EVALUATION OF TREATMENTS FOR CORONARY ARTERY DISEASE UTILIZING CONTEMPORARY STATISTICAL METHODS

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Cardiovascular disease is the leading cause of mortality worldwide, and approximately half of all cardiovascular deaths are attributed specifically to coronary artery disease (CAD). Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) procedures play a prominent role in managing the heavy burden of CAD. The purpose of this dissertation was to evaluate revascularization treatment in patients with multivessel coronary disease. Specifically, predictors of long-term prognosis and factors related to selection of revascularization strategy were investigated in the BARI and BARI 2D cohorts, respectively.

In BARI, treatment with CABG was associated with a significantly lower risk of sudden cardiac death, but did not impact any other causes of mortality. Moreover, protection conferred by CABG was observed in patients regardless of diabetes status.

Following successful initial PCI in BARI, male gender, proximal LAD disease, and incomplete revascularization were associated with an increased risk of a first subsequent revascularization event but not latter events. Diabetes and extensive CAD, on the other hand, demonstrated an incremental impact on the number of repeat procedures over 10 years of follow-up.

Among patients with diabetes and stable CAD in BARI 2D, angiographic features associated with the extent and location of coronary disease greatly influenced the decision to perform CABG over PCI. Geographic region, independent of patient characteristics, was also a driving factor in treatment selection,

with a greater propensity to recommend PCI in the US. In all countries of origin, we observed substantial variation across individual clinical sites in this decision-making process.

Results in the BARI cohort may have clinical implications on guiding initial revascularization strategy and underscore the importance of intensive management of atherosclerotic risk factors in order to limit disease progression. Our investigation of BARI 2D demonstrate the need for rigorous evaluation of optimal CAD treatment approaches in diabetic patients and factors that guide this decision-making process in current practice. Overall, these findings may be useful for devising long-term treatment strategies that address the chronic, progressive, and systemic nature of coronary disease, which will be of great public health importance as medical advances continue to extend the lives of individuals with CAD.

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1.0 DISSERTATION OVERVIEW AND OBJECTIVE

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, and approximately half of all cardiovascular deaths are attributed specifically to coronary artery disease (CAD). Myocardial revascularization has a prominent role in managing the heavy burden of ischemic heart disease and an increasing number of these procedures are performed each year. Given the chronic and progressive nature of atherosclerosis, long-term outcomes following coronary intervention are of great interest. On the other hand, evolution of therapy, PCI in particular, requires continual reassessment of treatment strategies and the factors related to their use.

The purpose of this dissertation is to evaluate coronary revascularization treatments in patients with multivessel disease utilizing contemporary statistical methods. Specifically, the following questions are addressed in a series of three research papers:

1. In patients with treated diabetes, revascularization with CABG (versus balloon-only PCI) has been shown to significantly increase long-term survival in the BARI trial, by conferring protection against cardiac death. Although a modest survival benefit of CABG has been reported in the overall coronary revascularization patient population, this finding has been less consistent across clinical trials. What is the impact of treatment with CABG on specific causes of death? Does CABG have a differential effect on cause-specific mortality?

2. A recognized limitation of percutaneous intervention is the need for additional revascularization procedures, which pose an increasing economic and health burden on individual patients as well

as health care systems. Among patients who undergo successful initial PCI, what factors are associated with the need for additional revascularization treatments? Do these predictors have a different effect on the *number* of repeat procedures?

3. Advances in PCI technology and adjunctive therapies over the last decade have markedly lowered rates of short-term complications and restenosis. As a result, percutaneous interventions are increasingly used to treat select high-risk subsets of patients who have traditionally undergone bypass surgery. In contemporary practice, what factors influence the selection of CABG over PCI in patients with diabetes and stable coronary disease? Do practice patterns vary across geographic regions?

Research questions for the first and second papers were evaluated in the Bypass Angioplasty Revascularization Investigation (BARI), which compared an initial revascularization strategy of CABG versus balloon PCI in patients with multivessel disease. Research questions for the third paper were examined in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, which was designed to simultaneously compare diabetes and CAD treatment strategies in patients with diabetes and stable coronary disease.

2.0 BACKGROUND

2.1 CARDIOVASCULAR DISEASE

2.1.1 Epidemiology of Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death in nearly every region of the world according to the World Health Organization, accounting for an estimated 30% of all mortality.[1] In sub-Saharan Africa, the sole exception, CVD is expected to surpass infectious disease, the current leading cause of death in this region, within the next decade. A marked rise in the burden of CVD is anticipated globally, as the proportion of cardiovascular deaths is projected to increase from 29% in 1990 to 36% in 2020.[2] The detrimental impact of cardiovascular disease is far-reaching, and the notion that atherosclerosis is a disease of affluent, industrialized countries is no longer accurate.

In the United States, cardiovascular disease affects an estimated 71.3 million individuals.[3] As the leading cause of mortality in both men and women, 37% of all deaths in 2003 were attributed to CVD.[4] Coronary artery disease (CAD) comprises half of all cardiovascular events, including death, among adults under 75 years of age.[5] According to the National Health and Nutrition Examination Survey (NHANES 1999-2002), an estimated 53% of all cardiovascular mortality was due specifically to CAD, followed by 18% for stroke.[6]

The economic burden of cardiovascular disease further demonstrates the scope of CVD as a major public health problem. In 2006, the direct and indirect cost of CVD is estimated at $403.1 billion, of which $142.5 billion is for CAD alone.[5] In a rating of the most costly medical conditions in the US,

ischemic heart disease, the uncontested leader, was associated with an 8% increase in total healthcare spending between 1987 and 2000.

Despite an increasing prevalence of CAD, mortality from coronary heart disease in the US has actually declined in recent decades.[3, 7, 8] From 1968 to 1981, age-adjusted CAD mortality decreased at a rate averaging 3% per year.[8] A steady decrease in stroke deaths during this period resulted in substantial reduction in death rates from major cardiovascular and all causes, which was observed in all regions of the country. According to more current estimates from the Framingham Heart Study, a 59% decrease in CAD mortality was reported between 1950 and 1999.[4] The sizable and sustained decline in CHD and CVD mortality have been attributed largely to improved management of cardiovascular risk factors and progress in the diagnosis and treatment of coronary disease over the last 3 decades.[9, 10]

As medical advances lead to increased longevity, the elderly will comprise a growing proportion of the general population. According to the US Census Bureau, approximately 40 million Americans will be over the age of 65 by 2010, which represents a dramatic demographic shift that has been underway since the 1950s.[6] Aging of the population is expected to be a driving factor in the escalating health and economic burden of cardiovascular disease for years to come.

2.1.2 Risk Factors for Cardiovascular Disease

Extensive epidemiologic research has led to identification of cardiovascular risk factors. Determinants with proven causality include: high low-density-lipoprotein (LDL) and low high-density-lipoprotein (HDL) levels, type 2 diabetes (which is related to hyperglycemia and hyperinsulemia), hypertension, cigarette smoking, and obesity.[11-13] In recent years, studies carried out simultaneously in basic science laboratories have identified a number of new candidate risk factors, including elevated levels of prothrombotic factors (e.g. fibrinogen and PAI-1), inflammatory markers (e.g. C-reactive protein), homocysteine, and lipoprotein(a).[14, 15] Although causation has not yet been established between these

emerging risk factors and cardiovascular disease, there is mounting evidence of a real cause-and-effect relationship.[14-17]

2.1.3 Pathophysiology of Coronary Artery Disease

CAD generally refers to the pathological condition in which atherosclerotic progression in the coronary arteries restricts blood flow to the myocardium. Early pathogenesis is characterized by endothelial dysfunction, vascular inflammation, and build-up of lipids, calcium, and cellular debris in the intimal lining of the vessel wall.[18, 19] During positive remodeling, fibrous plaque deposits outside of the lumen and extends outward, allowing the diameter of the lumen to be maintained. With progression of atherosclerosis, the plaque mass extends into the lumen, decreasing its diameter and obstructing blood flow through the coronary arteries.[20] Endothelial erosion or rupture of the fibrous cap can cause plaques to become 'vulnerable' and encroached in the vessel wall.[18, 19] Vulnerable plaques may not be obstructive, and therefore remain undetected until they rupture and become clinically apparent. Severe narrowing of the coronary arteries and rupture of vulnerable plaques ultimately lead to restricted blood flow, and thus, inadequate oxygenation of the myocardium.

2.2 DIABETES AND CORONARY HEART DISEASE

2.2.1 Epidemiology of Diabetes and Coronary Disease

Type 2 diabetes is an established and powerful predictor of coronary disease that has evolved into a major public health concern in recent years. Diabetes affects more than 150 million adults worldwide, and prevalence is expected to reach 300 million by 2025.[21] The rising burden of diabetes is even more alarming in the US where prevalence is currently estimated at 17 million,[22] representing a more than 2-fold increase over the last decade.[23, 24] The total economic burden of diabetes was estimated at $98 billion

in 2003, accounting for approximately 1 of every 10 dollars allocated to health care. More than half of this expenditure covered indirect costs (i.e. temporary or permanent disability and premature deaths), and nearly one-fifth of the direct medical costs was for management of cardiovascular complications.[5]

Epidemiological studies have played an important role in elucidating the relationship between diabetes and cardiovascular disease. Diabetic individuals typically have an increased number of atherogenic risk factors including hyperglycemia, insulin resistance, hypertension, dyslipidemia, heart failure, autonomic dysfunction, peripheral vascular disease, cerebrovascular disease, microvascular disease, a prothrombotic state, and nephropathy.[25, 26] Diabetes has been associated with a 2- to 3-fold increase in the risk of cardiovascular disease in the Framingham Study [27] and a 2- to 4-fold increase in the risk of developing ischemic heart disease in the Atherosclerosis Risk in Communities (ARIC) study.[28] Moreover, individuals with diabetes manifest symptoms earlier in life and more severely compared to those without diabetes. In fact, it has been reported that diabetic patients without a history of MI have a similar likelihood of experiencing an MI as non-diabetic patients with a prior MI, emphasizing the importance of aggressive treatment of CVD risk factors in diabetic patients regardless of MI history.[29] More than 80% of the diabetic population ultimately die as a result of CVD.[26] The Multiple Risk Factor Intervention Trial (MRFIT) reported that the absolute risk of cardiovascular mortality among men was 3-times higher in diabetics compared to non-diabetics. Even after adjusting for effects of age, race, income, blood pressure, cholesterol level, and smoking, diabetes remained a potent predictor of cardiovascular disease.[30]

Recently, the NHANES cohort was examined to determine whether diabetic individuals benefited from the decline in CAD mortality observed in the US population in recent decades.[31] Between the early 1970s and 1980s, non-diabetic men experienced a 36% decline in age-adjusted CAD mortality compared with only a 13% decline in those with diabetes. During the same period, the age-adjusted CAD death rate among women decreased 27% in non-diabetic but increased 23% in diabetic women. Based on their findings, the NHANES researchers concluded that improvements in treatment of CVD (which resulted in

marked decline in CAD mortality in the overall population) appeared to be less effective in individuals with diabetes, particularly women.

2.2.2 Pathophysiologic and Anatomical Features of CAD in Diabetes

Unique pathophysiologic and anatomical features of coronary disease in diabetic patients contribute to their worse prognosis. Hyperglycemia is believed to play a central role in atherosclerotic progression by contributing to endothelial cell dysfunction, which inhibits vasodilation and increases vascular smooth-muscle proliferation, thrombogenesis, and proatherogenic cellular processes.[32] Enhanced platelet aggregation mediated by increased expression of glycoprotein (Gp) IIb/IIIa receptors further contributes to endothelial cell dysfunction, accelerated disease progression, and coronary thrombosis.[33] Individuals with diabetes have elevated levels of fibrinogen,[34] coagulation factor VII,[35] and von Willebrand factor.[36] These haemostatic abnormalities lead to a prothrombotic state which likely contributes to the problem of restenosis in diabetic patients. Dyslipidemia also plays a role in pathogenesis of CVD via glycosylation of LDL particles which stimulate smooth muscle cell migration and proliferation.[37] These are some of the biological and metabolic abnormalities that are thought to promote restenosis and accelerate disease progression in persons with diabetes.

Diabetic individuals typically bear a greater atherosclerotic burden that is characterized by multivessel disease,[38, 39] obstructions in left main coronary artery,[40, 41] presence of diffuse lesions,[42] more totally occluded segments,[43] and lipid-rich plaques vulnerable to rupture.[44] In addition, diabetic patients have an impaired ability to develop coronary collaterals[45] and undergo favorable remodeling,[46] which are two intrinsic mechanisms for alleviating the burden of atherosclerosis. Taken together, these anatomic features explain, at least in part, the more frequent and severe occurrence of ischemic coronary events and a generally poor prognosis in patients with diabetes, particularly following cardiac intervention.

2.3 MYOCARDIAL REVASCULARIZATION FOR TREATMENT OF CAD

Coronary revascularizations play a prominent role in managing the heavy burden of CAD and in 2003, an estimated 467,000 coronary artery bypass grafting (CABG) surgeries and 664,000 percutaneous coronary intervention (PCI) procedures were performed in the US.[5] With mean costs exceeding $30,000 per CABG and $12,000 per PCI (including hospital and physician fees), the total direct cost for coronary revascularization in the US is more than $28 billion annually.[47] Selection of the preferred strategy is often determined by the severity of disease and feasibility of PCI based on coronary anatomy and lesion morphology. Other factors, such as patient's age and comorbidities, may also play a role in selecting the more appropriate method of revascularization.[48, 49]

2.3.1 Coronary Artery Bypass Grafting Surgery

Approximately 10% of patients with coronary disease undergo CABG in the US,[50] which is considered the standard approach for treatment of significant left main disease and multivessel disease, especially when the proximal left anterior descending (LAD) artery is involved. During surgical revascularization, most of the epicardial vessel is bypassed, including symptom-causing culprit lesions and, more importantly, "future" culprit lesions which are thought to be responsible for most mid- and long-term coronary events.[51] In this way, patients who are treated with CABG generally receive a more complete and durable revascularization, particularly when internal mammary artery (IMA) grafts are used, and therefore, less frequently need additional subsequent procedures. These benefits, however, come at the cost of CABG being a major surgical procedure with attendant risks, including perioperative myocardial infarction (MI), stroke, and death, as well as potential complications of general anesthesia and cardiopulmonary bypass such as cognitive impairment.[52] These factors translate into a longer hospitalization and overall recovery and higher initial cost, compared to percutaneous intervention.

2.3.2 Percutaneous Coronary Intervention

In the US, approximately 1 in 3 patients with CAD undergo less invasive percutaneous coronary intervention which is directed at treating culprit lesions.[50] For patients with extensive and diffuse coronary disease, or complex lesions that are not amenable to treatment with balloon angioplasty or stenting, PCI is a suboptimal strategy. But for suitable candidates, PCI offers the advantages of lower periprocedural risk, shorter recovery, and lower initial cost. However, since the focalized approach results in a less complete revascularization than bypass surgery, a major limitation of percutaneous intervention is the need for additional procedures to address restenosis (re-narrowing of lumen to >50% occlusion which occurs in 30% to 57% of patients after PCI)[53-55] and atherosclerotic progression in native vessels.

For many years, these two revascularization strategies have been considered complementary, with the less invasive PCI generally well-suited for patients with limited lesions and CABG reserved for those with more severe and extensive coronary disease. Advances in PCI technology and adjunctive therapy in the last decade have narrowed this gap, and as a result, indications for percutaneous intervention have expanded to include those who would have, historically, been treated with bypass surgery. Drug-eluting stents have dramatically lowered incidence of restenosis,[56] and use of Gp IIb/IIIa receptor inhibitors has improved short-term event rates.[57, 58] Furthermore, refinements in PCI devices and techniques have enabled interventionalists to treat increasingly complex and severe lesions, leading to a drastic increase in the number of PCI performed each year. In 2002, the number of PCI procedures performed in the US reportedly increased 326% over the previous 15 years.[5]

2.3.3 Review of Randomized Trials Comparing CABG versus PCI

Randomized controlled trials (RCTs) conducted in the past two decades provide considerable evidence regarding efficacy of CABG versus PCI procedures in the overall CAD patient population, and several of the more prominent trials are briefly introduced in this section. Since these RCTs differ from each other

in terms of target study population, sample size, primary endpoint, and duration of follow-up, this review is limited to randomized trials comparing CABG versus PCI (balloon-only and with stenting) in patients with multivessel coronary disease, who are the focus of this dissertation.

2.3.3.1 CABG versus Balloon-Only PCI

The Bypass Angioplasty Revascularization Investigation (BARI), the largest of these trials in the pre-stent era, was designed to compare an initial revascularization strategy of CABG versus balloon-only PCI in patients with multivessel disease amenable to treatment by both procedures. The main finding in BARI was that mortality in the two treatment arms was not significantly different at 5 years (10.7% vs. 13.7%, respectively; P=0.19)[59] and significantly lower in the CABG group at 7 years (15.6% in CABG vs. 19.1% in PCI; P=0.043).[60] The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI)[61] and the Emory Angioplasty versus Surgery Trial (EAST),[62] which both enrolled patients similar to BARI, reported that mortality was not significantly different following CABG versus PCI at 1- and 3- years, respectively. Lack of a statistically significant difference in treatment effect was likely due, at least in part, to insufficient power arising from small sample size and relatively short follow-up periods. In all three trials, patients treated with CABG consistently reported a significantly lower recurrence of anginal symptoms, and therefore, less frequent need for further revascularization.[60-62] A meta-analysis which included these and several other randomized trials evaluating patients with multivessel coronary disease reported trend of a survival advantage of 2.3 percent at 5 years (P=0.03) and 3.4 percent at 8 years (P=0.03) conferred by CABG.[63]

2.3.3.2 CABG versus PCI with Coronary Stents

In recent years, CABG versus PCI randomized trials have incorporated the use of intracoronary stents as an adjunct to percutaneous intervention. In the Arterial Revascularization Therapy Study (ARTS), the incidence of death, MI, or stroke as a combined endpoint at 1- and 3-years of follow-up was not significantly different in patients assigned to CABG versus PCI with stenting; however, 1-year event-free

survival was significantly higher among surgically treated patients (87.8% vs. 73.8%).[64] The Stent or Surgery (SoS) trial also reported comparable rates of death or MI in the two treatment arms at 2 years (P=0.80).[65] In contrast, the Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multivessel Disease (ERACI II) trial reported significantly lower 1.5-year rates for death (3.1% vs. 7.5%, P<0.017) and MI (2.3% vs. 6.6%, P<0.017) in the PCI versus CABG groups, respectively.[66] Consistent with RCTs conducted in the pre-stent era, all three trials reported significantly higher rate of repeat revascularization following PCI compared to CABG (ARTS: 16.8% vs. 3.5%; SoS: 21% vs. 6%; ERACI II: 16.8% vs. 4.8%; all P<0.01).

