjustment for Lost to Follow-up

We expect that a certain percentage of patients will be lost to follow-up. Other studies have had lost-to follow-up rates which varied between 1% and 10%. For the V.A. patients, vital status at least will be available on all lost patients using the BIRLS system. If a cumulative loss to follow-up rate of 10% is factored in for the duration of the trial, then assuming rates of 14% and 11% and intake/follow-up durations as specified in the previous section, we would need to enroll 3,260 patients to achieve the required number of endpoints.

D) Expected Number of Endpoints

With a sample size of 3,260 patients and an average 3 year event rate of 12.5%, we anticipate that 217 events will occur in the patients randomized in the first year, 177 events in the patients randomized in the second year, and 136 events in the patients randomized in the third year for a total of 530 events. Allowing for 10% of these events to be "lost" we anticipate that we will observe 477 patients with documented first events by the conclusion of the trial.

E) Feasibility and Number of Sites

It is anticipated that 36 enrolling sites (12 V.A., 12 U.S. non-V.A., and 12 Canadian) will be needed to accrue 3,260 patients. Thus, each site would be expected to enroll a total of 90 patients. If patient intake for the trial were to be 3 years, each site would be required to enroll an average of 30 patients/year.

1) Evidence to support feasibility of proposed enrollment goals

During the ACME trial, a study of PCI versus Medicine in stable CHD patients with predominantly single-vessel CAD (some double-vessel CAD as well), which used short-term, functional trial endpoints, we screened all patients who underwent cardiac catheterization at the eight participating sites during the 3 year period (1987-1989) of intake. Of the 9,573 patients who were screened, 328 were ultimately randomized. Using the information obtained on the screening form for the 9,245 patients who were not randomized and the 328 who were, we applied the exclusion criteria for the COURAGE study to these patients.

From our analysis it appears that about 40% of the patients who were screened for ACME would have been excluded from COURAGE. Some of these patients are excluded because they could not exercise or had a negative exercise test, but it may have been possible to show myocardial ischemia by some alternate method that would satisfy the CSP #424 inclusion criterion of inducible ischemia. Therefore, some of these excluded patients would be COURAGE trial-eligible.

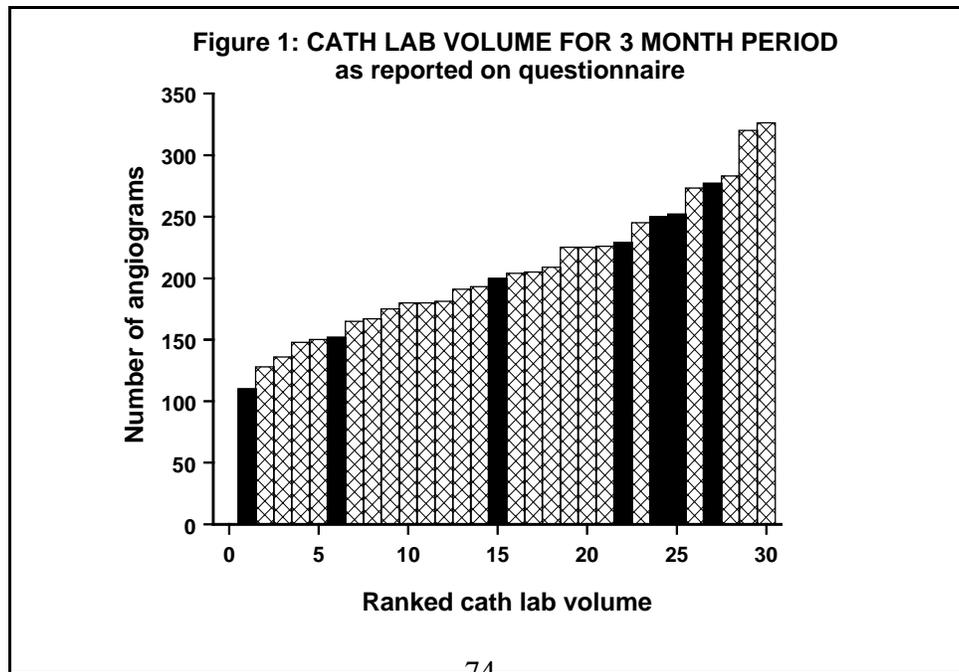
Alternatively, three vessel CAD was an exclusion from ACME but is not an exclusion for CSP #424. From the information on the forms, although we know who had triple vessel disease, we do not know what proportion of the three vessel disease patients would have been "technically unsuitable for PCI," a CSP #424 exclusion or would have required revascularization.

Assuming, however, that these respective exclusions to ACME and COURAGE offset each other to some extent, and that an additional 15%-20% would be excluded owing to situations unmeasured in ACME, such as elevated serum creatinine in diabetics, we estimate that 60-65% would be excluded, i.e. that about 40% of the screened patients would be eligible for COURAGE.

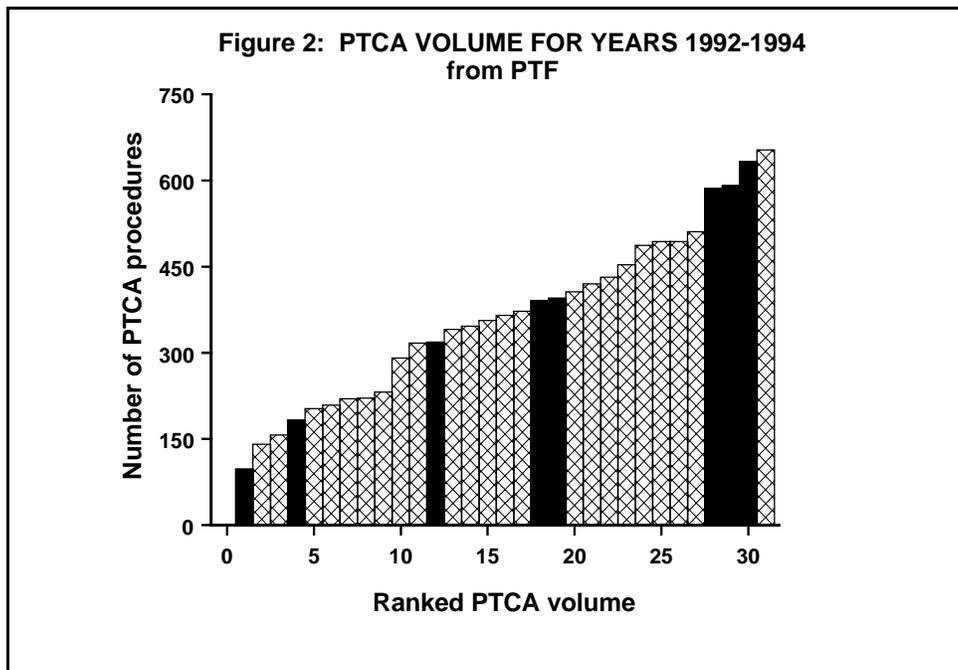
If 50% of those eligible agree to randomization (in the ACME trial the consent rate was > 60%) then the estimated number of patients from these eight sites would be about 1,915 (9,573 [screened] x 0.4 [eligible] x 0.5 [consent]). Thus based on the volume and data from the ACME trial experience approximately 240 patients per site (or 85 per site per year) would be randomizable. In the ongoing VANQWISH Trial of non-Q-wave MI (CSP #368) the enrollment rate among 15 enrolling sites was 62 patients per site during 2 years of intake (31 patients per year per site) and the consent rate was > 80%. Thus we feel that our projected rate of 90 patients per site during the 3 years of intake (30 patients per year / site) appears feasible.

2) *Extrapolation to non-ACME VA Enrolling Sites:*

Is it likely that these numbers can be extrapolated to other, non-ACME VAs? According to the questionnaire completed by prospective CSP #424 enrolling site investigators and submitted to us (See Volume 2- Section C), the ACME sites did not routinely have the highest 3-month volume of angiograms among the 30 VA sites that have expressed interest in COURAGE.



This is displayed in Figure 1 where the ACME sites are shown in solid black bars. The ACME sites are distributed over the range of volumes among the sampled sites, so it is likely that the results obtained from the ACME screening forms would be typical of the other VAs. Further data to support the extrapolation of the data to other VAs were obtained from the volume of PCI procedures done at all of these sites during the 3 year period from 1992 to 1994 inclusive. These data, obtained from the PTF files using the ICD-9 codes for PCI and therefore not subject to investigator bias or optimistic self-reporting, are displayed in Figure 2. The ACME sites, depicted in solid black bars as before, are again distributed among the interested CSP #424 enrolling sites.



It would appear from these analyses that 30 patients per site per year is a realistic and feasible goal. We are currently conducting a 1-month prospective survey at the interested sites. The results of this survey will be available and distributed prior to the CSEC review.

The criteria we specified in Section X, Part D of the protocol for the selection of the sites includes >150 diagnostic catheterizations in a 3 month period for the laboratory. This catheterization volume should allow us some leeway in the selection process, as volume is not the only consideration. Experience in performance of procedures among the operators is also important for the credibility of the study. The operators must perform at least 100 procedures annually (>300 total) with acceptable complication rates and must have experience in the newer techniques including atherectomy, rotoblator, and stents.

F) Other Evidence To Support Event Rate Projections

To investigate whether our projected event rates might be reasonable, we used the DVA databases to follow CHD patients who had previously undergone PCI. From the Patient Treatment File (PTF), which is the database of all DVA hospital discharges, we identified a total of 3,723 patients who had undergone a PCI procedure during FY92. During that fiscal year, 440 of these patients had an additional PCI. Following these patients using both PTF and BIRLS, we estimated the number of events--revascularizations, MIs and deaths--during the subsequent 3 years.

Table 11: Events in FY 93-95 in 3,723 patients who had PCI in FY 92			
		Number of patients	Percent of patients
Revascularizations	CABG	271	7.3
	PCI	481	12.9
	CABG or PCI	683	18.3
Events	Non-fatal MI	589	15.8
	Death	510	13.7
	Death or MI	990	26.6

While it is likely that we have identified > 95% of the deaths in this actual analysis, it is also likely that we have underestimated the true number of MIs. (In another study being conducted by the West Haven CSPCC, the DVA-based PTF captures only about 70% of the MIs; silent MIs and MIs occurring at non-V.A. hospitals may be missed.) Thus the true event rate of interest in these patients is likely to be higher than the **26.6%** demonstrated here.

The patients identified in this analysis are *unselected* PCI patients. We anticipate that a major reason for excluding patients from our study will be unstable angina. These unstable patients are likely to be those patients at highest risk for an event, if they are not revascularized. Thus, the event rate we encounter in the COURAGE Trial may be lower than that found in this analysis. In addition, we will be aggressively treating **all** the patients in the study with medical therapy and attempting maximum lifestyle changes. This also will lower the event rate. The event rates in this analysis of PCI in the V.A. in FY92, however, *do* include patients who have been revascularized previously. Thus, it would appear that our projected rates of 14% and 11% are appropriately conservative, in that they are approximately *half* the rate observed in this analysis.

A concern in using a combined endpoint of death or non-fatal MI is that one of the components, in this case infarction, will excessively dominate the primary event rate, but we believe this is not justified. The actual MI event rate observed in the V.A. PCI database analysis is higher than the mortality rate, but it is not overwhelming so. In addition, we postulate that aggressive medical therapy, as planned in the COURAGE Trial, will have a proportionately greater effect on reducing the infarction rate and less impact on the death rate. Thus we believe that in our trial combined primary endpoint, MI may be even less important than it was in this

analysis.

G) Power for Secondary and Tertiary Endpoints

1) Health Economics

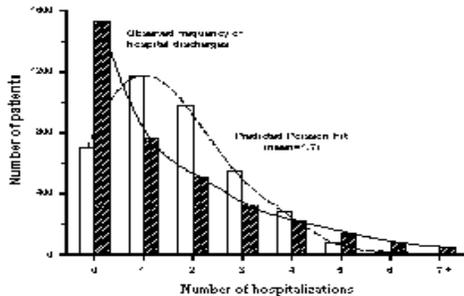
The standard deviation of the total cost estimates for both arms of the recently reported studies of PCI and CABG surgery³²⁻³⁴ varied between \$7,000 and \$10,000. If the standard deviation (SD) of the cost estimate is \$7,000 then the sample size that would be needed to be able to detect a difference of \$500 between the two groups is 6,154, for a difference of \$1,000 it is 1,539 and for a difference of \$1,500 it is 684 ($\alpha=0.05$, 80% power). If the SD is \$8,000, then for these same differences the required sample size ranges from 8,083 to 894 and for a SD of \$10,000, it ranges from 12,559 to 1,396 (See Volume 2, part A). Stated in another way, for a difference of \$1,000 between the two groups we would need from 1,539 to 3,140 patients depending on the variability of the estimates. Thus, with an effective sample size of 2,964, we should have ample power to detect an important difference in costs anticipating that the variability in COURAGE is similar to that seen in other studies.¹⁰⁵

2) Quality of Life

For the quality of life endpoint, using results from the SF-36, the sample size that would be necessary to detect a 2 point difference between two groups in the improvement in a subscale (using a repeated measures design, a two-sided test at 0.05, and 80% power) ranges from 1,308 to 3,652, depending on the subscale, and for a 5 point difference it ranges between 165 and 585.¹⁰⁶ Thus with an effective sample size of 2,964 we will have sufficient power to detect meaningful differences for most domains in our final quality of life questionnaire.

3) Tertiary Endpoints

For MI alone, if the rates are 8.4% and 6.6% (i.e. 60% of the combined rates) for the two arms, with our proposed sample size the power is 71%. For death alone, if the rates are 7% and 5.5%



(i.e. 50% of combined) the power is 53%.

For the other tertiary endpoints, some (such as stroke) will be much less prevalent than either death or MI and will thus have much less power and some (such as exercise duration) will have >95% power to detect meaningful

differences, should they occur. Repeat hospitalizations are unlikely to follow a Poisson distribution as can be seen in the accompanying display of hospitalizations over the subsequent 3 years for the 3,723 V.A. patients identified in the previous section. It is thus difficult to determine the power for this endpoint.

