GENDER BIAS IN TREATMENT OF CARDIOVASCULAR DISEASE IN NEWFOUNDLAND AND LABRADOR

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GENDER BIAS IN TREATMENT OF CARDIOVASCULAR DISEASE IN NEWFOUNDLAND AND LABRADOR

by

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ABSTRACT

Rationale: Cardiovascular disease (CDV) is the leading cause of mortality and morbidity in Canada. Mortality from cardiovascular disease is higher in Newfoundland and Labrador (NL) than other Canadian provinces. Gender differences in the treatment of and assessment of CVD have been repeatedly demonstrated in clinical trials.

Objective: 1) To determine the existence and impact of gender bias in the treatment of Acute Myocardial Infarction (AMI) in NL. 2) To determine if male gender is associated with inappropriate use of surgical revascularization in NL.

Design: Two observational studies: 1) Prospective cohort study; 2) Cohort study with retrospective data collection.

Setting: University based tertiary referral center in St. John's, NL.

Participants: 1) AMI patients admitted between May 24, 1990 and June 30, 1993 and followed for 3 years.
2) Patients referred for Coronary Angiography (CA) between April 1, 1994 and March 31, 1995 who subsequently underwent Coronary Artery Bypass Grafting (CABG).

Measurements: 1) The gender rates of risk factors, post-MI complications, CA, pharmacologic interventions, CABG, Percutaneous Transluminal Coronary Angioplasty (PTCA), functional class assessment using Goldman scales and mortality for three years following AMI were compared.

2) CAD risk factors, angina severity, coronary anatomy, medical therapy, CABG indication, appropriateness and necessity of CABG and operative risk and post operative complications were compared by gender.

Results: 1) During the AMI admission 9.4% of women compared to 3.9% of men had recurrent MI ($p=0.04$), 12.6% of women and 7.4% of men died ($p=0.03$). With the exception of heparin (67% male vs. 58% female $p = 0.02$), pharmacologic intervention was comparable in men and women. CA was performed in 31 % of women and 41.9% of men ($p = 0.007$). Men were more likely to be revascularized during the AMI admission (19.3 vs. 12.2, $p= 0.02$) but there was no gender difference in revascularization up to three years post-MI. Multiple logistic regression analysis (MLR), which included demographic and clinical characteristics, revealed that male sex was a strong predictor of CA and revascularization post-MI. During follow-up women consistently reported a statistically significant reduced functional capacity. Survival analysis revealed that women had significantly reduced likelihood of survival ($p=0.004$) independent of age and Angiotensin Converting Enzyme (ACE) inhibitor therapy.

2) Although there was no gender difference in angiographic findings of patients referred for CABG, 88.5% of women compared to 78.9% of men were referred for CA due to Class IV angina (p=0.006) and 49.9% of women versus 30.1% of men were at moderately to very high operative risk (p=0.000). CABG was deemed highly appropriate in 96.8% of women versus 99.5% of men (p=0.066) and highly necessary in 92.7% of women versus 94.2% of men (p=0.66).

Conclusions: 1) In Newfoundland and Labrador, Canada, despite more complicated post-MI courses, women were as likely as men to receive standard pharmacologic intervention but significantly less likely to undergo CA and revascularization following AMI.

2) Furthermore women referred for CABG had more advanced and severe CHD than men. It is possible that gender bias in the utilization of coronary revascularization may contribute to excess CHD mortality observed in women.

Caution must be exercised in generalizing the results of these studies of highly selected populations to the overall population of NL.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACC/AHA TF	American College of Cardiology/ American Heart Association Task Force
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AMI	Acute Myocardial Infarction
ASA	Acetyl Salacylic Acid (Aspirin)
AV	Atrio-ventricular
AVR	Aortic Valve Replacement
BARI	Bypass Angioplasty Revascularization Investigation
BC	British Columbia
BSA	Body Surface Area
CA	Coronary Angiography
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Grafting
CAMI	Canadian Assessment of Myocardial Infarction
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CK	Creatinine Kinase
CK-MB	Creatinine Kinase Myocardial Band
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
COPD	Chronic Obstructive Pulmonary Disease
DM	Diabetes Mellitus
ECG	Electrocardiograph
EPS	Electrophysiologic Studies
ER	Emergency Room
FDA	Food and Drug Administration
HERS	Heart and Estrogen/Progestin Replacement Therapy
HOPE	Heart Outcomes Prevention Evaluation
IV	Intravenous
LAD	Left Anterior Descending Coronary Artery
LVD	Left Ventricular Dysfunction
MI	Myocardial Infarction
MLR	Multiple Logistic Regression
MVR	Mitral Valve Replacement
NCEP	National Cholesterol Education Program
NL	Newfoundland and Labrador
NLMI	Newfoundland and Labrador Myocardial Infarction Study
NIH	National Institute of Health
ORWH	Office of Research on Women's Health
PTCA	Percutaneous Transluminal Coronary Angioplasty
PCI	Percutaneous Coronary Intervention

RAND/UCLA	Research and National Defense/University of California at Los Angeles
SAGES	Signal Averaging ECG Study
SAVE	Survival And Ventricular Enlargement
SHOCK	Should we emergently revascularize Occluded Coronaries for cardiogenic shocK
SOLVD	Studies of Left Ventricular Dysfunction
TAMI	Thrombolysis and Angioplasty in Acute Myocardial Infarction
TRACE	Trandolopril Cardiac Evaluation
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WATCH	Women's Atorvastatin Trial on Cholesterol
WHI	Women's Health Initiative

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PREFACE

The first data set analyzed for the purpose of satisfying the requirements for this thesis was collected from 1990 to 1995 (Newfoundland and Labrador Myocardial Infarction study) and the second was collected in 1996 (Newfoundland and Labrador Coronary Artery Bypass Grafting Study). These data sets may be considered by some to be dated. However, since there are no other published data offering discussion of gender bias in the treatment of cardiovascular disease, as it relates to the population of Newfoundland and Labrador, this thesis serves to fill a significant void in this area. Additionally, regardless of the age of the data sets analyzed, the requirements of the thesis may be fulfilled in the analysis and interpretation of these data sets.

1 Introduction

1.1 THE BURDEN OF CARDIOVASCULAR ILLNESS

Nearly twice as many women die from cardiovascular disease (CVD) in North America than all forms of cancer combined, yet only a very small percentage of women perceive heart disease to be a significant health threat (Legato, Padus & Slaughter, 1997; Heart and Stroke Foundation of Ontario, 2000). Despite overwhelming evidence to the contrary, many physicians still believe CVD to be primarily a disease of men and are not sufficiently attentive to the potential burden of CVD in females (Legato et al, 1997).

Mortality from CVD in Canada is declining (Merkatz, Temple, Sobel et al, 1993; Fallen, Armstrong, Cairns et al, 1991). Most of this decline is due to fewer deaths from myocardial infarction (MI) and the reduction is more pronounced in men (Brophy, 1997). Cardiovascular disease remains the leading cause of death among Canadians (Heart and Stroke Foundation of Canada, 1996).

Cardiovascular disease is the leading cause of hospitalization among women in Canada, despite the fact that women develop coronary artery disease (CAD) less frequently and later in life than men (Lerner & Kannel, 1986). In the FASTRAK database, a national registry of acute coronary syndromes, women accounted for almost one third of patients admitted with acute myocardial infarction (AMI) in 1998 (Heart and Stroke Foundation of Canada, 1999). In 1992, more than 39,000 men and nearly 37,000 women died from CVD. In Canada, 41 % of deaths in women and 37 % of deaths in men resulted from cardiovascular related diseases in 1993 (Heart and Stroke Foundation of Canada, 1995). Independent of age and other contributing factors, Ontario women were shown to have 2-3 % higher hospital mortality than men (Naylor & Chen, 1994). In addition, significant

costs associated with morbidity and mortality related to CVD in Canada.

In 1998 the total cost of illness in Canada was similar for males and females ($62.9 billion versus $57.5 billion) (Health Canada, 2002). These estimates include direct costs, (hospital care expenditures, physician care expenditures and drug expenditures) and indirect costs (those related to mortality and long- and short-term disability). The distribution of cost-by-cost component varies considerably so that 32.8 % of the total cost for males and 42.5 % of the total cost for females is allocated to direct costs while the remainder is allocated to indirect costs. The per capita direct costs of illness are essentially equal for all Canadian provinces and territories (Health Canada, 2002).

In 1998, direct costs attributable to CVD were approximately $6.81 billion dollars while the indirect costs were approximately $11.65 billion dollars (Health Canada, 2002). Direct costs of CVD in Canadian women in 1993 were approximately $3.23 billion and indirect costs were $4.72 billion (Heart and Stroke Foundation of Canada, 1996). The measurement of indirect costs of CVD in women does present some difficulty, as women represent a sizeable unpaid workforce potentially resulting in falsely low estimates (Heart and Stroke Foundation of Canada, 1996; Health Canada, 2002).

Two studies have estimated that the annual cost of CVD in Canada exceeds 19.7 billion dollars (Moore, Mao, Zhang et al, 1997; Chan, Coyote & Heick, 1996). A third Canadian report demonstrated that in 1998 the total cost of illness attributable to CVD was 18.5 billion dollars. This accounted for 11.6 % of the overall cost of illness in 1998. The costs have remained relatively stable since 1986 (Health Canada, 2002).

In Canada, mortality related to CVD is influenced by geography and age-standardized female mortality seems to follow an east-west gradient, with higher rates in Newfoundland and Labrador (NL) women (241 per 100,000) and lower rates in British Columbia (BC) women (164 per 100,000) (Heart and Stroke Foundation of Canada, 1999).

Data from the Newfoundland & Labrador Center for Health Information show that, in NL in the last six years, there has been a dramatic increase in the annual number of patients having coronary angiograms (CA), coronary artery bypass grafts (CABG's) and percutaneous transluminal coronary angioplasties (PTCA's). For example 1,363 CA's, 346 CABG's and 307 PTCA's were performed in 1995/1996, while 2001 CA's, 553 CABG's and 502 PTCA's were performed in 2000/2001. The number of CA has remained constant since 1998 while the number of CABG's continues to increase annually and the number of PTCA's seems to have peaked in 1998/1999 and fallen in the following two years (D. MacDonald, Director, Product Development Division, Newfoundland and Labrador Center for Health Information, personal communication, January 17, 2003).

Gender distribution remains the same for all procedures during that six-year period, with approximately 70 % of all CA and PTCA's and 75 % of all CABG's performed on men. When gender is additionally divided by ages of less than 70 years, age 70 to 74 years and age greater than 74 years, it becomes clear that the greatest differences in gender distribution of procedures is seen in the younger age groups. This is particularly evident in the group over 74 years where gender distribution of CA and PTCA is approximately equal. Gender distribution of CABG in this age group varies widely from 56 % male to 79 % male but consistently more males than females receive CABG (D. MacDonald, personal communication, January 17, 2003).

Life expectancy of Canadians is gradually increasing. Women outlive men by an average of 7.5 years (Gurwitz, Nananda & Avron, 1992). This results in increasing numbers of women with coronary heart disease. Since it appears that recognized treatments are generally underutilized in women, and that women are disproportionately affected by age-based rationing of health care dollars (Jecker, 1991) female access to these treatments requires particular attention.

As this will impact delivery of health care, appropriate use of recognized treatments for coronary heart disease requires further examination. In Canada, Newfoundland and Labrador is disproportionately affected by morbidity and mortality as well as increasing use of health care resources to treat CVD in women. Consequently, assessment of gender-based differences in the management of CVD in Newfoundland and Labrador is of utmost importance.

2 Bias

2.1 BIAS IN CLINICAL RESEARCH

For hundreds of years scientists have attempted to assess the value of therapies, however, it was not until 1938 that the first law, requiring establishment of drug safety prior to marketing, was passed (Neal, 1968). In 1979, publication of the Belmont Report, a comprehensive review of human experimentation, exploring ethical and human rights considerations, resulted in greater protection for human research subjects (The Belmont Report, 1978). Considering the fairly recent development of standards in performing clinical trials, it is not surprising that the science of clinical trials is imperfect and that problems such as bias have not been eliminated from the process.

Bias in clinical research introduces systematic error that may prejudice the outcome in such a way that results are no longer valid. Bias may be introduced at any phase in development, execution, or interpretation of a clinical trial (Spilker, 1991; Sachett, 1979).

Since differences in treatment outcome may occur due to chance, treatment effect, or bias, recognition, avoidance, and minimization of bias should be a primary concern for all investigators from inception of a clinical question to publication of the data. Proper execution and accurate interpretation of significance tests should be able to determine if differences can be explained by chance. Elimination of all possible systematic error should effectively reduce the possibility that differences in treatment are due to bias.

Sackett maintains that bias can occur at all stages of clinical trials. He has catalogued fifty-seven biases and provided a definition and an example for many (Sachett, 1979). Following his work in 1979, he and others have attempted to describe new, or redefine

old, biases and develop standards for prevention of bias in clinical trials (Spilker, 1991).

It is generally agreed that the best way to prevent bias is to be knowledgeable about the sources of bias and methods of prevention. Retrospective case-control or cohort studies are most susceptible to introduction of bias. Prospective randomized controlled trials provide the greatest assurance against bias. However these trials are not always possible or practical and are not entirely exempt from the influence of bias. Spilker provides an excellent resource guide for reducing bias in this type of trial (Spilker, 1991).

Even results from prospective randomized, controlled clinical trials are only generalizable to populations similar to those under study. Restrictive inclusion criteria produce a homogeneous study population but may restrict the ability to extrapolate study results to patients with characteristics that differ from the population studied. Therefore, selection of study samples must be broad enough to be applicable to the population of interest. The majority of biases detailed in Sackett's catalogue of biases fall under the heading of bias in selecting the study sample (Sachett, 1979). This provides evidence to the complexity of selection bias in clinical trials and makes it easy to see how selection criteria can influence study results.

Referral of subjects to clinical facilities may also distort study conclusions if study samples are selected from only one institution. Typically the most complex cases are referred to facilities equipped to handle them (Greenberg, Daniels, Flanders et al, 1996). The unique geography, as well as population and healthcare resource distribution of Newfoundland and Labrador has the potential to introduce bias in the assessment and treatment of patients in this province. Concentration of cardiac facilities and specialists in one tertiary

referral centre introduces selection biases into cardiac patient referral in this province.

Clinicians can feel secure in evaluating treatment modalities and make objective inferences based on the outcome of clinical trials only when every effort has been made to eliminate bias. Despite many advances in design methodologies, publication of contradictory results from clinical trials propagates skepticism among clinicians and investigators alike (Horwitz and Feinstein, 1979). This may be partly responsible for failure to implement clinical trial results into medical practice and, in particular, failure to implement the results of cardiac trials into standard treatment for female cardiac patients. Newfoundland and Labrador offers a unique opportunity to assess the impact of selection bias on treatment of cardiac disease in women.

2.2 GENDER BIAS IN CLINICAL RESEARCH

Women's cardiovascular health needs are poorly understood because less clinical information is available regarding coronary artery disease in women. Treatments, which have proven to be safe and efficacious in male populations, may not have the same benefits in female populations. Failure to conduct gender specific research may result in ill-defined criteria for diagnosis and treatment of heart disease in women (Levy, 1991).

