Quality of Life Outcomes Following Treatment for Coronary Artery Disease

by

Colleen Marie Norris ©

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DEDICATION

This is dedicated to my beautiful sister Frances who always believed in my abilities. She was and will always be the angel on my shoulder.

ABSTRACT

For many patients with multi-vessel coronary artery disease (CAD), coronary artery bypass grafts (CABG), percutaneous coronary interventions (PCI), and/or medical management are all clinically feasible treatment options. Given the increasing prevalence of treatment strategies as well as the lack of significant evidence regarding treatment supremacy, this present research evaluated the quality of life (QOL) outcomes one year following catheterization in an inception cohort of Alberta patients with multi-vessel CAD.

This study was divided into three distinct stages. First, a method of enhancing missing clinical data with administrative data was developed and validated. Second, a comprehensive literature review of all studies that cited and/or used the Seattle Angina Questionnaire (SAQ) identified that while the SAQ has been and continues to be in widespread use, investigators need to increase their attention to the distributional characteristics of their SAQ QOL data before applying parametric tests. Furthermore, when there is pronounced non-normality in the SAQ scale distributions, the proportional odds ordinal regression model appears to be responsive to the characteristics, specifically the ordinality, of the SAQ data. Third, using enhanced data and ordinal regression, a study was done to measure and compare the QOL outcomes of patients with CAD, treated with different strategies.

The analytical cohort for this study included 3392 patients from the Alberta Provincial project for Outcome Assessment in Coronary Heart Disease (APPROACH) who responded to the follow-up survey one year following their index catheterization. Results indicated that those patients who were revascularized either with PCI including PTCA or stents, or CABG tended to have better QOL at follow-up when compared to patients treated with medical management. As well, men reported better QOL at follow-up compared to women. Younger respondents reported the highest exertional capacity at one-year follow-up, yet also reported the least satisfaction with treatment and the most perceived burden of disease.

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CHAPTER 1

INTRODUCTION

1.0 Overview

The thesis introduction presents an overview of the issues surrounding the quality of life (QOL) outcomes of treatment for coronary artery disease (CAD). The specific aims of the research are subsequently discussed. This is followed by a literature review and the series of papers relating to risk-adjusted quality of life (QOL) following treatment of coronary artery disease. These include a) a comparison of methods to deal with missing data needed for risk-adjustment in observational health care outcome analysis, b) critique of the methods used for comparing Seattle Angina Questionnaire (SAQ) scores in published papers and, a comparison of the results of different statistical methods for comparing SAQ scores, and c) comparison of risk adjusted SAQ data for Coronary Artery Bypass Graft (CABG), Percutaneous Coronary Intervention (PCI) including both percutaneous coronary balloon angioplasty (PTCA) and stents (Stent), and medically treated patients with CAD. Each of the three papers is complete within itself, yet contributes to the overall evaluation of QOL outcomes for patients undergoing treatment for CAD. The final section draws links between the papers and makes recommendations for future research. The results from all three papers are discussed in relation to existing literature.

1.2 Preamble

The objective of this thesis was to use the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database to risk adjust and compare the QOL outcomes of patients treated for CAD. The realization of the analysis to a seemingly straightforward clinical research question yielded a number of

obstacles that needed to be overcome prior to attempting to discern whether there truly were QOL differences among CAD treatment groups.

The first hurdle of this methodological journey became apparent when it was discovered that the APPROACH data, a relatively new database, contained a substantial amount of missing data. As the objective of the research was to risk adjust the SAQ QOL outcome scores by controlling for clinical variables, the missing data issue needed to be resolved in order to proceed. Missing data replacement methods were explored and a "data enhancement" methodology whereby APPROACH data was 'enhanced' with Administrative data, was developed and validated.

The next obstacle was discovered when descriptive statistics of the QOL outcome SAQ scale scores indicated that the data was not normally distributed. As a result, a comprehensive literature review was done to determine how the SAQ had been analyzed in published outcome studies to date. The literature review failed to identify the most appropriate statistical analysis for SAQ outcome data. Consequently, a second methodological study was undertaken to compare 4 methods for analyzing SAQ outcome data. Based on the results of that study, ordinal regression modeling was used to compare QOL outcomes for patients treated for CAD.

It was now possible to turn to the original question of this research: Using 1) "enhanced APPROACH clinical data" and 2) ordinal regression analysis, 3) compare SAQ QOL outcome scores of patients treated for CAD controlling for baseline clinical variables.

1.2 Statement of the Problem

1.2.1 Treatment for CAD

CAD is the leading cause of death and disability in Canada and the United States and therefore continues to be the focus of intensive research efforts aimed at improving the treatment of patients with this chronic disease. Over the last 20 years, there has been

a shift in the management of CAD from predominantly medical therapy to an increasing use of revascularization procedures (1, 2). As a result, diagnostic cardiac catheterization (CATH), PCI, and CABG have become very common procedures. A CATH is an invasive diagnostic test used to identify ischemic changes in the coronary arteries whereas PCIs, CABGs and medical management are treatments for CAD. A PCI can be 1) PTCA, a procedure in which a specially constructed catheter with a small balloon on the tip is inserted in an artery in the groin or arm, threaded into a coronary artery and used to open up a blockage or 2) the deployment of a Stent – a coil-like device which opens and holds the blockage back against the wall of the artery. In a CABG procedure, blood flow to the heart is re-routed around the site of the coronary artery blockage by bypassing the blockage via anastomosed saphenous veins or arteries arising from branches off the aorta. These vessels are then connected to the coronary arteries downstream from the blockage. Medical management consists of using pharmacological agents to control the progression of CAD and reduce the symptoms associated with the disease.

For many patients with multi-vessel CAD, CABG, PCI, and/or medical management are all clinically feasible treatment options. A Medline search identified seven randomized control trials (RCTs) (3-8) and one meta–analysis (9), comparing the outcomes of CABG versus PTCA treatments for multi-vessel CAD. Primary and secondary outcomes in the trials included mortality at one year, revascularization rates, anginal frequency post procedure, and/or combined endpoints including all three. Even though there were important differences in the design and endpoints of all of the RCTs, their results measured at follow-up, consistently showed *non-significant differences in survival*, and *non-significant differences in the incidences of nonfatal myocardial infarctions* of patients treated with CABG or PTCA. In spite of the positive outcomes for revascularization treatments of multi-vessel CAD, as yet no clear criteria exist for the choice of which treatment option is the most appropriate based on the patient's presenting

symptoms and the results of the CATH. The controversy over the best treatment for CAD was evidenced by a recent consensus study, which reported that coronary revascularization 'experts' failed to agree in strategy appropriateness in 40 - 60% of clinical scenarios presented to them (10). This difference in agreement as to the most appropriate therapeutic option for patients with CAD is reflected in the CATH and treatment numbers for the province of Alberta.

With a population of approximately three million people, Alberta has two centers that perform catheterizations and subsequently treat patients with CAD. From January 1st 1997 until December 31st 2000, the total number of diagnostic cardiac catheterization procedures performed in Edmonton (n=18139), was relatively similar to the Calgary total (n=20883). Subsequent treatment strategies differed. Whereas the Edmonton cardiovascular surgical center performed slightly more CABG procedures relative to the number of catheterization, than the total at the Calgary center, (27% to 22%), Edmonton centers performed almost one quarter less angioplasty procedures relative to catheterizations, than did the Calgary centers (37% to 40%). The percent of catheterized patients treated medically in Edmonton and Calgary were 36% and 38% respectively. These differences, as well as the need for evidence about the relative effectiveness of different treatment options were the impetus for the development of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH).

1.2.2 Clinical data used to risk adjust QOL data

The APPROACH Project, a province-wide inception cohort of all adult Alberta residents undergoing cardiac catheterization, was initiated to study provincial outcomes of care and facilitate quality assurance/quality improvement for patients with coronary artery disease in Alberta. The APPROACH database contains detailed clinical information on adult patients with known or suspected CAD. Patients in APPROACH are followed longitudinally after cardiac catheterization, thus allowing for assessment of subsequent

procedure use (i.e., PTCA, stent or CABG), as well as outcomes such as mortality and quality of life. The use of the APPROACH database, which includes the total population of patients catheterized in Alberta, offers a unique opportunity to compare quality of life outcomes of patients treated with the therapeutic treatment options. One of the limitations of the APPROACH database prior to 1999, (inclusive of the sample used in this analysis) was that there were no measures of patients socio-economic status or ethnicity. APPROACH now includes those important variables. As well although information on smoking history and current status is collected, this variable was not included in the analysis due to concerns about the validity of these data.

In the process of attempting to study the QOL outcomes two separate yet related issues were identified that needed to be addressed prior to moving ahead. These included 1) how to deal with missing clinical data used to adjust the QOL scores and 2) the most appropriate statistical tests to use in the analysis of the Seattle Angina Questionnaire.

Prospective clinical databases like APPROACH are potentially valuable tools for studying outcomes of health care. Much of the published outcome research in health care relies on administrative databases with limited clinical information about patients. Multivariable risk adjustment based on administrative data is therefore constrained from the outset by the lack of details on important prognostic factors. Clinical databases like APPROACH are better able to explain inter-provider differences in outcomes than are administrative databases. As Hannan et al.(11) have demonstrated, the advantage of clinical databases comes from the ability to select and capture prospectively those clinical variables that are important prognostically and have no comparable diagnostic code in administrative data. However, when more detailed databases are developed, costs rise as does the likelihood that some data for some patients will not be collected. Cases with missing values for any one of the variables entered into a model

unfortunately cannot be used in multivariable analysis, unless the missing data is replaced.

1.2.3 Replacing missing data in APPROACH

Common methods for handling missing covariate values include stratification on missing-data status, conditional-mean imputation, and complete subject analysis in logistic regression. More sophisticated methods include multiple-imputation methods, maximum likelihood or pseudo maximum-likelihood methods, and weighted estimating equation methods (12). However, the validity of all methods for handling missing data depends on meeting certain assumptions (12), the most stringent being the assumption that the data as a whole are "missing completely at random" (i.e., whether or not a given variable is missing is entirely independent of the values of other variables, and also independent of whether other variables are missing). A less stringent assumption is that the data are "missing at random" (i.e., whether or not a given variable is missing is entirely independent of the values of any other unobserved variables, although it can depend on the values of observed variables). In their review of methods for handling missing covariates in epidemiology, Greenland and Finkle argue that if the "missing-at-random" assumption fails, none of the above-mentioned missing data methods can be applied (12).

The APPROACH data collection process began in January of 1995. Among 6276 patients tracked in 1995, only 4629 had complete data for a logistic regression analysis predicting one-year mortality. These data were missing in a non-random manner with a higher frequency of missing data in one of the four hospitals studied, and more missing data earlier in 1995 relative to later in the year. As well, certain values within each facility were missing more often than others, often in non-random "clusters" of variables (e.g., the variables prior myocardial infarction and prior thrombolytic therapy were often simultaneously missing). Consequently, the data were certainly not "missing

completely at random", and were possibly also not "missing at random", both key assumptions for imputation analyses. Alternative methods for replacing the missing values were required.

Facing a clearly non-random pattern of missing data in the APPROACH database, a study was undertaken to develop a method for replacing missing data by drawing on administrative data for the same patients. As a result the "data enhancement", method for replacing missing data was developed (14) therefore maximizing the use of *all cases* in our cohort containing APPROACH clinical data necessary for the risk adjustment of the outcome QOL data. The development and testing of the enhancement method of data replacement is explained in Chapter 3.

1.2.4 Analysis of SAQ QOL data

Outcome QOL data in the APPROACH database was collected by means of a self reported questionnaire mailed to patients on the anniversary of their initial cardiac catheterization. This includes the Seattle Angina Questionnaire (SAQ) (Appendix A), a disease specific QOL scale. Disease specific measures of QOL are used for patients with diseases and symptoms that alter their QOL and are designed to address selected changes that are unique to an identified population or illness (15). The SAQ is a 19 item self-administered, questionnaire that measures five dimensions of CAD: exertional capacity, anginal stability, anginal frequency, disease perception and treatment satisfaction generating five independent scales. The SAQ, is sensitive to clinical changes in patient's coronary artery disease, and focuses on symptoms and impairments in health that are unique to coronary disease (16).

While analysing SAQ data gathered from our cohort of Alberta patients who had undergone cardiac catheterization (17), we noticed that each of the five dimensional scores of the SAQ were non-normally distributed and had marked ceiling effects. Given

the non-normal distributions for the SAQ dimensions for our cohort, we were concerned that the assumptions of parametric tests would be violated if we used t-tests to compare mean group scores or general linear modelling to risk adjust the SAQ scores. Consequently, the use of appropriate analysis methods for the SAQ became an important issue.

A comprehensive review of the literature on the SAQ, presented in Chapter 4 identified 9 studies that used the SAQ to measure QOL outcomes in patients with CAD (18-26). Although favourable results were found in assessing the outcome following *individual* treatment strategies, for example patients undergoing a CABG (19, 22), Stent (20, 23), or medical management (18, 21), there were no studies that addressed the QOL outcomes *comparing* treatment options for patients with multi-vessel CAD. Additionally perhaps more importantly, the comprehensive literature review of the SAQ demonstrated that parametric tests were used to compare SAQ scores. This was problematic considering the potentially non-normal distributions of the SAQ scale scores. Only one of the nine studies identified in the comprehensive literature review, addressed the issue of analyzing non-normally distributed SAQ scores (24) and used non-parametric statistics to compare scores between baseline and three months for patients with medically refractory angina, treated with transmyocardial revascularization and continued medical therapy.

1.2.5 Comparison of methods for analyzing SAQ data

For these two reasons: 1) results of the comprehensive literature review as well as 2) the distributions of our own SAQ data, an exploration of the most appropriate statistical analysis for SAQ data was undertaken. Four strategies for analysis were explored. The first strategy was to use linear regression based on the application of the central-limit theorem. This states that where one has a large dataset (large number of cases), despite the non-normality of the raw responses and the residuals, statistical inferences can be made based on the approximate normality of the regression estimates. The second and third strategies

involved dichotomizing the SAQ outcome data by two separate methods and using binary logistic regression analysis and the fourth strategy was to use ordinal logistic regression. The comparison of the 4 models used to analyze SAQ exertional capacity dimensional scores is presented in Chapter 5.

1.2.6 QOL outcomes of patients treated for CAD

Using enhanced data and ordinal regression, a risk-adjusted analysis of follow-up QOL outcomes of patients in Alberta treated for CAD was undertaken, the results of which are presented in Chapter 6. The purpose of this study was to compare the cardiac related QOL outcomes one year after initial catheterization of patients undergoing PCI, CABG or medical treatment after adjustment for known demographic, co-morbid, and clinical predictors of outcome. Cardiac related quality of life was measured using the Seattle Angina Questionnaire (SAQ).

The research questions of this study were:

A) Are scores for the five dimensions of the Seattle Angina Questionnaire (exertional capacity, anginal frequency, anginal stability, disease perception, treatment satisfaction) different for adult Alberta residents treated with CABG, PCI or medical management?

B) What clinical factors are significantly associated with exertional capacity, anginal frequency, anginal stability, disease perception, treatment satisfaction after statistical adjustment, one year following catheterization and treatment of CAD

For many patients with CAD, revascularization options of CABG, PCI, and/or medical management are clinically feasible options. The combined evidence comparing CABG and PTCA shows no difference in the survival outcomes of these two treatment strategies. Consequently, future selection of a revascularization strategy may be determined by the quality of life of patients following different treatment options. The aim

of this study was to determine if there is an association between the choice of treatment and the quality of life outcomes as measured by exertional capacity, anginal stability, anginal frequency, treatment satisfaction and disease perception dimensions of the SAQ measured one year following the diagnostic catheterization for CAD. These findings should provide cardiologists further motivation to consider including patient reported QOL one-year follow-up outcome data when undertaking the complex therapeutic decision-making process for patients with multi-vessel CAD.

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CHAPTER 2

LITERATURE REVIEW

2.0 Coronary Artery Disease Risk Factors

The Framingham Heart Study was the definitive study that identified the issues for epidemiological investigations of coronary artery disease. Between 1948 and 1949 a prospective cohort of 5,209 people, living in Framingham Massachusetts, aged 30 to 59 and free from cardiovascular disease were enrolled. The accumulated data indicated that more than one factor was associated with the risk of myocardial infarction and of dying from heart disease. At the time when reports began to be released on the Framingham results, it was known that various factors were statistically and temporally related to heart disease but it was not known whether the factors actually 'caused' heart disease. [1] In fact the Framingham report of 1961 actually coined the phrase "risk factors" in describing the associations identified [1]. As a result of the Framingham study, an immense number of studies have confirmed what we accept today as the risk factors for heart disease. These include unmodifiable risk factors such as age, sex, and race. As well behaviors such as smoking, alcohol consumption, diet, psychosocial factors, and exercise and physiological conditions such as hypertension, hypercholesterolemia, obesity, and diabetes, were identified as modifiable risk factors.

2.1 Treatment for Coronary Artery Disease

Over the last 20 years, there has been a shift in the management of coronary artery disease (CAD) from predominantly medical therapy to increasing use of

revascularization procedures [1],[2]. As a result, cardiac catheterization, percutaneous transluminal coronary angioplasty (PCI), and coronary artery bypass grafting (CABG) have become very common procedures. In 1995, for example, approximately 16,000 PCI and 19,000 CABG procedures were performed in Canada. CABG and PCI, are widely used procedures that provide at least a temporary mechanical solution to the fundamental problem of inadequate nutritive flow to the heart muscle. A CABG is a surgical procedure whereby 1-5 vessels are grafted to coronary arteries and blockages are "bypassed". A PCI is an interventional procedure where a catheter is inserted into the coronary artery and a balloon inflated resulting in flattening of the coronary lesion and clearing of the coronary artery. Although these procedures are often very effective, the relative merits of the two approaches remain controversial [2].

The quality of life (QOL) outcome benefits of PCI as compared with CABG or medical therapy for patients with multi-vessel coronary artery disease has not been firmly established [1] . A Medline search of the medical literature identified nine randomized control (RCTs) and one meta–analysis comparing the outcomes of CABG versus PCI for single and multi-vessel coronary artery disease [2-11]. Two trials, the Lausanne Trial [7], and the MASS trial [8] included only patients with single vessel disease. As this study assessed the QOL outcomes of patients with multi-vessel disease, these studies were not reviewed. Length of time to measure outcomes varies for each of the trials. One further study looked at the immediate revascularization results [3], three studies addressed one-year outcomes, [4,11,5], one study reported on the outcomes at a mean follow-up of 2.7 year [6], one study, [9] had a follow-up of 3 years, and one trial, [10] measured outcomes at 5 years. These studies are summarized in table 2-1. Sample sizes ranged from 52 patients per group in the Toulouse trial [3] to the

largest sample in the BARI trial [10] of 915 per group. All seven trials randomized patients appropriately and demonstrated that the groups were similar at the start of the trials. Intention to treat strategy was used in all seven trials. Blinding of investigators involved in the treatment strategies was not possible as all trials involved surgical interventions. The BARI trial [10], RITA trial [6] and EAST trial [9] minimized bias by blinding the investigators and follow-up personnel who assessed the clinical outcomes of the treatments.

The Toulouse trial sets the stage for comparing the RCTs of treatment modalities for multi-vessel disease. As the first of several different follow-up time frames studied, the Puel et al study [3] reported in abstract form, compared the revascularization results, calculated as a rate (successfully grafted or dilated/attempted vessel x 100) immediately following PCI or CABG treatment procedures. Patients were randomly assigned to PCI (n=57) or CABG (n=52) and inclusion criteria included patients with multi-vessel disease. The investigators stated that both groups were similar in respect to age, sex, risk factors, and symptoms, and left ventricular function. Four sub-groups emerged for comparison as a result of the number of diseased vessels involved. These included 2 vessel disease having PCI, 2 vessel disease having CABG, 3 vessel disease having PCI and 3 vessel disease having CABG. There were no significant differences in the angiographic type of lesions among the groups. There was no significant difference in the rate of successfully dilated/grafted vessels between the 2 VD subgroups. There was a marginally (73.8%-PCI vs. 96.6%-CABG, $p \leq 0.05$) significant difference associated with the treatment sub groups with 3 vessel disease, but the authors state that larger numbers are required in order to draw any firm conclusions.

Three RCTs looked at the one-year outcomes, comparing CABG versus PCI treatments. The German GABI trial [4], the ERACI Argentinean trial [11], and the European CABRI trial [5] all have important differences in design and end points. The GABI study collected data at 8 centers in Germany, and randomized a total of 338 patients, 176 to PCI, and 161 to CABG. Selection criteria were similar to both the ERACI and the CABRI trial but the primary end point of the GABI trial was freedom from angina (CCS class <2) one year after the intervention. Secondary endpoints included the incidence of major cardiovascular events (death or myocardial infarction); procedure related complications and the rate of further interventions. A unique inclusion in the GABI trial was a 6-month angiography at a central lab. Although only 219 patients agreed to participate in this part of the study, and it would be obvious at angiography which treatment the patients had received, this procedure provided a clinically objective measurement of comparison between occluded grafts (20%) and occluded vessels (16%) that had been revascularized with PCI. Results of the GABI trial showed that PCI and CABG are equally effective treatments for relieving angina. The most prominent difference between the GABI trial and the CABRI and ERACI trials aside from the primary endpoint is the percentage of patients in each trial whose clinical indication for treatment was unstable angina. These differences (GABI-5%, CABRI-55%, ERACI-83%) would suggest that the populations are different and there may have been unique selection differences among the trials. The differences in the populations would likely account for the differences in the findings between the studies, specifically the difference in the increased presence or absence of angina at one year associated with PCI.

The ERACI trial's first publication was a one-year report of a study designed to compare freedom from combined cardiac events (death, angina, and MI) at 1, 3 and 5-year follow-ups. The randomized sample included patients from one hospital in Argentina. There

were no significant differences in the treatment groups at the beginning of the trial. All analysis used intention to treat criteria. Similar to the CABRI trial, the ERACI results indicated non-significant differences between the PCI and CABG treatment groups for death and MI. ERACI results did demonstrate that levels of angina, repeat revascularization, and combined events were significantly higher for patients treated with PCI. The ERACI trial although small (PCI-62 patients and CABG-64 patients) supports the results demonstrated in the CABRI trial. Of note, the ERACI sample had a higher than usual presence of patients with unstable angina which may have biased the overall results. Rodriquez et al [12] note that it has been well established that patients with unstable angina are known to suffer from a greater number of complications from the revascularization procedure and that these results might be better in studies with fewer patients with unstable angina.

The CABRI trial randomized 1054 patients from 26 different centers across Europe. One of the main strengths of this particular RCT aside from it's substantial size was that each center had knowledge of its own results alone, and therefore could not influence its own results by knowing those of the other centers. The primary outcome that was compared between the PTCA and CABG groups was mortality and anginal symptoms at one year. Secondary outcomes included MI's, requirements for revascularization, and requirements for medications. The randomization successfully distributed the sample into equal groups on all risk factors identified. The results indicated that there was a non-significant higher relative risk of death (1.42, 95% CI 0.731-2.76), for the PCI group and a significantly higher relative risk of angina (CCS CLASS $\geq$1) associated with the PCI treatment strategy (RR=1.54 p=0.012). The CABRI trial also identified that the patients in the PCI group had a risk of re-intervention 5 times greater than the patients in the CABG

group (RR=5.23 95%CI=3.90-7.03, p<0.001). As a result of the PCI patients experiencing significantly more angina, it is not surprising that the PCI treatment group took significantly more anti-anginal drugs. Finally the CABRI trials noted that females were more likely to have clinically significant angina at one year, and were at significantly higher risk for one-year mortality. The association identified with the female sex is unique to this trial.

The RITA trial designed as a five-year outcome study published an interim report [6] for patients with a mean follow-up time of 2.5 years. Sixteen participating hospitals across the United Kingdom and Ireland participated in the study. Every center employed a research assistant to coordinate the study and collect the data. All patients were examined and interviewed at 1, 6, and 12 months following the initial intervention and then follow-up at 2, 3, 4 and 5 years. The primary endpoint was the combined 5-year incidence of death and MI. A reviewer blinded to the treatment strategy independently assessed all deaths and MI. 1011 patients were successfully randomized as evidenced by equality of prevalence of risk factors and analyzed by intention to treat criteria. No patients were lost to follow-up. To date there were no differences between the CABG and PCI groups in the combined primary end-point. There is no evidence to suggest any treatment difference, depending on the number of diseased vessels. There was a significant difference in the number of PCI vs. CABG patients undergoing a second revascularization procedure (PCI-38%, cabg-11.5%, and p <0.001). The authors noted a striking improvement in reported angina in both treatment groups but state that at every follow-up point there was a significant excess of patients with angina in the PCI group. As well, patients receiving PCI had a much greater use of anti-anginal drugs during follow-up compared to CABG patients.

The EAST trial [9] was a three-year prospective trial that compared the clinical benefits of PCI and CABG for multi-vessel disease. 392 patients were randomized into two

groups. There were no significant differences between the two groups. All patients were recruited from a single center in Atlanta, GA. An independent biostatistical center at Emory University verified the data and provided analysis as required. Throughout the trial, all clinical investigators were blinded for outcomes of the two treatment groups. The primary endpoint included a composite of death, including mortality from all causes, a Q wave MI and a large ischemic burden detected by thallium scanning at three years. Data were analyzed according to the intention-to-treat principle. The results of the EAST trial led the investigators to conclude that CABG and PCI did not differ significantly (p=. 73) with respect to the occurrence of the composite primary end point. Consequently, the selection of one procedure over the other should be guided by patients' preferences regarding the QOL and the possible need for subsequent procedures.

One trial used five-year follow-ups to determine if there was a difference in endpoints for the patients treated with CABG vs. PCI. The BARI trial [10] randomized 1829 patients to CABG and PCI groups recruited from 16 centers across the United States and 2 centers in Canada. The Primary endpoint was mortality from all causes. Subgroups of patients, defined by five factors: the severity of angina, the number of diseased vessels, diabetics treated with the use of insulin or oral hypoglycemic, left ventricular function, and complexity of lesions, were identified a priori for analysis. There was no statistically significant difference in the cumulative survival curves for the two treatment groups, (CABG-111 deaths, PCI-131 deaths, p-0.19). The rates of survival free MIs also did not differ significantly between assigned treatment groups. Eight percent of CABG patients underwent additional revascularization procedures within the first five years as compared to 54% of patients in the PCI group (p>0.001). The only significant difference occurred in the five-year survival in the subgroup of patients with treated diabetes. 5-year survival was

65.5% among patients with treated diabetes who were assigned to PCI as compared to 80.6% among diabetics assigned to CABG. The researchers note that as compared to the CABRI, RITA, EAST, GABI, MASS and ERACI trial, the one-year mortality of the BARI trial appeared to be higher. The BARI trial enrolled older patients, a higher proportion of patients with a history of myocardial infarction, hypertension, congestive heart failure, diabetes and poor left ventricular function. The conclusions reached in the BARI trial suggested that for patients, who prefer to avoid major surgery, PTCA may offer a reasonable alternative with an expectation of similar overall survival rates and survival rated free of Q-wave infarction.

Finally, Pocock et al [2] completed a meta-analysis of eight of the above RCT comparing CABG and PCI treatment strategies. The meta-analysis focuses on outcomes of treatment including mortality, MIs, additional interventions, and angina post procedure. In order to seek consistent reporting of information a standard proforma was sent to each of the principal investigators. This information included the number randomized, the median length of follow-up, number receiving the randomized procedure, and the distribution of angina grade (CCS CLASS) at one and three years. Pocock 's meta-analysis concludes that there is no evidence of a treatment difference in mortality, and no overall difference in cardiac death/MI rates between CABG and PCI groups. They did however identify a significant difference in re-intervention rates ranging from 3.2% for CABG vs. 34.5% for PCI. Of note is the highly significant heterogeneity between trials, (p=0.006). All trials had a higher prevalence rate of angina in the PCI group at one year that diminished substantially at three years (Table 2-2).