H) Data Analysis

All major analyses will be done using the intent-to-treat policy, and all statistical tests will be two-sided. Data will be analyzed primarily with the SAS[®] statistical package. Other packages, including BMDP and S-Plus will also be used. Patient characteristics in the randomization groups will be compared. Descriptive statistics, tables and graphs will be used^{107,108} Nonparametric tests will be used when necessary.¹⁰⁹

The primary outcome measure, time to first cardiac event (all-cause mortality; nonfatal

MI) will be analyzed by standard failure time methods--Kaplan-Meier procedures and Cox regression techniques.¹¹⁰ The Kaplan-Meier estimate will be used to display the estimated probability of the freedom from events across time. Standard errors of this estimate will be computed using the modified Greenwood formula. The unadjusted comparison of the freedom from event curves will be performed using the log-rank statistic. Similar methods will be used for freedom from revascularization.

The multivariate (adjusted) comparison of the freedom from events will be performed using the Cox proportional hazards regression, where the hazard of an event is modeled. The Cox analysis will allow for adjustment for pertinent covariates such as angina class, ejection fraction, anti-anginal medication intake, comorbidity, and others. Estimates of the relative risks will be obtained from the Cox analysis. The Cox regression will also be used to identify subsets of patients for whom the effects of the two treatment strategies are more, or less, pronounced.¹¹¹ The subgroups of particular interest are defined by extent of disease, diabetes, age, gender, race, LV function, prior MI, and the strata incorporated into the design of the trial.

The validity of the assumption of the proportionality of hazards will be investigated for each considered model.¹¹¹ If necessary, time dependent covariates will be considered. The diagnostics of all the models will be performed to detect possible outliers and/or influential points using S-Plus. For the continuous covariates, the assumption of the linear effect will be checked. Interactions between covariates will also be investigated.^{108,112}

Binary outcomes (such as freedom from angina), where the time of occurrence of the outcome is not available or where the occurrence is measured at specific time points, will be analyzed using logistic regression.¹¹³ Linear regression, and/or additive regression (which

incorporates smoothing) will be used to model continuous variables of interest.¹¹⁴ Diagnostics of all models will be performed.

Time to hospitalizations will be also be analyzed by time-to-failure methods. Counts of repeat hospitalizations and repeat procedures will be analyzed assuming the distribution to be Poisson. If the Poisson distribution does not appear to be valid, then permutation and bootstrap methods will be used.¹¹⁵ Total hospital days and other resources used will be accumulated over all patients in each treatment arm and compared using t-tests or Wilcoxon rank sum tests. These outcomes will be compared over subgroups using analysis of variance techniques or the Kruskal-Wallis test. The p-values in subgroups will be adjusted using the "FDR" techniques.¹¹⁶

The QOL measures and changes in these from baseline values will be analyzed using longitudinal methods.¹¹⁷ At any one time point, standard t-tests or, for subgroups, analysis of variance techniques or the nonparametric analog will be used, with the p value adjusted for multiple endpoints. Patient scores for each quality of life domain measure will be examined in relation to performance of instruments in the trial (reliability), randomized treatment groups, patient characteristics, health resource utilization, and other significant clinical variables.

VIII. PATIENT SAFETY AND TRIAL MONITORING

A) Adverse Events

If there is a serious clinical event after randomization (procedural or otherwise), the site institutional investigator will contact the Study Chairman's Office by telephone, as well as reporting it through the usual data gathering mechanisms. The study medication(s) may be stopped, if necessary, but the patient will remain in the trial and will, if possible, have remaining

follow-up visits completed. Analysis by intention to treat will not be affected. It is anticipated that all drugs used in the study will have indications for which they are being prescribed. Thus only serious events that are reasonably thought to be related to one of the drugs that are distributed by the Pharmacy Coordinating Center will be reported on study adverse event forms.

B) Data Monitoring Board

The CS #424 Trial will be overseen by an independent Data Monitoring Board (DMB) which, in addition to seeing that the trial is being conducted in the manner proposed, will be responsible for the ethical conduct of the study. This board will consist of 5 - 6 experts in the fields of cardiovascular clinical trials, interventional cardiology, health economics, and biostatistics. These experts will not be participants in the trial and will not have participated in the review process of the protocol. This board will make recommendations to the Chief, Cooperative Studies Program, regarding continuation or discontinuation of the trial. Initially, the DMB will meet at least semi-annually, and may have quarterly conference calls, which will be arranged by the chairman.

C) Human Rights Committee

The West Haven Human Rights Committee will meet at least annually in conjunction with the DMB to review all issues regarding adverse events and endpoints. In addition, a member of the Human Rights Committee will site visit one site each year and interview 5-6 patients about their understanding of the study and their treatment by the study team.

D) Monitoring of Trial Procedures

The Executive Committee is responsible for initial monitoring of trial procedures. It is responsible for assessing whether a trial procedure should be changed and proposing this change to the DMB. It is responsible for overseeing the performance of each participating site and for instituting measures to correct deficiencies. If the deficiencies do not appear to be correctable, the Executive Committee may propose termination of the site to the DMB.

E) Monitoring of Intake

The intake rate and operational aspects of the study will be monitored continuously by the Study Chairman and Study Biostatistician. Participating medical centers will continue in the study only if adequate patient intake is maintained. Probation, study hold at the site, and suspension or reduction of funds are all possible actions. The Executive Committee will only take procedures leading to termination of a center with the concurrence of the DMB and the Chief, CSP. A great deal of attention will be paid to the performance of each site in the initial stages of patient enrollment, as this is when most of the problems are identified.

F) Interim Monitoring of Adverse Events and Endpoints

At each meeting during the intake period, the DMB will review the randomization rates and assess the difference between the actual and projected rates, as well as the impact of these assessments on overall trial size. If it is inadequate, the reasons for exclusion may be scrutinized and actions may be suggested. An assessment of whether the trial should be continued will be made followed by a recommendation, as appropriate.

Since the therapy being used in this trial is that recommended by committees of the AHA it is unlikely that any unanticipated adverse events will occur. Serious adverse events, both procedural and clinical, however, will be reported to the DMB and, if appropriate, to the FDA.

At each meeting after 18 months, the accumulating information on endpoints will be reviewed. At its first meeting, the DMB will decide on the method that they would prefer to use to adjust for the "multiple looks" at the accumulating evidence. It is suggested here that the method proposed by Lan & DeMets¹¹⁸ be used. In this procedure, a use function determines how the α , or type I probability, is used up over time. For example, a common use function is

$$\mu^*(t) = \mu t.$$

In this function, time is represented by the proportion of total expected events that have occurred up to the time of analysis. For instance, with observation of 20/140 failures, $t=0.14$. The quantity t is often referred to as the "percent of information" as it represents the amount of variance that is proportional to the number of failures for the logrank test under a proportional hazards assumption. This approach allows some flexibility in the timing and frequency of the interim analyses. Presuming this will be the method utilized in the COURAGE Trial, no adjustment has been made to the sample size calculations to allow for multiple looks at the data. In addition, the actual event rate and the projected sample size based on current accrual rates will also be investigated. An estimate of the probability of crossing a boundary will be provided to assist the DMB in their deliberations.¹¹⁸

G) Incentives

Allowance has been made in the budget for incentives for the sites during both the

randomization period and the follow-up period. This may take the form of cash awards or adjustments in the proportion of time the program assistant is employed at the site.

IX. ORGANIZATIONAL STRUCTURE

The trial will be run by the *Executive Committee* with the cooperation of the West Haven Coordinating Center. Reporting to the Executive Committee will be the sites, the Endpoints Committee, the Publications Committee, the Coordinating Center, and the Albuquerque Pharmacy Drug Distribution Center. In addition, the COURAGE Trial Core laboratories (Health Economics, Coronary Angiography, Electrocardiography, Nuclear, and Lipid) will also report to the Executive Committee. The Executive Committee will provide overall scientific direction at the operational level. Members of the Executive Committee will include selected representatives of the CS #424 Planning Committee, key investigators representing the V.A., U.S. non-V.A. and Canadian enrolling sites, members of the West Haven CSPCC, and non-voting representation from industrial sponsors. The Executive Committee will oversee all substudy and/or ancillary study requests, and will appoint a subcommittee to critique and review submitted requests for scientific merit. The Executive Committee will meet semiannually and will have biweekly conference calls to deal with ongoing trial issues and developments during the first year of the study. Additional videoconferences or meetings will be scheduled as needed. After the first year, meetings will be held annually and the conference calls bi-weekly to monthly.

The entire *Study Group*, with representatives from each site will meet annually. Divided conference calls (12-15 sites per call) will be held regularly during the first year and, if necessary, for the duration of the study.

The Executive Committee will nominate an independent Endpoints Committee. Membership may include representatives from the Executive Committee or from outside investigators. This committee will establish guidelines for coding cause of death, diagnosing myocardial infarctions, and evaluating other trial cardiac events. These guidelines will be communicated to the Executive Committee and ultimately to the Study Group. The Endpoints Committee will meet regularly to review and adjudicate suspected trial endpoints, and the results of these deliberations will form part of the reports submitted to the DMB. Insofar as is possible, the Endpoints Committee will be presented with blinded data for both fatal and nonfatal cardiac events.

A *Publications Committee* will be established to develop guidelines for the development of papers (abstracts) for presentation at national meetings, as well as the development of manuscripts for peer review publication. Any publication related to the major endpoints during the active phase of the study **must** have prior approval of the Data Monitoring Board. All publications are to be approved by the Chief at the Coordinating Center before submission for publication. The Publications Committee will be expected to develop guidelines to protect patient confidentiality, to prevent unwarranted release of study information, and to prevent conflict of interest. The Publications Committee will also be expected to resolve problems of authorship and to maintain the quality of publications. All publications will acknowledge appropriate funding sources.

Publications could include:

- Effect of PCI in addition to Medical Therapy on Long-Term Health Care Outcomes

- Differential Resource Utilization Among CHD Patients Undergoing PCI in the United States and Canada
- Relationship between Quality of Life and Resource Utilization among CHD patients.

The data derived from the clinical trial is considered the property of the Cooperative Studies Group, not the property of the individual participating investigator or health care facility where the data were generated.

Individual investigators may propose substudies. Before they are instituted the Executive Committee must approve them. No substudy will be initiated until the overall study procedures are in place and operational, and no substudy will be approved if it interferes with the primary goals of the study. Possible substudies could include:

- Health Outcomes in PCI Patients with Impaired LV Function
- Non-Invasive Risk Stratification of CHD Patients Who Undergo PCI

- Effect of PCI and Medicine on Holter Monitoring in Patients with Silent Ischemia
- Effect of folate on the primary outcome.

Dr. William S. Weintraub of Emory University will coordinate the Health Economics/Resource Utilization component of the study.

Four other core laboratories are anticipated: a LIPID Core Lab, a Coronary Angiographic Core Laboratory, an Electrocardiography Core Laboratory, and a Nuclear Core Lab. Each laboratory will develop standards for the measurement, review, and systematic coding of relevant material or will document that these are in place. If special procedures are required at the study sites these will be clearly outlined. Competitive bids from experienced laboratories will be solicited and submitted to the Coordinating Center for their review and approval. Specific details and operational activities of the proposed core laboratories are described in Section XIII.

X. QUALITY CONTROL

A) Data Quality Control

After the study is approved, the data forms will be field tested prior to study start-up. Most forms will be printed on NCR paper to alleviate the need for Xeroxing.

During the trial the study coordinator at each medical center will assemble the completed data forms for each study patient. The participating investigator has overall responsibility for the data from the site. One copy of the forms will be kept at the participating investigator's office, one a copy sent to the Coordinating Center and a third copy to the Study Chairman's office on a monthly basis.

All forms received at the Coordinating Center will be reviewed manually by a statistical

assistant for consistency and completeness. Problems discovered by the statistical assistant will be resolved by telephone calls to the study coordinator or deferred to computer data-checking procedures. The data will then be keyed and re-keyed for verification. Data files on an in-house mini-computer containing the accumulated patient information will be updated at monthly intervals. Newly keyed information will be screened by a computer program to check for missing and out-of-range values. Machine-generated notices will be mailed to the study coordinators requesting completion, correction or verification of specific data items. A computer-generated edit message indicating the questionable data will be used to monitor coding errors and edit the data on the main computer file when the requested information is returned. Data found to be irretrievable will be assigned a code to distinguish the value from pending data. A computerized record will be kept of types of errors to ensure a high level of data integrity. A cumulative record of errors will be kept and interim progress reports regarding data quality will be sent to the Participating Investigator, the Study Chairman, and to the Data Monitoring Board.

The quality of life forms that are completed by the patient will not be on NCR paper. These data will be checked for consistency but will not be data checked in the same manner as information provided by the study personnel. Study nurses should check the forms for missing entries before the patient completes the clinic visit.

B) Missing Data

The progress of data collection will be monitored with computerized data from inventory programs which will produce a summary of patient follow-up, a profile of all forms received for a patient indicating which forms should be on file according to the patient's scheduled follow-up.

A "missing-forms report" will be generated and sent to the study coordinators in order to obtain complete patient follow-up. A follow-up schedule will be generated by the Coordinating Center and sent to the study coordinators on a monthly basis to assist in the contacting of patients and the scheduling of follow-up visits.

Missing data within forms will be identified either by the statistical assistant's review or by the data checking procedure and, if appropriate, the study coordinators will be requested to supply or retrieve the missing items. Summary reports of the completeness of the data will be provided to the Executive Committee and the DMB.

C) Quality Control of the Process

After the study is approved, the principal proponent and co-proponents will prepare an Operations Manual which will be provided to the investigators and the clinical coordinators as a guide to the operation and management of the study as well as a technical reference manual. At the study kick-off meeting, all study criteria and procedures will be discussed and the methodology explained with this manual providing a basis for the discussion. Training will also be provided for all study participants in both patient management and data collection procedures in an attempt to assure uniformity across centers and over time. The study coordinators will also be trained in interview techniques and questionnaire administration.

Study procedures will be reinforced by the use of regular conference calls, particularly in the first few months of the study and by the regular distribution of a study newsletter. All participants will attend a meeting after 1 year when study procedures again will be discussed in detail.

If it is determined by the Executive Committee that a procedure must be changed, participants will be informed by conference call and/or newsletter and eventually an updated section of the Operations Manual will be provided.

D) Site Selection

Sites will be selected based on volume of **diagnostic** angiograms and PCI procedures performed in the laboratory, **interest** of the site investigators, and **experience** of the proposed operators.