2.3.4 Coronary Revascularization in Patients with Diabetes

Diabetic individuals account for an increasing proportion of patients undergoing coronary revascularization. Of the estimated 1.5 million revascularization procedures performed each year in the US,[67] approximately 25% are in diabetic patients who experience worse short- and long-term outcomes after both CABG and PCI, compared to those without diabetes.[68-70] In particular, diabetic patients have a significantly higher risk of long-term mortality following coronary revascularization.[71]

An unexpected finding in BARI was that among patients with treated diabetes, a 15% absolute survival advantage was associated with CABG versus balloon PCI (P=0.003).[59, 60] Moreover, improved survival in the CABG arm was attributed specifically to a reduction in cardiac deaths and was limited to patients who received at least one IMA graft. Subgroup analyses of diabetic patients in the EAST and CABRI trials also suggested trend of improved long-term survival following CABG (vs. PCI); however, results were not statistically significant in either trial due to smaller sample sizes resulting in less statistical power to detect treatment differences. Meta-analyses of these trials in the diabetes subset revealed a trend toward reduction in mortality following revascularization with CABG versus balloon-only PCI at 4 years (P<0.01) but not at 6.5 years (P=0.71).[63]

2.3.5 Bypass Angioplasty Revascularization Investigation 2 Diabetes

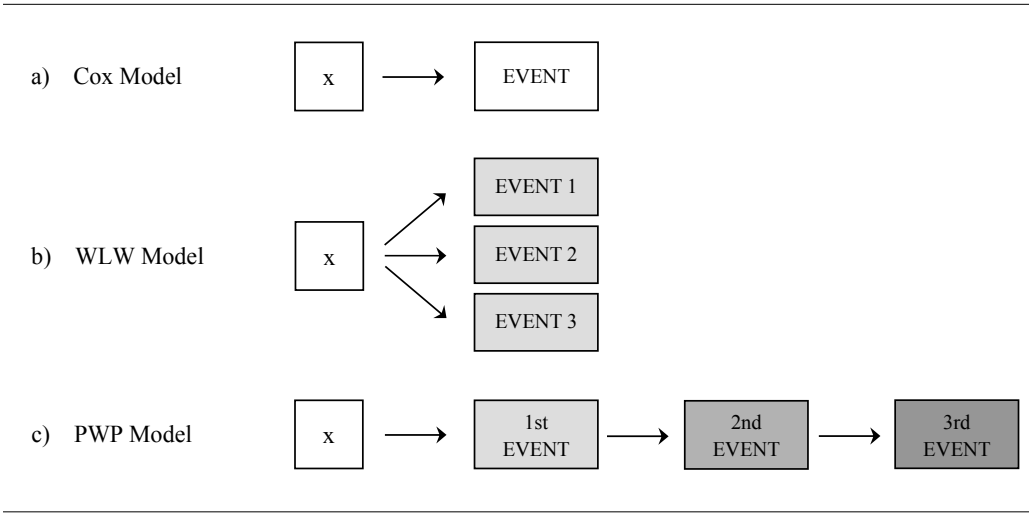
Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) is a currently ongoing trial based on the results of BARI regarding treatment of coronary disease in patients with diabetes. Using a 2x2 factorial design, patients with diabetes and stable coronary disease were randomly assigned to intensive medical therapy alone versus intensive medical therapy plus immediate coronary revascularization for treatment of CAD; and an insulin-sensitizing versus an insulin-providing strategy for diabetes management.[72] Although treatment strategy for coronary disease was dictated by random assignment, selection of the mode of revascularization among patients randomized to the invasive intervention arm was at the discretion of treating physicians. BARI 2D is expected to elucidate the optimal timing of coronary revascularization in patients with diabetes and stable CAD with respect to cardiac mortality.

2.4 APPLICATION OF CONTEMPORARY STATISTICAL METHODS

An appropriate and rigorous statistical analysis is an integral part of clinical research, and an important feature of this dissertation was the application of contemporary statistical methods to the BARI and BARI 2D datasets. This section introduces the three research papers at the heart of this dissertation and highlights the statistical procedure that was utilized in each.

2.4.1 Multiple Failure-Time Analyses

Extensions of traditional Cox proportional hazards regression were applied to model multiple *competing* outcome events in *Research Paper 1* and recurrent events of the same type in *Research Paper 2*. Figure 2.1 illustrates how these multiple failure-time models differ from standard Cox regression and how they differ from each other.



WLW indicates Wei-Lin-Weissfeld; PWP Prentice-Williams-Peterson

Figure 2.1 Schematic diagram of three time-to-event regression models

2.4.1.1 Modeling Multiple Competing Endpoints using WLW Regression

In *Research Paper 1*, the impact of treatment with CABG on specific causes of long-term mortality was evaluated in the BARI cohort. Four causes of death were modeled simultaneously using Wei-Lin-Weissfeld (WLW) competing risks regression.[73] Since causes of death are mutually exclusive *competing* outcomes, the occurrence of one event type removes the individual from being at risk for all other events. Therefore, patients were considered to be at risk for all four outcome events (or causes of death) until they either: 1) died, at which time the patient was considered to have had the 'event' for a specific cause of death and censored for the other 3 endpoints; or 2) stopped being followed in the study, at which time the patient was censored for all 4 endpoints.

Fitting a single WLW model with four endpoints is, essentially, like fitting four separate Cox models, one for each defined endpoint. A key advantage of WLW regression is that it allows multiple endpoints to be modeled simultaneously in the presence of competing risks, efficiently and without losing statistical precision. In addition, having multiple endpoints in the same model allows for statistical tests

that would not be possible otherwise, such as testing whether the effect of a given predictor on each of the defined endpoints are significantly different from each other.

2.4.1.2 Modeling Recurrent Events using PWP Regression

In instances where patients experience multiple adverse events of the same type, analysis of the time-to-first event is commonly undertaken using Kaplan-Meier[74] and Cox proportional hazards regression[75] methods. However, by ignoring the subsequent events, this approach does not make full use of the available data, and therefore, may not tell the full story of the treatment effect.

In *Research Paper 2*, predictors of repeat revascularizations after successful initial PCI were examined in the BARI cohort. The number (or *count*) of subsequent procedures was modeled as a recurrent events outcome using methods described by Prentice, Williams, and Peterson (PWP).[76] PWP 'conditional' regression assumes that a patient cannot be at risk for a subsequent event until a prior event has occurred, and in effect, estimates the probability of having a subsequent revascularization event conditional on having experienced a prior event. Interpretation of PWP models provides the following information: In patients who undergo successful percutaneous intervention, what is the probability of a first subsequent revascularization event? *Among* patients who received one additional procedure, what is the probability of a second repeat revascularization event? And *among* those who received at least two subsequent procedures, what is the probability of a third event?

2.4.2 Multilevel Modeling using GEE

Multilevel models were first used by sociologists to examine how students' educational achievement (a student-level endpoint) is influenced by factors such as the student's race, class characteristics, and racial composition of the school (student-level and higher-level predictors).[77] Similarly, multicenter studies also give rise to a hierarchical structure in the data, where patients are nested in clinical sites. Data indicating that patients in the same clinical site tend to be more similar with respect to the outcome of interest

violates the assumption of independent observations, which is one of the most fundamental assumptions underlying traditional linear and logistic regression methods. Ignoring correlation in the data leads to underestimated standard errors, and therefore, erroneously low p-values and narrow confidence intervals. Multilevel models take into account correlation in the data and provide correct parameter estimates.

In *Research Paper 3*, we evaluated what factors influence the selection of CABG over contemporary PCI in patients with diabetes and stable multivessel disease in the BARI 2D trial. Preliminary analyses indicated considerable correlation in the treatment selection outcome among patients clustered in clinical sites, and variable degrees of correlation between sites. This led us to conclude that multilevel modeling using generalized estimating equations (GEE)[78] which accounts for correlation within and between clinical sites would be the appropriate statistical procedure for multivariable analysis.

3.0 IMPACT OF CABG ON SPECIFIC CAUSES OF LONG-TERM MORTALITY IN THE BYPASS ANGIOPLASTY REVASCULARIZATION INVESTIGATION (BARI)

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3.1 INTRODUCTION

Cardiovascular disease is the leading cause of mortality in western countries.[1] The specific causes of death vary and may be the result of sudden cardiac death, myocardial infarction (MI), and congestive heart failure (CHF). Although the effect of coronary revascularization on all-cause and cardiac mortality has been previously described,[2-5] there are limited data on the effect of revascularization on specific causes of death in patients with coronary artery disease (CAD). Results from CASS[6] and other studies[7, 8] indicate that revascularization with coronary artery bypass grafting (CABG) may impact specific causes of mortality, in particular sudden death. Evaluation of cause of death may help elucidate the mechanism of disease processes and have important clinical implications for developing optimal treatment strategies to improve long-term survival after coronary revascularization.

The Bypass Angioplasty Revascularization Investigation (BARI) study has data for cause-specific death in 3610 patients undergoing initial revascularization with either CABG or percutaneous transluminal coronary angioplasty (PTCA).[2] The main finding in the BARI randomized trial was a significantly lower 7-year mortality in the CABG treatment arm compared to PTCA (16% and 19%, p=0.04).[9] Among patients with treated diabetes at baseline, 7-year mortality was also significantly lower in those randomized to CABG versus PTCA (24% and 44%, p=0.001), which was attributed to a reduction in cardiac deaths.[10] However, there was no treatment difference in mortality among patients without diabetes (14% in CABG vs. 13% in PTCA; p=0.72).

The purpose of this manuscript is to investigate the impact of revascularization with CABG on specific causes of mortality in the BARI cohort.

3.2 METHODS

3.2.1 Study Design

BARI was an IRB-approved, multicenter clinical trial designed to compare an initial revascularization strategy of CABG versus PTCA on long-term mortality in selected patients with multivessel coronary artery disease judged suitable for both procedures. A detailed description of the study aims, eligibility criteria, and patient selection procedures has been published previously.[11] In brief, symptomatic patients with multivessel CAD were randomly assigned to treatment with either CABG or PTCA and followed after revascularization. Eligibility criteria included clinically severe angina or evidence of ischemia requiring revascularization and angiographically documented CAD involving 2 or 3 vessels amenable to revascularization by either CABG or PTCA.

Participants were enrolled from 18 clinical sites in the United States and Canada between August 1988 and August 1991. Of the 4107 eligible patients identified, 1829 patients gave written informed consent and were randomized to receive either CABG or PTCA. Eligible patients who declined randomization were given the opportunity to participate in the BARI "Eligible Not Randomized" (ENR) registry, in which the patients and their physicians selected the initial treatment but had similar follow-up schedules as the randomized patients. 2010 patients gave informed consent to participate in the BARI ENR registry. The BARI cohort of revascularized patients is the focus of this analysis, specifically, those who received their assigned revascularization treatment in the randomized trial and those who were revascularized within 3 months of enrollment in the registry.

Identical baseline data were collected for all patients, which include demographic descriptors, clinical history, 12-lead electrocardiogram (ECG), coronary angiography measurements, angina, functional status, medications, risk factors, and quality of life. All ECGs were interpreted by a core laboratory. Although angiograms were evaluated by a central laboratory for the randomized patients, only clinical site evaluations were obtained for the registry patients; therefore, angiographic data based

on clinical site interpretation were used in this analysis. In this analysis, CABG was defined as revascularization with CABG at any time during the BARI study. Thus, patients who initially received PTCA, either by random assignment or by choice, and subsequently underwent CABG during follow-up are classified as having received CABG.

Follow-up data were obtained at 4 to 14 weeks and at 1, 3, and 5 years, and telephone contacts at 6 months and at 2 and 4 years. After 5 years, follow-up contacts were made annually by telephone, and vital status was obtained for 98% of the patients as of September 15, 1997.

3.2.2 Classification of Cause-of-Death Outcomes

Deaths were classified by an independent Mortality and Morbidity Classification Committee (MMCC) using the following documents, if available: death certificate; report from the clinical site's principal investigator; coroner's report; surgical and catheterization laboratory reports if death occurred within 30 days of a coronary revascularization procedure; ECG and cardiac enzyme levels measured within 24 hours of death; and in-hospital data ascertained from medical records. Each death was reviewed independently by 2 members of the MMCC and classified into one of the following primary classifications: direct or contributory cardiac, atherosclerosis-related non-cardiac, non-cardiac medical (e.g. cancer, pulmonary disease), non-cardiac trauma, accident, suicide, and other, unknown, or unclassifiable causes.[11] Disagreements between reviewers on the primary cause of death were resolved by full committee consensus.

Deaths determined to be of cardiac origin received one of the following secondary classifications: sudden death, death secondary to MI, CHF, cardiogenic shock, unwitnessed beyond 1 hour, and other documented cardiac causes. Agreement between the 2 reviewers on the secondary classifications was not required in BARI, and thus 2 reviewers could assign different secondary causes to the same patient death. For patients with multiple secondary causes, the following hierarchy was applied in order to determine the cause of death classification to be used in this analysis: unwitnessed beyond 1 hour was preferred over MI

death which was preferred over sudden death which was preferred over CHF and finally over other cardiac causes. Using these classifications, the following 4 endpoints were defined for this analysis:

Sudden death includes deaths within 1 hour of the onset of cardiac symptoms and deaths unwitnessed beyond 1 hour.

MI death includes deaths within 30 days of documented or probable MI, and deaths resulting from cardiogenic shock.

CHF and other cardiac death includes deaths due to CHF and all other documented cardiac causes.

Non-cardiac death includes deaths resulting from atherosclerosis-, medical-, and trauma-related non-cardiac causes, accidents, suicides, and other, unknown, or unclassifiable causes.

3.2.3 Statistical Analyses

Baseline characteristics are presented by vital status and by cause of death. Statistical comparisons were made between groups of patients defined by the 4 mutually exclusive causes of death (alive patients were excluded). Chi-square test was used to compare categorical variables, and Wilcoxon non-parametric test was used to compare continuous variables.

For all time-to-event analyses, the date of the initial revascularization procedure was considered time "zero," and patients remained in the "no CABG" group until the time that they received a CABG, at which point they joined the "CABG" group. Cumulative mortality rates in the CABG and no CABG (i.e. PTCA only) groups were estimated using the transient-state method[12] and compared using the log-rank test.[13]

Multivariate analysis was conducted using Wei-Lin-Weissfeld (WLW) competing risks regression,[14] which is an extension of the traditional Cox proportional hazards regression that allows multiple competing outcomes to be modeled simultaneously.[15] Patients were considered to be at risk for all cause-specific mortality outcomes until the time of either censoring or death. Since the 4 causes of

death are mutually exclusive endpoints, patients who died were considered to have had an "event" for the specific cause of their death and censored for the other 3 endpoints at the time of death. An initial competing risks model was constructed to estimate the unadjusted effect of CABG (vs. no CABG) on the 4 causes of death and to test for departures from the proportional hazards assumption. The multivariate model was then built by allowing potentially confounding baseline characteristics to enter in using forward selection (entry criterion $p<0.05$ for main effects). Known predictors of mortality,[16] age, gender, race, diabetes status, hypertension, CHF, renal dysfunction, peripheral vascular disease (PVD), and malignancy, were forced in the model if they did not enter in during the forward selection procedure. The time-dependent CABG variable was then added to the model, and covariates with $p>0.01$ were removed using backward selection. Missing values (<3% of values for any variable) for clinical history variables included in the final multivariate model were set to the mean value for continuous variables and zero for binary variables; thus, binary covariates may be interpreted as the known presence of the respective risk factors. Differential effects of CABG on the 4 cause-specific mortality outcomes were tested in the multivariate model. Statistical interactions between CABG and diabetes status on each cause of death were also tested. In the presence of any significant interactions, two separate multivariate models were constructed, one for patients with diabetes and one for those without diabetes. Lastly, standard Cox regression was utilized to estimate the independent effect of CABG on all-cause mortality.[17]

Estimates of relative risk (RR), 95% confidence intervals (CI), and p-values are reported. $P<0.05$ are considered statistically significant. All statistical analyses were performed using SAS version 8.2 (Cary, NC).

3.3 RESULTS

Three thousand-six hundred-and ten (N=3610) BARI participants underwent initial coronary revascularization and were followed for an average of 7.7 years. Patients receiving CABG included those

who received CABG as the initial revascularization (n=1517), and those who received PTCA as the initial procedure and "crossed over" to CABG during follow-up (n=722), 52% of which occurred within 6 months of initial treatment with PTCA. There were a total of N=1371 patients who received only PTCA during the course of follow-up.

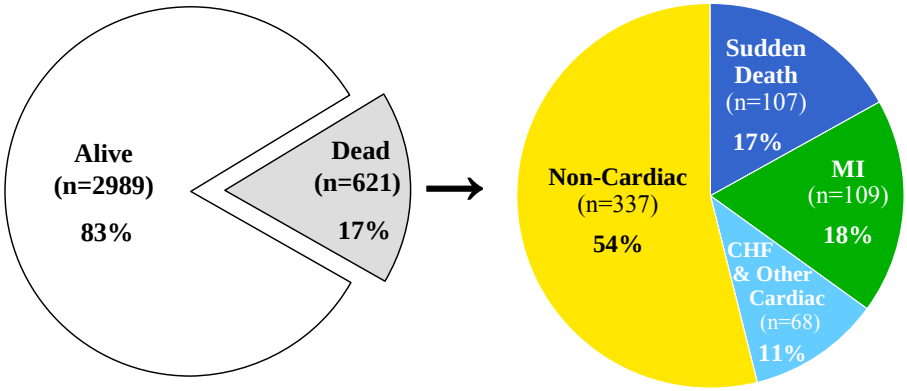

Figure 3.1 Vital status and causes of death (among patients who died) over 7.7 years of follow-up

At the end of the follow-up period, 83% of patients (n=2989) were alive and 17% (n=621) had died (Figure 3.1). Three percent (n=107) of patients died of sudden cardiac death, 3% (n=109) MI, 2% (n=68) CHF and other cardiac causes, and 9% (n=337) non-cardiac causes. Of all deaths, 17% were attributed to sudden cardiac death, 18% to MI, 11% to CHF and other cardiac, and 54% to non-cardiac causes.

Comparison of baseline characteristics by cause of death is presented in Table 3.1. Among patients who died, mean age at baseline, presence of diabetes, history of MI, CHF, angina duration of at least 1 year, ST-segment depression on baseline ECG, and ejection fraction (EF) <50% differed significantly by cause of death. Those patients who died suddenly were younger than patients who died of other causes. Compared to surviving patients, those who died from sudden cardiac death had more extensive CAD, depressed LV function, prior MI, and abnormalities on the resting electrocardiogram and more persistent angina over the year before revascularization.

3.3.1 Unadjusted Effect of CABG on Causes of Death

Unadjusted mortality rates were 17% (251/1517) among patients who underwent CABG as the initial revascularization, 13% (97/722) among patients who received CABG as a subsequent procedure, and 20% (273/1371) among patients who never received CABG. Transient-state Kaplan-Meier curves comparing cardiac and non-cardiac death rates between the CABG and no CABG groups are presented in Figure 3.2.

