UNDERSTANDING SEX/GENDER IN CARDIOVASCULAR DISEASE

UNDERSTANDING SEX/GENDER IN CARDIOVASCULAR DISEASE

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A Thesis

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Abstract

There has been much controversy in the cardiovascular literature regarding sex/gender differences in the presentation of coronary artery disease and downstream implications. The aim of this thesis is not to resolve this controversy, but rather to assess and critique potential sex/gender similarities and differences from a variety of perspectives, explored through various methodologies.

This thesis contains four main studies, each employing different quantitative and qualitative methods. An overarching framework was developed to contextualise each study presented in this thesis. The first main study entitled, the *"RACE CAR"* trial assessed physician opinion *prospectively* observing that women are perceived to benefit less from cardiac catheterization compared to men, while controlling for age, TIMI risk and preference for cardiac catheterization. The *"Identifying women with severe angiographic coronary disease"* study observed physician referral patterns *retrospectively* and determined that although women are less likely to have severe angiographic disease compared to men, the traditional risk factors and CCS Class IV angina are significant predictors of severe angiographic disease. This is an important finding to help physicians better identify women at risk. The findings from these two studies identified the need for the cardiovascular research community to better define angina, particularly among women. Using qualitative methodology, a new theory of angina emerged, illustrating symptoms along a *gender continuum*. Based on the findings from the qualitative study, the final study of this thesis developed an assessment tool to test the symptom parameters along the *gender continuum*. The findings confirm that the symptoms of women and men represent more *shared experiences* rather than differences, particularly among patients with obstructive coronary artery disease.

These studies collectively address knowledge gaps and add new information to various stages of patient cardiac care within the sex/gender programme of cardiovascular research.

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Sincerely with gratitude,

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2.2

2.3

2.4

2.4.1

2.4.2

Table of Contents

Title	Pageii
Desc	riptive Noteiii
Absti	activ
Ackn	owlegementsvi
Table	e of Contentsvii
Table	of Tablesxiv
Table	of Figuresxvi
List o	f Abbreviations xvii
Decla	ration of Academic Achievementxix
Chapt	er 1: General Introduction and Thesis Overview1
1.0	General Introduction1
1.1	Introduction1
1.2	Outline of Thesis Studies
1.2.1	Chapter 2: Literature Review
1.2.3	Chapter 3: The RACE CAR trial
1.2.4	Chapter 4: Identifying women with severe angiographic disease9
1.2.5	Chapter 5: Understanding Chest-Related Symptoms According to Gender10
1.2.6	Chapter 6: McMaster University Symptoms in Cardiac Assessment (MUSICA) Tool11
1.2.7	Chapter 7: Discussion12
1.2.8	Chapter 8: Conclusions12
Refere	ences13
Chapt	er 2: Literature Review
2.0	Literature Review15
2.1	Cardiovascular Disease Mortality15

Coronary Artery Disease Presentation......17

2.4.3	Diabetes Mellitus	29
2.4.4	Dyslipidemia	33
2.4.5	Excess weight: Overweight and Obesity	38
2.4.6	Physical activity	44
2.4.7	Psychosocial differences in CAD according to sex	48
2.4.8	Social determinants of cardiovascular disease	51
2.5	Differences in Cardiovascular Symptom Presentation in Women and Men	53
2.5.1	Differences in ACS symptoms among women and men	56
2.5.2	Differences in MI presentation among women and men	59
2.5.2	Sex Differences in Evaluation and Outcomes Presenting to the ER	62
2.5.2	Differences in Outcomes After Catheterization among Women and Men	64
2.6	Biological differences in coronary anatomy between the sexes	65
2.7	The Age-Sex/Gender Relationship	67
2.7	Gender Affecting Physician Recommendations	70
Refere	nces	73

CHAPTER 3	95
3.0 Referrals in Acute Coronary Events for CARdiac Catheterization: The RACE CAR Tr	rial95
CHAPTER 3: The RACE CAR Trial	96
3.1 Summary	97
3.2 Structured Abstract	98
3.3 Introduction	100
3.4 Methods	102
3.5 Design of Survey Instrument	
3.6 Survey Administration	
3.7 Controlled Patient Factors	104
3.8 Description of Physician and Hospital Characteristics	104
3.9 Survey Questions	
3.10 Statistical Considerations	
3.11 Results	107
3.12 Physician Characteristics	
3.13 Hospital Factors	
3.14 Referral Decisions Based on Gender, Age, Patient Preference, and Risk	

3.15 Interactions Between Patient Factors Influencing Referral Decisions	109
3.16 Secondary Objectives	110
3.17 Characterization of chest pain	111
3.18 Estimated probability that patient has significant obstructive CAD	111
3.19 Influence of patient opinion for referral for CC	112
3.20 Discussion	113
3.21 Limitations	116
3.22 Conclusion	117
Reference List	

CHAPTER 4	. 127
4.0 Identifying Women with Severe Angiographic Coronary Disease	
Identifying Women with Severe Angiographic Coronary Disease	128
4.1 Abstract	
4.2 Introduction	
4.3 METHODS	
4.3 Data Collection	
4.4 Statistical Analysis	
4.5 RESULTS	
4.6 Patients Identified with Angiographically Severe CAD	
4.7 Risk Factors Among Young Women Versus Older Women	
4.8 Angina Severity in Patients with Severe CAD Stratified by Age	
4.9 Angina Severity Among Young Women versus Young Men	
4.10 Angina Severity Among Young Women versus Older Women	139
4.11 Risk Factors Associated with Severe Angiographic CAD	
4.12 Discussion	140
4.13 Conclusion	144
Reference List	145

Chapter 5: Understanding Cardiac-Related Symptoms According to Sex/Gender....157

5.0	Introduction	157
5.1	Sex and Gender Differences	157
5.1.	Sex Differences in Angina	162

5.1.1	A Brief History of Angina	
5.1.2	Defining Typical versus Atypical Angina Today	166
5.2	Clinical implications of sex differences in angina	169
5.3	Study Rationale	171
5.4	Research Study Objective	173
5.5	Study Design	174
5.6	Selection of Patients	175
5.6.1	Patient Screening and Study Site	175
5.6.2	Inclusion Criteria	176
5.6.3	Exclusion Criteria	177
5.7	Data collection	178
5.8	Qualitative Data Analysis	179
5.8.1	Analysis of data	179
5.9	Study Results	
5.9.1	Description of Study Population	
5.9.2	Main Study Findings	
5.9.3	Symptoms parameters on the gender continuum	
5.9.4	Symptomatic Tipping Point	198
5.9.4	Model of the Symptomatic Tipping Point Process	199
5.10	Discussion	208
5.11	Limitations	217
5.12	Conclusions and Future Directions	219
Refere	ences	

1.0	Introduction	231
1.1	Early Angina Studies	231
1.2	The impact of early angina studies	234
1.3	Angina 'Re-Constructed'	236
2.0	Study Rationale	238
3.0	Study Objectives	240
4.0	Methods	240

4.1	Brief overview of study design	240
4.2	Selection of Patients	241
4.2.1	Study Site	241
4.2.2	Inclusion Criteria	242
4.2.3	Exclusion Criteria	243
4.3	Assessment tool development and administration	243
4.3.1	Assessment tool development	243
4.3.2	Administration of assessment tool MUSICA	245
4.4	Collection of Coronary Angiography Results	245
5.0	Statistical Considerations	246
5.1	Sample Size	246
5.2	Statistic Analytical Plan	247
6.0	Study Results	248
6.1	Baseline characteristics of study population	248
6.2	Symptom Parameters	249
6.2.1	Descriptive Terms of Sensations in the Chest-Region Among All Patients	249
6.2.2	Descriptive Terms of Sensations in the Chest-Region Among Patients with Obstructive CAD	250
6.2.3	The Gender Continuum	251
6.2.4	Non-Chest Region Pain/Discomfort Among All Patients	251
6.2.5	Non-Chest Region Pain/Discomfort Among Patients with Obstructive CAD	252
6.2.6	Gender Continuum of Pain/Discomfort in the Non-Chest Region	252
6.2	7 Other Symptoms Associated with Chest-Related Sensations/Symptoms Among All Patients	253
6.2.8	Other Symptoms Associated with Chest-Related Sensations/Symptoms Patients with Obstructive CAD	253
6.2.9	Gender Continuum of Other Symptoms Associated with Chest-Related Symptoms	254
6.3	Severity of Symptoms According to CCS Angina Classification	254
6.3.1	Patient and Physician CCS Angina Classification Rating Among Men	254
6.3.2	Patient and Physician CCS Angina Classification Rating Among Women	255
6.3	3.3 The Association of CCS Angina Classification with Obstructive CAD According to Patient and Physician Ratings	256
7.0 I	Discussion	256

References	265
Chapter 7: Conclusions and Epilogue	287
Appendix A	300
Appendix B	307
Appendix C	315

Table of Tables

TABLE 1-1- PARTICIPATING PHYSICIAN DEMOGRAPHICS AND HOSPITAL FACTORS	123
TABLE 3-1- BENEFIT FROM CARDIAC CATHERIZATION CONTROLLED FOR GENDER, AGE, TIMI RISK SCORE AND PATIENT PREFERENCE	124
TABLE 3-2- INTERACTION OF PATIENT BENEFIT FROM CARDIAC CATHERIZATION(CC) REFERRAL BETWEEN TIMI RISK SCORE, AND GENDER, AGE, AND PATEINT PREFERENCE	125
TABLE 3-3- INFLUENCE OF SECONDARY OBJECTIVES CONTROLLED FOR GENDER, AGE, TIMI RISK SCORE, AND PATIENT PREFERENCE	126
TABLE 4-1– BASELINE CHARACTERISITCS OF PATIENTS IN THE HAMILTON HEALTH SCIENCES CORONARY ANGIOGRAPHY REGISTRY	150
TABLE 4-2- CORONARY ANATOMY DIFFERENCES BETWEEN MEN AND WOMAN	151
TABLE 4-3- FREQUENCY OF CCS CLASS* ANGINA SYMPTOMS ACCORDING TO SEX AND AGE	152
TABLE 4-4- PROPORTION OF RISK FACTORS IN YOUNGER PATIENTS VERSUS OLDER PATIENTS WITH SEVERE CAD	153
TABLE 4-5- UNIVARIATE AND ADJUSTED MULTIVARIATE LOGISTIC REGRESSION MODEL OF VARIABLES ASSOCIATED WITH SEVERE CAD	154
TABLE 5-1- CLINICAL DIAGNOSIS, MEAN, AGE AND SEX DISTRIBUTION	165
TABLE 6-1- BASELINE DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION	273
TABLE 6-2- MORPHOLOGICAL DIFFERENCES BETWEEN MEN AND WOMEN OR CORONARY ANATOMY	274
TABLE 6-3- DESCRIPTIVE TERMS OF SENSATIONS/SYMPTOMS IN THE CHEST-REGION AMONG ALL PATIENTS	275
TABLE 6-4- DESCRIPTIVE TERMS OF SENSATIONS/SYMPTOMS IN THE CHEST-REGION AMONG PATIENTS WITH OBSTRUCTIVE CAD	276
TABLE 6-5- NON-CHEST REGION PAIN/DISCOMFORT AMONG ALL PATIENTS	278
TABLE 6-6- NON-CHEST REGION PAIN/DISCOMFORT AMONG PATIENTS WITH OBSTRUCTIVE CAD	278

TABLE 6-7- OTHER SYMPTOMS ASSOCIATED WITH CHEST-RELATED SENSATION/SYMPTOMS AMONG ALL PATIENTS	280
TABLE 6-8- OTHER SYMPTOMS ASSOCIATED WITH CHEST-RELATED SENSATION/SYMPTOMS AMONG PATIENTS WITH OBSTRUCTIVE CAD	280
TABLE 6-9- CCS ANGINA CLASSIFICATION ACCORDING TO PHYSICIAN AND PATIENT ASSESMENT	282
TABLE 6-10- COMPARISION OF PATIENT RATINGS TO PHYSICIAN RATING OF CCS ANGINA CLASSIFICATION USING WILCOX ON SIGNED RANKS TEST	285
TABLE 6-11- REGRESSION MODEL OF CCS ANGINA CLASSIFICATION PHYSICIAN AND PATIENT RATINGS ASSOCIATED WITH OBSTRUCTIVE CAD	286

Table of Figures

FIGURE 1-1: FRAMEWORK OF PATIENT CARDIAC CARE	6
FIGURE 4-1: ADJUSTED SEX X CCS CALASS IV INTERACTION	155
FIGURE 5-1: GENDER CONTINUUM OF SYMPTOMS	185
FIGURE 5-2: LOCATION OF CHEST PAIN/DISCOMFORT DESCRIBED BY PATIENTS ON GENDER CONTINUUM	187
FIGURE 5-3: NON-CHEST LOCALIZED AREAS OF PAIN.DISCOMFORT	188
FIGURE 5-4: DESCRIPTION OF PAIN/DISCOMFORT	191
FIGURE 5-5: OTHER ASSOCIATED SYMPTOMS	194
FIGURE 5-6: ORIGINALLY ATTRIBUTED CHEST-PAIN/DISCOMFORT	195
FIGURE 5-7: PHYSICAL LIMITATIONS	197
FIGURE 5-8 SYMPTOMATIC TIPPING POINT	200
FIGURE 6-1 POWER CALCULATIONS TO DETECT ODDS RATION OF 2.0 FOR ONE S INCREASE IN PAIN SEVERITY	247
FIGURE 6-2: GENDER CONTINUUM OF DESCRIPTIVE TERMS OF SENSATIONS/SYMPTOMS IN THE CHEST REGION AMONG ALL PATIENTS	277
FIGURE 6-3: GENDER CONTINUUM OF DESCRIPTIVE TERMS OF SENSATIONS/SYMPTOMS IN THE CHEST REGION PATIENTS WITH OBSTRUCTIVE CAD	277
FIGURE 6-4: GENDER CONTINUUM OF PAIN/DISCOMFORT IN THE NON-CHEST REGION AMONG ALL PATIENTS	279
FIGURE 6-5: GENDER CONTINUUM OF PAIN.DISCOMFORT IN THE NON-CHEST REGION AMONG PATIENTS WITH OBSTRUCTIVE CAD	279
FIGURE 6-6: GENDER CONTINUUM OF OTHER ASSOCIATED SYMPTOMS WITH CHEST RELATED SENSATIONS/SYMPTOMS AMONG ALL PATIENTS	281
FIGURE 6-7: GENDER CONTINUUM OF OTHER ASSOCIATED SYMPTOMS WITH CHEST-RELATED SENSATIONS/SYMPTOMS AMONG PATIENTS WITH OBSTRUCTIVE CAD	281
FIGURE 6-8: PATIENT AND PHYSICIAN CCS ANGINA CLASSIFICATION RATINGS AMONG TOTAL MEN	283
FIGURE 6-9: PATIENT VERSUS PHYSICIAN CCS ANGINA CLASSIFICATION RATINGS AMONG TOTAL WOMEN	284
FIGURE 6-10: COMPARISION OF PATIENT RATINGS TO PHYSICIAN RATINGS OF CCS ANGINA CLASSIFICATION	285

List of Abbreviations

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
Аро А	Apolipoprotein A
BMI	Body mass index
CAD	Coronary artery disease
CABGS	Coronary artery bypass graft surgery
СС	Cardiac catheterization
CCS	Canadian Cardiovascular Society
CCHS	Canadian Community Health Survey
CHHS	Canadian Heart Health Survey
CHMS	Canadian Health Measures Survey
CVD	Cardiovascular disease
ECG	Electrocardiogram
HDL	High density lipoprotein
LAD	Left anterior descending (artery)
LDL	Low density lipoprotein
MI	Myocardial infarction
MET	Metabolic equivalent
MUSICA	McMaster University Symptoms in Cardiac Assessment
NPHS	National Population Health Survey

- NSTEMI Non-ST elevation myocardial infarction
- PAR Population-attributed risk
- PCI Percutaneous coronary interventions
- PTCA Percutaneous transluminal coronary angioplasty
- RACE CAR Referrals in Acute Coronary Events for CARdiac catheterization
- SHARE Study of Health Assessment and Risk Evaluation
- SHARE-AP Study of Health Assessment and Risk Evaluation of Aboriginal Peoples
- STEMI ST elevation myocardial infarction
- TIMI Thrombolysis in Myocardial Infarction
- WC Waist circumference
- WHO World Health Organization
- WHR Waist to hip ratio
- WHtR Waist to height ratio

Declaration of Academic Achievement

I have been the principal and sole writer of all the contents of this thesis. For the multi-authored publications the candidate's role are described in detail below.