- The laboratories must have a volume exceeding 150 diagnostic catheterizations in a 3-month period documented by hospital reporting procedures.
- The investigators must demonstrate interest by responding to questionnaires and by being willing to count patients prospectively for a limited time.
- The operators must perform at least 100 procedures annually and have experience in the newer techniques including DCA, rotoblators, and stents. Ideally the operator will have performed a minimum of 300 elective revascularization procedures of which at least 80 were multivessel disease patients. Further, the per lesion success rate will be $\geq 90\%$ for subtotal lesions and the overall incidence of procedure related acute myocardial infarction, emergency coronary bypass surgery and death will be $<5\%$, $<3\%$, and $<2\%$ respectively.

E) Proposed Enrolling Sites:

V.A. Sites

Albuquerque	Houston	Nashville
Ann Arbor	Iowa City	New York
Atlanta (Decatur)	Lexington	San Antonio
Durham	Little Rock	Seattle

U.S. non-V.A. sites

University Hospital, Ann Arbor Institute	Mayo Clinic	Mid-America Heart
Duke University Delaware	Boston Medical Center	Medical Center of
Cleveland Clinic Hospital	Emory University	The Rhode Island
Hospital of the University of PA University of Wisconsin, Milwaukee	Jewish Hospital of St. Louis University of Syracuse	

Canadian Sites

St. Paul's Hospital, Vancouver Vancouver Hospital and Health Sciences Center	St. Boniface General Hospital, Edmonton The Toronto Hospital, Toronto	Ottawa Heart Institute, Montreal Heart Institute New Halifax Infirmary (Dalhousie University)
Foothills Hospital, Calgary University of Alberta Hospital, Edmonton London Ontario	Sunnybrook Hospital, Toronto Sudbury Memorial Hospital	Hamilton General Hospital University Hospital,

XI. STUDY TERMINATION

After study completion, whether normal or premature, patients enrolled in the study will be returned to their usual source of care.

After all patient follow-up is completed and major analyses are performed, a letter will be sent to each patient thanking him/her for participating in the study

and informing him/her of the study results. The approach and content of this letter will be discussed with the Study Group, Executive Committee and the Human Rights Committee toward the end of the study.

XII. HEALTH ECONOMICS ASSESSMENT

The COURAGE Economic, Quality of Life and Cost Effectiveness Study Investigators

William S. Weintraub, M.D., PI & Study Director, Emory University, Atlanta

Edmund Becker, Ph.D., Emory University, Atlanta

Stephen Culler, Ph.D., Emory University, Atlanta

Andrzej Kosinski, Ph.D., Emory University, Atlanta

Elizabeth Mahoney, Sc.D., Emory University, Atlanta

Sandra Dunbar, D.S.N., Emory University, Atlanta

Christi Warner, Ph.D., Emory University, Atlanta

Laura Kimball, Ph.D., Emory University, Atlanta

Leslee Shaw, Ph.D., Emory University

Joy Burnette, R.N., Emory University, Atlanta

Paul Barnett, Ph.D., Palo Alto VA, Stanford University, Palo Alto, CA

Bernard O'Brien, Ph.D., McMaster University, Hamilton, Ontario

Robert Nease, Ph.D., Washington University, St. Louis, MO

John Spertus, M.D., M.P.H., University of Missouri, Kansas City, MO

Patrick D. Mauldin, Ph.D., Medical University of South Carolina, Charleston

Stan Kaufman, M.D., Epimetrix Corporation, Seattle Washington

Walton Sumner, Washington University, St Louis, MO

Mark Hlatky, M.D., Stanford University, Palo Alto, CA

Dan Mark, M.D., Duke University, Durham, NC

David Cohen, M.D., Harvard University, Boston, MA

Milton Weinstein, Ph.D., Harvard University, Boston, MA

John Miyamoto, Ph.D., University of Washington, Seattle

Jinook Jeong, Ph.D., Ajou University, Seoul, Korea

Stephen Boccuzzi, Ph.D., Merck-Medco, White House, PA (ex officio)

Joanne Palmisano, M.D., Merck, West Point, PA (ex officio)

Pamela Hartigan, Ph.D., Yale University-West Haven VA, West Haven, CT

Koon Teo, M.D., University of Alberta, Edmonton, Canada

Robert O'Rourke, M.D., University of Texas-San Antonio VA, San Antonio,

TX

William Boden, M.D., COURAGE PI, SUNY Syracuse-Syracuse VA,

Syracuse, NY

A) Overview

National PTCA data first became available in 1983 when 32,300 procedures were performed. Currently, there are in excess of 400,000 coronary interventional procedures performed annually. While PTCA is recognized to be expensive, there are little data to justify this expense. In this section we present background information, measurements of cost, quality of life assessment and methods for integrating cost and quality of life. It is necessary to measure quality of life because this is in large measure what patients really care about. This being the case, event rates for death, MI and revascularization do not adequately describe outcome. There are complementary reasons for including cost data and for integrating cost and outcomes. Economic theory is based on the notion of scarcity of resources. In an era in which we must make choice of how to use scarce resources the only scientific method for doing so is to assess cost and then analyze the benefit to be obtained from resources spent. Thus the economic and cost-effectiveness analyses to be described should be viewed as not only complementary, but also part of an integrated whole within COURAGE which will allow society to assess the use of angioplasty.

B) Economics of PTCA

The determinants of the costs of PTCA have been analyzed in several studies. Mark et al¹¹⁹ have proposed analyzing the cost determinants of PTCA in four major categories: patient-specific, hospital-specific, treatment-specific, and geographic-specific. Topol et al⁴⁰ evaluated some of these factors in a private insurance claims database; for patient-specific factors, the charges for PTCA were higher in older patients, in women, and in patients with a history of prior MI; for hospital-specific factors, teaching hospitals had lower charges than nonteaching hospitals except in the Midwest; for geographic factors, the West had the highest charges, the Midwest the lowest.⁴⁰

As might be expected, complications increase costs. Reeder and co-workers¹²⁰ found that unsuccessful PTCAs more than doubled hospital charges compared with an initially successful procedure. Barbash et al found higher charges for nonelective procedures, for procedures in patients with more severe symptoms, and in older patients.¹²¹

In a 1988-89 investigation, Topol et al found that average hospital charges in a database of 2,100 PTCA patients were around \$10,000 for the baseline hospitalization (which included the preceding diagnostic catheterization), plus another \$4,000 for physician fees.⁴⁰ Within one year, Topol et al found \$4,000 to \$5,000 more in charges for these PTCA patients.⁴⁰ Weintraub et al studied the costs associated with new devices. There was increased cost with devices, but the major contributor was prolonged length of stay after the placement of an intra-coronary stent.¹²² In the multicenter CAVEAT randomized trial, mean hospital costs were \$10,300 with a median of \$8,500.⁴⁹ Hlatky et al examined in-hospital resource utilization in patients undergoing CABG and PTCA.¹²³ These investigators developed 4 scales to compare the economic costs of the two procedures: 1) cost of supplies, 2) cost of personnel and supplies, 3) average direct costs, and 4) average direct costs plus hospital overhead. While none of these scales was established as the best measure of marginal costs, the authors maintained that any one of these was superior to hospital charges, and they drew several conclusions: 1) the difference between CABG surgery and PTCA is overstated when charges are used as a proxy for economic costs when compared to any of these accounting methods; 2) the estimated differences between CABG surgery and PTCA are smaller the more stringent the definition of marginal costs, i.e., the differences are smallest using scale 1 and greatest using scale 4.¹²³

Several studies have analyzed data using the charges for PTCA and CABG.^{40,124-128}

Given the methodologic problems in these investigations (use of charges to estimate costs, problems in measuring charges/costs, length of follow-up periods, potential bias in samples, dates of analysis, differences among institutions, etc.) any summary comparisons across these studies must be viewed with skepticism.

Overall, the studies indicate that the initial charges for CABG are substantially higher than those for PTCA. The estimates from these investigations suggest that CABG surgery costs are about two to three times higher than those for PTCA are. The major factors in the cost of PTCA were the need for subsequent revascularization and the 30%-40% restenosis rate. Weintraub et al¹²⁶ estimated costs for 787 2-vessel CAD patients treated with either PTCA or CABG. The authors found a cumulative increase in costs for the PTCA group over time but, at five years, the overall costs of PTCA were still significantly lower than CABG costs.

At present, there are two randomized, controlled trials in the U.S. studying the short-term and long-term cost differences of PTCA and CABG in multivessel CAD: the EAST Trial³⁴ and the BARI Substudy of Economics and Quality of Life (SEQOL).¹²⁷ In the EAST trial Weintraub et al¹²⁸ examined the in-hospital and three year costs of patients randomized to revascularization with coronary surgery or coronary angioplasty. While the in-hospital costs of surgery were higher than those of angioplasty, there was little difference in 3-year costs. This was due to the need for additional procedures in many of the angioplasty patients. BARI¹²⁷ is a multicenter trial with 1,829 patients and includes prospective information on economic costs and quality of life in 934. The initial cost of angioplasty was \$21,113 and or coronary surgery \$32,247 ($p < 0.001$). However, by 5 years the costs were much closer, \$56,225 for angioplasty and \$58,889 for surgery ($p = 0.047$). The costs were surprisingly and disturbingly high in both treatment arms, and there was considerable

overlap. Two European randomized trials of PTCA and CABG have included economic endpoints, the RITA Trial³² of 1,011 patients and the GABI Trial³³ of 358 patients. In the GABI Trial, the initial procedural costs were \$16,562 for CABG and \$5,000 for PTCA. After one year, the authors found that there was little increase in cumulative costs in the CABG group, while the cumulative costs for PTCA were \$11,250.³³ Similar results were found in the RITA trial, where initially there were much higher costs in the CABG group, but by 2 years the cumulative costs of PTCA were 80% of those for CABG.¹²⁹

In summary, the descriptive studies clearly demonstrate the nature of the problem. These procedures are complicated, with multiple different events occurring over time. The literature reveals only a modest amount of descriptive data or methodologic approaches that are useful in evaluating PTCA costs and outcomes. The vast majority of the literature has limited generalizability or comparability. While most available data focus on hospital charges, it is well known that charges are an uncertain surrogate for true economic costs.

The Prospective Payment Assessment Commission (PROPAC) has identified numerous problems with such approaches. While the literature hints at numerous variables that appear to influence the outcome and costs of these procedures--patient demographic characteristics, clinical characteristics, and physician characteristics--few have been analyzed systematically or comparatively from one study to another. Moreover, there are virtually no economic data, which can be used for medical decision making regarding interventions in CHD management and the choice between medical therapy, or medical therapy combined with PTCA. While the in-hospital costs of medicine should be lower than for medicine combined with PTCA, to date, there are no economic comparisons that could be used in decision making. In the descriptive cost studies

concerning PTCA, hospital and professional costs are not available generally, or if they are available, researchers have often reported charge data. Clearly, more comprehensive and systematic investigations are required.

C) Quality of Life Assessment

Overview

Quality of life has become an important and essential outcome variable in the evaluation of interventions,¹³⁰ and it is considered a significant endpoint of medical care--specifically for patients with cardiovascular disease.^{131,132} The focus of cardiovascular patient care is not cure but rather management of chronic illness including alleviation of symptoms, improvement of functional capabilities and retardation of disease progression.^{131,132} Historically, quality of life measures in cardiovascular studies focused on reduction of anginal symptoms^{133,134} and return to work.^{135,136,128} Using these indicators, revascularization procedures have clearly improved the quality of life as it relates to symptom relief and whether patients perceive treatment to be beneficial.¹³⁷ Return to work rates was low in some studies,¹³⁸⁻¹⁴⁰ but remarkable high in the EAST trial in patients who were working when they entered the trial.¹²⁸ More contemporary thoughts about quality of life, however, suggest that it is more than just the presence or absence of symptoms, but rather a multi-dimensional construct involving health and satisfaction with aspects of life that are important to the individual.^{141,142} At its fundamental level, quality of life is both multidimensional and subjective; thus health status is best measured from the patient perspective (while utility is best measured from both a patient and community perspective, see below).¹⁴³ Health related quality of life is characterized by its application to well-being and satisfaction associated with how an individual's life is affected by disease, accidents and treatment.¹⁴⁴ Assessment of quality of life complements

the more traditional sources of information for evaluating therapies by providing a more comprehensive evaluation of therapy.¹⁴⁵

The assessment of economic and quality of life outcomes is moving into a new era as clinical trials attempt to intertwine these two domains in analyzing the effectiveness and utility of interventions. Two major approaches have emerged, including psychometric methods and utility assessment.¹⁴⁶ This trial will effectively intertwine quality of life assessments from these two approaches with economic measures to determine overall cost-quality outcomes (see sections E and G). Inclusion of both the psychometric and utility approaches to quality of life will enhance interpretation of the trial outcomes in terms of both the usefulness of interventions to patients and to society which will significantly increase the value of the data for health policy implications.

Quality of Life in Patients with Heart Disease

Regarding the psychometric approach and evaluation of global aspects of quality of life, Cella¹⁴² describes four areas, which are highly relevant for patients with CHD: physical, functional, emotional and social. The physical domain refers to perceived alterations in body function and includes both disease symptoms and side effects. Along with anginal symptoms, CHD patients may experience multiple medication and interventional treatment side effects. It has been documented that cardiac medications such as beta blockers, nitrates, anti-lipidemics, and calcium antagonists do cause a wide array of side effects,^{147,148} and side effects may be the leading reasons that patients are not compliant with an effective therapeutic regimen. In the early recovery period following PTCA, over 50% of subjects reported having side effects, with the most frequently reported as bruising, pain or swelling at the groin arterial puncture site.¹⁴⁹ While these tend to subside within several weeks, fatigue has also been reported in the 2-3 month period following PTCA.¹⁵⁰

The functional domain refers to abilities to perform activities of daily living and perform responsibilities at home and work. Measuring both physical and functional dimensions is important when it is considered that CHD patients with more sedentary jobs might be able to continue performing adequately at work despite great discomfort from either symptoms or side effects of treatment.¹⁴²

The third domain of quality of life is emotional function. Emotional function includes both positive and negative affect. In general, emotional distress has been most apparent in CHD patients following salient negative CHD-related events such as myocardial infarction;¹⁵¹ however, the impact of repeat CHD treatment events on emotional function has not been studied. Depression has been documented to have an independent impact on cardiac mortality during the first 6-18 months after acute myocardial infarction.¹⁵² In a study of 113 consecutive patients prior to and six months after PTCA, patients 70 years and older showed significant improvement in emotional role score (measured by the Medical Outcomes study Short Form 36 questionnaire) after PTCA. Younger patients had no difference in emotional role scores.¹⁵³ Recent data reported by Spertus and colleagues¹⁵⁴ revealed depression to be associated with very significant decreases in disease specific functional status in patients with documented coronary artery disease. Changes in depression status over time were accompanied by changes in cardiac-specific functional status. These findings add compelling reasons to examine the full array of quality of life domains and their interrelationships.