Recruitment may bias trial data if subjects differ greatly from others with the disease. This is known as selection bias and is the most likely explanation for exclusion of women from clinical trials. Women have traditionally been underrepresented in clinical trials of CVD and data have not been analyzed by gender (Douglas, 1986; Horton, 1994). The most cited explanations for exclusion of women from clinical trials includes fear of teratogenicity, hormonal fluctuations, cardiovascular protection by estrogen and low incidence of measured outcomes (Levy, 1991; Fetters, Peterson, Shaw et al, 1996; Horton, 1994; Ryan, Anderson, Antman et al, 1996). The claim of cardiovascular protection by estrogen has been refuted by Heart and Estrogen/progestin Replacement Study (HERS) investigators who noted increased cardiovascular events in the first year of hormone replacement therapy (Hulley, Grady, Bush et al, 1998). Others note that it is difficult to recruit women into clinical trials (Legato, 1994); Johnson and colleagues however, report that women were as likely as men to consent to follow-up in observational studies (Johnson, Goldman, Orav, et al, 1996).

Trials with age-based exclusions have fewer female subjects than those without. The results of one study suggest that over 60 % of randomized controlled clinical trials of MI treatments exclude persons over 75 years of age, and up to 50 % exclude persons over 70.

Age-based exclusions in clinical trials have increased significantly since 1979. Since women comprise the largest percentage of the population over 75 years, age-based exclusions in CVD trials eliminate women from clinical studies of a disease process by which they are disproportionately affected in old age (Gurwitz, 1992; Jecker, 1991). In addition, five percent of studies exclude women totally, and 7.5 % exclude women of childbearing potential because of contraceptive requirements for inclusion (Cain, Lowell, Thorndyke et al, 2000).

The majority of MI related deaths occur in patients over 65 years of age. Sixty-four percent of those who die of acute myocardial infarction over the age of 85 years are female. By virtue of this fact, age bias equates to gender bias. The elderly are more likely to be excluded from trials using thrombolytic therapy or invasive procedures (Gurwitz, 1992; Jecker, 1991). Reluctance to use these treatments in the elderly puts the population most affected by the disease at a decided medical disadvantage.

Women's health issues have received increasing attention since the 1980's. Following the report of a Public Health Service Task Force on Women's Health Issues in 1985, The US National Institutes of Health (NIH) strengthened its policies regarding inclusion of women and minorities in clinical trials (Levy, 1991; Manolio & Harlan, 1993; Healey, 1991, JAMA). Following adoption of the Women's Health Equity Act in 1990, the Office of Research on Women's Health (ORWH) was established at the NIH (Beery, 1995) and is responsible for the administration of three Centers of Excellence in Women's Health Research. As part of its mandate, ORWH is charged with ensuring that women participate in clinical research, and that trial data is analyzed and reported by gender to ensure that differences in drug safety and efficacy are identified (Becker, 1995). In 1993, the Food

and Drug Administration (FDA) revised its policy to ensure that women of childbearing potential who use accepted methods of birth control are included in early phase clinical trials (Merkatz et al, 1993).

The Women's Health Initiative (WHI), one of the first projects to be undertaken by the NIH, is a fifteen-year prospective study (including 160,000 women) that will assess the effect of hormone replacement therapy, aspirin, antioxidant therapy, low fat diet, and lifestyle changes on cardiovascular and other diseases (Legato, 1994; Becker, 1995).

In Canada, a Federal / Provincial / Territorial Advisory Committee on Health Infostructure was convened at the Conference of Deputy Ministers of Health in 1997. This group provided a framework for developing policies and programs pertaining to sharing information on the health of all Canadian. This stimulated national discussion regarding consolidation of major health databases and development of a central registry of all Canadian clinical trials. This would facilitate review of data relevant to women's health and results of clinical trials that include female subjects (Kanzanjian, 1998).

Although Canadian researchers are aware of the importance of including women into clinical trials, analysis of data by sex is declining (Marrocco & Stewart, 2001). Women remain underrepresented in clinical trials, and publication of gender-related information remains inadequate, despite established guidelines for inclusion of women in clinical trials and reporting of gender differences in drug responses (Josephson, 1997; Birmingham, 1997; Recruitment of women to clinical trials (editorial), 2001).

Comparatively small numbers of women have been enrolled in clinical trials on which

treatment of coronary heart disease is based. Consequently, depending on patient gender, physicians may offer different treatment options, or they may generalize study results and apply identical treatment options without conclusive evidence of effectiveness. This has a significant impact on patterns of practice in the treatment of CAD in the female population (Heston and Lewis, 1992). Confirmation of the effectiveness of coronary artery disease therapies in women might improve use of proven effective therapies in females.

2.3 GENDER BIAS IN CLINICAL PRACTICE

During the 1980's and 1990's women's health issues have received a great deal of attention. This has increased awareness that some therapeutic options are not distributed equally among the sexes. Women are less likely to receive intensive management options at several junctures in health care delivery.

Many controversies still exist regarding the outcome of myocardial infarction in women. This is probably due to lack of definitive post myocardial infarction studies done in women. Most current data is based on post-hoc analysis of small numbers of women enrolled in predominantly male clinical trials. Other data has been derived from administrative databases or retrospective chart reviews with their inherent methodological flaws.

2.3.1 Intervention in Unstable Angina and Acute Myocardial Infarction

The proportion of Canadian females admitted to hospital with AMI is increasing (Kannel & Thom, 1990; Naylor & Chen, 1994). Canadian in-hospital revascularization rates are higher than they were 10 - 15 years ago. This, combined with introduction of numerous other interventions, is responsible for improvement in post-myocardial infarct prognosis (Heidenreich & McClellan, 2001). Most experts agree that prognosis after myocardial infarction (MI) is worse in Canadian women (Tsuyuki, Koon, Ikuta et al, 1994; Naylor & Chen, 1994; Rouleau, Talajac, Sussex et al 1996), but it remains uncertain whether this is related to age, severity of coronary artery disease or the presence of more active risk factors. This may be partly due to sex-related differences in assessment and treatment (Jenkins, Flaker, Nolte, et al, 1994).

Improvements in survival following AMI have been most dramatic in the past two decades, since adoption of treatments such as aspirin, thrombolytics, anticoagulants and beta-blockers (Naylor & Chen, 1994; Rouleau et al, 1996). Standard intervention for patients with acute coronary syndromes (ACS) includes establishing patency of the infarct related artery and reducing the extent of myocardial ischemia and/or necrosis. Development of time-dependent treatments, such as thrombolytic agents for AMI, makes rapid assessment and intervention of the essence. Expeditious and universal use of reperfusion therapies is the goal of care for AMI patients with ST elevation on ECG.

2.3.1.1 Emergency Management

Little information is available regarding presentation, assessment and treatment of women with chest pain in emergency rooms. Studies examining gender bias in diagnostic and therapeutic approach to patients with new onset non-traumatic chest pain report contradictory findings. At least one report suggests that no gender bias exists in the evaluation and treatment of patients presenting to emergency departments with chest pain (Silbergleit & McNamara, 1995). The preponderance of evidence suggests that women and men with similar age, risk factor profiles, presenting complaints, and co-morbid illnesses, are assessed and managed differently (Heston & Lewis, 1992; Lehman, Wehner, Lehman et al, 1996; Jackson, Anderson, Peacock, Vaught, Carley and Wilson, 1996).

Although not validated by other studies, it has also been reported that patients who have a MI confirmed by electrocardiograph (ECG) or cardiac enzyme evidence, are probably treated with equal aggression regardless of gender (French, Williams, Hart et al, 1996). It has also been claimed that a large majority of patients presenting to emergency departments with acute myocardial infarction are properly diagnosed and admitted

regardless of sex (Karlson, Herlitz, Hartford and Hjalmarson, 1993). Others suggest that men are evaluated earlier (Heston & Lewis, 1992; Lehman et al, 1996), treated more aggressively, and admitted more frequently than women (Lee, Gregory, Weisberg et al, 1987; Heston & Lewis, 1992; Lehman et al, 1996; Chandra, Ziegelstein, Rogers et al 1998). Some studies have shown that MI is confirmed more often in men, than women (Karlson, 1993; Heston & Lewis, 1992; Silbergleit & MacNamara, 1996), and that the difference in management is appropriate (Karlson et al, 1993).

Emergency assessment and subsequent management play a vital role in patient outcome. The optimum benefit of intervention for acute coronary syndromes is achieved if treatment with thrombolytics, acetylsalacylic acid (ASA), beta-blockers, and angiotensin converting enzyme (ACE) inhibitors is initiated soon after onset of symptoms. However, delay in patient presentation, treatment, and under-utilization of these pharmacologic interventions (Goldberg, Gurwitz, Yarzebski et al, 1993; Barron, Bolby, Breen et al, 1998; Chandra et al, 1998) continue to be important problems with many contributing factors.

2.3.1.2 Thrombolytics

There is no evidence to suggest that coronary thrombosis evolves differently in males and females. There is considerable evidence that women, despite increased risk of bleeding, gain substantial benefit from thrombolytic therapy (Becker, Terrin, Ross et al, 1994; White, Barbash, Modan et al, 1993) and that aggressive reperfusion therapy yields similar outcomes for men and women (Becker, 1995). Current guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) recommend administration of thrombolytic therapy to all patients without contraindications, in whom AMI is suspected, regardless of age, sex, or race (Barron et al, 1998). However, women

and the elderly are more often considered ineligible for thrombolytics due to age, delayed presentation, nondiagnostic ECG's, and medical contraindications. Even when eligible, they are less often treated with thrombolytics (Maynard, Althouse, Cequeria et al, 1991). While the Thrombolysis and Angioplasty in AMI (TAMI) trials demonstrated that controlling for clinical and angiographic differences produced similar mortality and thrombolytic utilization rates in men and women (Lincoff, Califf, Ellis et al, 1993), a similar approach in a retrospective cohort Japanese study of post MI patients showed that even after adjustment for baseline characteristics, women had higher mortality and lower thrombolytic utilization rates than men (Matsui, Fukui, Hira et al, 2002).

Delays before and after presentation contribute to patient outcome. Over the last thirty years, public education has resulted in decreased delay between symptom onset and hospitalization. Patient delay in seeking attention and physician delay in referral continue to be major contributing factors in late intervention for acute myocardial infarction. Delays occur even in patients with well-known risk factors and frequent medical contacts (Goldberg et al, 1992) and are still more pronounced in women than men (Goldberg et al, 1992; Jenkins et al, 1994; Clarke, Grey, Keating et al, 1994; Karlson & Herlitz, 1996; Chandra et al, 1998).

Thrombolytics are more likely to be administered to patients presenting early after symptom onset. The greatest benefit is seen when thrombolytics are administered within six hours of symptom onset. In the Trandolopril Cardiac Evaluation (TRACE) study, 56 % of patients presenting within two hours, and only twelve percent of those arriving more than twelve hours after symptom onset, were treated with thrombolytic therapy. Longer delay was associated with higher mortality (Ottesen, Kober, Jorgenson et al, 1996).

Canadian physicians are reported to be significantly slower than their US counterparts in initiating thrombolytic therapy (Williams, 1997). Elderly and hypertensive patients are more likely to experience a delay in administration of thrombolytics therapy (Goldberg et al, 1992; Barron et al, 1998). As women presenting with MI are typically older and have higher incidences of hypertension than their male counterparts, delay in initiation of thrombolytics therapy is more likely to be seen in women. This may expose Canadian women to a greater risk of death than United States (US) women following AMI. Reductions in time-to-treatment with thrombolysis have been achieved by Canadian physicians in recent years (Markel, 1997).

It has been reported that, despite probable underutilization of most accepted post MI interventions, there appears to be no gender difference in the use of thrombolytics (Vacek, Handlin, Rosamond et al, 1995; French et al, 1996;). However, only 31 % of patients presenting with AMI in the US are considered eligible for thrombolytic therapy. Twenty four percent of patients are not treated despite being eligible. Underutilization is particularly evident in the elderly, minorities, and women (Rathore, Berger, Weinfurt et al, 2000). These groups are at the highest risk of in-hospital mortality (Clarke et al, 1994; Chandra et al, 1998; Rathore et al, 2002). Among women who are eligible for thrombolytic therapy, 60 % are not treated and this cannot be explained by age or delayed presentation (Barron et al, 1998). There has been at least one report of increasing numbers of women being treated with thrombolytics (Chandra et al, 1998).

2.3.1.3 ASA, Beta-blockers and ACE Inhibitors

Therapies for secondary prevention of MI, such as ASA, beta-blockers (Wegner, Speroff and Packard, 1993) and ACE inhibitors (Pffeffer, Braunwald, Moye et al, 1992) appear to

have comparable efficacy in both men and women. Despite temporal trends for increased utilization of effective AMI therapies in North America (Pagley, Yarzebski, Goldberg et al, 1993; Tsuyuki et al, 1994; Martinez, Agusit, Arnau et al, 1998), Canadian patients are prescribed fewer medications than American patients following MI. In the SAVE study, Canadian patients were significantly less likely than US patients to be prescribed cardiac medications, including beta-blockers, during hospitalization (Rouleau, Lemuel, Pfeffer et al, 1993). Gan and colleagues demonstrated that, including only ideal candidates for receiving standard post-MI pharmacologic interventions eliminated gender differences in administration of beta-blockers and ACE inhibitors (Gan, Beaver, Houck, MacLehose, Lawson and Chan, 2000).

ASA

The primary protective effects of aspirin have not been demonstrated in females and the results of two primary prevention studies in men are conflicting (Steering Committee of the Physicians' Health Study Research Group, 1989; Peto, Grey, Collins et al, 1988). The British male doctors study, which failed to demonstrate beneficial effects of aspirin in reducing coronary events (Peto et al, 1988), had a lower incidence of non-fatal MI than the United States trial, which demonstrated about a 30 % reduction in non-fatal MI (Steering Committee of the Physicians' Health Study Research Group, 1989). This supports positive finding of the US trial. However, the women nurses study noted a statistically significant reduction in risk of myocardial infarction in women who took low-dose aspirin. Women who reported taking higher doses of aspirin were noted to have increased risk of hemorrhagic stroke (Manson, Stampfer, Colditz et al, 1991). Some authorities have argued however, that because this was an observational study, it provides insufficient evidence for the cardio protective effect of low-dose aspirin in women (Appel

and Bush, 1991). Randomized data from women's studies are not available. The Women's Health Study, a randomized trial of low-dose aspirin will provide more definitive data on primary prevention of MI in women (Women's Health Study Research Group, 1994).

A review of randomized trials of antiplatelet therapy showed that aspirin reduces the odds of recurrent events following MI by as much as 34 % (Antiplatelet Trialists Collaboration, 1994; Tsuyuki et al, 1994). It is clear that following acute MI, regardless if sex significant risk reduction is achieved through aspirin use (Hennekens, 1999). It is recommended that all post MI patients receive aspirin unless contraindicated (Fallen et al, 1991; Ryan et al, 1996). Evidence of aspirin's role in secondary prevention of coronary artery disease is based primarily on trials involving men, but additional evidence supports it has clear benefits in reducing risk of events in men and women (Yusuf, Collins, MacMahon et al, 1988; Antiplatelet Trialists' Collaboration, 1994).

Some reports suggest that, during hospitalization post MI patients are prescribed aspirin equally regardless of gender (French et al, 1996; Wilkinson, Laji, Ranjadayalan, et al, 1994). Following referral to an outpatient cardiologist, males are more frequently prescribed ASA than females (Jaglal, Slaughter, Baigrie, Morgan, and Naylor, 1995). In the SAVE study, men received more ASA than women in the weeks preceding MI (Pfeffer et al, 1992). Lehman and coworkers reported that only 12 % of women compared to 26 % of men received ASA when presenting to the emergency room (ER) with chest pain (Lehman et al, 1996). Most reports indicate that during hospitalization (Chandra et al, 1998; Rathore et al, 2000) and on discharge following AMI, significantly fewer women than men were prescribed aspirin (Clarke et al, 1994; Rathore et al, 2000).