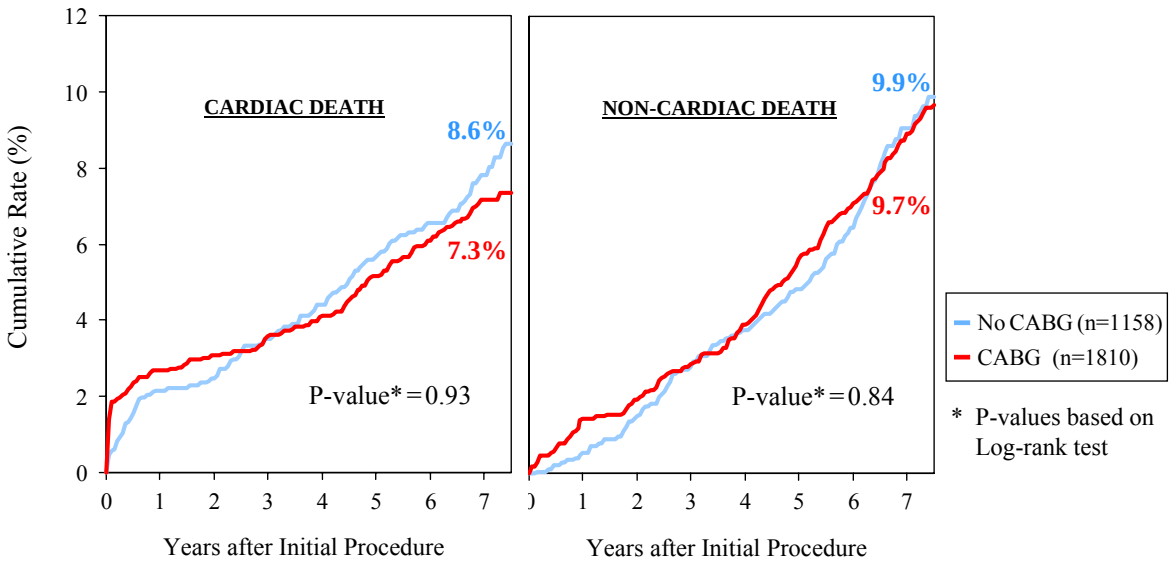

Figure 3.2 Kaplan-Meier curves for cardiac and non-cardiac death by CABG status

Cardiac mortality among patients who underwent CABG and those who did not were similar over time, with an early preponderance of events and a steady increase over the remaining follow-up period. 7.5 years after initial revascularization, cardiac death rates in the CABG and no CABG groups were 7.3% and 8.6%, respectively (p=0.93). Non-cardiac death rates were also similar in the CABG and no CABG groups throughout the follow-up period and at 7.5 years (9.7% vs. 9.9%, respectively; p=0.84).

Kaplan-Meier rates for specific causes of death at 7.5 years are presented in Figure 3.3.

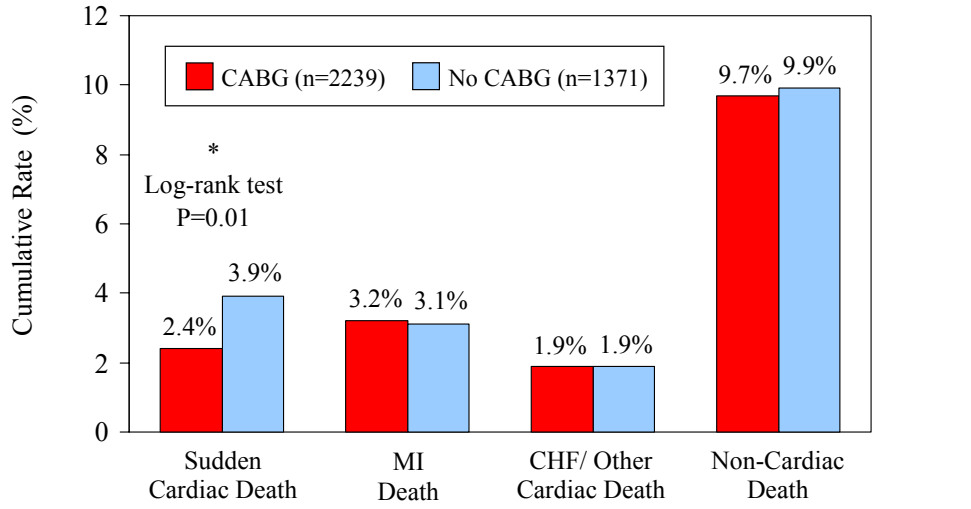

Figure 3.3 7.5-Year cumulative rates for specific causes of death by CABG status

Patients who underwent CABG (compared to those that did not) had a significantly lower incidence of sudden cardiac death (2.4% vs. 3.9%, p=0.01) but similar rates of death due to MI (3.2% vs. 3.1%, p=0.64), CHF and other cardiac (1.9% vs. 1.9%, p=0.59), and non-cardiac causes (9.7% vs. 9.9%, p=0.84). Unadjusted competing risks analysis demonstrated consistent results. Revascularization with CABG was associated with a significantly lower relative risk of sudden death (RR=0.62, 95% CI 0.42-0.91, p=0.01) but was not associated with the other causes of death individually (MI: RR=1.10, 95% CI 0.75-1.61, p=0.63; CHF and other cardiac: RR=1.14, 95% CI 0.70-1.87, p=0.59; non-cardiac: RR=0.98, 95% CI 0.79-1.22, p=0.84) or these 3 causes of death combined (RR=1.02, 95% CI 0.86-1.22, p=0.80).

3.3.2 Multivariate Analyses

Adjusting for confounding predictors of mortality had little effect on the relative risks for CABG on the mortality outcomes (Table 3.2). Revascularization with CABG did not significantly impact all-cause

mortality (RR=0.90, 95% CI 0.77-1.06, p=0.19). Examination of the cause of death indicated that CABG was associated with a significantly lower risk of sudden cardiac death (RR=0.60, 95% CI 0.41-0.88, p=0.01) but was not associated with other causes of death individually (MI: RR=1.06, 95% CI 0.72-1.56, p=0.76; CHF and other cardiac: RR=1.10, 95% CI 0.67-1.79, p=0.72; non-cardiac: RR=0.93, 95% CI 0.75-1.16, p=0.93) or combined (RR=0.98, 95% CI 0.82-1.17, p=0.83). Moreover, the impact of CABG on sudden cardiac death was significantly different than the effect of CABG on all other causes of death combined (RR=0.60 vs. 0.98, p=0.02). The multivariate model also revealed a statistically significant interaction between CABG and diabetes status for death due to MI (test of interaction p=0.04) but not any of the other causes (sudden death p=0.92; CHF/other cardiac p=0.19; non-cardiac p=0.53). Therefore, we examined the effect of CABG on cause-specific mortality separately for non-diabetic and diabetic patients. Multivariate competing risks models stratified by diabetes status are presented in Table 3.2.

Among patients without diabetes, revascularization with CABG significantly decreased the risk of sudden cardiac death (RR=0.61, 95% CI 0.38-0.97, p=0.04) but did not significantly impact any of the other causes of death (MI: RR=1.51, 95% CI 0.92-2.46, p=0.10; CHF/other cardiac: RR=1.49, 95% CI 0.74-2.99, p=0.26; non-cardiac: RR=0.99, 95% CI 0.77-1.29, p=0.96) or overall mortality (RR=1.01, 95% CI 0.83-1.23, p=0.94) . In diabetic patients, CABG was associated with a 32% lower risk of long-term mortality (RR=0.68, 95% CI 0.52-0.90, p=0.01), and there was a statistically non-significant trend of a protective effect on sudden death (RR=0.55, 95% CI 0.28-1.10, p=0.09) and also MI death (RR=0.54, 95% CI 0.28-1.02, p=0.06). Revascularization with CABG was not associated with CHF-related (RR=0.69, 95% CI 0.34-1.39, p=0.30) or non-cardiac (RR=0.80, 95% CI 0.54-1.19, p=0.27) mortality in diabetic patients.

3.3.3 Further Examination of Sudden Cardiac and MI Deaths

Kaplan-Meier curves were created to further investigate the impact of CABG on sudden cardiac death and MI death stratified by diabetes status (Figures 3.4 and 3.5).

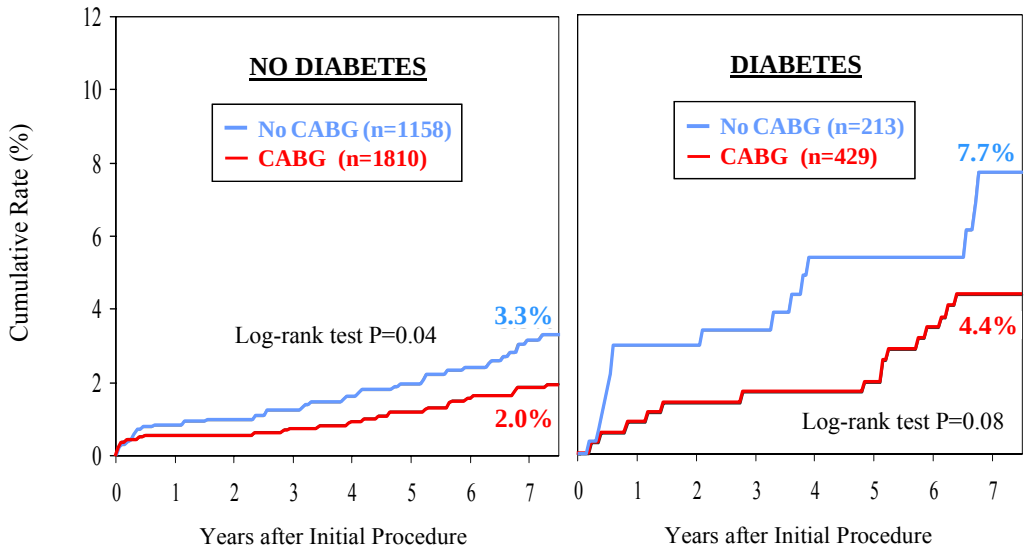

Figure 3.4 Comparison of sudden death rates in CABG and No CABG groups stratified by diabetes

In patients without diabetes, the sudden death event curves diverged steadily over time, and 7.5 years after initial revascularization, the cumulative rate of sudden cardiac death was significantly lower in patients who underwent CABG versus no CABG (2.0% vs. 3.3%, respectively, p=0.04). A similar effect of CABG was observed in patients with diabetes, with 7.5-year sudden death rates of 4.4% and 7.7% (p=0.08) in the CABG and no CABG groups, respectively.

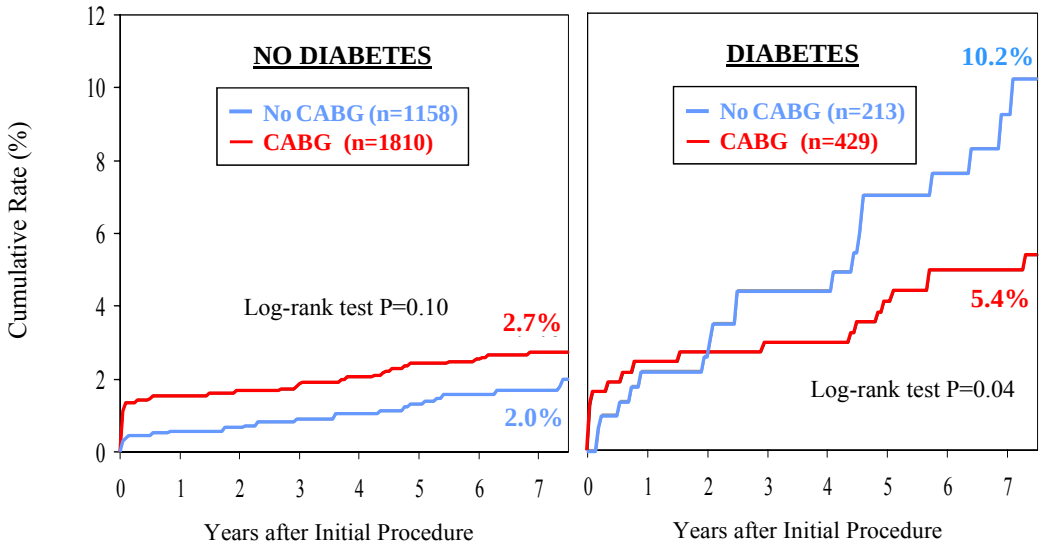

Figure 3.5 Comparison of MI death rates in CABG and No CABG groups stratified by diabetes

MI-related mortality among patients without diabetes occurred more frequently in the first several weeks after the initial procedure in the CABG group; during 7.5 years of follow-up, the cumulative event rate curves converged such that the MI death rate was 2.7% in the CABG group and 2.0% in the no CABG group (p=0.10). In contrast, among patients with diabetes, the MI death rate was slightly higher in the CABG group during the first 2 years of follow-up; however, by 7.5 years, the cumulative MI death rate was significantly lower in patients who underwent CABG compared to those that did not (5.4% vs. 10.2%, p=0.04).

3.4 DISCUSSION

CABG had differential effects on various causes of long-term mortality in the BARI cohort of revascularized patients. Revascularization with CABG significantly decreased the risk of sudden cardiac

death but did not impact other causes of death. Furthermore, the protective effect of CABG on sudden death was observed in patients regardless of the presence or absence of treated diabetes.

Why might one expect CABG to reduce the risk of sudden cardiac death, but not necessarily other specific causes of cardiac death? While the mechanism of sudden death in the setting of coronary artery disease is complex, it commonly occurs secondary to ventricular arrhythmias[18, 19] (often ventricular tachycardia that degenerates into ventricular fibrillation[20]), triggered by myocardial ischemia.[21] In general, patients receiving CABG are more completely revascularized and have the advantage of a greater relief of myocardial jeopardy than those receiving PTCA which targets a more limited extent of a given coronary artery.[22, 23] Thus, we suggest that patients in the BARI cohort who received CABG had greater and more durable protection against myocardial ischemia which preferentially protected against acute environmental events which may heighten susceptibility to a ventricular arrhythmia.

Our results may have important clinical implications for guiding CAD treatment strategies. Specifically, revascularization with CABG may be preferred in patients who are identified as having an increased risk of sudden cardiac death due to extensive CAD,[6, 24] history of ventricular arrhythmia,[25] ECG abnormalities, and impaired LV function.[26] If PCI is the intervention ultimately chosen in patients at particularly high risk for sudden death, more complete revascularization may be wise. Prior studies in CASS emphasized the importance of complete surgical revascularization in patients with depressed LV function. However, as noted in the BARI cohort of patients with multivessel disease, the majority treated with PTCA had less complete revascularization than CABG-treated patients, and even in current practice, many PCI-treated patients receive treatment in only one coronary segment. While this approach to PCI does not appear to compromise overall survival, as per BARI in those without treated diabetes, the current study suggests that PTCA as performed in 1988-1991 left patients at risk for sudden death in contrast to those revascularized with CABG. Patients who are not suitable candidates for bypass surgery may benefit from added measures to prevent sudden death, such as prophylactic placement of implantable cardiac defibrillators, which has been shown to substantially improve survival in the CAD population by preventing sudden death.[27]

Of note, PTCA in BARI preceded the routine use of both bare metal and drug-eluting stents, and similarly, CABG has continually progressed with better perioperative management, a higher use of arterial grafting, and improved techniques with minimally invasive and off pump surgery as options.[28, 29] In the context of these developments, are the BARI results relevant? Yes – as described above, the subset of patients who benefited most from CABG were those at high risk of sudden cardiac death, as characterized by extensive CAD, depressed LV function, abnormalities on the resting electrocardiogram, etc. By way of analogy, PCI is currently challenging CABG as an alternative for revascularization of high-risk patients with triple vessel disease or left main disease, domains historically reserved for CABG. Whether or not current methods of PCI will eliminate or minimize the historical advantage of CABG in selected high-risk subsets is under study in several current large randomized trials. To this end, our data corroborate the need for rigorous evaluation of revascularization strategy of very high risk patients, in particular, those at high risk of sudden cardiac death.

Multivariate analysis of cause-specific mortality also revealed a statistically significant interaction between diabetes status and CABG for MI death, indicating a differential impact of CABG on MI death in patients with and without diabetes. Although the relative risks associated with CABG for MI death were not significantly different from one (i.e. no effect) in the two stratified models, it is notable that in the non-diabetic population CABG was associated with a greater long-term risk of MI death while in the diabetic population CABG was associated with a lower long-term risk of MI death. This is consistent with the previous report by Detre et al.[30] that demonstrated that among revascularized patients who have an MI, CABG offered greater protection against long-term mortality in diabetic patients compared to non-diabetic patients.

Whereas comparison of the *strategy* of initial revascularization with CABG versus PTCA is best accomplished in an intention to treat analysis of a randomized clinical trial, the purpose of this analysis was to evaluate the impact of receiving (versus not receiving) a CABG on various causes of mortality. Therefore, undergoing CABG, as either an initial procedure or a subsequent procedure, was the exposure of primary interest. Since BARI registry patients met every eligibility criteria for the randomized trial

except a willingness to be randomly assigned to treatment, our purpose was best served by including both the randomized and registry cohorts in this analysis and by considering treatment with CABG at any time during the BARI study as our key covariate. The same patient sample and methodology were used in BARI report by Detre et. al. to evaluate the effect of CABG on survival after MI.[30]

Competing risks analysis of cause-specific mortality in the BARI study provided additional information beyond standard Cox regression analysis of overall mortality or even cardiac mortality. All-cause mortality is a common primary endpoint in clinical studies, including BARI, since death, regardless of its cause, is an important and clinically meaningful outcome. This pertains especially to studies that evaluate medical treatments designed to prolong survival. From a methodologic perspective, clearly defined endpoints such as all-cause mortality are more easily verified, and the data will more often be complete. Despite such advantages, important implications of the disease process and treatment effect may be missed by not considering specific causes of death. Holmes et al. reported that the ratio of cardiac to non-cardiac death rates tends to decrease as patients age within a study cohort and as follow-up time increases.[4] This was evident in BARI, and a preponderance of non-cardiac deaths may obscure accurate interpretation of studies investigating long-term treatment effects, particularly in an aging patient population.

The study shares the weaknesses of an observational study in addition to the difficulty of determining the actual cause of death. A strength of the BARI study however is the manner in which cause of death was determined. An independent Morbidity and Mortality Committee comprised of cardiologists was included in the original design of BARI, and the initial five year results showing a survival benefit with CABG in patients with treated diabetes was greatly enhanced by determining that the difference was entirely due to cardiac mortality.

3.5 CONCLUSION

In BARI, revascularization with CABG had a different impact on specific causes of long-term mortality in patients with multivessel coronary artery disease. CABG significantly decreased the risk of sudden cardiac death, irrespective of diabetes status, while not significantly altering the risk of other causes of death. Evaluation of specific causes of death provided insights that may be useful for guiding treatment selection and developing strategies to improve long-term survival after coronary revascularization.

3.6 ACKNOWLEDGEMENT

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Table 3.1 Baseline characteristics by vital status and cause of death

	Alive	Dead (Cause of Death)				
		Sudden Death	MI	CHF/Other Cardiac	Non-Cardiac	*P**
	(n=2989)	(n=107)	(n=109)	(n=68)	(n=337)	
Demographic profile						
Age, in years	61±10	62±9	64±10	67±9	66±9	<0.01
Male	75	77	63	60	68	0.09
White race	93	82	89	85	89	0.31
Black race	4	12	10	10	8	
Post high school education	36	28	26	25	29	0.33
Medical history						
Treated diabetes	15	31	36	47	30	0.04
Myocardial infarction	51	65	64	62	51	0.01
Congestive heart failure	5	14	23	25	14	0.03
Peripheral vascular disease	13	21	26	29	29	0.40
Hypertension	46	55	64	69	58	0.20
Renal dysfunction	1	7	6	12	5	0.21
Malignancy	4	7	6	10	12	0.16
Clinical profile						
Former smoker	46	50	40	44	47	0.52
Current smoker	23	25	27	21	26	
Stable angina class 1 or 2	16	10	13	12	13	0.27
Stable angina class 3 or 4	15	9	16	24	15	
Unstable angina/ non-Q-MI	68	80	72	65	71	
Angina duration ≥1 year	39	34	55	43	49	0.01
Major Q-wave	16	23	25	22	23	0.96
ST depression	5	12	8	21	6	<0.01
Major ECG abnormality	40	54	52	54	52	0.97
Angiographic profile						
Triple-vessel disease	37	49	46	49	40	0.28
Proximal LAD disease	38	38	43	25	40	0.12
Ejection fraction <50% †	14	28	24	34	20	0.02
Left-sided/ mixed dominance	14	23	26	12	17	0.06

Categorical variables are presented as column percentages, continuous variables as mean±SD.