Social functioning is the final quality of life domain suggested by Cella.¹⁴² It refers to maintaining satisfying relationships with family and friends. Social support, a separate construct, has been also demonstrated to be an important variable in reducing morbidity and mortality in CHD patients.¹⁵⁵

Very few studies have addressed quality of life following PTCA or medical therapy from a multi-dimensional perspective. Although sample sizes were quite small, findings suggest that PTCA patients demonstrated improvement in the areas of health and functioning^{150,156} and increased participation in recreational activities.^{151,157} Papadontonaki and Stotts¹⁵⁸ found that patients who underwent CABG and PTCA were similar in terms of small improvements in perceived quality of life. However, PTCA patients reported greater improvement in mood and physical functioning than surgical patients did at three weeks after hospital discharge, which would be expected due to differences in the recovery process. This study did not examine long-term events or changes in quality of life.

The three year outcomes of the EAST Trial³⁴ found that PTCA patients were more likely to take anti-anginal medications, to have higher (worse) functional anginal classifications, were less likely to classify themselves as completely recovered, and had a greater number of hospitalizations for chest pain than CABG patients. However, more PTCA patients than CABG patients were optimistic about their health which may reflect the difference in invasiveness and meaning of the procedures to the patient.¹²⁸ Other aspects of quality of life such as emotional and social functioning were not reported in the EAST data.

Quality of life comparisons between PTCA patients and those treated with medical therapy were reported from the ACME trial in the unidimensional form of psychological well-being.³⁷ Angioplasty patients had significantly greater improvement in psychological well-being which was accounted for primarily by improvements in perceptions of general health and vitality. The major limitations of this report were the single dimension measure of quality of life, as well as the limited (6 month) time frame for examining outcomes. A more recent report from ACME described improvement in both physical and psychological measures in the angioplasty group at 6 months after randomization.¹⁵⁹

In summary, major gaps in knowledge about quality of life following CHD treatment with PTCA or medical therapy have occurred for three major reasons: 1) when larger samples were used, as in clinical trials, quality of life was not assessed from a *multi-dimensional* perspective; 2) in studies where multiple domains of quality of life after treatment were assessed, *sample sizes were too small to generalize findings*; 3) although pre- and post-treatment assessments of quality of life were made, few studies measured quality of life at *multiple time points* to assess differences in quality of life in the early and late post-treatment periods, and 4) multifactorial analysis of quality of life including treatment and mediating variable effects has not been addressed.

Consequently, the effects of these treatments on the multiple domains of quality of life and relationships with other demographic and clinical variables remain unclear. In addition, it has not been demonstrated how subsequent occurrence of CHD-related events following randomized treatment or the demands of that treatment affect quality of life, and the impact of CHD patients' quality of life on health resource utilization is unknown.

D) Proposed Economic Analysis

Overview

In COURAGE we will determine the cost and effectiveness of the PTCA in the setting of optimal medical therapy. Comprehensive information will be gathered on cost over 3 years for all health care resources on all patients in COURAGE. We will determine the direct in-hospital cost of angioplasty as well as cumulative health costs over 3 years. While we will include all health care costs, cardiovascular costs can be expected to dominate¹²⁸ over a 3-year period. The reason for including all costs is that it is sometimes difficult to distinguish cardiac from non-cardiac events.

However, we will attempt to separate hospitalizations and office visits associated with a patient's cardiac problems from non-cardiac episodes of care. The type of office visit will be based on patient reporting and the type of hospitalization will be adjudicated, permitting us to look both at total and cardiac specific costs. In addition we will examine the effectiveness of PTCA through the clinical endpoints discussed above and multiple quality of life measures. We will use quality adjusted life years (QALYs) as a morbidity-adjusted measure of survival. A cost-effectiveness analysis will be used to estimate the cost-effectiveness of PTCA in dollars per QALY gained. This results of this analysis may be used by health care decision-makers to compare the cost-effectiveness of PTCA to other health care interventions. In addition we will use a econometric model (MIMIC) to assess the cost-effectiveness within COURAGE. This model will permit assessment of the cost-effectiveness using multiple measures of outcome and for subgroups in a multivariate manner not possible with standard cost-effectiveness analysis. MIMIC does not provide a measure, such as cost/QALY, that permits a comparison to other competing claims for scarce health care dollars. Thus, the models of cost/QALY and MIMIC should be seen as complementary forms of analysis, with MIMIC looking internally within COURAGE, while the results of the cost-effectiveness analysis in cost/QALY gained from PTCA providing our most generalizable measure.

Primary Aims

- 1) To compare the total cost of treating randomized patients with coronary disease with both angioplasty and medical management to the total cost of medical management alone over 3 years.
- 2) To compare the outcomes, using quality of life measures, of randomized patients in the two treatment arms.
- 3) To determine the incremental cost-effectiveness of angioplasty in dollars/QALY.

Secondary Aims

- 1) To estimate the differences in types of resource utilization between the two arms of the trial, including hospitalizations, procedures, length of stay, time to first hospitalization/procedure, anti-anginal medications, diagnostic procedures, rehabilitation, and outpatient visits.
- 2) To determine the effect of angioplasty on a range of outcomes, including physical, functional and emotional as well as global well-being.
- 3) To determine the cost, effectiveness and cost-effectiveness of angioplasty in the three different health care systems (VA, Canada, U.S. non-VA).
- 4) To compare the cardiac specific cost of treating randomized patients with coronary disease with both angioplasty and medical management to the cardiac specific cost of medical management alone over 3 years.

Costs/Resource Utilization

Overview

The COURAGE economic study will first focus on cost and resource utilization. Thus the first question is "What are the costs and resources used in the treatment of patients from the two arms of the trial during the 3 years of the study period?" To answer this question, we will focus on calculating direct costs (hospital, physician, and outpatient), and patient indirect cost. This is complicated in COURAGE by the inclusion of sites with different economic systems requiring different methods to determine cost. Table 11 shows a general conceptual overview of our approach to the cost analysis. We will develop estimates of cost based on this model for each therapy and for

each cost system

Table 11: Conceptual Overview of Major Cost Components and Time Periods for Analysis

Type of Resource	Information Retrieval	Time	Scope of Cost Included
Hospital US-Non VA VA Canada	Hospital Billing Systems UB-92 VA Cost System Canadian Cost System	3 years	All Hospitalizations
Physician US-Non VA VA Canada	Resource Base Relative Value Scale VA Cost System Canadian Reimbursement Rates	3 years	All Cardiac and Non-Cardiac Physician Services
Outpatient	Patient self reported office and clinic visits	3 years	All Cardiac and Non-Cardiac Physician Services
	Patient self reported prescription drug use	3 years	All Cardiac Related Prescription Pharmaceuticals
Patient indirect costs	Productivity instrument	3 years	Travel & Lost Productivity

U.S. Non-VA Hospital and Physician Cost

Overview:

A combination of hospital bills (UB-92s), modeling and chart review, as well as cost-charge ratios will be used to derive hospital costs, and resource-based relative values (RBRVS) will be used to generate physician resource use.^{160,161} Outpatient utilization will be determined using patient self reporting of office visits, while medication costs and patient indirect costs will be analyzed by Patient Productivity Instrument.

US Hospital Cost:

One problem common to all empirical studies evaluating the cost effectiveness of any medical procedure that involves hospital services is that the actual cost of the services is not available. The typical solution to this problem in the literature is to approximate the cost of a patient's hospitalization using charge information obtained from claims data sets.¹²³ Previous researchers have obtained estimates of the total cost of a hospital episode by adjusting charge information using one of two approaches: 1) Hospital Wide Cost-to-Charge Ratios - in this approach, the total cost of each hospitalization is calculated as the product between total billed charges during the hospital episode found in the claims data base and the hospital's overall cost-to-charge ratio available from the Medicare cost report¹⁶²⁻¹⁶⁴; and 2) Department Wide Cost-To-Charge Ratios - in this approach, the total cost of each hospitalization is obtained by adjusting hospital charges to costs at the departmental level using the appropriate departmental cost-to-charge ratio.¹²⁸ This study will use the latter approach. Hospital cost from U.S. non-V.A. sites will be estimated by collecting UB92 forms for each hospitalization. Costs will be derived from charges using the appropriate departmental cost-to-charge ratio. To test the sensitivity of the hospital cost

estimates, hospital costs will be estimated using overall hospital cost-to-charge ratios for at least 10 hospital sites.

Professional Costs:

Physician professional costs will be estimated using a resource-based relative value scale (RBRVS) methodology. There are a number of steps involved in the process. First, from the hospitals with centralized billing, we get all physician services, defined by current procedure terminology (CPT) codes, CPT modifiers, and physician charges. We next merge RBRVS physician work relative value units (RVUs), practice cost RVUs, malpractice RVUs, and total RVUs from the Medicare Fee Schedule (MFS). We will use the latest MFS for obtaining RVUs given that the RBRVS values in the most current MFS reflect the most up-to-date perspective on the level of physician inputs to CPT services and procedures.

Because the anesthesia codes for the RBRVS are computed based on both physician work and time, for the anesthesia CPT codes, the anesthesia RVUs from the 1995 Federal Register will be used.¹⁶⁵ In the 1995 Federal Register, the Health Care Financing Administration (HCFA) imputed RBRVS physician work units and time units. The 1995 anesthesia units will be updated to correspond to RVUs for the other specialties.

The next step involves listing all CPT services without a corresponding RBRVS. These services can include local codes or services that are used in a unique way by a particular institution. These services will be reviewed and RBRVS weights assigned in one of two ways. First, for small groups of services from an institution (10 or less), we will initially use all physician services from the institution where we have relative values and charge data and calculate a mean physician charge per RVU. Using the mean physician charge per RVU, we will divide the total charges for the specific services without RVUs by the corresponding mean physician charge per RVU to calculate an imputed RBRVS for the services without an RBRVS.

Another method for services where there are greater than 10 services, is to use a small panel of knowledgeable physicians to review the services and match them up with CPT codes that have similar levels of physician work and practice costs. These RBRVS values will then be assigned for the services missing RBRVS values.

A further issue relates to all the physician services that have CPT modifiers. CPT modifiers are added to the CPT code and provides a means by which the reporting physicians can indicate a service or procedure that has been performed has been altered by some specific circumstance but not changed in its CPT definition or code. For example, a modifier can be used to indicate that: 1) a service has both a professional and technical component, 2) a service was performed by more than one physician, 3) a bilateral service was performed, or 4) a service was performed by an assistant at surgery. In these cases, RBRVS units will be assigned based on the modifier and the payment rules in MFS. That is, for instance, if an assistant at surgery is used on a procedure and HCFA pays 16% of the cost of the surgeon, we would adjust the RBRVS units to 16%. A similar process would be followed for other modifiers. An example of using this RBRVS methodology is presented in Becker, et al.¹⁶⁶

To convert the service RVUs into cost estimates; we will analyze the costs using two different conversion factors. The first conversion factor will be the Medicare national conversion factor for the latest year available (to make the results as current as possible). A second conversion factor will be the national conversion factor based on Blue Cross - Blue Shield (BCBS) or the Health Insurance Association of America (HIAA) data. By using two conversion factors in our analysis, we seek to accomplish several objectives. Two conversion factors will provide professional cost estimates for both Medicare and a major private payer. The difference between these two cost estimates should provide us with an indication of the additional professional costs for private payers compared to Medicare. Moreover, the difference between the professional costs in

each arm using the two conversion factors should indicate the sensitivity of the cost estimates to the value of the conversion factor and how critical the professional component is to the total cost estimate. In order to come up with one final estimate, we will determine whether to use the BCBS or HIAA conversion factor after discussions with representatives from both organizations about the extent to which each conversion factor is reflective of professional costs.

Costing in the VA

Although the Department of Veterans Affairs (VA) keeps careful account of the resources used by each of its medical centers, it has no comprehensive source of information on the costs incurred by individual patients. It does have a cost-accounting system and clinical and administrative databases that contain detailed utilization data. We have designed a method to determine costs that uses these data in a way that is especially sensitive to differences in resources use associated with the interventions being under study, medical management and PTCA.

VA Utilization Data:

VA maintains several centralized databases of utilization data, including the Patient Treatment File (PTF), the Outpatient Care file (OPC), and the Patient Assessment File (PAF); the National Patient Care Database (NPCD) is under development. The PTF is the VA database of hospital discharges. It includes a unique patient identifier, patient demographics, length of stay, and the Diagnosis Related Group (DRG) for each hospitalization. A related file contains procedures performed during the hospital stay. The OPC contains information on outpatient

visits, including patient demographics information, the date of the encounter, and the type of clinic visited. Complex ambulatory procedures are also reported.

The VA is adopting a new database to record ambulatory care encounters. Scheduled to be implemented on October 1, 1996, the National Patient Care Database will have a record for each outpatient visit, with fields to identify patient and practitioner, the diagnosis, and the service provided, recorded as a HCPCS procedure code. HCPCS is the Health Care Financing Administration Procedure Coding System, the system used by Medicare, which is similar to the Common Procedure Terminology (CPT) code system developed by the American Medical Association. The database will include radiology and laboratory services provided to ambulatory patients, but it will not include pharmacy.

Each medical center records clinical data in the Decentralized Hospital Computer Program (DHCP). DHCP contains unique information not available from the centralized databases; data on a particular patient may be retrieved via Patient Data Exchange, a program, which responds to remote, inquires with an e-mail message containing clinical information. Extracting data from these messages can be labor intensive.

Cost Data:

All VA medical centers complete the Cost Distribution Report (CDR), a cost-allocation system that assigns costs to different patient care units.¹⁶⁷ The VA is in the process of implementing a state-of-the-art cost-accounting system, called Decision Support System (DSS), that will determine the cost of each service provided to each patient. In order to fully realize the potential of DSS, medical centers must undertake extensive effort to account for the expenses used within each department and

by each patient. Because of the magnitude of this effort, it takes at least one year after installation before DSS can accurately determine costs. DSS is fully operational at more than 30 medical centers, including several of the sites being considered for this trial (Albuquerque, Denver, Little Rock, Seattle and Tampa were among the first 30 sites to implement DSS) and is being installed at new sites. Although DSS will eventually be implemented at all VA medical centers, this will not occur soon enough to provide complete cost data at all study sites.