Beta-Blockers

The role of beta-blockers in post-infarction mortality reduction has been clearly established in clinical trials (Sial, Malone, Freeman et al, 1994;Yusuf et al, 1988, Martinez et al, 1998). It is generally accepted that, except when contraindications exist, beta-blockers should be administered to all AMI patients (Fallen et al, 1991; Ryan et al; 1996) early in the post MI period and continued for two to three years thereafter (Hennekens, Albert, Godfried et al, 1996). However, following AMI, beta-blockers are underutilized in general (Sial et al, 1994; Rouleau et al, 1993) and withheld from patients with diabetes and left ventricular dysfunction. Women are significantly less likely than men to receive beta-blockers during hospitalization (French et al, 1996; Chandra et al, 1998; Rathore et al, 2000) and on discharge (Jenkins et al, 1994; Wilkinson et al, 1994; Sial et al, 1994, Clarke et al, 1994). Yet there are no randomized clinical trials specifically addressing the role of beta-blockers in females following AMI.

ACE Inhibitors

The role of ACE inhibitors in prevention of cardiac remodeling in AMI has been clearly established in clinical trials since the early 1990's (Pfeffer et al, 1992; French et al, 1996) and reinforced in the more recent Heart Outcomes Prevention Evaluation (HOPE) trial (Yusuf, Sleight, Pogue et al, 2000). Improved survival following AMI has been shown to be associated with the use of ACE inhibitors in the early post MI period (Pffeffer et al, 1992). In addition, ACE inhibitors have been shown to improve long-term survival in patients with left ventricular dysfunction. This is reflected in increased ACE inhibitor prescription in secondary prevention after MI (Martinez et al, 1998). It has been recommended that all patients without contraindications receive ACE inhibitors for at least

six weeks following MI (Hennekens et al, 1996). From the HOPE trial, it is evident that ACE inhibitors should be used in a broad spectrum of patients at risk of cardiac events (Sleight, 2002). However, data from randomized trials of ACE inhibitors in post-MI females are lacking. A recent Quebec study has reported that post MI patients, admitted to tertiary care settings, were significantly less likely to be prescribed ACE inhibitors than those admitted to community hospitals (Beck, Lauzon, Eisenberg et al, 2000).

2.3.1.4 Nitroglycerine, Heparin and Calcium Channel Blockers

Some drugs previously touted for universal use in post-MI patients, have only limited use in special situations. Among these are nitroglycerine, heparin and calcium channel blockers. Nitrates are indicated in the treatment of angina but have no effect in progression of CAD and do not reduce morbidity or mortality post-MI (Anonymous, 1996). Post-MI women have been shown to receive more nitrates than men (Clarke et al, 1994). The effects of heparin on mortality are less certain than those of ASA, beta-blockers and ACE inhibitors (Heidenreich & McClellan, 2001). Heparin may be used as antithrombotic therapy, in those not receiving thrombolytics, or as adjuvant to thrombolytic therapy. Treatment with heparin is less frequent in women (Chandra et al, 1998). Calcium channel blockers have not been demonstrated to decrease mortality and have a role only when beta-blockers are contraindicated. Women have been shown to receive calcium channel blockers more often than men (Clarke et al, 1994).

2.3.2 Noninvasive IschemicTesting (NIIT)

Early detection of CAD through effective use of noninvasive ischemic testing (NIIT) has the potential to increase identification of patients at risk. During the last two decades several noninvasive diagnostic tests have become widely used in cardiac patients. These

tests are reported to have varying sensitivities and specificities, particularly in women, may influence their use in the female population. Noninvasive testing includes exercise stress electrocardiography (ECG), stress echocardiography, and nuclear cardiac imaging (thallium and sestamibi) tests. Overall the prognostic value of these tests in women is improving (Merz, Johnson, Kelsey et al, 2001).

Exercise stress ECG is the least reliable of noninvasive tests. This test has poor sensitivity and specificity and a higher rate of false positives in women than in men (Sketch, Mohiuddin, Lynch et al, 1994). Stress echocardiography has improved sensitivity and specificity over stress ECG and it provides additional information regarding cardiac function. However, it requires that the patient exercise and develop ischemia in order to identify wall motion abnormalities. This may result in false negatives if target exercise level is not reached. Image quality can also influence diagnostic value of the test. Stress echo is widely used and a recent publication suggests that it has value in identification of women with severe CAD (Merz et al, 2001).

Nuclear tests are favored in diagnosing CAD in women because they have superior sensitivity and specificity to stress tests and have been demonstrated to be effective in stratifying women according to degree of risk (Hachmanovitch, Berman, Kiat et al, 1995). These tests are useful in identifying patients who require more invasive testing. In addition, images can also be gated thereby separating attenuation defects from infarcts and allowing assessment of heart function. Nuclear tests are also more beneficial in situations where patients are unable to exercise (Cequeria, 1995). Until recently, women were generally underrepresented in clinical trials of these diagnostic tests or the data was not analyzed by gender. In spite of this, there have been reports that the results were used in

the same manner in women as in men (Shaw, Miller, Romeis et al, 1994).

An Ontario based observational study demonstrated rapid growth in the use of noninvasive cardiac diagnostic tests with the highest growth rate (157%) being exhibited in myocardial perfusion scans. A proportionately greater use of many procedures, most notably myocardial perfusion scans in women, contributed to increased utilization rates (Chan, Cox and Anderson, 1996). At least one other study has demonstrated increasing utilization of perfusion scans in women (Miller, Roger, Hodge et al, 2001).

The optimal diagnostic strategy in evaluation of chest pain in women is sequential testing with referral of women with positive tests to the next level of evaluation (Shaw, Hachmanovitch and Redberg, 2000). Women are often deemed to have abnormal noninvasive test responses. This, combined with lower CAD prevalence reduces the ability of stress tests to accurately diagnose CAD in women. These issues may influence the physician's decision to refer women for noninvasive cardiac diagnostic tests (Mark, Shaw, DeLong et al, 1994). Myocardial perfusion scans appear to have similar prognostic accuracy regardless of gender (Marwick, Shaw, Lauer et al, 1999).

Following presentation to emergency departments for acute chest pain, women are less likely than men to be admitted to hospital or to undergo stress tests in the first month following the event. Women, who are admitted to hospital, are as likely as men to undergo stress testing but less likely than men to undergo nuclear imaging or CA (Johnson et al, 1996).

Since findings of noninvasive tests are often used in determining the need for more

invasive testing, the impact of patient referral for noninvasive testing has a significant impact on access to myocardial revascularization.

2.3.3 Coronary Angiography and Revascularization

The American College of Cardiology and American Heart Association Task Force (ACC/AHA TF) on Practice Guidelines (Committee on Management of Acute Myocardial Infarction) recommend that following MI, patients who develop recurrent angina or evidence of ongoing ischemia or left ventricular dysfunction (LVD) should undergo CA (Ryan et al, 1996). Coronary angiography has been shown to be associated with lower mortality regardless of sex (Kostis, Wilson, O'Dowd, 1994). Although there are reports which indicate that coronary artery disease severity is similar in women and men following AMI (Jenkins et al, 1994), referral of females for CA has been influenced by studies that reported finding normal coronary flow in a high percentage of women referred for evaluation of chest pain (Fisher et al, 1982).

It has been long demonstrated that grouping women on the basis of severity of anginal symptoms is effective in identifying those with critical coronary artery stenosis (Welsh, Proudfit and Sheldon, 1975). After adjustment for age and thallium results, Lauer found that women were referred for coronary angiogram as frequently as men (Lauer, Pashkow, Snader et al, 1996). Both Hachmanovitch and Duca found that controlling for severity of abnormality on cardiac perfusion scans eliminated the difference in referral rate for cardiac catheterization and frequency of cardiac events between men and women (Hachmanovitch et al, 1995; Duca, Travin, Herman et al, 1996).

Regardless of country and type of healthcare system (Jaglal, Goel, Naylor et al, 1995), the

majority of studies report that women are referred for CA significantly less often than men (McGlynn, et al, 1994) even when age, functional disability, and comorbid illness are accounted for (Steingart et al 1991; Anyan and Epstein, 1991; Pfeffer et al, 1992; Maynard, Litwin, Martin et al, 1992; Kee, Gaffney, Curry et al, 1993; Johnson et al, 1996) or when CA is deemed *necessary* by objective assessment of need (Garg, Landrum, Normand, et al, 2002).

Utilization of CA in patients with chest pain and no previous history of CAD has not been the subject of many studies. This group comprises a large segment of the population referred for invasive diagnosis. Studies refute the presence of referral bias in this patient population. One such study reveals that in all decades of life, a greater proportion of women than men were referred for CA. Significantly greater numbers of women had normal coronary arteries and the extent of disease and LVD was comparable in both sexes also refuting the claim of later referral in women (Vaitkus, 1995)

In contrast, a Canadian study suggests bias may be operating at all levels of the referral chain. This study found that, even when angina severity was accounted for, females with newly suspected CAD were significantly less likely than men to have had referrals for noninvasive diagnostic testing, or for CA when noninvasive testing was positive (Jaglal et al, 1995). In similar groups of patients in other studies, it has been reported that men were significantly more likely than women to be referred for CA following abnormal cardiac noninvasive perfusion tests (Tobin, Wassertheil, Wexler et al, 1987; Shaw, Miller, Romeis et al, 1994; Miller et al, 2001).

It has been suggested that once women present with definite diagnosis of AMI or have

undergone invasive diagnosis and are shown to be as sick as men they are treated with equal aggressiveness (Healey, 1991; Maynard et al, 1992; Demirovic, Blackburn, McGovern et al, 1995). In these patients, CA is generally used to determine disease severity and help select the best treatment option. Gender difference in referral for CA should not be evident in this population (Bell, 1996).

There are many reports of similar rates of CA in post MI patients. A study by Krumholtz and coworkers found, that by controlling for age, they were able to eliminate differential referral rates for CA and PTCA and reduce differential referral rates for CABG to borderline statistical significance (Krumholtz, Douglas and Lauer, 1992). A study by Mark and others revealed that after accounting for lower pre-test probability of coronary disease and lower rate of positive exercise tests, gender was not related to referral for cardiac catheterization (Mark et al, 1994). A recent publication by Rathore finds that risk-standardization of rates for cardiac catheterization reduced most of the sex differences in procedure utilization in elderly post MI patients. Rates of use were similar between men and women with strong indications, whereas rates were slightly lower in women with equivocal indications for cardiac catheterization (Rathore, Wang, Radford et al, 2002). The SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) trial, which included patients from five Canadian centres, revealed that, after adjusting for demographics and treatment approaches, women were more likely to undergo CA than men (Wong, Sleeper, Monrad et al, 2001).

PTCA has demonstrated improved survival in high-risk post myocardial infarction patients (Vacek et al, 1995) and is now the procedure of choice in treating AMI (Azar, Waters, McKay et al, 2000). Procedural success rate is similar in women and men (Azar et al,

2000; Peterson, Lansky, Kramer et al, 2001). Higher risk of female mortality and post procedural complications have been seen (Wegner et al, 1993; Azar et al, 2000; Peterson et al, 2001) in several studies, but more recent data suggest similar short-term, medium-term, and long-term outcome for both sexes, after controlling for demographic and clinical variables and body surface area (BSA) (Philippides and Jacobs, 1995; Jacobs, Kelsey, Brooks et al, 1998; Azar et al, 2000; Peterson et al, 2001). In one study of very early revascularization with percutaneous intervention (PCI), women were shown to have better long-term outcome than men (Mueller, Neumann, Roskamm et al, 2002).

Two studies found that women were as likely as men to undergo PTCA but less likely to have CABG (Bell, Berger, Holmes et al, 1995; Bergelson and Tommaso, 1996). While the difference in revascularization strategy was unexplained in one study (Bergelson and Tommaso, 1996) clinical differences, making women less desirable surgical candidates, were evident in the other (Bell et al, 1995). Another study noted that over time a significant increase was seen in the number of PTCA's performed in women and a significant decrease was seen in the number of CABG's performed in men (Roeters van Lennep et al, 2000).

Coronary artery bypass grafting is effective in reducing angina and prolonging life in patients with severe disease. Throughout the last decade there has been progressive increase in the number of women having CABG (Abramov, Tamariz, Sever et al, 2000). Women have consistently been reported to have higher perioperative complications than men, including mortality (Wegner et al, 1993; Tan, van der Meer, de Kam et al, 1999; Abramov et al, 2000). It has been demonstrated that less favorable clinical outcome is related, not to gender, but to unequal distribution of risk factors (Tan et al, 1999;

Abramov et al, 2000). A recent study reports that, while women were more likely to require inotropic support and to have longer hospital stays, controlling for differences in risk factors eliminated the sex difference in death, perioperative MI, and cerebrovascular accident (CVA) (Aldea, Gaudiani, Shapira et al, 1999). Long-term mortality for women who undergo CABG has been demonstrated to be similar to that of men (Philippides and Jacobs, 1995). A Canadian study of almost 5,000 CABG patients, followed for up to nine years, showed actuarial survival at sixty months to be greater in women than men, when adjustment occurred for other risk variables (Abramov et al, 2000). The authors wondered if this was related to later disease onset and greater longevity in women. Similar results were seen in the Bypass Angioplasty Revascularization Investigation (BARI) study but this was a selected group of patients amenable to both CABG and PTCA (Jacobs et al, 1998). Graft patency at one year has been shown to be similar in men and women undergoing CABG (Tan et al, 1999).

Several studies have found evidence that North American women have less access to revascularization after CA than men (Pffeffer et al, 1992; Naylor et al, 1993; Jaglal et al, 1994; Schulman, Berlin, Harless et al, 1999; Chandra et al, 1998). It has been claimed that when the survival benefit is low, women are more often treated medically while men are referred for surgical intervention (Tobin et al, 1987; Bickell, Pieper, Lee et al, 1992) and that this reflects appropriate treatment (Bickell et al, 1992). Without outcome data it is difficult to determine whether this is true. In many studies, revascularization rates have been reported to be similar in men and women with known or suspected CAD (Tobin et al, 1987; Chriboga, Yarzebski, Goldberg et al, 1993; Johnson et al, 1996; Bell, Berger, Holmes et al, 1995; Bergelson and Tommaso, 1996; Roeters van Lennep, Zwinderman, Roeters van Lennep et al, 2000; Miller et al, 2001). Some have suggested that gender bias

in referral to revascularization is not evident when disease severity is considered (Tobin et al, 1987; Bell, Berger, Holmes et al, 1995; Bergelson and Tommaso 1996; Roeters van Lennep et al, 2000). An Alberta study of revascularization after CA, has demonstrated that adjusting analysis for clinical variables, especially the extent of coronary disease, can eliminate the differences in revascularization rates between women and men, regardless of revascularization strategy (Ghali, Faris, Galbright et al, 2002). Likewise in the SHOCK study, where, once adjustments were made for patient characteristics, no gender bias was seen in selection of patients for revascularization (Wong et al, 2001).

2.3.4 Appropriateness of Revascularization

Rates of coronary revascularization vary widely between and within countries. A 1997 report indicates that, in 1992, the rate of combined CABG and PTCA varied from 515 per million in the United Kingdom to 2676 per million in the United States (Meijler, Rigter, Bernstein, et al, 1997). Two Canadian studies show that rates of CABG vary by province (McGlynn, Naylor, Anderson, et al, 1994; Anderson, Pinfold, Hux, et al, 1997). This makes it somewhat difficult to define the optimal rate at which CABG should be utilized.

Consequently, during the last ten years attention has been focused on devising appropriateness scores for revascularization decisions. This is of particular importance when specialized care is regionalized, potentially influencing access to procedures such as coronary revascularization. Also, when limited resources are available, these ratings may help to ensure that overuse and underuse of coronary revascularization is minimized.