Two aspects of all the RCTs stand out as important limitations to the studies. Firstly, all of the studies randomized a small (4% to a maximum of 54%) percentage of eligible patients and consequently, the randomized patients represent only a small portion

of total number of patients who were screened for the studies. Secondly, each study's design albeit slightly different, utilized agreement between surgeons and interventionalists (physicians trained to perform angioplasty) as to whether or not each patient was suitable to both treatments prior to randomization. A patient may have met the inclusion criteria but was at risk of being randomized contrary to the treatment method deemed by the clinician to be in the patients best interest. For example, some clinicians may prefer to treat younger patients with PCI and to delay surgical interventions for as long as possible. Disagreement between the surgeon and interventionalist resulted in patients not meeting the eligibility criteria for randomization. Consequently this further constraint on the patients available for randomization severely limited the generalizability of the results.

Even though there were important differences in the design and endpoints of all of the RCTs, their results measured at follow-up, consistently showed non-significant differences in survival, and non- significant differences in the incidences of nonfatal myocardial infarctions of patients treated with CABG or PCI, at follow-up. As well, when measured at follow-up, patients undergoing CABG, as compared to those undergoing PCI were less likely to have angina and less likely to undergo additional coronary revascularization procedures. Given the differences in inclusion criteria, and follow-up, the consistency of these results of the trials is striking.

Three of the 7 trials, the CABRI trial, the BARI trial and the RITA trial comparing CABG versus PTCA included sub-studies on quality of life outcomes [13-15]. The CABRI and RITA sub-studies concluded that there was no difference at 1 and 3 years respectively in the health related quality of life outcomes following surgery or angioplasty treatments for CAD. In contrast, the BARI trial found an association between treatment with CABG surgery and "better quality of life" as measured by functional status scores,

at three years as compared to patients treated with angioplasty. One cohort study [16] used a repeated measures design to assess the QOL changes at baseline, 6 months and 1 year in terms of functional capacity in 280 patients (100 CABG, 100 PTCA, & 80 medication only) undergoing treatment for CAD. Results of the study indicated that the QOL of the patients who had undergone CABG and PTCA was significantly better at 6 months and one year in the dimensions of energy, pain and mobility at one year. In the Medically managed group, the only improvement took place in the dimension of social isolation. The dimensions of energy and mobility for this treatment group in fact deteriorated. Unfortunately the patients in the study groups (CABG, PCI and medically managed) were notably different at the beginning of the study and risk adjustments were not done to attempt to control for the differences. As well patients in the PTCA group who then went on to have a CABG were dropped from the analysis potentially altering the results of this group.

2.2 Measuring the Quality of Life in Patients with Coronary Artery Disease

Although it was Socrates who exclaimed "We should set the highest value, not on living, but on living well", medical interest in Quality of Life (QOL) issues, is a relatively recent development, that has been significantly roused as technological advances result in care that prolongs survival yet fails to address the 'quality' of the survival. Debate regarding the quality of life following medical treatment and the appropriate medical treatment in relation to consideration of quality of life outcomes rages on. MacDowell and Newell in their book on measurements of health, note that although the debate is not new "What is new is the development of formal ways to measure quality of life and their routine application in outcome evaluation."[17]. QOL questionnaires are particularly beneficial at enhancing the scope of outcome measures

beyond the traditional ones of disability and/or death. Of particular interest though, is the fact that frequently, QOL measures also provide a means whereby a patients' own judgment can be measured and in ideal circumstances influence treatment. This has intuitive appeal for outcomes research, as patients are considered better at judging when they are better or worse off.

QOL scales can be classified as generic, covering health in general, or disease specific. Global or generic QOL measures address a variety of dimensions of health including physical functioning, social and emotional functioning, perceived health status, life satisfaction and interpersonal relationships. Some QOL instruments designed for general use include: the Duke Health Profile, the Nottingham Health Profile, the McMaster Health Index Questionnaire and the popular Medical Outcomes Study sf surveys, the SF-36, SF-20 and now the SF-8.Generic scales generally describe a subjects physical, social and mental well-being. Disease specific scales as the name implies were developed to be used for patients with specific diseases and symptoms that alter their QOL. They are designed to address selected changes that are unique to an identified population or illness. Examples include the Arthritis Impact Scale, the Functional Living Index-Cancer, and the Seattle Angina Questionnaire. QOL measurement is valuable in comparing treatments that are equivalent in terms of other indices [17]. Ultimately, in health outcomes research, a QOL measure should ascertain if a patient has received medical treatment that they determine has been beneficial, at the very least non-maleficent. "In a sense, patients statements about how they feel about the quality of their own lives could be considered the GOLD standard itself. After all can a patient have a good quality of life without knowing it?" [62].

2.3 Measures

2.3.1 The Seattle Angina Questionnaire

In 1994 Spertus et al published "a disease-specific functional status measure, to quantify the physical and emotional effects of coronary artery disease"[18]. The Seattle Angina Questionnaire is a 19 item self-administered questionnaire. Five dimensions of coronary artery diseases are measured, generating five independent scales including exertional capacity, anginal stability, anginal frequency, and disease perception and treatment satisfaction. Each of the questions is measured on an ordinal scale with 1 indicating the lowest/poorest response. The questions specific to each dimension are summed and then converted to a 0 to 100 range. As each ordinal scale measures a unique dimension, the five scales have been tested for validity, responsiveness, and reproducibility independently using different patient groups including:

1) Patients with CAD undergoing an exercise treadmill test at a Veterans Affairs medical center and a university-affiliated outpatient clinic,
2) Outpatients with self-reported CAD from a survey of all enrollees in an internal medicine clinic.
3) A cohort of patients with initially stable coronary artery disease identified from the Seattle Veterans Affairs Medical Center's computerized database who met the following criteria I) a discharge diagnosis in the previous 5 years of coronary artery disease. II) A current prescription for nitroglycerine, III) no change in anti-anginal medicines within the previous 9 months, IV) no hospital admissions with the 2 months and V) no diagnostic tests for evaluation of cardiac disease during the 2 months proceeding the study.

4) Patients undergoing percutaneous coronary angioplasty enrolled from a cardiac catheterization laboratory of a Veteran Affairs Medical center and a university medical center.

The results of these studies are summarized in Table 2-3 and indicate that for all dimensions the SAQ appears to be a satisfactory scale for measuring the quality of life in cardiac patients. Pearson correlations were used to compare clinically accepted measures (gold standards) with the dimensional scores of the 5 SAQ subscales. The exertional capacity scores were correlated with exercise treadmill times resulting in a Pearson r = 0.42 (p=0.001). Anginal frequency scores were correlated with the number of nitro-glycerine refills reported over a one year period (r=0.31,p=0.006). The anginal stability score were correlated with patient's global perceptions of change (r=0.70, p<0.0001). The treatment satisfaction scores were correlated with the American Board of Internal Medicine patient satisfaction questionnaire scores and demonstrated a correlation of r= 0.67 (p<0.0001) and the disease perception scale was correlated with the SF-36 general health scale resulting in an r=0.60 (p<0.0001). The most notable limitation regarding the SAQ was that all of the validation studies for the SAQ dimensions were performed on a sample of elderly men. One further limitation of the SAQ is the absence of scales measuring the psychological and social dimensions both of which have important ramification regarding a patient's QOL.

Spertus further tested the SAQ in a comparison study of the SAQ and the SF 36, a generic measure of health status [19]. Both questionnaires were administered to 2 groups of patients. The first group was 45 patients who underwent successful angioplasty whereby it was anticipated that the patients would experience substantial improvement in their symptoms. Baseline and three-month follow-up SAQ and SF-36

forms were completed and evaluated with paired t-tests. As well, Guyatt's responsiveness statistic, a ratio of the mean change in score among patients who improve clinically, divided by the standard deviation of the change in score observed among stable patients, were also calculated. The higher the responsiveness statistic, the more sensitive the measure is in detecting change. For the scales that changed significantly over three months, the responsiveness statistics of the SAQ scales were considerable higher than those of the SF-36 (Table 2-4).

The second group of patients included 130 patients with stable CAD. This group was chosen to demonstrate the responsiveness of the questionnaires to smaller clinical changes. Three months following the completion of the SAQ and SF-36, this group was mailed a 5-point global question inquiring about changes in the patient's CAD. Linear regression analyses in which all 8 SF 36 scales were entered into a model with the patients' responses to the global follow-up question as the dependent variable were completed. According to the responses, patients were grouped into three groups including patients who felt they had gotten worse, patients who felt they were unchanged and patients who felt they had gotten better in the 3-month interval. The multiple-partial F test was highly significant ($p<0.001$), suggesting that the SAQ added significantly to the SF-36 in explaining patients' self-report change. Contrary to the SAQ, the SF-36 added no significant additional information to the SAQ in explaining the patients' self-reported change in their CAD. The preliminary results of these studies indicate that the SAQ is a valid scale for different populations of patients with CAD (Personal Communication: John Spertus, Oct 1996).

2.3.1 Reported Use of the Seattle Angina Questionnaire

Electronic databases (Medline, Psychlit, Embase, Cinahl, Health star, Pubmed, Ageline, Cochrane, Sociological abstracts, MD consult) were searched using "Seattle angina questionnaire" as the key words as well as various combinations of Seattle, angina

and questionnaire. Web of Science (Scientific Citation Index) was searched to identify any manuscripts that cited either one of the two developmental articles authored by JA Spertus.

The electronic database search identified a total of six studies . Two of the six were the SAQ development studies [18,19]. Three studies employed the SAQ as a measure of QOL in patients with CAD [20, 21, 22] and one study [23] compared the SAQ to two other QOL measures. Searching the Scientific Citation Index identified a further 31 articles that cited one or both of the two Spertus SAQ developmental articles [18,19] (Table 2-5). Of those 31 studies an additional four articles were identified as having used the SAQ as a measurement tool in the studies. Thirteen articles referred to the SAQ as a disease-specific tool for assessing QOL in patients with CAD. Ten articles use the results of the developmental SAQ article as validation for their own particular study. Examples included indicating that the scores of the SF-36/MOS scores used in the validation of the SAQ, were comparable to the SF-36 scores achieved in the particular study in question and for justification that mortality is no longer justifiable as the sole endpoint in CAD treatment assessment. Two articles were published in non-English journals, German and Spanish, and were not assessed. Two article were planning to use the SAQ in planned RCTs (Table 2-5). Further results of this comprehensive literature review are presented in Chapter 4.

2.4 APPROACH

The Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease (APPROACH), a population-based inception cohort of all Alberta residents undergoing cardiac catheterization for CAD provides a unique opportunity to study many aspects of CAD management. All APPROACH patients at present are treated at three

sites: the University of Alberta Hospitals (Edmonton), the Royal Alexandra Hospital (Edmonton), and the Foothills Hospital (Calgary). Up until March 31st 1996, patients were also treated at the Holy Cross Hospital (Calgary). Patients in APPROACH are followed longitudinally after cardiac catheterization, thus allowing for assessment of subsequent treatment (i.e., PCI or CABG or medical treatment). The significant strength of the APPROACH database is that it is very large (about 7000 new cases a year) and contains detailed information for each patient including sociodemographic characteristics, presence or absence of co-morbidities, disease specific variables, coronary angiography results, post-catheterization referral decisions, records of actual revascularization events (including dates), and survival and quality of life. The ongoing involvement of cardiologists and cardiac surgeons at all three sites in the APPROACH project has ensured the clinical relevance of the data collected.

2.5 Dealing with Missing Data in an Observational Database

Much of the published outcomes research in health care relies on administrative databases with limited clinical information about patients. Multivariable risk adjustment based on administrative data is therefore constrained from the outset by the lack of details on important prognostic factors. Clinical databases are better able to explain inter-provider differences in outcomes than are administrative databases. As Hannan et al. [58] have demonstrated, the advantage of clinical databases comes from the ability to select and capture prospectively those clinical variables that are important prognostically and have no comparable diagnostic code in administrative data. However, when more detailed databases are developed, costs rise as do the chances that some data for some patients will not be collected. Cases with missing values for any one of the variables entered into a model unfortunately cannot be used in multivariable analysis, unless imputation is used.

Common methods for handling missing covariate values include; stratification on missing-data status which is equivalent to creating an additional "missing category" for the covariates ; conditional-mean imputation whereby the concept is to fill in (impute) missing values for each subject with the mean value of the cases with the variable present ; and complete subject analysis in which only subjects with all values recorded for all covariates are retained in the logistic regression analysis. These methods can be biased under reasonable circumstances and are often unsatisfactory [59]. More sophisticated methods include; multiple-imputation methods where multiple copies of the original dataset are generated, each with missing values replaced by values randomly generated according to a model for the distribution of incomplete regressors and its dependence on complete regressors and the outcome variable; maximum likelihood or pseudo maximum-likelihood methods in which a joint model for the outcome under study,; the covariate distribution and possibly the missing data process is fit , and ; weighted estimating equation methods in which a model for the missing-data process is used to provide special weights and covariates for the outcome regression analysis [59]. These three groups of advanced methods require considerable theory and statistical sophistication and contain many variants. Notwithstanding this, the validity of all methods for handling missing data depends on meeting certain assumptions [59], the most stringent being the assumption that the data as a whole are "missing completely at random" (i.e., whether or not a given variable is missing is entirely independent of the values of other variables, and also independent of whether other variables are missing). A less stringent assumption is that the data are "missing at random" (i.e., whether or not a given variable is missing is entirely independent of the values of any other unobserved variables, although it can depend on the values of observed variables). In their review of methods for handling missing covariates in epidemiology, Greenland and Finkle argue

that if the "missing-at-random" assumption fails, none of the above-mentioned missing data methods can be applied [59].

If the data are non-randomly missing, then the impact of exclusion will be non-random, with resultant biases in any analyses. Another approach is to impute the lowest level of severity for a given missing variable. In this instance, the goal is to provide an incentive for participating centers or health care providers to be more assiduous about data capture in the future. A third possibility is using alternative data sources to 'fill in the blanks'. For example, Smith et al. [60] recently demonstrated that significantly more accurate estimates of probabilities of death are possible with administrative data when limited clinical information from clinical databases is merged with the administrative data. The converse (using administrative data to fill in gaps in clinical registry data) is also feasible. Chapter 3 presents the method and validation of replacement of missing data that was used in this study.

2.6 Summary

Randomized controlled trials comparing the survival benefits between treatment modalities for CAD do not provide definitive evidence of which intervention (CABG vs. PTCA) is superior. Even though there were important differences in the design and endpoints of the RCTs, their results measured at follow-up, consistently showed non-significant differences in survival, and non- significant differences in the incidences of nonfatal myocardial infarctions of patients treated with CABG or PTCA, at follow-up. As well, patients undergoing CABG, as compared to those undergoing PTCA were less likely to have angina and less likely to undergo additional coronary revascularization procedures. Given the differences in inclusion criteria, and follow-up, the consistency of these results of the trials is striking. Due to the lack of significant evidence regarding treatment

supremacy, for mortality and myocardial infarction, one group of investigators was led to conclude " although absolute treatment survival differences were modest, treatment decisions should be based not only on survival differences, but also on symptom relief, *quality of life outcomes* and patient preferences." [25]Of particular note is that no published studies have compared all three treatment modalities (CABG, PTCA and Medical Management) for efficacy or effectiveness with respect to quality of life.

Prior to being able to compare the QOL outcomes of patient treated for CAD, two issues required attention. The first of these was to replace the missing clinical data that was required to risk adjust the SAQ QOL dimensional scores. Chapter 3 presents the development and testing of the 'enhancement method' used to replace the missing data in the APPROACH database. The second issue involved determining the most appropriate statistical analysis of the SAQ QOL scores. Chapter 4 presents a comprehensive literature review of the studies that have used and analyzed SAQ data and Chapter 5 compares 4 methods of data analysis for SAQ data and presents the most appropriate method of statistical analysis.

The primary aim of this study is to measure the QOL outcomes, specifically the exertional capacity, anginal stability, disease perception, anginal frequency and treatment satisfaction of patients undergoing treatment for CAD while controlling for disease severity. The evaluation of health-related QOL for patients treated for CAD is crucial particularly in light of the fact that there are diverse treatment options. Disease-specific QOL outcomes are important to determine whether the treatment modalities improve in specific dimensions known to limit patient activities of daily living and ultimately their quality of life. In view of the gains attained with the treatments for CAD, further information regarding patient characteristics predictive of exertional capacity,

anginal stability, disease perception, anginal frequency and treatment satisfaction will provide patients and clinicians with another important facet of the outcome of treatment for CAD.

Table 2-1. Summary table of randomized controlled trial for treatment of coronary artery disease.

Study	Inclusion Criteria	Sample Size		% randomized from eligible pool	1.Primary endpoint 2.Secondary endpoint	ntention To Treat analysis	Results
Toulouse Trial 1 centre	multi-vessel	CAB 52	PCI 57		1. Revascularization rate (successfully dilated-grafted /attempted vessels)* 100	✓	1) 2 vessel disease no significant difference 2) 3 vessel disease PCI- 73.8% CABG-96.6% p<0.05
GABI trial 8 centres in Germany	No Left main,< 75 yrs. 2 major arteries CCS>2 Stenosis > 70%	CAB 161	PCI 176	4 % of total	1.Freedom from angina at one-year 2. Combined Death or MI	✓	1) No significant difference in Primary endpoint 2) Significant difference in combined rate CAB>PCI 11%:5% p=.047
ERACI Trial 1 centre in Argentina	Severely limited stable angina Rest unstable angina >=70% stenosis in more than one epicardial artery,	CAB 64	PCI 63	5.8% of total • High incidence of patients with unstable angina –83%	1) Freedom from combined coronary events at one-year death, MI, & angina 2) In hospital complications (death MI and ER revascularization, completeness of revascularization, in hospital and late costs.	✓	1.1) Death –NS difference. 1.2) AMI – NS difference 1.3)Freedom from angina CAB-85% PCI-65% p<0.02 1.4 Freedom from combined events CAB 85% PCI 65% p< 0.005 2.1)
CABRI Trial 26 European centers	LEF >= 35% < 76 years pain at rest > 50% stenosis in 2 or more vessels	CAB 513	PCI 541	54% of total	1) Mortality and symptom status (based on angina class) at one-year 2) MI, requirements for antianginal medications, revascularization	✓	1.1) death – NS difference 1.2)angina PCI:CAB RR=1.54 (1.09-2.16), p=0.012 2.1) MI - NS difference 2.2) meds- PCI:CAB RR= 1.30 (1.18 – 1.43) p<0.001 2.3) reintervention- PCI:CAB RR=5.23 (3.90-7.03) p<0.001

RITA 16 cardiothoracic centres in the UK and Ireland	Arteriographically proven CAD Stable or unstable angina One or > vessels with 70% stenosis in one view or 50% in two views	CAB 501	PCI 510	3% of total	1) Combined death or MI –2.5 year report 2) Subsequent interventions and angina 3) Self reported health status & return to work (QOL)	✓	1.1)Combined death and MI CAB: PCI RR=.88 (.59 – 1.29)p=.47 2.1)Subsequent interventions PCI-38% CAB-11% p<0.001 2.2) Angina –PCI-31.3% CAB-21.5% @ 2 yrs. P=0.007 3.1) NS differences between two treatment strategies
EAST trial Single centre trial US	All patients with Unstable and Stable Angina Any age 2 or 3 vessel disease EF > 25 %	CAB 194	PCI 198	7.7% or total	4) Composite of death or Q wave MI at 3 years 5) Reintervention and angina	✓	1) Composite NS difference 2.1) Re-intervention CAB-1% PCI-22% p<0.001 2.2)Angina (CCS class >= II) – CAB-12% PCI 20% p=0.039
BARI trial 18 centres in the US and Canada	Multi-vessel coronary disease Clinically severe angina	CAB 914	PCI 915	Apriori Subgroup Severity of angina Number of diseased vessels LV function Lesion complexity Treated Diabetes	1) All cause mortality within 5 years. 2) All cause mortality by subgroups 3) Repeat revascularization, Angina at 5 years, 4) QOL –return to work rates, rate own health, limitations on daily life	✓	1.1)All cause mortality- NS difference between CAB and PCI p=0.19 2.1) Diabetes –CAB 80.6% PCI 65.5% p=0.003 3.1) Repeat Revascularization CAB 3% PCI 19% p<0.001 3.2) Angina at 5 years CAB:PCI RR=.738 p=.003 4) NS differences at 5 years

Table 2-2 Size and precision of treatment effects of seven multi-vessel RCTs and one meta-analysis

TRIAL	NUMBER OF PATIENTS		Number of patients having cardiac death or MI in first year		RR Significance CABG:PCI		Significance used	
	cabg	PCI	cabg	PCI			α	power
CABRI	513	541	29	43	.817	NS	p<.05	.80
RITA	501	510	31	34	.972	NS	p<.05	.80
EAST	194	198	33	24	1.20	NS	p<.05	.83**
GABI	177	182	18	10	1.34	NS	p<.05	.80
TOULOUSE	76	76	6	6	1.00	NS	p<.05	.11**
ERACI	64	63	7	8	.917	NS	p<.05	.70
BARI	914	915	52	27	1.37	P<0.01	p<.05	
Meta-analysis*[1]	1661	1710	127	135	.97	NS	P<.05	.63 ***

*Included 2 trials (single vessel-MASS, Lausanne): did not include BARI trial.

**Power calculated based on results of trial

*** Power calculated to detect 2% difference in rates.

Table 2-3 Validation Studies- Seattle Angina Questionnaire

Dimension	Sample	References	Analysis	Statistic	Significance
Physical Limitation	Patients with CAD undergoing ETT	ETT *duration COMPARED TO: SAQ physical limitation Duke Activity Status Index Specific Activity Scale Canadian Cardiovascular Society Classification SF-36	Pearson r coefficient	 .42 .40 .36 .21 .024	 (0.001) (0.001) (0.02) (0.11) (0.93)
Anginal Frequency	Patients with initially stable CAD	Number of nitro-glycerine refills in 1 year	Pearson r coefficient	.31	(0.0006)
Anginal Stability – Lower scores=more frequent angina	1. Patients undergoing PCI 2. Patients with initially stable CAD	1. Diagnosis of unstable angina (UA) 2. Patients global perception of change	1. t test of mean scores 2. Pearson r coefficient	UA-21.4 SA-39.8 .70	(0.03) <(0.0001)
Treatment Satisfaction	Resident patients with self-reported CAD	American Board of Internal Medicine Patient Satisfaction Questionnaire	Pearson r correlation	.67	<(0.0001)
Disease Perception	Patients with initially stable CAD and PCI	SF-36 general health scale	Pearson r coefficient	.60	<(0.0001)

Taken from Spertus et al 1994

Table 2-4 Mean Change in Functional Status Score of Patients Undergoing Successful PCI

Scale	Mean Difference Baseline & 3 months	P value	Responsiveness Statistic
SAQ			
Physical Limitation	17.9	<0.0001	1.2
Anginal Stability	46.3	<0.0001	2.2
Anginal Frequency	33.3	<0.0001	2.0
Treatment Satisfaction	-1.5	.66	0.1
Disease Perception	36	<0.0001	2.3
RAND SF-36			
Physical Functioning	10.6	0.02	0.8
General Health	-1.2	0.64	0.1
Mental Health	5.4	0.07	0.4
Bodily Pain	23.1	<0.0001	1.1
Role-emotion	18.5	0.04	0.5
Role-physical	20.3	0.003	0.5
Social Functioning	11.6	0.008	0.6
Vitality	10.7	0.005	0.9

Table 2-5 Results of literature search

Use of SAQ in Manuscripts	Electronic Databases N (reference)	Web of Science N (reference)	Total
SAQ Development Studies by Spertus et al	2 [18,27]		2
Used SAQ as a measure for QOL	***3 [20,22,23]***	***6 [28-33]***	***9***
Plans on using SAQ in future study	1 [21]	1 [34]	2
Articles refer to SAQ as disease specific tool for measuring QOL. (do not actually use SAQ)		17 [35-51]	17
Use the results of SAQ developmental article as validation for another QOL measure		6 [52-57]	6
Identify and review the treatment satisfaction scale of the SAQ		1 [34]	1
Articles published in non-English journals (not assessed)		2	2
Total	6	33	39

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CHAPTER 3

DEALING WITH MISSING DATA IN OBSERVATIONAL HEALTH CARE OUTCOME ANALYSES.

3.0 Introduction

Observational outcome studies appear frequently in the clinical and health services research literature. The objectives of these studies typically are hypothesis generation about optimum management of illness, or analyses of the quality of medical care. As Iezzoni notes, meaningful assessments of patients' outcomes in observational studies require two basic procedures [1]: a reliable and accurate measure of the outcome itself; and a method of adjusting for factors affecting that outcome, other than the variable(s) of primary interest. For example, where mortality is the outcome under scrutiny, multivariable models are constructed to determine which variables predict individual patients' probabilities of dying, and the expected mortality rates for two or more groups of patients.

Much of the published outcomes research in health care relies on administrative databases with limited clinical information about patients. Multivariable risk adjustment based on administrative data is therefore constrained from the outset by the lack of details on important prognostic factors. Clinical databases are better able to explain inter-provider differences in outcomes than are administrative databases. As Hannan et al. [2] have demonstrated, the advantage of clinical databases comes from the ability to select and capture prospectively those clinical variables that are important prognostically and have no comparable diagnostic code in administrative data. However, when more detailed databases are developed, costs rise as do the chances that some data for some patients will not be

collected. Cases with missing values for any one of the variables entered into a model unfortunately cannot be used in multivariable analysis, unless imputation is used.

Common methods for handling missing covariate values include stratification on missing-data status, conditional-mean imputation, and complete subject analysis in logistic regression. These methods can be biased under reasonable circumstances and are often unsatisfactory [3]. More sophisticated methods include multiple-imputation methods, maximum likelihood or pseudo maximum-likelihood methods, and weighted estimating equation methods [3]. However, the validity of all methods for handling missing data depends on meeting certain assumptions [3], the most stringent being the assumption that the data as a whole are "missing completely at random" (i.e., whether or not a given variable is missing is entirely independent of the values of other variables, and also independent of whether other variables are missing). A less stringent assumption is that the data are "missing at random" (i.e., whether or not a given variable is missing is entirely independent of the values of any other unobserved variables, although it can depend on the values of observed variables). In their review of methods for handling missing covariates in epidemiology, Greenland and Finkle argue that if the "missing-at-random" assumption fails, none of the above-mentioned missing data methods can be applied [3].

We recently faced the problems of non-random patterns of missing data in a new clinical registry and therefore decided to test three strategies for dealing with missing data. The first method tested was to exclude cases with missing data therefore modeling only those cases with complete covariate data. The second method tested was to impute the lowest level of severity for a given missing variable. The third method used an alternative data source and 'filled in the blanks'. Smith et al. [4] recently demonstrated that significantly more accurate estimates of probabilities of death are possible with administrative data when limited clinical information from clinical databases is merged with the administrative data.

The converse (using administrative data to fill in gaps in clinical registry data) is also feasible. We report here on the findings and also reflect on the lessons that other health services research might draw from our experience.