Overview of Cost Finding Approach:

We will determine health care costs by multiplying utilization times a standard cost for each service. We will determine utilization from the databases available at all sites. We will expend most of our cost-finding effort on services that are the most frequently utilized, that is, the care related to coronary artery disease. This approach is designed to ensure that our method is sensitive to the variation in the amount of resources used in the different arms of the trial. We will find the standard cost of these high volume services from the DSS. We will find the standard cost of other types of care using a statistical analysis of the CDR.

Cost of Frequently Utilized Services:

We will obtain detailed information on the services frequently used by patients in the study including visits to medicine and cardiology clinics, ambulatory procedures, medication and hospitalizations involving a diagnosis of heart disease. We will use the PTF and DHCP to characterize inpatient episodes, including diagnosis, complicating co-morbidities, length of stay,

procedures, and use of high cost ancillary services. We will use the DHCP and NPCD (or if the latter is not fully operational, the OPC) to characterize outpatient care, including the procedure code, diagnosis, use of laboratory and radiology, and prescriptions filled, including drug, dosage and quantity.

We will use the DSS to determine the standard cost of services (since it will be available only at a few sites, we cannot use it to find costs directly). We will obtain detailed cost information at the sites using DSS, and compare these costs to utilization as measured by the universal databases, the PTF, DHCP, NPCD, and OPC. We will undertake a series of patient level statistical analyses using DSS costs as the dependent variable, and the universal utilization variables as independent variables. The result will be an estimate of the standard cost associated with each type of service.

Standard Costs of VA Inpatient Care:

It is not possible to undertake such a detailed analysis for all possible services, however. For the types of utilization that occur less frequently-- hospitalizations for other conditions, utilization of mental health, and long-term care-- we will use standard cost estimates for VA hospitals.¹⁶⁸ These estimates are based on program level statistical analyses that assume that the costs of medical and surgical hospitalizations are proportional to the "DRG weight", the relative quantity of resources used by patients treated in each Diagnosis Related Group (DRG). These weights are published annually by the Health Care Financing Administration. This method also considers how much the patient's length of stay deviates from the VA average length of stay for that DRG. The cost of long-term care is based on length of stay, and weights from the Resource

Utilization Grouping, ratings given to all long-term care patients and recorded in the VA Patient Assessment File.

Cost of Utilization of Non-VA Providers:

Veterans who receive health care from VA also visit non-VA providers. We will ask study subjects to provide information about their use of other providers. We will contact inpatient providers to obtain the total charges for hospitalization, and adjust those charges for the hospital specific ratio of cost to charges, as calculated from the hospital's Medicare cost report. For outpatient visits, we will determine the specialty of the clinician visited, and use the average costs of a visit to that type of clinician in the rest of the trial.

Costing In Canada

Background on Hospital Costs:

In Canada, hospitals are funded through governmental global budgets. As a result, hospital billing records for patients are not available. Since costs of medical resources were not required, costs of hospital services in Canada have traditionally been estimated through the construction of hospital costing models. With this type of approach, cost accounting methodologies are applied to hospital financial data to produce unit costs for patient services. Although this process is quite time consuming, it does offer the advantage of producing estimates based on hospitals costs (including a share of hospital overhead and support) rather than hospital charges.

Recently, a number of Canadian hospitals have developed integrated sophisticated costing and inpatient resource information systems. Most of these hospitals are participants in the

Ontario Case Costing Project (OCCP). These hospitals have the capability to provide details of both resource use and resource costs for individual inpatient episodes. This information is primarily used to produce price weights for inpatient episodes by Case Mix Group (similar to DRG's).

Analysis Plan:

For patients recruited at hospitals participating in OCCP, patient-level hospital costs will be available. For patients recruited at hospitals not participating in OCCP, we will estimate costs for measured items of resources used. Our strategy is to use data from OCCP Hospitals to create a Canadian-specific regression model of hospitalization costs for patients in the COURAGE trial. For each patient in COURAGE in whom costs are directly measured, total per patient hospital cost will be used as the dependent variable. Independent variables will include utilization data collected in the hospitalization case report form (total length of stay, ICU days, catheterization, PTCA, CABG, MRI, Holter Monitor etc.) along with other demographic covariates (sex, age, outcome.) This modeling strategy is similar to the costing approach being applied to the VA hospital sites.

At non-OCCP sites, the regression model will be used to determine costs. The covariates from the regression model will be available at all sites, allowing patient level costing to either be measured or estimated in all patients. The regression model will be validated by dividing the OCCP hospitals into a test and validation group. The model will first be developed in the test group and validated against patients in the validation group. This will provide an r^2 value allowing estimation of error in non-OCCP hospitals. The final model for the non-OCCP

hospitals will be developed from all OCCP hospitals.

Canadian Physician Fees:

In Canada, physician reimbursement is reported separately from hospital accounts. Physicians submit claims directly to provincial Ministries of Health. These claims are based on billings specified in ‘fee schedules’. There are unique ‘fee schedules’ for each province which identify standard billings for specific surgical procedures, radiological examinations, diagnostic & therapeutic procedures, consultations, and other physician services provided to patients.

Fee schedule(s) will be used to establish billings for the physician services provided to the COURAGE trial participants. Physician service utilization information for patients will be obtained from the study research data forms.

Estimating billings for therapeutic and diagnostic procedures will be straightforward. For example, if a patient receives a CT scan during the trial, the standard fee specified for this procedure will be applied. Physician billings for surgeries and patient consultations however will require some additional considerations. In many provinces anesthetist billings depend not only on the type of surgical procedure performed, but also on the length of time of the procedure. A number of cardiologists will be contacted to determine the average length of surgical procedures performed on patients in the trial (CABG, IABP etc...).

In addition to diagnostic and surgical procedures, physicians can claim for consultations and assessments given to patients while they are in hospital. The study research data forms do not (and cannot reasonably) include information on the number of physician consultations or assessments provided to patients. We will consult with cardiologists to produce a protocol of the type and

number of consultations/assessments normally claimed for cardiac hospitalizations in Canada. This protocol will be applied to each hospitalization and will vary according to length of stay. (i.e. a patient in hospital for 20 days will likely receive less assessments per day than a patient hospitalized for 5 days).

Medications and Indirect Costs

Medication use will also be tracked in COURAGE. Cost for pharmaceuticals may be estimated using the available retail prices for drugs (Red Book prices).

Indirect costs will be estimated using a patient productivity tool, which will estimate income and lost time from work. Indirect costs in Canada will be estimated from published data in *Statistics Canada* on Canadian salaries and earnings. Total societal indirect costs, which include such items as the impact of loss of time at work on an employer, cannot reasonably be calculated. Travel time and expenses for outpatient visits will be simulated from the number of office visits from published data on distances between zip codes.

Analytic Overview of Costs

Costs finally will be discounted to the year of initiation of the study termination to control for differences in timing of events during the 6-year study period. Costs will also be discounted at 3% per year (a generally agreed to number, people seek to defer costs to the future) and adjusted for the effect of inflation by using the Medicare inflation rate. Cost data will be displayed in tables, divided by treatment arm to highlight the extent to which costs cluster around the initial hospitalization, initial physician costs, outpatient costs, medications and readmission(s). Costs will

also be displayed graphically in a cumulative fashion by treatment arm, with cost on the horizontal axis and percent of patients with a specified or lower cost on the vertical axis. Finally costs will be displayed over time, with time on the x-axis and mean cost on the y-axis. The difficulties in aggregating costs from the three different health care systems are well recognized. Thus, the cost analysis will naturally consider each system separately as well as data aggregated across the three systems using the methods presented above. Currency differences with Canada will be accounted for.

The primary cost comparison will be performed using the two sample t-test if data will be approximately normally distributed in each group or Wilcoxon two sample test if marked non-normality will be present. A secondary analysis of costs will be performed using linear regression with cost as the outcome. Diagnostics of the model, including detection of possible groups of outliers will be performed. We will use the Least Trimmed Squares regression technique for such a robust analysis. Subsequently, Least Squares regression will be performed with weights based on the size of the residuals from the Least Trimmed Squares regression.

We will present means and standard deviations of costs for the two randomized groups. We will also present trimmed means and standard deviations of costs when 10% largest values and 10% smallest values are ignored. This way the summary statistics are less influenced by a small number of extreme outliers. Another possibility is to consider median as a measure of location and interquartile range as a measure of variance. However the usual or trimmed means and standard deviations seem more appropriate here because health care providers and payers may be concerned more about average cost, not median cost.

Power computations assume a 0.05 level two sided test and equal number of patients in each of the two randomized groups. Based on the three year physician charges with hospital costs in the EAST PTCA group we estimate that the average costs in the PTCA treatment of the COURAGE trial will be about \$23,000 with standard deviation of \$16,000.¹²⁸ The COURAGE study will then have an 80% power to detect a difference of \$1,570 in costs between the PTCA and Medicine groups. However if we consider data with 10% of the smallest and 10% of the largest values removed from the PTCA population, the average cost in the EAST PTCA group was \$21,400 with a standard deviation of \$8,300. This is reasonable, because the patients in EAST all had multivessel disease, were sick enough to at least warrant coronary surgery, and some 20% crossed over to coronary surgery by 3 years and there were many repeat angioplasties, providing for a highly skewed distribution of costs. With a standard deviation of \$8,300, the COURAGE study will have 80% power to detect a difference of \$815 in costs between the PTCA and Medicine groups.

E. Cost-Utility Analysis

Overview

Cost-effectiveness analysis is a method of comparing cost and effectiveness of alternative forms of health care. In a variant cost-utility analysis, several measures of outcome are aggregated to create an overall measure of effectiveness. In this study utility will be measured as well as the overall summary measure quality adjusted life years (QALYs). This study will permit the cost and outcome of angioplasty to be compared to medical management alone. Angioplasty will be preferred if it is as more effective than medicine alone and less costly. This is the principle of strong dominance. Alternatively, medical management alone may strongly dominate angioplasty. Perhaps more likely, given data from the ACME study, angioplasty will be found to

be both more costly and more effective than medicine alone. In such a case strong dominance will not apply, and the incremental cost-effectiveness of angioplasty must be considered. This will be expressed in cost per quality adjusted life years, which can then be used by policy makers to compare angioplasty to other competing therapies for scarce health care dollars.

Expected Utility Theory and the Definition of QALYs

Quality of life and functional status instruments can describe ‘how patients are doing’ with regards to their current disease status. As described below, quality of life measures will be used to illustrate the relative differences in outcomes of an initial treatment strategy of medical vs. percutaneous revascularization in the COURAGE trial. When used as outcomes, they can illustrate the frequency of symptoms, the physical or emotional limitations of a disease, and other qualities that influence patients’ lives. Whereas functional status measures describe the quality of people’s lives, mortality specifies how many enrollees have died. These 2 outcomes, mortality and functional status, provide different but complementary descriptions of treatment outcomes. Consequently, it would be very useful to distill the broad characteristics of quality of life into a single value that can be combined with mortality to describe the overall outcome of treatment.

Quality-adjusted life years (QALYs) are one approach to accomplishing this goal. QALYs modify the duration of patients’ survival by the quality of that survival. QALYs is a fundamental concept in expected utility theory; a theory of rational preferences among risky options that can be used to describe and understand patients’ decision making processes. According to expected utility theory, QALY is defined by multiplying a health state utility¹⁴⁹ by patients’ survival (discounted over time), Y , as shown below:

$$U(Y,Q) = Y*H(Q) \quad \text{(Equation 1)}$$

H(Q) is the utility of health state Q. It is a description of patients' health status that is anchored by an upper bound of 'perfect' health and a lower bound that is usually considered to be death. Numerical values are assigned to health states along a continuum of 0 - 1, where 0 represents death and 1 represents a state completely free of disease (i.e. H(death) = 0 and H(perfect health) = 1.0). In essence, a utility represents the distillation of all aspects of a patient's quality of life into a single numerical value between 0 and 1. For any given Q, H(Q) measures the utility of living in health state Q relative to the utility of living in perfect health. Therefore, the QALY utility model incorporates the tradeoff between patient longevity and quality of life by integrating mortality and attitudes towards morbidity into a single measure. To determine the QALYs for each arm of the COURAGE trial requires an estimate of Y, the expected survival duration, and H(Q) the health state utilities throughout Y.

Acquisition of Required Components for QALY Determination

Survival Duration:

Survival duration will not be observed within COURAGE because of the short time duration of the study (3 years). Survival up to 3 years will be needed to calculate QALYs during this period, and an estimate of expected survival beyond 3 years will be need to estimate QALYs after this time. Survival may be estimated with the use of covariates predicting survival and an exponential decrease in survival after 3 years.

Utility Determination:

Measuring a patient's utility of health state Q ($H(Q)$ from equation 1 above), can be theoretically and practically challenging. Several techniques have been developed to assist in the acquisition of patient utilities. The most widely accepted approach is the Standard Gamble, a technique originating with the work of von Neumann and Morgenstern.¹⁷⁰ The Standard Gamble presents patients with a choice: either accept a given health state or risk a chance of death to have perfect health. By continually altering the risk of dying in order to achieve a perfect state of health, a point of equivalence should be reached at which a patient cannot decide which is a better choice, perpetuation of a given health state or an immediate risk of death to achieve perfect health. The point of indifference between a health state and a risk of death is the patient's utility for that health state and is interpreted to be a patient's 'percentage' of perfect health. In essence, a patient's willingness ($1 - (\text{the risk of death that they would accept})$) to attain perfect health is equivalent to the quality of their life on a scale of 0-1. For example, a patient who already perceives their health to be perfect would accept no risk of death in order to attain perfect health and would have a utility of 1 (1-0). Conversely, a patient willing to accept a 95% chance of dying in order to attain perfect health would have a utility of 0.05 (1-0.95) indicating that their current health is only 5% of perfect health.