The RAND/UCLA (Research and National Defense/University of California at Los Angeles) appropriateness method, which requires a panel of experts to review and rate the

appropriateness of indications for a medical procedure in two rounds, has been applied to a variety of medical procedures (Rigter, Meijler, McDonnell, et al, 1997). While this method received some criticism of its ability to identify overuse, it has been shown to have highly reproducible results in detecting underuse of revascularization (Shekelle, Kahan, Bernstein et al, 1998). This method has been used as the basis for developing Canadian appropriateness criteria for CA and CABG (McGlynn et al, 1994).

It has been demonstrated that Canadian physicians in two provinces make similar decisions regarding appropriate use of CABG (Anderson et al, 1997). Several studies have found that rates of inappropriate revascularization, especially inappropriate CABG, are as low as two to five percent in Canadian provinces and generally less than ten percent in the United States and Europe (McGlynn et al, 1993; Meijler et al, 1997; Bernstein, Brorsson, Aberg et al, 1999).

It should be expected that patients receiving revascularization, in whom it is considered appropriate, would have better outcomes than those in whom it is considered inappropriate (Rigter et al, 1997; Hemingway, Crook, Dawson et al, 2001). Substantial underuse of coronary revascularization in patients considered appropriate has been identified and found to be associated with poor clinical outcomes. Patients who received medical management, despite being classified as appropriate for CABG, were more likely to have angina, MI, or to have died at follow up than those who received CABG. This demonstrates the clinical validity of appropriateness ratings (Hemingway, Crook, Feder, et al, 2001). There are no published data addressing gender and appropriateness of coronary revascularization.

The literature includes many explanations for lower rates of CA in women including perception of more severe CAD in men, inaccurate noninvasive testing, poor outcome in women and referral at a later stage in the disease process. It has also been suggested that differences in treatment approach could be explained by gender bias (Johnson et al, 1996). Although earlier publications claimed lower rates of CA and revascularization in women, later studies have demonstrated that gender becomes less important when clinical differences, disease severity, and appropriateness of procedures are considered (Azar et al, 2000; Rathore et al, 2002;Ghali et al, 2002).

3 Gender Bias in Newfoundland and Labrador

3.1 GENDER AND CLINICAL OUTCOMES, TREATMENT AND MORTALITY FOLLOWING ACUTE MYOCARDIAL INRFARCTION (NLMI STUDY)

3.1.1 Context

Coronary artery disease is the leading cause of morbidity and mortality in Canada. As the population ages, the severity of this problem will become more evident, particularly in women who live longer than men. As female mortality due to cardiovascular disease is higher in NL than other Canadian provinces, this province will be disproportionately affected by this problem.

Gender bias in delivery of medical care to cardiac patients is controversial. Little is published about the association between gender and delivery of cardiac care in Canadian institutions. The province of NL has a high prevalence of cardiovascular disease but there is little information regarding gender bias in treatment, or impact on outcome, in cardiovascular patients in this province.

3.1.2 Objective

To determine if gender bias exists in the treatment of AMI in Newfoundland and Labrador.

3.1.3 Hypothesis

Female sex is associated with less aggressive treatment and assessment and poorer outcome following myocardial infarction in Newfoundland and Labrador.

3.1.4 Methods

These data were originally collected in the context of the (Signal Averaging ECG) SAGES study and subsequently stratified by sex and reanalyzed for the purpose of this study. The

SAGES study was undertaken to determine if it was possible, using signal averaging electrocardiography (SAECG), to predict which patients were at the greatest risk of developing ventricular arrhythmias following MI.

Between May 24, 1990 and December 31, 1992, 698 consecutive patients presenting to two tertiary referral centres in St. John's, NL with an AMI were documented in a prospective fashion. One of these hospitals contained the only provincial facility for cardiac catheterization and cardiac surgery. Patients were identified by a daily review of admissions to the coronary care unit, intensive care unit, and the cardiology ward. In addition, all patients undergoing bypass surgery were reviewed to identify perioperative myocardial infarction. All deaths in the emergency department were also reviewed and all patients meeting the study criteria were included in the study. Exclusion criteria were limited to patient or physician refusal, permanent pacemaker dependant, malignant neoplasm or other criteria making the patient unsuitable for study.

Prior to October 1991, patients greater than 75 years of age were excluded. Due to slow study enrollment it was subsequently decided to include subjects regardless of age.

Data were collected by trained research nurses and verified by a cardiologist. All data were collected prospectively using uniform procedures for data collection and entry which were outlined in a protocol and reinforced with training sessions before the start of patient enrollment and at annual meetings thereafter. Information was obtained from chart review, patient and family interviews and physician interviews.

Demographic variables included age, gender, family history, diabetes (DM), hypercholesterolemia, hypertension and smoking. Cardiac history included previous

angina, MI, congestive heart failure (CHF), angiographic evidence of CAD, CABG, PTCA, aortic (AVR) or mitral (MVR) valve replacement or other relevant conditions. It was also determined whether the patient was transferred from another institution.

Acute myocardial infarction was defined as having at least two of the following: 1) chest pain lasting at least 20 minutes, 2) new Q wave of at least 0.04 seconds in at least two contiguous leads on 12-lead ECG, or 3) creatinine kinase (CK) $\geq$ 1.5 times the upper limit of normal or creatinine kinase myocardial band (CK-MB) positive when CK was greater than the upper limit of normal. Probable acute myocardial infarction was defined as someone who died within four hours after having at least twenty minutes of chest pain and continuous ST segment elevation in at least two contiguous leads on a 12-lead ECG, but who did not meet the above criteria for an acute myocardial infarction. Definite and probable myocardial infarctions were considered together in this data analysis.

Killip class was assigned to each patient on the basis of severity of signs of heart failure at first assessment. Killip 1 is defined as absence of rales in the lung fields and absence of an S_3 heart sound; Killip 2 is defined as rales in $\leq$ 50% of the lung fields and presence of an S_3 or jugular venous distention; Killip 3 is defined as rales in > 50% of the lung fields; and Killip 4 is defined as presence of pulmonary edema with hypotension. For the purposes of this study, Killip class of at least 2 was defined as CHF.

Complications of MI, including recurrent angina (> 48 hours after the qualifying infarct), recurrent angina with ECG changes (>1mm ST segment shift, relative to the painfree ECG that resolves within 30 minutes of the pain termination), recurrent MI (post index MI) and cardiac arrest were documented. Additionally, electrical complications including Mobitz

II second degree atrioventricular (AV) block, third degree AV block, Left bundle branch block, Right bundle branch block, left anterior or posterior hemiblock, ventricular tachycardia (VT) and ventricular fibrillation (VF) were documented. Interventions used to treat acute myocardial infarction were assessed. These included electrical interventions (chemical and electrical cardioversion, defibrillation and pacemakers), coronary angiograms, revascularization (CABG and PTCA), other surgical interventions (valve replacements) and pharmacological interventions (thrombolysis, IV heparin, IV nitroglycerine, IV beta-blockers). All other pharmacological treatments administered during hospitalization were tabulated. There were no predefined criteria for receiving CA, CABG or PTCA.

Patients who survived for five days were asked to participate in more in-depth evaluation, including SAECG, twenty-four-hour Holter monitoring and left ventricular ejection fraction before hospital discharge. Additionally they were invited to participate in a thirty-six-months follow-up program.

During 36 months of follow-up, patients visited the clinic or were contacted by telephone at six, twelve, 24, and 36 months following the index MI. During clinic visits, patients again underwent SAECG. Using the Goldman scale (Goldman, Cook, Mitchell, Flately, Sherman and Cohn, 1982), a specific activity scale, data was collected regarding current functional class. The Goldman scale uses external objective standards based on patient interview as a reference by which to measure current disability. With the Goldman scale, higher scores indicate greater functional impairment. Goldman functional status class of at least two indicates some activity limitation. Patients were also interviewed to determine the cause of activity limitation. Details of the Goldman scale are outlined in Appendix 1.

Information was also collected regarding complications (angina, unstable angina, MI, loss of consciousness, VT and VF) and procedures (CA, PTCA, CABG, aortic valve replacement, mitral valve replacement, permanent pacemaker, cardioversion, defibrillation and electrophysiologic studies (EPS), current medications, exercise routine, smoking status and vital status. Details concerning death were ascertained and classified by an independent mortality committee according to a predefined classification. Death was first classified as cardiovascular or non-cardiovascular. Cardiovascular death was then sub-classified as 1) recurrent MI, 2) low output, 3) arrhythmic, 4) procedural, and 5) other cardiovascular (cerebrovascular accident (CVA), aneurysm, pulmonary emboli, cardiac rupture, peripheral, or renovascular disease).

By December 1995 all patients had at least 36 months of follow-up.

3.1.5 Statistical Analysis

The study population was stratified by gender. Differences between males and females were evaluated for statistical significance by use of the Chi-square statistic for categorical variables and by Student's t-test for continuous variables. In multivariate analysis, logisitic regression models were developed to estimate association between sex and post-MI treatments, after adjusting for possible confounding variables. In these models, the treatments were the dependent variables and sex was among the independent variables. In addition to sex, the models included the following possible confounding variables: age, diabetes, hypertension, previous MI, previous angina, and previous CHF. Cox regression analysis was used to identify independent predictors of hospital readmission and death following the initial MI. Gender, age, diabetes, hypertension, CHF, previous MI, previous

angina, recurrent MI in hospital, recurrent angina in hospital, CHF in hospital, revascularization following MI and treatment with ASA, ACE inhibitors, beta-blockers and calcium channel blockers were entered into the model. Cumulative survival curves for time to death and time to hospitalization following MI were constructed using the Kaplan-Meier method. A *p* value of less than 0.05 was considered to indicate statistical significance for all comparisons in the study. The SPSSX program was used for all statistical analysis.

3.1.6 Results

3.1.6.1 Demographics

The study population was comprised of 214 (30.7 %) females and 484 (69.3 %) males. Approximately equal percentages of men and women (25.2 % versus 24.3 % respectfully) were transferred from another facility. Women were significantly older (65 $\pm$ 11 years; p = 0.005) than men (60 $\pm$ 12 years) on presentation. As documented in Table 1, comparison of patient characteristics showed that, although fewer women smoked, they were more commonly hypertensive or diabetic. Incidence of previous angina, previous MI or CHF was not significantly different between women and men.

Table 1. *Gender and Risk Factors for MI*

Risk Factor	Male N (%)	Female N (%)	P value
Family History IHD	234 (48.8)	112 (54.1)	NS
Hypertension	117 (36.6)	119 (55.6)	< 0.001
Diabetes	112 (23.1)	72 (34)	0.003
Previous Angina	210 (43.8)	104 (48.6)	NS
Previous MI	139 (28.8)	63 (29.4)	NS
CHF	50 (10.4)	33 (15.6)	NS
Smokers	420 (87.5)	106 (51.2)	< 0.001

Significantly more men than and women had previous angiographic evidence of coronary artery disease, defined as at least 70 % occlusion of at least one coronary vessel. Likewise, significantly more men than women had previous surgical coronary revascularization (see Table 2).

Table 2. *Gender and Invasive Interventions Prior to MI*

Procedure	Male N (%)	Female N (%)	P value
CAD on CA	117 (24.5)	17 (36)	0.03
CABG	51 (10.6)	4.2 (9)	0.006
PTCA	17 (3.5)	6 (2.8)	NS

From Table 3, it is evident that significantly more men had a Q-wave myocardial infarction. Within the Q-wave infarct group, it was found that a statistically significant number of men had suffered an anterior wall MI. There was no gender difference in occurrence of inferior, lateral, or posterior wall infarcts. However, after controlling for

infarct type, it was found that women with Q-wave infarcts were significantly more likely than men with Q-wave infarcts to develop recurrent angina and recurrent MI's. Regardless of infarct type, women were more likely to develop moderate to severe CHF, defined as Killip Class 3 or higher. As expected, clinical and laboratory characteristics of index myocardial infarction were similar in both groups.

Table 3. *Gender and Description of Current AMI*

MI Characteristic	Male N (%)	Female N (%)	P value
Q-wave MI	262 (54.1)	97 (45.3)	0.03
Anterior MI	107 (22.1)	31 (14.5)	0.02
Non-Q-wave MI	222 (45.9)	117 (54.7)	0.03
Enzyme rise	480 (99.2)	212 (99.1)	NS
Chest pain	469 (96.9)	207 (96.7)	NS

During AMI admission, significantly more women had recurrent angina and recurrent MI. There was no gender difference in the incidence of CHF when defined as Killip Class of $\geq$ 2. However, women were significantly more likely to suffer from more severe CHF, defined as Killip Class $\geq$ 3. Female mortality was also significantly higher than male mortality during the post MI admission (see Table 4).

Table 4. *Gender and Post-MI Complications in Hospital*

Complication	Male N (%)	Female N (%)	P value
Recurrent Angina	137 (28.9)	78 (37.5)	0.03
Recurrent Angina with ECG changes	42 (8.8)	28 (13.3)	NS
Recurrent MI	19 (3.9)	20 (9.4)	0.04
Killip Class ≥ 2	215 (44.4)	104 (48.6)	NS
Killip Class ≥ 3	60 (12.4)	46 (21.6)	0.002
Death	36 (7.4)	27 (12.6)	0.03

3.6.1.2 Treatment for Current Myocardial Infarction

3.6.1.2.1 Noninvasive Treatment

As shown in Table 5, comparable use of pharmacologic interventions was seen in men and women during post-MI hospitalization. However, beta-blockers and ACE-inhibitors were underutilized in both groups. Despite evidence of CHF (Killip Class ≥ 2) in 44.4 % of males and 48.6 % of females, less than 25 % in each group received ACE-inhibitors following MI. Beta-blockers were administered to only 29 % of males and 27 % of females. Further analysis showed that there was no significant difference in the beta-blocker prescription rate between diabetics and non-diabetics or patients with and without historic CHF. Chi-square analysis of beta-blocker prescription rates in patients suffering post-MI CHF, defined as Killip Class 2 or higher, however revealed that only 28 % of those receiving beta-blockers had Killip Class ≥ 2 ($p < 0.01$). A significant gender difference was seen in heparin administration. Men were significantly more likely than women to receive IV heparin following MI.

Table 5. *Gender and Noninvasive Post MI Treatment*

Treatment	Male N (%)	Female N (%)	P value
Thrombolytics	173 (35.9)	60 (28.3)	NS
IV Heparin	322 (67.2)	122 (57.8)	0.02
IV Nitroglycerine	339 (70.5)	141 (66.8)	NS
ASA	284 (79.8)	104 (75.4)	NS
Beta-blockers	104 (29.2)	37 (26.8)	NS
ACE inhibitors	78 (21.9)	33 (23.9)	NS
Calcium channel blockers	127 (35.7)	62 (44.9)	NS

Tables 6 to 10 include results of logistic regression analysis on relationship of demographic and clinical characteristics to prescription of standard post-MI medical treatments. Each model included the baseline variables sex, age $\geq$ 65 years, diabetes, hypertension, previous MI, previous angina and CHF. Multiple logisitic regression (MLR) analysis revealed that age $\geq$ 65 years (OR 0.3; 95% CI 0.2 to 0.5; $p < 0.001$) and diabetes (OR 0.5; 95% CI 0.3 to 0.8; $p = 0.003$) were negative predictors of receiving IV thrombolytics; age $\geq$ 65 years (OR 0.6; 95% CI 0.4 to 0.8; $p < 0.001$) was the only predictor of receiving IV nitroglycerine; age $\geq$ 65 years (OR 0.5; 95% CI 0.3 to 0.7; $p < 0.001$) and a history of CHF (OR 0.3; 95% CI 0.2 to 0.6; $p < 0.001$) were negative predictors of receiving IV heparin; a history of hypertension (OR 2.3; 95% CI 1.5 to 3.7; $p < 0.001$) or CHF (OR 3.6; 95% CI 1.7 to 7.4; $p < 0.001$) were associated with receiving ACE-inhibitors, while a history of previous angina (OR 1.8; 95% CI 1.0 to 3.1; $p = 0.03$) was a positive predictor and CHF (OR 0.4; 95% CI to 0.2 to 0.9; $p = 0.03$) was a negative predictor for being prescribed ASA. None of the demographic or clinical

variables included in the regression models were found to be associated with prescription of beta-blockers or calcium channel blockers (results not shown). Gender did not prove to be an independent predictor for receiving any pharmacologic intervention following myocardial infarction. However, younger age (≤ 65 years) was associated with receiving more aggressive acute medical interventions (thrombolytics, IV nitroglycerine and IV heparin).