3.1 Methods

3.1.1 APPROACH Project

The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH Project) is a province-wide inception cohort of all adult Alberta residents undergoing cardiac catheterization for ischemic heart disease. The APPROACH project was initiated to study provincial outcomes of care and facilitate quality assurance/quality improvement for patients with coronary artery disease in Alberta. The APPROACH database contains detailed clinical information on adult patients with known or suspected coronary artery disease (CAD). Patients in APPROACH are followed longitudinally after cardiac catheterization, thus allowing for assessment of subsequent procedure use (i.e., percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG)), as well as outcomes such as mortality and quality of life. New patient data continues to be added to the APPROACH database.

3.1.2 Clinical Variables

Clinical data were obtained for 6276 adults (age $\geq$ 18 years), undergoing cardiac catheterization at one of the four hospitals performing this procedure. Data elements include patients' age, sex, and presence of the following risk factors: cerebrovascular disease (CEVD), congestive heart failure (CHF), chronic pulmonary disease (COPD), renal disease, type I diabetes, type II diabetes, dialysis, hyperlipidemia, hypertension, liver/gastrointestinal disease, malignancy, prior coronary artery bypass graft surgery, prior angioplasty, coronary anatomy as defined by the Duke Index [5], clinical indication for catheterization, left

ventricular ejection fraction, prior lytic therapy, prior myocardial infarction and peripheral vascular disease.

3.1.3 Missing data

The APPROACH data collection process began in January of 1995. Among 6276 patients tracked in 1995, only 4629 had complete data for a logistic regression analysis predicting one-year mortality. These data were missing in a non-random manner (Table 3-1), with a higher frequency of missing data in one of the four hospitals studied (hospital D in Table 3-1) and more missing data earlier in 1995 relative to later in the year. As well, certain values within each facility were missing more often than others, often in non-random "clusters" of variables (e.g., the variables prior myocardial infarction and prior thrombolytic therapy were often simultaneously missing). Consequently, our data were certainly not "missing completely at random", and were possibly also not "missing at random", both key assumptions for imputation analyses. Alternative methods for replacing the missing values were required.

3.1.4 Administrative Data Source

We obtained administrative data coded according to the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) [6] for all four participating hospitals. Hospitals are required to submit discharge abstracts to the provincial Ministry of Health and the Canadian Institute for Health Information for each acute care separation (discharge, transfer, or death) and for major outpatient procedures. Data elements acquired from this source included the patients' unique provincial personal health care number, the hospital chart number, sex, birth date, admission category, admission date, procedure date, discharge date, up to 16 ICD-9-CM diagnostic codes and up to 10 ICD-9-CM procedure codes.

Unlike many administrative databases that do not allow for distinction between pre-existing conditions and complications arising post-admission, Canadian hospital discharge data contain a 'diagnosis-type indicator' that permits this distinction. However, this diagnosis-type indicator was not used in our analyses, because an important use of the prospectively collected APPROACH data is to predict long-term outcomes such as one-year mortality based on clinical factors present *around the time* of catheterization. Our decision to extract information from all diagnoses regardless of type in the administrative data was thus intentional, as it mimics the capture in APPROACH data of both pre-existing conditions and conditions diagnosed post-admission.

3.1.5 Data Merging

The first step was to develop ICD-9-CM definitions for the clinical variables identified in the APPROACH database. To do this, we used the ICD-9-CM co-morbidity coding scheme derived by Deyo et al. [7], a validated translation of the original Charlson index [8]. Variables in the APPROACH data that could not be matched to the Deyo coding algorithms (e.g. hyperlipidemia or prior bypass surgery) were matched with ICD-9-CM codes by two individuals (CMN, WAG) who independently reviewed the ICD-9-CM coding manual [6] to select representative codes for each of the clinical variables. A final ICD-9-CM coding algorithm was developed by consensus between these two individuals (Table 3-2).

The merging of records by hospital ID and provincial personal health numbers matched a total of 6065 APPROACH patients' clinical data with ICD-9-CM administrative discharge data. A total of 211 records from the APPROACH data (3.4%) did not have matches in the administrative data. A comparison of matched and unmatched cases revealed no statistically significant differences in clinical characteristics, aside from a higher prevalence of prior lytic therapy in the unmatched cases.

3.1.6 Logistic Regression Models

We then constructed 3 logistic regression models for predicting death within 1 year of the index procedure. These models each used one of the following databases: 1) the dataset of 4629 cases from APPROACH with complete clinical data (APPROACH 4600), 2) a dataset (n=6065) of APPROACH variables in which missing predictor variables were assumed to be at the reference level of risk and coded as '0' (APPROACH 6000), and 3) a combined dataset (n=6065) that included clinical variables collected at catheterization enhanced by the administrative database (enhanced data). In this final "enhanced" database, variables were coded as '1' if either the administrative or clinical data sources indicated a variable to be present; if absent in both data sources, the final variables in the "enhanced" data base were coded as '0'.

For this study, all potential predictor variables were modeled, because our objective was to determine which database provides the most clinical information to predict mortality at one year. The final models included two variables, ejection fraction and coronary anatomy, for which we were unable to obtain any information from administrative data, and therefore were unable to fill missing data fields. For these two variables (and only these two variables), we modeled dummy variables for missing values. We caution readers that while this approach to modeling clinical variables has been used in published work using prospective cardiovascular data registries [9,10], such analyses can yield, for the variables handled in this manner, distorted parameter estimates that are difficult to interpret [11]. This distortion is particularly concerning if a study has as its focus the evaluation of parameter estimates and odds ratios for specific variables modeled in this manner, whereas there is perhaps less concern when the parameter estimates simply become part of a model that is used primarily for prediction.

3.1.7 Parameters Used for Model Comparison

The models' discrimination and goodness-of-fit were assessed using the c statistics and the Hosmer-Lemeshow (H-L test), respectively. The c statistic corresponds to the area under the receiver operating characteristic (ROC) curve and is a measure of model discrimination [1]. If all predicted probabilities of mortality for cases that die are higher than the predictions for mortality of those who live, the c statistic takes on a maximum value of 1.0. A model with no ability to discriminate has a c statistic of 0.5. H-L tests were used to assess the models' goodness of fit. The H-L test computes a summary measure of the discordance between the expected and the observed number of deaths for cases in deciles of increasing predicted risk [1]. Models with significant H-L chi square values (i.e. $p<0.05$) are rejected for poor fit. We chose to use this test because of its widespread use in the literature, but draw readers' attention to published studies raising concern regarding the Hosmer-Lemeshow test's stability and power [12]. We also used the decile framework of the H-L analysis to calculate, for each model, the mean absolute value of observed minus expected mortality across deciles (an analysis that is not sensitive to sample size). As well, gradients of risks were calculated from the H-L decile-of-risk tables. Gradients of risk were calculated by dividing the expected number of deaths in the 10^{th} (high-risk) decile by the expected number of deaths in the 1^{st} (low risk) decile. This gradient indicates how well the model spreads out the expected risk of death. Finally, minus 2-log likelihood (-2LL), or residuals, in each model were compared against the null model. Large values indicate large decreases in deviance attributable to the model [13].

We performed a simple bootstrapping procedure with 80 replications, so that approximate 95% confidence intervals for c statistics, H-L gradients of risk, and changes in –2LL could be identified by dropping the two lowest and two highest observations [1]. The third lowest and highest c statistic, H-L gradient of risk, and –2LL values define lower and upper

bounds for approximate 95% confidence intervals. (It should be noted that the c statistic, gradient of risk, and –2LL values generated by the simple bootstrapping procedure used here tend to be overestimates of models' true performance on cross validation testing, because we did not account for "optimism" in our bootstrapping method [14].) All statistical analyses were performed using SPSS, version 8.0.

3.2 Results

A total of 6065 patients (71.5% male) with a mean age 62.1 years (Standard Deviation=11.3 years) were used for these analyses. Table 3-3 indicates the prevalence of the predictor variables in each of the three datasets examined in our analysis. With the exception of prior PTCA, CABG, and lytic therapy, the enhanced database demonstrates a consistently higher prevalence for each of the predictor variables. This suggests that assuming a negative or '0' code when data are missing or unknown underestimates the true prevalence of risk factors. On the other hand, dropping the cases with missing data may over-estimate the prevalence of certain risk factors.

Table 3-4 lists the areas under the ROC curves (c-statistics) for each of the three predictive models. The use of the APPROACH 6000 data, with its imputations of absent (i.e., «zero») values for missing data, resulted in the least accurate mortality prediction (c-statistic = 0.755). The model using enhanced data (c =0.770) had the best discrimination, and also the largest gradient of risk across deciles (46.25 vs. 45.03 for the «APPROACH 4600' data, and 42.16 for 'APPROACH 6000' data).

The model using enhanced data also demonstrated the best model calibration in the H-L decile of risk analysis where we found the lowest mean absolute mortality difference across deciles in the model using enhanced data. The corresponding H-L p-value indicates that the actual and the predicted death rates within each of the ten deciles were not significantly different (P=0.59). Finally, the model using enhanced data resulted in the largest

decrease in deviance from the null model (change in –2LL = 406.17 vs. 305.12 for 'APPROACH 6000', and only 242.16 for 'APPROACH 4600').

Table 3-5 presents the logistic regression model derived using enhanced data. Odds ratios and the associated 95% confidence intervals are presented for each predictor variable. The odds ratios for mortality at one year for each of the modeled variables are generally «clinically» credible. Two possible exceptions are the protective odds ratio for hyperlipidemia and malignancy (see Discussion).

Table 3-6 presents the H-L decile of risk table for the model derived using enhanced data. This table is included to display the goodness-of-fit of our best model. The non-significant H-L statistic (p=0.59), indicates that there is no significant difference between the observed and expected (estimated probability) deaths over the 10 deciles. A comparison of the observed and expected frequencies over each of the 20 cells in the 10 deciles shows that the model fits within each decile of risk. The table also demonstrates the large gradient of risk across deciles.

3.3 Discussion

Prospective clinical databases like APPROACH are potentially valuable tools for studying outcomes of health care. However, missing data present major challenges to researchers wishing to develop risk adjustment algorithms to take advantage of clinical databases. As noted earlier, the standard methodologies for handling missing data presuppose that the data are at least "missing at random"— an assumption that is frequently violated in clinical and health care research. In the APPROACH database, we faced a clearly non-random pattern of missing data, and were left with the choice of 1) not using the data, 2) assuming that missing data meant the patients did not have the risk factor in question, or 3) developing a method for replacing missing data by drawing on administrative data for the same patients.

As shown in table 3-4, a predictive model based on enhanced data performed better than the alternatives based on excluding cases with any missing values or imputing baseline (zero) values for missing variables. We acknowledge, however, that the model parameters presented in Table 3-4 are only marginally better for the enhanced data than for the other two data sources. It could be argued that such small improvements in discrimination, goodness-of-fit, and gradient of risk are hardly worth the effort and expense of data merging. We would nonetheless propose that the data merging is worthwhile for the following reasons: 1) All measures of model performance improved, indicating that several aspects of model prediction were individually improved by the data merging methodology. 2) While the APPROACH 4600 data yielded a model with reasonably favorable properties (generally the second best across the three data sources), we had to exclude more than 1400 cases from that analysis – an exclusion that has the potential to introduce bias, considering the non-random nature of missing data. 3) In our case, the data merging process was not excessively effortful or expensive, and alternate methods of imputation would have been problematic for reasons discussed earlier.

The model generated with the enhanced data has clinical face validity (i.e. most of the odds ratios in table 3-5 are clinically credible). Two possible exceptions are the protective odds ratios for hyperlipidemia and malignancy. For hyperlipidemia, it is possible that the APPROACH database captures only *identified* hyperlipidemia, which is likely to be treated. The reference group without coded hyperlipidemia in APPROACH may, on the other hand, include patients who actually have untreated hyperlipidemia. Another consideration is that some secondary diagnoses (usually chronic asymptomatic conditions) tend to be under coded in the administrative data records of patients who experience adverse outcomes [15]; this may have contributed to the protective odds ratio for hyperlipidemia. As for malignancy, we first draw attention to the wide confidence intervals of its odds ratio (0.4 – 1.6).

Furthermore, it is possible that only healthier patients with less advanced malignancies are undergoing cardiac catheterization, a patient subset for whom we expect low 1 year mortality.

We did lose 211 APPROACH patients because of failed linkage to administrative data, but this loss was far smaller and had far less impact on generalizability of the findings than the exclusion of more than 1500 patients, as would have been the case had we only analyzed patients with complete data sets. Reassuringly, the unmatched cases had generally similar characteristics to matched cases.

3.4 Conclusions

Iezzoni [16] has stated that although the clinical content of administrative data may be criticized, administrative data are readily available, computer readable, encompass large populations, and are useful for supporting research on outcomes of care. In this instance, we have demonstrated benefit from the combined use of clinical and administrative data in an ongoing prospective data collection initiative. Our positive experience with administrative data cannot automatically be generalized to other databases, and we caution that this solution should be tested empirically against strategies that are more conventional. Researchers should, for example, be aware that administrative data may be problematic in analyses predicting short-term outcomes such as in-hospital mortality, because it is often not possible to distinguish pre-existing conditions from complications arising after admission. This was not a problem in our analyses, because we wanted to capture all clinical risk factors present *around the time* of cardiac catheterization as predictors of a long-term outcome – one year mortality. (Canadian administrative data actually contain a diagnosis-type indicator that allows us to distinguish between co morbidities and complications; we did not use this because of our objective of capturing all clinical risk factors present around the time of catheterization.) As well, researchers should also be aware that incorrect coding of diagnoses in the administrative database may result in the enhanced database yielding false positive

results. Familiarity with the coding methodology of the institution whose administrative database is used may reduce the risk of this occurring.

Of interest, a model run on the administrative data alone resulted in a c statistic of 0.721, significantly lower than the c statistics for the clinical data models. This was not surprising as important predictors in the model using the enhanced data were left ventricular ejection fraction, and the coronary anatomy index; such variables are generally not collected in administrative databases. We emphasize, therefore, that the ultimate objective of prospective clinical registries such as APPROACH remains the collection of complete data on all cases. However, given the cost of clinical databases, and the usual problems of incomplete data capture in the start-up phases of any clinical registry, our experience may be valuable to other researchers.

Table 3-1 Frequencies of missing data (overall and by hospital) for each of the clinical variables collected in APPROACH.

Independent Variable	Percent Missing Overall	Percent Missing by Hospital A	B	C	D
Cerebrovascular Disease	5.8%	2.8%	1.7%	8.8%	9.8%
Congestive Heart Failure	5.2%	0.5%	1.1%	8.9%	10.1%
Pulmonary Disease	10.7%	6.1%	5.1%	17.2%	14.9%
Renal disease	15.2%	8.8%	4.5%	11.6%	34.5%
Diabetes Type I	5.8%	2.8%	1.7%	8.8%	9.8%
Diabetes Type II	5.8%	2.8%	1.7%	8.8%	9.8%
Dialysis	15.2%	8.8%	4.5%	11.6%	34.5%
Hyperlipidemia	5.8%	2.8%	1.7%	8.8%	9.8%
Hypertension	5.8%	2.8%	1.7%	8.8%	9.2%
Prior CABG	10.7%	6.1%	5.1%	17.2%	14.9%
Prior PTCA	10.7%	6.1%	5.1%	17.2%	14.9%
Prior Infarction	5.8%	2.8%	1.7%	8.8%	9.8%
Liver/Gastrointestinal Disease	14.5%	10.6%	9.3%	20.4%	18.1%
Malignancy	10.7%	6.1%	5.1%	17.2%	14.9%
Peripheral Vascular Disease	5.8%	2.8%	1.7%	8.8%	9.8%
Prior Lytic Therapy	10.7%	6.1%	5.1%	17.2%	14.9%
Left Ventricular Ejection Fraction	18.5%	19.1%	7.6%	20.1%	28.0%
Coronary Anatomy	9.2%	4.0%	2.8%	2.7%	25.5%

Table 3-2 Coding scheme used to define variables in the administrative database

VARIABLES	ICD-9-CM CODE
CEREBROVASCULAR DISEASE*	430-438
CONGESTIVE HEART FAILURE*	428
PULMONARY*	490-496, 500-505, 5064
RENAL DISEASE	584, 582, 583.0 - 583.7, 585, 586, 588
DIABETES TYPE I	250.0-250.9 with 5th digits 1 & 3
DIABETES TYPE II	250.0-250.9 with 5th digits 0 & 2
DIALYSIS	V42.0,V45.1,V56.0,V56.1,V56.8 OR procedure 39.27, 39.42, 39.9
HYPERLIPIDEMIA	272.0-272.4
HYPERTENSION	401-405
PRIOR CABG	V45.81
PRIOR PTCA	V45.82
PRIOR INFARCTION*	412
PRIOR THROMBOLYTIC THERAPY	E934.4
LIVER/GASTROINTESTINAL DISEASE*	456.0 - 456.21, 572.2 - 572.8, 571.2, 571. 4 – 571.49, 571.5, 571. 531-534
MALIGNANCY/METASTATIC DISEASE*	140-172, 174 - 208
PERIPHERAL VASCULAR DISEASE*	441,443.9, 785.4, V43.4
CLINICAL INDICATIONS FOR CATHETERIZATION	410
MYOCARDIAL INFARCTION	411.1, 411.81, 411.89, 413.0
UNSTABLE ANGINA	413.1, 413.9
STABLE ANGINA	NONE OF THE ABOVE CODES FOR INDICATION PRES
OTHER	

* Used codes as defined by Deyo et al. [7].

Table 3-3. Frequencies of clinical characteristics in each of the three databases

Independent variable	APPROACH 4600	APPROACH 6000	ENHANCED DATA
Cerebrovascular Disease	3.8%	3.6%	4.7%
Congestive Heart Failure	8.0%	8.6%	13.9%
Pulmonary Disease	4.3%	4.5%	8.1%
Renal disease	1.6%	1.4%	2.1%
Diabetes Type I	1.4%	1.6%	2.5%
Diabetes Type II	4.9%	13.9%	15.1%
Dialysis	0.9%	0.7%	0.8%
Hyperlipidemia	35.7%	32.9%	37.4%
Hypertension	46.8%	43.9%	50.3%
Prior CABG	8.3%	7.5%	7.9%
Prior PTCA	14.8%	12.4%	13.1%
Prior Infarction	41.1%	37.6%	53.4%
Liver/Gastrointestinal Disease	1.8%	1.6%	2.9%
Malignancy	2.0%	2.2%	2.7%
Peripheral Vascular Disease	5.5%	5.5%	5.9%
Prior Thrombolytic Therapy	11.7%	10.5%	10.5%

Table 3-4. Parameters of model performance

Dataset	c-statistic	Hosmer-Lemeshow decile of risk analysis[a]		Change in deviance (⇓) from null model
		Mean absolute difference (%)[b]	Gradient of risk	
APPROACH 4600 (n=4629)	0.766	1.01%	45.0	242.2
	(0.724 – 0.823)		(34.46 – 138.65)	(215.86 – 364.16)
APPROACH 6000 (n=6065)	0.755	2.06%	42.2	350.1
	(0.732 – 0.803)		(31.98 – 83.84)	(324.94 – 474.22)
ENHANCED DATA (n=6065)	0.770*	0.33%*	46.3*	406.2*
	(0.758 – 0.807)		(32.34 – 92.00)	(344.10 – 535.06)

*Indicates best model according to specific parameters.

[a] p values from the Hosmer-Lemeshow test were 0.39, 0.24, and 0.59 for the APPROACH 4600, APPROACH 6000, and enhanced data models, respectively. The models are all therefore not rejected, but we draw readers' attention to published criticisms of the Hosmer-Lemeshow test [12].

[b] This column presents the mean absolute value of observed minus expected mortality (%) across deciles. Lower values indicate better fit.

Table 3-5. Multivariable model derived from enhanced data.

VARIABLES	Odds Ratio	95% Confidence Interval
AGE for each 10 yr.	1.4	(1.2 - 1.6)
CEREBROVASCULAR DISEASE	2.1	(1.4 - 3.3)
CONGESTIVE HEART FAILURE	2.7	(1.9 - 3.6)
PULMONARY DISEASE	1.4	(0.9 - 2.0)
RENAL DISEASE	5.6	(3.4 - 9.1)
DIABETES MELLITUS	1.2	(0.8 - 1.6)
DIALYSIS	1.3	(0.5 - 3.3)
HYPERLIPIDEMIA	0.8	(0.6 - 1.0)
HYPERTENSION	1.1	(0.8 - 1.4)
LIVER/GASTROINTESTINAL DISEASE	1.0	(0.5 - 2.0)
MALIGNANCY	0.8	(0.4 - 1.6)
PRIOR CABG	1.2	(0.8 - 1.8)
PRIOR MYOCARDIAL INFARCT	1.1	(0.8 - 1.6)
EJECTION FRACTION		
<30%:>50%	2.6	(1.6 - 4.4)
30-50%:>50%	1.6	(1.0 - 2.4)
V-gram not done:>50%	3.6	(1.9 - 6.9)
missing:>50%	2.1	(1.5 - 3.1)
CORONARY ANATOMY		
1&2 vessel disease: normal	1.3	(0.6 - 2.9)
2 vessel disease PLAD%: normal	2.3	(0.8 - 6.5)
3 vessel disease: normal	3.2	(1.5 - 7.0)
3 vessel disease PLAD%: normal	3.4	(1.5 - 7.6)
LEFT MAIN: normal	4.9	(2.2 - 11.2)
Missing:normal	2.1	(0.8 - 5.6)
PRIOR PTCA	0.9	(0.6 - 1.4)
PERIPHERAL VASCULAR DISEASE	1.5	(0.7 - 1.8)
PRIOR THROMBOLYTIC THERAPY	1.4	(0.9 - 2.2)
SEX female: male	1.3	(1.0 - 1.8)
CLINICAL INDICATION		
Myocardial infarct: Stable angina	1.2	(0.8 - 1.8)
Unstable angina: Stable angina	1.0	(0.7 - 1.4)
Other: Stable angina	1.4	(0.9 - 2.2)

Abbreviations: PLAD= Proximal Left Anterior Descending Artery; V-gram=ventriculogram, PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting.

Table 3-6. Goodness-of-fit across deciles of model-predicted risk*

DECILE	OBSERVED	EXPECTED	TOTAL
1	5	2.69	607
2	5	4.35	607
3	3	5.92	607
4	5	7.86	607
5	7	10.30	607
6	13	13.69	607
7	19	18.49	607
8	30	25.99	607
9	44	41.56	607
10	124	124.18	602

* Hosmer-Lemeshow Chi-Square statistic = 6.53 (p=0.59) ; Gradient of risk - 124.2/2.7 = 46.3

3.5 References

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CHAPTER 4

COMPREHENSIVE LITERATURE REVIEW OF STATISTICAL METHODS USED TO ANALYZE SEATTLE ANGINA QUESTIONNAIRE SCORES.

4.0 INTRODUCTION

Treatments provided to patients with coronary artery disease (CAD) are often performed with the objective of prolonging life by eliminating or slowing down the stenosis in the coronary arteries thereby increasing the blood flow to the heart. For many patients with CAD, treatment options of coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and/or medical management are all clinically feasible options. The evidence comparing CABG and PCI shows little difference in survival between patients treated with these two treatment strategies[1]. Due to the lack of significant evidence regarding the supremacy of one treatment over another, it has been suggested that "....treatment decisions should be based not only on survival differences, but also on symptom relief, quality of life outcomes and patient preferences" [2].

Spertus et al have developed a disease-specific functional status instrument measure, the Seattle Angina Questionnaire (SAQ) [3]. The SAQ was developed to measure the quality of life (QOL) outcomes of patients with CAD. The developers established the reliability and validity of the SAQ as a disease-specific QOL instrument. The SAQ is a 19 item self-administered questionnaire. Five dimensions of the functional status of patients with CAD are measured generating five independent scales: physical limitations, anginal stability, anginal frequency, disease perception and treatment satisfaction. Each of the questions is measured on an ordinal scale with 1 indicating the lowest/poorest response.

The questions specific to each dimension are summed and then converted to a zero to 100 range. As each scale measures a unique dimension, the five scales have been tested for validity, responsiveness, and reproducibility independently using different patient groups [3].

Based on the results of the validity, responsiveness, and reliability testing, the SAQ has been judged to be a valid, responsive, and reliable instrument. Specifically, it has been demonstrated that the SAQ is sensitive to clinical changes in a patient's coronary artery disease, and that it focuses on symptoms and impairments in health that are unique to coronary disease[3]. The Medical Outcomes Trust adopted the SAQ as a QOL measure for patients with CAD. The SAQ has been translated into 16 languages for use in Europe, Scandinavia, the Middle East, and North America [4], and is in widespread use worldwide (Spertus, Personal communication June 1999).

While analyzing SAQ data gathered from a population based cohort of Alberta patients who had undergone cardiac catheterization [5], we noticed that each of the five dimensional scores of the SAQ were non-normally distributed and had marked ceiling effects [6]. Interestingly, no mention is made in either of the SAQ scale developmental studies[3,8] of the typical distributions of the dimensional scale scores. Parametric tests were used in all of the analyses done to validate the SAQ. Mean values were reported without standard deviations therefore making it difficult to assess the distributional properties of the scales. Given the non-normal distributions for the SAQ dimensions for our cohort, the assumptions of parametric tests would have been violated if we used t-tests to compare mean group scores or general linear modeling to risk adjust the SAQ scores. Consequently, the use of appropriate analysis methods for the SAQ became an important issue. The purpose of this paper is to identify all published studies analyzing SAQ scores, and to compare and contrast the statistical methods used in studies that utilized the SAQ to compare QOL scores in patients with CAD.

4.1 METHODS

4.1.1 Literature Search

The literature search of the articles that cited or used the SAQ scale as a QOL outcome measure, performed in May 2000, included all years from the development of the SAQ (1994) to present. Electronic databases (Medline, Psychlit, Embase, Cinahl, Health star, Pubmed, Ageline, Cochrane, Sociological abstracts, MD consult) were searched using "Seattle angina questionnaire" as a key word, text word or MESH heading as well as combinations of Seattle, angina, and questionnaire. Web of Science (Scientific Citation Index) was searched to identify any manuscripts that cited either one of the two developmental articles authored by JA Spertus and colleagues [3,8]. Relevant manuscripts were identified as any studies that used the SAQ as a measurement tool for QOL outcome data.

4.1.2 Data Extraction

For each of the manuscripts, we recorded the type of study, purpose, how and when in the study the SAQ was completed. All relevant manuscripts were further reviewed to identify the method(s) of statistical analysis used in the analysis of SAQ data and the appropriateness of the method(s) selected based on the statistical tests' analytical assumptions.

4.2 RESULTS

A total of 39 articles cited and/or used the SAQ scale (Table 4-1). The electronic database search identified six studies. Two of the six were the SAQ development studies [3, 8]. Two studies employed the SAQ as a measure of QOL in patients with CAD [9,11], one study provided an overview of the health-related QOL methods for a future study [10] and one study [12] compared the SAQ to two other QOL measures. Searching the Scientific Citation Index identified a *further* 33 articles that cited one or both of the two

Spertus SAQ developmental articles [3, 8]. Of those 33 studies, six articles were identified as having used the SAQ to measure QOL outcomes [13-18]. Seventeen articles referred to the SAQ as a disease-specific tool for assessing QOL in patients with CAD[19-35]. Six articles used the results of the developmental SAQ article as validation for their own particular study [36-41]. One article identified and reviewed the treatment satisfaction dimension of the SAQ [42]. Two articles were published in non-English journals, German and Spanish, and were not assessed. One article planned to use the SAQ in an upcoming RCT [43].