Chapter 3: Referrals in Acute Coronary Events for CARdiac catheterization: The *RACE CAR* Trial

Kreatsoulas, C., Sloane, D., Pogue, J., Velianou, J. L., & Anand, S. S. (2010). Referrals in acute coronary events for CARdiac catheterization: The RACE CAR trial. *The Canadian journal of cardiology, 26*(8), 290-296.

Candidate's role: I designed and implemented the study, conducted all the statistical analysis and was the primary author of this publication.

Chapter 4: Identifying women with severe angiographic coronary disease

Kreatsoulas, C., Natarajan, M. K., Khatun, R., Velianou, J. L., & Anand, S. S. (2010). Identifying women with severe angiographic coronary disease. *Journal of internal medicine*, *268*(1), 66-74.

Candidate's role: I was initially involved in the establishment of the database many years prior to this analysis, however I conducted the statistical analysis and was the primary author of this publication.

Chapter 5: Understanding Cardiac-Related Symptoms According to Sex/Gender

Candidate's role: Although not yet published, I was designed the study, conducted qualitative interviews, coded and analysed the data and was the primary author of this paper.

Chapter 6: Understanding Cardiac-Related Symptoms According to Sex/Gender using the McMaster University Symptoms in Cardiac Assessment (MUSICA) Tool

Candidate's role: I developed MUSICA, collected and analysed the data and was the primary author of this paper.

Chapter 1: General Introduction and Thesis Overview

1.0 General Introduction

Cardiovascular disease (CVD) is a common disease among women, accounting for the leading cause of death among women in the western world. Despite this, knowledge of CVD progression has largely been established on disease presentation in men. It is possible that differences in the presentation, symptoms, diagnosis, treatments and outcomes may be different in women compared to men. These issues will be outlined and explored in this thesis.

1.1 Introduction

Since the mid-twentieth century, cardiovascular disease (CVD) has been the leading cause of morbidity and mortality among both men and women in the western world, accounting for approximately one-third of total deaths annually and it is predicted that by 2020 or sooner, it will be the leading cause of death worldwide (Levenson, Skerrett, & Gaziano, 2002; Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; Murray & Lopez, 1997; *Social Determinants of Health: THE SOLID FACTS*, 2003). Although it is often not realized, the percentage of total deaths from CVD is slightly higher in women than in men, and specifically in 2007 in Canada, 30% of women succumbed to CVD, compared to 29% in men (Statistics, 2007). Specifically, CVD accounts for the greatest proportion of deaths among adult women of all ages, (Hochman et al., 1999; Lerner & Kannel, 1986; Mosca et al., 2000; Shaw

et al., 2006; Smith et al., 2001; Statistics, 2004; Thom et al., 2006) including the younger age subset (i.e. 35-55 years). Despite this, there has been a widespread perception that CVD is a "man's disease".

Over the past half century this perception has become well-entrenched among the medical community and general public. This perception has resulted in much controversy and as a result, the repercussions of this perception have had deleterious downstream effects where CVD is under-appreciated, under-recognized, under-diagnosed and evidently, under-treated among women, often interpreted as the "sex/gender bias" in the CVD literature. In the past twenty years, this controversy has engrossed a large proportion of the CVD literature, exploring issues of bias and equality, and the many avenues of health care. Although there are many similarities between the sexes in the determinants and symptoms of CVD, differences have been observed in the form of bias, negatively impacting selfreferral and/or physician referral for examinations, referral for diagnostic technologies and treatment strategies among women. Despite various hypotheses put forth, there is no clear consensus why this perception persists, ironically among the most prevalent disease that claims the most lives among women. Further compounding the issues are flaws in the underlying philosophical construct in studying the disease process and methodologic limitations comprising the CVD sex/gender body of literature. Our current knowledge of CVD is largely based on the underlying male construct as most of the early studies recruited patient populations mostly comprised of men. The disease was expected to progress similarly in women

and when discrepancies in disease presentation occurred, women were labelled as "atypical", and the comparison group whether realised or not meant, "atypical compared to men". At the same time, women appeared to not suffer from the same complications from the disease as men, and the disease course was determined to be "uncomplicated" among women (Campeau et al., 1968; Dawber, Moore, & Mann, 1957; Proudfit, Shirey, & Sones, 1966).

As the CVD literature began to proliferate, women were underrepresented in studies and to determine if the study findings were equivalent in women, investigators began to perform subgroup analyses in clinical trials according to sex, which were never adequately powered to reliably detect if a sex difference exists. As a result, discordant findings began to amass where some studies reported sex differences in symptoms/ treatment/outcome while others reported minimal to no differences between sex symptoms/ treatment/ outcomes, further fuelling the sex/gender controversy.

Intrigued by the controversy in the literature, this PhD thesis began as a very broad question, *"Are there differences in cardiovascular disease symptoms according to sex/gender?"* and eventually evolved into a journey of more questions and discoveries. During the first course in the Health Research Methodology (HRM) Doctorate Programme, HRM 700 *The Philosophy of Science*, I first began to question the underlying assumptions and philosophical underpinnings in this area. Collectively this questioning, along with the skills developed en route (i.e. courses, comprehensive exams, discussions with thesis committee, anonymous reviewers PhD Thesis

comments), helped to shape the type of approach, study design and methodology that I felt would best answer my questions. As a result, this thesis represents a twofold exploration; one, of the topic area itself analysed from a variety of perspectives, complemented by an exploration of various methodologies which helped inform the map and directions of this journey. Assembled as a sandwich thesis, each chapter represents a segment of my journey.

The aim of this thesis is not to resolve the controversy whether there is a sex/gender bias in the diagnosis and treatment of CVD, but rather to assess and critique aspects of how this perception may impact cardiac diagnosis and treatment. In very broad terms, the studies comprising the first half of this thesis will seek to delve deeper to determine to what degree a sex/gender bias in the physician approach to evaluation in the symptomatic presentation of CVD exists and whether this perception is substantiated among patients with confirmed disease. For the independent study component of the PhD programme (a component of the comprehensive exam process not included in this thesis) my project entitled "Deconstructing Angina in Women", sought to historically de-construct the initial conceptualisation of coronary artery disease (CAD), how it was first approached, identified and studied, to better understand the assumptions/interpretations that led to the perception that CAD is a "man's disease". The findings from this independent study established the roadmap for the last two thesis studies that explore reconstructing symptoms, perceptions and knowledge of CVD from the patient's perspective. The final study of this thesis seeks to collectively link the

avenues of this journey by testing the concepts that have emerged from the preceding studies tested or summarized in an assessment against cardiac morphologic angiographic outcomes, the gold standard of diagnosing heart disease.

To better understand the controversies and to contextualise the studies comprising this thesis, I have developed a framework, describing the stages and various factors that influence patient cardiac care (Figure 1). Each thesis study chapter will be discussed against the backdrop of this framework. Figure 1:1

Figure 1: Framework of Patient Cardiac Care



The *framework of patient cardiac care* illustrated above (Figure 1) will be discussed in greater detail in the upcoming chapters as each study explores the components of the framework from a different perspective. Briefly, a patient with/ without risk factors, may be experiencing some symptoms and limitations with their functional ability (i.e. shortness of breath, angina) either acutely or over a period of time. 'Something' unusual (an event/feeling of being compromised/ concerned with their symptoms or functional ability/ concern based on their health knowledge/ advice from family or friend/ a change from the patient's acceptable level of 'normal') provokes the patient to seek medical attention, described as the "tipping point". Once the patient experiences the 'tipping point', presumably with symptoms and/or risk factors, the patient seeks medical attention. Patients in an acute state typically go to the emergency room, while patients that feel their condition is not urgent usually visit their family practitioner. At this point, the emergency room physician or family practitioner may feel that further non-invasive diagnostic testing is necessary, which is often followed by a cardiology consult by an internist or cardiologist. Once the specialist assesses the patient's clinical history which include risk factors, symptoms, functionality and the patient's concerns (initiating the "tipping point"), collectively with the outcomes of any diagnostic tests (i.e. electrocardiogram, stress test, echocardiogram) that may have been ordered, the specialist then may refer the patient for cardiac catheterization. Cardiac catheterization is the gold standard in the diagnosis for coronary artery disease (CAD). However cardiac catheterization is not a procedure without risks. The

physician must evaluate the benefit of the cardiac catheterization to the patient as being greater than the risk of the test. Once the patient has been identified and diagnosed as having significant CAD, they are recommended either medical therapy alone, percutaneous coronary intervention (PCI) with medical therapy or coronary artery bypass graft (CABG) surgery with medical therapy. This thesis will focus exclusively on the patient's route to cardiac catheterization and not on the recommended therapies after cardiac catheterization.

1.2 Outline of Thesis Studies

1.2.1 Chapter 2: Literature Review

This chapter will review trends in CVD prevalence and incidence, in Canada and worldwide. A brief history on the early conceptualisation of the risk factors will be presented followed by an in-depth exploration of specific risk factors, highlighting sex/gender discrepancies. Lastly, sex/gender differences in the clinical arena will be explored, including differences in the presentation of myocardial infarction, outcomes including cardiac catheterization, and the influence of sex/gender on physician recommendations.

1.2.3 Chapter 3: The RACE CAR trial

The first study of this thesis entitled, *"Referrals in Acute Coronary Events for CARdiac Catheterization: The RACE CAR trial"* is a conceptual experiment designed to prospectively assess if there is a sex/gender difference in the perceived benefit of

8

cardiac catheterization by physicians assessing patients with suspected cardiac disease. In reference to the *framework of patient cardiac care* illustrated above (Figure 1), this study is designed to assess if specialists/cardiologists perceive a sex/gender bias when assessing clinical vignettes controlled for risk factors, symptoms and functionality, in their perceived benefit of cardiac catheterization. Methodologically, one of the unique features of this study is that it includes a *prospective* conceptual framework, as most sex/gender studies consist of retrospective analyses of large datasets plagued with inherent limitations, or underpowered subgroup analyses. Employing quantitative methods, the analysis of this study consists of multi-level regression modelling. *The RACE CAR trial* has been published in the Canadian Journal of Cardiology and is presented in Appendix B.

1.2.4 Chapter 4: Identifying women with severe angiographic disease

The second study of this thesis entitled, "Identifying women with severe angiographic disease" examines the characteristics including the distribution of risk factors according to age, severity of functional angina symptoms (CCS classification) and pattern of angiographic disease of over 23,000 men and women referred for their first cardiac catheterization. In reference to the *framework of patient cardiac care* (Figure 1), in this study analyse the effects of risk factors, symptoms and functionality on the outcome, cardiac catheterization. The methodology of this study consisted of stratification according to sex and age, and univariable and multivariable logistic regression modelling. This paper was published in the Journal of Internal Medicine and is presented in Appendix C.

1.2.5 Chapter 5: Understanding Chest-Related Symptoms According to Gender

The next three studies evolved from insights gained from the independent study of the comprehensive exam process (not included in this thesis). By opening the "black box" of CAD knowledge construction, it was apparent that there were gaps in CAD knowledge, and biases that have been inherently embedded over the past half century particularly among symptoms in women. To overcome some of these embedded limitations, it is necessary to re-examine and re-define chestrelated symptoms in a gender-centered language. In reference to the *framework of* patient cardiac care (Figure 1), this study seeks to re-define symptoms and functionality from the perspective of a patient who has already been referred for cardiac catheterization (either through the emergency department or from a specialist/cardiologist), while developing the concept of the "symptomatic tipping" point", the incident/sensation/knowledge that persuades a patient to initiate the process for cardiac care. Using qualitative methodology, drawing on concepts from feminist epistemology and using a modified grounded theory approach, over thirty patients were interviewed to gain a deeper understanding of their symptoms and circumstances surrounding their referral for cardiac catheterization. This paper has been prepared in manuscript form for journal submission.

10

1.2.6 Chapter 6: McMaster University Symptoms in Cardiac Assessment (MUSICA) Tool

The results from the two qualitative studies, "Chapter 4: Understanding chest-related symptoms according to gender" and "Chapter 5: Patient perspectives in cardiac care according to gender" were collated and summarized to inform the cardiac symptom assessment tool, MUSICA, comprising the final study of this thesis. MUSICA in itself represents a summary of this PhD journey; it seeks to collectively assess physician perception, risk factor profile, symptomology re-defined according to gender, while incorporating patient perspective, knowledge and literacy in predicting angiographically significant disease (gold standard). In reference to the framework of patient cardiac care (Figure 1), this study seeks to assess the reconstructed inputs (risk factors, symptoms, functionality and "tipping point") prior to cardiac catheterization predictive of significant angiographic CAD. Although the tool itself is informed by qualitative methods, the analytical methodology for this study consists of univariable and multivariable linear and logistic regression modelling. This paper has been prepared in manuscript form for journal submission.

11

1.2.7 Chapter 7: Discussion

Although each chapter is has a discussion section respective to the specific study, this chapter will seek to provide an overview of all the studies in the thesis and how they relate to progressing knowledge forward.

1.2.8 Chapter 8: Conclusions

The last and final chapter of this thesis will discuss some broad conceptual conclusions summarizing the route of this journey.

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Chapter 2: Literature Review

2.0 Literature Review

2.1 Cardiovascular Disease Mortality

Cardiovascular disease is the leading cause of mortality and morbidity for over half of the past century in the western world and by 2020 it will be the leading cause of death worldwide (Michael Marmot, Friel, Bell, Houweling, & Taylor, 2008; Mathers & Loncar, 2006). The current trends indicate a decline for the past three decades in CVD mortality rates in North America and Europe; however CVD mortality rates have been climbing in middle-income countries, including Eastern Europe, India and China (Pilote et al., 2007; Tunstall-Pedoe et al., 1994). Historically in westernized countries, men have higher rates of CVD mortality than women (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; M. G. Marmot & Bell, 2009; Mathers & Loncar, 2006; Tunstall-Pedoe et al., 1999). However, in recent times the gap between the sexes has been narrowing and in some western countries CVD mortality rates among women have even surpassed those of men (L. Mosca et al., 2000; Pepine, 2004; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006). To exemplify these trends, specifically in the United States, since 1984 CVD mortality rates among women have exceeded those in men, and in 2005, women represented 52.6% of all CVD deaths (American Heart, 2009). Similarly in Canada, comparable trends have been observed. For the past 25 years,

15

PhD Thesis

CVD has been the leading cause of death among Canadian men and women, historically claiming more lives among men than women (Pilote et al., 2007; Public Health Agency of, 2009a).