Table 6. *Logisitic Regression Analysis of demographic and clinical characteristics predicting administration of IV Thrombolytics post-MI.*

Variable	Odds Ratio	95% CI	P value
Sex (male)	0.9	0.6 - 1.4	NS
Age ≥ 65	0.3	0.2 - 0.5	< 0.001
DM	0.5	0.3 - 0.8	0.003

* DM indicates Diabetes Mellitus.

Table 7. *Logisitic Regression Analysis of demographic and clinical characteristics predicting administration of IV Nitroglycerine post-MI.*

Variable	Odds Ratio	95% CI	P value
Sex (male)	1.1	0.7 - 1.6	NS
Age ≥ 65	0.6	0.4 – 0.8	< 0.001

Table 8. *Logisitic Regression Analysis of demographic and clinical characteristics predicting administration of IV Heparin post-MI.*

Variable	Odds Ratio	95% CI	P value
Sex (male)	1.3	0.9 - 1.9	NS
Age ≥65	0.5	0.3 – 0.7	< 0.001
CHF	0.3	0.2 – 0.6	< 0.001

* CHF indicates Congestive Heart Failure

Table 9. *Logisitic Regression Analysis of demographic and clinical characteristics predicting administration of Angiotensin Converting Enzyme (ACE) Inhibitors post-MI.*

Variable	Odds Ratio	95% CI	P value
Sex (male)	1.1	0.6 - 1.8	NS
Hypertension	2.3	1.5 - 3.7	< 0.001
CHF	3.6	1.7 - 7.4	< 0.001

* CHF indicates Congestive Heart Failure.

Table 10. *Logisitic Regression Analysis of demographic and clinical characteristics predicting administration of ASA (Acetylsalacylic acid) post-MI.*

Variable	Odds Ratio	95% CI	P value
Sex (male)	1.2	0.7 - 1.9	NS
CHF	0.4	0.2 - 0.9	0.03
Angina History	1.8	1.0 - 3.1	0.03

* CHF indicates Congestive Heart Failure.

3.1.6.2.2 Invasive Treatment

Significantly more men underwent coronary angiography during post-MI hospital admission. When CABG and PTCA were considered separately, there appeared to be no gender difference in invasive intervention for myocardial revascularization. However, when they were combined, it was found that a significantly greater number of males were revascularized during the post-MI period (see Table 11). Seven males and two females underwent both CABG and PTCA following MI. Since these were considered as one revascularization, this explains the difference in numbers of CABG and PTCA when analyzed separately versus combined.

Table 11. ***Gender and Invasive Post MI Treatment***

Intervention	Male N (%)	Female N (%)	P value
CA	201 (41.9)	66 (31)	0.007
CABG	57 (11.8)	17 (7.9)	NS
PTCA	43 (8.9)	11 (5.2)	NS
Revascularization	93 (19.3)	26 (12.2)	0.02

In a model including only baseline characteristics (sex, age > 65 years, CHF, diabetes, hypertension, previous MI and previous angina) multiple logistic regression analysis revealed that age $\geq$ 65 years, CHF and previous MI were negative predictors, whereas a history of angina was a positive predictor of receiving CA following MI. Male sex (OR 1.4; 95% CI 1.0 to 2.1; p = 0.049) was of borderline significance in predicting CA (Table 12).

Table 12 demonstrates that adding post-MI complications of CHF (Killip Class 2 or

greater), recurrent MI and recurrent angina to the regression model increased the significance of male sex as a predictor of CA (OR 1.8; 95% CI 1.2 to 2.7; p = 0.00). Men were 80 % more likely than women to have CA in the immediate post-MI period. Age ≥ 65 years (OR 0.3; 95% CI 0.2 to 0.5; p < 0.001), CHF (OR 0.3; 95% CI 0.2 to 0.7; p = 0.00) and previous MI (OR 0.6; 95% CI 0.4 to 0.9; p = 0.02) continued to be independent negative predictors for CA while a history of angina (OR 2.1; 95% CI 1.4 to 3.2; p < 0.001) and recurrent angina following MI (OR 5.5; 95% CI 3.7 to 8.4; p < 0.001) were strong positive predictors for CA. Recurrent MI and CHF following MI were not predictive of CA in the post-MI period.

Table 12. *Two Separate MLR Models to Predict CA following MI*

Baseline characteristics predictive of CA

Variable	Odds Ratio	95% CI	P value
Sex (male)	1.4	1.0 - 2.1	0.05
Age ≥ 65	0.3	0.2 – 0.5	< 0.001
CHF	0.3	0.2 - 0.7	0.00
Angina History	2.1	1.4 - 3.2	<0.001
Previous MI	0.6	0.4 – 1.0	0.03

Table 12 (cont). ***Two Separate MLR Models to Predict CA following MI***

Baseline characteristics and Post-MI complications predictive of CA

Variable	Odds Ratio	95% CI	P value
Sex (male)	1.8	1.2 - 2.7	0.005
Age ≥ 65	0.3	0.2 – 0.5	< 0.001
CHF	0.3	0.3 – 0.7	0.01
Angina History	2.1	1.4 – 3.2	< 0.001
Previous MI	0.6	0.4 – 0.9	0.02
Recurrent Angina	5.5	3.4 – 8.4	< 0.001

* CHF indicates Congestive Heart Failure; MI indicates Myocardial Infarction.

In a model including only baseline characteristics (age ≥ 65 years, sex, diabetes, hypertension, CHF, previous MI and previous angina), logistic regression analysis revealed that male sex (OR 1.8; 95% CI 1.0 to 3.0; p = 0.02) and previous angina were strong positive predictors, whereas CHF was a strong negative predictor for revascularization (see Table 13). Men were 80 % more likely than women to be revascularized during the immediate post-MI period. Addition of post-MI complications of recurrent angina, recurrent MI and CHF to the MLR model increased the predictive value of male sex (OR 2.3; 95% CI 1.3 to 3.9; p= 0.03). Angina history continued to be an independent predictor and recurrent angina emerged as a strong positive predictor for revascularization. Historic CHF continued to be a negative predictor for revascularization during the post-MI period. Recurrent MI and CHF following MI were not predictive of revascularization in the post-MI period.

Table 13. *Two separate MLR Models to predict revascularization following MI*

Baseline characteristics predictive of revascularization

Variable	Odds Ratio	95% CI	P value
Sex (Male)	1.8	1.1 - 3.0	0.02
CHF	0.4	0.2- 0.9	0.02
Angina History	3.1	1.9 – 4.9	< 0.001

Baseline Characteristics and Post-MI complications predictive of revascularization

Variable	Odds Ratio	95% CI	P value
Sex (Male)	2.2	1.3 – 3.8	0.00
CHF	0.2	0.1- 0.7	0.01
Angina History	3.0	1.7 – 5.0	< 0.001
Recurrent Angina	7.0	4.3 – 11.0	< 0.001

* CHF indicates Congestive Heart Failure; MI indicates Myocardial Infarction.

3.1.6.3 Clinical Picture During Follow-up

Table 14 demonstrates that, evidenced by Goldman scores of at least two, women consistently had significantly poorer functional capacity than men throughout thirty-six months of follow-up. Except for the category other, it was not possible to isolate one consistent causal factor in activity limitation. Other was a non-specific category and included patient fear, family fear, and physical impediments such as arthritis and previous hip injuries. The percentage of men reporting angina as the cause of limitation, remained relatively stable (21% at 6 months versus 27 % at 36 months). The percentage of women attributing limitation to angina gradually increased (22 % at 6 months versus 37 % at 36 months) throughout the study, becoming statistically significant at 36 months post-MI (see Table 15). MLR analysis revealed that age $\leq$ 65 (OR 0.4; 95% CI 0.3 to 0.7; p = 0.001)

was negatively associated and female sex (OR 2.9; 95% CI 1.6 to 5.0; $p < 0.001$) was positively associated with poorer Goldman scores (results not shown).

Only 124 patients (male = 88, female = 36) were followed for four years. Women in this group continued to have significantly reduced functional capacity but equal proportions of men (23.5 %) and women (25 %) attributed the activity limitation to angina.

Table 14. *Gender and Functional Capacity During 36 Months of Follow-up*

Goldman Score ≥ 2	Male N (%)	Female N (%)	P value
6 months	134 (40.7)	95 (74.2)	< 0.001
12 months	117 (36.9)	89 (71.7)	< 0.001
24 months	121 (39.5)	83 (68.5)	< 0.001
36 months	112 (38.8)	82 (73.2)	< 0.001

Table 15. *Gender and Cause of Activity Limitation During 36 Months of Follow-up*

Six months post-MI

Cause	Male N (%)	Female N (%)	P value
Angina	73 (21.4)	29 (21.8)	NS
Dyspnea	69 (21.2)	38 (29.5)	NS
Fatigue	32 (16)	29 (22.5)	NS
Doctors advice	31 (15.7)	26 (20.3)	NS
Other	87 (26.6)	58 (45.3)	< 0.001

Table 15 (cont). *Gender and Cause of Activity Limitation During 36 Months of Follow-up*

Twelve months post-MI

Cause	Male N (%)	Female N (%)	P value
Angina	72 (22.1)	37 (29.8)	NS
Dyspnea	70 (22)	47 (38.2)	< 0.001
Fatigue	57 (17.9)	40 (33.3)	< 0.001
Doctors advice	33 (10.5)	30 (25.2)	< 0.001
Other	76 (24.1)	50 (41.3)	< 0.001

Twenty-four months post-MI

Cause	Male N (%)	Female N (%)	P value
Angina	69 (22)	35 (28.7)	NS
Dyspnea	93 (30.5)	43 (35.3)	NS
Fatigue	51 (16.7)	38 (31.4)	0.001
Doctors advice	11 (3.6)	9 (7.5)	NS
Other	67 (22)	45 (37.2)	0.001

Thirty-six months post-MI

Cause	Male N (%)	Female N (%)	P value
Angina	78 (26.8)	42 (36.5)	0.04
Dyspnea	76 (26.4)	45 (39.8)	0.007
Fatigue	34 (11.8)	31 (27.4)	< 0.001
Doctors advice	12 (4.2)	17 (15)	< 0.001
Other	81 (28.2)	49 (43.4)	0.004

3.1.6.4 Treatment During Follow-up

Except at thirty-six months follow-up, when men were significantly more likely to be prescribed ASA, the rate of ASA prescription remained constant and no gender difference in ASA use was seen. There appeared to be a relationship between symptoms and prescriptions throughout most of the follow-up period. Reflecting the clinical picture in terms of angina, and dyspnea six months following MI, there was no difference in medical therapy with respect to gender. At twelve months, women reported significantly more dyspnea and fatigue, and significantly more ACE-inhibitors were prescribed to women. At twenty-four months, activity limitation was not related to dyspnea or angina and there was no difference in prescriptions between men and women. Thirty-six months following MI was the exception. Women again suffered significantly more activity limitation due to angina, dyspnea, and fatigue and this was reflected only in the prescription of significantly more calcium channel blockers to women (see Table 15 and 16).

Table 16. *Gender and Pharmacotherapy During 36 Months of Follow-up*

ASA

Timeline	Male N (%)	Female N (%)	P value
6 months post-MI	251 (78.7)	96 (75.6)	NS
12 months post-MI	254 (79.9)	96 (78)	NS
24 months post-MI	246 (81.7)	93 (79.5)	NS
36 months post-MI	236 (85.8)	85 (77.3)	0.04

Table 16 (cont). *Gender and Pharmacotherapy During 36 Months of Follow-up*

Beta-blockers

Timeline	Male N (%)	Female N (%)	P value
6 months post-MI	133 (41.7)	51 (40.2)	NS
12 months post-MI	122 (38.4)	56 (45.5)	NS
24 months post-MI	120 (39.9)	48 (41)	NS
36 months post-MI	117 (42.5)	41 (37.3)	NS

ACE inhibitors

Timeline	Male N (%)	Female N (%)	P value
6 months post-MI	89 (27.9)	44 (34.6)	NS
12 months post-MI	87 (27.4)	48 (39)	0.017
24 months post-MI	95 (31.6)	37 (31.6)	NS
36 months post-MI	94 (34.2)	42 (38.2)	NS

Calcium Channel Blockers

Timeline	Male N (%)	Female N (%)	P value
6 months post-MI	115 (36.1)	57 (44.9)	NS
12 months post-MI	106 (33.3)	51 (41.5)	NS
24 months post-MI	102 (33.9)	45 (38.5)	NS
36 months post-MI	86 (31.3)	50 (45.5)	0.01

3.1.6.5 Invasive Intervention during follow-up

With respect to gender, there was no difference in the rate of CA or coronary revascularization, when CABG and PTCA were separate, or combined, throughout the entire follow-up period (see Table 17). However, the number of patients

revascularized may have been too small to detect a statistically significant difference.

Table 17. *Gender and Invasive Intervention During 36 Months of Follow-up*

6 months post MI

Procedure	Male N (%)	Female N (%)	P value
CA	46 (13.3)	19 (14.3)	NS
CABG	25 (7.2)	4 (3.0)	NS
PTCA	16 (4.6)	4 (13)	NS
Revascularized	38 (11)	8 (6.1)	NS

12 months post MI

Procedure	Male N (%)	Female N (%)	P value
CA	15 (4.6)	5 (4)	NS
CABG	5 (1.5)	3 (2.4)	NS
PTCA	3 (0.9)	2 (1.6)	NS
Revascularized	8 (2.5)	5 (4)	NS

24 months post MI

Procedure	Male N (%)	Female N (%)	P value
CA	13 (4.1)	2 (4.2)	NS
CABG	5 (1.6)	1 (0.8)	NS
PTCA	3 (0.9)	3 (2.4)	NS
Revascularized	6 (1.9)	3 (2.4)	NS

Table 17 (cont). *Gender and Invasive Intervention During 36 Months of Follow-up*

36 months post MI

Procedure	Male N (%)	Female N (%)	P value
CA	6 (2.0)	2 (1.7)	NS
CABG	1 (0.3)	0	NS
PTCA	3 (1.0)	0	NS
Revascularized	4 (1.4)	0	NS

3.1.6.6 Mortality

Table 18 demonstrates that the rate of in-hospital mortality was significantly higher in females than in males. Multiple logistic regression analysis of baseline clinical characteristics showed that age $\geq$ 65 years was the only independent predictor of in-hospital mortality (OR 2.6, 95% CI 1.4 to 4.9, p = 0.002) following AMI. A trend for increased mortality in females persisted throughout follow-up but did not reach statistical significance until 36 months when 24 % of males and 32.4 % of females had died.