Of the nine studies that used the SAQ as a QOL outcome measure (Table 2), three studies [13, 16, 18] did not explicitly describe how the results of the SAQ questionnaires were analyzed. General statements such as the following were often used: "...for each of the 15 components of the SAQ, (3 groups compared on 5 SAQ scales)... TMR was associated with a significantly better result than medical management" [13]. Five studies [10,12,14,15,17] used parametric tests that require normally distributed data. However, assumptions required for the use of parametric tests were not specifically discussed or addressed. Although none of the studies explicitly discussed the distributions of the SAQ scores, mean scores (when presented), e.g. 88+/- 18 (S.D.) [14] indicate that the upper limit of intervals defined by the reported standard deviations exceeded the maximal score possible for the scales (100). As well, standard deviations presented [10] were over half of the mean SAQ score. Altman states that for measurements that cannot be negative ... we can infer that the data have a skewed distribution if the standard deviation is more than half the mean. [7] This suggests that the SAQ scale scores may not have been normally distributed.

While it is true in small samples that data should be normally distributed for use of t-tests, linear regression, and ANOVA, this is not an absolute requirement of the analysis

in large samples because of the Central Limit Theorem. However, sample sizes for the studies that used parametric statistics in their analysis of the SAQ scores ranged from 10 to 78 patients (Table 2). One of the studies with 78 patients in the sample [10] used t-tests to determine the differences between baseline and 3 month SAQ scores. The second study with 78 patients [15] presented mean SAQ scores taken at one year follow-up. The SAQ scores presented in both studies suggest that the scores were skewed [7] and in both cases no apparent attempt was made to transform the data. Of further note is that the two studies with the largest samples [10,15] were prospective cohort studies. As with any cohort study, comparisons of outcomes can prove misleading without first adjusting for patient's characteristics. Although the sample sizes may have been sufficient for the tests used, the statistical analyses should have included the presentation of *adjusted* as opposed to crude SAQ scores.

Only one of the nine studies that used the SAQ addressed the issue of analyzing non-normally distributed SAQ scores [9]. Reporting on the results of a randomized controlled trial that compared transmyocardial revascularization with continued medical therapy in patients with medically refractory angina, Burkoff et al noted that the SAQ, completed by the patients at baseline and three months, was analyzed using median scores with inter-quartile range scores. Changes in the SAQ scores from baseline were compared using the non-parametric Wilcoxon's test.

4.3 DISCUSSION

Our review demonstrates that the SAQ is recognized as a QOL measure for patients with CAD and further, that parametric tests are used to compare SAQ scores. This is problematic considering the potentially non-normal distributions of the SAQ scale scores. Bivariate analyses of non-normally distributed data are reasonably straightforward using non-parametric tests such as the Mann-Whitney test. Methods to control for covariates in a

multivariate analysis prove to be somewhat more challenging. Several different strategies can be considered including 1. Logistic regression using patients who scored 100 (the maximum) versus patients who scored less than 100 as a dichotomous outcome measure. 2. Logistic regression using patients who scored at or above the median and patients who scored below the median as a dichotomous outcome variable. 3. Ordinal regression whereby dimensional scores are categorized into ordered categories and mean dimensional scores are used as independent variables in the regression analysis [44].

Although this paper focuses on the SAQ, the issue of the most appropriate statistical analysis for disease specific QOL scales may not be unique to this particular scale. Ordinal scales (particularly common in QOL instruments) even when transformed, risk generating skewed results [45]. The 'average' scores for patients with chronic diseases may be concentrated at the top of the scale (ceiling effect) or the bottom of the scale (floor effect) severely limiting the range of scores possible. This then makes it difficult using parametric methods to describe differences in QOL post-treatment or changes in QOL over time.

A review of the literature shows that the assumptions of the statistical tests used for the analysis of SAQ scores may have been violated leading to questionable results. As the SAQ is becoming a widely recognized instrument for measuring the QOL of patients with CAD, results of this research suggest that investigators may need to increase their attention to the distributional characteristics of their QOL data before applying parametric tests.

Table 4-1 Results of literature search

Use of SAQ in Manuscripts	Electronic Databases N (reference)	Web of Science N (reference)	Total
SAQ Development Studies by Spertus et al	2 –[3,8]		2
Used SAQ as a measure for QOL	***3 [9,11,12]***	***6 [13-18]***	***9***
Plans on using SAQ in future study	1 [10]	1 [42]	2
Articles refer to SAQ as disease specific tool for measuring QOL.(do not actually use SAQ)		17 [19-35]	17
Use the results of SAQ developmental article as validation for another QOL measure		6 [36-41]	6
Identify and review the treatment satisfaction scale of the SAQ		1 [42]	1
Articles published in non-English journals (not assessed)		2	2
Total	6	33	39

Table 4-2 Studies that used the SAQ as a QOL measurement tool

Author	Type of study	Purpose	SAQ completion	Analysis of SAQ
Blum et al [18]	Prospective case-control pilot study Sample size 10 patients	Assess the effects of oral L-arginine on the clinical inflammatory state of patients with CAD and intractable angina pectoris	Patients filled out SAQ before treatment, 1month post and 3 months post treatment.	ANALYSIS NOT DESCRIBED Results: Assessment of changes in SAQ demonstrated improvement in all 5 aspects of angina
Fruitman et al [15]	Cohort of 127 CABG patients > 80 years. Between March 1995 to Feb 1997. SAQ follow-up = 78 CABG only patients.	Stated that they wished to look at whether health care resources spent on elderly patients were cost effective in maintaining a meaningful QOL	Telephone interview (mean follow-up time 15.7 months, standard deviation = 6.9 months)	PARAMETRIC TEST USED Mean scores of QOL dimensions presented. No reference to distributions or normal scores for octogenarians - "very good scores in all areas ... generally good enjoyment of life"
MacDonald P. et al [10]	Prospective cohort Jan 1995-Feb 1996. 100 patients > 75 years. Follow-up on 78 patients.	1.Examine the impact of CABG surgery on the QOL of elderly patients with CAD. 2. compared different QOL measurements 3. examined predictors of poor QOL outcomes assessed clinical ratings to identify patients at high risk	Mailed questionnaires at three months	PARAMETRIC TEST USED Mean change scores between baseline and 3 months using (effect size mean change)/(standard deviation of mean change). *t*-tests for determinations of differences between baseline and 3 month scores. Logistic regression to identify risk adjusted odds of no change in scores.
Jeremias et al [16]	Prospective cohort of 145 stent/PCI/catheterization patients. From Mar 97-Aug 97. Compared SAQ scores in 3 groups. 51-stent group, 33 PCI group, and 61 Diagnostic Catheterization group.	Evaluate the frequency of nonischemic post procedural chest pain in patients after stent implantation compared with patients undergoing PCI or diagnostic catheterization.	SAQ used for assessment of post-procedural chest pain within 24 hours of procedure.	ANALYSIS NOT DESCRIBED Implied non-parametric but not conclusive. Only states that 3 of the scales were "comparable in all groups"
Kimble, and Kunik [17]	Descriptive correlational design. 95 patients with chronic Angina. SAQ scores compared on 45 women and 50 men	Purpose was to explore relationship among knowledge and use of sublingual nitroglycerine and QOL	SAQ used to measure QOL in interview conducted by phone (98%) or face to face.	PARAMETRIC TEST USED Compared mean scores between genders. Pearson r used to examine relationship between sublingual nitroglycerine use and QOL
Simes et al [14]	Used patients from randomized control trial of Stenting in Chronic Coronary Occlusion study (SICCO). 117 patients. SAQ scores compared on two groups: 59 control group and 57 stent group.	Assessed the long-term clinical outcomes of stenting chronic occlusions	Used SAQ sent as questionnaire or solicited by telephone 2 years post randomization	PARAMETRIC TEST USED SAQ scores presented as means. Statistical methods states used *t*-test with means. Anginal stability scale missing.

Frazier et al [13]	Randomized controlled multicenter trial of 192 patients. Follow-up on 3 groups of patients: 67 patients in TMR group, 37 patients in medical group with crossover and 30 patients in the medical group with no crossover.	Purpose was to examine the efficacy and safety of Transmyocardial Revascularization in patients with refractory angina and left ventricular free wall ischemia that was not amenable to direct coronary revascularization and to compare to medical management.	SAQ questionnaire completed at enrollment, 3,6, and 12 months	ANALYSIS NOT DESCRIBED General discussions of all statistical analysis. Results indicated that for each of the 15 components of the SAQ (3 groups of patients with 5 SAQ scores each), "Transmyocardial revascularization was associated with a significantly better result that medical management."
Burkhoff et al [9]*	Prospective randomized controlled trial of 182 patients assigned to transmyocardial revascularization & medications or medications alone	To compare transmyocardial revascularization with continued medical therapy for patients with medically refractory angina	SAQ questionnaires completed at baseline, and 3 months.	NON-PARAMETRIC TESTS USED Analyzed changes in SAQ scores between groups using Wilcoxon's rank-sum test. Presented as medians and inter-quartile ranges.

*Used non-parametric statistics to analyze data.

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CHAPTER 5

COMPARISON OF FOUR DIFFERENT STATISTICAL ANALYSIS STRATEGIES FOR ANALYZING SEATTLE ANGINA QUESTIONNAIRE QUALITY OF LIFE DATA

5.0 INTRODUCTION

The Seattle Angina Questionnaire (SAQ) is being used with increasing frequency in clinical research to address the quality of life (QOL) outcomes of patients with coronary artery disease (CAD). Results of a comprehensive literature review identifying all published studies analyzing the SAQ demonstrated that inappropriate analysis methods are commonly used to analyze SAQ scores [1]. Our results of a preliminary analysis of a large population based cohort of patients undergoing cardiac catheterization for CAD indicated that as high as 35% of patients selected 100 (the best possible score) for one of the dimensions [2]. The resulting ceiling effect produced a strongly skewed dataset creating graphically non-normal distributions in all five SAQ dimensions. Transformation of the data using log transformation, squared and square root transformations failed to yield normally distributed data. The distribution of the data led to an exploration of the most appropriate statistical analysis for multivariate modeling of the predictors of QOL outcomes. Four strategies for analysis were explored. The first strategy was to use linear regression relying on the central-limit theorem that states that where one has a large dataset (large number of cases), despite the non-normality of the raw responses and the residuals, statistical inferences can be made based on the approximate normality of the regression estimates. The second and third strategies involved dichotomizing the outcome data by two separate methods and using binary logistic regression analysis. The fourth strategy was to use ordinal logistic regression.

5.1 The SAQ

The SAQ is a 19 item self-administered questionnaire. Five dimensions of CAD are measured, generating five independent scales measuring exertional capacity, anginal

stability, anginal frequency, disease perception and treatment satisfaction. Each of the questions is measured on an ordinal scale with one indicating the lowest/poorest response. The questions specific to each dimension are summed and then converted to a zero to 100 range. As each scale measures a unique dimension, the five scales have been tested for validity, responsiveness, and reproducibility using different patient groups [3].

Based on the results of the validity, responsiveness and reliability testing, the SAQ was determined to be a valid, responsive and reliable instrument. The research by Spertus et al [3] suggested that the SAQ was sensitive to clinical changes in patient's coronary artery disease, and that it focused on symptoms and impairments in health that are unique to coronary disease. [3] The Medical Outcomes Trust adopted the SAQ as a QOL measure for patients with CAD. The SAQ has been translated into at least 16 languages for use in Europe, Scandinavia, the Middle East and North America [4], and is in widespread use worldwide (Spertus, Personal communication).

The purpose of this paper was to compare four different statistical analysis strategies for analyzing skewed SAQ QOL data including 1. Linear regression using the SAQ scoring method set out by Spertus et al. [3] 2. Logistic regression using patients who scored 100 (the best score) versus patients who scored less than 100 as the outcome variable. 3. Logistic regression using patients who scored at or above the median versus patients who scored below the median as the outcome variable. 4.Ordinal regression whereby dimensional scores were categorized into ordered categories with those in the lowest category having the lowest QOL scores while those in the highest category had the highest QOL scores.

5.2 METHODS

5.2.1 APPROACH Project

The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) is a province-wide inception cohort of all adult Alberta residents undergoing cardiac catheterization for ischemic heart disease. The APPROACH project was initiated to study provincial outcomes of care and facilitate quality assurance/quality improvement for

patients with CAD in Alberta. The APPROACH database contains detailed clinical information on adult patients with known or suspected CAD. Outcome QOL data were collected by means of a self reported questionnaire mailed to patients on the anniversary of their initial cardiac catheterization. The self reported questionnaire includes the SAQ. Participants were provided with two options for completing the follow-up questionnaire. Participants could complete the questionnaire and mail it back in a stamped envelope or they could telephone a toll free line and respond to a verbally administered questionnaire that is recorded and transcribed daily. A second questionnaire was sent to non-respondents with the same options for completion. In the case of the questionnaires failing to reach subjects due to the wrong addresses, letters were sent to the referring cardiologist/family doctor to attempt to get a more current/correct mailing address and if available questionnaires were resent.

5.2.2 Sample

Eligible subjects included all consenting adult Alberta residents over the age of 18 years, with CAD (Duke Coronary Index coded between 1 and 13) [5], without a previous catheterization, or surgical intervention, undergoing cardiac catheterization in Alberta, from January 1st, 1995 to December 31st, 1997. The cohort for this study comprised 3523 adults who responded to the one-year follow-up QOL questionnaire.

5.2.3 Clinical Variables

Clinical data were obtained from the APPROACH database on adults who had undergone cardiac catheterization. Data elements collected at catheterization include patients' age, sex, and presence of the following risk factors: cerebrovascular disease (CEVD), congestive heart failure (CHF), chronic pulmonary disease (COPD), renal disease, peripheral vascular disease (PVD) type I diabetes, type II diabetes, dialysis, hyperlipidemia, hypertension, liver/gastrointestinal disease, malignancy, coronary anatomy as defined by the Duke Index, [5] clinical indication for catheterization, left ventricular ejection fraction,

prior lytic therapy, prior myocardial infarction, prior coronary artery bypass graft surgery, and prior angioplasty.

5.2.4 Quality of Life Data

The QOL paradigm of patients with CAD as identified by Spertus in the SAQ [3] is made up of a combination of dimensions including the exertional capacity, anginal stability/frequency, treatment satisfaction and disease perception. One of the most directly quantifiable measurements, the exertional capacity scale, determines the exertional capacity of patients with CAD. Consequently, the Exertional Capacity (EC) scale scores of the SAQ were used for the purposes of these analyses. The EC score is composed of nine questions specific to the exertional capacity dimension. The nine questions were summed and then transformed to a zero to 100 range as indicated by the authors' method for scoring the SAQ [3]. This score, along with three new variables, were created for each of the four models compared. For the linear regression model 'ECSCORE' was used as the outcome variable. For the first logistic regression model a binary variable 'EC100' was created with respondents who scored 100 (no limitations to exertional capacity) coded as '0' and respondents who scored less than 100 coded as '1'. A second variable was created for the outcome variable of the second logistic model 'ECMEDIAN' whereby respondents who scored higher than the median score were coded as '0' and respondents scoring less than or equal to the median score were coded as '1'. Finally, an outcome variable 'ECCAT' was created for the ordinal regression model. Each of the 9 items that comprise the exertional capacity score is a five-point item with a maximum score of 5. The original scores from the 9 exertional capacity dimension questions were added together and divided by 9 to create a mean exertional capacity score. The set of mean scores was then separated into quintiles to produce 5 equal groups. This categorization reflected the scale itself with the lowest group (category 1) having the overall lowest scores continuing up to category 5, the group with the highest overall score.

5.2.5 Models

Four regression models were constructed. For this comparison, all potential predictor variables collected at catheterization were entered into the models. One linear regression model was run using the ECSCORE as the outcome variable. Two logistic regression models were run using 1) EC100 and 2) ECMEDIAN as the outcome variables. One ordinal regression model was fitted using the variable ECCAT as the outcome variable. The logit link function was used in the ordinal regression modeling. Approximate odds ratios and confidence limits based on the linear regression results arise from viewing the proportional odds model in terms of a latent logistic error model. A crude conversion factor, π { 3*sresid* }, where *sresid* is the residual standard deviation, results from matching variances between logistic and normal distribution curves. To get a rough estimate of the odds ratio, the negative of the coefficients from the linear regression were divided by 10 and exponentiated ($^{(-\text{coefficient})/10}$). All statistical analyses were performed using SPSS version 10.0.7.

5.3 ASSESSMENT CRITERIA FOR MODEL FIT.

5.3.1 Linear Regression Model

If the linear regression model is indeed appropriate for the data under analysis, the observed residuals should exhibit properties in keeping with the assumptions for regression analysis [6]. These include that the unobserved error terms of the residuals are independent, have a mean of zero, a common variance and follow a normal distribution. An analysis of the residuals from the fitted model was performed specifically examining the variance, skewness and kurtosis of the residuals. As well a normal plot of the residuals was produced to verify that the residuals had an approximately normal distribution as well as to check the overall fit of the model. The fit of the model was also assessed by considering the proportion of the total sum of squares that was explained by the regression using the adjusted R^2 statistic. The adjusted R^2 is the more appropriate statistic to use as it compensates for the expected chance prediction when the null hypothesis is true. [7] In

order to maintain consistency among the 4 models, all possible explanatory variables were left in the model. Although R^2 is a valuable summary measure of model performance, Iezzoni [8] notes that it provides little intuitive feel for the model's ability to discriminate among cases with high or low values of the outcome variable. Accordingly, we also examined the actual and predicted mean exertional capacity scores within quintiles.

5.3.2 Logistic Regression Models

The -2 log likelihood change in deviance was used to examine the fit of the binary logistic models. The models' discrimination and goodness-of-fit were assessed using the c statistics and the Hosmer-Lemeshow (H-L test), respectively. The c statistic corresponds to the area under the receiver operating characteristic (ROC) curve and is a measure of model discrimination [8]. If all predicted probabilities for cases coded as 1 are higher than the predictions for those who were coded as 0, the c statistic takes on a maximum value of 1.0. A model with no ability to discriminate has a c statistic of 0.5. H-L tests were used to assess the models' goodness of fit. The H-L test computes a summary measure of the discordance between the expected and the observed number of outcomes for cases in deciles of increasing predicted risk [8]. Models with significant H-L chi square values (i.e. $p<0.05$) are rejected for poor fit. We chose to use this test because of its widespread use in the literature, but draw readers' attention to published studies raising concern regarding the Hosmer-Lemeshow test's stability and power [9]. We also used the decile framework of the H-L analysis to calculate, for each model, the mean absolute value of observed cases minus expected cases across deciles (an analysis that is not sensitive to sample size). Finally, minus 2-log likelihood (-2LL), or residuals, in each model were compared against the null model. Large values indicate large decreases in deviance attributable to the model [10].

5.3.3 Ordinal Regression Model

The proportional odds model sometimes referred to as the "ordinal logistic model" [11] is an extension of binary logistic regression. The -2 log likelihood change in deviance was used to examine model fit. A significant ($p < 0.05$) change in the -2 log likelihood statistic between the baseline model and the final model demonstrates that the predictors were jointly significant based on the likelihood ratio test. The model fit was also assessed using a cross-tabulation of the predicted outcome categories with the observed categories. As the model attempts to predict cumulative probabilities rather than category membership, two steps are involved in predicting categories. First, for each case, the probability is estimated by using the predictor values for a case in the model equations and taking the inverse of the link function. Second, the predicted probabilities are used to select the most likely outcome category, that being the category with the highest probability given the pattern of the predictor values for each case. Finally, the test of parallel lines was examined to determine whether the proportional odds assumption was satisfied. The proportional odds assumption for modeling ordinal data suggests that the cut-point specific odds ratios are homogeneous and uses a chi-square statistic to compare the estimated model with one set of coefficients for all categories to a model with a separate set of coefficients for each category.

5.4 RESULTS

A total of 3523 patients (73.3% male) with a mean age of 62.1 years (SD= 10.7 years) were used for this analysis. Table 5-1 describes the study population. Fifty percent of the patients were hypertensive, 45.3% were hyperlipidemic, while 37.4% had experienced a myocardial infarction within 3 months before their admission for catheterization. Forty-two percent of the patients had undergone catheterization for stable angina. Results of the cardiac catheterization demonstrated that 41.7% of the patients had 2 to 3 vessel disease and 63.9% had an ejection fraction of >50%.

5.4.1 Linear Regression Model Performance

The normal plot of residuals from the linear regression fit revealed a pattern that was much closer to normal than the SAQ scores. However, there remained a pronounced degree of skewness (-0.57) in that the left tail was much longer than the right. The Normal plot of the residuals against the fitted values is very close to a straight line; again suggesting that the model provides a good fit to the data. The adjusted R^2 was 0.54 indicating that 54% of the variance in exertional capacity score was explained by the independent variables in the model. Table 5-2 presents the predicted scores divided into quintiles, cross-tabulated with the actual scores also divided into quintiles. The model does a reasonably good job of predicting the exertional capacity scores by predicting the largest percentage of correct outcome categories in all 5 categories. Category 1 (lowest/worst exertional capacity scores) is the best predicted category (60.5% correctly predicted) followed by Category 5 (highest/best exertional capacity scores) with 56.5% correctly predicted.

5.4.2 Comparison of the two logistic regression models

Binary logistic regression modeling of the data revealed that the use of the median score (EC median) to split the exertional capacity scores into a binary outcome, resulted in a higher c statistic (c=0.874) then did the use of EC100 as the outcome variable. Conversely the median split model demonstrated slightly less model calibration with the H-L decile of risk analysis having a higher mean absolute difference across deciles (2.0%). The corresponding p value (p= 0.20) indicated that the actual and predicted numbers of patients above the median within each of the 10 deciles were not significantly different. The split using less than complete exertional capacity versus complete exertional capacity (EC100), resulted in a slightly lower c statistic of 0.856, yet the H-L decile of risk analysis yielded a lower mean absolute difference of 1.3%. The corresponding p value (p= 0.21) indicated that the actual and predicted EC100 scores within each of the 10 deciles were not significantly different.

5.4.3 Ordinal regression model performance

The ordinal regression model had a highly significant change in deviance score (-2 Log likelihood score) of 7814.88 ($p < 0.0001$). The significant chi-square indicates that the model gives a statistically significant improvement over the baseline intercept-only model. Table 5-3 presents a cross-tabulation of the predicted exertional capacity categories with the actual exertional capacity categories. This table shows that the model predicts the largest percentage of correct outcome categories for all categories, except category 3 (middle category). Categories 1 and 5 were the best predicted with 61.5% and 59.3% predicted in each category respectively. Despite the less than perfect prediction, the majority of cases in all categories were predicted to fall in the adjacent category (i.e. +/- one category) rather than in more distant categories on the ordinal scale. The assumption of homogeneity of the proportional odds ratio over all cut-points was tested with SPSS test of parallel lines yielding a chi-square of 121.25 ($p<0.03$) for the full model.

5.4.4 Comparison of Odds Ratios from the four models

Table 5-4 presents the odds ratios, 95% confidence intervals and confidence interval widths (ratio of the upper confidence interval divided by the lower confidence interval) for all of the variables analyzed in each of the three logistic models and the linear regression model. The linear regression model and the proportional odds model clearly achieved more stable estimates compared to the two binary logistic models as demonstrated by the smallest ratios of the upper confidence intervals to the lower confidence intervals. The linear regression model and the proportional odds model consistently ranked 1st (smallest ratio) or 2nd . The linear regression model, produced the smallest ratios for 11 of the predictor variables while the proportional odds model produced the smallest ratios for 7 of the predictor variables. Both models attained equal ratios for the remaining 6 predictor variables in the models. The binary logistic models yielded much larger ratios and in some instances (e.g. renal disease), the binary logistic models produced confidence intervals that were sufficiently large to suggest that the coefficient of the predictor variables were so unstable that they were uninterpretable.

5.5 DISCUSSION

The SAQ is being used with increasing frequency in clinical research addressing the QOL outcomes of patients with CAD. A review of the literature indicated that inappropriate statistical methods for the analysis of SAQ scores are prevalent. [1] Although the SAQ scores are transformed from ordinal scales to seemingly continuous scales, the non-normal distributions of the SAQ dimensional scores suggested that applying linear regression models to assess predictors of SAQ scores may not be the most suitable statistical analysis to use. With the APPROACH database, we faced a wealth of clinical variables to model outcomes and apparently non-normally distributed SAQ dimensional scores. We were therefore left with the choice of 1) using linear regression after testing model assumptions, 2) assuming that the patients responding to the 1-year SAQ indicating that they had complete exertional capacity (score of 100) were unique and using logistic regression modeling to define the difference, 3) assuming that there was a difference in the patients who responded above the median score as compared to those at or below the median score and using logistic regression analysis, or 4) using the ordinality of the ranked SAQ responses and controlling for the clinical variables using ordinal regression analysis. Globally, all four modeling methods compared in this paper produced acceptable parameters used for measuring model performance. Analysis of the residuals of the linear regression model indicated that these data follow an approximately normal distribution and therefore the assumptions for the use of parametric statistics are met. The adjusted R^2 (0.54) also suggests that the model fits the data reasonably well. This is further evidenced by the fact that the predicted scores for exertional capacity are fairly good especially in the lowest and the highest categories. Both logistic regression models yielded similar discriminative abilities, although the median model discriminated slightly better than the model using the patients who scored 100 (c-statistics: 0.875 and 0.857 respectively). On the other hand, the difference in the H-L goodness of fit statistic, and the mean absolute difference would suggest that the use of a score of 100 in the exertional capacity score to dichotomize the data slightly improved model performance and model prediction. Findings from both

models are valid, yet the dilemma arises when researchers are then faced with making an arbitrary choice as to which cut point to use in order to dichotomize the data.

The highly significant change in the deviance score produced by the ordinal regression model suggests that the model fits the data better than the intercept only model. This is further evidenced by the fact that the predicted scores for exertional capacity do a satisfactory job of predicting the data. A preliminary test for homogeneity of the odds ratios over the various cut points in the ordinal regression model suggested that the model failed to meet the assumption required for use of the model (chi-square=121.24 p=0.03). However, the score test used to evaluate this assumption has a number of limitations. As described by Scott et al [11] zero cells for a regressor variable at an inner value of the outcome variable may produce spuriously high chi-square values. A similar problem may result when data are generally sparse or when one of the values of the outcome represents only a small fraction of the total sample size. In fact, in this analysis, there were 12568 (80.0%) of cells of the dependent variable levels by the combinations of predictor variable values with zero frequencies. Secondly, the score test is a global test of non-proportionality and cannot distinguish heterogeneity associated with the exposure variable from those associated with other covariates. Results from the method suggested by Brant [12] to assess the proportionality assumption demonstrated that the low p value from the score test of the adjusted model was due to sparse data rather than significant heterogeneity. Thirdly, the score test is sensitive to sample size and may produce statistically significant p values between the cut-points where there is little practical difference.

A comparison of the odds ratios and 95% confidence intervals of the four models demonstrated that the linear regression model and the proportional odds ordinal regression model shared in producing the smallest 95% upper confidence interval to lower confidence interval ratios. The linear regression model and the proportional odds ordinal regression models have the additional advantage over the logistic regression models as inferences from the former can be made across the range of outcomes while inferences from the logistic

regression models are limited to comparisons across single cut-points. The within-sample predictive fit was similar for ordinal and linear regression models.

Based on the inherent information loss in grouping, the statistical efficiency of the linear model approach is higher, as can be seen in the relative narrowness of the 95% confidence intervals of the linear regression odds ratio approximations. In addition, the regression slopes are immediately interpretable in terms of the differences in mean SAQ scores between variously defined patient sub-groups. These advantages, however, may be outweighed by issues of lack of fit in other applications where the residual pattern of dispersion is strongly non-normal or in smaller samples where large sample hypothesis tests and interval estimates may be invalid.