With the advent of improved diagnostic technology, advances in prevention and treatment, the CVD mortality rate among Canadians has been steadily declining (Pilote et al., 2007; Public Health Agency of, 2009a; Statistics, 2010). These improvements in cardiac care are linked to a steady decline in the CVD mortality rate. However, there has been a sharper decline in CVD deaths observed among Canadian men than women, narrowing the gap between the sexes, and since 1997 the number of CVD deaths between men and women have been approximately equal (Heart and Stroke Foundation of Canada et al., 2003). From the year 2000 to 2004, cumulatively 370.861 Canadians died from CVD: 184.282 men compared to 186.579 women (Public Health Agency of, 2009a). The annual number of CVD deaths in this period decreased by 4.9% among all Canadians; CVD deaths among men fell 5.5% compared to slightly less of a decline among women, 4.3% (Public Health Agency of, 2009a). The age-standardized mortality rates declined from the year 2000 to 2004 by 16% in both sexes from 268 to 224 CVD deaths per 100,000 in men compared to 164 to 138 CVD deaths per 100,000 in women (Public Health Agency of, 2009a). There are regional differences in mortality rates within Canada, with the highest rates of deaths attributed to CVD observed in Newfoundland and Labrador, and the other Atlantic provinces, and the sex difference between men and women remained (Filate, Johansen, Kennedy, & Tu, 2003).
2.2 Coronary Artery Disease Presentation

Specifically within CVD, coronary artery disease (CAD) symptoms can vary from silent ischemia to acute coronary syndrome (ACS). ACS covers a broad spectrum of pathologic conditions that include acute myocardial infarction (AMI), unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). Traditionally the risk factors, symptom presentation and treatment process for ACS was assumed to be equal between the sexes, however a multitude of studies have demonstrated sex/ gender differences in various stages of the disease process, including onset of disease, access to health services and differences in referral and preferences for cardiac procedures (Alter, Navlor, Austin, & Tu, 2002; S. S. Anand et al., 2005; Beery, 1995; Bell et al., 1995; DeVon & Zerwic, 2002; Douglas & Ginsburg, 1996; Ghali et al., 2002; Glaser et al., 2002; Grundy et al., 2001; Hochman et al., 1999; Kreatsoulas, Natarajan, Khatun, Velianou, & Anand, 2010; Lerner & Kannel, 1986; Malenka et al., 2002; Miller et al., 2001; Roger et al., 1998; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Wise, 2006). Differences between the sexes and controversies in the sex/gender literature will be highlighted in the discussion below.

2.3 Sex differences in cardiovascular disease prevalence

Although the CVD mortality rate is declining, it remains unclear if the incidence rate is also declining or if the declining mortality reflects an increase in survivorship. This discrepancy is particularly difficult to discern, as current disease surveillance systems are not structured to easily determine disease incidence; current systems require costly record linkage and determine the presence of CVD on presentation of an acute event through a probabilistic algorithm (Heart and Stroke Foundation of Canada et al., 2003; Pilote et al., 2007). Most incidence and prevalence data is informed through public health surveys such as the Canadian Heart and Stroke Surveillance System (CHSSS), the National Population Health Survey, The Canadian Community Health Survey (CCHS) in Canada, and the Behavioural Risk Factor Surveillance System (BRFSS) and National Health and Nutrition Examination Survey (NHANES) in the United States. Internationally, the World Health Organization (WHO) organized in the early 1980's the Multinational MONItoring to prospectively monitor trends in CVD and determinants in the CArdiovascular disease (MONICA) Project. The study sample consisted of ten million men and women, ages 35-64, across 37 populations in 21 countries, for a span of ten years. Over the course of 371 population years, 166,000 fatal and nonfatal myocardial infarctions were documented. Despite regional variations, men in western countries including North America, Europe and Australasia, were reported to have a higher prevalence of CVD compared with women (Tunstall-Pedoe et al., 1994; Tunstall-Pedoe et al., 1999). However, in a study analyzing data from 1988

PhD Thesis

and 1998 in the United States, the incidence rates of fatal and non-fatal coronary disease (myocardial infarction, sudden death or any CAD) declined in men and vounger persons and remained stable or increased in women and older persons (Arciero et al., 2004). The relationship between sex and age in CAD is important to consider; despite being the leading cause of death among women of all ages, the incidence of CAD varies greatly between the sexes according to age and not accounting for this relationship has likely contributed to the perception that CAD is a "man's disease". Specifically, the incidence of CAD in premenopausal women is lower than men, but rises steadily after the fifth decade and nearly equalises between the sexes by the seventh decade of life (Bairey Merz et al., 2006; Grundy et al., 2001; Lerner & Kannel, 1986; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006; Smith et al., 2001). It is likely that the delayed onset of the disease has reinforced the perception that CAD is a man's disease by estimating an overall lower risk for CAD. The temporal trend of CAD prevalence is rising among women, and declining among men (Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006; Stramba-Badiale et al., 2006). It is postulated that this is due to the declining rate of MI among younger men with a concomitant increase among older women (Arciero et al., 2004; D. S. Lee et al., 2009; Stramba-Badiale et al., 2006).

PhD Thesis

2.4 Sex Differences in CAD Risk Factors

Mortality statistics indicate that by the mid 1940's in the United States, death from CVD was escalating sharply and the United States Public Health Service decided it was imperative to undertake a large-scale study to investigate this This growing concern eventually led to the conceptualization of the further. Framingham Heart Study. The Framingham Heart Study, initiated in 1948, was the first CAD prospective cohort study that developed a framework to systematically follow a cohort of 5,209 men and women to identify the precipitating conditions/factors that eventually develop into CAD, working with the underlying assumption that it is unlikely that chronic diseases have a single causal agent. The contributions of the Framingham Heart Study have been momentous in cardiology; over 1.100 papers have been published and currently the study is following the grandchildren of the original cohort (Generation III Cohort). Today, the Framingham Heart Study is arguably most recognized for identifying and coining the term "risk factors" which include hypertension, elevated cholesterol, smoking, obesity, diabetes and physical inactivity. The risk factors identified by Framingham are currently referred to as the "traditional" risk factors and can be classified as modifiable and non-modifiable risk factors. The identification of the risk factors led to the advancement of the concept of "preventative medicine"; by treating or modifying the risk factor(s), one could "prevent" the disease from occurring. The Framingham Heart Study is internationally recognized for their risk factor prediction charts and risk factor scoring tool which is designed to help estimate an individual's risk of developing CAD based on their risk factor profile.

Despite their immense contribution to the knowledge of risk factors and development of CAD, unfortunately some of the initial biases and assumptions (which will be explored later in this thesis) have also infiltrated the scoring charts and today, the Framingham risk score has been particularly criticized for underestimating risk among low-scoring women and among some ethnic groups (L. Mosca, 2007). As the prevalence of CAD varies between men and women across age ranges, not surprisingly the distribution of CAD risk factors also varies between men and women across age ranges and failure to consider these differences may have contributed to the belief that women are less likely to suffer from CAD compared to men (Alter et al., 2002; L. Mosca, 2007). In a recent paper by Lee et al (D. S. Lee et al., 2009), examining temporal trends in risk factors among Canadians, the traditional risk factors, hypertension, diabetes, obesity are all on the rise, among both men and women, although current smoking is declining in both sexes. This section will discuss some sex/gender differences in the most common CVD (traditional) risk factors.

2.4.1 Hypertension

Historically, hypertension was the first identified cardiac risk factor and the importance of maintaining a healthy blood pressure has been well-established in the medical literature. Despite this, hypertension is considered the leading risk factor

for death in the world, causing an estimated 7.5 million deaths worldwide, each year (Danaei et al., 2011; Stevens, Mascarenhas, & Mathers, 2009; Wilkins et al., 2010). Surveillance of hypertension at a population level is an important tool for prevention and control, however there are challenges associated with trying to establish hypertension prevalence rates. Symptoms associated with hypertension are predominately "silent" or asymptomatic, and so, self-reported measurements are often unreliable and/or underreported. The National Population Health Survey (NPHS) (conducted by Statistics Canada), established in 1996 that the overall prevalence of hypertension amongst Canadians was 10%; 12% for women and 9% for men (Canada, 1998; Carew, Molnar-Szakacs, & Walsh, 1999). However the NPHS relied largely on self-reported data and is considered a conservative estimate of the population prevalence of hypertension. Since then, the reported prevalence rate of hypertension has nearly doubled in both men and women (D. S. Lee et al., The most recent nationwide population survey, the Canadian Health 2009). Measures Survey (CHMS), collected direct measures of blood pressure from a representative sample across Canada and found that the overall prevalence of hypertension among Canadians in 2007-2009 was 19%, with nearly identical prevalence rates in both men and women (19.7% in men and 19.1% in women) (Wilkins et al., 2010). The prevalence of hypertension increases with age in both men and women; among individuals 20 to 39 years hypertension was reported in 2% of the population, rising to a prevalence of 18% by age 40 to 59 years, and by

age 60 and older, over half of the population (53%) was found to be hypertensive (Wilkins et al., 2010).

Hypertension is defined as a systolic blood pressure >140 mmHg or diastolic blood pressure >90mmHg, and it increases overall CVD risk by two to three fold (Heart and Stroke Foundation of Canada et al., 2003; Wolf-Maier et al., 2003), independently of the other CVD risk factors. Although hypertension is considered independently an important risk factor for CVD, atherosclerosis, stroke and renal disease, it is often associated with obesity, physical inactivity, alcohol consumption, diabetes and dyslipidemia (Heart and Stroke Foundation of Canada et al., 2003). Prehypertension, defined as a systolic blood pressure of 120 to 139 mmHg or a diastolic blood pressure of 80 to 90 mmHg (Wilkins et al., 2010), is normally not medically treated however this is subject to much debate as it is highly predictive of hypertension (Rust & Rao, 1996; Shields & Tiepkema, 2006; Wilkins et al., 2010) and adverse CVD events (Vasan et al., 2001). At this time, prehypertensive individuals are strongly advised to make lifestyle modifications to their diet, alcohol consumption, weight, smoking, exercise and stress to help prevent hypertension (Wilkins et al., 2010). The CHMS study found that although 61% of Canadian adults had blood pressures in the normal range, 20% had blood pressure values in the prehypertensive category, and men had a higher likelihood of prehypertension than women (25% vs. 15%, respectively) (Wilkins et al., 2010). Although the significance of prehypertension is unclear at this time, it may be important to note that among individuals over age 60, there are equal numbers of individuals with normal blood

pressure and prehypertension (23% versus 24% respectively) (Wilkins et al., 2010). However, since the long-term outcome of individuals with prehypertension is currently unknown, following the prehypertensive group warrants future research.

The prevalence of hypertension between the sexes varies according to age; among younger individuals (<60 years) women have lower mean systolic blood pressure than men, however women over age 60 have higher mean systolic blood pressure than men (126.9 mmHg in women age 60-79 compared to 122.4 mmHg in men age 60-79, p<0.05) (Wilkins et al., 2010). This age-sex interaction has been reported across many studies (assessed by both self-reported and direct blood pressure measures) and the Women's Ischemia Syndrome Evaluation (WISE) study investigated whether the relationship between hypertension is modified by age in women (Gierach et al., 2006). Among women undergoing coronary angiography, premenopausal women had a lower mean systolic blood pressure (132 mmHg versus 139 mmHg, p<0.0001) and lower pulse pressure (54mmHg versus 62 mmHg, p<0.001) compared to post-menopausal women (Gierach et al., 2006). Interestingly, elevated systolic blood pressure was prognostically a significant risk factor for CAD in premenopausal women (p=0.002), but not postmenopausal women (p=0.13) (Gierach et al., 2006). Currently it remains unclear if hypertension is a different disease process in younger women compared to older women or whether it is modified or confounded by other unmeasured factors.

The INTERHEART study, a case-control study which examined the effect of risk factors among patients with acute myocardial infarction (AMI) in 52 countries,

found an overall higher prevalence of hypertension among women compared to men (28.3% women versus 19.7% men). Among patients with AMI, the differences between the sexes were accentuated (53.0% women compared to 34.6% men). Further, there were dramatic differences according to ethnicity in the prevalence of hypertension. For example, the population-attributed risk (PAR) of hypertension on AMI was highest in both men and women of Southeast Asian and Japanese ethnicity (PAR= 34.3% among Southeast Asian and Japanese men compared to 56.3% among Southeast Asian and Japanese women) and lowest among Middle Eastern men (PAR=5.8%) and Western European women (PAR=25.9%) (Yusuf, Hawken, Ounpuu, et al., 2004). Despite ethnicity, hypertension contributed to the PAR in women to a greater degree compared to men (29.0% vs. 14.9%) even when adjusted for other eight other risk factors (D. S. Lee et al., 2009; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsev, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006; Yusuf, Hawken, Ounpuu, et al., 2004). Consistent with Canadian trends, the difference in hypertension between the sexes has been largely attributed to the higher prevalence of hypertension among older women (D. S. Lee et al., 2009; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006; Yusuf, Hawken, Ounpuu, et al., 2004; Yusuf, Hawken, Ounpuu, et al., 2004).

2.4.2 Smoking

The association between tobacco smoking and adverse cardiac events was firmly established as a CAD risk factor by the Framingham Heart Study (Lerner & Kannel, 1986) and since then has been regarded as the single most preventable cause of death (due to CVD and cancer). Traditionally, the prevalence of cigarette smoking is higher among men compared to women, worldwide (Office on Smoking and Health, 2001; Stramba-Badiale et al., 2006; Yusuf, Hawken, Ounpuu, et al., 2004). Despite much research and attention devoted to this potent risk factor since the 1950's, the Surgeon General of the United States did not include much information on the effects of smoking in non-pregnant women until the second official report was released in 1980. Smoking peaked for men in the 1960's and the rates for women did not begin to decline until the late 1970's. At the time of the first report's release, most studies informing the Surgeon General's recommendations were based on studies comprised almost exclusively of men and as the evidence was beginning to accumulate, a preface to the 1980 report was appended entitled, "The Fallacy of Women's Immunity" (Office on Smoking and Health, 2001). The implication of this delay is important as smoking-attributable mortality reflects the smoking behaviour of the population two to three decades earlier. Today, deaths due to CVD among women have yet to significantly decrease (Pilote et al., 2007). Although women and men share many of the same smoking related risks including CVD, cancer and emphysema to name a few, women also experience unique smoking-related diseases such as CVD and stroke related to pregnancy, menstrual function, oral contraceptives and hormone-replacement therapy use (Office on Smoking and Health, 2001; Pilote et al., 2007). The Atherosclerosis Risk in Communities (ARIC) study recruited 15,792 men and women from four geographically distinct communities in the United States and found that smoking was a significantly stronger predictor of CAD in women compared to men (Hazard Ratio HR =2.95 versus 1.55, p<0.01, respectively) and was independently biologically supported with distinct gender differences in the intimal medial thickness of the extracranial carotid arteries, which is a well-established proxy marker for CAD (Richey Sharrett, Coady, Folsom, Couper, & Heiss, 2004).

Historically, cigarette smoking has always been more prevalent among men however smoking prevalence rates are declining. Despite declining rates, the sex/gender gap has remained constant in North America. Great effort has been dedicated to smoking cessation, including pharmacologic and population-level interventions (i.e. workplace programs, government policies, media campaigns, and taxation, to name a few) and these efforts have experienced some success in North America. Specifically in Canada, smoking prevalence in 1994 was 25.5% among men compared to 23.3% in women; in 2005 smoking had decreased to 19.7% among men and 16.7% among women, resulting in a 23% and 28% relative change among men and women respectively (p=0.006) (D. S. Lee et al., 2009). This decreasing trend has been observed among across all age groups (D. S. Lee et al., 2009). However, smoking prevalence rates vary significantly according to age, and in Canada smoking prevalence peaks in the age group 20 to 29 years in both men and women (37.3% in men versus 30.9% in women) (Tanuseputro et al., 2003). Of particular concern is the slightly rising prevalence of smoking among teenage girls age 12 to 19 (19.9% girls compared to 17.7% boys) (Tanuseputro et al., 2003). However, by age 55 and older in both sexes, the prevalence of smoking is half of the 20 to 29 age group (Pilote et al., 2007; Tanuseputro et al., 2003). There may be multiple reasons for this decline including successful smoking cessation and healthy survivor benefit. The high prevalence of smoking among the young age group is particularly concerning especially among women, as cardiovascular mortality in the less than 50 age group is largely attributed to smoking (Office on Smoking and Health, 2001).