When time to death was examined as an endpoint, Kaplan-Meier analysis showed that women had reduced likelihood of survival (Log rank statistic 8.31; p = 0.004) compared to men (See Figure 2). Multivariate Cox regression showed that a history of previous MI was a positive predictor for death (OR 1.9; 95%CI 1.1 to 3.4; p = 0.03). Those having previous MI were nearly twice as likely as those without MI history to die. Within the model, treatment with ACE inhibitors (OR 2.0; 95%CI 1.2 to 3.6; p = 0.01) was a positive predictor of survival. Other variables entered into the analysis included sex, age, hypertension, diabetes, CHF, previous angina, recurrent MI, recurrent angina, post-MI CHF and treatment with ASA, beta-blockers and calcium channel blockers, none of which

were predictors for survival.

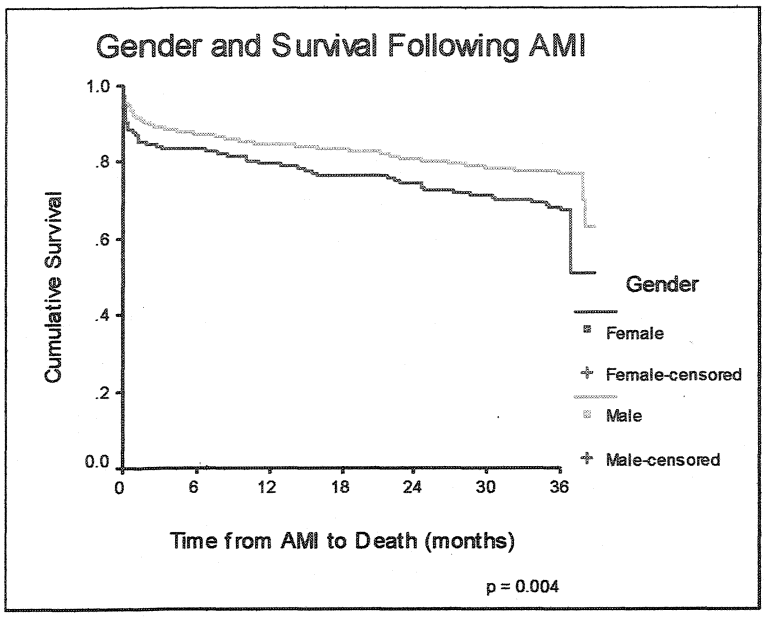

Figure 1. *Cumulative probability of survival for women and men following AMI*

Table 18. *Comparison of Cumulative Mortality Rates by Gender*

Time post-MI	Male N (%)	Female N (%)	P value
In hospital	36 (7.4)	27 (12.6)	0.03
6 months	60 (12.4)	35 (16.4)	NS
12 months	73 (15.2)	43 (20.1)	NS
24 months	92 (19.2)	55 (25.7)	NS
36 months	114 (24)	69 (32.4)	0.02
48 months	125 (25.8)	73 (34.1)	0.03

As seen in Table 18, within four years following MI, 125 men and 73 women were dead. A greater percentage of female deaths were cardiac in origin (69.8 % versus 61.6 %) but

this was not statistically significant. When cardiac death was subdivided, it was evident that a significant majority of female deaths were secondary to acute MI. Aside from MI no gender difference was seen in cause of death (see Table 19).

Table 19. *Cause of Cardiac Death by Gender*

Cause of Death	Male N (%)	Female N (%)	P value
Acute MI	16 (17)	17 (32.1)	0.04
CHF	33 (35.1)	19 (35.8)	NS
Arrhythmia	16 (17)	8 (15.1)	NS
Procedural	6 (6.4)	2 (3.8)	NS
Other Cardiac	6 (6.4)	5 (9.4)	NS

3.2 Gender and Appropriateness of Coronary Artery Bypass Grafting in Newfoundland and Labrador (NLCABG Study)

3.2.1 Context

Between and within country differences in CABG rates render it difficult to determine the optimal rate at which to apply this treatment to patients with CVD. Limitation in government funding may interfere with ability to deliver optimal rate of CABG. Perhaps women fare worse than men in distribution of limited health care resources.

3.2.2 Objective

To determine if gender is associated with inappropriate use of surgical revascularization in NL.

3.2.3 Hypothesis

Male gender is associated with inappropriately high use of CABG in NL.

3.2.4 Methods

These data were originally collected in the context of the Coronary Artery Bypass Grafting in Newfoundland (CABG) study and subsequently stratified by sex and reanalyzed for the purpose of this study. The CABG study was undertaken at the request of the Health Care Corporation of St. John's to assist in decisions regarding the allocation of resources for the CABG program in NL.

To determine annual need for CABG, all patients who had cardiac catheterization in St. John's in one year (April 1994 -April 1995) were identified. Those with significant disease on CA were divided into those referred for PTCA, considered inappropriate for revascularization, and those in whom CABG was feasible. Those without CAD and those with non-critical stenosis (<50 % LAD stenosis, < 70 % stenosis of other vessels) along

with those referred for angioplasty (other than failed angioplasties) were excluded. This study included those who were referred for CABG after coronary angiography and those who were on the waiting list for CABG and underwent the procedure during the study period.

Chart reviews using cardiac catheterization report, hospital chart, cardiologists' chart, and minutes from weekly cardiac surgery conferences were undertaken. Data abstracted included CAD risk factors, angina symptoms, indication for CABG, coronary anatomy, ejection fraction, medical therapy, operative risk and contraindications to surgery, and postoperative complications. Refer to Appendix 2 for definitions of terms used to describe patients.

Using the guidelines of a Canadian panel (McGlynn, Naylor, Anderson et al, 1994; Naylor, McGlynn, Leape et al, 1993), each patient was assigned appropriateness and necessity scores from 1-9. Appropriateness was defined to mean that expected benefit exceeded expected negative consequences by a margin that made treating physicians believe that surgery was worthwhile. Necessity was defined to mean that the physician felt obligated to offer the surgical option to the patient as the best clinical option available given that there was a high probability of benefit in patients with similar presentation. Appropriateness ratings tend to err on the side of intervention, whereas necessity ratings provide a more stringent risk-benefit ratio.

Appropriateness score is based on a scale of one to nine, with one being extremely inappropriate and nine being extremely appropriate. Generally a score of one to three is considered inappropriate, four to six intermediate, and seven to nine appropriate.

Necessity score is based on a scale of one to nine, with one being extremely unnecessary and nine being extremely necessary. Generally a score of one to three is considered unnecessary, four to six intermediate, and seven to nine necessary.

3.2.5 Statistical Analysis

The study population was stratified by gender. Differences between males and females were evaluated for statistical significance by the Chi-square statistics for discrete variables and by t-test for continuous variables. A p value of less than 0.05 was considered to indicate statistical significance for all comparisons in this study. The SPSSX statistical package was used for all statistical analysis.

3.2.6 Results

3.2.6.1 Demographics

For 338 of 342 patients there was information on clinical presentation, medical treatment, coronary anatomy, cardiac function, ischemic risk and operative risk. Males comprised 72 % of the group. Females were significantly older than males with average ages being 65 ($\pm$ 9) and 59 ($\pm$ 10) years respectively.

As shown in Table 20, women suffered significantly more severe angina symptoms prior to coronary angiogram. Eighty-nine percent of women and 79 % of men had Class IV angina. However there was no gender difference in application of maximal medical therapy. There was no gender difference in thrombolytic use, frequency of MI, or results of exercise stress tests prior to coronary angiogram.

Table 20. *Gender, Demographic and Clinical Characteristics and Treatment Prior to CA*

Factor	Male N (%)	Female N (%)	P value
Previous MI	148 (61)	48 (50)	NS
Class IV Angina	191 (78.9)	85 (88.5)	0.01
Thrombolytic	17 (7)	14 (6)	NS
Maximal Medical Therapy	203 (83.8)	86 (89.5)	NS
Strongly positive stress test	122 (85.9)	39 (82.9)	NS

The majority of patients, regardless of sex were referred for CABG due to unstable angina with 79% of women and 73% of men having this documented as the indication for CABG (See Table 21).

Table 21. *Gender and Indication for CABG*

Indication	Male N (%)	Female N (%)	P value
Chronic Stable Angina	25 (10.3)	9 (9.4)	NS
Unstable Angina	176 (72.7)	76 (79.2)	NS
Post MI	26 (10.7)	7 (7.3)	NS

As shown in Table 22, there was no gender difference in severity of CAD on coronary angiogram. Eighty-eight percent of men and 91 % of women had significant CAD defined as double vessel disease involving the proximal left anterior descending artery (LAD), triple vessel disease or left main disease. Groups were also similar in terms of left

ventricular function measured on coronary angiogram (see Table 23).

Table 22. *Gender and Angiographic Findings*

Finding	Male N (%)	Female N (%)	P value
Left Main Disease	49 (20.2)	14 (14.5)	NS
3 Vessel Disease	130 (53.7)	59 (61.4)	NS
2 Vessel Disease with LAD	35 (14.5)	14 (14.6)	NS
2 Vessel Disease without LAD	20 (8.3)	4 (4.2)	NS
1 Vessel Disease	6 (3.3)	5 (5.2)	NS
EF < 35 %	61 (25.4)	23 (23.9)	NS

Table 23 shows that a significantly higher number of women were considered to be at greater operative risk than men. Fifty percent of females and 30 % of males were at moderately high to very high operative risk.

Table 23. *Gender and Operative Risk*

Risk Group	Male N (%)	Female N (%)	P value
Normal/low	169 (69.8)	48 (50)	< 0.001
Moderately high	55 (22.7)	30 (31.2)	< 0.001
Very high	18 (7.4)	18 (18.7)	< 0.001

There were no cases in which surgery was considered inappropriate. There was no gender difference in appropriateness score or necessity score. More than 96 % of surgeries in

females and 99 % of surgeries in males were considered highly appropriate with appropriateness score of at least seven. More than 92 % of surgeries in females and more than 94 % of surgeries in males were considered highly necessary with necessity scores of at least seven. The remaining surgeries were considered to be of intermediate risk and necessity (see Table 24).

Table 24. *Gender and Appropriateness/Necessity of CABG*

Score	Males N (%)	Females N (%)	P value
Appropriateness ≥ 7	241 (99.5)	93 (96.8)	NS
Necessity ≥ 7	228 (94.2)	89 (92.7)	NS

4 Discussion and Conclusions

4.1 NLMI study

The NLMI study population was demographically similar to other studied populations in many ways. Women were older and had more diabetes and hypertension (see Table 1) prior to study entry. Similarly, men were significantly more likely to be smokers and to have angiographic evidence of CAD prior to MI (Greenland, Reicher-Reiss, Goldbourt, Behar et al, 1991; Steingart et al, 1991; Rathore et al, 2002; Mueller et al, 2002). Men were significantly more likely than women to have had CABG prior to the current MI (Mueller et al, 2002; Azar et al, 2002). Men were more significantly more likely than women to have Q-wave infarcts involving the anterior cardiac wall. Women also suffered more recurrent angina, recurrent MI, and a higher incidence of moderate to severe CHF and were more likely than men to die during the immediate post-MI period (Maynard et al, 1992, Becker et al, 1994; Jenkins et al, 1994; Greenland et al, 1991).

Comparing men and women in NL reveals some important gender differences in clinical characteristics and management. Despite increased likelihood to suffer ischemic complications and death in hospital, women in the MI study received medical intervention that was similar to that of men and invasive assessment and intervention that was less aggressive than that provided to men (see Table 5 and Table 11). While older age was associated with less aggressive intervention, gender was not an independent predictor of noninvasive treatment once age was taken into account. The opposite was true when CA and coronary revascularization were considered. Younger age and male sex were strong independent predictors of invasive assessment and intervention. Long-term mortality was higher and functional limitation was greater in women than men.

Several studies have reported improved survival in association with frequent use of pharmacologic and invasive interventions in MI patients (Pfeffer et al, 1992; The SOLVD investigators, 1992; Clarke et al, 1994; Tsuyuki et al, 1994; Rouleau et al, 1996). Underutilization of proven efficacious post-MI therapies has likewise been the finding of several studies (Rouleau et al, 1993; Clarke et al, 1994; Wilkinson et al, 1994; Tsyuki et al, 1994). Many studies have reported gender differences in the use of standard post-MI medical therapies (Clarke et al, 1994; Sial et al, 1994; Tsuyuki et al, 1994; Wilkinson et al, 1994, Chu et al, 1998). Consistent with the findings of these studies, NLMI women were significantly less likely than men to receive heparin (Chandra et al, 1998) following MI. Like the NLMI study, these studies were conducted in the early 1990's and included consecutive patients with definite diagnosis of acute MI. This should reduce the impact of temporal trends and selection bias in the application of standard therapies between these studies and the NLMI study.

It is evident that, with the exception of post-MI beta-blockers, NL patients are treated similarly to other Canadian patients. For example, FASTRACT II (Heart and Stroke Foundation of Canada, 1999) showed that in 1998, in Canada, 46.3 % of patients were prescribed ACE-inhibitors, 72.9 % were prescribed beta-blockers and 82.7 % were prescribed ASA following AMI (Heart and Stroke Foundation of Canada, 1999). The CAMI study, like the NLMI study, reflects prescribing patterns in the early 1990's, thereby accounting for temporal trends and changes in post MI treatment. It shows that, following AMI, 24 % of Canadian patients were prescribed ACE-inhibitor, 61 % were prescribed beta-blockers and 86 % were prescribed ASA (Rouleau et al, 1996). In comparison, following AMI, 22.5 % of NL patients were prescribed ACE-inhibitors, 28.5 % were prescribed beta-blockers and 78.5 % were prescribed ASA (see Table 5 and Table

25).

Table 25. *Comparison of Post-MI treatment in Canada versus N L*

Source	Fastrack II	CAMI	NLMI
Year	1998	1990 to 1993	1990-1993
Population	Canadian	Canadian	Newfoundland & Labrador
% ACE	46.3	24	22.5
% BB	72.9	61	28.5
% ASA	82.7	86	78.5

** CAMI = Canadian Assessment of Myocardial Infarction; NLMI = Newfoundland and Labrador MI study; ASA = Acetylsalacylic Acid; BB = beta-blocker; ACE = angiotensin converting enzyme inhibitor.*

While it appears that appropriate CHF treatment is not reflected in ACE-inhibitor utilization, this probably reflects a temporal trend in the data. Studies Of Left Ventricular Dysfunction (SOLVD) investigators reported that, from 1988 to 1989, the overall utilization rate for ACE-inhibitors in CHF treatment was only 30 % (Bourassa, Gurne, Bangdiwala et al, 1993), and Martinez et al reported only 23 % use in post-MI patients in 1994 (Martinez et al, 1998). Therefore, apparent low ACE-inhibitor utilization in the NLMI study may simply reflect practice patterns in the early 1990's. This is supported by comparable ACE inhibitor utilization in the CAMI study (Rouleau et al, 1996). SOLVD investigators did find higher utilization of ACE-inhibitors in more seriously ill patients (Bourassa et al, 1993). Twenty-four percent of women and 22 % of men in the NLMI study received ACE-inhibitors, while 22 % of women and 12 % of men in the NLMI study had more severe CHF. This is more in keeping with findings of the SOLVD investigators

in this subpopulation. Studies of ACE-inhibitor utilization in post-MI patients with left ventricular dysfunction were ongoing at the study center at the same time as the NLMI study. This may have favorably impacted ACE-inhibitor administration in patients with more severe CHF by influencing the rate at which research findings were incorporated into clinical practice.

The rate of beta-blocker use in the NLMI study is dramatically lower than that of the CAMI study (Rouleau et al, 1996). At least one other study has reported utilization of beta-blockers that was comparable to that seen in the CAMI study during the same time period (Martinez et al, 1998). In the NLMI study, historic CHF or diabetes were not related to beta-blocker utilization. However, there was a statistically significant relationship between post-MI CHF and beta-blocker administration thus providing some explanation for the low rate of beta-blocker use.