Obviously, explaining the concept of the Standard Gamble and asking patients to choose between a risk of death and the perpetuation of a given health state is a time-consuming and cognitively challenging process. To overcome these obstacles, an efficient and reproducible method for administering this instrument has been developed. A computer program, U-Titer,¹⁷¹

will be embedded within an Epimetrics™-designed computer application used to solicit patients' quality of life and utilities for the COURAGE trial. The use of a computerized method for utility assessment offers several distinct advantages. First, this approach will facilitate standardized utility solicitation among all 40 sites of the COURAGE trial. Given the complexity of eliciting utilities, the importance of standardizing the assessment and removing inter-site variability can hardly be overemphasized. In addition, it will allow patients to have a well encapsulated summary of their current health state with which to compare their decision against the concept of perfect health. This description will be individualized for each patient by basing these descriptions upon patients' responses to the SF-36 and the Seattle Angina Questionnaire. Such a process makes the Standard Gamble decision-making process far more applicable to each patient and should elevate the validity of the utility determinations.

Computerized acquisition of patient utilities has been performed in smaller studies¹⁷¹ and has been well accepted by both patients and study coordinators. For patients who are unfamiliar with the use of a computer, the study coordinator at each site will facilitate their completion of the utility assessment protocol. The study coordinator at each site will be equipped with a Fujitsu-510 pen-based, portable computer that will enable proper functioning of the Epimetrics™ program. In addition, the coordinators' will receive extensive training in the use of this computer, the Epimetrics™ software designed for the COURAGE trial and the study manual at the initial kick-off meeting. Individual training will be provided to each subsequent study coordinator who enters the project. Furthermore, an infrastructure will be established to code and evaluate data quality from the utility assessments on an ongoing basis throughout the study protocol.

In the COURAGE trial, the time trade-off method of utility assessment will be performed on all 3,260 participants at baseline, 3 and 6 months, 1, 2, and 3 years. These time frames were selected to document patients' health state utility at the time of randomization, at a period early enough to capture an early potential difference in the health status of the 2 treatment arms and annually after the time of randomization.

Utility Analyses

Specific Aims

Primary Aim:

To define the difference in quality-adjusted life years, over 3 years, between strategies of medical and percutaneous revascularization in patients with coronary artery disease. The use of QALYs will permit an integration of both mortality and quality of life into a single analysis. This is the primary aim because it involves measurements made during the course of the study and involves less assumptions than are involved in projecting beyond the end of the follow-up period. Furthermore, it seems likely to capture most of the benefit of angioplasty.

Secondary Aim:

To define the projected difference in quality-adjusted life years, not only for the period of direct observation but also into the future, between strategies of medical and percutaneous revascularization in patients with coronary artery disease. The secondary aim is recognized to involve assumptions about survival and utility after 3 years. However, it will allow calculation

of total QALYs in each arm, will require no additional data collection and no additional expense.

Analytic Overview:

In the COURAGE trial we plan to measure utility at several prespecified times to avoid the need to assume constant utility. QALYs are computed as the area under the utility function over the time interval from zero (baseline) to a specified time. The utility function will be prospectively ascertained for the COURAGE trial patients during the first three years.

With no censoring in observation times we can use the observed survival time for each patient and obtain individual QALYs as the area under this patient's utility curve over the interval from 0 through the time of interest. However the situation can be more complicated because of the presence of censored observation times where the patient's survival time is unknown. As commonly accepted we assume non-informative censoring. This means that censored patients experience the same survival as similar observed patients. In other words the fact of censoring should not be related to the likelihood of survival. A person who missed a follow-up visit because she was too sick to come to the hospital would violate the assumption of non-informative censoring.

Because we do not know the actual survival times for censored patients, we will need to estimate their survival time. To this end we will consider an exponential parametric survival model with a constant hazard rate (force of mortality). After completion of the 3-year follow-up we will fit such a model with all possible relevant covariates which impact survival. Thus, we will be able to estimate expected survival for each pattern of the considered covariates.

Primary Analysis, Calculation of QALYs during the 3 years of observation:

We will know the actual 3-year survival times for patients who were not censored within

the 3-year time frame of the COURAGE trial. Thus we will estimate survival times only for patients censored within 3 years from baseline. Thus, we will be able to estimate the area under the utility curve as follows. As demonstrated in equation 1, QALYs are the product of patients' utilities multiplied by their survival. During the first 3 years after randomization, patients' survival and utilities are known. Therefore, QALYs during this period will be determined as follows:

1. The first 2 weeks of patients' post-randomization course will be assigned the baseline utility weight.
2. Weeks 2-8 (2 months) will be assigned the 1 month utility weight.
3. Months 2 – 4.5 will be assigned the 3 month utility weight.
4. Months 4.5 – 9.0 will be assigned the 6 month utility weight.
5. The period from 9 months - 1.5 years will be assigned the 1 year utility weight.
6. From 1.5 - 2.5 years, the 2-year utility weight will be used.
7. From 2.5 - 3.0 years, the 3-year utility weight will be used.

For each censored patient we will enter the covariate values into the model and obtain the expected survival time. If this time is less than 3 years than it will be substituted for the unobserved survival time and if it is larger than 3 years we will treat such a patient as alive throughout the study. We will use the utility function for the censored patients over the unobserved time as the average utility function of patients with that particular pattern of covariates (or as similar a pattern as possible).

QALYs during each period will be calculated by multiplying the time duration of that period by the assessed utility for that time period, which, in turn, will be multiplied by a discount

rate for the period that accounts for the greater near-term value of a higher quality of life. A 3% discount rate per year will be used. Each patient's QALYs for the first three years of the study will be determined by summing QALYs from steps 1 - 5. Patients who expire during this time period will be assigned utility weights of 0 for all time periods subsequent to their death. $U_{PTCA} - U_{MED}$ is the adjunctive benefit of PTCA over medicine alone over 3 years. If survival and utility after 3 years are unaffected by the treatment arm, then the calculations in the primary analysis represent the complete adjunctive benefit of PTCA.

Analytic Plan:

The QALYs will be presented graphically as cumulative distribution plots, with mean and median points noted. A Student's t-test will be used to compare the calculated utilities over the 3 years of direct observation of the 2 arms of the COURAGE trial. If, however, the QALYs deviate substantially from a normal distribution, a Wilcoxon Rank Sum test will be used. As for the rest of the trial, a two-sided probability of <0.05 will be considered a statistically significant difference between the groups.

Secondary Analysis, Projecting QALYs Beyond Year 3:

Although definitive QALY assessments will be available during the initial 3 years of observation, it is also desirable to predict patients' QALYs beyond these 3 years. The importance of this analysis lies in the need of health policy planners to know the impact of treatment strategies for the entire lives of the patients for whom they need to establish policy. For example, if health policy planners need to allocate resources between treatment programs for

different diseases or social priorities (e.g. renal dialysis programs, better housing, vocational training etc.), it is necessary to have a common metric that incorporates all future benefits of a program to treat coronary artery disease so that it can be compared with the same metric of benefits for other programs. Because COURAGE will follow patients for only 3 years, it will be necessary to project both future survival and future utilities in order to estimate total QALYs associated with each arm of the COURAGE trial. Accordingly, a secondary analysis will be performed to model future QALYs of the surviving population at the conclusion of the COURAGE trial. The limitations and assumptions of this approach are clearly recognized. If, however, there appears to be a substantial difference in utility or survival at 3 years, then there would be a strong impetus to extend the trial.

Determining an estimate of QALYs beyond the 3-year follow-up period is difficult. The easiest subset of patients to account for are those who die during the initial 3-years of the trial because we will know the survival times and utilities of these patients. For these patients we will compute QALYs as the area under their individual utility curves. For all other patients, censored during the trial or at the end of the trial (alive at 3 years), we will need to compute their estimated survival time as well as their estimated utilities. Survival can be predicted using the regression model, generated during the first 3 years of the study, and assuming an exponential approximation of life expectancy. We will fit a model with baseline covariates to the 3-year survival data. We will consider all patients in the trial for fitting this model. We will use a parametric model with time assumed to be exponentially distributed. After fitting the model, for each pattern (i) of baseline covariates describing a patient, we will obtain an estimate of survival curve $S_i(t) = \exp(-m_i \cdot t)$ or equivalently the hazard $m_i = \int_0^{\infty} \exp(-m_i$

. t) dt. This allows us to compute expected survival time $1/m_i$ for the i -th pattern of covariates. Then the QALYs for this pattern of covariates is computed as the area under the utility curve over the interval from zero to the expected survival time $1/m_i$.

Patients enrolled in COURAGE may have projected survival durations of up to 20 or more years after enrollment in COURAGE. Knowing what the utilities of these patients will be in the future is difficult to predict because projecting future health state utilities has never been done before. The COURAGE trial will attempt to model future utilities using a cross-sectionally designed substudy to define the shape of the utility function over time. This curve will then be applied to the COURAGE population in order to estimate the utilities of survivors over time.

Although the utilities of both arms of the COURAGE trial will be explicitly followed for 3 years, beyond 3 years the utilities of both treatment arms will be assumed to be the same. This assumption is made because it is likely that patients' whose coronary artery disease is significantly limiting their health state utility would have 'crossed-over' by this time to the other treatment arm to maximize their functional status. This will blur any associated differences in utilities between the 2 treatment groups beyond 3 years and will create a more homogenous range of utilities among the entire COURAGE population. The primary determinant of projected utilities will then be assumed to be the variation due to time since enrollment and aging rather than the assigned treatment regimen. The first step in utility assignment will be to project the utilities of patients who have survived 5, 10, and 20 years after enrollment in COURAGE. These projected utilities can then be applied to the projected survivors, as described above, to determine the projected QALYs of COURAGE patients.

A cross-sectionally designed substudy will be used to define the utility weights that

should be applied to patients at times in the future. In order to estimate the utility values that survivors will have, the COURAGE investigators will use the Emory databank to identify patients who would have met the COURAGE entry criteria at the time of their enrollment in the Emory database. Ten patients will be identified that would have met COURAGE entry criteria and who have survived 1, 3, 5, 7, 9, 11 and 13 years. These 70 patients will have formal utility assessments performed using the same Epimetrics™ designed computer application as used for the rest of the COURAGE trial. The utilities of the patients who have been followed at Emory for 1 and 3 years will be used to compare with the 1 and 3 year utilities of the COURAGE population to insure similarity between Emory and COURAGE patients. If they are similar, then mean utilities at years 5 through 13 will be applied to the entire COURAGE population. The utilities of COURAGE patients beyond 13 years will be assumed to be the same as the 13-year utilities. These mean weights will then be applied to the COURAGE treatment groups projected survivals, as described in the preceding paragraph, to determine the QALYs of each arm of the COURAGE trial. The exploratory nature of the secondary analysis is recognized. The utilities are assumed to be the same in both treatment arms and while survival for each patient will be individually predicted from the regression analysis, randomization would be expected to produce populations with similar a priori survival estimates.

Analytic Plan:

Because of the degree of estimation required (including the assumption that the patients have the same utility), formal statistical analyses comparing the projected QALY differences between medical and percutaneous revascularization treatment strategies will not be performed.

Rather, descriptive analyses that state the projected QALYs of each treatment strategy will be presented. If QALYs after 3 years are equal in the two arms, then the full benefit of PTCA will be described in the first three years as per the primary analysis. This analysis will provide an estimate of total QALYs to be expected in each arm, an estimate the primary analysis cannot provide.

Cost-Utility Analyses

Overview:

The purpose of the cost-utility analysis is to define the incremental cost of one therapeutic arm over another divided by the incremental benefit of the same therapy.^{172, 173} Such an analysis relates the economic resources consumed by treatment to the benefits attained by that treatment.

This is illustrated in equation 2:

$$CE_{PTCA} = \frac{C_{PTCA} - C_{MED}}{U_{PTCA} - U_{MED}} \quad \text{(Equation 2)}$$

where CE_{PTCA} is the cost-effectiveness of PTCA, C_{PTCA} = The mean cost of PTCA in addition to medical therapy, C_{MED} = the mean cost of medical therapy alone, U_{PTCA} = the mean utility of PTCA in addition to medical therapy, and U_{MED} = the mean utility of medical therapy alone.

Primary Analysis:

In the primary analysis, the mean costs for each arm over the 3 years of the study will be used in the numerator and the mean QALYs of each treatment arm, as directly measured over the 3 years of the trial, will be used in the denominator. We will also employ median costs and QALYs as an alternative estimate of the cost-effectiveness ratio. These analyses will provide the best estimates of the cost-effectiveness of percutaneous revascularization relative to medical therapy over a 3-year period. Both the standard deviation and the distribution of cost effectiveness (CE) are presently unknown for the type of patients who will be enrolled in COURAGE. Thus we do not feel one can obtain a meaningful estimate of the power to detect a difference in CE from zero (or from any arbitrary value). We propose to compute the CE after the completion of the trial, and then use the bootstrap technique to obtain a 90% Confidence Interval (CI) around the estimated CE. We will need to use the bootstrap technique because, as noted, the distribution of CE is presently unknown.

To gain further insight into the variation in the cost-effectiveness of percutaneous revascularization relative to medical therapy, we will perform several sensitivity analyses. Sensitivity analysis involves systematically altering our assumptions about the costs and health effects of percutaneous revascularization and medical therapy and noting the effect on the resulting incremental cost-effectiveness ratio. We will perform two types of sensitivity analyses. The first set of calculations will be one-way sensitivity analyses. In one-way sensitivity analysis, the assumption about each parameter (e.g., total cost of medical therapy) is varied over a reasonable range of values with all other parameters fixed. Specifically, we will vary one-by-one our estimates of the total cost of medical therapy over three years, the total cost of percutaneous revascularization over three years, the QALYs associated with medical therapy over three years,

and the QALYs associated with percutaneous revascularization over three years. We will use the 25th and 75th percentiles for each parameter as the range for one-way sensitivity analysis. For the second set of analyses, we will perform two-way sensitivity analyses. In these analyses, estimates for two parameters are varied simultaneously. Because costs and QALYs are likely to vary substantially among subjects in the study in ways that may not be related to treatment assignment, we will first vary the total cost of medical therapy and the total cost of percutaneous revascularization in tandem, setting both to their 25th percentile values, then both to their 75th percentile values. This analysis will allow us to estimate the incremental cost-effectiveness of percutaneous revascularization relative to medical therapy as our assumptions about total cost move together. We will perform a similar two-way sensitivity analysis on the QALYs associated with medical therapy and percutaneous revascularization. Finally, we will develop favorable and unfavorable scenarios for percutaneous revascularization based on various assumptions about total cost and QALYs. Because the specifics of these scenarios will depend on the nature of our findings, we cannot describe fully these analyses a priori. Nonetheless, these scenarios will reflect our understanding of the variation surrounding the cost and QALY estimates and the correlation among those parameters. For example, if our data suggest that total cost and QALYs are correlated among those undergoing percutaneous revascularization (i.e., longer life is associated with higher costs), that total cost is driven primarily by the intervention (i.e., medical therapy versus percutaneous revascularization), and that variation in QALYs is due primarily to variation in utilities across subjects, an unfavorable scenario for percutaneous revascularization might use the 75th percentile on total revascularization cost, the 75th percentile on QALYs for percutaneous revascularization, the 25th percentile on total cost for medical therapy, and the 75th

percentile on QALYs for medical therapy. Thus, we will perform extensive sensitivity analyses to test robustness of our findings concerning the cost-effectiveness of percutaneous revascularization relative to medical therapy.