Smoking prevalence rates have been observed to vary geographically within Canada and worldwide. Specifically in Canada, smoking prevalence rates are highest in Nunavut, the Northwest Territories, Quebec and the Atlantic provinces (Tanuseputro et al., 2003), with a higher prevalence among men. The robustness of the smoking trend in men is observed worldwide; despite regional variations, the prevalence of smoking is consistently higher among men (Tunstall-Pedoe et al., 1999; Yusuf, Hawken, Ounpuu, et al., 2004). Geographic differences in smoking prevalence among women however can vary dramatically, ranging from a low of 7.1% among South Asian women compared to 40.7% among women in Australia and New Zealand (Yusuf, Hawken, Ounpuu, et al., 2004; Yusuf, Hawken, Ounpuu, et al., 2004). There are regional differences in smoking prevalence rates observed also among men although they do not vary to the same degree as in women (i.e. smoking

prevalence rates range from a low of 30.9% among North American men compared to 51.4% of Middle Eastern men) (Yusuf, Reddy, Ounpuu, & Anand, 2001). It is reasonably well-established that smoking is more socially acceptable among men compared to women worldwide (Yusuf, Hawken, Ounpuu, et al., 2004). Yet despite regional differences, the overall prevalence of smoking among controls was substantially higher in men compared to women worldwide (33.0% versus 9.3%, respectively) (Yusuf, Hawken, Ounpuu, et al., 2004). There is much opportunity to thwart further increases in smoking worldwide.

One of the strongest predictors of smoking is social and economic disadvantage. An inverse social gradient has been observed in smoking prevalence rates; as income decreases, smoking prevalence rates increase (Kreatsoulas et al., 2010; D. S. Lee et al., 2009). This trend has also been observed among single or divorced parents, the unemployed and those with low levels of education (Kirkland, Greaves, & Devichand, 2004; D. S. Lee et al., 2009; Pilote et al., 2007; Watson et al., 2003). Smoking prevalence is nearly threefold higher among women who have 9 to11 years of education compared to those have 16 years of education or higher (32.9% versus 11.2%, respectively) (Office on Smoking and Health, 2001). Targeting socially disadvantaged groups may improve smoking cessation efforts.

2.4.3 Diabetes Mellitus

Adult onset diabetes mellitus, also referred to as type 2 diabetes, is also a well-established risk factor in the development of CVD. People with diabetes have a

PhD Thesis

two to four-fold greater risk of developing CVD, and CVD is the leading cause of morbidity and mortality among diabetics (Pilote et al., 2007). Diabetes is also a significant risk factor in the development of other CVD risk factors and related disease conditions including hypertension, stroke and vascular disease (Heart and Stroke Foundation of Canada et al., 2003; Pilote et al., 2007).

Diabetes is a highly prevalent disease with over 285 million people affected worldwide and by the year 2030, this number is expected to reach 438 million (International Diabetes Federation, 2006). Traditionally the prevalence of diabetes was lower in the developing world, however these trends have been rapidly changing and many of the developing countries now face challenges with dramatic increases in the prevalence of diabetes, including Southeast Asia, Africa and the Middle East (International Diabetes Federation, 2006; Pilote et al., 2007; Yusuf, Hawken, Ounpuu, et al., 2004). In the United States, over 25 million people or 8.3% of the population have diabetes. In Canada, similar trends are observed, where approximately 1.8 million people are diagnosed with diabetes, a prevalence rate of approximately 5.5% (Public Health Agency of, 2009b). According to the Canadian National Diabetes Surveillance System, the prevalence of diabetes is greater in men compared to women (5.8% men versus 5.2% in women) (Public Health Agency of, 2009b) and has been increasing among Canadians of all ages (D. S. Lee et al., 2009; Public Health Agency of, 2009a). From 1994 to 2005 in Canada, there is an overall increase of 52% in men and 37% increase among women (D. S. Lee et al., 2009). As with many of the other traditional CVD risk factors (with the exception of smoking)

PhD Thesis

the prevalence of diabetes increases with age in both men and women (Heart and Stroke Foundation of Canada et al., 2003; D. S. Lee et al., 2009). Along with the myriad of health concerns that independently affect people with diabetes, women with diabetes are at especially higher risk for CVD than men with diabetes, often with more co-morbidities (Hu et al., 2001; C. H. Lee et al., 2008; Pilote et al., 2007; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Wise, 2006; Yusuf, Hawken, Ounpuu, et al., 2004). The pronounced risk of CVD among women with diabetes has recently been supported by several meta-analyses (of prospective studies). A meta-analysis by Lee and colleagues (2000) report a relative risk RR= 2.58 (95% CI 2.06-3.26) in diabetic women compared to non-diabetic women which was significantly higher even when compared with diabetic men (RR=1.85, 95% CI 1.47-2.33) (C. M. Y. Lee, Huxley, Wildman, & Woodward, 2008). Similarly in a metaanalysis of 447,064 patients, an increased risk of CVD mortality was observed among diabetic women; women had RR=3.5 (95% CI 2.70- 4.53) increase in CVD mortality compared with non-diabetic women and diabetic men (RR= 2.06, 95% CI 1.81-2.34) (Huxley, Barzi, & Woodward, 2006). The relationship between diabetes in women is especially marked among young women, eliminating the "female advantage" of being at lower risk for CVD compared to young men (Kreatsoulas et al., 2010; Pilote et al., 2007; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006).

Several biological mechanisms have been postulated to play a role in the sex differences observed, including changes in endothelial dysfunction, dyslipidemia, loss of vasodilation and thrombosis, each believed to explain some of the sex differences in CVD mortality among patients with diabetes (Pilote et al., 2007; Sowers, 1997). However, these mechanisms are difficult to discern from diabetes as they interact with other CVD risk factor processes including dyslipidemia, obesity, physical inactivity and hypertension (Pilote et al., 2007; Sowers, 1997).

There also appears to be a wide variation in prevalence rates among different ethnic groups. The INTERHEART study observed that although diabetes is an overall potent risk factor for CAD, there is great variation between world regions, particularly according to sex. For example, the prevalence of diabetes among controls in women was 8.0% compared to 7% among men. However among the patients that experienced an AMI, 26% of women were diabetic compared to 16% of men, OR= 4.3 (95% CI 3.5-5.2) in women compared to OR=2.7 (95% CI2.4-3.0) in men (Yusuf, Hawken, Ounpuu, et al., 2004). Marked differences were also observed between ethnic groups, with PAR's varying from 7 % among Australian and New Zealanders, up to a PAR of 21% among South Asians and Japanese people (Yusuf, Hawken, Ounpuu, et al., 2004). Ethnic variation has also been observed within countries including the United States and Canada, where in the United States, the prevalence of diabetes is 7% among non-Hispanic whites, 8% among Asian Americans, 13% in non-Hispanic blacks and 12% in Hispanics) (Diabetes Facts, In Canada, 80% of the total prevalence of diabetes is comprised from 2011).

populations that are at higher risk for type 2 diabetes including people of Aboriginal, Hispanic, Asian, South Asian and African descent (Arto, Philip, Scot, & Jeffrey, 2004).

2.4.4 Dyslipidemia

The abnormal lipoprotein cholesterol profile is a well-known predictor of atherosclerosis, CAD, stroke, CVD and peripheral vascular disease, and is often associated and accentuated in the presence of diabetes, hypertension, smoking and obesity (Connelly, Stachenko, MacLean, Petrasovits, & Little, 1999). The traditional abnormal cholesterol profile typically consists of elevated levels of total cholesterol, low density lipoprotein (LDL) and/or triglycerides, and/or decreased levels of high density lipoprotein (HDL). Dyslipidemia is a significant risk factor in all populations and it is reported that 56% of the global CVD is attributed to elevated cholesterol (Pilote et al., 2007). Likely coinciding with the higher prevalence of the other traditional risk factors, dyslipidemia is particularly prevalent in western countries. The Canadian Population Heart Health Survey reported that 45% of men and 43% of women had a total plasma cholesterol level above the desired level (5.2 mmol/L), while 30% of men and 27% of women were in a moderate risk group (5.2 - 6.1)mmol/L) and 18% of men and 17% of women were in the highest risk group (≥ 6.2 mmol/L) (Plotnikoff, Hugo, Wielgosz, Wilson, & MacQuarrie, 2000). Similar to many of the risk factors, the prevalence of elevated total blood cholesterol in women rises with age, and by age 55 women are reported to have higher concentrations than

men. However, there is some controversy regarding the associated CVD risk with the lipid profile; some studies suggest that a high total cholesterol in women is not considered as potent of a CVD risk factor as it is in men (Bass, Newschaffer, Klag, & Bush, 1993). Rather, the specific combination of low HDL and elevated triglycerides has been reported to increase a women's risk of CVD mortality ten-fold (Austin, 1998; Bass et al., 1993; La Rosa, 1988). Similar to many of the traditional CVD risk factors there is an interaction of the lipid profile according to age. Total cholesterol levels are often higher in young men, however levels peak in women between ages 55 and 65, almost a decade later than men (Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006; Stramba-Badiale et al., 2006) where sex differences in HDL diminish with advancing age.

Low-density Lipoprotein (LDL)

Elevated LDL has been considered the primary culprit in the development of atherosclerosis and CVD, and lowering LDL with statin therapy has been a primary target in preventative therapy for CVD. Elevated LDL levels have been found to be more predictive of CAD risk in men than in women, and premenopausal women in particular have been found to be at lowest risk (Bass et al., 1993). The CPHHS found that 32% of women have elevated LDL (>3.4 mmol/L) (Plotnikoff et al., 2000). An age-sex interaction demonstrates that women have lower LDL levels in the premenopausal years compared to equal age male counterparts. However, after age 50, LDL levels plateau in men and increase in women, surpassing the concentrations seen in men (Johnson et al., 1993). It is believed that the interaction between elevated LDL in postmenopausal women is a result of diminishing levels of estrogen influencing the decreased clearance of LDL cholesterol from the serum (Pilote et al., 2007).

High-density Lipoprotein (HDL)

Low levels of HDL is an important predictor of CVD risk in both men and women, however low HDL is a particularly potent predictor among women (Connelly et al., 1999; MacLean et al., 1999; Plotnikoff et al., 2000). This was relationship was unexplored for years as many of the early landmark cholesterol clinical trials, including the British Regional Heart Study, the Lipid Research Clinics Coronary Primary Prevention Trial and the Multiple Risk Factor Intervention Trial, collectively enrolled over 15,000 men and no women (Gordon, Knoke, Probstfield, Superko, & Tyroler, 1986; "Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group," 1982; Pocock, Shaper, Phillips, Walker, & Whitehead, 1986), resulting in profound gaps in knowledge while fuelling the perception that "CAD is a man's disease". Since the interaction of age on many of the CVD risk factors was observed, exploration of cholesterol levels by age also revealed age-effects. Specifically, HDL levels on average are 0.25mmol/L higher in premenopausal women than in men, which may contribute to the lower incidence of CVD in premenopausal women. The

CPHHS study found that 4% of Canadian women have depressed HDL levels (Plotnikoff et al., 2000). The Lipid Research Clinics Prevalence Mortality Follow-up Study found that a 0.025mmol/L increase in HDL was associated with a 4.7% reduction in CVD mortality in women (p=0.002) compared to a 3.7% reduction among men (p<0.001) (Gordon et al., 1989). Current clinical guidelines urge physicians to aggressively treated decreased HDL, particularly in women (Lori Mosca, Appel, et al., 2004).

Triglycerides

For over 40 years the role of triglycerides as a CVD risk factor was more elusive compared to the well-defined role of LDL, HDL and total cholesterol. Data was often conflicting and similar to many of the other lipid studies, study populations consisted overwhelming of men. The relationship between triglycerides and CVD has recently been more firmly established and elevated triglycerides are an independent risk factor for CVD for both sexes (Pilote et al., 2007). A meta-analysis of 17 prospective studies consisting of 46,413 men and 10,864 women found that elevated triglycerides, adjusted for elevated HDL posed a 32% (RR= 1.32, 95% CI 1.26-1.39) increase in CVD risk in men compared to a 76% (RR=1.76, 95% CI 1.50-2.07) increase in women (Hokanson & Austin, 1996). When elevated triglycerides were adjusted for other variables including elevated HDL despite attenuating the relative risk, the relationships remained statistically significant (RR=1.14, 95% CI1.05-1.28 in men compared to RR=1.37, 95% CI 1.13-

1.66 in women) (Hokanson & Austin, 1996). Consistent with the lipid profiles of LDL, HDL and other CVD risk factor, there appears to be an interaction with age, where higher mean concentrations of elevated triglycerides have been repeatedly observed among post-menopausal women (Connelly et al., 1999).

Apolipoprotein B/ Apolipoprotein A 1 Ratio

More recently, the ratio of Apolipoprotein B (ApoB), a component involved in the transport of atherogenic lipoproteins, and Apolipoprotein A1 (ApoA1), a key component in the transport of antiatherogenic HDL, referred to as the ApoB/A1 ratio, has been identified as a powerful predictor and perhaps better marker than traditional cholesterol lipids for risk of CVD. More recent trials have further supported the predictive power of the ApoB/A1 ratio as a superior predictor of fatal stroke, MI and CVD compared to other lipid measures (Walldius & Jungner, 2005). Among the mounting evidence for this predictor, the INTERHEART study, which identified risk factors predictive of AMI in 52 countries in the world, identified ApoB/A1 as "the most important risk factor in all geographic regions" (Yusuf, Hawken, Ounpuu, et al., 2004). The ApoB/A1 ratio demonstrated a graded relation with AMI and had no evidence of a threshold (OR= 4.7, 99% CI 3.9-5.7), comparing highest versus lowest deciles of ApoB/A1 ratio). Further, the ApoB/A1 ratio, in concert with current smoking were found to be the two strongest predictors of AMI. independent of geographic regional differences (Yusuf, Hawken, Ounpuu, et al.,

2004). An interaction of age with ApoB/A1 ratio was also detected in both men and women; the odds of AMI was higher in both younger men and women with elevated ApoB/A1 (PAR=58.9%, 99% CI 50.9-66.5) in young compared to (PAR=43.6% 99% CI 36.6-50.8) in older patients (Yusuf, Hawken, Ounpuu, et al., 2004).

2.4.5 Excess weight: Overweight and Obesity

As with many of the CVD risk factors there is great overlap and co-presence among them and excess bodyweight has been strongly associated with diabetes, hypertension, hypercholesterolemia, cancers and musculoskeletal disorders causing an estimated 3 million deaths worldwide (Ezzati, Lopez, Rodgers, Vander Hoorn, & Murray, 2002; Finucane et al., 2011; Ni Mhurchu, Rodgers, Pan, Gu, & Woodward, 2004; Organization., 2009; Prospective Studies et al., 2009). The relationship between excess weight and a higher CVD risk has been established for some time (Heart and Stroke Foundation of Canada et al., 2003; Kannel, D'Agostino, & Cobb, 1996; Organization., 2009; Rexrode, Manson, & Hennekens, 1996). The most common measure of excess weight is the body mass index (BMI) which calculates weight in relation to height (BMI=weight/height⁻²) and classifies individuals into underweight, normal weight, overweight and obese categories. Although BMI ranges are not standardized per se, the values set by the World Health Organization (WHO), adopted by Health Canada (Belanger-Ducharme & Tremblay, 2005; H. Canada., 2003) classify obese adults with a BMI \geq 30.0 kg m⁻² and overweight as BMI

25.0 -29.9 kg m⁻². There are inherent flaws in the prevalence estimates of BMI as most data is accumulated from various national surveys relying on self-reported data. Further, it is well documented that prevalence data based on self-reported height and weight data are grossly underestimated compared to measured data (Belanger-Ducharme & Tremblay, 2005). Specifically, self-reported weight data is commonly underestimated by women, and height data is often overestimated in men, making gender-specific analysis of self-reported data particularly difficult (Belanger-Ducharme & Tremblay, 2005).