***** Compares 4 causes of death among patients who died.

† Ejection fraction data was missing for 462 patients.

Table 3.2 Relative Risks Associated with CABG for Overall and Specific Causes of Death

	All Patients (N=3610)				**No Diabetes** (n=2968)				**Diabetes** (n=642)			
	No. of Events	RR*	95% CI	*P*	No. of Events	RR*	95% CI	*P*	No. of Events	RR*	95% CI	*P*
Impact of CABG (vs. no CABG) on:												
All-cause mortality	621	0.90	0.77-1.06	0.19	416	1.01	0.83-1.23	0.94	205	0.68	0.52-0.90	0.01
Sudden cardiac death †	107	0.60	0.41-0.88	0.01	74	0.61	0.38-0.97	0.04	33	0.55	0.28-1.10	0.09
MI death ‡	109	1.06	0.72-1.56	0.76	70	1.51	0.92-2.46	0.10	39	0.54	0.28-1.02	0.06
CHF/other cardiac death	68	1.10	0.67-1.79	0.72	36	1.49	0.74-2.99	0.26	32	0.69	0.34-1.39	0.30
Non-cardiac death	337	0.93	0.75-1.16	0.54	236	0.99	0.77-1.29	0.96	101	0.80	0.54-1.19	0.27

CABG indicates coronary artery bypass graft; RR relative risk; CI confidence interval

* Adjusted for: diabetes, age, gender, race, smoking, congestive heart failure, hypertension, major ECG abnormality, peripheral vascular disease, renal dysfunction, left/mixed dominance, ejection fraction, and malignancy.

† Among all patients, the impact of CABG on sudden cardiac death was significantly different than on all other causes of death combined (test of interaction p=0.02).

‡ The impact of CABG on MI death was significantly different in non-diabetic and diabetic patients (test of interaction p=0.04).

4.0 PREDICTORS OF REPEAT REVASCULARIZATIONS AFTER SUCCESSFUL INITIAL PTCA: LONG-TERM EVALUATION OF THE BARI COHORT

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4.1 INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) is an established and effective revascularization strategy for patients with coronary artery disease (CAD).[1, 2] The appeal of achieving desirable results by a minimally invasive means is, however, offset by the need for subsequent procedures due to restenosis and atherosclerotic disease progression. In the NHLBI[3] and Mayo Clinic[4] PTCA Registries, 35-50% of patients who underwent an initially successful balloon angioplasty required subsequent coronary artery bypass surgery (CABG) or repeat PTCA over the next 5 to 10 years. Factors that have been shown to significantly increase the long-term risk of repeat revascularization include male gender, diabetes, unstable angina, lesion length, and not fully successful initial dilation.[5-8]

Predictors of recurrent coronary interventions have been previously described in the PTCA population. However, these analyses have generally been limited to the first subsequent procedure event, and thus, may not have considered the full impact of various risk factors on recurrent revascularizations. Although percutaneous coronary intervention has evolved substantially since balloon angioplasty, evaluation of multiple subsequent revascularization procedures over an extended period of time among patients who underwent successful initial PTCA may provide information regarding the impact of specific risk factors on the progression of CAD and, to a lesser degree, on restenosis. Given the substantial long-term cost associated with PCI treatment driven largely by subsequent interventions,[9, 10] identification of factors that impact recurrent revascularizations may provide useful insights for predicting patient prognosis as well as for guiding treatment strategies. We analyzed the Bypass Angioplasty Revascularization Investigation (BARI) cohort for this purpose.

The specific aim of this analysis was to identify factors related to repeat revascularization after successful initial PTCA, and to evaluate the impact of these predictors on multiple revascularization outcomes occurring over 10 years of follow-up.

4.2 METHODS

4.2.1 Study Design

BARI was designed to compare an initial revascularization strategy of CABG versus PTCA on long-term mortality in patients with multivessel coronary artery disease. A detailed description of the trial has been published previously.[11] In brief, eligibility criteria included clinically severe angina or evidence of ischemia requiring revascularization and angiographically documented CAD involving 2 or 3 vessels amenable to revascularization by either CABG or PTCA. Exclusion criteria included severe left main disease, prior coronary revascularization, and acute myocardial infarction (MI) 24-hours prior to the initial procedure. Participants were enrolled from 18 clinical sites in the United States and Canada between August 1988 and August 1991. Of the 4107 eligible patients identified, 1829 patients gave written informed consent and were randomized to either CABG or PTCA. Eligible patients who declined randomization were given the opportunity to participate in the BARI registry, in which the patients and their physicians selected the initial revascularization strategy but had similar follow-up schedules as the randomized patients. This analysis includes participants in the BARI randomized trial and registry who underwent initial PTCA.

Identical baseline data were collected for BARI randomized and registry patients, which included demographic descriptors, clinical history, 12-lead electrocardiogram (ECG) parameters, coronary angiography measurements, angina, and other risk factors. Although baseline and procedural angiograms were evaluated by a central laboratory for patients in the randomized trial, only clinical site evaluations were obtained for the registry participants. Therefore, angiographic data based on site interpretation were used in this analysis. Patients with missing baseline angiograms were excluded (n=38). Follow-up data were obtained during clinic visits at 4 to 14 weeks and at 1, 3, and 5 years, and telephone contacts at 6 months, 2, 4, 5 years, and annually thereafter. At the time of a vital status sweep undertaken on March

31, 2000, BARI patients who had reached 10 years of follow-up were censored, and patients who fell short of the decade mark continued to be followed until their 10-year anniversary.

The present analysis is a long-term evaluation of factors related to repeat revascularizations including insight regarding restenosis and disease progression. Since cardiovascular complications occurring during or shortly after percutaneous intervention are generally attributed to procedural factors (i.e. technical failure, operator skills, and inadequate completeness of revascularization), this analysis was limited to patients who underwent a successful initial PTCA, which was defined as having at least one ≥50% lesion successfully dilated and not experiencing MI, subsequent revascularization, or death within 30 days of the index procedure. Patients were excluded due to at least one of the following early failure (in-hospital) events: total angiographic failure (n=201), MI (n=58), subsequent CABG (n=185), subsequent PTCA (n=105), and death (n=17). This analysis also excluded patients who received new interventional devices during the initial PTCA procedure, including: atherectomy (n=33), bare metal stent (n=11), and laser (n=6). Thus, the present study evaluates patients who underwent balloon angioplasty in the pre-stent era.

4.2.2 Angiographic Definitions

Diseased vessels were determined from the anterior, lateral, and inferoposterior coronary perfusion territories supplied by a vessel with a significant lesion. Lesions residing in a vessel with reference diameter >1.5mm were considered significant if stenosis was ≥50% and totally occluded if stenosis was ≥99%. Successful lesion dilation was characterized by residual stenosis <50%, ≥20% reduction in stenosis, and TIMI grade 3 flow. Angiographic success of the index procedure was considered to be 'partial' if some but not all attempted significant lesions were successfully dilated, and 'total' if all attempted significant lesions were successfully dilated. Lastly, the initial PTCA was considered an incomplete revascularization (IR) if any significant lesions were left remaining.

4.2.3 Statistical Methods

Baseline clinical and angiographic characteristics were compared using the Chi-square test for categorical variables and the Cochran-Armitage trend test for ordinal variables. For angiographic data, we were interested in assessing the presence of disease at baseline, as well as any residual disease following initial revascularization. Therefore, lesion characteristics were examined as binary variables (indicating presence vs. absence) and as 3-level categorical variables (absent, present and attempted, and present but not attempted).

The main outcome was time-to-repeat revascularization with either CABG or PTCA. For all time-to-event analyses, the date of the initial PTCA was considered to be time "zero." PTCAs performed in multiple stages were counted as a single procedure, and the date of the first stage was considered to be the date for that procedure. Patients were censored at the time of death. Kaplan-Meier[12] curves were constructed to examine temporal trends in the first repeat revascularization event. Nelson-Aalen curves were created to estimate the cumulative number of repeat revascularization procedures received per 100 patients over time.

Multivariate analyses were initiated by identifying predictors of the first repeat revascularization event using Cox proportional hazards regression.[13] Clinical and angiographic characteristics were allowed to enter into the model using forward selection (entry criterion $p<0.10$) and then, angiographic PTCA procedural variables were allowed to enter (entry criterion $p<0.10$). Covariates with $p\geq0.05$ were later removed using backward selection. A separate Cox model was constructed using "second repeat revascularization" as the endpoint with the same model-building procedures but forcing in predictors of the first event. The final model included variables identified by either model-building process. We tested for possible interactions between covariates in the main effects model based on biological plausibility (i.e. diabetes and evidence of diffuse disease), and statistical interactions with $p<0.05$ were retained. Missing values (<3% for any variable) were set to the mean value for continuous variables and zero for binary

variables, and the proportional hazards assumption was checked for each covariate in the model by examining Kaplan-Meier curves.

A multiple outcomes model was created using methods described by Prentice-William-Peterson (PWP)[14] an extension of Cox regression that allows multiple recurrent events to be modeled simultaneously using robust variance estimates. The PWP (or 'conditional') approach estimates the probability of having a subsequent event conditional on having experienced a prior event. Compared to other statistical methods for analyzing multiple outcome events data, the PWP approach is efficient and powerful in detecting differences between exposure groups.[15] The time to each subsequent revascularization events is measured as the time since the previous event. We initially considered modeling the first 4 repeat revascularization events per patient. Preliminary PWP models indicated that none of the predictor variables had a significantly different impact on the third and fourth events (all $p>0.10$). Therefore, PWP analysis was limited to the first 3 repeat revascularizations, which ensured sufficient sample size for analysis in each of the latter event categories

Multivariate PWP regression was utilized to investigate the effect of each predictor on the first, second, and third repeat revascularization events. The PWP model initially allowed for separate associations between each covariate and the 3 outcomes; only those covariates with a significantly different impact on the defined endpoint, or combination of endpoints, are presented as outcome-specific estimates (test of equal associations $p<0.05$). Relative risk estimates for such 'uncommon effect' predictors may be interpreted as the probability associated with a given factor of having: a first repeat revascularization event; a second repeat revascularization event among those who had a first event; and a third event among those who experienced the first and second events. Covariates that had a similar impact on the 3 outcomes were included in the model as a single common-effects variable indicating an average effect of the predictor on the long-term subsequent revascularization rate.

Since patients may not receive subsequent revascularization because they die before having an opportunity to be treated or because they are poor candidates for subsequent revascularization due to increased perioperative risk, we were concerned that our results may be affected by the occurrence of

deaths (survival bias) as well as the perceived risk of death based on comorbidities (selection bias). To address this concern, we compared PWP regression results in the overall cohort with a subgroup of patients who had lower risk of long-term mortality based on propensity scoring.[16] The probability of death (the propensity score) was estimated for each patient using a multivariable model for 5-year mortality previously reported in BARI;[17] the "lower risk" strata was defined by propensity scores in the lower 70th percentile.

Estimates of relative risk (RR), 95% confidence intervals (CI), and p-values are reported, and $p<0.05$ is considered statistically significant. All statistical analyses were performed using SAS 9.1 (Cary, NC).

4.3 RESULTS

4.3.1 Repeat Revascularizations Over 10 Years of Follow-Up

In BARI, 1606 patients underwent successful initial PTCA and were followed over an average of 10.6 years. Subsequent revascularizations received are presented in Figure 4.1.

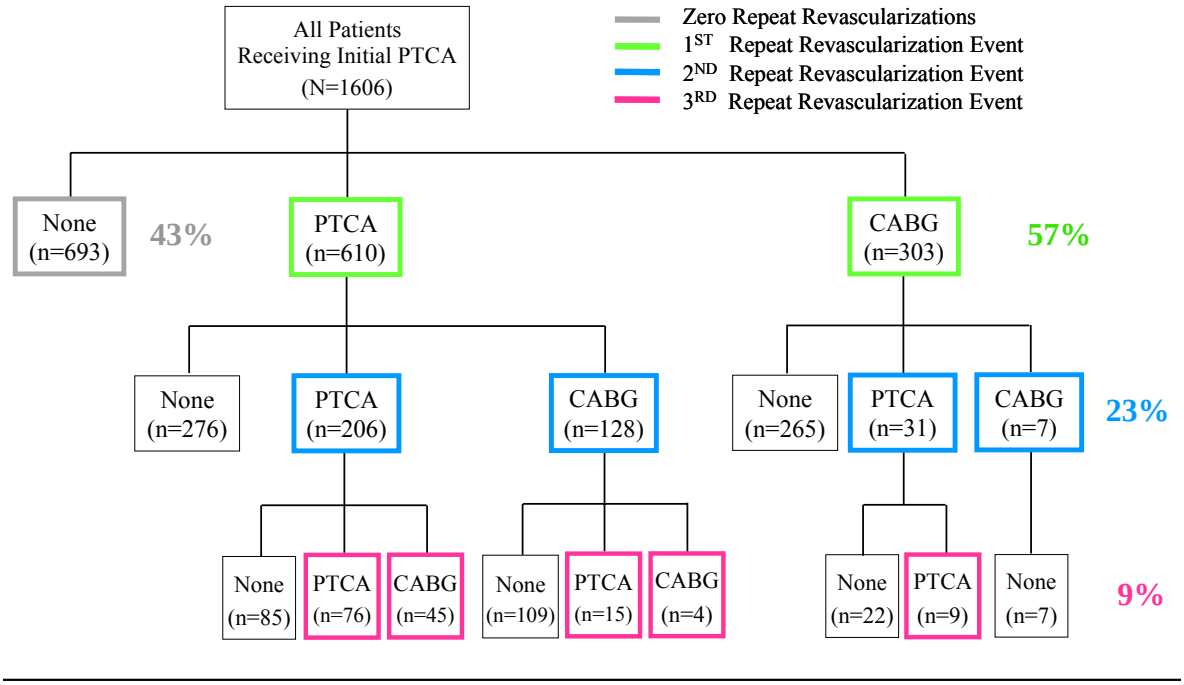

Figure 4.1 Subsequent revascularizations received over 10 years after successful initial PTCA

Following initial treatment, 43% of patients (n=693) did not undergo any additional procedures and 57% (n=913) received a first repeat revascularization, 38% (n=610) with PTCA and 19% (n=303) with CABG. Among those who underwent a first repeat PTCA, 55% (n=334) received a second subsequent procedure (206 with PTCA and 128 with CABG), of which 42% (n=140) went on to receive a third procedure (91 with PTCA and 49 with CABG). Among patients who received CABG as the first repeat revascularization, 13% (n=38) underwent a second subsequent procedure (31 with PTCA and 7 with CABG), and 24% (n=9) of these patients underwent a third procedure.

4.3.2 Baseline Characteristics

Baseline characteristics associated with repeat revascularization with either CABG or PTCA are presented in Table 4.1. Gender was significantly related to a first procedure, with 60% of men undergoing additional procedures compared to 50% of women ($p<0.001$). Other clinical characteristics

that were associated with a significantly greater risk of a subsequent revascularization included diabetes ($p=0.04$), unstable angina ($p=0.03$), and angina duration of at least 1 year ($p=0.03$). The subsequent procedure rate was significantly lower in patients 65 years and older ($p<0.001$), former and current smokers versus never smokers ($p<0.001$) and in patients without, compared to those with, ST elevation on baseline ECG ($p<0.001$).

Angiographic predictors of subsequent revascularization are presented in Table 4.2. Myocardial jeopardy index demonstrated a significant relationship between overall angiographic severity at the time of initial PTCA and the need for additional treatment ($p=0.01$). Nearly one-third of patients had triple vessel disease at baseline, which was associated with a higher incidence of subsequent revascularization compared to double vessel disease (61% vs. 55%, $p=0.04$). All BARI participants had multivessel disease by eligibility criteria; thus, we examined the disease distribution at baseline by forming mutually exclusive categories of the diseased coronary vessels. Among patients with double vessel disease, the subsequent revascularization rate was 60% in those with significant lesions in the left anterior descending (LAD) and left circumflex (LCx) arteries, 54% in LAD and RCA, and 52% in LCx and right coronary artery (RCA). LAD disease appeared to play an important role in the need for further interventions, such that presence at baseline ($p=0.03$) and evidence of residual LAD disease after initial PTCA ($p=0.05$) were associated with a higher repeat revascularization rate over long-term follow-up. In particular, proximal LAD disease that was present at baseline or left untreated was related to a subsequent procedure ($p=0.02$ and $p=0.06$, respectively).

4.3.3 Kaplan-Meier and Nelson-Aalen Curves

A Kaplan-Meier curve of the proportion of patients who underwent at least one repeat revascularization is presented in Figure 4.2.

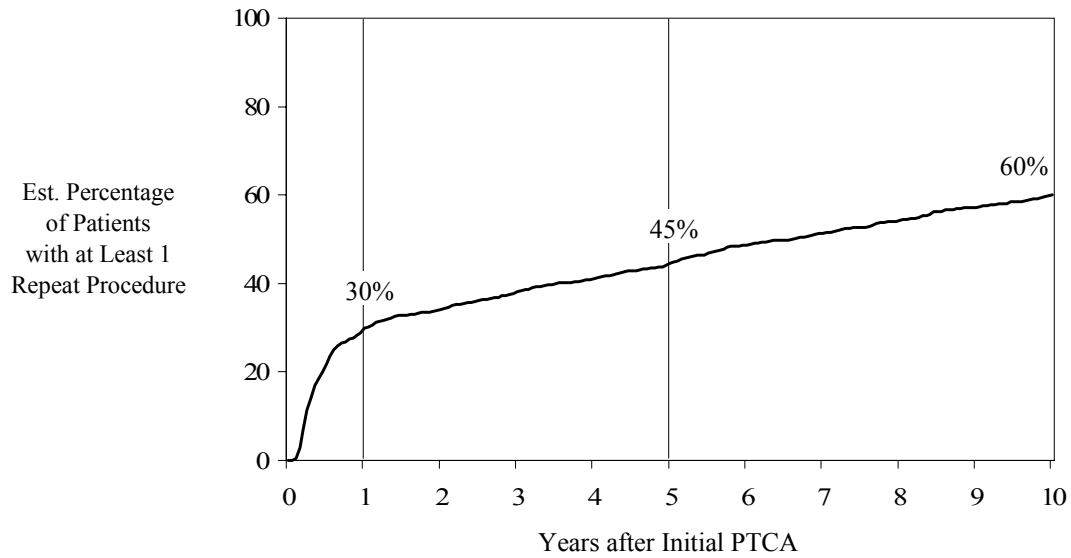

Figure 4.2 Kaplan-Meier curve for time to the first repeat revascularization event

Following successful initial PTCA, there was a steep, early rise in the percentage of patients who received additional procedures, such that nearly half of all patients who underwent subsequent revascularization did so within one year of the index PTCA procedure; a more gradual increase was observed over the remaining follow-up period. Among patients who underwent at least one subsequent revascularization, the median time to the first event was 7 months for those receiving PTCA (n=610) and 28 months for those receiving CABG (n=303).

A Nelson-Aalen curve for the estimated cumulative number of repeat revascularizations per 100 patients is presented in Figure 4.3.