In general, there is merit to considering the use of the proportional odds ordinal regression model when there is pronounced non-normality as in the case at hand. It must be noted though that odds ratios, unless they meet the rare disease assumption and approximate relative risks (when the risk of the outcome is low), are not readily interpretable from a practical perspective. Notwithstanding this potential for misinterpretation, the odds ratio has found wide spread use in epidemiology. The constraint placed on the use of the ordinal model is that the log odds does not depend on the outcome category and therefore inferences from fitted proportional odds ordinal models lend themselves to a general discussion of *direction* of response [14].

In conclusion, comparison of 4 models used to analyze SAQ exertional capacity dimensional scores demonstrated that all 4 models were successful at fitting the data. However, the ordinal regression model and the linear regression model were superior to the logistic regression models. The choice between the use of the ordinal regression model or a linear regression model is not as clear-cut. On the one hand, the proportional odds ordinal regression model appears to be more sensitive to the characteristics, specifically the ordinality, of the SAQ data. Scott et al [11] argue persuasively that while ordinal regression modeling retains the inherent ordinality of the data, it neither imposes the loss of information by treating

the outcome as dichotomous, nor the unjustified quantification of category differences when ordinal data are treated as continuous. On the other hand where the residual patterns of dispersion are close to normal or in samples where the large sample hypothesis testing and interval estimates are valid, the regression slopes from the linear regression model are easily interpretable in terms of differences in mean scores between subgroups of interest. These latter points lead us to conclude that in the absence of a breach of the models' assumptions, a combination of the results derived from a linear regression model and an ordinal regression model (adjusted SAQ scores and odds ratios) may produce the most comprehensive interpretation of the data from a quantitative as well as qualitative perspective. Furthermore, analysis of the SAQ using a combination of models will assist in the interpretation, presentation and ultimately the understanding of QOL results for patients with CAD.

Table 5-1 Sample Demographic Data

Independent Variables	Number (overall N= 3523)	Percentage
Age (mean)	Mean:62.1	Std.dev:10.7
Sex	Male: 2583	73.3%
Cerebrovascular Disease	161	4.6%
Pulmonary Disease	253	7.2%
Heart failure	323	9.2%
Renal Disease	45	1.3%
Diabetes Mellitus	519	14.7%
Dialysis	31	0.9%
Hyperlipidemia	1597	45.3%
Hypertension	1763	50.0%
Prior Myocardial Infarction	1305	37.4%
Liver/Gastro Intestinal Disease	105	3.0%
Malignancy	104	3.0%
Peripheral Vascular Disease	211	6.0%
Indications for catheterization		
Unstable Angina	961	27.3%
Myocardial Infarction	676	19.2%
Stable Angina	1462	41.5%
Other	424	12.0%
DUKE INDEX		
Left Main Disease	1043	29.6%
2 & 3 Vessel Disease	1468	41.7%
I Vessel Disease	705	20.0%
Missing	307	8.7%
Ejection Fraction		
<30%	135	3.8%
30-50%	705	20.0%
>50%	2250	63.9%
Ventriculogram not done due to instability	98	2.8%
Missing	335	9.5%

Table 5-2 Crosstabulations of the predicted scores (divided into quintiles) from the linear regression model by the actual scores

	Predicted category 1	Predicted category 2	Predicted category 3	Predicted category 4	Predicted category 5	Total
Actual category 1	399	173	64	19	5	660
N (%)	(60.5%)	(26.2%)	(9.7%)	(2.9%)	(0.4%)	(100%)
Actual category 2	167	222	169	87	15	660
N (%)	(25.3%)	(33.6%)	(25.6%)	(13.2%)	(2.3%)	(100%)
Actual category 3	45	142	188	156	60	591
N (%)	(7.6%)	(24.0%)	(31.8%)	(26.4%)	(10.2%)	(100%)
Actual category 4	13	58	141	204	201	617
N (%)	(2.1%)	(9.4%)	(22.9%)	(33.1%)	(32.6%)	(100%)
Actual category 5	4	34	66	163	347	614
N (%)	(0.7%)	(5.5%)	(10.7%)	(26.5%)	(56.5%)	(100%)
Total	628	629	628	629	628	3142

Table 5.3 Crosstabulations of the predicted scores from the ordinal regression model by the actual scores

	Predicted category 1	Predicted category 2	Predicted category 3	Predicted category 4	Predicted category 5	Total
Actual category 1	406	178	50	17	9	660
N (%)	(61.5%)	(27.0%)	(7.6%)	(2.6%)	(1.4%)	(100%)
Actual category 2	174	252	119	96	19	660
N (%)	(26.4%)	(38.2%)	(18.0%)	(14.5%)	(2.9%)	(100%)
Actual category 3	48	170	134	170	69	591
N (%)	(8.1%)	(28.8%)	(22.7%)	(28.8%)	(11.7%)	(100%)
Actual category 4	17	67	107	211	215	617
N (%)	(2.8%)	(10.9%)	(17.3%)	(34.2%)	(34.8%)	(100%)
Actual category 5	5	37	52	156	364	614
N (%)	(0.8%)	(6.0%)	(8.5%)	(25.4%)	(59.3%)	(100%)
Total	650	704	462	650	676	3142

Table 5-4 Odds Ratios and 95% Confidence Intervals (CI) of three models

Independent Variables	Log regression (EC100) less than complete EC vs. complete EC	Ratio of Upper CI to Lower CI	Log Regression (ECmedian) At or Below Median score vs. Above median score	Ratio of Upper CI to Lower CI	Ordinal Regression Best to worst	Ratio of Upper CI to Lower CI	Linear Regression (mathematical conversion)	Ratio of Upper CI to Lower CI
Male	0.35 (0.26,0.47)	1.80	0.34 (0.27,0.42)	1.55	0.35 (0.30,0.41)	1.36	0.44 (0.38,0.50)	1.32*
Age in years	1.07(1.06,1.08)	1.01	1.09 (1.07,1.10)	1.02	1.07(1.06,1.08)	1.01	1.06 (1.05,1.06)	1.01
Cerebrovascular Disease	1.55 (0.80, 3.00)	3.75	1.29 (0.81, 2.05)	2.53	1.43 (1.03,1.99)	1.93	1.48 (1.32,1.66)	1.26*
Pulmonary disease	1.41 (0.87,2.30)	2.64	1.34 (0.91,1.97)	2.16	1.42 (1.08, 1.86)	1.72	1.29 (1.15,1.45)	1.26*
Heart failure	1.17 (0.71, 1.93)	2.74	1.72 (1.17, 2.52)	2.15	1.68 (1.28,2.20)	1.72*	1.60 (1.15,2.24)	1.95
Renal Disease	17.88 (1.49, 214.17)	143.7	4.47 (1.37, 14.56)	10.62	4.86 (2.15,10.99)	5.11	2.83 (2.03,3.95)	1.95*
Diabetes Mellitus	1.06 (0.76,1.48)	1.95	1.59 (1.21,2.08)	1.72	1.56 (1.28,1.89)	1.48	1.48 (1.26,1.75)	1.39*
Dialysis	0.63 (0.13, 3.07)	23.62	1.62 (0.50, 5.28)	10.56	1.13 (0.48, 2.66)	5.54	1.85 (1.45,2.35)	1.62*
Hyperlipidemia	0.92 (0.74,1.14)	1.54	0.90 (0.76, 1.09)	1.43	0.88 (0.77, 1.01)	1.31*	0.85 (0.65,1.12)	1.72
Hypertension	1.37 (1.10,1.70)	1.55	1.27 (1.05, 1.53)	1.46	1.20 (1.04,1.37)	1.32*	1.15 (0.92,1.44)	1.56
Prior Myocardial Infarction	1.04 (0.80,1.37)	1.71	1.15 (0.91, 1.46)	1.51	1.15 (0.97,1.37)	1.40	1.16 (1.01,1.34)	1.33*
Liver-Gastro Intestinal Disease	0.91 (0.47,1.75)	3.72	1.03 (0.58, 1.83)	3.16	1.15 (0.77,1.73)	2.25*	1.22 (0.65,2.30)	3.56
Malignancy	1.21 (0.61, 2.40)	3.04	0.69 (0.40, 1.20)	3.00	0.84 (0.57,1.25)	2.19	0.77 (0.61,0.95)	1.55*
Peripheral Vascular Disease	1.39 (0.79, 2.45)	3.10	2.16 (1.42, 3.26)	2.30	2.07 (1.54,2.78)	1.80*	1.80 (0.88,3.67)	4.17
Time from catheterization to follow-up (days)	1.00 (1.00,1.01)	1.01	1.00 (1.00, 1.00)	1.00	1.00 (1.001,1.004)	1.00	1.00 (1.001,1.003)	1.00
Time from treatment to follow-up (days)	1.00 (0.99,1.00)	1.01	0.99 (0.99,1.00)	1.01	1.00 (1.00, 1.00)	1.00	1.00 (1.00,1.00)	1.00
Indications for catheterization								
Other : SA^	0.79 (0.54,1.15)	2.13	0.95(0.68, 1.31)	1.93	0.90 (0.71,1.14)	1.60	1.04 (0.85,1.26)	1.48*
UA" : SA	0.97 (0.74, 1.26)	1.70	0.77(0.60, 0.97)	1.61	1.01 (0.85,1.19)	1.40	1.03 (0.89,1.18)	1.33*
MI° : SA	1.15 (0.81, 1.62)	2.00	0.79 (0.58, 1.08)	1.86	0.82 (0.66,1.03)	1.56	0.81 (0.67,0.97)	1.45*
DUKE INDEX								
1VD : <50%DISEASE & 2 VD : <50%DISEASE	0.82 (0.61,1.11)	1.82	0.77 (0.59, 1.02)	1.73	0.87 (0.71, 1.05)	1.48	0.86 (0.73,1.02)	1.39*
	1.30 (0.91,1.85)	2.03	0.97 (0.71,1.32)	1.86	1.13 (0.91, 1.41)	1.48	1.09 (0.90,1.31)	1.45*
LEFT MAIN: <50%DISEASE	1.22 (0.78,1.92)	2.46	1.25 (0.84, 1.85)	2.20	1.31 (0.98, 1.75)	1.78	1.26 (0.99,1.61)	1.63*
Ejection Fraction								
Unstable: >50%	2.02 (0.92,4.45)	4.84	1.78 (0.97, 3.25)	3.35	2.04 (1.32,3.17)	2.40	1.81 (1.26,2.61)	2.07*
30-50% : >50%	1.73 (1.29,2.32)	1.80	1.76 (1.37, 2.26)	1.65	1.65 (1.37, 1.97)	1.44	1.49 (1.28,1.74)	1.36*
<30% : >50%	2.02 (0.94, 4.40)	4.68	2.28 (1.31, 3.94)	3.01	3.00 (2.02,4.43)	2.19	2.22 (1.62,3.03)	1.88*
Missing : >50%	1.19 (0.82,1.74)	2.12	1.30 (0.93,1.80)	1.94	1.25 (0.99, 1.56)	1.56	1.19 (0.96,1.48)	1.54*
Anginal stability score	0.99 (0.98, 1.00)	1.02	0.99 (0.98, 0.99)	1.01	0.99 (0.98,0.99)	1.00*	0.99 (0.99,1.00)	1.01
Anginal frequency score	0.96 (0.95, 0.98)	1.03	0.98 (0.97,0.98)	1.02	0.98 (0.97,0.98)	1.00*	0.98 (0.97,0.98)	1.01
Disease Perception score	1.00 (0.99,1.01)	1.02	0.95 (0.95, 0.96)	1.01	0.95 (0.95,0.96)	1.01	0.96 (0.95,0.970	1.01
Treatment Satisfaction score	1.00 (0.99,1.01)	1.02	1.00 (0.99,1.01)	1.02	1.00 (1.00, 1.01)	1.01	1.49 (1.48,1.50)	1.01

SA^ =stable angina, UA"= Unstable Angina, MI°= Myocardial Infarction, VD$= Vessel disease,* =lowest CI ratio among three models

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CHAPTER 6

QUALITY OF LIFE OUTCOMES OF PATIENTS WITH CORONARY ARTERY DISEASE, TREATED WITH SURGERY, PERCUTANEOUS INTERVENTION OR MEDICAL MANAGEMENT.

6.0 Introduction

For many patients with coronary artery disease (CAD), coronary artery bypass grafts (CABG), percutaneous coronary intervention (PCI), (including percutaneous transluminal angioplasty (PTCA) and percutaneous placement of a stent (Stent)) and medical management are clinically feasible treatment options. Studies comparing CABG and PTCA show no difference in the mortality outcomes between these two treatment strategies [1]. Due to the lack of significant evidence regarding treatment supremacy, one group of investigators was led to conclude "although absolute treatment survival differences [are] modest, treatment decisions should be based not only on survival differences, but also on symptom relief, *quality of life outcomes* and patient preferences" [2]. To date no published studies have been found that compared adults catheterized patients for all three treatment modalities (CABG, PCI and Medical Management) for differences with respect to quality of life (QOL). The purpose of this study was to compare the QOL outcomes of patients in Alberta treated with CABG, PCI (PTCA &/or Stent), or medical therapy, at or near one-year following initial catheterization, after adjustment for known demographic, co morbid, and disease severity predictors of outcome using data from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH).

APPROACH is a province-wide inception cohort of all adult Alberta residents undergoing cardiac catheterization for ischemic heart disease. The APPROACH project was initiated to study provincial outcomes of care and facilitate quality assurance/quality improvement for patients with CAD in Alberta.[3] Briefly, the APPROACH database contains detailed clinical information collected at catheterization and treatment on adult patients with known or suspected CAD. Missing data are a common problem in any clinical registry, and continue to pose a threat to the validity of observational outcomes analyses. The use of the APPROACH project clinical data for this study yielded the same missing data issues. To contend with this concern a new method for data enhancement was applied.[4] Administrative data collected from participating hospitals was merged with the APPROACH clinical data to fill in variables where data was missing.

The Outcome QOL data were collected by means of a self-reported questionnaire mailed to patients on or near the one-year anniversary of their initial cardiac catheterization. The questionnaire included the Seattle Angina Questionnaire (SAQ). Notification regarding death occurred either through the family by return mail or through a bi-annual merge with data from the Alberta Bureau of Vital Statistics.

The SAQ is a 19 item self-administered questionnaire. Five dimensions of CAD are measured: exertional capacity, anginal stability, anginal frequency, disease perception and treatment satisfaction generating five independent scales. Each question is measured on an ordinal scale with 1 indicating the lowest/poorest response. Based on the results of the validity, responsiveness and reliability testing, the SAQ was judged to be a valid, responsive and reliable instrument. Specifically, it has been suggested that the SAQ is sensitive to clinical changes in patient's CAD, and that it focuses on symptoms and impairments in health that are unique to coronary disease. [5] The Medical Outcomes Trust adopted the SAQ as a QOL measure for patients with CAD. Furthermore, the SAQ

has been translated into 16 languages for use in Europe, the Middle East and North America [6], and is in widespread use worldwide (Spertus, Personal communication).

6.1 Methods

6.1.1. Selection of patient population

Eligible subjects included all adult Alberta residents over the age of 18 years, with CAD (Duke Coronary Index between 3 and 13 [7]), without a previous catheterization, referred for cardiac catheterization, between January 1,1996 and December 31, 1998, to one of the three tertiary care centers in Alberta, who were found to have 2 or more diseased coronary vessels at catheterization who consented to become part of the APPROACH cohort.

6.1.2 Collection of data

Data collection sheets were completed at the time of catheterization by the referring cardiologists and were entered by cardiac catheterization laboratory staff into on-site computers, linked via Ethernet to a server located at the University of Alberta. Data collected at catheterization included; sociodemographic characteristics (sex, age, residence address and postal code), presence or absence of co morbidities (renal insufficiency, hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, smoking status, pulmonary disease, liver/gastrointestinal disease, malignancy), disease specific variables (congestive heart failure, prior myocardial infarction, prior thrombolytic therapy, Canadian Cardiovascular Society angina class, results of previous non-invasive cardiac tests), and coronary angiography results (coronary anatomy, extent of coronary stenosis, left ventricular ejection fraction).The treatment modality group was identified as the first treatment the

patient received following the initial cardiac catheterization. Results of subsequent interventions and subsequent catheterizations were also collected in the APPROACH database.

Participants were provided with two options for completing the follow-up questionnaire sent one year after the initial catheterization. They could complete the questionnaire and mail it back in a stamped addressed envelope or they could telephone a toll free line and respond to a verbally administered questionnaire, which was recorded and transcribed daily. A second questionnaire was sent to non-respondents, 13 months post-catheterization with the same options for completion. In the case of a questionnaire being returned due to a wrong address, letters were sent to the referring cardiologist to obtain current/correct mailing addresses and questionnaires were resent. Finally, at 15 months post-catheterization, a third reminder was sent to non-responders.

6.3 Statistical Analysis

6.3.1 Scoring the SAQ

The SAQ is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning, and summing across items within each of the five dimensional scales. Scale scores are then transformed to a 0 to 100 range by subtracting the lowest possible score, dividing by the range of the scale and multiplying by 100. [5] Although the SAQ scores are transformed from ordinal scales to seemingly continuous scales, the non-normal distributions of the SAQ dimensional scores suggested that applying linear regression models to assess predictors of SAQ scores was not the most suitable statistical analysis to use [8].

With the APPROACH database, we faced a wealth of clinical variables with which to model outcomes but SAQ dimensional scores that appeared to have non-normal distributions. Transformation of the data using log transformation, squared and square root transformations failed to produce normal distributions. [9] Consequently, the original scores from each of the 5 scale scores were added together and divided by the number of questions that made up the scale to create a mean dimensional score for each respondent. Frequencies of the scores were run for each of the 5 scales and categories were created based on quintiles.

6.3.2 Risk adjusting the SAQ scores

Baseline clinical and demographic characteristics of patients who completed the survey (responders) and those with surveys that remain outstanding (non-responders) were compared. The proportional odds (PO) model, sometimes referred to as the "ordinal logistic model"[10], was used in modeling the risk-adjusted associations between treatment modalities and SAQ. The PO model produces a summary odds ratio or adjusted estimate of effect by modeling the dependence of an ordinal variable. Maximum likelihood estimates were used to estimate summary odds ratios. Five regression models were constructed, one model for each SAQ dimensional scale. For each of the models all demographic, co-morbid and clinical variables were included and entered at the same time into the ordinal regression models.

All variables included in the bivariate analyses were entered simultaneously into the multivariate models for a number of reasons. First, all variables were considered to be clinically relevant irrespective of statistical significance in the bivariate analysis. Second, we wanted to have the same independent variables in all models. Third, the objective of the modeling was to determine the difference in QOL among treatment groups as

opposed to developing parsimonious models for predictive purposes. Finally, a sensitivity analysis performed using backward elimination of non-significant variables, yielded similar proportional odds ratios for treatment modalities. All statistical analyses were conducted using SAS® version 8.2.

6.4 Results

A total of 10,108 consenting patients underwent cardiac catheterization between January 1st 1996 and December 31st 1998 in the province of Alberta were sent follow-up surveys. Of these, 4,344 patients who had 2 or more diseased coronary arteries and no prior CABG, PCI or thrombolytic therapy were eligible for this study. 3392(78.1%) patients responded to the follow-up survey while 952 (21.9%) surveys remained outstanding. 3243 surveys were returned completed and 149 surveys were returned with a notice that the patient had died prior to completion of the survey.

An analysis of the differences in the baseline demographic and clinical characteristics of responders and non-responders demonstrated few significant differences (Table 1). Compared with respondents, non-responders tended to be younger and were more likely to have diabetes mellitus and a lower ejection fraction. As well, non-respondents were more likely to have been treated with medical therapy during the first year following their index catheterization (35.1% versus 26.7% $p<0.001$).

The mean age of the study population at the time of the index catheterization was 64.6 years and the median age was 65.7 years. Seventy-eight percent of the sample were male. Thirty nine percent were in the CABG group, 34.0 % had a PCI as the first treatment and 27.0% were medically managed for the first year following the index catheterization. Baseline demographic and clinical characteristics of the analytic cohort grouped by the first treatment received after catheterization are described in Table 2.

Patients in the PCI treatment group were significantly younger, and were more likely to be female compared to the CABG and medically managed treatment groups. The PCI group had a higher percentage of patients who had 2-vessel disease, and the largest percentage of patients with a left ventricular ejection fraction of greater than 50%. Finally the PCI group had the highest percentage of patients who underwent catheterization for myocardial infarction (PCI-29.7%, CABG- 18.5%, medicine – 20.3% $p<0.001$), and were significantly more likely to have had a second treatment prior to follow-up as compared to the other two treatment groups. Patients in the CABG treatment group were more likely to be male and had the largest percentage of patients older than 60 years of age (CABG-75.1%, Medicine-72.1%, PCI- 60.7% $p<0.001$). Respondents who were treated with CABG were significantly more likely to have cerebrovascular disease, congestive heart failure, hyperlipidemia, peripheral vascular disease and diabetes mellitus. The CABG treatment group had the largest percentage of patients with 3 vessel and left main disease and a left ventricular ejection fraction between 30 and 50 percent. The most notable differences of the respondents who were treated with medical management were that they had the largest percentage with a left ventricular ejection fraction of less than 30 % (medicine- 7.2%, CABG- 4.0%, PCI –2.7% $p<0.001$), and were originally catheterized for stable angina (medicine – 45.2%, CABG – 41.8%, PCI – 32.0%).

Proportional odds ratios for the treatment modalities, sex, age and follow-up time categories following adjustment for all independent variables in the 5 models are presented in Table 3. For the overall study population, the adjusted proportional odds controlling for demographic and clinical characteristics indicated that those patients who were revascularized either with PTCA, Stent or CABG tended toward higher scores (better QOL) on all 5 SAQ dimensions as compared to patients treated with medical management. Patients treated with CABG tended to significantly higher scores in all dimensions compared

to patients treated with PTCA or Stent, although this relationship was non-significant in the exertional capacity scale.

Men reported higher scores in all 5 QOL dimensions as compared to women. Younger respondents reported higher scores in the exertional capacity dimension, as well as the anginal frequency scale (higher scores indicate less anginal frequency) compared to older respondents. Conversely older patients reported higher treatment satisfaction scores as well as higher disease perception scores (less perceived disease) compared to younger patients. Finally, those patients who responded to the follow-up questionnaire closest to one year following catheterization reported higher scores in all QOL dimensions compared to those who responded at or greater than 16 months post catheterization.

6.5 Discussion

Little is known about the QOL outcomes after treatment with different modalities for CAD. Results from this study demonstrated that while controlling for the demographic and/or clinical characteristics, and co morbidities present at catheterization, the treatment decision to revascularize the coronary vessels, whether with PTCA, Stent or CABG, consistently yielded significantly higher SAQ dimensional scores (better QOL) compared to respondents who were medically managed. As both PTCA, Stent and CABG aim to revascularize the myocardium, it is naturally appropriate that respondents who underwent any of these procedures reported more exertional capacity, more anginal stability and less anginal frequency compared to respondents who were pharmacologically managed. It is also not surprising that respondents who were not mechanically revascularized reported less satisfaction with treatment and higher perceptions of their disease status.

The treatment options for CAD have been well publicized particularly in light of the medical treatment waiting time projects presently underway in Canada [11]. Consequently, as

a result of the media attention on treatments for CAD, there exists a "technological imperative" whereby there is an expectation by health care consumers that something must be actually *done* in order for a 'treatment' to be beneficial. With this awareness, it is understandable that respondents who were medically managed would not be "satisfied ...that everything possible is being done to treat your chest pain, chest tightness, or angina" (question 6 SAQ), regardless of the appropriateness of the treatment. In addition if medically managed respondents report more anginal frequency and less anginal stability and exertional capacity at follow-up compared to respondents who were revascularized they would also *perceive* that they continue to have considerable disease.

Respondents who underwent CABG surgery reported significantly more anginal stability, less anginal frequency, more treatment satisfaction, and less perceived disease as compared to respondents who underwent either a PTCA or Stent. A meta-analysis of eight randomized controlled trials comparing CABG and PTCA treatment strategies identified a significant difference in re-intervention rates ranging from 3.2% for CABG vs. 34.5% for PTCA. As well all trials included in the analysis reported higher prevalence rates of angina in the PTCA groups at one year.[1] It is noteworthy that the studies and resulting conclusions upon which the above mentioned meta-analysis was based were during the pre-stent era. Nonetheless even though our cohort included patients who were stented, this increased frequency of angina was also present in our study as evidenced by the respondents in the CABG group having significantly higher scores (better QOL) in the anginal frequency and anginal stability scales as compared to the PTCA and the Stent groups. Interestingly though, the magnitude of the POR comparing the CABG group to the Stent group was substantially less than the POR comparing the CABG group and the PTCA group. Additionally, the Stent group did report higher scores in all SAQ scales compared to the PTCA group albeit only statistically significant in the treatment satisfaction dimension.

The introduction of glycoprotein IIb/IIIa inhibitors administered adjunctively with PCI procedures followed closely on the heels of the introduction of stents. Based on the results of a number of definitive clinical trials [12-16], demonstrating significantly less angina as well as reduced re-intervention rates following the use glycoprotein IIb/IIIa inhibitors, the interventional community widely embraced the addition of these interventional advancements to PCI treatments. As this sample was selected prior to these now standard methods of care it is possible that the PCI and CABG treatment groups of cohorts selected after 1998 may not report the differences in QOL noted in our study. It should also be noted that while stents were a treatment modality in this study, due to their novelty, they were used on a selective group of patients who were typically selected due to their apparent lower risk (high-quality coronary arteries). This may have influenced the reported higher QOL scores noted in the stent group.

Male respondents reported overall higher scores in all of the five QOL dimensions as compared to females after adjustment for treatment modality, co morbidities and clinical variables. It has been suggested that this noted difference in QOL between men and women might be a result of overall patient size rather than gender.[17] Further investigation into the association between a patient's general size and more importantly their heart size, and the outcomes of treatment for CAD is warranted. A second hypothesis suggested to explain the male/female difference in follow-up QOL is that the disparity may be a result of variations in social support between genders. A comprehensive review by Toobert et al [18] indicated the need to take psychosocial gender differences into account in the course of CAD. They state that despite a number of reports finding that being divorced and/or living alone and being female increased the risk for further cardiac events, research evidence on social support and CAD is inconclusive and more work is needed to determine how social support relates to the development and progression of CAD.

Age demonstrated significant associations in at least one of the age categories with the exertional capacity, anginal frequency, and disease perception SAQ dimensions following adjustment. In the exertional capacity dimension the youngest age quintile had the highest exertional capacity scores (most exertional capacity) compared to the eldest quintile (POR 3.37). As the age quintiles increased there was a decreasing stepwise progression of the POR (decreasing levels of exertional capacity) for each of the increasing age quintiles (53- 59 years compared to > 72 years- POR 3.33, 60-65 years compared to >72 years – POR 2.19 and 66 to 72 years compared to > 72 years 1.61). In other words, as age increased exertional capacity at one-year follow-up decreased. Interestingly, but intuitively understandable was the inverse relationship that was demonstrated between the age quintiles and the treatment satisfaction dimension. The youngest age group reported the lowest treatment satisfaction compared to the eldest quintile (POR 0.78) with progressively increasing levels of treatment satisfaction as the age quintile increased. Similar to the treatment satisfaction dimension, the youngest respondents reported the highest perceived level of disease as compared to the eldest age group. Although younger respondents reported more exertional capacity at follow-up compared to the eldest respondents they in turn reported more anginal instability, more anginal frequency, the least satisfaction with treatment and the most perceived disease. It would appear that the expectations of what is physically possible are relative to ones age, which in turn affects the expectations of medical care and consequently the satisfaction with that care.