Using measured anthropometric data comparing trends from the 1970-72 National Canada Survey data to the Canada Heart Health Survey (CHHS) of 1988-1992, the prevalence of obesity increased from 8% to 13% in men, and 13% to 15% in women. The proportion of overweight individuals also increased in both men and women during the same time period; 47% to 58% in men and 34% to 41% in women (Belanger-Ducharme & Tremblay, 2005). The 2003 Canadian Community Health Survey (CCHS) using self-reported data classifies 41% of men and 26% of women as overweight and 16% of adult men and 14% of adult women obese. Despite discrepancies in self-reported prevalence of excess weight between the CHHS and the CCHS, the high prevalence of excess weight is undisputable. The prevalence of obesity increases until the fifth decade of life, peaking between age 55-64 among men and women (20%) and declines sharply as age increases beyond 65 (Belanger-Ducharme & Tremblay, 2005; S. Canada. & Information., June 2004.) regardless of ethnicity (Tremblay, Perez, Ardern, Bryan, & Katzmarzyk, 2005).

There are regional differences in obesity prevalence rates within Canada, the highest rates reported in Nunavut (26%), the Northwest Territories (23%) and Atlantic Canada (19% -21%), and the lowest levels of obesity reported in Quebec (13%) and British Columbia (13%) (S. Canada. & Information., June 2004.; Tanuseputro et al., 2003). Rural communities have higher prevalence rates of overweight and obese individuals than the national average and in contrast, large urban and metropolitan areas (including Toronto, Montreal and Vancouver) have prevalence rates of obesity and overweight less than half the national average (Belanger-Ducharme & Tremblay, 2005). Northern remote communities, characterized by a high proportion of Inuit and Aboriginal peoples, have the highest obesity rates in Canada (Belanger-Ducharme & Tremblay, 2005; Tanuseputro et al., 2003). In the Study of Health Assessment and Risk Evaluation of Aboriginal Peoples. known as the SHARE-AP Study, 62% of Aboriginal men and 56% of Aboriginal women had obese BMI profiles compared to 32% Canadian men and 24% Canadian women of European descent, an absolute difference over 30% (p<0.01) (Sonia S. Anand et al., 2001). Similarly, the 2000/2001 and 2003 CCHS self-reported survey describe almost 50% of whites (representing approximately 80% of the study population) as overweight. The lowest rate of overweight individuals was reported among East/Southeast Asians (22%) and the highest rates of overweight among offreserve Aboriginal people (63%). Among those who fall into the obese BMI category, these differences were further magnified where only 3% East/Southeast Asians reported obesity compared to 17% of Whites and 28% of Aboriginal people, with parallel distributions among both sexes (Tremblay et al., 2005).

High obesity rates have often been associated with low socio-economic status. Among Canadians, the Yukon First Nations and Inuit communities have the highest obesity prevalence rates while also the lowest education and income strata in Canada (Kuhnlein, Receveur, Soueida, & Egeland, 2004; Tanuseputro et al., 2003). The socio-economic relationship in obesity is well documented in Canada (and other westernized countries) where the highest absolute rate of obesity is observed among the lowest income group (D. S. Lee et al., 2009; Tanuseputro et al., 2003). However, low income appears to be protective from being overweight, but not obesity (Tremblay et al., 2005). Although the absolute rates of obesity remained highest among low-income groups, there has been a rise in obesity among all income groups, suggesting that the wealthy are not exempt from the effects of an obesogenic environment (D. S. Lee et al., 2009; Physiology, 2011; Rosengren, 2009a). In 1994, in Canada, the difference in the prevalence of obesity between the lowest income quartile and the highest income quartile was 14% versus 11% (p=0.035) and in 2005 the difference in obesity between the lowest and highest income guartile was 18% versus 15% (p=0.11) (D. S. Lee et al., 2009). In addition to low household income, low levels of physical activity and education are also powerful predictors of being overweight and obese in both men and women regardless of ethnicity in Canada (Tremblay et al., 2005). However, the repercussions of excess weight and obesity are especially concerning for CVD risk as

co-morbidities such as diabetes and hypertension have experienced the most dramatic increases among obese people (Rosengren, 2009b).

The relationship between excess weight and socioeconomic status has also been observed among previously healthy immigrants in Canada which may be confounded later by socioeconomic pressures and other co-morbidities. The prevalence of overweight and obesity was higher among long-term immigrants (greater than 11 years) than more recent immigrants (10 years or less) (Tremblay et al., 2005). The length of time since immigrant (10 years or less) (Tremblay et al., 2005). The length of time since immigrant women, and specifically among immigrant men of Asian origin (Belanger-Ducharme & Tremblay, 2005). This relationship, where the "healthy immigrant" effect fades over time, suggests a temporal component independent of ethnicity, as it has been observed among all ethnic groups in both Canada and the United States (Cairney & Ostbye, 1999; Lauderdale & Rathouz, 2000; Tremblay et al., 2005). It has been suggested that the increase in BMI is likely due to a transition away from traditional cultural diets and a more sedentary lifestyle (Tremblay et al., 2005).

Not surprisingly, ethnic differences in the prevalence of excess weight have been observed around the world. In a recent study that analysed BMI among 9.1 million patients across 199 countries, the mean BMI increased by 0.4kg/m² per decade (95% CI 0.2-06) and 0.5kg/m² per decade (95% CI 0.3 -0.7) for women, worldwide (Finucane et al., 2011). The age-standardised prevalence of obesity was 9.8% (95% CI 9.2%-10.4%) in men and 13.8% (95% CI 13.1-14.7%) in women in PhD Thesis

2008, which is nearly a two-fold increase since 1980 in both men and women (4.8% men versus 7.9% women). Despite global temporal trends in the increase of BMI and obesity, this varied dramatically by world region. For example, age-standardised BMI in 2008 was highest among men in North America (28.4 kg/m², 95% CI 27.9-28.7 kg/m²) and lowest among sub-Saharan African men and men from east, south and southeast Asia (BMI ranging from 20.6-22.9 kg/m²) (Finucane et al., 2011). Women on the other hand, faced the largest increases in BMI in Oceania (BMI increase of 1.8 kg/m² per decade) and south and central America (BMI increase of 1.3 kg/m² per decade) (Finucane et al., 2011). Despite men having a slightly lower BMI than women globally (23.8 kg/m² in men versus 24.1 kg/m² in women), BMI trends varied in parallel with national income; among high income countries, men had a higher BMI than women but had a lower BMI in low-income and middle-income regions (Finucane et al., 2011).

One of the observed difficulties with the interpretation of ethnic-specific weight data is that while prevalence of excess weight between ethnic groups is generally consistent, BMI may be a poor indicator predicting the CVD risk of excess weight among certain ethnic groups. Generally speaking, BMI offers little insight into the potential differences of abdominal weight distribution and absolute levels of adiposity. For example, BMI has been criticized for its inability to distinguish between someone with excess adipose tissue and an athlete with a high muscle mass. Further, BMI has also been criticised for not capturing ethnic-specific distributions of body weight such as Asians, who have been shown to have a higher percentage of body fat than their European/white counterparts even after adjusting for BMI (Deurenberg, Deurenberg Yap, Wang, Lin, & Schmidt, 1999; Deurenberg & Deurenberg-Yap, 2003; Deurenberg-Yap, Schmidt, van Staveren, & Deurenberg, 2000; Tremblay et al., 2005). For this reason, alternative measures of weight distribution such as waist-circumference (WC) and the waist-hip ratio (WHR) and waist to height ratio (WHtR) have been proposed. A meta-analysis comparing the pooled results of studies analysing BMI, WC, WHR and WHtR compared the discriminatory power of ROC analysis to compare their impact on CVD risk, diabetes, hypertension and dyslipidemia (Huxley et al., 2006; C. M. Y. Lee et al., 2008). The meta-analysis found that among studies conducted between 1990 and 2004 across nine countries that included 88,514 subjects, the alternate measures of central obesity, particularly WHtR predict obesity CVD risk better than BMI (Huxley et al., 2006; C. M. Y. Lee et al., 2008). Future studies should consider using one of these markers of weight-distribution in lieu of BMI.

2.4.6 Physical activity

The positive effects of physical activity on health are well-known for both men and women of all ages and include reducing CVD risk of premature mortality, hypertension, insulin resistance and diabetes, serum cholesterol, thrombogenic factors, colon cancer, and depression to name a few (Heart and Stroke Foundation of Canada et al., 2003; Office on Smoking and Health, 2001; Pilote et al., 2007; Plotnikoff et al., 2009). The Canadian guidelines recommend for adults over 18 PhD Thesis

years of age to engage in at least 150 minutes of aerobic physical activity of moderate-to-vigorous intensity per week, in bouts of 10 minutes or more and to complement this with muscle and bone strengthening exercises at least two times per week (Physiology, 2011). Similarly, the Surgeon General of the United States and the US Department of Health and Human Services recommend that a modest increase in daily activity can improve the health and quality of life, by including moderate activity such as 30 minutes of brisk walking, 15 minutes of running, or 45 minutes of playing volleyball on most, if not all days of the week (Haskell et al., 2008). However, despite these recommendations, physical activity goals are poorly met in both Canada and the United States. The NPHS of 1996/97 reported that over half of adults (57%) were physically inactive in their leisure time. Similar trends have been reported from the CCHS 2000/01 data, indicating that more than half of Canadians ages 12 and older are physically inactive (Tanuseputro et al., 2003). Overall, the prevalence of physical inactivity is greater among women than men (p < 0.05) with the greatest difference between the sexes in the youngest and oldest age groups. Physical inactivity generally increases with age in both sexes (with some exceptions) and women are more physically inactive than men in every age group (Tanuseputro et al., 2003). The link between excess weight and physical inactivity has been firmly established and not surprisingly these two trends parallel each other.

The pattern of lower physical activity levels in women than in men has been observed around the world. The ATTICA study used a validated questionnaire

which assessed the frequency, duration and intensity of physical activity during a usual week, in over 3000 randomly sampled Greek men and women. The investigators found that 52% of men and 48% of women were physically active (p<0.05) and men were more physically active than women across all age groups (Panagiotakos et al., 2008). Rates of physical inactivity were highest in the 40-49 age group (C. Pitsavos, Panagiotakos, Lentzas, & Stefanadis, 2005). Physical activity was independently associated with lower odds of having hypertension, hypercholesterolemia and depression. An inverse relationship between obesity, hypertension, hypercholesterolemia, diabetes and physical activity was reported even after adjusting for age, sex and smoking (partial rho= -0.33, p<0.001) (C. Pitsavos et al., 2005). Further, socio-demographic risk factors associated with increased physical activity include higher occupation skills, living in rural areas. unmarried, non-smoker and healthier dietary pattern (all p<0.05), across all age groups and sex (C. Pitsavos et al., 2005).

Similarly, the INTERHEART study, collected physical activity information defined as regular moderate exercise(walking, cycling or gardening) or strenuous exercise (jogging, football, vigorous swimming) for more than four hours per week, among 9459 cases (patients with AMI) and 10,851 matched controls (patients without AMI) across 52 countries. Among controls, 20.3% of men engaged in weekly exercise compared to 16.5% of women (Yusuf, Hawken, Ounpuu, et al., 2004). However among individuals with AMI, despite the sex/gender gap, the prevalence of exercise was lower in both sexes (15.8% men compared to 9.3% in

women) (Yusuf, Hawken, Ounpuu, et al., 2004).

Similarly, the Greek Study of Acute Coronary Syndromes (GREECS) Study found that among patients who had an AMI there was an inverse association between physical activity level and a cardiac biomarker (Troponin I). Physically active patients had a 53% (OR=0.53, 95% CI 0.30-0.93) less likelihood of dying during hospitalization, compared to physically inactive patients (Christos Pitsavos et al., 2008). The overall death rate among patients that were physically inactive was 4.2% compared to 2.0% of minimally active and 0% among active patients (Christos Pitsavos et al., 2008).

One of the limitations of assessing physical activity is the lack of standardization of what comprises 'physical activity' and therefore it is difficult to compare the results of studies. The most common unit used to measure energy expenditure during physical activity is the metabolic equivalent (known as a MET) and is calculated by evaluating the oxygen uptake of 3.5 millilitres per kilogram of body weight, per minute. The intensity of physical activity level is often classified according to METS (World Health, 2010). However, a multitude of physical activity assessment tools have been developed including questionnaires and scales which vary widely in their physical activity criteria including whether METs are included and what role METs may play in the tool. Despite this limitation, the importance of physical activity as a CVD risk factor is widely acknowledged and has been incorporated into guidelines around the world, including the WHO, American Heart Association, British Heart Foundation and government agencies (i.e. Centres for

Disease Control and Health Canada) to name a few (Haskell et al., 2008; Ness, 2004; Physiology, 2011; World Health, 2010).

2.4.7 Psychosocial differences in CAD according to sex

In addition to the traditional CVD risk factors, psycho-social factors, including emotional factors and chronic stress, have also been found to play an important role in the development of CAD and adverse cardiac events (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). Emotional factors include affective disorders such as major depression and anxiety, and chronic stressors include factors such as low social support, low socioeconomic status, work and marital stress to name a few (Brezinka & Kittel, 1996; Rozanski et al., 2005).

Of the emotional factors, depression in particular, is more common in patients with CAD than in the general population and over 20% of patients hospitalized for MI meet the criteria for major depressive disorder (Nancy Frasure-Smith & Lesperance, 2010; Thombs et al., 2006). There has been much support for the role of depression in heart disease as depression itself is also associated with an increased probability of developing CAD in healthy subjects (Nancy Frasure-Smith & Lesperance, 2010; Lesperance & Frasure-Smith, 2000). There is substantial evidence from the literature that there is a strong relationship between depression and CVD however the directionality of this relationship remains unclear at this time. Several studies suggest that patients (of similar CAD profile) report more chest pain intensity and severity when depressed compared to non-depressed patients (Plach, Napholz, & Kelber, 2001; Stewart, Abbey, Shnek, Irvine, & Grace, 2004; Tsouna-Hadjis et al., 1998). Also, ACS patients with depression have an increased risk for mortality and morbidity (N. Frasure-Smith, Lesperance, & Talajic, 1993, 1995; Ladwig, Kieser, Konig, Breithardt, & Borggrefe, 1991; Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002). Studies demonstrate a strong gradient between depression severity and prognosis in patients with CAD (Nancy Frasure-Smith & Lesperance, 2010; N. Frasure-Smith et al., 2000; Lesperance & Frasure-Smith, 2000; Rozanski et al., 2005). The pooled results from meta-analyses support the role of depression in the development of CAD, reporting effect sizes between 1.5-2.7 (depending mostly on definitions and statistical adjustments for covariates) (Nancy Frasure-Smith & Lesperance, 2010; Nicholson, Kuper, & Hemingway, 2006; Rugulies, 2002; Van der Koov et al., 2007; Wulsin & Singal, 2003). Further, the results from several meta-analyses also support the predictive importance of depression in patients with CAD, reporting effect sizes ranging from 1.6 -2.2 (depending on covariate adjustments) (Barth, Schumacher, & Herrmann-Lingen, 2004; Nancy Frasure-Smith & Lesperance, 2010; Nicholson et al., 2006; van Melle et al., 2004). Despite much support for the relationship between depression and CAD, there is still much caution in declaring depression a "CVD risk factor" as the biological mechanisms remain unclear or if they are mediated by a common cause such as genetic factors (McCaffery et al., 2009).