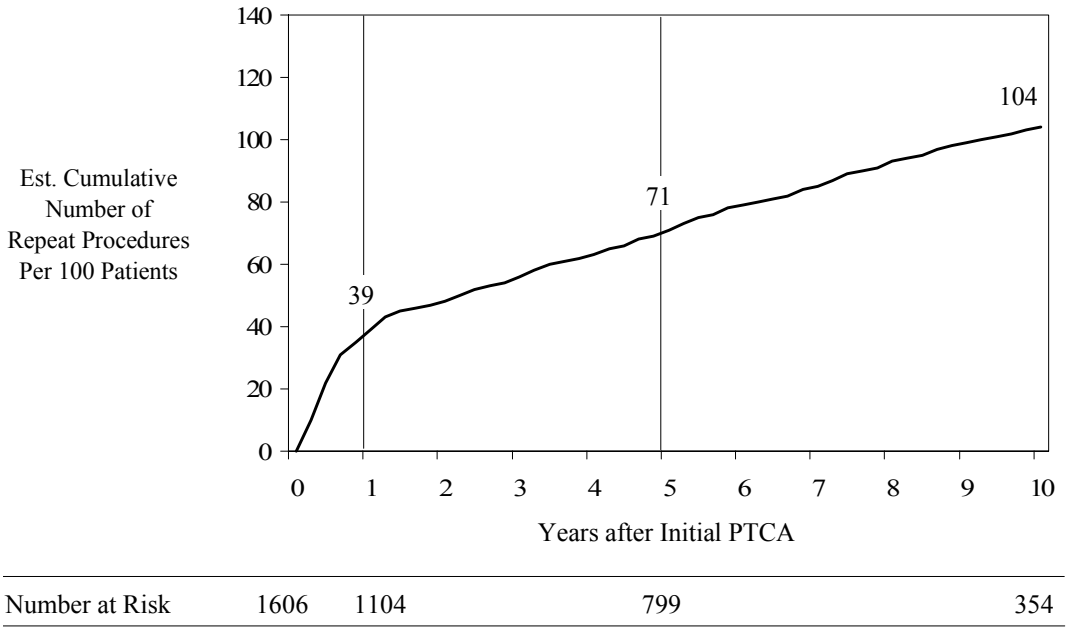

Figure 4.3 Nelson-Aalen estimates for cumulative number of repeat procedures per 100 patients

The cumulative number of repeat procedures increased markedly during the first year, and continued to rise steadily throughout the follow-up period, reflecting patients who underwent a first subsequent revascularization and also those who received multiple additional procedures.

4.3.4 Cox Model for the First Repeat Revascularization Outcome

Several predictors of the first subsequent revascularization were identified using multivariate Cox regression analysis (Table 4.3). Following initial treatment with PTCA, male gender, diabetes, and unstable angina (compared to stable or atypical angina) were associated with a significantly increased risk of repeat revascularization, and age ≥65 years, smoking history, and ST-segment elevation were associated with a significantly lower risk. Angiographic characteristics that were independently

predictive of the need for additional treatment included proximal LAD disease, presence of diffuse lesions, and an incomplete revascularization during the index PTCA. Renal dysfunction was not related to the first repeat revascularization event but was associated with a significantly increased risk for the second event.

4.3.5 PWP Model for Multiple Repeat Revascularization Outcomes

PWP model estimates for differential covariate effects on the multiple repeat revascularization outcomes are presented in Table 4.4. Among patients who underwent successful initial PTCA, fewer than 5% had 4 or more procedures, and 80% of the observed subsequent procedures were accounted for in this analysis (Table A6.1). Consistent with Cox regression analysis, men were more likely than women to undergo a first subsequent revascularization (RR=1.44, $p<0.001$). However, *among* patients who received a first repeat procedure, the risk of undergoing a second procedure did not differ by gender (RR=1.00, p=0.97), and then *among* those who received a second repeat procedure, men were significantly less likely to undergo a third revascularization compared to women (RR=0.64, p=0.01). The differing effect of gender on the number of recurrent treatments was significant (test of equal associations: RR=1.44 vs. 1.00 vs. 0.64, $p<0.001$). Similarly, incomplete revascularization was associated with a higher risk of a first repeat revascularization event (RR=1.13, p=0.07), but conditional on having received one subsequent treatment, incompletely revascularized patients had a marginally lower likelihood of undergoing second and third repeat procedures (RR=0.86, p=0.09). The impact of IR on the number of subsequent revascularizations was significantly different (RR=1.13 vs. 0.86, p=0.01). Proximal LAD disease and smoking history were significantly associated with the first repeat revascularization event (RR=1.24, $p<0.01$ and RR=0.71, $p<0.001$, respectively), but were not associated with subsequent procedures beyond the first (RR=0.95, p=0.58 and RR=0.96, p=0.63, respectively).

The PWP conditional model demonstrated a significant common effect of several predictors on the number of repeat revascularizations. Diabetes was associated with an estimated 43% increase in the

subsequent revascularization rate over 10 years after initial PTCA (RR=1.43, p<0.001). This means that diabetes increased the risk of a first repeat revascularization event, and then *among* patients who experienced a first event, diabetes was again significantly related to higher rates of a second subsequent procedure, and similarly for a third procedure. A sustained effect was also demonstrated for renal dysfunction (RR=1.75, p<0.001), unstable angina (RR=1.15, p=0.01), and presence of diffuse lesions (RR=1.13, p=0.03). Age ≥65 years and ST elevation were associated with a lower common effect on the subsequent revascularization rate (RR=0.84, p<0.01 and RR=0.52, p<0.001, respectively).

4.3.6 Assessment of Survival and Selection Bias

Ten-year cumulative mortality rate was markedly higher among patients who did not receive subsequent revascularization compared to those who did (32% vs. 21%, log-rank p<0.001), which suggested a potential survival bias. Multivariate PWP analysis of a subgroup of patients with a lower predicted probability of death, which addressed both survival bias and treatment selection bias, resulted in estimates that were consistent with estimates in the overall cohort (Table A6.2). The notable exception was age ≥65 years, which was not significantly associated with subsequent revascularizations among patients with a lower predicted probability of death (RR=0.93, p=0.31).

4.3.7 Examination of Subsequent Revascularization Strategy

To illustrate the changing effect of gender, proximal LAD disease, and incomplete revascularization on the multiple subsequent procedure outcomes, we compared event rates and mode of revascularization (either CABG or PTCA) for these patient groups. As shown in Figure A6.1, men were more likely to undergo a first subsequent procedure compared to women (60% vs. 50%, p<0.01) and, in particular, to receive CABG for the first treatment (21% vs. 14%, p<0.01). Among patients who had a first subsequent revascularization event, gender was not related to a second event (p=0.90), but of those who received a

second repeat procedure, a smaller proportion of men underwent a third procedure (36% vs. 52%, $p<0.01$).

A similar pattern was observed for proximal LAD disease and incomplete revascularization (Figures A6.2 and A6.3, respectively). Patients with proximal LAD disease (compared to those without it) more frequently underwent a first repeat procedure (61% vs. 55%, p=0.02), particularly with CABG (21% vs. 18%, p=0.04). However, among patients who had a first event, proximal LAD disease was not predictive of further interventions (p=0.51 and p=0.20). Patients who received an incomplete (versus complete) initial revascularization were somewhat more likely to undergo a first subsequent procedure (58% vs. 54%, p=0.13) and significantly more likely to be treated with CABG (23.0% vs. 12.2%, $p<0.001$). Conditional on the first repeat procedure, IR was associated with a marginally lower second event rate (39% vs. 44%, p=0.11), but, once again, incompletely revascularized patients were more likely to receive CABG for the second procedure (15.4% vs. 13.7%, p=0.06). Among patients who underwent two repeat procedures, an incomplete initial revascularization was not predictive of a third intervention (39% vs. 41%, p=0.71).

4.4 DISCUSSION

Among patients who underwent successful initial PTCA in BARI, an estimated 57% received at least one subsequent procedure and 23% received two or more procedures over 10 years of follow-up. The long-term repeat revascularization rate in BARI was comparable to what has been reported from the NHLBI[3] and Mayo Clinic[4] PTCA Registries in similar subset of patients (i.e. those with multivessel disease and successful initial balloon angioplasty). Factors that were associated with a significantly greater risk of repeat revascularization included: male gender, diabetes, renal dysfunction, unstable angina, proximal LAD disease, diffuse disease, and incomplete revascularization.

Evaluation of the multiple repeat revascularization events revealed a significantly different effect of gender, proximal LAD disease, and completeness of initial PTCA on the first versus latter events. In BARI, patients who were male, with proximal LAD disease, and received an incomplete revascularization were more likely to undergo a first repeat procedure, and more importantly, to be revascularized with CABG for this procedure. Given this subsequent treatment with CABG, a more durable revascularization strategy than PTCA,[4, 18, 19] these 3 predictors were either not related or negatively associated with the need for additional coronary interventions. Prior percutaneous intervention studies have reported that men are more frequently referred for repeat procedures compared to women,[4] including more frequent subsequent surgical revascularization.[20] Although the underlying reasons remain unclear, a possible explanation may be that female gender has been identified as an independent risk factor for major in-hospital CABG complications in both the Society for Thoracic Surgeons risk modeling[21] and the EuroSCORE risk algorithm.[22]

Consistent with previous reports,[23-26] measures of extent and severity of CAD at the time of initial PTCA treatment were associated with a significantly increased risk of repeat revascularizations in BARI. Among these multivessel disease patients, the location of the disease was a stronger independent predictor than the number of lesions or diseased vessels. Significant LAD disease, particularly in the proximal segment, was related to subsequent revascularization. Much of the difference in repeat revascularization rates between patients with and without LAD disease occurred early in the follow-up period (<1 year), which may reflect higher incidence of restenosis in patients who had LAD lesions treated during the index procedure or the need to treat residual disease in those with LAD lesions that were left untreated.

PWP analysis demonstrated a persisting detrimental impact of diabetes on the increasing number of recurrent procedures. Diabetes was associated with a significantly greater risk of restenosis following balloon angioplasty[6, 8, 27-29] and accelerated disease progression, which are mediated by hyperreactive platelets that exhibit increased adhesion, aggregation, and platelet-dependent thrombin generation.[30] Our findings support what has been previously described regarding the role of diabetes in CAD progression,

and underscore the importance of intensive risk factor modification in diabetic patients undergoing coronary revascularization in order to maintain the benefits of initial treatment.

Investigation of factors related to subsequent procedures also allowed us to characterize patients who are likely to attain long-term success after undergoing initial percutaneous intervention. Even in the presence of multivessel disease, 43% of patients who had a successful initial PTCA in BARI received no subsequent revascularization. Our analyses indicate that percutaneous coronary intervention may be particularly effective for women and patients without the presence of diabetes, renal disease, and advanced CAD (as indicated by presence of unstable angina, diffuse lesions, and proximal LAD disease), and those in whom complete revascularization can be achieved.

Importantly, our findings were confirmed in a subgroup of patients with a relatively lower mortality risk who were, therefore, less subject to survival and treatment selection bias. Overall, there was minimal evidence to suggest that early deaths and reluctance to revascularize high risk patients influenced the results of this analysis in a meaningful way. The only covariate that differed meaningfully between the 2 models was age, indicating that the seemingly 'protective' effect of older age may be due to early deaths or a reluctance to revascularize high risk patients. A similar explanation was not evident for smoking history and ST elevation, established cardiovascular risk factors related to lower revascularization rates. A biologically plausible explanation of our finding on smoking is a "preconditioning-like" effect of nicotine on the myocardium. Animal studies suggest that brief ischemic episodes may promote the formation of collateral vessels and thereby increase myocardial tolerance to subsequent periods of prolonged ischemia.[31] Smoking history may, in fact, have a lower risk of repeat procedures because of protection derived from collaterals vessels. This postulate, however, cannot be verified due to an absence of specific angiographic data on collateral vessels. Regarding ST elevation, it is possible that patients with ST elevation on baseline ECG received more aggressive medical therapy after initial PTCA compared to others.

4.4.1 Extending Study Results to the Current Era

The introduction of drug-eluting stents in the last decade has drastically lowered restenosis rates following percutaneous intervention.[32-34] Despite overcoming a major limitation of conventional balloon angioplasty, benefits conferred by drug eluting stents and adjunctive therapies (namely, the use of glycoprotein IIb/IIIa inhibitors) are limited to the short-term. Even in the absence of definitive data, there is little reason to believe that contemporary PCIs alone (i.e. notwithstanding advances in pharmacological therapy) will diminish the long-term need for additional procedures, which is driven mainly by native disease progression in the coronary arteries.[25, 35, 36] Therefore, generalizeability of our findings to the current PCI patient population are less likely to be affected by improvements in PCI technology and adjunct therapy, and more likely to be influenced by the widespread use of statins, anti-platelet medications, and other anti-atherogenic agents.

4.4.2 Study Limitations

Although extensive baseline and procedural angiographic data were obtained, follow-up angiograms were not systematically collected in BARI. Without knowing which target lesions were treated during subsequent revascularizations, it is difficult to offer more definitive explanations and possible underlying mechanisms for our findings. Nevertheless, it has been well-established that restenosis occurs most frequently during the first 6 months and up to 1 year after balloon angioplasty.[6, 37-39] Given this timeframe and the fact that majority of repeat procedures during the first year were percutaneous interventions, which is the standard approach for treating primary restenosis,[40] it is likely that in BARI, subsequent revascularizations during the first year were to address restenosis and those occurring after the first year were to treat native disease progression. This is supported by results from a BARI ancillary study, which included approximately 400 patients from the randomized trial, indicating that angiographically-documented CAD progression exceeded failure of initial revascularization as the cause of recurrent angina at 5-year follow-up.[36]

4.5 CONCLUSION

Among patients who were successfully treated with initial PTCA in BARI, independent predictors of a first repeat revascularization event included male gender, diabetes, renal dysfunction, unstable angina, proximal LAD disease, diffuse disease, and incomplete revascularization. Evaluation of multiple repeat revascularization events occurring over 10 years of follow-up demonstrated a significantly different effect of several predictors on the number of recurrent outcomes. Male gender, proximal LAD disease, and incomplete revascularization were associated with a significantly increased risk of a first repeat procedure but were either not related or inversely related to the need for additional procedures. Examination of revascularization strategy revealed that patients with these characteristics in BARI were more likely to receive CABG as their first subsequent treatment, and this strategy substantially decreased the need for further revascularizations. Diabetes, renal dysfunction, unstable angina, and diffuse disease, on the other hand, had a consistent detrimental impact on the number of repeat revascularizations. These findings underscore the importance of glycemic control and intensive modification of risk factors that promote atherosclerotic progression. These data also indicate that women and patients with an absence of extensive coronary disease, diabetes, and renal disease are less likely to need further revascularizations and, therefore, may be particularly good candidates for initial PCI treatment.

Recent advances in PCI technology have significantly improved short-term outcomes but have not markedly decreased the long-term need for additional procedures which are driven primarily by disease progression. Given the substantial economic and health burden associated with subsequent revascularizations, an aggressive approach to limiting disease progression is paramount. Similarly, devising optimal long-term treatment plans that address cardiovascular disease as a chronic, progressive, and systemic condition is of great public health importance.

4.6 ACKNOWLEDGEMENT

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Table 4.1 Baseline characteristics associated with repeat revascularization after successful initial PTCA

		No. of Patients (N=1606)	Repeat Procedure (n=913)	P-value*
BARI study	Randomized trial	717	56%	0.44
	Registry	889	58%	
Gender	Female	432	50%	
	Male	1174	60%	<0.001
Age	< 65 y/o	992	61%	<0.001
	≥ 65 y/o	614	51%	
Race	White	1481	57%	0.56
	Non-white	125	54%	
Education	< High school	1019	55%	0.09
	≥ High school	566	60%	
Prior MI	No	773	58%	0.34
	Yes	815	56%	
CHF	No	1499	57%	0.08
	Yes	103	49%	
PVD	No	1363	58%	0.26
	Yes	237	54%	
Hypertension	No	825	56%	0.55
	Yes	778	58%	
Treated Diabetes	No	1327	56%	0.04
	Yes	279	62%	
Renal Dysfunction	No	1569	57%	0.98
	Yes	35	57%	
Smoking History	Never	478	65%	<0.001
	Former	724	53%	
	Current	404	54%	
ST Elevation	No	1539	58%	<0.001
	Yes	64	36%	
Angina Status	Stable/ Non-Q-MI	768	54%	0.03
	Unstable	838	59%	
Angina Duration ≥ 1YR	No	992	55%	0.03
	Yes	611	60%	

Row percentages are presented.

* P-values are based on chi-square test

Table 4.2 Baseline and procedural angiographic factors associated with repeat revascularization

		No. of Patients (N=1606)	Repeat Procedure (n=913)	P-value*	P-value†
Myocardial Jeopardy Index ‡	< 50%	473	51%	0.01	
	50-65%	613	57%		
	66-100%	520	61%		
Ejection Fraction <50%	No	1194	57%	0.79	
	Yes	248	56%		
Vessel Disease	Double	1101	55%	0.04	
	Triple	470	61%		
Diseased Vessels	LAD & LCx only	379	60%	0.02	
	LAD & RCA only	390	54%		
	LCx & RCA only	332	52%		
	LAD & LCx & RCA	470	61%		
LAD Disease	No	358	52%	0.05	0.03
	Yes/None Attempted	213	62%		
	Yes/ ≥ 1 Attempted	1035	58%		
LCx Disease	No	408	54%	0.38	0.21
	Yes/None Attempted	268	59%		
	Yes/ ≥ 1 Attempted	930	57%		
Proximal Disease	No	516	56%	0.75	0.49
	Yes/None Attempted	167	56%		
	Yes/ ≥ 1 Attempted	923	58%		
Proximal LAD Disease	No	1033	55%	0.06	0.02
	Yes/None Attempted	80	61%		
	Yes/ ≥ 1 Attempted	493	61%		
Any Total Occlusions	No	1048	58%	0.24	0.28
	Yes/None Attempted	380	53%		
	Yes/ ≥ 1 Attempted	178	59%		
Any Diffuse Lesions	No	1169	56%	0.26	0.10
	Yes/None Attempted	424	60%		
	Yes/ ≥ 1 Attempted	13	62%		
Angiographic Success	Partial	161	60%	0.45	
	Total	1443	57%		
Incomplete Revascularization	No	615	54%	0.13	
	Yes	991	58%		
No. of Significant Lesions Remaining	0	615	54%	0.47	
	1	578	59%		
	2	275	57%		
	3+	138	57%		

Row percentages are presented.

* Chi-square test p-value compares the presented categories; † Chi-square test p-value compares presence versus absence of the lesion characteristic; ‡ Cochran-Armitage trend test $p<0.01$.

Table 4.3 Cox model estimates for the first repeat revascularization event

	Adjusted RR	95% CI	P-value
Male	1.44	1.23 - 1.69	<0.001
Diabetes	1.46	1.24 - 1.73	<0.001
Renal dysfunction	1.51	0.97 - 2.36	0.07
Age ≥ 65 years	0.82	0.71 - 0.94	<0.01
Smoking history	0.70	0.61 - 0.81	<0.001
ST elevation	0.47	0.31 - 0.71	<0.001
Unstable angina	1.16	1.02 - 1.32	0.03
Proximal LAD disease	1.25	1.09 - 1.42	<0.01
Diffuse disease	1.18	1.02 - 1.37	0.02
Incomplete revascularization	1.13	0.99 - 1.30	0.07

RR indicates relative risk; CI confidence interval

Table 4.4 PWP model estimates for multiple repeat revascularization events

	Event Number	RR (95% CI)	P-value	P-value* for Equal Assoc
Male	1	1.44 (1.23-1.69)	<0.001	<0.001
	2	1.00 (0.78-1.28)	0.97	
	3	0.64 (0.45-0.91)	0.01	
Diabetes		1.43 (1.25-1.64)	<0.001	-
Renal dysfunction		1.75 (1.27-2.41)	<0.001	-
Age ≥ 65 years		0.84 (0.75-0.94)	<0.01	-
Smoking history	1	0.71 (0.61-0.81)	<0.001	0.01
	2 and 3	0.96 (0.79-1.15)	0.63	
ST elevation		0.52 (0.37-0.74)	<0.001	-
Unstable angina		1.15 (1.04-1.28)	0.01	-
Proximal LAD disease	1	1.24 (1.09-1.42)	<0.01	0.02
	2 and 3	0.95 (0.79-1.14)	0.58	
Diffuse disease		1.13 (1.01-1.27)	0.03	-
Incomplete Revascularization	1	1.13 (0.99-1.30)	0.07	0.01
	2 and 3	0.86 (0.72-1.03)	0.09	

PWP indicates Prentice-Williams-Peterson; RR relative risk; CI confidence interval

* P-value tests the null hypothesis that the respective predictor has the same impact on all repeat revascularization events.