Lastly, the relationship between the SAQ dimensional scores and the time period when the follow-up survey was returned warrants further investigation. The consistent pattern, that participants who completed the follow-up survey closest to the one-year anniversary yielded higher SAQ scores compared to participants who returned the survey at or greater than 16 months following the index catheterization is of interest. Two potential

explanations include 1) the possibility that those with the most health related QOL were up and about and therefore filled out the form and returned it as soon as it arrived or conversely, 2) At one year, respondents who felt well (high levels of health related QOL) did not respond to the QOL questionnaire, but as time increased beyond one year post catheterization their health deteriorated to the point where they felt compelled to reply to the survey noting their physical limitations and dissatisfaction with the treatment they received.

6.6 Study Limitations

The observed differences between treatment groups may be due to residual confounding. Since the choice of treatment for CAD may be associated with a variety of demographic and clinical characteristics, we attempted to adjust for baseline differences in our analysis. Nonetheless, it is possible that our adjustment methods were inadequate and that other unmeasured confounders accounted for the observed differences. For instance patients waiting to undergo CABG may have attempted to improve their health in preparation for the surgery through diet and exercise, which may have resulted in greater gains in health-related QOL at follow-up. Although we cannot entirely exclude such unmeasured confounding, one could postulate that patients who underwent PCI or medical management could also have attempted to improve their overall health status as a result of the diagnosis at catheterization of multi-vessel CAD.

6.7 Conclusions

Cardiac care providers continue to be faced with evolving indications, techniques and operator experience, making it nearly impossible to define the most appropriate treatment option for patients with CAD. There are however recurrent themes or factors that are considered important in the process of selecting the most appropriate treatment/revascularization option for patients with multi-vessel CAD. Currently these factors include the age, sex, ejection fraction, coronary anatomy and the co-morbid

conditions of the patient being catheterized. The results of this study have demonstrated that even when controlling for all of the above-mentioned factors, respondents who were revascularized either with CABG or PCI reported better QOL at follow-up as compared to respondents who were medically managed. These findings should provide cardiologists with further motivation to consider incorporating information from studies on patient reported one-year follow-up QOL outcome data when undertaking the complex therapeutic decision-making process for patients with multi-vessel CAD.

Table 6-1. Difference in demographic data and co morbidities between eligible patients who returned 1-year QOL questionnaire and those who did not return questionnaire.

Variables	Returned (N=3243)	Not returned (N=952)	P value
Sex (% Female)	22.2%	20.7%	0.322
Age Category (% per Quintile)			
30-57 years	25.0%	36.3%	<0.001
58-65 years	25.0%	24.8%	
66-75 years	25.0%	20.6%	
> 75 years	25.0%	18.3%	
	6.9%	6.3%	0.514
Pulmonary disease			
Cerebrovascular Disease	4.8%	5.9%	0.198
Renal Disease	1.7%	1.6%	0.849
Congestive Heart Failure	10.5%	11.4%	0.413
Dialysis	1.0%	0.90	0.844
Hypertension	53.6%	56.8%	0.081
Hyperlipidemia	47.9%	46.5%	0.442
Liver/Gastrointestinal Disease	2.9%	3.6%	0.313
Malignancy	3.3%	2.2%	0.085
Prior Myocardial Infarction	43.2%	45.9%	0.144
Peripheral Vascular Disease	7.5%	8.2%	0.495
Diabetes Mellitus	18.0%	23.7%	<0.001
Left Ventricular Ejection Fraction			
>50%	58.0%	59.1%	0.001
<30%	4.4%	6.6%	
30-50%	24.6%	25.1%	
V-gram not done due to instability	2.7%	2.4%	
Missing	10.3%	6.7%	
Coronary Anatomy			
2 Vessel Disease	37.1%	39.1%	0.124
3 Vessel Disease	50.0%	50.0%	
Left Main Disease	12.9%	10.5%	
Treatment within 1st year following			
Index catheterization			
Medical Management	26.7%	35.1%	<0.001
Cabg/Valve	38.6%	32.6%	
PCI	34.7%	32.4%	

Table 6-2 Baseline Demographic Characteristics According to First Treatment Received following Catheterization.

Variables	PCI/STENT N=1125	CABG N=1252	Medical N=866	P value
Sex (Female %)	23.9	18.3	25.6	<0.001
Age Category (% per Quintile)				
16-52 years	17.9	9.3	10.9	
53-59 years	21.8	15.5	17.7	
60-65 years	20.9	21.6	19.9	<0.001
66-72 years	20.0	26.8	22.4	
>72 years	19.8	26.7	29.8	
Total	100.0	100.0	100.0	
Variables				
Pulmonary disease (%)	6.0	7.6	7.0	0.328
Cerebrovascular Disease (%)	3.4	5.8	5.4	0.017
Renal Disease (%)	1.2	2.2	1.6	0.162
Congestive Heart Failure (%)	6.6	11.8	13.9	<0.001
Dialysis (%)	0.9	1.0	1.3	0.678
Hypertension (%)	51.7	55.0	54.2	0.272
Hyperlipidemia (%)	49.4	49.4	43.9	0.020
Liver/Gastrointestinal Disease (%)	2.8	3.2	2.7	0.753
Malignancy (%)	2.9	3.5	3.5	0.695
Prior Myocardial Infarction (%)	43.2	42.5	44.3	0.700
Peripheral Vascular Disease (%)	4.7	8.9	9.1	<0.001
Diabetes Mellitus (%)	13.9	20.2	20.2	<0.001
Left Ventricular Ejection Fraction				
>50%	65.3	53.4	55.2	
<30%	2.7	4.0	7.2	
30-50%	19.8	29.0	24.4	<0.001
V-gram not done due to instability	2.4	3.2	2.5	
Missing	9.8	10.5	10.7	
Coronary Anatomy				
2 Vessel Disease (%)	58.6	11.6	44.0	
3 Vessel Disease (%)	39.3	58.7	48.2	<0.001
Left Main Disease (%)	1.2	28.3	5.0	
Clinical Indication for catheterization				
Unstable angina (%)	32.9	30.8	21.2	
Myocardial Infarction (%)	29.7	18.5	20.3	
Stable Angina (%)	32.0	41.8	45.2	0.004
Other (%)	5.4	9.0	13.3	
Second treatment prior to follow-up (% yes)	20.4	2.2	0.8	<0.001

Table 6-3. Proportional Odds Ratios for Treatment, Age, Sex and Time from Catheterization to Follow-up, Adjusted for ALL Clinical, Demographic and Co morbid Variables.

Variable	Exertional Capacity		Anginal Stability		Anginal Frequency		Treatment Satisfaction		Disease Perception	
TREATMENT	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI
PTCA: Medical Management	1.77	1.32-2.37	1.48	1.13-1.94	1.92	1.48-2.51	1.42	1.10-1.83	1.57	1.23-2.00
Stent: Medical Management	2.05	1.62-2.59	1.81	1.46-2.24	2.39	1.93-2.95	2.02	1.64-2.48	1.98	1.63-2.40
CABG: Medical Management	2.48	1.99-3.09	3.39	2.76-4.17	4.21	3.44-5.15	3.12	2.56-3.79	2.62	2.19-3.14
CABG: PTCA	1.40	1.04-1.90	2.29	1.73-3.05	2.19	1.65-2.90	2.20	1.68-2.88	1.67	1.31-2.14
CABG: Stent	1.21	0.95-1.54	1.88	1.49-2.37	1.77	1.40-2.22	1.55	1.24-1.93	1.33	1.09-1.61
Stent: PTCA	1.16	0.87-1.55	1.22	0.94-1.59	1.24	0.95-1.62	1.42	1.10-1.83	1.26	0.99-1.60
Sex Male: Female	3.43	2.79-4.22	1.22	1.02-1.46	1.69	1.43-2.01	1.26	1.06-1.49	1.75	1.49-2.05
Age Category	3.24	2.46-4.27	0.84	0.65-1.10	0.96	0.75-1.24	0.78	0.69-1.08	0.48	0.38-0.61
	3.23	2.51-4.17	0.89	0.70-1.12	1.19	0.95-1.50	0.87	0.82-1.26	0.69	0.56-0.85
16-52 years:>72 years	2.16	1.70-2.75	1.03	0.82-1.29	1.23	0.99-1.53	1.01	0.90-1.35	0.87	0.71-1.05
53-59 years:>72 years	1.60	1.27-2.02	1.05	0.84-1.30	1.25	1.02-1.54	1.10	0.86-1.51	1.11	0.92-1.34
60-65 years:>72 years										
66-72 years:>72 years										
Time from catheterization to Follow-up										
12 mths < 14 mths: 16 mths	1.33	1.06-1.66	1.23	0.99-1.53	1.24	1.00-1.54	1.21	0.98-1.49	1.27	1.05-1.53
14 mths < 15 mths: 16 mths	1.24	1.00-1.54	1.14	0.93-1.40	1.22	1.00-1.49	1.24	1.02-1.51	1.23	1.03-1.47
15 mths < 16 mths: 16 mths	1.03	0.83-1.28	0.96	0.78-1.17	1.07	0.88-1.31	1.07	0.88-1.30	1.13	0.94-1.34

Highlighted areas indicated statistical significance

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CHAPTER 7

GENERAL DISCUSSION AND CONCLUSIONS

7.0 Overview

For many patients with multi-vessel CAD, treatment options of CABG, PCI, and/or medical management are all clinically feasible options. Given the increasing prevalence of treatment strategies as well as the lack of significant evidence regarding treatment supremacy, this present research addressed the QOL outcomes one year following catheterization in an inception cohort of Alberta patients with multi-vessel CAD.

Prior to researching this seemingly straightforward clinical question, two distinct yet crucial methodological issues were addressed. First, a method to replace missing data by enhancing clinical data with administrative data was developed and validated. Second, a comprehensive literature review identified that investigators may have neglected to take the distributional characteristics of their SAQ QOL data into consideration before applying parametric tests. Consequently, based on the pronounced non-normality of the QOL SAQ scale distributions, a comparison of 4 statistical analyses identified that the proportional odds ordinal regression model was the most appropriate method for analyzing SAQ QOL outcome data. This methodological journey facilitated the main objective of this thesis, by making it possible to measure and compare the QOL outcomes of patients with CAD, who underwent different treatment modalities while controlling for baseline clinical data.

7.1 Missing Clinical Data

Missing data are a common problem in any clinical registry, and continue to pose a threat to the validity of observational outcomes analyses. The APPROACH project clinical data in this study yielded the same missing data issues. To contend with this concern a new method for data enhancement was applied. Administrative data were merged with the APPROACH clinical data to fill in variables where data were missing. To test the new enhancement method three possible responses: exclude cases with missing data; assume

that the missing data indicated absence of risk; or merge the clinical database with an existing administrative database, were compared. The superior performance of the enhanced data model supported the use of this "enhancement" methodology for this present study.

7.2 Analyses of SAQ Data

In Chapter 4, a comprehensive literature review was done that identified all published studies analyzing SAQ scores, and reviewed the appropriateness of the statistical methods used. A total of 39 articles cited and/or used the SAQ scale. Nine studies used the SAQ as a QOL outcome measure in the analysis of the data (1-9). Three of those did not describe how the results of the SAQ were analyzed (1, 4, 7). Five used parametric tests to analyze the data (2, 3, 5, 6, 8). One study used non-parametric tests (9). Assumptions required for the use of parametric tests were not addressed nor was there any explicit mention of the distributions of the SAQ scores. The results of the review demonstrated that inappropriate analytic methods are employed to analyze SAQ scores.

The SAQ continues to be used with increasing frequency in clinical research to address the QOL outcomes of patients with coronary artery disease (CAD). A search of the Web of Science records identified a further 25 studies published since May 2000 that cited or used the SAQ scale as a QOL outcome measure. Five of those studies used the SAQ as an outcome measure (10-14). Similar to studies published prior to May 2000, the entire group of studies failed to discuss the distributions of the SAQ data. In contrast to the first comprehensive literature review, two of the five outcome studies (10, 11) had large enough samples sizes to warrant the use of parametric statistics. One of the studies used non-parametric statistics (12). In light of the recently published studies citing or using the SAQ, the conclusion reached in Chapter 4, that investigators need to increase their attention to the distributional characteristics of their QOL data before applying parametric tests remains valid.

Chapter 5 presents four different statistical analytic strategies that were compared for analyzing skewed SAQ QOL data. Comparisons demonstrated that all 4 models were successful at fitting the data. Clearly, though, the ordinal regression model and the linear regression model

were superior to the logistic regression models. In general it was determined that in view of the pronounced non-normality of the SAQ dimensional scores, there was merit to using the ordinal regression model.

7.3 Quality of life at one-year follow-up.

Improving QOL and functional status are primary goals in treating patients with CAD (14). For the overall study population, results (presented in Chapter 6) indicated that those patients who were revascularized either with PCI including PTCA or stents, or CABG tended to have better QOL outcomes at one-year following catheterization as compared to patients treated with Medical management. The results of a Medline search completed in October 2001, of studies comparing QOL outcomes of patients with CAD treated with CABG, PCI and medical management identified one study limited to patients over 75 years of age. The results of this study published in The Lancet compared invasive treatments (revascularization) versus medical therapy in the elderly (75 years or older) (15). Similar to this study, the TIME investigators noted reported benefits of being revascularized and further suggested that if the coronary anatomy is suitable for revascularization, patients with multi-vessel disease should be offered an invasive assessment. No other published study using patient subjective QOL outcome data comparing treatment modalities for CAD was identified.

Sex and age continued to play significant roles in the perception of QOL. Men reported better QOL at follow-up compared to women even after adjustment for co- morbidities and clinical variables. Younger respondents reported more exertional capacity at one-year follow-up, yet also reported the least satisfaction with treatment and the most perceived disease when compared to older respondents.

7.4 Strengths and Limitations of this study.

First and foremost, the strongest feature of this study was the use of the APPROACH database. The APPROACH database captures the entire population of patients undergoing

catheterization and treatment for CAD in the province of Alberta. Consequently we can be assured that the data includes the full spectrum of patients catheterized for CAD and can therefore be generalized to all patients who undergo catheterization and treatment for CAD in Alberta. Unfortunately, the follow-up for patients with 2 vessel disease or greater, who were catheterized for the first time (no previous interventions for CAD) did not achieve a 100% response rate. Nonetheless, considering the size of the cohort in this study (reducing the potential for random error) and the level of detail of the clinical data collected at catheterization, our 78% response rate at one year compares favorably with previous QOL outcomes in patients with heart disease (14, 22, 23). Furthermore, the demographic and clinical data in APPROACH for patients with multi-vessel disease is similar in age, sex, as well as the percentage with co-morbid conditions such as hypertension, diabetes mellitus, and prior infarction, when compared to the demographic and clinical data provided in six of the RCTs comparing patients undergoing CABG and PTCA (16-21).

A limitation of this study is that observed differences may be due to residual confounding. The choice of treatment for CAD may be associated with a variety of demographic and clinical characteristics, consequently, an attempt was made to statistically adjust for baseline differences in our analysis. Nonetheless, it is possible that our adjustment methods were inadequate and that other unmeasured confounders accounted for the observed differences.

7.5 Implications for Future Research

The most noteworthy finding in this study was, regardless of age, sex, co-morbid conditions or severity of CAD, patients with multi-vessel CAD who were treated with revascularization reported *better quality of life* outcomes at follow-up compared to those who were medically managed. If we accept that the risk adjustment did in fact statistically control for all baseline demographic and clinical differences among patients thus "leveling the playing field", (25) then we can compare QOL outcomes of this cohort of multi-vessel CAD patients based on

treatment. The implication of this finding is that revascularization should be considered and presented as a viable option to patients with multi-vessel CAD. Future research is required to attempt to identify which variable or variables, included in the risk adjustment model, were predictive of medical management as the first treatment received for CAD. A better understanding as to the clinical factors that influence the physician's decision regarding choice of treatment may support or deny clinical scenarios that have been used in the past to select the treatment of choice for patients with multi-vessel CAD.

A number of other areas requiring further investigation were identified in this study. The first of these is the distributional properties of the SAQ data. The SAQ data collected in this study yielded highly skewed data with marked dimensional ceiling effects. With between 25% and 40% of patients reporting the highest SAQ dimensional scores possible, it would appear that the SAQ might not be discriminating sufficiently between the patients at the highest functional level. Further research is required addressing the number of levels available in the questions of the SAQ.

Similar to the findings of a recently published study investigating adaptations to the SAQ instrument (24), there were significantly more missing data in the 7^{th} ,8^{th} and 9^{th} questions of the exertional capacity scale of this study. This resulted in having to drop a number of cases in the analysis of that particular scale. Future analysis investigating methods of replacing the missing exertional capacity scale data are warranted.

Finally, following the risk adjustment analysis of the outcome QOL data, it was discovered that several important independent variables remained significantly associated with the SAQ scales. Specifically sex and age continued to demonstrated statistically significant proportional odds ratios following adjustment. Further investigation is required to attempt to explain the sex and age differences observed in adjusted SAQ QOL outcome data.

7.6 Concluding remarks

The primary aim of this study was to measure the QOL outcomes, specifically the exertional capacity, anginal stability, disease perception, anginal frequency and treatment satisfaction of patients undergoing different treatment for CAD while controlling for demographics, co-morbidities, and disease severity. Cardiologists continue to be faced with evolving indications, techniques, and operator experience, making it nearly impossible to define the most appropriate treatment option for patients with CAD. The evaluation of health-related QOL for patients treated for CAD is crucial particularly in light of the fact that there are diverse treatment options available to patients with multi-vessel disease. Disease-specific QOL outcomes are crucially important to determine which of the treatment modalities demonstrates the most significant improvement in functional status, activities of daily living, treatment satisfaction and ultimately the quality of life of CAD patients. This study provides an important, critical and to date unmeasured facet of the outcome of adult patients catheterized and treated for CAD.

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APPENDIX A

SEATTLE ANGINA QUALITY OF LIFE QUESTIONNAIRE

The Seattle Angina Questionnaire

1. **The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had due to chest pain, chest tightness, or angina over the past 4 weeks.**

Place an x in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a block at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your chest pain, chest tightness, or angina?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your chest pain, chest tightness, or angina?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the <u>past 4 weeks</u>, how much has your chest pain, chest tightness, or angina limited your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your chest pain, chest tightness, or angina the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I can't stop thinking or worrying about it	I often think or worry about it	I occasionally think or worry about it	I rarely think or worry about it	I never think or worry about it
☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have chest pain, chest tightness, or angina when doing your most strenuous activities?

I have had chest pain, chest tightness, or angina...

Much more often	Slightly more often	About the same	Slightly less often	Much less often
☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina?

I have had chest pain, chest tightness, or angina...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your chest pain, chest tightness, or angina?

I have taken nitroglycerin...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for chest pain, chest tightness or angina as prescribed?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not bothersome at all	My doctor has not prescribed pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your chest pain, chest tightness, or angina?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

APPENDIX B

Method of Patient Selection

VARIABLES: Source and Classification

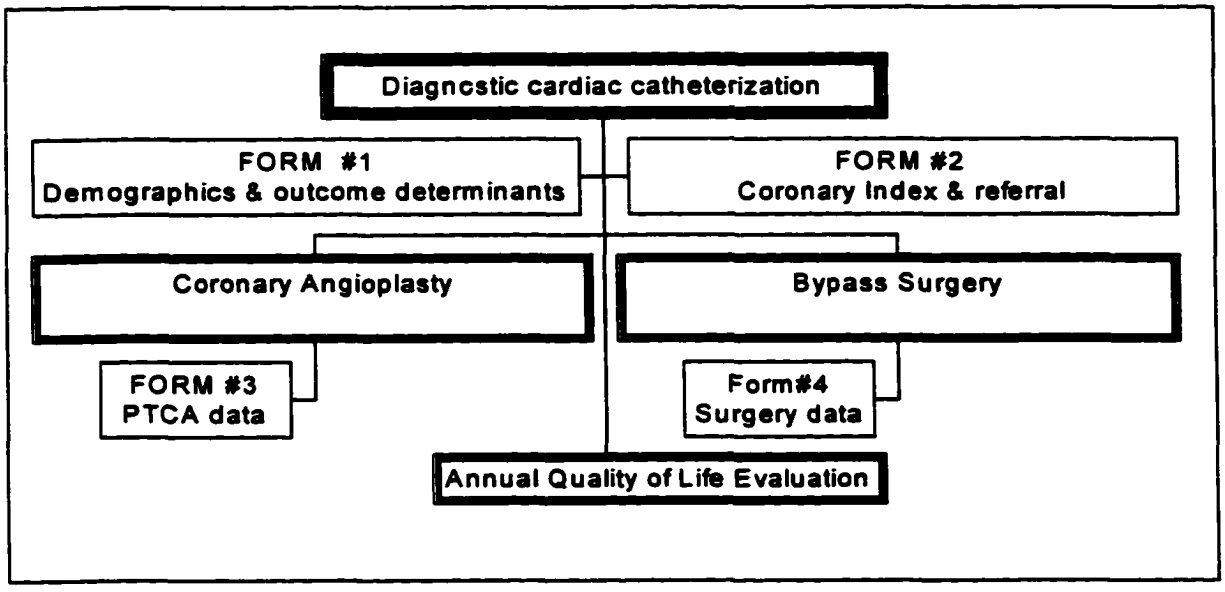
METHODS

Selection of patient population

Eligible subjects included all consenting adult Alberta residents over the age of 18 years, with CAD (Duke Coronary Index between 3 and 13), without a previous catheterization, referred for cardiac catheterization, from January 1,1996 and December 31, 1998, to the University of Alberta Hospital (Edmonton), the Royal Alexandra Hospital (Edmonton) and the Foothills Hospital (Calgary) who were found to have a 2 or more-vessels diseased on catheterization.

Collection of data

Data collection sheets were completed by the referring cardiologists and were entered by cardiac catheterization laboratory staff into on-site computers, linked via Ethernet to a server located at the University of Alberta. Data collected at catheterization includes; sociodemographic characteristics (sex, age, residence address and postal code), presence or absence of co morbidities, (renal insufficiency, hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, smoking status, pulmonary disease, liver/gastrointestinal disease, malignancy, disease specific variables (congestive heart failure, prior myocardial infarction, prior lytic therapy, Canadian Cardiovascular Society angina class, results of previous non-invasive cardiac tests), and coronary angiography results (coronary anatomy, extent of coronary stenosis, left ventricular ejection fraction). The treatment modality group was identified as the first treatment the patient received following the initial cardiac catheterization. Results of subsequent interventions and subsequent catheterizations were also collected in APPROACH. The dates and procedures of subsequent catheterizations, PCIs, CABGs and/or other hospitalizations were collected at one-year to validate the data as well as provide new data should the patients have had a procedure outside of Alberta. The following figure indicates the points of data collection.



Outcome quality of life (QOL) data is collected by means of a self reported questionnaire mailed to patients on the anniversary of their initial cardiac catheterization. The self reported questionnaire includes Information regarding procedures and dates of procedures subsequent to their index catheterization, and the Seattle Angina Scale (SAQ), a generic health-related quality of life (QOL) questionnaire. Participants were provided with two options for completing the follow-up questionnaire. Participants could complete the questionnaire and mail it back in a stamped envelope or they could telephone a toll free line and verbally respond to a verbally administered questionnaire, which is recorded and transcribed daily. A second questionnaire was sent to non-respondents with the same options for completion. In the case of the questionnaires being returned due to wrong addresses, letters were sent to the referring cardiologist to attempt to get a more current/correct mailing address and questionnaires were resent. Finally, a third reminder was sent to non-responders.

Definitions of Outcomes of Interest

The outcome measures of interest were the 5 SAQ scales including 1) the exertional capacity scale, 2) the anginal stability scale, 3) the anginal frequency scale, 4) the treatment satisfaction scale, and 5) the disease perception scale.

Description of Independent variables

The focus of this analysis was to determine if the first treatment that a patient received following the index catheterization was associated with the SAQ outcome scores. Index catheterization dates were subtracted from CABG and/or PCI dates. The treatment with the minimum number of days from index catheterization within a 365-day limit was used to create a variable that identified the first treatment a patient received following the index catheterization. Patients who had a CABG were coded as 1. Patients who had a PCI were coded as 2 and patients who had neither a CABG nor a PCI were coded as 0 indicating that they were in the medically managed group. Patients who had both a PCI and a CABG on the same day were coded in the PCI category.

Age was originally coded in years, captured at the time of catheterization. Age was re-coded into a 5 level categorical variable by dividing the range of ages into Quintiles. This was done for two reasons: 1) the sparseness of outcome data, particularly in the lowest (worst) category of the 5 SAQ scales, and 2) certain fit statistics for ordinal models (used in the regression analysis) depend on aggregating data based on unique predictor and outcome patterns. For example all cases where the respondents have the same predictor variables are combined to form one cell. Age is calculated based on subtracting the participants birth date from their catheterization date. As a result there are very few duplicate ages. A histogram of the continuous age variable revealed that the distribution of age resembled a normal distribution. Consequently age was categorized into 5 equal categories. This categorization resulted in the following categories:

1. 18 years - 52 years, 2. 53 years – 59 years, 3. 60 years – 65 years,
4. 66-72 years and 5. Greater than 72 years.

Sex was coded as an indicator variable with males coded as 1 and females coded as 2.

All of the comorbidities recorded at catheterization were dichotomous variables with 1 indicating the presence of the condition, and 0 the absence of the condition.

Left ventricular (LV) ejection fraction (EF) was coded either as categorical or continuous in the APPROACH database. All EFs were re-coded into a categorical variable including EF >50%, 30-50%, <30%, and not done due to instability at catheterization. This "instability" includes patients who were deemed too sick to have a ventriculogram done. Data were missing for 9.5% of respondents. Non-parametric Kruskal-Wallis tests produced unique mean ranked scores for the 'missing' EF category for each of the 5 SAQ scales. As a result the missing cases were treated as a separate category. This strategy was consistent with that reported and published previously. [1]

Data on coronary anatomy recorded in APPROACH at the time of catheterization was classified according to a 15 level coronary artery disease severity class index developed at Duke University [2].

APPROACH collects data on the clinical indication that led to the index catheterization. This variable is considered to be an indicator of the patient's coronary artery disease severity. There were 4 categories in the clinical indication variable including in order of severity 1) myocardial infarction, 2) Unstable Angina, 3) Stable Angina, and 4) other.

Three new variables were created for inclusion as predictor variables. A binary variable labeled 'Crossover' was created whereby respondents who had had a revascularization procedure following their first treatment prior to completing and returning the questionnaire were coded as 1. Those who did not crossover to a second treatment group during that time period were coded as 0. A second variable 'length of time from treatment to follow-up questionnaire' was calculated in days based on the belief that a respondent's QOL would be affected depending on when they were treated for CAD and when the questionnaire was completed. This variable was then categorized into: 1) < 6 months, 3) 6 months & < 9 months, 4) 9 months & < 12 months, 5) 12 months. Finally a variable was calculated 'time to follow-up' to account for the differences in the measured QOL that may be due to the length of time since catheterization. This variable was

also categorized into 5 categories: 1) returned in<13 months, 2) 14 months & < 15 months, 3) 15 months & < 16 months,4) 16 months .