As the biological mechanism in depression and CVD remain unclear at this time, further complicating this relationship is the role of chronic stress in the development/progression of CVD, likely impacting this relationship. Chronic stressors such as low levels of social and functional support have been consistently linked to cardiac-death and all-cause mortality. This relationship has been demonstrated in a number of studies including the effect of CVD and living alone (Case, Moss, Case, McDermott, & Eberly, 1992), lack of available support (Williams et al., 1992), low emotional support (Barefoot et al., 2000; Brezinka & Kittel, 1996), marital stress (Blom, Janszky, Balog, Orth-Gomer, & Wamala, 2003; Orth-Gomer et al., 2000) and care-giving for an ill or disable spouse (Berkman, Leo-Summers, & Horwitz, 1992; Wang et al., 2007). Often the emotional factors and chronic stressors are thought of as separate entities, however they often overlap and cluster together (Rozanski et al., 2005; Yusuf, Hawken, Ounpuu, et al., 2004). The INTERHEART study developed a psycho-social index that was based on a combination of depression (versus no depression), stress at work/home, moderate/severe financial stress, one or more life events and a low locus of control (Yusuf, Hawken, Ounpuu, et al., 2004). The association of psycho-social factors was high (OR=2.51 (99% CI 2.15-2.93), adjusted for age, sex and smoking and remained a robust predictor of MI independent of geographic region or ethnicity. However, when analysed according to sex, the psycho-social factors contributed to the PAR in women to a greater extent (45.2%) compared to men (28.8%) (Yusuf, Hawken, Ounpuu, et al., 2004). Other studies also support a sex difference where women report more depression and

PhD Thesis

anxiety after a cardiac event than men (Plach et al., 2001). Although the precise mechanism of psycho-social factors in CVD remains unknown at this time, a deeper understanding of this relationship is an important area for future research.

2.4.8 Social determinants of cardiovascular disease

Among the most important advances in cardiovascular research has been the identification of risk factors and treatments developed towards modifying risk factors with the goal of preventing CVD. The INTERHEART study examined over 27,000 cases and controls from 52 countries and found that more than 90% of the PAR for AMI is explained by nine potentially modifiable individual-level risk factors (Yusuf, Hawken, Ounpuu, et al., 2004). However despite identifying individual-level risk factors and advances in the primary and secondary prevention of CVD, as is evident from this review of the literature thus far, there are marked disparities in the distribution of cardiovascular risk factors, with varying trends among populations worldwide and even within Canada (D. S. Lee et al., 2009; M. Marmot & Wilkinson, 2006). Although the underpinnings behind these disparities are currently not well understood, it is postulated that many of the individual risk factors are influenced by environmental and behavioural factors that likely interact with genetic factors throughout life. However further examination of predictors of the risk factors, or the "causes of the causes/upstream causes", including the social determinants of health, is necessary to bridge the knowledge gap in the whole chain of causation for CVD (Yusuf & Anand, 2010).

The term 'social determinants of health' is used to describe the health impact of the social environment which people share when living in a certain community (Social Determinants of Health: THE SOLID FACTS, 2003). Specifically, they include the conditions in which people are born, grow, live, work and age and are shaped by the distribution of money and resources at a global, national and local level (M. Marmot & Wilkinson, 2006; Social Determinants of Health: THE SOLID FACTS, 2003). The social determinants of health (including the health care system) are mostly responsible for health inequities between and within countries (Yusuf & Anand, 2010). Historical research has well established the impact of economic development and social organization on health (Social Determinants of Health: THE SOLID FACTS, 2003). Since the prevalence of some cardiovascular risk factors (i.e. obesity, hypertension and diabetes) are rising worldwide (Lopez et al., 2006; Social Determinants of Health: THE SOLID FACTS, 2003), it is necessary to focus efforts in understanding the role of the 'causes of the causes' or the social determinants of health to help bridge the current gap in equality. Our current concepts of how social and environmental determinants (e.g. income, education, occupation, geography) and the environment interact with health remain unclear when considering only the independent effects of individual-level risk factors (Chow et al., 2009). Further, it has been argued that analysis of individual risks may be subject to the atomistic fallacy, where the analyses of individual-level risks may be inappropriate if we are seeking to determine social/ environmental causes of illness (Berkman & Kawachi, 2000). Even within the context of preventative therapy, the social determinants of
health, including social contextual factors (i.e. education, socioeconomic status, role responsibilities, living circumstances) and psychosocial factors (i.e. coping, adjustment), play an important role in the adoption and maintenance of preventative behaviours (Berkman & Kawachi, 2000). Research to date has largely ignored the role of these "upstream" factors through which the larger social context affects individual behavioural and psychological factors (Berkman & Kawachi, 2000). These trends become even more complex when taking into account the large variation in the prevalence rates of social factors among different sex/gender and race/ethnic groups. It is likely that these social factors intersect with sex/gender and race/ethnicity contributing to disparities in health observed among these groups (Armstrong, Strogatz, & Wang, 2004). For more on the role of the social determinants in cardiovascular disease, please refer to my paper published in the Canadian Journal of Cardiology (Kreatsoulas & Anand, 2010) (Appendix A).

2.5 Differences in Cardiovascular Symptom Presentation in Women and Men

Understanding the role of the CVD risk factors is an essential component to understanding the canvas of heart disease. Some risk factors may be associated with symptoms (i.e. physical inactivity, depression) while other risk factors can be relatively symptom-less (i.e. hypertension, dyslipidemia). Presentation of symptoms can prompt people to seek medical attention for them. However most

people cannot cite their cholesterol or blood pressure values, even when being treated for it (Lori Mosca, Ferris, Fabunmi, & Robertson, 2004; Nash et al., 2003). Further, people also lack the general knowledge of most CVD risk factors (Lori Mosca, Ferris, et al., 2004; Lori Mosca et al., 2000). Rather, most people exclusively associate chest pain/discomfort, known as angina pectoris, as the cardinal (and often only) manifestation of CAD (Lori Mosca, Ferris, et al., 2004; Patel, Rosengren, & Ekman, 2004).

Early landmark studies investigating angina focused on populations of mostly European origin and found that angina occurred more often in women than in men (Dawber & Kannel, 1966; Kannel & Castelli, 1972). A recent meta-analysis analyzing the prevalence of angina across 31 countries was able to reaffirm this finding, demonstrating that the prevalence of angina is higher among women and this finding was consistent across geographic regions, over four decades (Hemingway et al., 2008). Despite this, the perception that CAD is a "man's disease" persists. There are several reasons why this perception exists and amongst them, early landmark studies reported that men had a higher incidence of myocardial infarction subsequently concluding that women "enjoyed immunity from CAD" (Kannel & Castelli, 1972). This notion gained support when early landmark cardiac catheterization studies correlated "typical angina" symptoms, the symptoms most commonly experienced in men, with angiographic disease and concluded that CAD was more evident in men (Campeau et al., 1968; Proudfit, Shirey, & Sones, 1966). Bolstering this perception further is the confounding effect of differences in

incidence rates according to age; the incidence of CAD in women is lower than men, but rises steadily after the fifth decade and nearly equalises between the sexes by the seventh decade of life (Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Ouvvumi, Sopko, & Investigators, 2006; Smith et al., 2001). Correspondingly, the distribution of CAD risk factors in men and women also varies according to age and failure to consider these differences may have contributed to the perception that women are less likely to suffer from CAD compared to men (Herrmann, 2008; Lori Mosca, Ferris, et al., 2004; Lori Mosca et al., 2000). The downstream implications of these perceptions have had a huge impact in the cardiac care of women from both a medical community and patient perspective. Even though women have a one in two lifetime risk of dving from CAD, many women and health care providers alike do not realize that CAD is the greatest health risk for women ("Assessing the odds," 1998; Lori Mosca, Ferris, et al., 2004; Lori Mosca et al., 2000). Furthermore, women are referred less than men for angiography, and receive less medical therapy and fewer invasive procedures (Bell et al., 1995; King et al., 2004; Lagerquist et al., 2001; Malenka et al., 2002; Roger et al., 2000; Roger et al., 2002; Vaccarino et al., 2005; Weintraub, Kosinski, & Wenger, 1996) even among women with acute coronary syndromes (ACS) (S. S. Anand et al., 2005; Roger et al., 2000; Vaccarino et al., 2005).

The upcoming sections will review some of these sex/gender differences, unique challenges and potential biases as they relate to and impact patients with ACS.

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2.5.1 Differences in ACS symptoms among women and men

Differences between the sexes in ACS and AMI symptom presentation have been observed and a substantial number of studies have directed their efforts to methodically assess these differences, attempting to categorize sex-specific symptoms. A review summarizing the results of 17,452 patients diagnosed with either unstable angina (UA) or AMI, concluded that despite many similarities, women typically suffer from more "atypical" symptoms than men (DeVon & Zerwic, 2002). Specifically, the authors summarize the "atypical" ACS symptoms more common in women as back and jaw pain, nausea/ vomiting, dyspnea, palpitations and indigestion (DeVon & Zerwic, 2002). However, it is important to note that there are a number of challenges in summarizing this type of data including the inability to control for possible confounding differences in baseline variables, geographical region differences, issues in methodology including differences in patient inclusion criteria and poor data collection, as most studies relied on data extraction from medical records.

Similarly, a more recent review by Patel et al (Patel et al., 2004) analysed the ACS symptoms for both men and women across fifteen studies. The most commonly reported symptom for both sexes was chest pain, however differences in symptom presentation between the sexes proved difficult to summarize across the studies. There were subtle differences even within "chest pain" where women reported more transient pain with a sharp, stabbing sensation compared to men and also used different descriptions of their chest pain, including terms such as "heaviness, pressure, tightness, squeezing in the chest" (Cunningham et al., 1989; Patel et al., 2004; Wenger, Speroff, & Packard, 1993). Despite discrepancies between studies and methodologic challenges encountered, similar to the study findings by DeVon (2002) (DeVon & Zerwic, 2002), Patel et al (2004) (Patel et al., 2004) conclude that although women experience more back pain, dyspnea, indigestion, jaw pain, nausea/ vomiting and palpitation during ACS compared to men and that men report more chest pain and diaphoresis compared to women during an MI, "the review failed to support the contention that atypical symptoms are more strongly related to ACS in women than in men" citing chest pain is the most notable symptom in men and women (Patel et al., 2004). However, the study authors also caution that patients are more likely to identify 'chest pain' as the cardinal symptom of heart disease and much attention was likely focused from their medical history interview on the presence or absence of this symptom rather than the symptom(s) that prompted the care-seeking behaviour of the patient (Patel et al., 2004).

However, there is a large body of literature, including a recent review of 69 studies describing the symptoms of ACS presentation and identified the lack of standardization of what constitutes "atypical" symptoms ACS presentation. It appears that the term "atypical" has become a catchall phrase for "different than classic MI symptoms in men, which include a constellation of symptoms usually without chest pain or discomfort" (Canto et al., 2007). The authors develop operational definitions of "typical" and "atypical" chest pain/discomfort and found more women presented with no chest pain/discomfort compared to men (37% vs.

27%, respectively) (Canto et al., 2007). This finding is particularly concerning as many ACS studies include patients based on the presence/absence of chest pain/discomfort and since more women than men have an absence of symptoms, this may be a source of bias leading to a systematic exclusion of women (Canto et al., 2007). Further, the absence of chest pain is most correlated with age rather than sex (Canto et al., 2007; Douglas & Ginsburg, 1996; Goldberg et al., 1998; Kyker & Limacher, 2002; Mehta, Rathore, Radford, Wang, & Krumholz, 2001; K. A. Milner et al., 1999; Nohria, Vaccarino, & Krumholz, 1998; Roger et al., 2000; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Wise, 2006; Vaccarino, Krumholz, Berkman, & Horwitz, 1995) and since women are generally older at time of presentation of MI, age may be a confounder of chest pain/discomfort (or absence of) in women. Support for this argument is well demonstrated in a retrospective analysis of landmark published studies (Canto et al., 2007).

Symptom studies raise some interesting questions including the importance of assessing atypical symptoms and non-cardiac pain. First, there is no standardization in data collection or in terminology of ACS in the absence of chest pain/discomfort (Canto et al., 2007; Shaw, Bugiardini, & Merz, 2009). Further, other centres of pain may not be captured in the absence of chest pain/discomfort, and they are rarely tested for their sensitivity/ specificity. Due to the nature of the ACS profile, most studies are comprised of retrospective analyses from medical records, which are plagued with inherent limitations such as incomplete records/ memories,

and a cascade of potential biases that may include the absence of the clinical historytaking of atypical symptoms.

Sex/gender-specific ACS symptomology is not well understood. Some investigators suspect that certain symptoms may occur more often in clusters or in the absence of chest pain (DeVon & Zerwic, 2002; Peterson & Alexander, 1998). Further complicating matters, atypical ACS symptoms overlap with many other diseases resulting in misdiagnosis, a delay in treatment time or referring patients for further testing. It is not surprising that the lack of clarity and understanding related to ACS symptoms in women has resulted in discrepancies in care. The follow section will review some of the landmark studies that have contributed to our current understanding of ACS symptoms in women.

2.5.2 Differences in MI presentation among women and men

Much of our current knowledge of ACS symptoms in women has been acquired through subgroup analyses of trials, not powered to determine if a sex/gender difference exists. For example, the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO) IIb trial assessed 12,142 patients, including 3662 women who presented with ACS symptoms (Hochman et al., 1999). The primary endpoint of the study consisted of a composite of death or non-fatal MI within 30 days after enrolment of being randomized to receive low-molecular weight heparin or unfractionated heparin. Patients were analyzed according to one of three groups; ACS presenting with ST

elevation MI (STEMI), ACS presenting with non-ST elevation MI (NSTEMI) and ACS presenting with unstable angina (UA). The study population represented a familiar clinical profile: at baseline women were older than men, had significantly higher incidence of diabetes, hypertension, and congestive heart failure while men had a prior history of MI and were more often smokers (Hochman et al., 1999). In the study, men presented more often with STEMI than women (37.0% vs. 27.2%, p<0.001). The baseline characteristics of patients that presented with STEMI differed than patients that presented with NSTEMI. After adjustments for the baseline differences, female sex was a significant predicator of NSTEMI at presentation (OR=1.5, 95% CI 1.3 - 1.7, p<0.01) and women were also more likely to present with unstable angina compared to men (OR=1.5, 95% CI 1.3 - 1.7, P<0.01). The decision to refer the patient for angiography was at the discretion of the attending physician and women were referred less often for coronary angiography than men (59% vs. 53%, p<0.01). Women had higher bleeding rates in all three groups, even after adjustments (p=0.04). With regards to the primary endpoint of the study, women had higher mortality at 30 days than men (6% vs. 4%, p < 0.01), but had similar rates of re-infarction (6%, p=0.19). However, after baseline characteristics were adjusted, the overall rates of death and MI at 30 days were similar between men and women. The findings from this study suggest that men and women have different clinical profiles and MI presentation in ACS. Such differences likely influence decisions in treatment and ultimately their outcomes.

Similar results, also from a sub-study of a larger trial were reported from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial. There were a total of 7,726 men and 4,836 women who presented within 24 hours of ACS symptoms, (including STEMI, non-STEMI and UA) that were randomized to either clopidogrel or placebo. The baseline profile of the patients was consistent with that of other studies: women were older, had higher rates of diabetes, hypertension and cholesterol even when adjusted for age, compared to men. Men, on the other hand, were more likely to be smokers, have peripheral vascular disease, and have a history of MI and stroke (S. S. Anand et al., 2005). Patients were stratified according to Thrombolysis in Myocardial Infarction (TIMI) risk score and there were no significant differences in the TIMI risk classification according to sex. Similar to the GUSTO IIb study, women were referred less for coronary angiography (39 % women versus 46% men, p<0.01), percutaneous coronary interventions (PCI) and coronary artery bypass graft surgery (CABG) compared to men (48% women versus 61% men, p < 0.01). However, women were more likely to have normal coronary arteries compared to men (27% women versus 13% men, p<0.01). Despite differences in procedure rates, no differences were observed in the primary composite outcome of death, MI or stroke at 30-days (4% women versus 5% men, p=0.23). However, women had a higher incidence of refractory angina or hospitalization for angina at 30-days compared to men (17% versus 14%, p<0.01, respectively) (S. S. Anand et al., 2005).