5.0 FACTORS RELATED TO SELECTION OF CABG VERSUS PCI IN PATIENTS WITH DIABETES AND STABLE MULTIVESSEL DISEASE IN BARI 2D

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5.1 INTRODUCTION

Patients with type 2 diabetes represent approximately 25% of the 1.5 million coronary revascularizations performed annually in the United States.[1-4] Diabetic patients, compared to those without diabetes, experience worse short- and long-term outcomes after both coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI);[4-6] hence, trying to determine which is the more appropriate strategy in diabetic patients requiring coronary revascularization is a complex issue. The original BARI trial was instrumental in shedding light on the issue in reporting a significantly lower long-term mortality in patients with diabetes and multivessel disease who underwent initial revascularization with CABG versus balloon-only PCI.[7] Similarly, the benefit of CABG was greater in patients with more extensive coronary disease.[8] These findings, particularly the former, prompted the National Heart, Lung, and Blood Institute (NHLBI) to issue a Clinical Alert recommending CABG over balloon angioplasty in patients with treated diabetes and multivessel CAD.[9]

In the years since BARI results were first reported, advances in PCI technology and adjunctive therapy have significantly improved peri-procedural and short-term outcomes. Use of glycoprotein (Gp) IIb/IIIa receptor inhibitors[10, 11] and drug-eluting stents,[12-15] in particular, have significantly decreased the rate of restenosis and other indications of early failure, and also improved short-term survival. In addition, there has been an increasing appreciation for the critical role of intensive medical management of atherosclerosis. Aggressive glycemic control,[16-18] lipid-lowering agents,[19, 20] beta-blockers,[21] and ACE inhibitors[22] have been shown to significantly lower cardiovascular events and mortality, and long-term use has become standard for patients undergoing coronary revascularization. These developments have overcome some of the main limitations of traditional balloon angioplasty, including: high incidence of restenosis,[23] inability to achieve a more complete revascularization,[24] and accelerated progression of atherosclerosis.[25-27] Although data from randomized trials and long-term studies are not yet available,

current trends indicate that these improvements may offset the advantage of CABG over PCI among patients with diabetes and multivessel CAD.

The current ACC/AHA guidelines on coronary revascularization are generally based on CAD severity, coronary anatomy and lesion morphology, as well as patient risk factors such as age.[28, 29] For patients with diabetes, CABG is preferred over PCI in the presence of left main disease, multivessel CAD involving the proximal left anterior descending (LAD) artery and moderate to severe symptoms. Although there are no clear recommendations for less severe indications, CABG is considered the standard treatment for non-selected patients with diabetes and multivessel disease.[26] Introduction of intracoronary stents and other developments have not changed recommendations for patients with either mild or very severe CAD; individuals with limited disease are generally treated with PCI and those with extensive disease are referred for CABG. But for the subset of patients with diabetes and stable multivessel disease whose risk profiles fall somewhere in between these ends of the spectrum, the decision is less straightforward. In the absence of compelling evidence to choose one revascularization treatment over another, clinicians make a judgment based on multiple patient-specific factors including: (i) anticipated feasibility of PCI to successfully dilate ischemia-producing lesions; (ii) prior medical history that may impact clinical outcome; and (iii) patient preference. While this global patient-specific assessment may appear straightforward, it is noteworthy that significant regional (i.e. geographic) differences in the treatment of ischemic heart disease have been previously described,[30-32] indicating that both patient-level and contextual (e.g. geographic region, clinical center) factors guide treatment decisions. This ambiguity exists among patients with diabetes and stable CAD where there is little consensus regarding the optimal method of revascularization, and factors influencing this decision are poorly understood.

Therefore, the purpose of this study was to investigate factors associated with the decision to perform CABG versus PCI in patients with diabetes and stable multivessel disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. An important feature of this

analysis was to describe how much of this decision-making process is driven by geographic region alone, independent of individual patient-level factors.

5.2 METHODS

5.2.1 Study Design

BARI 2D is a randomized clinical trial designed to simultaneously compare 2 treatment strategies in patients with type 2 diabetes and stable CAD: (i) coronary revascularization plus aggressive medical therapy versus aggressive medical therapy alone with the option for delayed revascularization for treatment of CAD; and (ii) an insulin-providing strategy versus insulin-sensitizing strategy for treatment of diabetes. A detailed description of the study has been published previously.[33] In brief, eligibility criteria included angiographically documented CAD involving at least one coronary vessel (≥50% stenosis) suitable for treatment with either medical therapy alone or elective revascularization by either CABG or PCI. Patients requiring coronary revascularization for prompt relief of symptoms were not eligible. Exclusion criteria included severe left main disease and prior CABG or PCI in the past 12 months. Participants were enrolled from 49 clinical sites in the United States, Canada, Czech Republic, Austria, Brazil, and Mexico from January 1, 2001 until March 31, 2005.

Although patients were randomly assigned to either immediate coronary revascularization plus intensive medical therapy or intensive medical therapy alone, selection of the revascularization strategy was at the discretion of the treating physicians. Moreover, all patients were evaluated to determine suitability for CABG or PCI, and prior to randomization, clinicians declared the intention to perform either CABG or PCI if the patient were ultimately randomized to the invasive intervention arm. In the present analysis, we were primarily interested in factors related to the *decision* to perform CABG (versus

PCI). Therefore, CABG and PCI revascularization strategies indicate the treatment that was intended prior to randomization, and not treatment that was ultimately received.

Baseline angiographic data were assessed locally by the clinical sites as well as a centralized core laboratory (Stanford University). Since clinicians based patient eligibility and the CABG versus PCI decision on site (non-core) evaluations, we first considered the use of angiographic data based on site interpretation. However, because only limited angiographic data were recorded by clinical sites on the case report forms, we secondarily used angiographic variables from the core lab that were not recorded by site evaluations, under the assumption that these characteristics were recognized and considered by clinicians during the initial evaluation. Patients with ≥80% missing baseline data were excluded from the overall analysis (n=47).

The myocardial jeopardy index (MJI) was a core laboratory measurement which reflects percentage of the myocardium that was jeopardized by significant lesions at baseline.[34] Because MJI did not take into account previously revascularized lesions that were patent, it did not reflect cumulative burden of coronary disease. Therefore, patients with prior PCI (n=285) were excluded in the presentation of MJI data.

Our primary interest was to evaluate factors related to the selection of CABG over PCI in moderate to high-risk patients with diabetes and stable CAD, for whom there is little consensus regarding optimal treatment. Since this decision is inherently biased toward PCI in patients who have previously undergone CABG, we excluded this subset (n=149). At the other extreme, patients with stable single vessel CAD, irrespective of the presence or absence of diabetes, are usually referred for PCI; therefore, this subgroup was also excluded from the analysis (n=601). By virtue of these selection criteria, which limited the analysis to patients with diabetes and multivessel CAD, this gave us an opportunity to indirectly evaluate the impact of the original BARI results on contemporary practice, a decade after the NHLBI issued a Clinical Alert regarding the superiority of CABG over balloon angioplasty in this patient population.

5.2.2 Statistical Methods

We started the analysis by examining selection of revascularization strategy by geographical region irrespective of patient characteristics. Although the percentage of CABG-intended patients varied across countries outside of the US (e.g. Canada versus Brazil), US versus non-US regions provided the most informative comparison, given the wide range in the numbers of patients within sites and sites within regions. Patient characteristics related to the decision to perform CABG were then assessed separately for US and non-US regions. Baseline clinical and angiographic characteristics were compared using the Chi-square test for categorical variables and the Cochran-Armitage trend test for ordinal variables.

Since patients were nested in clinical sites, and sites were nested in regions, we assessed the degree of correlation in treatment selection within and between individual clinical sites by fitting covariance patterns (residuals) using generalized estimating equations (GEE).[35] Preliminary analyses revealed considerable amount of correlation in our data, and we decided that multilevel modeling using GEE was the appropriate statistical procedure for multivariable analysis, which accounts for correlation and provides more accurate error estimates, resulting in p-values and confidence intervals that are unbiased with respect to correlation.[36] However, since our GEE modeling software did not support a forward selection procedure, the multivariable model was initially built using standard logistic regression,[37] ignoring clustering in our data. We expected this to result in erroneously low p-values, and therefore, a p-value cutoff of 0.01 was applied throughout the model-building procedure. In the final step, data were re-fitted using GEE.

Patient characteristics associated with the decision to perform CABG were identified using logistic regression by running 4 separate forward selections, one for each category of baseline variables: clinical, baseline medications, site angiographic data, and core lab angiographic data. We fitted a final forward selection procedure with patient-level characteristics identified in the previous steps as candidate variables. Region, a higher-level predictor, was then added to the model. In order to avoid imprecise estimates, we combined Canada and Europe, and also Brazil and Mexico, on the basis of similarities in

health care delivery systems as well as percentage of CABG-intended patients observed in this study. Therefore, geographic region was included in the final model as a 3-level variable (Canada and Europe; and Brazil and Mexico versus US). Variables with p>0.01 were subsequently removed using backward selection, and variables remaining in the model were assessed for multiple collinearity. Statistical interactions were initially tested between US (versus non-US) region and each variable in the main effects model. Any interaction terms with $p<0.01$ were tested in a second model with region as a 3-level variable, and only interactions with $p<0.01$ were retained in the final model. In the last step of the multivariable analysis, the data were refitted using GEE which accounted for between- and within-site correlations.

Missing values (<1% of values) for covariates included in the final multivariate model were set to zero for binary variables; thus, dichotomous covariates may be interpreted as the known presence of the respective characteristic. Estimates for odds ratios (OR), 95% confidence intervals (CI), and p-values are reported, and P<0.05 are considered statistically significant. All statistical analyses were performed using SAS 9.1 (Cary, NC).

5.3 RESULTS

5.3.1 Regional Variation in the Decision to Perform CABG versus PCI

Of the 2368 patients with diabetes enrolled in the BARI 2D trial, 1592 with multivessel disease and no prior history of CABG were included in this analysis. Patients were enrolled across 40 clinical sites in the US (n=910) and 9 sites in other parts of the world (n=682). As seen in Table 1.1, the decision to perform CABG versus PCI was made twice as often in patients seen outside of the US compared to those in the US (61% vs. 31%, $P<0.001$). The percentage of CABG-intended patients in regions outside of the US ranged from 47% in Canada, 56% in Europe, 73% in Brazil, and 76% in Mexico. Selection of

revascularization strategy differed significantly across the 5 geographic regions ($P<0.001$). GEE covariance estimates indicated that 29% of the variation in treatment decision was explained by US vs. non-US sites irrespective of patient characteristics; further distinguishing between the 4 non-US regions explained a slightly higher 34% of the variation.

To assess whether the substantial geographic variability in selection of revascularization strategy was due simply to patient differences in CAD severity between regions, we compared the percentage of CABG-intended patients across increasing levels of the myocardial jeopardy index (MJI) within- and outside of the US (Figure 5.1).

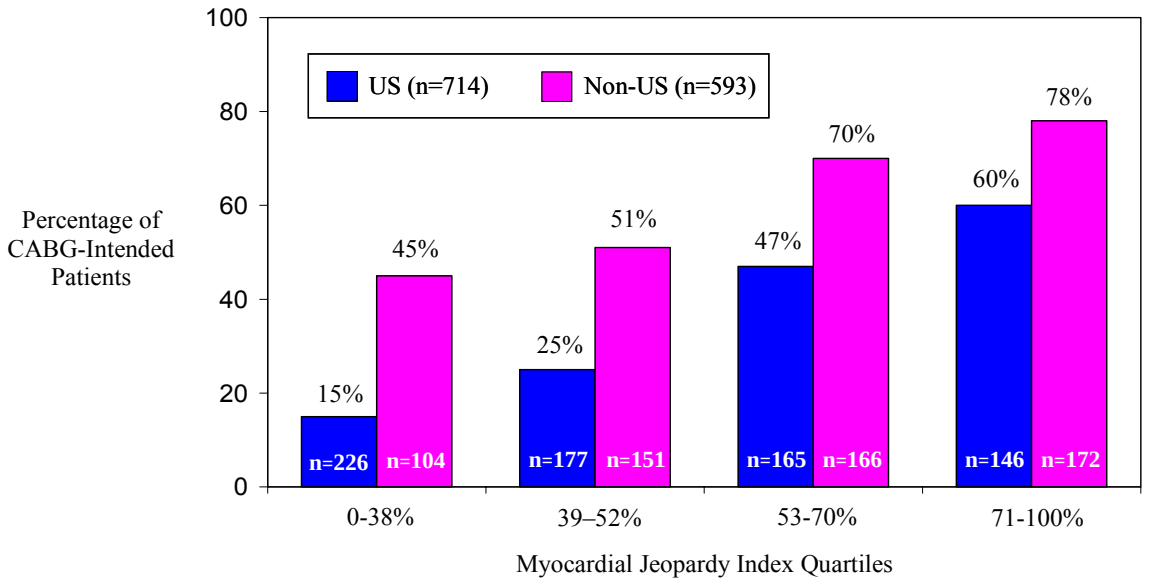
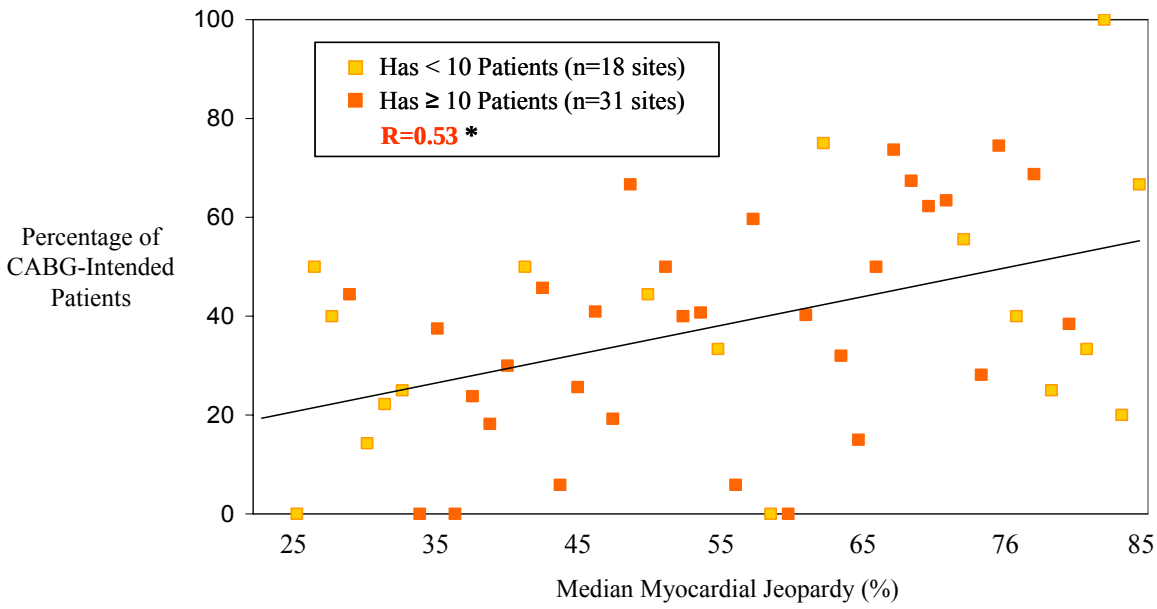


Figure 5.1 Intention to perform CABG within myocardial jeopardy quartiles in US and non-US sites

In both regions, the decision to perform CABG increased as disease burden increased, but within each MJI quartile, patients in the US were much less likely to be referred for surgical treatment compared to those in other countries ($P<0.001$).



Patients with prior PCI excluded (n=285)

* Correlation coefficient (R) calculated for clinical sites with 10 or more patients

Figure 5.2 Variation across clinical sites in the percentage of CABG-intended patients by median myocardial jeopardy index

Geographic region alone, however, did not explain all of the discordance. As seen in Figure 5.2, the median patient MJI at each clinical site was associated with the percentage of CABG-intended patients at each site (correlation coefficient R=0.53), yet there remained substantial variability in the decision to perform CABG across BARI 2D sites in both regions and at low and high levels of MJI. Among clinical sites with 10 or more patients, the percentage of CABG-intended patients varied from 0% to 74%, and notably, there were 3 sites (2 US and 1 non-US) in which no patients were recommended for CABG irrespective of the percentage of jeopardized myocardium.

We considered that this decision making process, particularly the US versus non-US variation, may have been influenced by factors related to the clinical sites per se rather than characteristics of individual patients. Unfortunately, very limited site-level data were collected in BARI 2D, including the ratio of surgeons to PCI operators, availability of off-pump surgery, and whether or not conduits other

than internal mammary artery and saphenous vein grafts (or 'alternate conduits') were used. Assessment of these site-specific characteristics as possible predictors of the treatment decision indicated minimal to no influence (data not shown).

5.3.2 Patient Characteristics Associated with CABG Selection

Patient characteristics related to intended revascularization with CABG (versus PCI) are presented in Table 5.2 for all patients, and separately for those in US and non-US regions. In the overall cohort, patients who were Hispanic or white (race), without a prior PCI and not taking anti-platelet agents at baseline were more likely to be recommended for CABG. In the US, patients who were male, age 65 years and older, and without a history of stroke or transient ischemic attacks were more likely to be deemed most suitable for surgical revascularization. These factors did not influence treatment selection outside of the US. Instead, demographic and clinical characteristics in non US regions that were associated with the decision to perform CABG included lower education, prior MI, and hypertension.

Angiographic characteristics associated with the decision to perform CABG are presented in Table 5.3. The prevalence of triple vessel disease was 53% overall, and nominally lower in the US compared to other regions (50% vs. 57%, respectively). Overall, angiographic factors related to treatment selection were consistent across US and non-US regions. Diabetic patients with triple (versus double) vessel disease were more likely to be recommended for CABG ($p<0.001$). Other angiographic characteristics associated with intended surgical revascularization included: number of vessels with ≥70% stenosis, increasing MJI, significant (≥50%) LAD and proximal LAD disease, presence of total occlusions and non-discrete lesions, and total number of lesions (irrespective of severity). Increasing number of class C lesions and significant lesions (≥50% or ≥70% stenosis), particularly those involving a proximal segment, were also associated with an increased likelihood of intended treatment with CABG. One angiographic factor that differed in its predictive value between the two regions was depressed left

ventricular function. Despite a very low prevalence of 5% in the overall cohort, ejection fraction <40% was related to recommendation for CABG in the US but not in non-US regions.