While, with the exception of heparin, no gender difference was seen in medical intervention in the NLMI study. One could argue that since women had had higher post-MI complication rates, they should probably have received IV thrombolytics, IV nitroglycerine, and IV heparin more frequently than men. However, since multiple logistic regression analysis revealed that sex was not an independent predictor for receiving any of these treatments, it appears that patient characteristics, rather than gender, provide an explanation for apparent underutilization in females with complicated post-MI courses.

Consistent with the findings of many other studies (Tobin et al, 1987; Ayanian et al, 1991; Steingart et al, 1991; Krumholz et al, 1992; Maynard et al, 1992; Bickell et al, 1992) including Canadian studies (Jaglal et al, 1994; Naylor et al, 1994) women in the NLMI

study were less likely than men to undergo invasive investigation following MI. Contrary to the recommendations of the ACC/AHA TF (Ryan et al, 1996), which suggests CA in patients with post-MI courses complicated by recurrent angina, recurrent MI and LVD, females were significantly less likely than men to have invasive investigation in the immediate post-MI period despite a significantly greater incidence of these exact complications.

After adjustment for demographic and clinical variables, male gender was reduced to borderline significance as an independent predictor for CA following MI. Controlling for clinical variables has produced similar results in other studies (Krumholz et al, 1992; Wong et al, 2001; Rathore et al, 2002). Unlike the studies of Tobin and Ayanian (Tobin et al, 1987; Ayanian et al, 1991), these studies, and the NLMI study, were all undertaken in patients with definite evidence of acute MI. All patients included in these studies were likely to have ischemic heart disease; therefore presumptions about pre-test likelihood of CAD should not have influenced the decision to refer patients for coronary angiography.

Controlling for post-MI complications increased the significance of male sex as an independent predictor of CA. Men were 80 % more likely than women to undergo CA during the post-MI period. This seems to suggest the presence of gender bias in referral of patients for CA. Previous data sets have not been analyzed in this fashion.

Twenty five percent of the patients included in our study were transferred from another facility. Because transfers are often made with further intervention in mind (Paul et al, 1995), this group may include patients with larger or more complicated MI's and may increase the rate of referral for CA. However, the CA referral rate was comparable to that

of Krumholz and colleagues who received equal number of referrals from family practitioners and specialists (Krumholz et al, 1992) and less than that of Wong and colleagues who included only patients with cardiogenic shock following MI (Wong et al, 2001).

Some studies suggest equal utilization of revascularization following coronary angiograms (Tobin et al, 1987; Bergelson et al, 1996; Bell et al, 1995; Wong et al, 2001; Ghali et al, 2002), but this was not the case in the NLMI study. These studies include a variety of patients with a variety of reasons for referral to CA. During post-MI hospitalization, NL men were significantly more likely than women to be revascularized. Even after controlling for a variety of clinical characteristics, men were more than twice as likely as women to be revascularized. In an Ontario study, Jaglal et al, also found that men were twice as likely as women to be revascularized in the post-MI period (Jaglel et al, 1994). In an Alberta study, adjustment for severity of CAD eliminated gender differences in referral to revascularization, however the study population included a cohort of patients referred to CA. This population differs from the NLMI study population who all had definite diagnosis of MI. Access to detailed clinical data, particularly on severity of vessel disease, may have eliminated this gender difference in the NLMI population (Ghali et al, 2002).

Krumholz and others found that even after controlling for age and severity of coronary artery disease on CA, there remained a borderline significant lower rate of CABG in females. Like the NLMI study, Krumholtz included post-MI patients rather than patients presenting with suspected cardiac ischemia (Krumholz et al, 1992). Unfortunately we do not have data on severity of vessel disease and are unable to determine the impact on referral to revascularization. Krumholtz however did not have information on clinical

variables other than age and CAD severity and was unable to control for these confounders.

Wong and colleagues and Steingart and colleagues have reported higher rates of revascularization in men and women; however both studies included highly selected population of patients (Wong et al, 2001; Stiengart et al, 1991). In the SHOCK study patients had post-MI cardiogenic shock (Wong et al, 2001), whereas in the SAVE study, only patients having post-MI LVD were included in the analysis (Steingart et al, 1991). Unfortunately, there is no available information regarding disease severity in the NLMI population, and appropriateness of referral to revascularization cannot be determined.

Newfoundland and Labrador's unique geography and population distribution has resulted in concentration of cardiac health care specialists and diagnostic facilities in the capital city. Like other Canadian provinces, Newfoundland and Labrador is experiencing increasing difficulty in providing necessary resources to meet demand for health care. Budgetary restraints impact patterns of practice by imposing limitations on availability of expensive procedures. The result is higher thresholds and longer wait lists for performance of these procedures (Rouleau et al, 1993; Bengston et al, 2000). However, it has been shown in at least one study that wait list time is similar for men and women (Bengston, Karlsson and Herlitz, 2000).

Because referrals for invasive coronary procedures are received in only one tertiary care hospital in NL, they are performed by priority and dependent on wait lists. Wait lists are growing and even very urgent cases are not receiving procedures within the recommended timeframes (Cohen, Ivanov, Weisel, Rao and Borger, 1996; Fox, O'Dea and Parfrey,

1998). It has been demonstrated that only 23 %, 24 % and 64 % respectively of NL patients in whom CABG was considered very urgent (within 24 hours), urgent (within 72 hours), or semi-urgent (within 14 days and during the same hospital stay), underwent the surgery within the recommended time (Fox et al, 1998). Because the NLMI study was conducted at this same tertiary hospital, and based on prolonged wait times for even very urgent cases, it would seem logical to perform fewer invasive procedures on stable patients on initial admission for AMI.

Due to limitation of health care resources in NL (Fox, O'Dea and Parfrey, 1998), those revascularized during MI admission should probably represent the most severe cases, but without information regarding vessel disease, surgical appropriateness, or necessity, this cannot be stated with certainty. Fox et al have demonstrated that, of those NL patients categorized for placement on the short wait (within 6 weeks) or delayed elective (within 6 months) wait lists, 50 % and 75 % respectively underwent CABG within the recommended time (Fox et al, 1998).

During follow-up, intensification of medical therapy appeared to be symptom-driven, as severity of angina and dyspnea were closely related to prescription of appropriate medical interventions. Throughout three years of follow-up, women continued to demonstrate poorer functional class than men. Dyspnea and fatigue were key contributors to increased Goldman scores. There is a paucity of data on functional limitation in post-MI patients so it is difficult to compare these findings to other studies.

Despite having no knowledge of Goldman scores, physicians prescribed beta-blockers and ACE inhibitors appropriately, according to the documented reason for activity limitation

on the Goldman scale. Calcium channel blockers were added to the regime at thirty-six months post-MI, when women reported that angina was a significant limitation to activity. It is unclear whether these were being used in lieu of beta-blockers for angina control in a female population, of whom 22 % were suffering from moderate to severe CHF (see Table 15 and Table 16).

A lower rate of invasive intervention has been shown to be associated with activity-limiting angina (Rouleau et al, 1993; Marl, et al, 1993). Bickell and others suggest that referral of low risk males for bypass could result in improved quality of life (Bickell et al, 1992). In keeping with these findings, Goldman scales provide evidence of significantly greater female disability from angina symptoms at thirty-six months following MI.

Two studies have reported that higher rates of invasive diagnostic and therapeutic interventions in the United States (compared to Canada), did not impact reinfarction or survival in post MI patients (Rouleau et al, 1993; Mark, Naylor, Califf, et al, 1993). Conversely, the CAMI study report indicated that revascularization was inversely related to mortality (Rouleau et al, 1996). The SAVE study included only those MI patients who had resolved ischemic events prior to the necessary randomization period. This was only a small proportion of all MI patients and may have resulted in reduced mortality in the SAVE study (Rouleau et al, 1993).

Following the index MI, there was no gender difference in rate of readmission to hospital. In the absence of mortality data this may seem to justify the more aggressive treatment of angina with revascularization in men. Assessment of mortality data however, reveals significantly poorer survival and a higher number of fatal out-of-hospital MI's in women.

With the absence of information regarding disease severity on CA or appropriateness of revascularization in this population, and are unable to determine whether these women were likely to have benefited from more aggressive intervention. However after controlling for clinical variables, revascularization was the only post-MI treatment to be related to sex.

The overall rate of in-hospital mortality was comparable that of an identical Canadian population, with the NL in-hospital death rate being 10.4 % and the Canadian in-hospital death rate being 9.9 %, as reported by Rouleau in the CAMI study. As with the CAMI study, in-hospital female mortality approximately doubled that of males and was statistically significant in both studies. The Canadian female mortality rate was 15.7 % compared to the male mortality rate of 7.7 %. The NLMI female mortality rate was 12.6 % compared to the male mortality rate of 7.4 % (Rouleau et al, 1996).

As both the NLMI study and the CAMI study are population-based including consecutive MI patients, selection biases inherent in clinical trials are reduced. It is expected that mortality in a population study would be higher than that seen in a highly selected clinical trial population (Naylor and Chen, 1994) such as the SAVE study. This probably explains comparable mortality in the NL study and the CAMI study and higher mortality than the SAVE study.

Mortality, one year following MI, was substantially higher in the NLMI population than in the overall Canadian population (16.5 % versus 7.1 %). Although cumulative mortality rates were consistently higher in females, no gender difference was seen in post-MI mortality in the NL population until three years post-MI when a significantly greater

number of deaths were seen in women (Table 18). Unfortunately, no comparable data is available for the Canadian population. While the CAMI study concludes that female gender is associated with increased in-hospital but not post-discharge death, the NLMI study suggests that, while there is no gender difference in short-term survival post-discharge, in hospital and long-term survival ($\geq$ 2 years) is significantly poorer in women than men. Patients in the CAMI study were followed for only one year and mortality results in the NLMI study at one year, similarly showed no significant difference in mortality by gender. Similar results may have been yielded in the CAMI study with longer follow-up. Female longevity dictates that longer trials are needed when comparing mortality in men and women (Merz, Johnson, Kelsey et al, 2001). Conversely, perhaps female mortality is related to lower rates of revascularization in females in the NLMI study.

4.2 NLCABG Study

The NLCABG study population is comparable to similar populations in several ways. This study demonstrates poorer clinical condition in women at time of coronary angiogram. Women were older and significantly more likely than men to have Class IV angina at time of presentation. However, there were no gender differences with regard to treatment with maximal medical therapy or thrombolytics, and women were no more likely than men to have had a previous MI or a strongly positive stress test prior to angiography. There were no gender differences in indication for surgery or in severity of vessel disease on coronary angiogram. A significantly greater number of women than men were at moderately high, to high operative risk. Appropriateness and necessity scores were high regardless of sex.

The proportion of females receiving CABG in NL was slightly higher (27 %) than that of Ontario or British Columbia (20 % versus 23 % respectively) in a study by Anderson and colleagues (Anderson et al, 1997). The results were similar for another Ontario study in which nineteen percent of those revascularized were female (Abramov et al, 2000). This may simply reflect the higher prevalence of CAD in NL females (Heart and Stroke Foundation, 1999).

Consistent with the findings of the NLCABG study, other studies have shown women to be older (Anderson et al, 1997; Aldea et al, 1999; Tan et al, 1999; Aquilar, Lazaro, Fitch et al, 2001) and to have more severe angina when presenting for revascularization (Aquilar et al, 1997, Tan et al 1999; Abramov et al, 1999). Similarly to study populations of Aquilar, Tan and Abramov the NLCABG study population was a retrospective cohort selected after CABG was performed. Since these populations have undergone CABG, it

is more likely that they are suffering from advanced CAD. These populations cannot be considered representative of all patients with CAD (Aquilar et al, 2001). Older age and severity of angina in females may indicate that women were referred for revascularization when coronary disease was more advanced. These findings are supported by several other studies suggesting later referral in women (Kee et al, 1995; Aguilar et al, 2001).

Newfoundland and Labrador patients have more severe angina than patients referred for CABG in other Canadian provinces. In the NLCABG study, there was no gender difference in indication for CABG with 79.2 % of women and 72.7 % of men being referred to CABG because of unstable angina, while 9.4 % of women and 10.3 % of men were referred to CABG for chronic stable angina. The finding of gender similarity in surgical indication has been seen in other studies of revascularized patients (Aquilar et al, 2001; Roeters van Lennep, 2000). Compared with Ontario and British Columbia data on main indication for CABG, a much higher proportion of NL patients were referred for CABG due to unstable angina. Seventy-seven percent of NL patients were referred to CABG because of unstable angina compared to 43 % for British Columbia (BC) patients and 20 % for Ontario (ON) patients (Anderson et al, 1997). The definition of unstable angina was the same in the NL study and the ON/BC study. Differences in indication for revasculaization between the Ontario and British Columbia population and the NLCABG population suggest provincial differences in the management and referral of patients.

Eighty-eight percent of men and 91 % of women in the NLCABG study had multivessel disease involving the left main coronary artery or the proximal left anterior descending artery. Gender similarity in the extent of vessel disease has been duplicated in other

studies of revascularized patients (Aquilar et al, 2001; Roeters van Lennep, 2000). In the Netherlands study of patients referred for CA over a sixteen-year period, no difference was seen in the extent or location of coronary artery lesions (Roeters van Lennep et al, 2000). In that study, referral to revascularization was associated with the extent of disease, which we are unable to determine in the NLCABG population, as the cohort was formed after referral for CABG. In contrast, Krumholtz and colleagues found that women had a significantly lower rate of severe CAD (OR 0.67), defined in the same way as the NLCABG study. However, Krumholtz included consecutive patients with AMI and the NLCABG study and the study of Aquilar and colleagues included cohorts of revascularized patients (Krumholtz et al, 1992; Aquilar et al, 2001). While, patients in Krumholtzs' study had a high probability of CAD, the selection process inherent in referral for CABG would probably dictate that NL patients have more severe vessel disease.

It has been shown that women have much higher surgical risk than men at the time of revascularization (Aquilar et al, 2002). This is likewise the finding of the NLCABG study. This strengthens evidence for later referral in women.

In NLCABG, there was no evidence of inappropriate referral for surgical revascularization, regardless of gender. This is consistent with other studies reporting that coronary revascularization does not tend to be overused following CA (Leape et al, 1993; McGlynn et al, 1994). In fact substantial underuse has been documented in patients considered appropriate for these procedures (Hemingway, Crook, Feder et al, 2001).

A Swedish study showed that eight percent of patients referred to continued medical therapy met necessity criteria for CABG (Bernstein et al, 1999). In a study by

Hemingway and others, 26 % of those considered appropriate for CABG received only medical treatment. These patients were more likely to have angina, non-fatal MI, or death than those who underwent CABG (Hemingway, Crook, Feder et al, 2001). Another study in the United Kingdom, demonstrates strong association between severity of vessel disease, appropriateness, and treatment (Hemingway, Crook, Dawson et al, 2001). These studies provide strong support for clinical validity of appropriateness ratings for referral to revascularization (Hemingway, Crook, Feder et al, 2001; Hemingway, Crook, Dawson et al, 2001; Bernstein et al, 1999).

Appropriateness of referral for CABG tends to be high (Leape et al, 1993; Naylor et al, 1994). More than 96 % of female referrals for procedures and more than 99 % of male referrals for procedures in the NLCABG study were considered highly appropriate. Likewise necessity scores exceeded North American averages of 70 % to 83 % (McGlynn et al, 1994). More than 92 % of female procedures and more than 94 % of male referrals were considered highly necessary. In other North American studies, the reported rate of inappropriate use of revascularization has been between two and six percent (McGlynn et al, 1994). A Canadian study of ON and BC patients reported 3.9 % and 2.4 % of CABG cases to be rated as inappropriate (Anderson et al, 1997). A Sweedish study, using conservative definitions, estimated inappropriate use of CABG to be ten percent (Bernstein et al, 1999), while a study in the Netherlands estimated that only four percent of CABG decisions were inappropriate (Meijler et al, 1997). The difference in findings between these studies and NLCABG may lie simply in the population under study. The Swedish study findings are based on all patients referred for CA, while the Netherlands study findings and the NLCABG study includes all those being referred to or having undergone CABG. Comparison of appropriateness at time of revascularization might have

yielded similar rates of inappropriateness.