We expect there to be missing cost and utility measures. Using the terminology of Little and Rubin¹⁷⁴, data are missing completely at random (MCAR) when the missing data mechanism is independent of observed and unobserved data (response and covariates). Data are missing at random (MAR) when the missing data mechanism depends only on the observed response and/or the observed covariates. In contrast to the ignorable mechanism (MCAR or MAR), a non-ignorable (NI) missing data mechanism is the one that depends on unobserved data (response or covariates). For example, quality of life measure could be not available because of underlying low quality of life.

In the presence of missing data, a simple and popular approach is to perform an analysis which deletes all subjects with any missing data, often called a "complete case" analysis. The complete case analysis is unbiased only if data is MCAR. However, the complete case analysis could be biased if the complete cases are not a random subset of patients. One can still perform an unbiased analysis if the MAR assumption is valid. However, the MAR assumption may not be realistic in practice and MAR analysis may be biased if the missing data mechanism is non-ignorable.

Under assumption of MCAR complete case analysis is valid. However, one loses precision due to reduced sample size. This may be particularly severe in an analysis such as this that requires repeated measures. To increase precision we will use imputation methods. As one approach, we will obtain a model for the missing variable using complete data. Subsequently,

the model will be used to predict the missing values. Then, complete data methods can be used to analyze the data containing observed and imputed information. We will also consider methods dealing with the MAR situation¹⁷⁵ or non-ignorable missing situation.¹⁷⁶ However, these methods are not currently available in statistical packages and the application of above methods will require customized programming. The latter approach emphasizes sensitivity analysis for different assumptions about the non-ignorable missing mechanism.

Secondary Analysis:

To compare the cost-effectiveness of percutaneous revascularization over medical therapy for the projected survival of patients enrolled in COURAGE, a secondary analysis using projected costs, survival and utilities will be performed. It will be assumed that future costs in the two treatment arms will be equal, and thus the numerator will be the difference in costs over 3 years. Projected QALYs, as described above, will be substituted into the denominator of equation 2. This will enable a cost-effectiveness analysis for the full projected future of treatment among the two arms of the COURAGE study. The resulting ratio differs from the primary analysis only in the calculation of survival.

F) Proposed Quality of Life Assessment Methods

Specific Aims

To address gaps in knowledge about the effect of PTCA on quality of life the following questions will be addressed:

- 1) What changes in global and CAD specific quality of life occur in the early and late post-treatment periods?
- 2) What changes in quality of life in the physical, (functional), emotional, social dimensions occur in the early and late post-treatment periods?

- 3) Do PTCA and optimal medical therapy patients differ in quality of life over time?
- 4) Does occurrence of CHD-related cardiac events following treatment randomization affect quality of life in the early and late post-treatment periods?
- 5) Are quality of life and utilization of health care resources related?
- 6) What demographic and clinical variables mediate quality of life outcomes in relationship to randomization?

Design and Instruments

A repeated measures survey design will be used to examine the effects of the randomized treatment on the various domains of quality of life in addition to the cost-utility assessment. Measures will be obtained through a battery of self administered instruments to evaluate the functional, physical, emotional and social domains of quality of life, symptom presentation, treatment satisfaction, and global perceptions about overall quality of life. Since no "gold standard" exists for assessing quality of life in CHD patients, we will include both generic and disease-specific questionnaires. Due to the focus on complex medication regimens and risk factor modification in this trial, the self-management demands of CHD and the randomized treatment will be assessed as a mediating variable.

The inclusion of multiple instruments that will address the multi-dimensional aspects of health-related quality of life will address gaps in knowledge concerning coronary disease patient's quality of life and how this is influenced by disease and treatment. As noted earlier, comprehensive evaluation of therapy mandates the inclusion of patient functional changes and perception of treatment value on their lives. Quality of life becomes even more meaningful when differences in clinical outcomes between two competing therapies are small. Understanding quality of life

outcomes measured from the patients perspective provides the context for understanding the cost-utility analysis and provides direction for future patient interventions and clinical care whereas the cost-utility analysis will inform health policy.

At a pragmatic level, the inclusion of patient subjective data has been observed to have a positive effect on patient participation in long-term studies. Patients may well appreciate being asked for information about issues of importance to them; e.g. their symptoms, satisfaction with treatment, daily activities, and emotions. In this way, patients are participants, rather than merely subjects in a study.

Table 12: Quality of Life Domains and Instruments

Domain	Instruments	Number of items	Time Points (months)
Functional status	Rand-36 Subscale SAQ	12 9	BL, 1, 3, 6, 12, 24 & 36 BL, 1, 3, 6, 12, 24, & 36
Emotional Function	Rand-36 Subscale Depression Screen	5 3	BL, 1, 3, 6, 12, 24 & 36 BL, 3, 6, 12, 24 & 36
Social & Role Functioning	Enriched Social Support Inventory RAND-36 Subscale	6 9	BL only BL, 1, 3, 6, 12, 24 & 36
Symptom Frequency & Distress	Symptom Distress Scale SAQ Subscale	18 2	BL, 3, 6, 12, 24 & 36 BL, 1, 3, 6, 12, 24 & 36
Global Health Perceptions	RAND-36 Subscale SAQ Subscale	5 3	BL, 1, 3, 6, 12, 24 & 36 BL, 1, 3, 6, 12, 24 & 36
Treatment Satisfaction	SAQ Subscale	4	BL, 1, 3, 6, 12, 24 & 36
Self Management	Self Management Demands	25	3, 6, 12, 24 & 36
Utility Assessment	Standard Gamble		BL, 1, 3, 6, 12, 24 & 36

BL: Baseline

This multidimensional approach to assessing quality of life and self-management demands will incorporate multiple measures of most domains. Table 12 displays the domains and instruments that may be used. Most measures will be obtained at baseline, and selected measures

will be repeated at 1, 3, 6, 12, 24 and 36 months as noted. These time points were selected because they represent critical time points for the overall trial, early recovery and adjustment periods and times in which clinical events (such as restenosis, rehospitalization, etc.) that may influence quality of life, may occur.

Items for the quality of life assessment will be derived from the following instruments:

a) *The Medical Outcome Study Short Form Health Survey (RAND-36)*¹⁷⁷

Designed for use in clinical practice and research, the RAND-36 has items assessing eight dimensions including activity limitations due to health, social limitations due to emotional or physical problems, role limitations due to health, pain, general mental well-being and distress, role limitations due to emotional problems, vitality (energy and fatigue), and general health perceptions. These subscales are particularly important in assessing the impact of the interventions on overall functional status and symptoms as well as perceptions about health. The dimensions of the RAND-36 are important domains related to quality of life.^{131,142} The RAND-36 has the advantages of brevity and comprehensiveness which serve to decrease respondent burden over the more elaborate Sickness Impact Profile.¹⁷⁸ The RAND-36 can be self-administered or completed by a trained interviewer and it is available in French and Spanish, in addition to English.

The RAND-36 has been used in multiple studies and has the advantage of serving as a useful index for comparison with related populations as it has been incorporated in many clinical databases. Reliability and validity are well supported.

¹⁷⁷ The total RAND-36 score will provide a general health status measure and will

help detect adverse effects of treatment outside of the cardiovascular system outcomes as well as integrate the effects of multiple medical conditions on overall quality of life. Subscale scores will also be analyzed to examine specific domains of quality of life. Three screening questions adapted from the Health Status Questionnaire will be used to assess risk of depression.

b) The Seattle Angina Questionnaire (SAQ)¹⁷⁸

The advantage of the RAND-36 is found in its global nature; the disadvantage is in the decreased sensitivity to disease-specific states. Thus, we will also use a disease-specific functional status measure for patients with CAD. The SAQ examines five clinically relevant domains of CAD including physical limitation, anginal stability, anginal frequency, treatment satisfaction, and disease perception. The SAQ was reported to be more sensitive than the RAND-36 in evaluation of change between BL status and one to three months after coronary angioplasty.¹⁷⁸ Although some redundancy with the RAND-36 exists in the questions related to ability to perform activities, the SAQ specifies activity limitation related to angina, and both scales will be useful to examine in relationship to the treatment and sensitivity in this patient population. The SAQ is currently being translated into French and Spanish versions.

c) Symptom Checklist or Distress Scale.¹⁷⁹

In addition to symptoms used in CCS classification, more specific

perceptions of the frequency and degree of distress associated with symptoms and the side effects of treatment will be obtained using a 18-item scale that includes 17 symptoms and a single item on the overall impact of symptoms on QOL. The symptom checklist was developed from the literature and tools used in clinical trials, and includes a frequency and distress assessment. Possible subscale scores range as follows: “symptoms” range from 0-17; “symptom distress” range from 1-255; total scores, 0-278. The importance of examining the frequency and degree of distress associated with symptoms is underscored in that symptoms influence quality of life by serving as a reminder of cardiac impairment and thus perpetuate concerns about health. Symptoms also serve as cues to self-management behaviors (such as taking nitroglycerin, changing diet, etc.), and may lead to patient decisions regarding compliance with medication and risk factor reduction strategies, or to seek health care. A greater understanding of the nature and impact of experienced symptoms and side effects in this trial will enhance interpretation of the effects of the randomized interventions.

d) Enriched Social Support Inventory¹⁸⁰ (ESSI)

The Enriched Social Support Inventory (ESSI) provides a measures of social support based on *whether* or not support is present regardless of *where* the support comes from. It is based on single items that predicted mortality post MI in several studies. Internal reliability (Cronbach's) alpha was 0.86, and it is correlated ($r = .62$) with the Perceived Social Support Inventory (PSSI).¹⁷⁷ Possible scores range from 8-

34. The social support data will be collected at baseline and will be examined in relationship to the other quality of life and outcome variables. We will examine if social support is related to the other outcomes as reported in previous studies, and ESSi score can be used as a covariate in the quality of life analyses and MIMIC model, if indicated.

e) Self Management Demands

The self-management demand scale was adapted from Irvine's tool examining diabetic self-care¹⁸¹ and revised for cardiac patients. Specific items were derived from CAD patient activities in the four domains of symptom and side effects, medications, risk factor modification, and communicating with health care providers. Participants rank each item according to the degree of time, effort and/or difficulty they have with the activity. Total and subscale scores will be obtained. The tool was developed by experts in cardiovascular care and content validity affirmed through a panel of experts.

The original Self-Management Difficulties Scale (SMDS) was pilot-tested with 12 subjects with a mean age of 63 ± 12 years prior to having PTCA. Eleven items had no variance within this sample and an additional item, "keeping track of my heart rate" had a moderately negative item to total correlation (-0.42). The instrument was revised and reduced to 25 items. The revised SMDS has a Cronbach's alpha of 0.77, acceptable for a newly developed instrument. Total scores range from 0-100, and subscale scores and ranges are: medications (0-32), symptom

management (0-24), diet (0-32), exercise (0-8), and smoking (0-4). We will obtain responses on the SMDS at follow-up only.

Collection of Data from Quality of Life Forms:

The items for the quality of life assessment will be incorporated from these scales into a form that can be completed during the follow-up visit at the designated time. The complete form will be pilot tested prior to the trial start-up and revised accordingly to maximize data and **minimize** respondent burden. We anticipate the final version will take the patients approximately 20-35 minutes to complete depending on the collection time point. In addition to these forms, the Health Utility Index will be collected to permit assessment of community weightings (see the appropriate section above). This will require just 8 additional fields. If reading comprehension is problematic, site coordinators can facilitate patient completion of materials by reading items to subjects. Specific training of site coordinators for this contingency will be provided at the kickoff meeting. Patient scores for each quality of life domain measure will be included in the overall project data base and will be examined in relation to performance of instruments in the trial (reliability), randomized treatment groups, patient characteristics, health resource utilization, and other significant clinical variables.