5.3.3 Multivariable Analysis Results

Adjusted odds of the intention to perform CABG versus PCI estimated using GEE are presented in Table 5.4. Among patients with diabetes and multivessel disease, angiographic characteristics indicating extent and severity of CAD were highly predictive of recommendation for CABG over PCI. The odds of selecting CABG was significantly higher among patients with triple (vs. double) vessel disease (OR=3.64, 95% CI 2.85-4.64; p<0.001) and presence (vs. absence) of proximal LAD stenosis ≥50% (OR=1.80, 95% CI 1.15-2.80; p=0.01), LAD stenosis ≥70% (OR=2.46, 95% CI 1.96-3.09; p<0.001), total occlusions (OR=1.78, 95% CI 1.30-2.44; p<0.001), and increasing number of class C lesions (OR=1.61, 2.13, and 3.62 for 1, 2, and 3+ lesions (vs. 0); all p<0.001). Several demographic and clinical factors were also predictive of treatment selection. The odds of selecting CABG over PCI was significantly higher in men (OR=1.25, 95% CI 1.03-1.51; p=0.02) and patients ≥65 years old (OR=1.38, 95% CI 1.11-1.73; p<0.01). Patients who had undergone prior PCI and those using antiplatelet agents were less likely to be recommended for CABG (OR=0.50, 95% CI 0.39-0.64, p<0.001; and OR=0.68, 95% CI 0.50-0.92, p=0.01, respectively). Independent of patient characteristics, this decision making process was significantly influenced by geographic region. Compared to the US, the odds of selecting CABG was significantly higher among patients seen in Canada and Europe (OR=1.81, 95% CI 1.03-3.20; p=0.04) and more than 4-times higher in Brazil and Mexico (OR=4.71, 95% CI 3.23-6.87; p<0.001).

5.4 DISCUSSION

In the present study, we evaluated factors influencing the selection of coronary revascularization strategy in patients with diabetes and stable multivessel disease in the BARI 2D trial. As expected, the decision to perform CABG over PCI was driven largely by angiographic features, reflecting existing limitations of PCI under certain anatomic circumstances, such as severe 3-vessel disease and total occlusions. Moreover, several angiographic characteristics that were closely related were independently predictive of treatment selection, suggesting that patient's anatomy is considered in aggregate in the treatment decision. For example, on average, patients with a total occlusion and a class C lesion are more likely to be recommended for CABG than patients with a single total occlusion alone.

In addition, several non-angiographic characteristics influenced treatment selection. In BARI 2D, men were more likely to be referred for CABG. It is well-recognized that women undergoing surgical revascularization experience worse perioperative outcomes compared to men,[38-41] and female gender has been identified as an independent risk factor in both the Society for Thoracic Surgeons risk modeling[42] and the EuroSCORE risk algorithm.[43] Clinicians may have taken this into consideration when deciding on treatment strategy. We also found that older age was associated with CABG selection. Although previous studies have shown old age to be a deterrent against surgical revascularization, BARI 2D has an inclusion criteria of 5-year expected survival and stable presenting clinical status; hence, age was apparently not judged to be a contra-indication to bypass surgery in this trial.

Patients who had undergone prior PCI and those using antiplatelet agents at baseline were less likely to be recommended for CABG. Per BARI 2D inclusion criteria, any previous revascularizations had to be at least one year prior to study enrollment, indicating that the most recent PCI was most likely initially successful without immediate need for re-intervention. In these patients, it is possible that clinicians and patients would be inclined to attempt PCI again. As for current patient use of antiplatelet agents, physician concern over an increased risk of perioperative bleeding is a possible explanation for selecting the less invasive percutaneous approach.

Importantly, not all factors influencing this decision-making process were features unique to individual patients, but rather, simply the individual clinical centers and geographic regions where patients were seen. Patients seen in countries outside of the US were much more likely to be selected for CABG compared to US patients even after taking into account differences in presenting profiles and disease severity. By covariance estimation, about one-third of the treatment decision process was made simply by the geographic region in which patients were seen. Moreover, even within individual regions, there were clear site differences in the preference for recommending CABG over PCI. These findings illustrate that in the absence of firm, unequivocal treatment guidelines, physician discretion plays a large role in determining patient revascularization treatment, and that factors (unidentified) associated with clinical centers and geographic regions augment, and possibly override, individual patient characteristics when there is no obvious clinical advantage for CABG over PCI.

5.4.1 Possible Explanations for Geographic Variation in Treatment Selection

Despite our in-depth multivariable analysis, it remains possible that regional variation in the decision to perform CABG over PCI can be explained primarily by intrinsic differences in patient risk profiles. Patients in the US (compared to those in other countries) did have, on average, less severe CAD and were slightly older and more educated, all of which seemingly influenced the more frequent recommendation for the less invasive and lower risk PCI. However, on the basis of our extensive individual-level dataset, differences in the distribution of the patient characteristics alone between US and non-US regions did not fully explain the variation in treatment decision. The greater reluctance to perform CABG in the US was demonstrated at every level of disease burden, and even after adjusting for patient characteristics and accounting for correlation within sites, region remained a strong independent predictor of treatment selection. Thus, we conclude that it is unlikely that the substantial influence of individual clinical center and geographic region on the selection of revascularization strategy is confounded by individual patient factors that were either not measured or controlled for in our analysis.

How might characteristics of the clinical centers and regions have played an influential role in the treatment decision of CABG versus PCI? First, differential access to invasive cardiac procedures outside of a research setting (such as BARI 2D) may be a factor. Previous studies have attributed the higher number of cardiac procedures performed in the US (compared to other countries) to greater availability of these procedures in the US.[30, 32] Given the potential for less, or delayed, accessibility to interventional procedures outside of the US (e.g. repeat procedures), we can speculate a predisposition toward recommending CABG, the more durable procedure, at centers outside of the US. This may be particularly likely given the higher rates of repeat revascularizations, primarily to treat target-vessel restenosis, among patients with diabetes following PCI.[44]

It is also possible that our observed site and regional variation in recommending CABG versus PCI was driven by unique characteristics of individual clinical centers, rather than geographic region per se. However, in BARI 2D, participating clinical sites had to meet minimal study-specific certification requirements for both PCI and CABG, including annual case volume. Thus, all participating centers were fully proficient in performing PCI and CABG. Moreover, among the few site-level variables collected, including the ratio of CABG surgeons to PCI operators, we found no association of such factors with treatment selection. Thus, there were no readily identifiable factors specific to individual clinical centers that appeared to influence treatment selection. Nonetheless, we cannot exclude unmeasured clinical and "corporate" climate, as well as financial considerations of individual hospitals, as being influential in the revascularization selection process.

Because the original BARI trial pre-dated the use of drug-eluting stents, Gp IIb/IIIa inhibitors, and other advances in coronary intervention, its recommendation for CABG over conventional balloon angioplasty in diabetic patients may have limited applicability to contemporary practice. McGuire and colleagues evaluated the influence of BARI results on practice patterns in the US two years after the Clinical Alert was issued.[45] They reported significant variability in revascularization strategy used to treat patients with diabetes and multivessel CAD and concluded that the original BARI results did not have an impact on practice patterns in the US. Nearly 10 years later, we find in the BARI 2D trial that there is

still little consensus regarding the most appropriate method of revascularization in diabetic patients with stable multivessel disease. We will look to the FREEDOM trial to help elucidate the optimal revascularization strategy in this high-risk population.

5.4.2 Study Limitations

Two issues may limit the generalizeability of our results. First, enrollment in the BARI 2D trial occurred as the first generation of drug eluting stents was introduced. Current trends demonstrate that indications for percutaneous intervention with DES have expanded to include patients who, historically, would have been treated with bypass surgery. This decision-making process continues to evolve since BARI 2D started, which may limit the relevance of our findings. Second, participating clinical sites in this trial are established centers of excellence that deliver quality medical care both in and outside of the US. As a result, practice patterns in these centers may not reflect general practice, which often include smaller community-based hospitals. In addition, our investigators and patients from Brazil and Mexico were from a single center, and it is unclear how representative these particular sites are of their respective countries at large. However, since the choice of revascularization strategy was at the discretion of local physicians, the decision to perform CABG observed in BARI 2D study centers likely reflect usual practice in these particular centers.

5.5 CONCLUSION

Among patients with diabetes and stable multivessel CAD in the BARI 2D trial, the decision to perform CABG over PCI was related to angiographic features associated with extent, location, and nature of CAD, as well as demographic and clinical factors. However, patient characteristics were not absolute in determining the method of revascularization. Treatment selection was also influenced by geographic

region, with a greater propensity to recommend PCI in the US. There was substantial variation in treatment selection across geographic regions, and among clinical sites within regions, indicating that physician discretion plays an important role in this decision making process.

5.6 ACKNOWLEDGEMENT

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Table 5.1 Intended revascularization strategy by geographic region

	No. of Sites	No. of Patients	CABG		PCI		*P*-value
			n	Row%	n	Row%	
US	40	910	283	31%	627	69%	<.001*
Non-US	9	682	419	61%	263	39%	
Canada	5	271	128	47%	143	53%	<.001†
Europe	2	57	32	56%	25	44%	
Brazil	1	292	212	73%	80	27%	
Mexico	1	62	47	76%	15	24%	
Total	49	1592	702	44%	890	56%	

Row percentages are presented.

Excludes patients with prior CABG (n=149) and single vessel disease (n=601)

***** Chi-square p-value compares treatment selection in US versus non-US regions.

† Chi-square p-value compares treatment selection across the 5 regions.

Table 5.2 Baseline characteristics associated with intention to perform CABG (versus PCI)

		All Sites (N=1592)			**US** (n=910)			**Non-US** (n=682)		
		No. of Patients	Intended CABG	*P**	n	Intended CABG	*P**	n	Intended CABG	*P**
DEMOGRAPHIC PROFILE										
Sex	Male	1149	46%	<.01	640	34%	<.01	509	62%	0.68
	Female	443	38%		270	24%		173	60%	
Age	< 65 y/o	949	42%	0.06	514	27%	<.01	435	60%	0.31
	≥ 65 y/o	643	47%		396	36%		247	64%	
Race	White (non-Hisp)	1054	47%	<.001	533	33%	0.04	521	61%	<.01
	Black (non-Hisp)	251	31%		208	24%		43	67%	
	Hispanic	198	48%		134	36%		64	75%	
	Other	89	36%		35	26%		54	43%	
≥ High School educ	No	619	55%	<.001	224	31%	0.90	395	68%	<.001
	Yes	968	37%		682	31%		286	52%	
Health insurance	Public	1155	49%	<.001	519	33%	0.26	636	61%	0.03
	Private	368	32%		330	28%		38	68%	
	None/ Self pay	67	27%		60	28%		7	14%	
CLINICAL HISTORY										
Prior MI	No	1065	41%	<.01	641	30%	0.35	424	58%	0.02
	Yes	501	50%		255	33%		246	67%	
Prior PCI	No	1306	47%	<.001	713	34%	<.001	593	63%	0.01
	Yes	285	29%		196	20%		89	48%	
Anti-platelet agent use	No	1304	47%	<.001	705	34%	<.001	599	63%	0.09
	Yes	285	30%		204	21%		81	53%	
Current insulin use	No	1170	47%	<.001	617	33%	0.06	553	62%	0.65
	Yes	422	37%		293	27%		129	60%	
Hypertension	No	271	41%	0.26	139	31%	0.97	132	52%	0.01
	Yes	1300	45%		766	31%		534	64%	
Stroke/ TIA	No	1425	45%	0.01	794	32%	0.02	631	61%	0.64
	Yes	160	34%		112	21%		48	65%	
Angina status	No angina	290	41%	0.09	170	29%	0.44	120	59%	0.15
	Atypical angina	348	43%		227	35%		121	57%	
	Stable class I/II	683	46%		336	32%		347	61%	
	Stable class III/IV	139	50%		69	29%		70	70%	
	Unstable angina	132	36%		108	26%		24	79%	

Row percentages are presented.

* Chi-square test p-values compare percentage of CABG-intended patients for groups defined by the variables listed

Table 5.3 Angiographic characteristics associated with intention to perform CABG (versus PCI)

		All Sites (N=1592)			**US** (n=910)			**Non-US** (n=682)		
		No. of Patients	Intended CABG	*P**	n	Intended CABG	*P**	n	Intended CABG	*P**
Clinical Site Measurements										
Vessel disease	Double	745	25%	<.001	453	16%	<.001	292	40%	<.001
	Triple	847	61%		457	46%		390	77%	
LAD ≥ 50% stenosis	No	202	17%	<.001	130	11%	<.001	72	29%	<.001
	Yes	1390	48%		780	34%		610	65%	
No. of vessels w/ ≥ 70% stenosis †	0	44	11%	<.001	32	0%	<.001	12	42%	<.001
	1	366	22%		242	14%		124	39%	
	2	712	39%		408	28%		304	53%	
	3	470	72%		228	59%		242	85%	
LAD ≥ 70% stenosis	No	510	24%	<.001	334	16%	<.001	176	39%	<.001
	Yes	1082	54%		576	40%		506	69%	
Any total occlusions	No	1015	34%	<.001	632	23%	<.001	383	52%	<.001
	Yes	577	62%		278	49%		299	74%	
Ejection fraction < 40%‡	No	1424	45%	0.47	794	30%	<.01	630	63%	0.55
	Yes	82	49%		64	47%		18	56%	
Core Lab Measurements										
Myocardial jeopardy †§	≤ 25%	158	18%	<.001	110	11%	<.001	48	33%	<.001
	26-50%	443	34%		262	22%		181	51%	
	51-75%	467	58%		242	45%		225	71%	
	76-100%	238	72%		99	65%		139	78%	
Total number of lesions †	≤ 3	301	26%	<.001	173	13%	<.001	128	43%	<.001
	4	325	38%		185	23%		140	57%	
	5	303	46%		175	31%		128	66%	
	6	248	49%		137	38%		111	63%	
	≥ 7	414	58%		239	46%		175	74%	
No. of lesions ≥ 50% †	≤ 1	272	17%	<.001	191	8%	<.001	81	37%	<.001
	2	401	33%		224	25%		177	44%	
	3	377	49%		213	34%		164	68%	
	≥ 4	541	62%		281	49%		260	77%	
Proximal LAD ≥ 50%	No	1363	41%	<.001	799	28%	<.001	564	59%	0.01
	Yes	228	62%		110	52%		118	72%	
No. of Proximal lesions ≥ 50% †	0	622	34%	<.001	373	20%	<.001	249	54%	<.001
	1	660	45%		371	32%		289	61%	
	2+	309	63%		165	53%		144	75%	
No. of Class C lesions †	0	678	29%	<.001	435	20%	<.001	243	45%	<.001
	1	567	50%		304	39%		263	64%	
	2	221	63%		109	50%		112	77%	
	3+	106	76%		44	59%		62	89%	
Any non-discrete lesions	No	781	39%	<.001	452	25%	<.001	329	58%	0.06
	Yes	791	50%		440	38%		351	65%	

Row percentages are presented.

***** Chi-square p-values compare percentage of CABG-intended patients for groups defined by variables listed; † Cochran-Armitage trend test $P < 0.05$; ‡ Ejection fraction missing for 86 patients; § Excludes patients with prior PCI (n=285)

Table 5.4 GEE model for predictors of intended revascularization with CABG (versus PCI)

	Adjusted OR	95% CI	*P* -value
Geographic Region			<0.01
Canada & Europe (vs. US)	1.81	1.03 - 3.20	
Brazil & Mexico (vs. US)	4.71	3.23 - 6.87	
Male gender	1.25	1.03 - 1.51	0.02
Age ≥ 65 years	1.38	1.11 - 1.73	<0.01
Prior PCI	0.50	0.39 - 0.64	<0.001
Use of anti-platelet agents	0.68	0.50 - 0.92	0.01
Triple vessel disease	3.64	2.85 - 4.64	<0.001
Proximal LAD ≥ 50% stenosis *	1.80	1.15 - 2.80	0.01
LAD ≥ 70% stenosis	2.46	1.96 - 3.09	<0.001
Any total occlusions	1.78	1.30 - 2.44	<0.001
No. of class C lesions *			<0.01
1 (vs. 0)	1.61	1.22 - 2.14	<0.001
2 (vs. 0)	2.13	1.37 - 3.32	<0.001
3+ (vs. 0)	3.62	1.77 - 7.41	<0.001

OR indicates odds ratio; CI confidence interval.

* Indicates core lab measurement; all other angiographic variables were based on site evaluation.

6.0 GENERAL DISCUSSION

6.1 SUMMARY OF FINDINGS

The objective of this dissertation was to evaluate myocardial revascularization in patients with multivessel coronary disease. Contemporary statistical methods were applied to investigate predictors of long-term prognosis and factors related to selection of revascularization strategy in the BARI and BARI 2D cohorts, respectively.

In *Research Paper 1*, treatment with CABG had a different effect on specific causes of death. Specifically, CABG was associated with a lower risk of sudden cardiac death, but did not significantly impact any other causes of long-term mortality. Moreover, the protective effect of surgical treatment was observed in patients with and those without diabetes. These results may have clinical implications for guiding revascularization strategy in individuals at high risk of sudden death. In this select group of patients, CABG may be the preferred method of initial revascularization.

Research Paper 2 evaluated the need for additional procedures following successful initial balloon angioplasty. In BARI, male gender, proximal LAD disease, and incomplete revascularization were associated with a significantly increased risk of a first repeat revascularization but not latter events. This may be explained by a higher likelihood, among patients with these characteristics, to receive CABG as the first subsequent treatment. Diabetes and extensive coronary disease were also predictive of a first repeat revascularization event, but the detrimental impact of these factors on the number of recurrent procedures remained consistent over time, underscoring the importance of intensive risk factor modification to limit disease progression.

In *Research Paper 3*, angiographic features associated with the extent and location of coronary disease greatly influenced the decision to perform CABG over PCI in patients with diabetes and stable multivessel disease. Gender, age, prior PCI, and use of anti-platelet agents at baseline also played a role in treatment selection. However, this decision making process was not entirely based on patient factors; geographic region also played an important role, with a greater propensity to recommend PCI in the US compared to other countries of origin. We also found that selection of revascularization strategy in varies substantially across individual clinical sites. These results demonstrate the need for rigorous evaluation of revascularization strategy in diabetic patients and other select high-risk subgroups and the factors that guide this decision making process in current practice.

6.2 IMPACT OF DIABETES ON LONG-TERM PROGNOSIS

Although diabetes was not the main focus of any of the papers, it turned out to be an important finding in both long-term evaluations of the BARI cohort. In *Research Paper 1*, diabetes was shown to be a powerful, independent predictor of overall mortality and each specific cause of death in patients with multivessel disease undergoing initial revascularization. Percutaneous intervention studies have consistently reported higher rates of subsequent revascularization in patients with, compared to those without, diabetes. *Research Paper 2* extended these previous findings by demonstrating a persisting effect of diabetes on the increasing *number* of additional procedures. Even after statistically adjusting for other confounding factors, diabetes was associated with an estimated 43% increase in the rate of subsequent revascularization over 10 years after initial PCI; in a 'lower risk' subgroup that was less subject to survival and selection bias, the risk increase was an estimated 74%. Overall, these results support prior studies demonstrating worse long-term prognosis for diabetic patients following coronary revascularization.

6.3 UTILITY OF CONTEMPORARY STATISTICAL PROCEDURES

Among clinical researchers, the importance of study design and methodological issues that may lead to bias are widely understood. This is one of the reasons BARI has been well received and cited in medical literature, and results from BARI 2D are anticipated. What is not as widely or uniformly appreciated is the important role of rigorous and appropriate statistical analyses. Conclusions drawn from a study are only as good as the quality of the data and the inferential procedures that are applied to them. The application of contemporary, computationally-intensive statistical methods in this dissertation illustrate what can be gained by exploring new ways of looking at data, and also the importance of applying the appropriate methods.