Table B-1 List of Independent Variables

Demographics

Age

Sex

Comorbidities recorded at catheterization

Cerebrovascular disease

Pulmonary disease

Renal disease

Diabetes mellitus

Dialysis

Hyperlipidemia

Hypertension

Liver/Gastrointestinal disease

Malignancy

Peripheral vascular disease

Myocardial infarction prior to catheterization

First Treatment Received within one year following Index Catheterization

- Medical Management
- Coronary Artery Bypass Grafting (CABG)
- Angioplasty
- Stent

Clinical variables collected at catheterization

Coronary Anatomy

- 2 vessel disease
- 2 vessel disease both 95%
- 1 vessel disease 95% PLAD
- 2 vessel disease 95% LAD
- 2 vessel disease 95% PLAD
- 3 vessel disease 1-95%
- 3 vessel PLAD
- 3 vessel 95% PLAD
- Left main disease
- Severe Left main disease

Left ventricular Ejection Fraction

- EF >50%
- EF<30%
- EF 31-50%
- Unable to measure due to instability

Clinical Indication for catheterization

- Myocardial Infarction
- Unstable Angina
- Stable Angina
- Other

Post Catheterization Clinical variables

Crossover to other treatment group prior to survey

Length of time from treatment to survey

Time from original catheterization to survey return

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APPENDIX C

Statistical Analysis

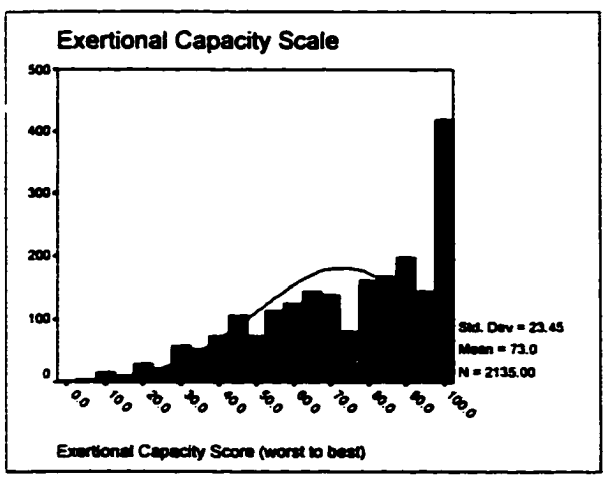
Statistical Analysis

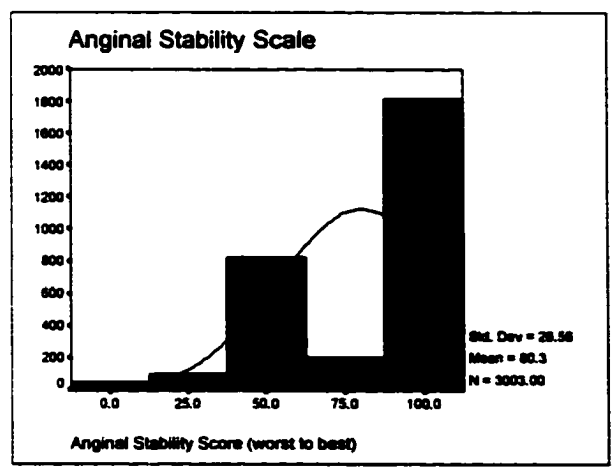
All statistical analyses were conducted using SAS® version 8.2.

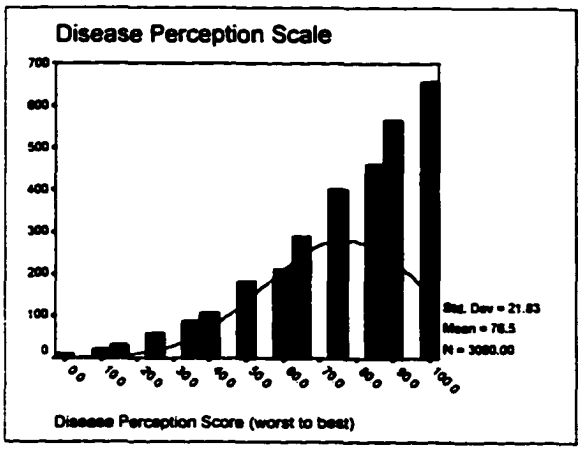
Scoring the SAQ

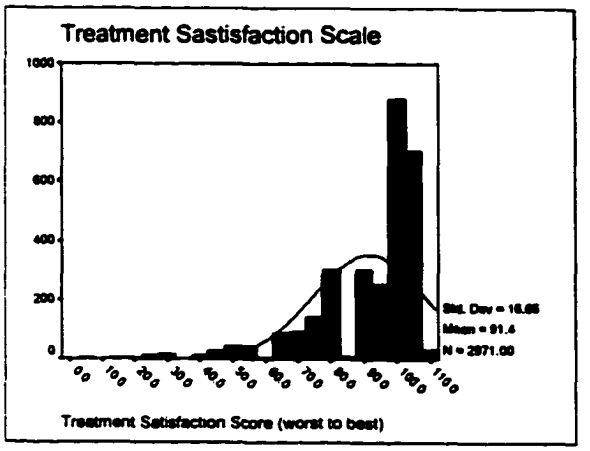
The SAQ questionnaire is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning, and summing across items within each of the five dimensional scales. Scale scores are then transformed to a 0 to 100 range by subtracting the lowest possible score, dividing by the range of the scale and multiplying by 100. Although the SAQ scores are transformed from ordinal scales to seemingly continuous scales, the distributions of the SAQ dimensional scores appear non-normal (Figure 4). Transformation of the data using log transformation, squared and square root transformations failed to normalize the distributions. Consequently, the original scores from each of the 5 scale scores were added together and divided by the number of questions that make up the scale to create a mean dimensional score for each respondent. Scores were then categorized into quintiles.

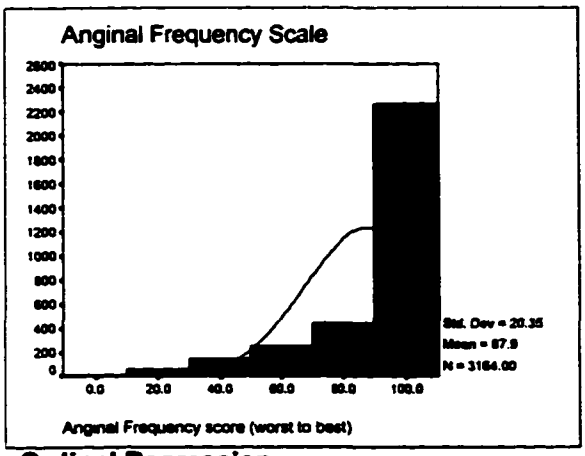
Figure C-1. Distribution of SAQ scores (0-100 scale)











Ordinal Regression

The proportional odds (PO) model sometimes referred to as the "ordinal logistic model" was used in the analysis of the SAQ data. The PO model produces a SUMMARY ODDS RATIO or adjusted estimate of effect by modeling the dependence of an ordinal variable. The PO model is linear and additive on a logit scale. Maximum likelihood estimates are used to estimate summary odds ratio. Odds ratios are formed over a series of incremental cut-points with each cut-point the level of severity required for categorization as a 'case' rather than a 'non-case' Each cut-point specific estimate is calculated using all observations in the sample at different dichotomization. For Example: SAQ responses categorized as 1=not limited, 2= a little limited, 3=somewhat limited, 4= moderately limited, 5= severely limited produce the following cut-points

1 versus 2,3,4,5

1,2 versus 3,4,5

1,2,3 versus 4,5

1,2,3,4 versus 5

The PO model predicts cumulative probabilities for the categories and produces separate equations for each category of the ordinal dependent variable. Each equation then gives a *predicted probability* of being in the corresponding category or any lower category. The prediction for the last category is always 1 since all cases must be in last category.

Basic form of the model

$\text{link}(\gamma j)=\theta j - [\beta_1\chi_1 + \beta_2\chi_2 \ldots + \beta_k\chi_k]$

γj = cumulative probability for jth category

θj =threshold for jth category

$\beta_1 \ldots \beta_k$ = regression coefficients

$\chi_1 \ldots \chi_k$ = predictor variables

k = the number of predictors

The PO model is based on the notion that there is some latent continuous outcome variable and that the manifest ordinal outcome variable arises from discretizing the underlying continuum into j ordered groups. The cutoff values on this continuous distribution that define the categories are estimated by the threshold θj. The threshold or constant in the model (like intercept in linear regression) depends ONLY on which categories probability is being predicted. The prediction part of the model ($[\beta_1\chi_1 + \beta_2\chi_2 \ldots + \beta_k\chi_k]$) depends ONLY on the predictors and is independent of the outcome category.

Determining the fit of the PO models

The –2 log likelihood change in deviance was used to examine model fit. Although the –2 log likelihood statistic may be suspect if there are a large number of empty cells, the difference of the log likelihood's between the baseline model and the final model with the predictors can still be interpreted as a chi square distributed statistic . A significant chi-square statistic indicates that the model demonstrates an improvement over the baseline intercept-only model. The fits of the models were also assessed using a crosstabulation of the predicted outcome categories with the observed categories. As the models attempt to predict cumulative probabilities rather than category membership, two steps are involved in predicting categories. First, for each case, the probability is estimated by using the predictor values for a case in the model equations and taking the inverse of the link function. Secondly, the predicted probabilities are used to select the most likely outcome category for each case. For each case the predicted outcome category is the category with the highest probability. Finally, the test of parallel lines was examined to

determine whether the proportional odds assumption was satisfied. The proportional odds assumption for modeling ordinal data suggest that the cut-point specific odds ratios are homogeneous and uses a chi-square statistic to compare the estimated model with one set of coefficients for all categories to a model with a separate set of coefficients for each category.

Multivariable analyses

Modeling was done by entering all variables into the models simultaneously. For each model produced during the modeling process the difference between the –2log likelihoods of the intercept only model and the final model were compared. The test of parallel lines will be examined to determine whether the proportional odds assumption was satisfied. Five ordinal regression models using each of the five SAQ ordinal scale scores as the dependent variables were constructed. The PO ordinal regression model was used to compare the summary proportional odds ratios of each of the four treatment categories (medical, CABG, PTCA and Stent) adjusted for predictor variables for each of the 5 SAQ scales.

Linear Regression Analysis

Multiple linear regression was run including all variables into each of the five models. Approximate odds ratios and confidence limits based on the linear regression results arise from viewing the proportional odds model in terms of a latent logistic error model. A crude conversion factor, $\pi \quad \{ \ 3sresid \ \}$, where *sresid* is the residual standard deviation, results from matching variances between logistic and normal distribution curves. To get a rough estimate of the odds ratio, the negative of the coefficients from the linear regression were divided by 10 and exponentiated ($^{(-\text{coefficient})/10}$).

APPENDIX D

SUMMARY OF DATA FOR TREATMENT COMPARISON ANALYSIS

Descriptive data on the study population

A total of 21,122 patients underwent a cardiac catheterization between January 1st 1996 and December 31st 1998. 9,959 patients were sent a follow-up survey. Descriptions of the exclusion criteria resulting in a patient not receiving a follow-up survey can be found in Table 1.

Table D-1 Selection of Sample for Follow-up Survey from APPROACH

Inclusion /exclusion criteria	Patients met inclusion criteria for sending follow-up survey		TOTAL
	No	Yes	
Sent – still out		2596 (26%)	2596
Returned		7363 (74%)	7363
Out of Province	1180		1180
Deceased prior to 1 year	1403		1403
Deceased (returned notice of death)	258		258
Not CAD	2018		2018
Consent not attained	4548		4548
Refused consent	609		609
Incorrect/incomplete address	998		998
Data updated post 1 year-died		149	149
	11014	10108	21122

Of the 10108 patients who were sent follow-up surveys, 4,344 had had no prior CABG, PCI or lytic therapy and had 2 or more diseased coronary arteries. This group made up the analytical cohort for this study (Table 2). 3392(78.1%) patients responded to the follow-up survey while 952 (21.9%) survey remained outstanding. 3243 surveys were returned completed and 149 surveys were returned with a notice that the patient had deceased prior to completion of the survey. Notification of the death occurred either through the family or the bi-annual merge with the bureau vital statistics.

Table D-2. Selection of Sample for Inclusion in QOL study

	Met inclusion criteria for QOL study (no prior CABG, PCI or Lytic Therapy, 2 vessel disease or greater)		Total
	No	*Yes*	
Sent – still out	1644	**952 (21.9%)**	2596
Returned	4120	**3392 (78.1%)**	7512
	5764	**4344**	10108

Table D-3. Difference in demographic data and comorbidities between APPROACH patients who returned 1 year QOL questionnaire and those who did not return questionnaire.

Variables	Returned (N=3243)	Not returned (n=952)	P value
Sex (% Female)	22.2%	20.7%	0.322
Age Category (% per Quintile)			
30-57 years	25.0%	36.3%	
58-65 years	25.0%	24.8%	
66-75 years	25.0%	20.6%	<0.001
> 75 years	25.0%	18.3%	
Pulmonary disease	6.9%	6.3%	0.514
Cerebrovascular Disease	4.8%	5.9%	0.198
Renal Disease	1.7%	1.6%	0.849
Congestive Heart Failure	10.5%	11.4%	0.413
Dialysis	1.0%	0.90	0.844
Hypertension	53.6%	56.8%	0.081
Hyperlipidemia	47.9%	46.5%	0.442
Liver/Gastrointestinal Disease	2.9%	3.6%	0.313
Malignancy	3.3%	2.2%	0.085
Prior Myocardial Infarction	43.2%	45.9%	0.144
Peripheral Vascular Disease	7.5%	8.2%	0.495
Diabetes Mellitus	18.0%	23.7%	<0.001
Left Ventricular Ejection Fraction			
>50%	58.0%	59.1%	
<30%	4.4%	6.6%	
30-50%	24.6%	25.1%	0.001
v-gram not done due to instability	2.7%	2.4%	
missing	10.3%	6.7%	
Coronary Anatomy			
2 Vessel Disease	37.1%	39.1%	
3 Vessel Disease	50.0%	50.0%	0.124
Left Main Disease	12.9%	10.5%	
Treatment within 1st year following Index catheterization			
Medical Management	26.7%	35.1%	
Cabg/Valve	38.6%	32.6%	<0.001
PCI	34.7%	32.4%	

Treatment Category

Of the patients who responded, 38.6% were in the CABG/Valve group, 34.7% had a PCI as the first treatment and 26.7% were medically managed for the first year following the index catheterization.

Age distribution of Patients

The Mean age of the study population at the time of the index catheterization was 64.6 years and the median was 65.7 years, indicating a non-skewed, and fairly normal distribution. The ages ranged from 33.6 years to 93.1 years with 4.7% of patients being over 80 years of age. An analysis of the treatment category by the re-coded age category indicated that respondents who received a PCI were more likely to be in the youngest age category whereas respondents in the oldest category were more likely to have received medical management as the first treatment within the first year following catheterization. Those in the older age categories were also more likely to have received a CABG as compared to younger participants.

Sex distribution of sample

Seventy-eight percent of the sample were male while the remaining twenty-two percent were female. Interestingly, these distributions changed when considering the association between a patient's age and the first treatment that they received following the index catheterization. Patients who received a CABG/Valve as the index treatment were 82% male, as compared to patients whose first treatment was PCI (76% male) or medical management (74% male).

Table D-4 Baseline Demographic and Clinical Characteristics According to First Treatment Received following Catheterization.

Variables	PCI N=1125	CABG N=1252	Medical N=866	P value
Sex (% Female)	37.4	31.8	30.8	<0.001
Age Category (% per Quintile)				
16-52 years	17.9	9.3	10.9	
53-59 years	21.8	15.5	17.7	
60-65 years	20.9	21.6	19.9	<0.001
66-72 years	20.0	26.8	22.4	
>72 years	19.8	26.7	29.8	
Pulmonary disease (%)	30.4	42.4	27.2	0.328
Cerebrovascular Disease (%)	24.2	45.9	29.9	0.017
Renal Disease (%)	24.1	50.0	25.9	0.162
Congestive Heart Failure (%)	21.7	43.4	34.9	<0.001
Dialysis (%)	30.3	36.4	33.3	0.678
Hypertension (%)	33.5	39.6	27.0	0.272
Hyperlipidemia (%)	35.8	39.8	24.4	0.020
Liver/Gastrointestinal Disease (%)	33.7	42.1	24.2	0.753
Malignancy (%)	30.8	41.1	28.0	0.695
Prior Myocardial Infarction (%)	34.7	37.9	27.4	0.700
Peripheral Vascular Disease (%)	21.7	45.9	32.4	<0.001
Diabetes Mellitus (%)	26.7	43.3	30.0	<0.001
Left Ventricular Ejection Fraction				
>50%	65.3	53.4	55.2	
<30%	2.7	4.0	7.2	
30-50%	19.8	29.0	24.4	<0.001
V-gram not done due to instability	2.4	3.2	2.5	
missing	9.8	10.5	10.7	
Coronary Anatomy				
2 Vessel Disease (%)	58.6	11.6	44.0	
3 Vessel Disease (%)	39.3	58.7	48.2	<0.001
Left Main Disease (%)	1.2	28.3	5.0	
Clinical Indication for catheterization				
Unstable angina (%)	32.9	30.8	21.2	
Myocardial Infarction (%)	29.7	18.5	20.3	
Stable Angina (%)	32.0	41.8	45.2	0.004
Other (%)	5.4	9.0	13.3	
Second treatment prior to follow-up (% yes)	20.4	2.2	0.8	<0.001

Analysis of responders compared to non-responders

An analysis of the differences in the baseline demographic data and clinical characteristics of the patients who completed the survey (responders) and those with surveys that remains outstanding (non-responders) demonstrated few significant differences (Table 2). Compared with respondents, non-responders tended to be younger (age 30-37 years 36.3% versus 25.0% p=<0.001), have diabetes mellitus (23.7% versus 18.0% p<0.001) and have lower ejection fractions (EF< 30% - 6.6% versus 4.4% p=0.001). As well, non-respondents were more likely to have been treated with medical therapy during the first year following their index catheterization (35.1% versus 26.7% p<0.001).

Table D-5. Difference in demographic data and co morbidities between APPROACH patients who returned 1-year QOL questionnaire and those who did not return questionnaire.

Variables	Returned (N=3243)	Not returned (N=952)	P value
Sex (% Female)	22.2%	20.7%	0.322
Age Category (% per Quintile)			
30-57 years	25.0%	36.3%	<0.001
58-65 years	25.0%	24.8%	
66-75 years	25.0%	20.6%	
> 75 years	25.0%	18.3%	
Pulmonary disease	6.9%	6.3%	0.514
Cerebrovascular Disease	4.8%	5.9%	0.198
Renal Disease	1.7%	1.6%	0.849
Congestive Heart Failure	10.5%	11.4%	0.413
Dialysis	1.0%	0.90	0.844
Hypertension	53.6%	56.8%	0.081
Hyperlipidemia	47.9%	46.5%	0.442
Liver/Gastrointestinal Disease	2.9%	3.6%	0.313
Malignancy	3.3%	2.2%	0.085
Prior Myocardial Infarction	43.2%	45.9%	0.144
Peripheral Vascular Disease	7.5%	8.2%	0.495
Diabetes Mellitus	18.0%	23.7%	<0.001
Left Ventricular Ejection Fraction			0.001
>50%	58.0%	59.1%	
<30%	4.4%	6.6%	
30-50%	24.6%	25.1%	
V-gram not done due to instability	2.7%	2.4%	
missing	10.3%	6.7%	
Coronary Anatomy			0.124
2 Vessel Disease	37.1%	39.1%	
3 Vessel Disease	50.0%	50.0%	
Left Main Disease	12.9%	10.5%	
Treatment within 1st year following Index catheterization			<0.001
Medical Management	26.7%	35.1%	
Cabg/Valve	38.6%	32.6%	
PCI	34.7%	32.4%	

Multivariate analysis

For the overall study population, the adjusted proportional odds controlling for demographic and clinical characteristics (Table D-6) indicated that those patients who were revascularized either with PTCA, Stent or CABG tended to higher scores (better QOL) on all 5 SAQ dimensions as compared to patients treated with medical management. Patients treated with CABG tended to significantly higher scores in all dimensions compared to patients treated with PTCA or Stent although this relationship was non-significant in the exertional capacity scale.

Proportional odds ratios for all the independent variables in the 5 models are presented in Table 5. Men reported higher scores in all 5 QOL dimensions as compared to women. Younger respondents reported higher scores in the exertional capacity dimension, as well as the anginal frequency scale (higher scores indicate less anginal frequency) compared to older respondents. Conversely older patients reported higher treatment satisfaction scores as well as higher disease perception scores (less perceived disease) compared to younger patients.

A respondent's left ventricular ejection fraction (EF) measured at catheterization remained significantly associated with the exertional capacity scale following risk adjustment. As the categories of EF worsened (v-gram not done due to instability, 30-50%, and <30%) respondents reported less exertional capacity at follow-up compared to respondents with an EF of >50%. Interestingly, co morbidities including pulmonary disease, cerebrovascular disease, heart failure, prior infarction, peripheral vascular disease, and diabetes mellitus measured at catheterization remained significantly associated with the exertional capacity scale in the final adjusted model (absence of the co morbidity yielded higher SAQ dimensional scores). Respondents who underwent catheterization for a myocardial infarction reported statistically significant higher scores in all 5 SAQ scales compared to respondents catheterized for stable angina. As well, respondents who did not undergo a second treatment (Medical, CABG, PTCA or Stent) reported higher scores in all 5 SAQ dimensions. Finally respondents who completed the follow-up questionnaire closer to the one year anniversary of their index catheterization (categories included completion within the 12th month to 13th month, 14th month, and 15th month since catheterization) reported higher scores in all 5 SAQ

dimensions when compared to respondents who returned the questionnaire at or greater than the 16th month following the index catheterization.

Table D-6. Adjusted Proportional Odds Ratios of Treatment Modalities by SAQ dimensions

Treatment comparisons	Exertional Capacity POR (95%CI)	Anginal Stability POR (95%CI)	Anginal Frequency POR (95%CI)	Treatment Satisfaction POR (95% CI)	Disease Perception POR (95%C
PTCA: Medical Management	1.77 (1.32-2.37)	1.48 (1.13-1.94)	1.92 (1.48-2.51)	1.42 (1.10-1.83)	1.57 (1.23-2.00)
STENT: Medical Management	2.05 (1.62-2.59)	1.81 (1.46-2.24)	2.39 (1.93-2.95)	2.02 (1.64-2.48)	1.98 (1.63-2.40)
CABG/valve: Medical Management	2.48 (1.99-3.09)	3.39 (2.76-4.17)	4.21 (3.44-5.15)	3.12 (2.56-3.79)	2.62 (2.19-3.14)
CABG/Valve: PTCA	1.40 (1.04-1.90)	2.29 (1.73-3.05)	2.19 (1.65-2.90)	2.20 (1.68-2.88)	1.67 (1.31-2.14)
CABG/Valve: Stent	1.21 (0.95-1.54)	1.88 (1.49-2.37)	1.77 (1.40-2.22)	1.55 (1.24-1.93)	1.33 (1.09-1.61)
STENT: PTCA	1.16 (0.87-1.55)	1.22 (0.94-1.59)	1.24 (0.95-1.62)	1.42 (1.10-1.83)	1.26 (0.99-1.60)

APPENDIX E

Results of Ordinal Regression Modelling;

Revascularized Treatment Groups Only

Table E-1 Final Models Adjusting for ALL Clinical, Demographic and Co morbid Variables Revascularized Groups Only

Variable	Exertional Capacity		Anginal Stability		Anginal Frequency		Treatment Satisfaction		Disease Perception	
	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI
TREATMENT										
CABG:PTCA	1.48	1.07-2.04	2.08	1.54-2.82	2.11	1.56-2.57	2.23	1.67-3.00	1.65	1.27-2.15
Stent:PTCA	1.16	0.87-1.56	1.26	0.96-1.64	1.24	0.95-1.62	1.48	1.15-1.91	1.27	1.00-1.61
CABG: Stent	1.18	0.92-1.52	1.81	1.42-2.33	1.68	1.31-2.14	1.46	1.16-1.84	1.25	1.01-1.53
Sex Male: Female	3.57	2.79-4.57	1.25	1.00-1.56	1.72	1.40-2.12	1.25	1.01-1.54	1.79	1.48-2.16
Age Category										
16-52 years:>72 years	3.26	2.36-4.52	0.75	0.54-1.02	0.92	0.68-1.26	0.74	0.55-1.00	0.43	0.33-0.56
53-59 years:>72 years	3.93	2.90-5.34	0.87	0.65-1.16	1.21	0.91-1.62	0.87	0.66-1.14	0.71	0.56-0.90
60-65 years:>72 years	2.46	1.84-3.27	0.92	0.69-1.21	1.17	0.89-1.54	1.05	0.80-1.37	0.88	0.70-1.10
66-72 years:>72 years	1.62	1.23-2.14	0.90	0.69-1.17	1.08	0.83-1.40	0.94	0.73-1.21	1.02	0.82-1.27
Pulmonary Disease NO: YES	1.92	1.30-2.82	1.24	0.88-1.77	1.22	0.87-1.73	1.27	0.91-1.78	1.54	1.14-2.07
Cerebrovascular Disease NO: YES	1.13	0.72-1.78	1.20	0.89-1.83	1.06	0.70-1.61	1.05	0.70-1.57	1.04	0.73-1.50
Renal Disease										
NO: On Dialysis	2.61	0.95-7.13	0.27	0.08-1.00	0.45	0.15-1.37	0.90	0.35-2.14	0.50	0.23-1.09
NO: renal disease no Dialysis	1.00	0.24-4.10	0.45	0.09-2.36	0.41	0.10-1.71	0.88	0.25-3.18	0.69	0.23-2.03
Heart Failure NO: YES	2.23	1.55-3.22	1.28	0.92-1.78	1.50	1.09-2.07	1.11	0.80-1.54	1.24	0.94-1.65
Hypertension NO: YES	1.18	0.97-1.42	1.03	0.86-1.24	1.06	0.88-1.27	1.07	0.90-1.27	1.07	0.92-1.25
Hyperlipidemia NO: YES	0.86	0.71-1.03	1.08	0.90-1.30	1.01	0.84-1.22	0.93	0.78-1.11	0.85	0.73-0.99
Liver/Gastrointestinal Disease NO: YES	1.12	0.65-1.92	1.06	0.64-1.75	0.92	0.55-1.53	0.92	0.56-1.52	1.07	0.69-1.65
Malignancy NO: YES	1.01	0.59-1.71	1.10	0.66-1.83	1.14	0.70-1.86	0.80	0.48-1.33	0.95	0.62-1.45
Prior Infarction NO: YES	1.21	0.96-1.52	0.94	0.75-1.24	1.10	0.88-1.37	0.99	0.80-1.23	0.94	0.76-1.12
Peripheral Vascular Disease NO: YES	2.00	1.37-2.92	0.86	0.59-1.24	0.91	0.64-1.31	1.13	0.81-1.59	1.07	0.80-1.45
Diabetes Mellitus NO: YES	1.73	1.35-2.22	1.10	0.87-1.40	1.19	0.95-1.51	1.06	0.84-1.33	1.28	1.05-1.60
Election Fraction at Catheterization										
V-gram not done d/t instability:>50%	0.72	0.40-1.29	1.77	0.96-3.29	1.93	1.03-3.63	2.10	1.16-3.96	1.40	0.87-2.27
30-50%:>50%	0.76	0.59-0.95	1.06	0.84-1.33	1.13	0.90-1.41	1.05	0.84-1.30	0.89	0.74-1.08
<30%:>50%	0.62	0.36-1.04	1.54	0.88-2.69	1.20	0.71-2.04	1.13	0.68-1.91	0.97	0.64-1.49
Missing:>50%	0.65	0.46-0.92	0.75	0.55-1.02	0.78	0.58-1.06	1.13	0.84-1.52	1.03	0.89-1.34
Coronary Anatomy at Catheterization										
2 vessel disease: Severe Left Main	1.39	0.82-2.38	0.83	0.48-1.42	0.90	0.53-1.56	0.85	0.50-1.44	0.79	0.51-1.24
2 vessel both 95%: Severe Left Main	1.40	0.87-2.27	0.93	0.57-1.53	0.86	0.52-1.40	0.84	0.52-1.35	0.75	0.51-1.12
1 vessel 95 % PLAD: Severe Left Main	2.03	1.25-3.31	1.10	0.66-1.81	1.00	0.61-1.66	0.60	0.37-0.96	0.91	0.61-1.36
2 vessel 95% LAD: Severe Left Main	1.29	0.81-2.04	0.84	0.52-1.34	0.91	0.56-1.46	0.75	0.47-1.17	0.87	0.60-1.28
2 vessel 95% PLAD: Severe Left Main	1.25	0.77-2.02	0.76	0.47-1.25	0.67	0.41-1.09	0.62	0.38-0.99	0.76	0.51-1.13
3 vessel 1-95%: Severe Left Main	1.12	0.75-1.65	0.72	0.47-1.09	0.75	0.49-1.14	0.63	0.42-0.94	0.74	0.53-1.03
3 vessel PLAD: Severe Left Main	1.16	0.68-1.97	0.55	0.32-0.94	0.70	0.43-1.20	0.76	0.46-1.28	0.83	0.54-1.27
3 vessel 95% PLAD: Severe Left Main	1.30	0.87-1.95	0.90	0.59-1.39	0.81	0.53-1.25	0.88	0.57-1.34	0.93	0.66-1.30
Left Main: Severe Left Main	1.00	0.63-1.60	0.74	0.45-1.21	0.80	0.49-1.31	0.58	0.36-0.93	0.91	0.62-1.34
Missing: severe Left Main	1.02	0.46-0.92	0.60	0.24-1.50	0.73	0.30-1.79	0.58	0.24-1.44	0.84	0.38-1.83
Indication for Catheterization										
Unstable Angina: Stable Angina	0.85	0.67-1.08	0.97	0.77-1.23	0.83	0.66-1.04	0.90	0.72-1.12	0.89	0.74-1.08
Myocardial Infarction: Stable Angina	1.32	0.99-1.78	0.98	0.73-1.30	1.23	0.92-1.64	1.08	0.82-1.42	1.13	0.89-1.43
Other: Stable Angina	1.03	0.70-1.52	1.13	0.76-1.66	1.15	0.78-1.70	0.98	0.68-1.43	0.90	0.55-1.24
Time from treatment to Follow-up										
12 mths < 14 mths: 16 mths	1.20	0.92-1.56	1.18	0.91-1.54	1.14	0.88-1.47	1.25	0.97-1.60	1.26	1.04-1.60
14 mths < 15 mths: 16 mths	1.12	0.87-1.44	1.20	0.94-1.54	1.34	1.05-1.71	1.25	0.99-1.58	1.30	1.06-1.60
15 mths < 16 mths: 16 mths	0.92	0.72-1.18	0.94	0.74-1.20	1.02	0.81-1.31	1.20	0.95-1.51	1.17	0.95-1.44
Second treatment before follow-up NO: YES	1.64	1.20-2.24	1.03	0.77-1.37	1.69	1.29-2.22	1.26	0.96-1.65	1.57	1.21-2.03