2.5.2 Sex Differences in Evaluation and Outcomes Presenting to the ER

It is presumed that for the most severe presentation of CVD ACS symptoms, when recognized should be treated equally between the sexes. A study by Roger et al (Roger et al., 2000) retrospectively examined sex differences in 2271 patients as they presented with their first ACS episode to the emergency room (ER) and followed their outcomes. The primary endpoint of this study was to assess the use of a cardiac procedure (including catheterization) within 90 days of the ER visit. The secondary endpoint sought to evaluate overall mortality and cardiac events compared by sex and risk category. The baseline characteristics of male and female patients are consistent with the trends reported in many other studies (Alter et al., 2002; Beery, 1995; Bell et al., 1995; Douglas & Ginsburg, 1996; Eaker, Packard, & Thom. 1989: Ghali et al., 2002: Glaser et al., 2002: Hochman et al., 1999: King et al., 2004; Lagerqvist et al., 2001; Malenka et al., 2002; Quaas, Curzen, & Garratt, 2004; Rathore, Wang, Radford, Ordin, & Krumholz, 2002; Roger et al., 2000; Steingart et al., 1991; Vaccarino et al., 1998; Vaccarino et al., 1995; Vaccarino, Krumholz, Yarzebski, Gore, & Goldberg, 2001; Weintraub et al., 1996), where women were older, hypertensive and had higher rates of hypercholesterolemia, while men were more likely to be smokers with typical angina (Roger et al., 2002). In this study, for equivocal symptoms, men were more likely than women to be referred for any noninvasive test (74% versus 62%, p<0.001) and coronary angiography (50% versus 33%, p<0.001). Moreover, the low referral of procedures among female patients could not be explained by the measured differences in baseline variables. The 6-

year overall survival rate was 78% for men and 71% for women (p<0.001), however after adjusting there was a trend towards an excess risk of death in men (except in high risk patients). The 3-year survival for women was 68% compared to 75% for men (p < 0.001). Even after adjustments, women fared worse than men, where male sex was univariately associated with a 31% decrease in risk of death. In terms of cardiac events, the 6-year survival free of cardiac events was 63% for females, and 70% for males. However, after adjustments, men fared worse than women with a 21% excess risk of developing a cardiac event. The results of this study indicate that there is an association between females and the lower use of cardiac procedures. This study supports the "Yentyl" syndrome, a term used to describe that for women to receive equal/similar treatment for ACS, she must present symptoms like a man There are some inherent limitations associated with the (Healv. 1991). interpretation of retrospective studies, including the possibility that the observed differences may be due to an unmeasured confounding variable(s), data was collected through medical records and patient preferences were not captured. However the authors caution that it is unknown whether a more aggressive approach in the management of women is necessary, or whether procedures are over-utilized in men. Although catheterization practices vary between countries, Graham and colleagues (Graham et al., 2005) found that as catheterization rates increased per region, the number of individuals with high-risk CAD increased linearly also, suggesting no evidence of reaching a "plateau" when more procedures were performed. The authors conclude that regional catheterization rates in the

province of Alberta (which are amongst the highest in Canada) may be suboptimal in detecting people with high-risk CAD. Unfortunately, the patients who are often referred for coronary angiography are not necessarily the higher-risk patients, but lower-risk patients (Natarajan, Gafni, & Yusuf, 2005). However, with the confusion surrounding the symptomology of ACS in women, it is not surprising that physicians are unclear in their selection of patients to refer for coronary angiography.

2.5.2 Differences in Outcomes After Catheterization among Women and Men

The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database contains detailed clinical data of 37,401 patients undergoing catheterization from 1995-2000 (King et al., 2004). A retrospective study analyzed all-cause mortality as it related to the extent of coronary disease, treatment strategy and follow-up time in male versus female patients who have undergone a catheterization. Baseline characteristics between the genders were consistent with previous studies. Also consistent with other studies, women had a higher LVEF and their coronary anatomy was lower risk than men. Despite this, women had a higher one-year overall mortality than men 6% versus 5%, p<0.01. When patients were stratified according to risk, there was little difference between low risk male and female mortality rates, however for patients in the higher risk category, women had significantly poorer early survival rates than men (χ^2 =83.2, p<0.01). Once patients were referred for PCI or CABGS, there was a marked increase in early risk mortality in female compared to male patients. However it is

important to note that this study only included patients who underwent catheterization and outcomes for women who were not referred to catheterization remain unknown. The study authors emphasize the importance of focusing future research to understand how to identify a woman at greater earlier risk when undergoing a revascularization procedure following catheterization.

2.6 Biological differences in coronary anatomy between the sexes

One of the great paradoxes in coronary artery disease in women is that despite having a lower prevalence angiographically assessed diseased arteries, women experience higher rates of angina compared to men (S. S. Anand et al., 2005; Berecki-Gisolf, Humphreves-Reid, Wilson, & Dobson, 2009; Berger et al., 2009; Bugiardini & Bairey Merz, 2005; Cannon, 2009; Douglas & Ginsburg, 1996; Hemingway et al., 2008; Kannel & Feinleib, 1972; Kerry A. Milner, Funk, Arnold, & Vaccarino, 2002; Proudfit et al., 1966; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Wise, 2006; Steingart et al., 1991; Wenger, 2010). Although some of the discrepancies have been attributed to differences between the sexes in CVD risk factor profile and symptom presentation, it is postulated that differences in the physiologic and biologic characteristics between the sexes also contribute. Specifically, physiologic and anatomical differences in coronary artery size have been observed in a study using intravascular ultrasound, concluding that women have smaller coronary arterial lumens than men, independent of body size (Sheifer

et al., 2000). This finding is of interest, particularly because there are theories which link smaller coronary arterial dimensions with adverse cardiac events. Specifically, there is a higher risk of total occlusion and MI when an atheromatous plaque ruptures within a smaller coronary arterial lumen as it is proportionally more flow-limiting (Sheifer et al., 2000). Also, restenosis, traditionally a limitation in PCI, has been positively correlated with smaller minimal lumen diameter or smaller arterial lumen (Mintz et al., 1998; Mintz et al., 1997). Similarly in CABGS, smaller target vessel size has also been correlated with poorer long-term graft patency (Fisher et al., 1982). This may have contributed to the perception that women are less likely to benefit. In addition to smaller coronary arterial lumen, women also have been noted to have less collateralization than men (Hochman et al., 1999). These anatomical differences may manifest as more ischemia during periods of exertion or stress and higher rates of complications especially when a chronic total occlusion occurs (DeVon & Zerwic, 2002; Sheifer et al., 2000). This finding is consistent and likely related to the higher rates of angina that women experience with less extensive CAD than their male counterparts (Hochman et al., 1999).

Biologically, women experience specific hormonal changes that differ from men. The incidence of CAD is lower in pre-menopausal women and rises in postmenopausal women (Mendelsohn & Karas, 1999; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006). This is reflected in an average of 10-15 more CAD-free years in women compared to men due to a later on-set of the disease (Mark, 2000; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006). It has been postulated that the protection against CAD is a result of endogenous estrogen however recent studies indicate that the relationship between estrogen and CAD protection is far more complicated than initially thought (Mendelsohn & Karas, 1999; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006). During menopause, estrogen levels are reduced, negatively affecting the profile of circulating lipoproteins, coagulation, the bioavailability of nitric oxide and vasodilatation factors that typically protect against the risk of developing CAD (Douglas & Ginsburg, 1996; Mendelsohn & Karas, 1999, 2007; Vaccarino et al., 2001).

2.7 The Age-Sex/Gender Relationship

There is an increasing body of evidence alluding to an age-sex interaction in mortality rates of post MI patients. A study by Vaccarino et al, (Vaccarino et al., 2001) investigated the 2-year mortality rates of 6826 post-MI patients stratified according to age and sex, over a 20 year time period. The overall hospital mortality was significantly higher in females than in males (21% versus 14%, p<0.01). Of particular concern is that women under 50 years of age had three times higher risk of death than their male counterparts. Of the in-hospital survivors, mortality was

still higher in women compared to men, 29% versus 20%, two years after their initial MI, [Hazard Ratio HR=1.5 (95% CI 1.4-1.6)]. This result is interesting since the "healthier survivor" effect would have been expected among the young female patients, since those at highest risk have been removed from the population pool however the higher mortality rate persisted for women under 60 years of age when compared to men of similar age. Interestingly, this effect seemed to diminish with age; as women's age increased, their mortality risk decreased when compared to men of the same age group. Specifically, the hazard ratios of female compared to male mortality at two years was HR=1.40 in the <60 year age group, 1.05 in the 60-69 year old group, and 0.95 in the >70 year olds. The interaction between sex and age was tested and found to be a statistically significant predictor, independent of baseline demographic, medical and treatment characteristics.

The results from this study indicate that younger women (<60 years) diagnosed with ACS are at higher risk of death than younger men (11% versus 7%) and as women's age increased, the risk of mortality decreased when compared to men (46% versus 51%). This interaction reflects two important epidemiologic issues. First, the higher unadjusted two-year mortality rate in women was fully explained by the confounding due to age (women were on average 8 years older than men per age cohort). And second, the age-sex interaction was a statistically significant effect modifier on mortality rates (Ayanian, 2001). The authors suggest that there is a possibility that previous gender studies may have masked the long-term risk of younger women by combining the analysis to include women of all age

groups (Vaccarino et al., 2001). Future research should aim to explore reasons for the increased mortality amongst younger women.

The age-sex/gender relationship was also examined in a cohort of 25,698 patients hospitalized for AMI in Ontario, between the years of 1992-1993 (Alter et al., 2002). Patients were analyzed according to their age cohort of 20-49, 50-64, 65-74 and >75. The results of the study confirmed previous studies findings, where women are older, even within age cohorts (p<0.01). Younger women were significantly poorer and sicker than younger men however this difference narrowed with age. The aggressiveness of referral for angiography was also measured, revealing that younger women were treated more aggressively than young male counterparts. Interestingly, despite efforts, younger women had lower survival rates than younger men (HR=1.7, 95% CI 1.2-2.3, p<0.01). Furthermore, survival differences in women improved with age, even though receiving less aggressive treatments (HR= 0.9, 95%CI 0.8-0.9, p<0.01). The age-sex/gender interaction was found to be a significant predictor. Furthermore, the study found that women were referred less often for angioplasty by 18% compared to men (p<0.01) and referrals also decreased as age increased. An interesting aspect of this study looked at the significance of several non-clinical factors as they related to the age-sex/gender interaction. The results of the non-clinical factors analysis revealed that older women were significantly less likely to be seen by a specialist, that younger women were at higher risk at a smaller volume hospital (<30 AMI/year) and if the hospital was >50 km away from their home. The presence of on-site revascularization

facilities, and hospital teaching status did not seem to significantly influence the results.

2.7 Gender Affecting Physician Recommendations

As the body of evidence grows, it is becoming increasingly apparent that there are disparities in the diagnosis and treatment of ACS between the sexes. However, a major limitation of the studies reviewing the gender issue thus far is that they consist largely of subgroup analyses of larger studies, not powered to detect differences in gender, or they are retrospective in nature, analyzing administrative databases. While these studies have been able to highlight some issues, there are inherent limitations associated with such study designs. The information derived from retrospective studies, although valuable is mostly descriptive in nature, with little insight or exploration for reasons of any differences noted. Furthermore, there are many possible covariate and confounding variables which are difficult if not impossible to fully account for, affecting the results to immeasurable levels. At this time, we also do not have a thorough understanding of ACS symptomologic differences between the sexes and how this may affect patient care.

An interesting study by Schulman et al (1999) (Schulman et al., 1999)sought to overcome some of the design limitations of previous gender studies by constructing a prospective study exploring the influence of a patient's race or sex has on a physician's decision to refer a the patient for cardiac catheterization. In this study, 720 primary care physicians were presented with case vignette videos of

actors portraying patients presenting with chest pain, varying six experimental variables; the patient's race (black/white), sex, age (55/75 years), level of coronary risk (low/high), type of chest pain (definite/possible/non-anginal) and the results of an exercise thallium test. Using a computerized survey instrument, physicians were required to characterize the type of chest pain, to estimate the probability that the patients had significant CAD (>70% lesion stenosis) and if they wished to refer the patient for cardiac catheterization. The results of this study revealed that physicians estimate a lower probability of CAD in women than in men (64% versus 69%, p<0.001) and in younger than older patients (64% versus 70%, p<0.01). The analysis further revealed that black women (79%) were significantly less likely to be referred for cardiac catheterization when compared to white females (91%). white males (91%) and black males (91%) (Schulman et al., 1999; Schwartz, Woloshin, & Welch, 1999). In addition, a two-part patient assessment survey was also completed by participating physicians. The survey included 10 items assessing physician judgement in predicting patient compliance, treatment outcomes, and individual patient characteristics using a 5-point or 7-point Likert scale. Small differences where found when the race and sex of the patient was combined and when these results were incorporated into the analysis, it did not change the main results.

The unique strength of this study design enabled to tap into physician decision-making while prospectively controlling for some known confounding variables, by presenting the clinical information using actors in a uniform manner,

removing effects of symptom differences in clinical presentation. Also, by asking the physicians to estimate the probability of CAD disease, the investigators were able to control for differences in their perception of CAD prevalence according to the sex/gender and race of the patient.

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CHAPTER 3

3.0 Referrals in Acute Coronary Events for CARdiac Catheterization: *The* **RACE CAR** *Trial*

The first study of my thesis entitled, *"Referrals in Acute Coronary Events for CARdiac Catheterization: The RACE CAR trial"* was a conceptual experiment designed to prospectively assess if there is a sex/gender difference in the perceived benefit of cardiac catheterization in patients with suspected cardiac disease. Canadian cardiologists and internal medicine specialists were presented a web-based tool illustrating clinical vignettes that were controlled for age, level of risk and patient preference for a cardiac catheterization procedure, manipulating only the assigned sex and gender of each scenario and were blinded to the primary objective of detecting a sex/gender difference. As physicians were requested to assess three clinical vignettes each, the analytical methodology consisted of multi-level regression modeling. This paper has been published in the Canadian Journal of Cardiology and is presented in Appendix B.

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CHAPTER 3: The RACE CAR Trial

Referrals in Acute Coronary Events for CARdiac Catheterization: *The* RACE CAR *Trial*

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3.1 Summary

Women with acute coronary syndromes (ACS) have lower rates of cardiac catheterization compared to men. One possible reason is the perception that women are lower risk. To determine factors which influence a physician's decision to refer ACS patients for cardiac catheterization, we designed 12 clinical scenarios controlling for sex, age, TIMI risk score and patient preference, administered them to specialists across Canada. "Sex" was randomly allocated to each scenario. We found that physicians perceive men to benefit more from cardiac catheterization than women. Our study is unique as it prospectively assesses physician decision-making with respect to ACS treatment.

3.2 Structured Abstract

Background: Women with acute coronary syndromes (ACS) have lower rates of cardiac catheterization (CC) compared to men.

Objective: To determine if sex, age, risk level and patient preference influence physician decision-making to refer patients to CC.

Methods: We designed 12 clinical scenarios controlling for sex, age (55 / 75 years old), TIMI risk score (low, moderate, high) and patient preference for CC (agreeable, refused/no preference expressed). Scenarios were administered to specialists across Canada using a web-based computerized survey instrument. Questions were standardized using five-point Likert scale ranging from 1 (very unlikely to benefit from CC) to 5 (very likely will benefit from CC). Outcomes were assessed using a two-tailed mixed linear regression model.