Multiple events modeling proved to be especially useful in the evaluation of long-term outcomes. Since cardiovascular disease is a progressive, life-long disease with multi-factorial etiology and concomitant risk factors, CVD trials often have long follow-up periods during which participants may experience various number and types of clinical events. Application of WLW and PWP regression allowed us to evaluate the incremental effect of risk factors (i.e. diabetes) and recurrence of adverse events (i.e. repeat procedures) as measures of increasing disease burden. As a result, we were able to gain new insights into the BARI cohort. Furthermore, incorporation of more clinical endpoints allowed us to make statistical inferences based on a larger data pool. A statistical advantage of modeling multiple events is the potential to add power to the analysis, which is particularly useful when modeling very rare outcomes or multiple recurrences of a single event type. Despite the apparent advantages, statistical methods for analyzing multiple events data are underutilized in clinical research. A likely explanation is that these are computationally intensive procedures that, until recently, were not widely supported by statistical software.

GEE models, on the other hand, are commonly used in clinical trials to analyze longitudinal or repeated measures data and, to a lesser extent, in multicenter trials when there is reason to believe that clinical outcomes may be related to the clinical center where treatment was administered. Whereas the

advantage of multiple events models have to do with increased efficiency and being able to examine the data in a new way, application of GEE models has to do with selecting the appropriate inferential procedure for the data at hand. Exploratory analysis of the BARI 2D cohort revealed substantial variation across clinical sites in selection of revascularization strategy and varying degrees of correlation within sites. As a result, GEE modeling was used to account for clustering in our data in order to obtain more accurate estimates for our patient-level outcome of interest. Failure to address this violation of independent observations would have resulted in underestimated standard errors, and thus, artificially low p-values and narrow confidence intervals, which may have led us to erroneously conclude that some relationships were statistically significant when in fact, they were not. This may be more than a minor technical issue in the field of interventional cardiology where fast-paced innovations necessitate continual re-evaluation of treatments, and in some instances, require practice guidelines to be updated in order to reflect the best available evidence. In this context, a series of reports committing a type I error as a result of inappropriate statistical analyses could have severe consequences.

6.4 RELEVANCE OF BARI RESULTS IN THE CURRENT ERA

Since BARI participants underwent initial treatment more than a decade ago according to the medical standards of that time, it is possible that recent advances in therapy (introduction of drug-eluting stents, in particular) may limit the generalizeability of BARI results to current practice. Reports from randomized trials of bare metal stents[79, 80] and drug-eluting stents[81, 82] have demonstrated superiority of intracoronary stents over conventional balloon angioplasty in drastically lowering the incidence of restenosis. Since restenosis is a time-related phenomenon that is limited to the early follow-up period, there is little reason to believe that our results on the *long-term* need for additional revascularizations, which is driven by progression of native disease, would be greatly altered by innovations in PCI. Additionally, contemporary and conventional PCIs have not been shown to have a significantly different effect on

mortality or MI, which suggests that our findings regarding specific causes of death may also be relevant in the current era.

6.5 ROLE OF BARI AND BARI 2D IN CORONARY INTERVENTION TRIALS

Randomized clinical trials and registries have provided extensive evidence regarding the effectiveness and preferred method of coronary revascularization in specified patient subgroups. The invaluable and unique contribution of BARI, in this broader context, was in establishing the role of diabetes in efficacy of revascularization treatment and atherosclerotic disease progression. BARI has been instrumental in identifying diabetic patients as a 'special' population who are not only higher-risk but also *different* in terms of disease mechanism and response to treatment. BARI 2D builds on these lessons learned from BARI and brings it into contemporary practice by incorporating new technologies and intensive modification of cardiovascular risk factors.

The BARI and BARI 2D trials represent a body of research encompassing over 20 years, and as such, evaluation of these cohorts provided a unique opportunity to investigate and address a variety of issues. As medical innovations continue to increase longevity, long-term outcomes are of great interest in coronary intervention studies. With over 10 years of follow-up, a major strength of BARI is the richness of the data which provide opportunities to dig deep into statistical analyses. However, evolution of coronary revascularization devices and techniques in the last decade naturally bring to question the relevance of BARI results to current clinical practice. Evidence to date suggests that contemporary and conventional percutaneous interventions do not differ with respect to death and MI, but to what extent innovations in PCI will challenge BARI results in the long run remains to be seen. Despite promising short-term results, use of drug-eluting stents and Gp IIb/IIIa are currently lacking in long-term outcomes data, and efficacy has yet to be determined from randomized trials which are still ongoing. In the

meantime, what factors should guide patient care? These are some of the important issues and questions that will continue to be addressed by BARI 2D and other coronary intervention trials in the future.

6.6 PUBLIC HEALTH SIGNIFICANCE

Diabetes has rapidly evolved into a major public health concern. Our findings in the BARI cohort support previous reports of a significantly worse prognosis in diabetic patients following myocardial revascularization. Even after statistically adjusting for other confounding factors, the detrimental impact of diabetes on mortality as well as need for multiple repeat revascularizations was apparent. These results underscore the importance of aggressive modification of CVD risk factors, especially glycemic control, to slow down the progression of atherosclerosis, which will be critical to long-term success in the diabetic population. Given the enormous scope of diabetes and CVD, even very modest improvements in clinical outcomes may translate into significant gains from a public health perspective.

For the population at large, coronary interventions are safer and more effective than ever before, and continued progress in tertiary care will be critical to maintaining the gains that have been made. However, there is an irony in the way in which the medical advances that help extend the lives of individuals with ischemic heart disease (which represents a *decrease* in disease burden) simultaneously create generations living longer with this chronic and debilitating disease (which represents an *increase* in burden). This 'shift' in the burden of CVD brings us back to the importance of disease prevention. The alarming rise in recent years in the incidence of diabetes, obesity, and other unattended risk factors in younger generations are a stark reflection of lagging public health efforts in the primary and secondary prevention of CVD.

6.7 FUTURE RESEARCH

Our findings bring to light several areas that warrant further research. There is a great need to find cost-effective approach to slowing down atherosclerotic disease progression, particularly in patients with diabetes. The BARI 2D and FREEDOM trials will help elucidate the optimal CAD treatment strategy in the diabetes population. By incorporating the latest technology and adjunctive therapies, these trials will provide invaluable information regarding whether, and to what extent, these improvements benefit patients with diabetes in the long-term, as these data will help guide clinical practice and future research. Since the number of studies dedicated to examining CAD in the diabetes population is very limited, much could be gained by encouraging future clinical and epidemiological studies to pre-specify an adequate number of participants with diabetes to allow for sufficiently powered subgroup analyses.

Improved management of cardiovascular risk factors in recent decades has led to marked declines in cardiac mortality in the general population but not in the diabetes subset, who bear a significantly greater CVD burden. In previous studies, aggressive medical management including strict glucose control,[83] angiotensin-converting enzyme (ACE) inhibitors,[84] beta-blockers,[85] and aspirin[84, 85] has been associated with significantly improved long-term survival following acute MI in patients with diabetes. In fact, use of ACE inhibitors was shown to be even more effective in diabetic versus non-diabetic patients.[84] These data suggest that failure to apply proven therapies may explain, at least in part, why the diabetic population has not benefited from the reduction in coronary deaths observed in the population at large. Further research is needed to better understand why this has been the case.

Lastly, application of contemporary statistical methods that maximally utilize existing data can offer new insights into disease processes. Compared to recommendations that require collection of new data, this recommendation is cost-effective, can be easily and readily implemented, and potentially lead to important findings. An increasing availability of user-friendly statistical software that supports these computationally-intensive methods will likely encourage wider application of these procedures in clinical research.

APPENDIX

ADDITIONAL TABLES AND FIGURES FOR *RESEARCH PAPER 2*

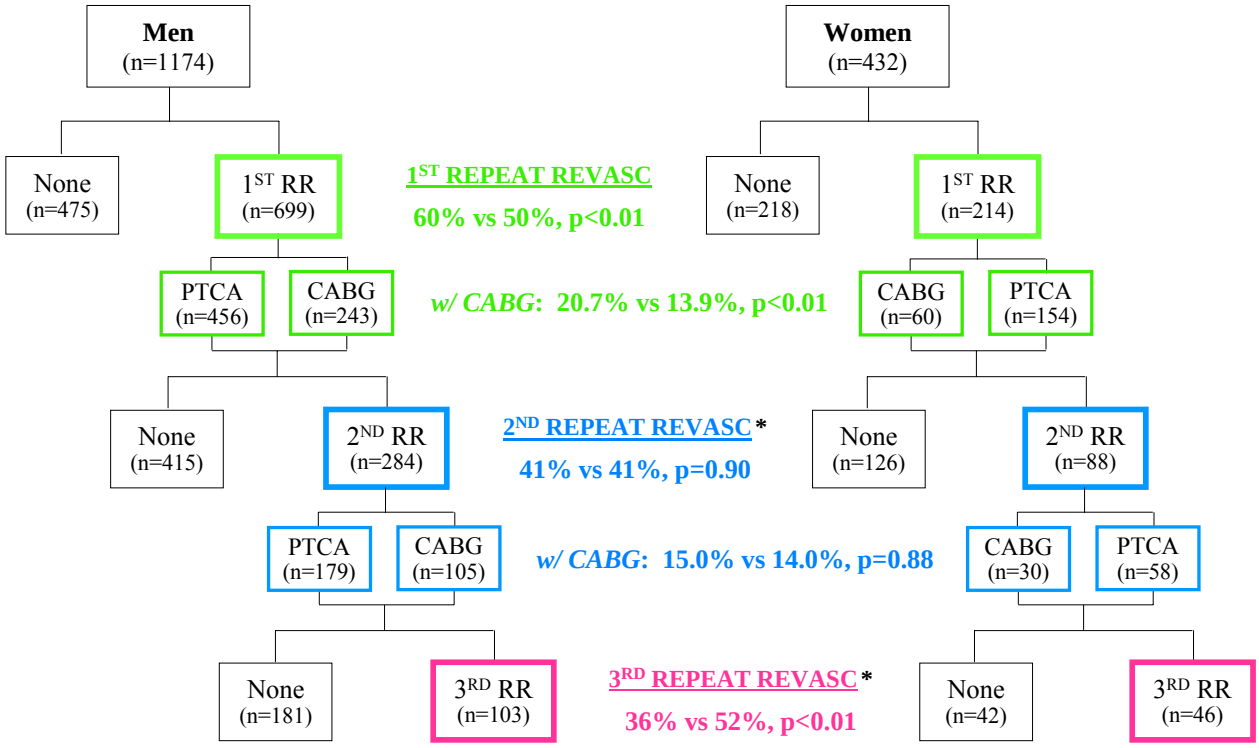
Table A6.1 Cumulative number of subsequent procedures over 10 years of follow-up

Number of Repeat Procedures	No. of Patients (N=1606)	Cum. Percent	Cum. Number of Procedures	Cum. Percent	
0	693	43%	0	0%	1236 Procedures Included in Analysis
1	541	77%	541	35%	
2	223	91%	987	64%	
3	83	96%	1236	80%	
4	32	98%	1364	88%	309 Procedures Not Included in Analysis
5	18	99%	1454	94%	
6	7	99%	1496	97%	
7	2	<100%	1510	98%	
8	4	<100%	1542	<100%	
9	0	<100%	1542	<100%	
10	1	<100%	1543	<100%	
11	1	<100%	1544	<100%	
12	1	100%	1545	100%	

Table A6.2 Comparison of PWP model estimates in the overall cohort and lower risk subgroup

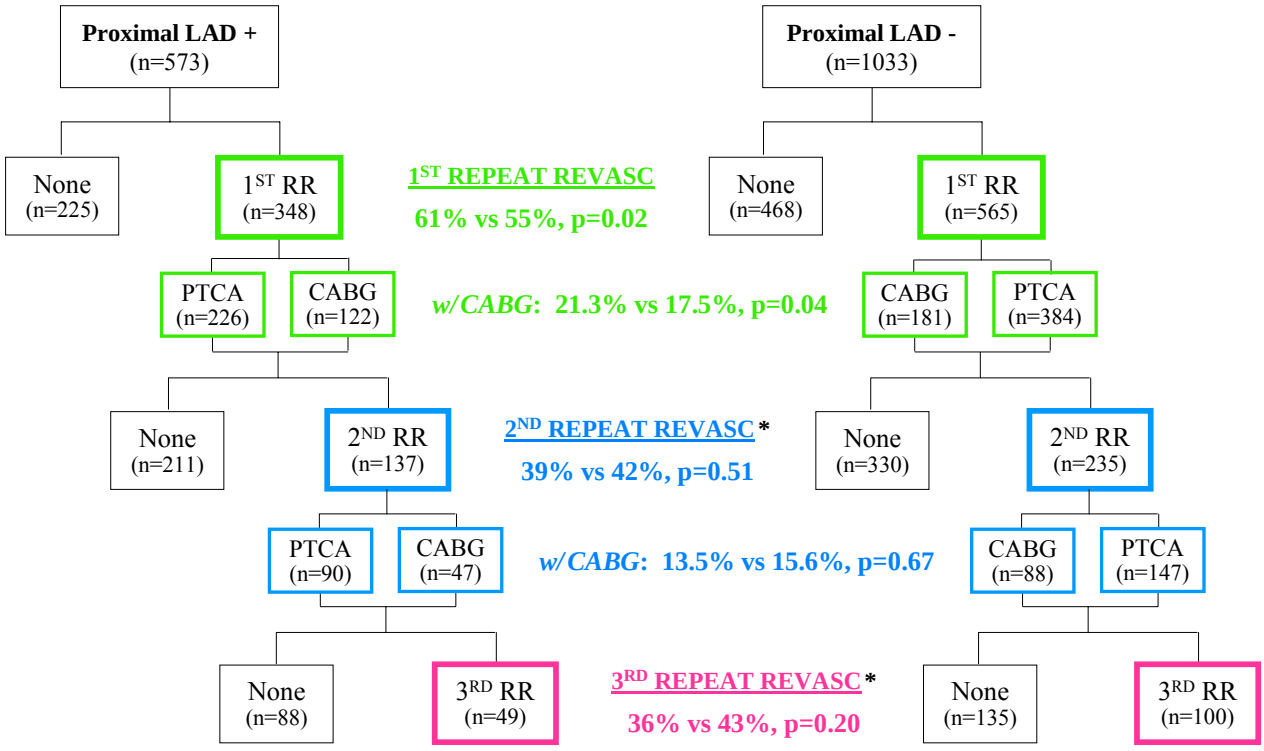
	Repeat Revasc. Event Number	**All Patients** (N=1606)		**Lower Risk*** (n=1124)	
		RR	P-value	RR	P-value
Male Gender	1	1.44	<0.001	1.57	<0.001
	2	1.00	0.97	1.08	0.64
	3	0.64	0.01	0.54	0.01
Diabetes		1.43	<0.001	1.74	<0.001
Renal Dysfunction		1.75	<0.001	4.01	<0.01
Age ≥ 65 Years		0.84	<0.01	0.93	0.31
Smoking History	1	0.71	<0.001	0.68	<0.001
	2 and 3	0.96	0.63	1.05	0.69
ST Elevation		0.52	<0.001	0.54	0.01
Unstable Angina		1.15	0.01	1.12	0.07
Proximal LAD Disease	1	1.24	<0.01	1.25	0.01
	2 and 3	0.95	0.58	0.90	0.31
Diffuse Lesions		1.13	0.03	1.15	0.05
Incomplete Revascularization	1	1.13	0.07	1.17	0.05
	2 and 3	0.86	0.09	0.83	0.07

* Patients with propensity scores in the lower 70th percentile were considered to have a lower predicted probability of death. Unadjusted 10-year mortality rates were 26% in the overall cohort and 16% in the lower risk strata; repeat revascularization rates in these groups were 42% and 41%, respectively.



* Percentages are among patients who had a prior repeat revascularization event within each strata

Figure A6.1 Comparison of repeat revascularization strategies by gender



* Percentages are among patients who had a prior repeat revascularization event within each strata

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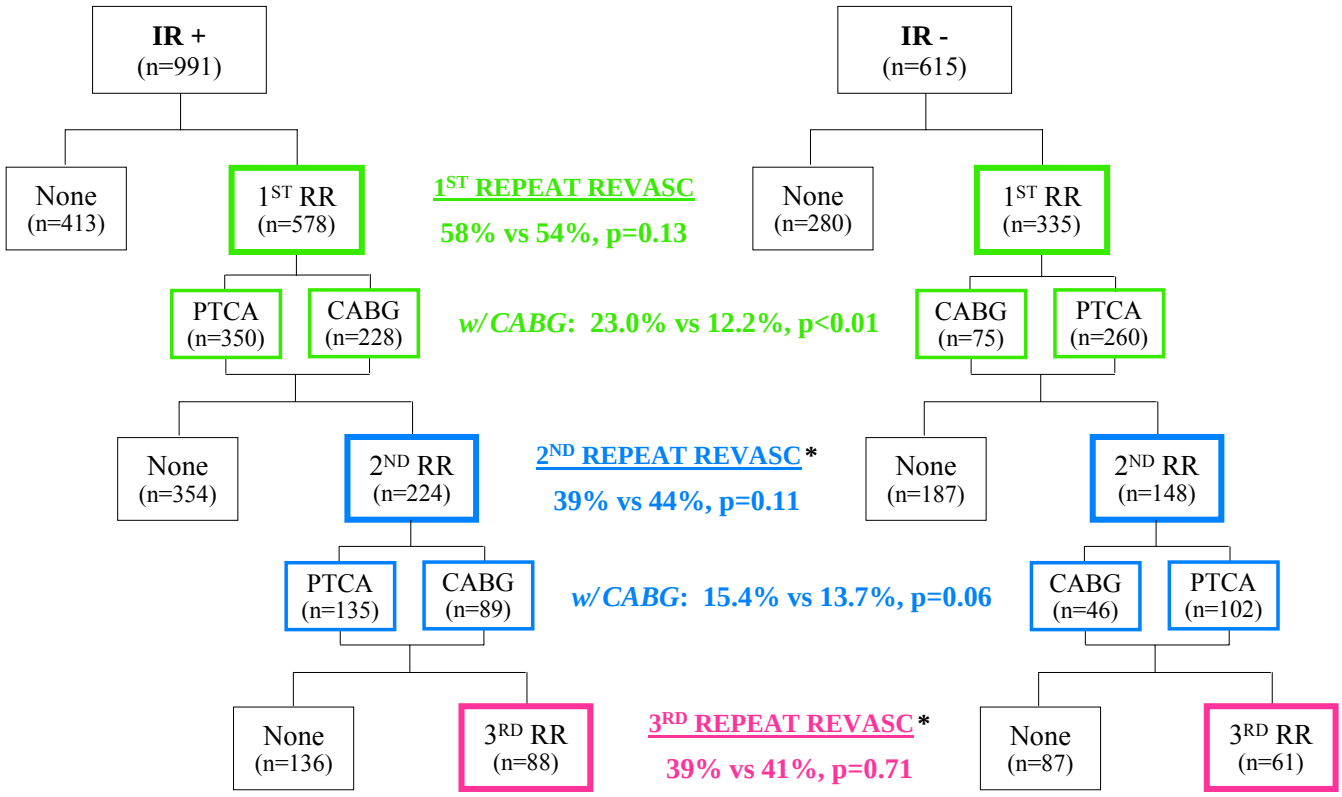
Figure A6.2 Comparison of repeat revascularization strategies by proximal LAD disease status



* Percentages are among patients who had a prior repeat revascularization event within each strata

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Figure A6.3 Comparison of repeat revascularization strategies by incomplete revascularization (IR) status

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