Highlighted areas indicated statistical significance

APPENDIX F

Results of Linear Regression Analysis

F-1 Distributional Analysis SAQ data

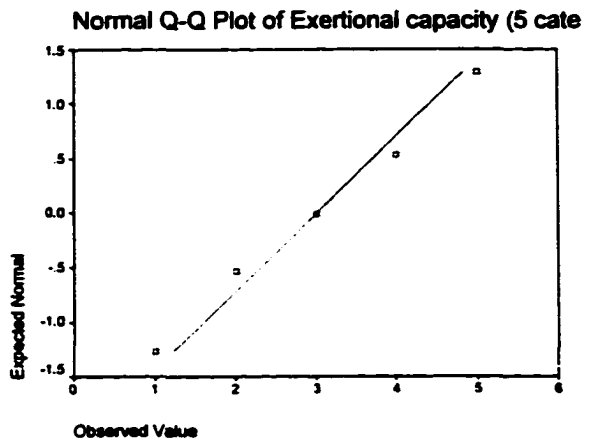
Descriptives

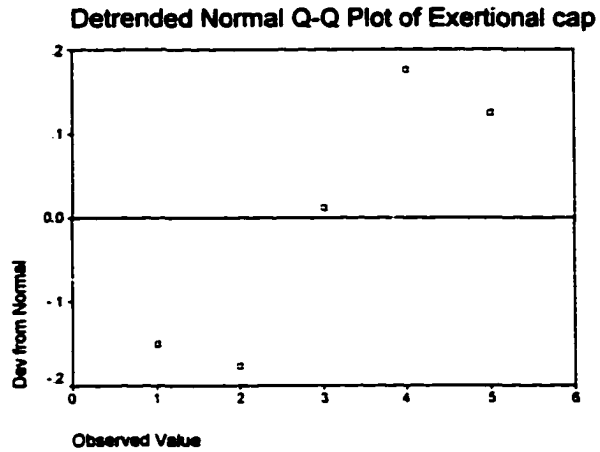
			Statistic	Std. Error
Exertional capacity (5 categories)	Mean		3.0000	3.058E-02
	95% Confidence Interval for Mean	Lower Bound	2.9401	
		Upper Bound	3.0599	
	5% Trimmed Mean		3.0000	
	Median		3.0000	
	Variance		1.993	
	Std. Deviation		1.4119	
	Interquartile Range		2.0000	
	Skewness		-.019	053
	Kurtosis		-1.285	105
Anginal stability (5-categories)	Mean		4.2105	1.939E-02
	95% Confidence Interval for Mean	Lower Bound	4.1724	
		Upper Bound	4.2485	
	5% Trimmed Mean		4.3086	
	Median		5.0000	
	Variance		1.129	
	Std. Deviation		1.0625	
	Interquartile Range		2.0000	
	Skewness		-.945	045
	Kurtosis		-.264	089
Anginal frequency (5 categories)	Mean		4.0044	2.634E-02
	95% Confidence Interval for Mean	Lower Bound	3.9528	
		Upper Bound	4.0561	
	5% Trimmed Mean		4.1160	
	Median		5.0000	
	Variance		2.196	
	Std. Deviation		1.4819	
	Interquartile Range		2.0000	
	Skewness		-1.160	044
	Kurtosis		-.251	087
Treatment satisfaction (5 categories)	Mean		3.7458	2.888E-02
	95% Confidence Interval for Mean	Lower Bound	3.6892	
		Upper Bound	3.8024	
	5% Trimmed Mean		3.8286	
	Median		5.0000	
	Variance		2.470	
	Std. Deviation		1.5716	
	Interquartile Range		3.0000	
	Skewness		-.749	045
	Kurtosis		-1.088	090
Disease perception (5 categories)	Mean		2.9220	2.656E-02
	95% Confidence Interval for Mean	Lower Bound	2.8699	
		Upper Bound	2.9741	
	5% Trimmed Mean		2.9133	
	Median		3.0000	
	Variance		2.179	
	Std. Deviation		1.4763	
	Interquartile Range		2.0000	
	Skewness		.099	044
	Kurtosis		-1.412	.088

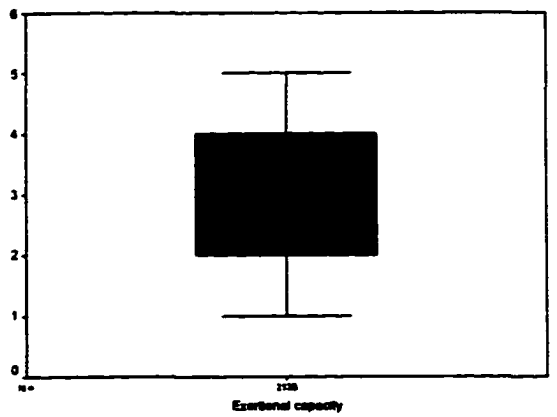
Exertional capacity (5 categories) Stem-and-Leaf Plot

Frequency	Stem & Leaf
438.00	1 . 0000000000000000000000000000000000000000000000
.00	1 .
.00	1 .
.00	1 .
.00	1 .
394.00	2 . 00000000000000000000000000000000000000
.00	2 .
.00	2 .
.00	2 .
.00	2 .
452.00	3 . 000000000000000000000000000000000000000G0000000
.00	3 .
.00	3 .
.00	3 .
.00	3 .
432.00	4 . 00000000000000000000000000000000000000000000
.00	4 .
.00	4 .
.00	4 .
.00	4 .
419.00	5 . 00000000000000000000000000000000000000000000

Stem width: 1.00
Each leaf: 10 case(s)



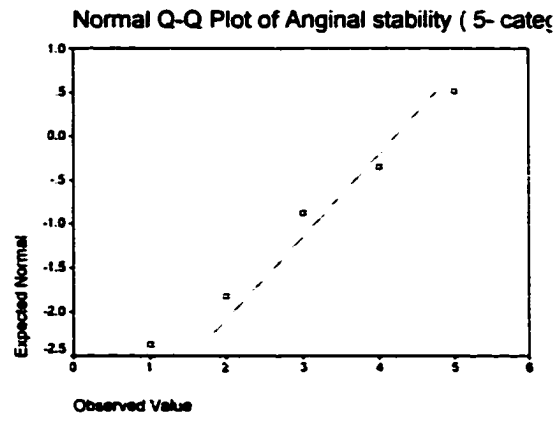


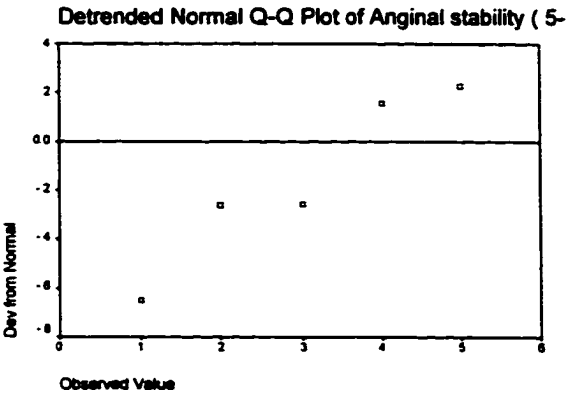


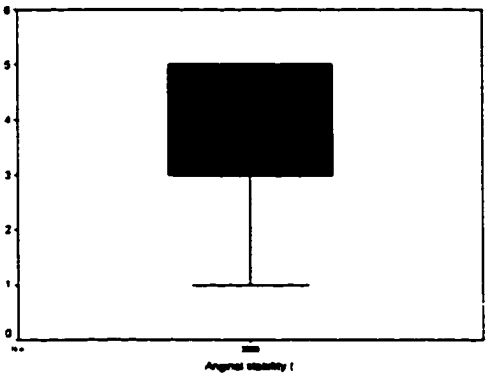
Anginal stability (5- categories) Stem-and-Leaf Plot

Frequency	Stem & Leaf
52.00	1 . 0
.00	1 .
.00	1 .
.00	1 .
.00	1 .
103.00	2 . 000
.00	2 .
.00	2 .
.00	2 .
.00	2 .
824.00	3 . 00000000000000000000
.00	3 .
.00	3 .
.00	3 .
.00	3 .
206.00	4 . 00000
.00	4 .
.00	4 .
.00	4 .
.00	4 .
1818.00	5 . 000000000000000000000000000000000000000000000000000

Stem width: 1.00
Each leaf: 38 case(s)



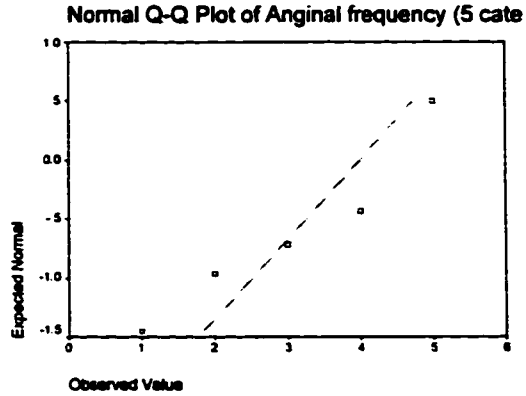


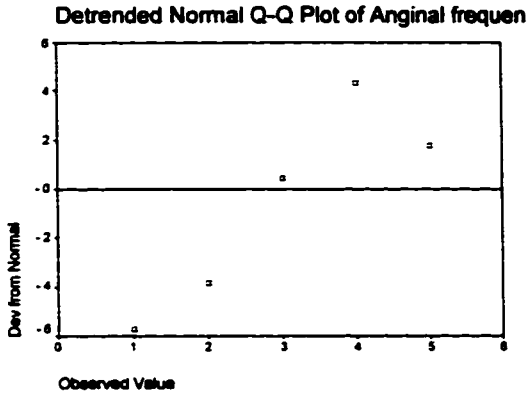


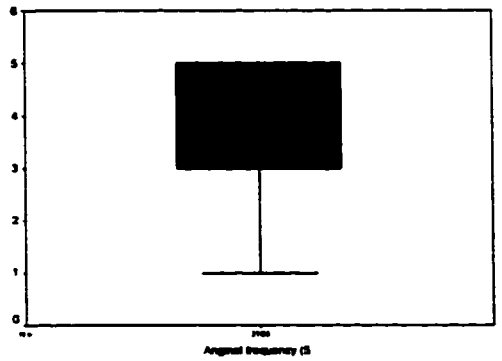
Anginal frequency (5 categories) Stem-and-Leaf Plot

Frequency	Stem &	Leaf
460.00	1 .	00000000000
.00	1 .	
.00	1 .	
.00	1 .	
.00	1 .	
135.00	2 .	000
.00	2 .	
.00	2 .	
.00	2 .	
.00	2 .	
301.00	3 .	0000000
.00	3 .	
.00	3 .	
.00	3 .	
.00	3 .	
303.00	4 .	0000000
.00	4 .	
.00	4 .	
.00	4 .	
.00	4 .	
1965.00	5 .	0000000000000000000000000000000000000000000000000000

Stem width: 1.00
Each leaf: 41 case(s)



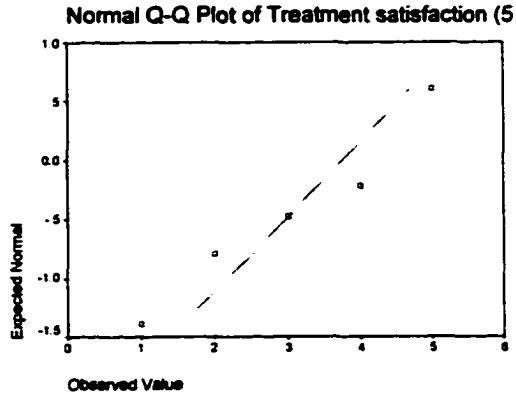


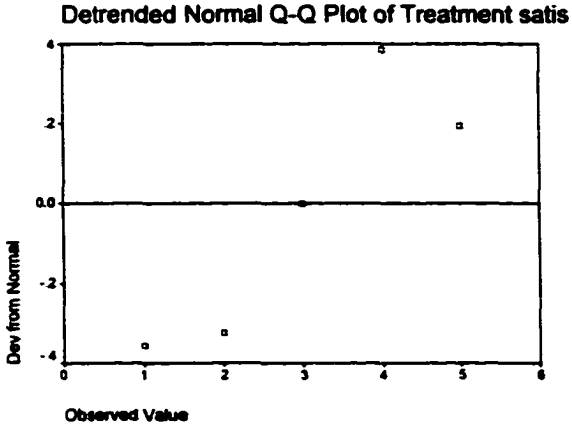


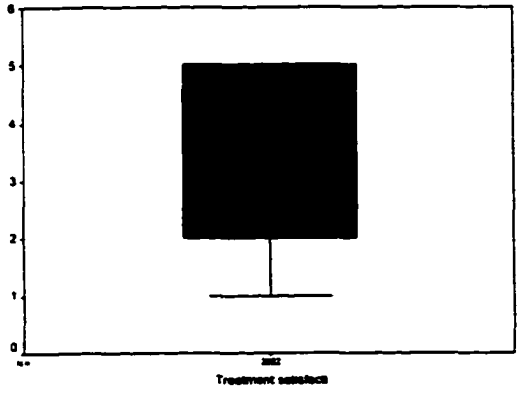
Treatment satisfaction (5 categories) Stem-and-Leaf Plot

Frequency	Stem &	Leaf
486.00	1 .	000000000000000
.00	1 .	
.00	1 .	
.00	1 .	
.00	1 .	
303.00	2 .	000000000
.00	2 .	
.00	2 .	
.00	2 .	
.00	2 .	
304.00	3 .	000000000
.00	3 .	
.00	3 .	
.00	3 .	
.00	3 .	
254.00	4 .	00000000
.00	4 .	
.00	4 .	
.00	4 .	
.00	4 .	
1615.00	5 .	000000000000000000000000000000000000000000000000000000000

Stem width: 1.00
Each leaf: 33 case(s)





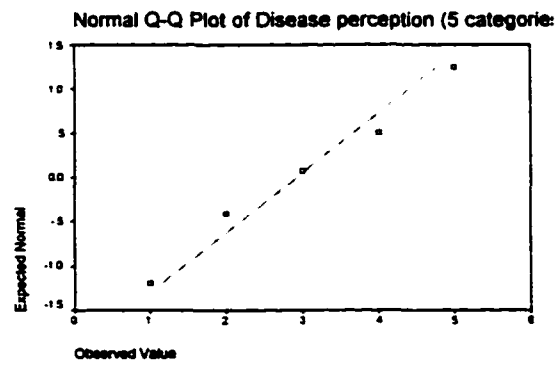


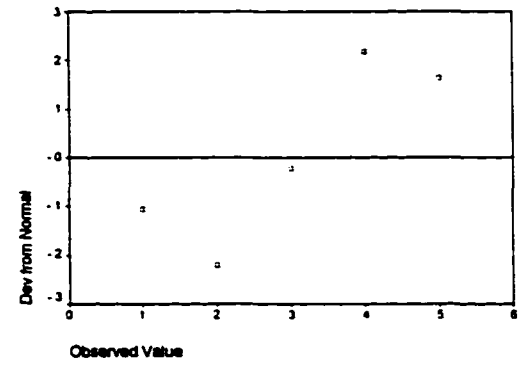
Disease perception (5 categories) Stem-and-Leaf Plot

Frequency Stem & Leaf

716.00 1 . 0000000000000000000000000000000000000000000000000000
.00 1 .
.00 1 .
.00 1 .
.00 1 .
690.00 2 . 0000000000000000000000000000000000000000000000000000
.00 2 .
.00 2 .
.00 2 .
.00 2 .
461.00 3 . 00000000000000000000000000000000
.00 3 .
.00 3 .
.00 3 .
.00 3 .
565.00 4 . 0000000000000000000000000000000000000000 .00 4 .
.00 4 .
.00 4 .
.00 4 .
658.00 5 . 0000000000000000000000000000000000000000000000000000

Stem width: 1.00
Each leaf: 15 case(s)





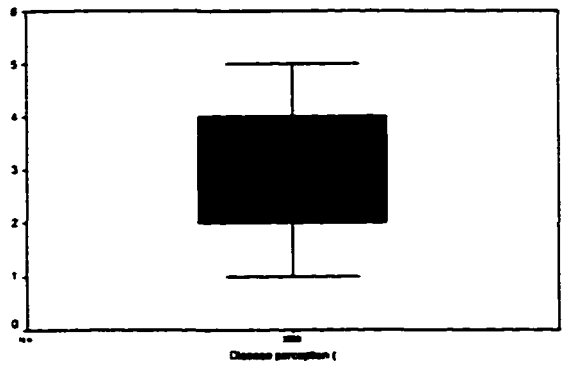


Table F-1 Odds Ratios and 95% Confidence Intervals for Linear Regression Models

Variable	Exertional Capacity		Anginal Stability		Anginal Frequency		Treatment Satisfaction		Disease Perception	
	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper CI	POR	95% lower and upper C
TREATMENT										
PTCA:MED	1.04	1.02-1.06	1.02	1.01-1.04	1.05	1.03-1.07	1.03	1.01-1.05	1.04	1.02-1.0
STENT:MEDICAL	1.05	1.03-1.04	1.03	1.02-1.04	1.07	1.06-1.09	1.06	1.04-1.08	1.05	1.04-1.0
CABG:MEDICAL	1.06	1.05-1.08	1.06	1.05-1.07	1.11	1.09-1.12	1.10	1.08-1.11	1.06	1.06-1.0
Stent:PTCA	1.01	0.99-1.03	1.01	1.00-1.02	1.02	0.84-1.22	1.03	1.01-1.05	1.02	1.00-1.0
CABG:PTCA	1.02	1.00-1.04	1.04	1.03-1.06	1.05	1.03-1.07	1.06	1.04-1.09	1.04	1.02-1.0
CABG:STENT	1.01	1.00-1.03	1.03	2.02-1.04	1.03	1.02-1.05	1.03	1.02-1.05	1.02	1.01-1.0
Sex Male: Female	1.09	1.07-1.10	1.01	1.00-1.02	1.04	1.03-1.05	1.02	1.01-1.03	1.05	1.03-1.0
Age Category										
16-52 years:>72 years	1.08	1.06-1.10	0.99	0.98-1.00	1.00	0.98-1.02	0.98	0.96-1.00	0.94	0.93-0.9
53-59 years:>72 years	1.08	1.07-1.10	0.99	0.98-1.01	1.01	0.99-1.03	0.99	0.97-1.01	0.97	0.96-0.9
60-65 years:>72 years	1.06	1.04-1.07	1.00	0.99-1.01	1.01	0.99-1.01	1.00	0.98-1.02	0.99	0.97-1.0
66-72 years:>72 years	1.03	1.02-1.05	1.00	0.99-1.01	1.01	0.99-1.01	1.01	0.99-1.02	1.01	0.99-1.0
Pulmonary Disease NO: YES	1.05	1.02-1.07	1.01	1.00-1.03	1.01	0.99-1.03	0.99	0.97-1.01	1.02	1.00-1.0
Cerebrovascular Disease NO: YES	1.03	1.00-1.05	1.01	0.99-1.02	1.01	0.99-1.04	1.01	0.99-1.04	1.01	0.99-1.0
Renal Disease NO: On Dialysis	1.08	1.02-1.14	0.99	0.95-1.03	0.98	0.98-1.04	1.01	0.96-1.07	0.98	0.98-1.0
Heart Failure NO: YES	1.04	1.02-1.06	1.01	0.99-1.02	1.01	0.99-1.03	0.99	0.97-1.01	1.01	1.00-1.0
Hypertension NO: YES	1.01	0.99-1.02	1.00	0.99-1.01	1.00	0.99-1.01	1.00	0.99-1.01	1.00	0.99-1.0
Hyperlipidemia NO: YES	0.99	0.98-1.00	1.00	0.98-1.01	1.00	0.99-1.01	0.99	0.98-1.01	0.99	0.98-1.0
Liver/Gastrointestinal Disease NO: YES	1.01	0.98-1.04	1.00	0.98-1.02	1.01	0.98-1.04	1.00	0.97-1.03	1.00	0.97-1.0
Malignancy NO: YES	0.99	0.96-1.02	1.01	0.99-1.04	1.00	0.97-1.03	0.99	0.96-1.02	1.00	0.97-1.0
Prior Infarction NO: YES	1.02	1.00-1.03	1.00	0.99-1.01	1.01	1.00-1.02	1.00	0.99-1.02	1.00	0.99-1.0
Peripheral Vascular Disease NO: YES	1.04	1.02-1.06	0.98	0.97-1.00	1.00	0.96-1.02	1.01	0.98-1.03	1.00	0.98-1.0
Diabetes Mellitus NO: YES	1.03	1.02-1.05	1.01	1.00-1.02	1.02	1.01-1.03	1.00	0.99-1.02	1.02	1.00-1.0
Ejection Fraction at Catheterization										
V-gram not done d/t instability:>50%	0.97	0.95-0.98	1.01	0.99-1.04	1.01	0.98-1.04	1.04	1.00-1.08	1.02	0.99-1.0
30-50%:>50%	0.98	0.93-1.00	1.00	0.99-1.01	1.04	1.03-1.05	1.00	0.98-1.01	0.99	0.98-1.0
<30%:>50%	0.95	0.97-1.00	1.01	0.99-1.03	1.01	0.98-1.04	1.00	0.97-1.03	0.99	0.96-1.0
Missing:>50%	0.96	0.93-0.98	0.98	0.99-1.02	0.97	0.97-1.00	0.98	0.98-1.02	1.00	0.98-1.0
Coronary Anatomy at Catheterization										
2 vessel disease: Severe Left Main	1.03	1.00-1.07	1.01	0.99-1.03	1.01	0.98-1.04	1.00	0.97-1.03	1.00	0.97-1.0
2 vessel both 95%: Severe Left Main	1.03	1.00-1.06	1.01	0.99-1.03	1.02	0.99-1.04	1.01	0.98-1.04	0.99	0.97-1.0
1 vessel 95 % PLAD: Severe Left Main	1.04	1.01-1.07	1.02	1.00-1.04	1.02	0.99-1.04	0.98	0.95-1.02	1.00	0.97-1.0
2 vessel 95% LAD: Severe Left Main	1.02	0.99-1.05	1.00	0.98-1.02	1.00	0.98-1.03	1.00	0.97-1.03	0.99	0.96-1.0
2 vessel 95% PLAD: Severe Left Main	1.02	0.99-1.05	1.00	0.98-1.02	0.99	0.98-1.02	0.99	0.96-1.02	0.98	0.96-1.0
3 vessel 1-95%: Severe Left Main	1.00	0.98-1.03	1.00	0.98-1.01	0.99	0.97-1.02	0.99	0.96-1.01	0.98	0.96-1.0
3 vessel PLAD: Severe Left Main	1.00	0.97-1.03	0.98	0.96-1.01	0.98	0.95-1.01	0.98	0.95-1.02	0.98	0.95-1.0
3 vessel 95% PLAD: Severe Left Main	1.01	0.98-1.03	1.00	0.99-1.02	0.99	0.97-1.02	0.99	0.97-1.02	0.99	0.97-1.0
Left Main: Severe Left Main	1.00	0.97-1.03	1.00	0.98-1.02	1.00	0.97-1.02	0.98	0.95-1.01	1.00	0.97-1.0
Missing: severe Left Main	1.06	1.01-1.11	1.03	0.99-1.06	1.05	1.00-1.10	1.01	0.96-1.06	1.01	0.96-1.0
Indication for Catheterization										
Unstable Angina: Stable Angina	1.00	0.98-1.01	1.00	0.99-1.01	0.99	0.98-1.00	1.00	0.99-1.02	1.00	0.98-1.0
Myocardial Infarction: Stable Angina	1.03	1.00-1.02	1.01	1.00-1.02	1.03	1.01-1.04	1.02	1.00-1.04	1.02	1.00-1.0
Other: Stable Angina	1.01	0.99-1.03	1.00	0.99-1.02	1.10	1.08-1.12	1.00	1.00-1.03	1.00	0.98-1.0
Time from treatment to Follow-up										
12 mths < 14 mths: 16 mths	1.02	1.00-1.03	1.01	1.00-1.02	1.02	1.00-1.03	1.01	1.00-1.03	1.02	1.00-1.0
14 mths < 15 mths: 16 mths	1.01	1.00-1.03	1.01	1.00-1.02	1.01	1.00-1.03	1.02	1.00-1.03	1.01	1.00-1.0
15 mths < 16 mths: 16 mths	1.00	0.99-1.02	1.00	0.99-1.01	1.01	0.99-1.02	1.00	0.99-1.02	1.01	1.00-1.0
Second treatment before follow-up NO: YES	1.04	1.01-1.06	1.00	0.99-1.02	1.04	1.02-1.06	1.02	1.00-1.04	1.03	1.01-1.0

Highlighted areas indicated statistical significance