G) Econometric Modeling in COURAGE

Overview

The aim of modeling cost-effectiveness is to provide insight into the medical decision making process. If one procedure has a higher clinical effectiveness at a lower cost, and the measure of effectiveness is clinically compelling, the decision is clear. If one procedure has a

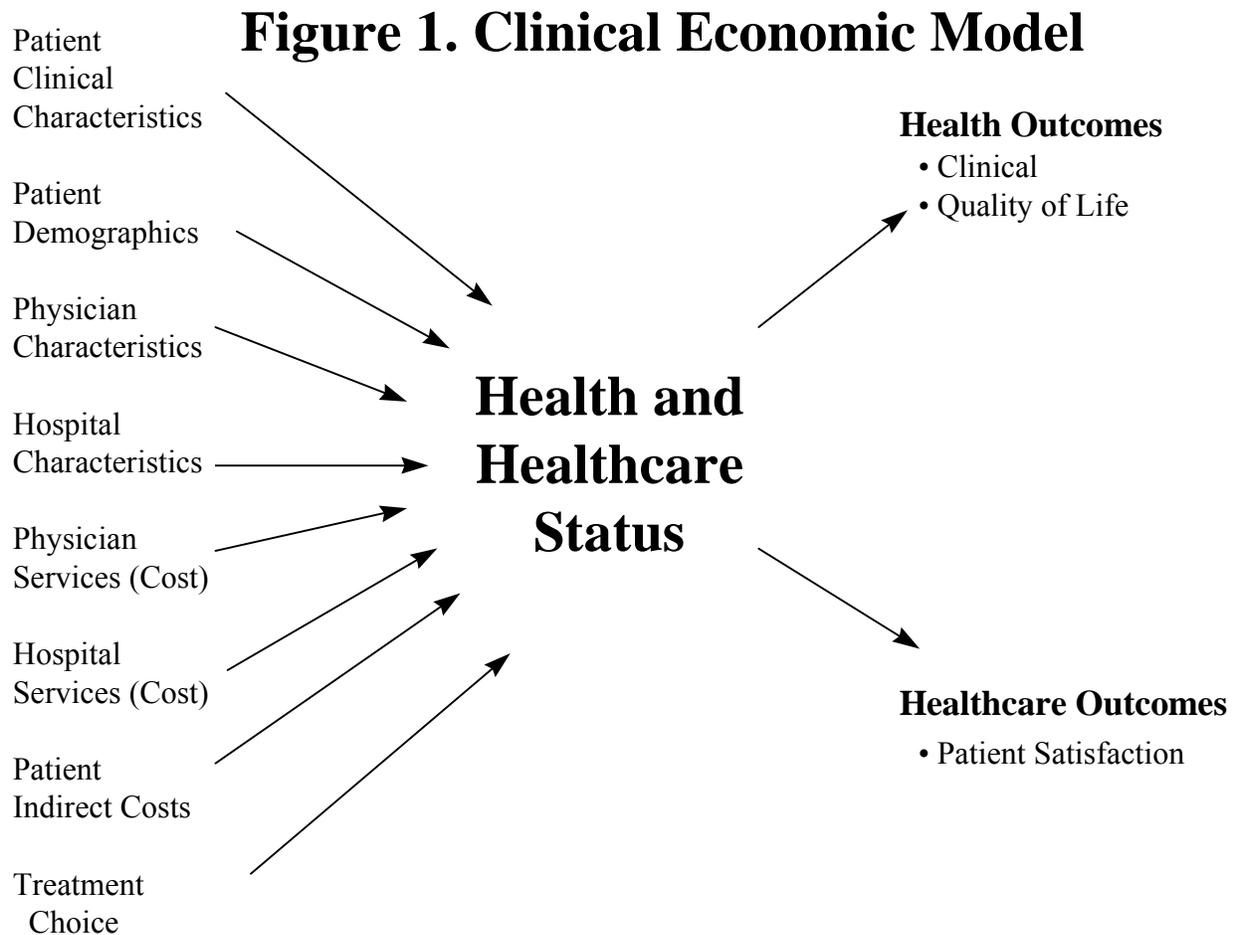
higher clinical effectiveness at a higher cost, then the decision will depend on the ability of society, the patient, and/or the payer to accept this cost. If the measure of effectiveness is ambiguous or not clinically compelling, then a multi-attribute proxy for quality health improvement, combining clinical outcome with patient's perception of well-being, may be helpful in illuminating the ambiguity, but more importantly, be crucial to the decision making process. Such an analysis should permit the assessment of the multiple domains of quality of life as presented above, as well as clinical endpoints. For COURAGE, we will employ an economic model that incorporates clinical, financial, and patient's perception of well-being data from a randomized clinical trial to assess the relative effectiveness and costs of patients in the two arms of the trial.¹⁸²⁻¹⁸⁴

Multiple-Indicator Multiple-Cause Model

The central questions in deciding treatment choice will include: 1) Which costs of alternative procedures are more reasonable in light of the clinical outcomes, quality of life, and patient satisfaction outcomes; 2) How do adverse medical outcomes associated with each procedures influence hospital, physician and patient costs; and 3) How do the probabilities of adverse outcomes change the patient's perception of the treatment choice? These questions all require a clinical decision model that incorporates multiple inputs and outputs.

Currently, most of the major methods for economic evaluation do not provide the level of sophistication needed to incorporate multiple costs and outcome indicators.¹⁸⁵ Most approaches would select certain outcome indicators and use them as proxies for effectiveness or develop a scale that incorporated the outcome measures. Recently, a clinical economic model has been developed,

and successfully applied in the EAST trial¹⁸⁶ to analyze the relationship among clinical and patient outcome measures and the cost factors and other variables hypothesized to influence the outcomes.



The clinical economic model depicted in Figure 1 is known as the multiple-indicator multiple-cause (MIMIC) model because the comparison is for multiple causes and multiple outcomes. MIMIC models were first developed in 1975 by Joreskog and Goldberger.¹⁸⁷ They were used in health economics by Van De Ven and Van Der Gaag¹⁸⁸ and Van De Ven and Hooijmans¹⁸⁹, among others with considerable success. (See manuscripts discussing the MIMIC model in Volume 2, Part E).

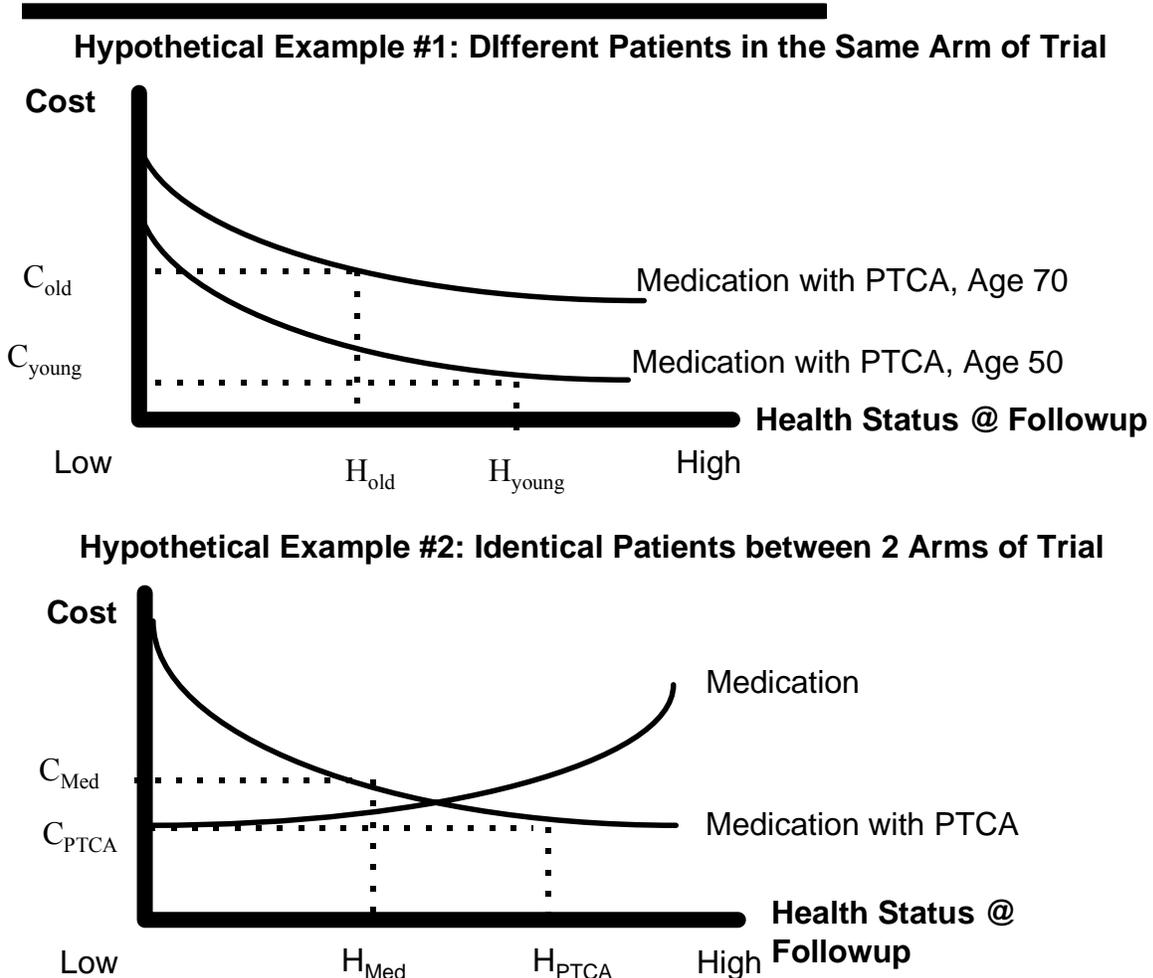
The clinical economic model assumes multiple causes affect multiple indicators through an

unobservable health effect. Because the true health improvement is not directly observed, multiple outcome indicators are used as proxies for health improvement. Through multivariate analysis, the MIMIC model can be used to estimate the sets of arrows in Figure 1.

Hypothetical results of MIMIC are displayed in the two examples in Figure 2. The points chosen represent mean health status (H) and cost (C). The potential results of the MIMIC model suggest possible relationships between cost and health status at follow-up. Note that the curves reflect the observed relationship between health status and cost, but do not imply cause and effect. Thus, it cannot be assumed that efforts to increase health status result in corresponding changes in cost described by the curves presented here. Example #1 shows hypothetically how different control variables (i.e., age) may impact cost at a given health status. This example indicates that a higher mean health status for a younger patient was achieved at a lower cost than for an older patient. Example #2 shows hypothetically how costs change with health status for patients in each arm of the trial. In this example the mean health status achieved in the PTCA patients was higher than in the medical therapy at a lower cost (strong dominance for PTCA).

Figure 2

MIMIC Model of Cost-Effectiveness of SMART



In addition to estimating the MIMIC model with all the outcome indicators combined, separate estimations can be performed for each group of outcomes. The separate estimations show the outcome-specific effectiveness of procedures and allow for the comparison of the influence of different factors for each treatment choice. For instance, medication with PTCA may be better in terms of clinical outcomes, but medication alone may turn out better for patient's satisfaction, and so

on.

Finally, interaction terms will be included in the analysis. They will capture the separate effect of, for example, medicine alone on subgroups of patients identified by specific exogenous variables. If it turns out that the average results suggest that medicine with PTCA is more effective, the interaction terms could identify certain types of patients who benefit more than average from medicine alone. If, for example, the interaction term of age is sufficiently positive, it would imply that older patients receive more health improvement with medicine alone than with medicine with PTCA, other things being equal.

The intent of this approach is to systematically define and analyze how the clinical and patient variables interrelate to obtain a better understanding of which factors are most powerful or the best predictors in explaining treatment costs and outcomes. By systematically analyzing the major factors which contribute to the cost and outcomes of alternative therapies and comparing these results on the dimensions of time, sample subsets, and variable subsets, we not only illuminate our overall understanding of the relationship between the cost and outcomes of these therapies, but also systematically evaluate which combinations of variables are most appropriate and useful. Comparison of the overall effectiveness and the individual outcome group effectiveness will provide a richer understanding on how the different factors contribute to the overall outcome of the therapy.

XIII. CORE LABORATORIES

A) Coronary Angiographic Laboratory:

Since coronary angiograms will be a pivotal factor in the decision to include a clinically eligible trial patient, it is essential that baseline cineangiograms be coded and interpreted in a rigorous, consistent fashion. All cineangiograms will be forwarded to a core laboratory, so that films can be reviewed by independent experts blinded to trial clinical information, and so that coronary stenoses can be classified according to accepted criteria and in a consistent manner for all patients across sites. Pre- and post-PCI cineangiograms for the initial PCI procedures will likewise be reviewed and coded. This should provide an independent and unbiased estimate of the success of the randomized procedures. Edited data will be forwarded to the West Haven CSPCC and incorporated into the CS #424 database for use in the analysis.

B) Electrocardiographic Core Laboratory:

Qualifying electrocardiograms will serve to quantify location and extent of myocardial ischemia, which will be potentially important predictors of outcomes in various high- and intermediate-risk CHD patients. In addition, non-fatal MI, as a trial primary endpoint, must be adjudicated by the Endpoints Committee, and proper coding/interpretation of MI by ECG will be vital to the committee's task of appropriately classifying clinical events.

C) Lipid Core Laboratory:

The lipid target is an important part of the aggressive medical therapy and a core laboratory will be required to regularly do the lipid profiles so that they are done in a standard manner across all sites.

IV. CLINICAL IMPLICATIONS AND SUMMARY

During the last 15 years, PCI has become a widely utilized, safe and effective procedure in the management of CHD patients with **symptomatic** myocardial ischemia. The advent of PCI has stimulated the development of additional new technologic advances in the field of interventional cardiology, which may permit even more sophisticated care of complex forms of coronary disease with an acceptable morbidity and mortality.

The explosive growth of angioplasty has resulted in the widespread application of this procedure to low-risk and even asymptomatic patients. This practice may well be encouraged by the ACC/AHA Joint Task Force Guidelines for PCI³ which recommends that asymptomatic or mildly symptomatic (CCS Class I) CHD patients with single-vessel or multi-vessel coronary artery disease (defined as $\geq 50\%$ diameter reduction stenosis) meet a "Class I" (or "Definite") indication for PCI. Thus, PCI is being utilized increasingly for the routine, prophylactic management of coronary anatomic findings in CHD patients--rather than for symptom relief--where outcomes-derived research has not yet demonstrated a conclusive benefit of reduced mortality or occurrence of MI in such CHD patients.

The results of several recent PCI versus CABG surgery trials³¹⁻³⁶ shows that long-term mortality or nonfatal MI is not significantly different between the two approaches of myocardial revascularization. It appears that although PCI may be a more cost-effective short-term strategy compared to CABG surgery, the differences in cost longer-term is small. These "procedure versus procedure" trials have helped to clarify the interventional approach to CHD; however, no studies to date comparing PCI with medical therapy have been "powered" to assess health care outcomes using "hard" endpoints as the trial primary endpoint.

Finally, given the fact that meaningful U.S. health care reform seems largely inevitable in the years to come, there are emerging, powerful financial incentives which may force cardiologists, hospitals, managed care providers and third party payers to seek out, proactively, more efficient and cost-effective approaches to health care delivery during an era of contracting health care resources. In the case of angioplasty, which costs the health care system billions of dollars annually, assessing prospectively its current use by employing a randomized, controlled, clinical trial of existing ACC/AHA Joint Task Force Class I PCI indications along with intensive medical therapy versus contemporary, intensive medical therapy seems long overdue.

Thus, until prospectively-acquired outcomes-based research can establish conclusively whether optimal catheter-based coronary revascularization ("PCI") + intensive medical therapy is superior to a strategy of intensive medical therapy alone in prolonging survival and reducing the incidence of nonfatal infarction, there will be a lack of evidence-based scientific information to guide therapeutic decision making and subsequent health care policy.

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