Because only patients who were already referred for CABG are included, NLCABG data do not allow for any assumptions about underuse of the surgical option. Given severity of angina and extent of vessel disease in those undergoing CABG, it is likely that the threshold for placement on the bypass list is high in NL. As the wait lists are long and growing, underuse is more likely to be the case. It has been demonstrated that coronary revascularization is underused in a population of CA patients in whom it was deemed to be highly appropriate (Hemingway, Crook, Feder, et al, 2001).

Likewise, the results of the NLCABG study indicate that, regardless of gender, the cardiac surgery program NL provides surgical intervention for patients in whom revascularization is highly appropriate and necessary. Despite being at significantly greater operative risk than men, women were offered and did accept the surgical option. Owing to wait lists and limited health care resources, these too probably represent the most urgent cases requiring CABG.

Older age and more severe symptoms suggest referral later in the disease process in women. It is arguable that based on symptom severity, women in the CABG study should have been referred for revascularization more often than men. Equal application of surgical intervention, despite more severe female symptoms, provides further support for reduced symptom-driven revascularization in women in this study. Surgical revascularization in women of high operative risk however, suggests physician support for the surgical option when symptoms and vessel disease are severe.

Delays in referral for revascularization may occur for many reasons including delayed seeking of medical attention by the patient, delayed referral for diagnostic tests, or delayed treatment once disease is identified. The CABG population represents a highly selected population having passed through several junctures in the referral process. This selection process may in fact have served to reduce potential gender bias in this population. Using this data set the author was unable to determine if late referral or treatment choices are based on patient or physician decision.

4.3 Summary

This review of two observational studies shows that, although not as dramatic as anticipated, there are some important gender differences in the treatment and clinical outcomes of patients with known cardiovascular disease in Newfoundland and Labrador. Differences in clinical characteristics fully explain the differences in medical management in this patient population. However men were significantly more likely than women to have invasive assessment and to be revascularized following the index MI. Women had higher in-hospital and long-term mortality from cardiac causes. They also had consistently poorer functional capacity and activity limiting angina than men throughout the follow-up period. Among patients who were surgically revascularized in NL, there was no indication of inappropriate utilization of CABG.

Pre-test likelihood of disease along with ACC/AHA guidelines for post MI treatment (Ryan et al, 1996) suggest that referral to CA should occur in equal proportions regardless of gender. Higher referral in men after consideration of all demographic and clinical factors suggests gender bias in the NLMI study population.

In the absence of information on disease severity in the MI population, we are unable to determine if they were surgical candidates. There are no published data addressing functional capacity and long-term activity limitation resulting from cardiac symptoms. The NLMI study is the first study having the ability to relate long-term functional capacity and mortality to cardiac intervention in such detail. The mortality and functional capacity data suggest underutilization of invasive interventions in NLMI women as opposed to over-utilization in men. The result is higher in-hospital and long-term mortality, and significant

functional limitation in women. The results of MLR showed that gender differences in the NLMI population were isolated to invasive intervention.

Reduced use of CA and myocardial revascularization in the NLMI study probably contributed to higher mortality particularly in females. Additionally, referral of a more ill female population for management of post MI complications may also have contributed to excess female mortality in this study. This is further supported by more severe angina and higher use of maximal medical therapy in females in the NLCABG study. Steingart and colleagues reported that drugs, rather than invasive interventions, were generally used to control cardiac complaints in women, even when their disability was greater than that of men (Steingart et al, 1991). Increased utilization of myocardial revascularization may have resulted in reduced mortality and improved quality of life in this patient population.

The NLCABG population was a highly selected patient group as they were primarily referred for urgent or emergent surgeries. This selection process may in fact have served to reduce potential gender bias in this population. However women were older and had more severe angina therefore were probably referred at a later stage than men (Kee, 1995).

Knowledge and attitudes among general practitioners and internists or cardiologists affects patient referral (Kee, Gaffney, Curry et al, 1993) and potentially other aspects of care. Rouleau and coworkers have suggested that marked bed restrictions increase the rate of definite MI admissions to Canadian versus US coronary care units (Rouleau et al, 1993). As observed by Every and colleagues, post MI patients are more likely to receive CA if they are admitted where facilities are available, than if they require transfer (Every,

Larson, Litwin et al, 1993). Sumita and others have claimed that patients transferred from outside hospitals are primarily admitted in consideration of further coronary intervention (Sumita et al, 1995). Kostis et al have suggested that women are less likely than men to be admitted to a facility equipped to perform invasive procedures (Kostis et al, 1994). All of these findings indicate a high degree of selection in the CA and revascularization referral process. Provincial differences in angina severity on referral to CABG demonstrate that NL patients are probably referred to revascularization when angina is more advanced (Anderson et al, 1997). This is probably because of availability of fewer acute care beds, cardiac catheterization and revascularization facilities in NL. It is evident from the NLCABG study that the patients referred for myocardial revascularization represent a highly selected population of the most severe cases.

It is clear that bias has the potential to influence all stages of referral in women who suffer from cardiovascular disease. Some selection bias has already occurred before a patient presents for hospital care. Such bias may occur for many reasons, but geographic and health resource allocation limitations probably play a vital role in selecting the population in both the NLMI and NLCABG studies.

From Sackett's table of selection biases (Sackett, 1979), three appear to be critical in defining the population included in these NL studies: 1) Centripetal bias may have influenced primary physicians to refer, or patients to gravitate towards, the only tertiary referral center in NL; 2) Referral filter bias may have resulted in the selection of more complex cases or more ill patients for referral to tertiary care; 3) Diagnostic access bias may have had an impact as geographic and economic access to diagnostic and invasive cardiac procedures is inequitably distributed.

In NL, gender bias is not evident in the medical management of post-MI patients. However in considering more invasive intervention, physicians are influenced by patient sex. Evidence suggests that quality initiatives may be useful in improving adherence to evidence-based guidelines (Haddad, Searles and Gillis, 2001). Adherence to clearly defined patterns of practice should improve the likelihood for patients to receive similar assessment and treatment regardless of gender.

The NL studies have several strengths compared to other studies in this area: 1) While it was analyzed retrospectively, the NLMI data was collected prospectively and was not dependent on chart reviews; 2) The NLMI study has lengthy follow-up and detailed clinical, treatment, and outcome data, allowing us to be one of the first to assess functional capacity as it relates to medical and invasive intervention in these patients. 3) The NLCABG study was among the first to address gender and appropriateness of revascularization and is the first in NL to address this issue.

Likewise these studies have some weaknesses: 1) The NLMI patients were a select group of patients who were enrolled in the SAGES study. Information on the overall population from which these 698 patients were selected is unavailable. Additionally, since a significant number of NLMI patients were probably referred to the study facilities because of post-MI complications, it is possible that selection of a higher risk female population has occurred through referral filter bias and diagnostic access bias. Likewise many of the NLCABG population was probably refereed for consideration of invasive intervention resulting in selection of a population with more advanced CAD. Therefore it may not be appropriate

to generalize the results of these studies to the remainder of Newfoundland and Labrador or to other provinces in Canada. The unique geographic distribution and availability of limited facilities for invasive intervention may affect treatment and influence outcomes in our studies. 2) These data are dated and in some cases are up to ten years old. The data do however help to fill a gap in the Canadian data, especially for this region. To avoid a disconnect between current consensus and decade-old thinking on appropriate therapy in patients with CAD, particular care is taken in comparing the NL data with data from studies conducted within the same time period. Temporal trends in prescribing patterns are discussed in detail. Likewise the consensus guidelines used to determine appropriate care in these studies were published in 1996 and based on formal literature reviews from publications up to 1995. This should reduce the difficulty in interpreting bias given that the time gap between the study treatment and treatment guidelines is small. 3) The NLCABG study is limited by use of retrospective chart review. Investigators were limited to information available from medical records. Non-documentation, misinterpretation and miscoding of data are particular weaknesses in this type of study. To reduce the impact of these problems, data were collected and analyzed by a specially trained research team using a Canadian tested chart abstraction instrument. After data abstraction two specialists independently determined appropriateness and necessity of each case using specific criteria developed by the RAND corporation. Nevertheless, given that risk adjustment is based on data from chart abstraction, the findings in this study should be interpreted with some caution.

Gender bias is evident in referral for invasive cardiac intervention in these populations of NL patients. It is difficult to determine at what point in the referral process this difference occurs. Further studies are needed to see if this is applicable to the overall NL population

and to identify at what juncture this arises.

Appendix 1: Goldman Scale

1.

Could the patient walk down a flight of stairs without stopping? Y N

If no, go to 4.

2.

Could the patient carry anything up a flight of 8 steps without stopping? Y N

Or can the patient:

a. Have sexual intercourse without stopping
b. Garden, rake or weed
c. Roller skate, dance foxtrot
d. Walk at 4 mph rate on level ground

If no, patient is class III, go to 6.

3.

Could the patient carry at least 24 lb. up a flight of 8 steps? Y N

Or can the patient:

a. Carry objects weighing 80 lb.
b. Perform outdoor work (e.g. Shovel snow, spade soil)
c. Participate in recreational activities such as skiing, basketball, touch football, squash, handball)
d. Jog/walk 5 mph

Goldman Scale: (continued)

If yes, patient is class I, go to 6.

If no, patient is class II go to 6.

4.

Could the patient shower without stopping? Y N

Or can the patient:

a. Strip and make a bed
b. Mop floors
c. Hang washed clothes
d. Clean windows
e. Walk at 2.5 mph
f. Bowl
g. Play golf (walk and carry clubs)
h. Push lawn mower

If yes, patient is class III, go to 10

If no, go to 5.

5.

Could the patient dress without stopping because of symptoms? Y N

If yes, patient is class III, go to 6

If no, patient is class IV, go to 6.

6. Provide Functional Status Class: I II III IV

Goldman Scale: (continued)

Was the limitation in activity in 1-5 above due to:

a. Angina

b. Dyspnea,

c. Fatigue

d. Physician instructions

e. Other

If yes, specify: _____

Appendix 2: Definitions for NLCABG Study

Coronary artery disease: Reduction in luminal diameter of Left main coronary artery of 50% or greater by visual inspection, or reduction in luminal diameter of one major coronary artery of 70% or greater by visual inspection.

Unstable angina: Chest pain thought to be due to myocardial ischemia, requiring hospitalization because of difficulty in control or concern about the possibility of myocardial infarction. This includes: (1) recent increase in intensity, frequency, or duration of chronic angina; (2) the development of angina at rest; or (3) new onset of severe chest pain ("acute coronary insufficiency"). Revascularization is carried out while the patient is in hospital or within 4 weeks of admission for unstable angina.

Angina Class I: angina on strenuous exertion.

II: angina on walking or climbing stairs rapidly

III: angina on walking one or two level blocks

IVa: unstable angina, pain resolved with intensified medical therapy, now stable on oral medication

IVb: unstable angina on oral therapy, symptoms improved but angina with minimal provocation

IVc: symptoms not manageable on oral therapy, requires coronary care or parenteral medication, may be hemodynamically unstable

Significant coronary artery disease:

a. **Left main disease**: Reduction in the luminal diameter of the left main coronary artery of 50 % or greater by visual inspection or formal calibration of angiographic findings. Protected left main disease is defined by the presence of a patent bypass graft to the LAD (left anterior descending) or circumflex arteries or by collateral flows to these arteries from a patent RCA (right coronary artery).

b. **Three-vessel disease**: Reduction in the luminal diameter of all three major coronary arteries of 50% or greater by visual inspection or calibration of angiographic findings. If measured by visual inspection, at least one vessel must have 80 % stenosis. The panel believed that these represented equivalent assessments of the extent of the disease.

c. **Two-vessel disease**: Reduction in the luminal diameter of two major coronary arteries of 50% or greater by visual inspection or calibration of angiographic findings. If measured by visual inspection, at least one vessel must have 70 % stenosis.

d. **One-vessel disease**: Reduction in the luminal diameter of one major coronary artery (not left main) of 70% or greater by visual inspection or 50 % by calibration.

e. **Proximal left anterior descending (PLAD)**: Viability of a major amount of the anterior wall of the left ventricles in jeopardy owing to reduction in luminal diameter of PLAD by 70% or greater by visual inspection or 50% by qualitative analyses. PLAD involvement that is proximal to the first septal perforator.

Operative risk score:

Female	+1
Weight > 1.5 ideal	+3
Diabetes mellitus	+3
Systolic BP > 140 mm HG	+3
Ejection Fraction mild impairment	+2
Ejection Fraction severe impairment	+4
Age 70-74	+7

75-79	+12
≥ 80	+20
First reoperation	+5
Second reoperation	+10
Pre-op intra aortic balloon pump	+2
LV aneurysm	+5
Emergency surgery following CA or PTCA	+10
Dialysis dependent	+10
Catastrophic state	+10-50
Rare problem	+2-10
Mitral valve surgery	+5
PA pressure ≥ 60	+8
Aortic valve surgery	+5
Aortic gradient > 120	+7
CABG at time of valve surgery	+2
Chronic obstructive lung disease	+4
Peripheral vascular disease with claudication or amputation	+3
Symptomatic carotid artery disease	+4

Maximal medical therapy:

a. Chronic stable angina: The patient has received drugs from at least two of the three major classes (nitrates, beta-blockers, and calcium antagonists) or the patient has received one class of medication, but there is a note in the chart that the patient is unable to tolerate the others.

b. Unstable angina: Must meet one of the following criteria:

1. The patient has received drugs from at least two of the following major classes of drugs: nitrates, beta-blockers, calcium antagonists, and intravenous heparin (except To Keep Open (TKO) Hep-lock), or
2. Receiving intravenous nitroglycerin, or
3. Receiving one of the three major classes of drugs (nitrates, beta-blockers, calcium antagonists), with a note in the chart indicating that the patient is unable to tolerate other drugs.

Contraindications to CABG:

a. Terminal illness, such as cancer, AIDS, severe COPD, hepatic failure, where a reasonable prognosis is six months or less.
b. Advanced dementia.
c. Severe impairment in ability to perform basic activities of daily living (Katz score of ≤ 3/6) because of noncardiac disease.

SCORING SYSTEM FOR RANKING RELATIVE URGENCE OF NEED FOR REVASCULARIZATION

	Stable Angina		Unstable Angina		
Anatomical Equivalent	I-II	III	IV-A	IV-B	IV-C
Left Main Stenosis	5.40	4.85	4.75	3.40	2.15
Multivessel, including proximal LAD stenosis	6.15	6.00	5.50	3.90	2.55
Three-vessel without proximal LAD stenosis	6.45	6.35	5.80	3.90	2.65
Single vessel proximal LAD stenosis	6.80	6.55	5.80	4.05	2.90
One or two-vessel disease, no proximal LAD stenosis	6.95	6.65	6.15	4.15	3.05
Number to be subtracted if non-invasive tests suggest high ischemic risk	0.90	0.75	0.75	N/A	N/A
Standard error of combined score (maximum)	0.11	0.06	0.08	0.03	0.03
Typical residula (mean squared error)	0.24	0.13	0.15	0.10	0.12
Maximum residual (predicted score vs trimmed mean rating)	0.45	0.32	0.45	0.28	0.28

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