Results: Of 237 scenarios physicians rated men more likely to benefit from CC compared to women $(4.44 \pm 95\%$ CI 0.14 vs. $4.25 \pm .15$, p=.03), adjusted for age, risk and patient preference. Low-risk men were perceived to benefit more than low-risk women $(4.20 \pm .13 \text{ vs.} 3.54 \pm .14, \text{ p<.01})$ and low-risk younger patients were perceived to benefit more than low-risk older patients $(4.52 \pm .17 \text{ vs.} 3.22 \pm .16, \text{ p<0.01})$. Regardless of risk, patients agreeable for CC were perceived more likely to benefit from CC than patients who were disagreeable, or made no comment at all $(5.0\pm .23, 3.67\pm .21, 2.95\pm .14, \text{ p<0.01})$.

Conclusion: Canadian specialists' decisions to refer patients for CC appear to be influenced by gender, age and patient preference in clinical scenarios where cardiac

risk is held constant. Future investigation of possible age and gender biases as proxies for risk is warranted.

Key words: acute coronary syndromes; cardiac catheterization; gender; decisionmaking

3.3 Introduction

It has been widely reported that coronary artery disease (CAD) is the leading cause of morbidity and mortality of both men and women in westernized countries. accounting for over one third of total deaths (1). Furthermore, CAD accounts for the greatest proportion of deaths among women of all ages, yet despite this, CAD has often been viewed as a 'man's disease'. Although there are similarities, differences do exist, particularly in symptom presentation and risk profile, as women characteristically present with CAD at older ages than men (2-23), and more often with atypical symptoms (2,8,10,13,17,18). However, women generally have less severe CAD as determined by angiography (4;8;10-12;16;22;23;28) contributing to the perception that they are "lower risk". Differences in physicians' interpretation of symptoms, risk assessment and patient preferences may contribute to sex differences in the diagnosis and treatment of CAD (29). Women generally receive less medical therapy, and are referred less frequently for angiography, percutaneous coronary interventions and bypass graft surgery than men (4:10-12:16:23:30). Even among women with acute coronary syndrome (ACS), studies have reported that women are referred less often for invasive procedures than men (16;31;32). The implication of these findings have been controversial, suggesting higher mortality and poorer long-term survival among women (2;10;16;21;31;32). Interestingly, a growing body of literature cautions that age may be an important confounder in the sex/gender literature. Studies have found that younger women with ACS are at three times higher risk for mortality than their young male

counterparts (21;22). The higher risk of mortality in these young women may be due in part to the *perception* that women, especially younger women, are at very low risk of CAD. At the same time, prior studies consisting mostly of retrospective analyses of administrative databases or subgroup analyses of clinical trials, have generally suffered from methodologic limitations including the lack of statistical power to determine if true differences exist (33).

The proposed study is an effort to prospectively assess if gender independently influences physician decision-making among various profiles of patients with acute coronary syndromes, with the following primary objectives: (i) to determine if there is a difference among Canadian cardiologists and internal medicine specialists' decision to refer for cardiac catheterization (CC) male and female patients of equal risk (ii) to determine patient factors which influence referral decisions including age, sex, risk level and expressed preference for catheterization. Secondary objectives include determining factors that influence (i) the perceived risk a patient will suffer from a myocardial infarction (MI) within the next 14 days; (ii) the characterization of chest pain; (iii) the probability a patient has significant CAD; and (iv) patient opinion in physician decision-making for referral to CC.

3.4 Methods

For the purpose of this paper, the term sex refers to the biological and physiologic determinants of disease, and gender refers to a person's social roles as expressed through their values and beliefs, psychosocial characteristics and behaviours (24).

3.5 Design of Survey Instrument

We designed 12 clinical vignette-scenarios describing patients presenting to the emergency room with chest pain, controlling for all combinations of patient factors, including two age categories (55 or 75 years of age), three TIMI risk levels (low, moderate and high) and two patient preferences (patient expressed preference/ no preference expressed) for catheterization. Due to sample size concerns, we designed the scenarios with blank fields in place of "gender" and designed a computer programme to randomly allocate gender and gender-specific pronouns to each scenario. In addition, gender specific terms were matched and tagged to the randomly assigned sex, to deliberately tap into physician perceptions that may be associated with gender. Each physician was required to review and assess three randomly allocated vignette-scenarios: one each of male, female and gender neutral. After reading each clinical vignette-scenario, physicians were required to answer a series of standardized questions of the patient. Physicians were blinded to the primary objective of the study. Physicians also provided demographic information about their practices. The scenarios were pre-tested for

face validity using the ACC/AHA criteria for referral for catheterization (34). Prior to initiation of the study, pilot testing was administered, appropriately modifying the scenarios and computer programme to work out any issues, such as the design of "limits" to ensure there were no missing data fields. The design of this study was inspired and modeled on a study by Schulman et al (29). An example of a clinical vignette scenario is illustrated in Appendix A.

3.6 Survey Administration

To recruit physicians for this study we sent an electronic mail with a link to our web-site to cardiologists and internal medicine specialists from across Canada using the following sources: 1) Canadian Cardiovascular Society (CCS) internal medicine and cardiology specialist regular members 2) a Canada-wide list using cardiologists listed with the Canadian Medical Association (CMA) directory (excluding prior CCS respondents) and 3) colleagues and collaborators across Canada, in addition to referring physicians at our institution who were not represented by CCS or our CMA list.

We sent up to three e-mails describing our study with a link to our web-site, each two weeks apart. Follow-up phone calls were made to physicians on our CMA, collaborators and colleagues list, subsequently followed with personally addressed e-mails as friendly reminders. There was no financial compensation for

participation in the study, however as an incentive we proposed a draw for a gift certificate to a bookstore.

3.7 Controlled Patient Factors

The scenarios contained patient factors representing all possible combinations of variables of interest. The scenarios were controlled for sex of patient (male, female, gender neutral), age (55 versus 75 years of age), level of TIMI risk score (low, moderate, high) and the patient's preference for a cardiac catheterization (no preference expressed or preference expressed which was further subdivided into agreeable/ refused for cardiac catheterization).

3.8 Description of Physician and Hospital Characteristics

Physician information was collected to understand and contextualize our sample population's demography and practice patterns, including physician sex, type of speciality (internal medicine, cardiology, or sub-specialities within cardiology), years since graduation from medical school, an estimate of the percentage of female patients seen in practice, an estimate of the percentage of non-white Caucasian patients seen in practice, and if the physician uses any type of risk assessment score in deciding whether to refer a patient for catheterization. Hospital factors included geographic region, the presence/absence of on-site catheterization facilities and type of practice (academic centre, community-based, out-patient clinic

only, other). The full list of physician demographics and hospital characteristics are available in Appendix B.

3.9 Survey Questions

Physicians were blinded to the primary objective of the study namely to detect a gender bias for cardiac catheterization. Physicians were asked to assess the likelihood that a patient would benefit from cardiac catheterization on a five point Likert scale ranging from 1 (very unlikely to benefit from cardiac catheterization) to 5 (very likely to benefit from cardiac catheterization). Physicians were also asked to characterize the patient's chest pain (non-cardiac, possible cardiac, definitely cardiac), the risk level of suffering a fatal or non-fatal MI in the next 14 days (low risk, moderate risk, high risk) and the probability that the patient has significant CAD (defined as a stenosis >70% of at least one major epicardial vessel) on a 5 point Likert scale ranging from 1 (very unlikely) to 5 (very likely). Physicians who decided not to refer the patient for cardiac catheterization, were asked if they would order any further tests and, if so, which tests. Physicians were also asked to report how much patient opinion influences their decision to refer a patient for cardiac catheterization, ranging from 1 (not much at all) to 5 (to a great extent). Lastly, physicians were requested to report if they required any other information to make their decision for catheterization referral. The full list of vignette questions and scaling are available in Appendix C.

3.10 Statistical Considerations

Statistical Power: We predetermined that 68 physicians completing 3 scenarios each for a total of 204 scenario assessments, would be required to provide 90% power to detect a minimum difference of 10% in cardiac catheterization rate between men and women. The sample size calculation included the clustering effect of physician, assuming an intra-cluster correlation coefficient of 0.5.

Analysis: To assess the differences in physician decision-making to refer a patient for cardiac catheterization, a mixed linear model was used. Patient factors were represented as covariates and analysed as fixed effects which included the controlled patient factors of gender, age, TIMI risk level and the patient's preference for catheterization. Interactions of all combinations of patient factors were also tested in the mixed effects model. Design variables were created for categorical variables. Since each physician answered standardized questions for three scenarios, scores for each physician rater were clustered and analysed as a random effect. Sidak's correction was employed to adjust for multiple testing. Significance testing was evaluated using two-tailed testing, with 95% confidence intervals. All analyses were performed using SPSS 16.0 statistical software (Chicago, Illinois).

3.11 Results

Baseline Demographics of Physicians and their Institutions:

After sampling almost 700 physician specialists across Canada at multiple time intervals, a total of 79 physicians (11%) each completed three randomly assigned scenarios for a total of 237 scenarios, between July and August 2006.

3.12 Physician Characteristics

The baseline demographic information of the participating physicians is outlined in Table 1. Briefly, physicians participating in this study were mostly male (87%) and specialized in cardiology (91%). Our sample of physicians were experienced, with the majority of participating physicians practicing for over 10 years; only one quarter of physicians reported having less than 10 years of cardiology work experience. The percentage of females seen in practice varied, with 72% of physicians reporting that women comprised \leq 50% of their practice, and only a quarter of physicians reported that women comprised \geq 50% of their practice. Similarly, the ethnic make-up of cardiology practices across Canada revealed non-white patients comprise less than 25% of physician practices in the majority of physician practices. In addition, when physicians were asked if they utilized a risk score when assessing their patients, approximately half reported that they used a risk score. Of the number of physicians that used a risk score, 74% reported the TIMI risk score as their risk assessment score of choice (Table 1).

3.13 Hospital Factors

Geographically, 70% of physicians practiced in Ontario/Quebec, 23% were in the western provinces and 6% of participating physicians were from Atlantic Canada. Also, two-thirds of physicians reported the presence of catheterization laboratories at their institutions, and 73% worked at academic centres (Table 1).

3.14 Referral Decisions Based on Gender, Age, Patient Preference, and Risk

Physicians rated men more likely to benefit from a CC than women (Mean score $\bar{x} = 4.44 \pm 95\%$ CI .14 versus $4.25 \pm 95\%$ CI \bar{x} .14, p=0.03), controlling for age, risk level and expressed preference for a catheterization procedure. Younger patients (age 55) were rated more likely to benefit from catheterization than older patients (age 75) controlled for all patient factors ($\bar{x} = 4.55 \pm .18$ versus $4.14 \pm .18$, p=0.01). Benefit from catheterization increased as the level of risk increased (low TIMI risk mean score = $3.87 \pm .2$, moderate TIMI risk $\bar{x} = 4.25 \pm .2$, high TIMI risk $\bar{x} = 4.98 \pm .16$, p<0.01). Patients who agreed to undergo CC were rated more likely to benefit from the procedure compared to patients who would not or expressed no opinion, even after controlling for gender, age and risk ('Agreeable' $\bar{x} = 4.65 \pm .24$ versus 'Refused' $\bar{x} = 4.17 \pm .25$ versus 'No opinion $\bar{x} = 4.21 \pm .15$, p=0.01) (Table 2).

3.15 Interactions Between Patient Factors Influencing Referral Decisions

Physicians rated low TIMI risk men as more likely to benefit from CC than low TIMI risk women ($\bar{x} = 4.20 \pm .27$ versus $\bar{x} = 3.54 \pm .25$, respectively, p<0.01) controlling for all other patient factors. No significant differences were detected among moderate and high TIMI risk men and women (Table 3).

Physicians rated younger, low TIMI risk patients more likely to benefit from CC than older, low-risk patients ($\bar{x} = 4.52 \pm .33$ compared to Likert= 3.22 $\pm .31$, respectively, p<0.01). There were no significant differences detected between moderate risk and high-risk, 55 year-old and 75 year-old patients (Table 3).

When analysing physician perception of CC benefit according to risk, patient preference influenced physician decision-making. Low TIMI risk patients who agreed to undergo CC were perceived more likely to benefit than low TIMI risk patients who would not undergo the procedure, or made no comment at all (all low-risk patients: 'agreeable' $\bar{x} = 5.0 \pm .45$ compared to 'refused' $\bar{x} = 3.67 \pm .41$ and 'no opinion' $\bar{x} = 2.95 \pm .27$, p<0.01). No significant differences were detected among high-risk patients, regardless of the patient's expressed preference for the procedure, as physicians rated all high-risk patients to significantly benefit from CC (Table 3).

When considering physician perception of benefit from CC according to patient preference, TIMI risk level did not seem to influence physician decisionmaking. Among patients agreeable for CC, low-risk patients were shown to benefit

more than moderate risk patients and equally as much as high-risk patients (all patients agreeable for CC: low-risk $\bar{x} = 5.0 \pm .45$ versus moderate risk $\bar{x} = 4.06 \pm .47$ and high-risk $\bar{x} = 4.88 \pm .34$, p<0.01). Among patients who did not want a CC or that did not express an opinion for the procedure, the benefit of catheterization reflected the main effects observed, where benefit from catheterization increased according to increasing risk (Table 3).

3.16 Secondary Objectives

Risk of suffering an MI within next 14 days

As an internal measure of validity of the TIMI risk score used to determine controlled risk in our scenarios, we asked physicians to rate the level of risk (according to the TIMI risk criteria) that the described patient would suffer a fatal or non-fatal MI in the next 14 days. We found that physicians in our study appropriately identified low, moderate and high-risk patients according to TIMI risk criteria (p<0.01) (Table 4). There were no statistically significant differences detected in the risk of suffering an MI according to gender, age or patient preference. However, an interaction was detected between age and gender; physicians rated 55 year-old men as more likely to be at risk for an MI than 55 year-old women controlled for all other patient factors ($\bar{x} = 2.62 \pm .18$ versus $\bar{x} = 2.32 \pm .18$, respectively, p<0.01).

3.17 Characterization of chest pain

Physicians were asked to characterize patient chest pain on a three-point Likert scale (1 representing non-cardiac to 3, definitely cardiac). Physicians rated chest pain among men as more likely to be cardiac compared to the same pain among women, even when controlled for all other patient factors (men $\bar{x} = 2.66 \pm$.08 versus women $\bar{x} = 2.53 \pm .08$, p=0.02). Patients were rated more likely to be experiencing cardiac pain if they were younger (55 years: $\bar{x} = 2.77 \pm .1$ versus 75 years: $\bar{x} = 2.43 \pm .1$, p<0.01) or had higher TIMI risk (low TIMI risk: $\bar{x} = 2.36 \pm .1$, moderate TIMI risk: $\bar{x} = 2.48 \pm .1$ and high TIMI risk: $\bar{x} = 2.95 \pm 0.1$, p<0.01). Physicians were more likely to characterize chest pain in an older low-risk patient as more cardiac in nature than in a young low-risk patient, even after controlling for all other patient factors ($\bar{x} = 1.93 \pm .14$ versus $\bar{x} = 2.79 \pm .18$, respectively, p<0.01). No differences were found among young and older age patients of moderate or high-risk. Physicians were not influenced by the patient's preference for CC (p=0.10) (Table 4).

3.18 Estimated probability that patient has significant obstructive CAD

When physicians were asked to estimate the probability that the described patient has significant CAD on a 5-point Likert scale (1, very unlikely to 5, very likely), physicians rated men as more likely to have significant CAD compared to women, controlling for all other patient factors (men $\bar{x} = 4.67 \pm .14$ versus women $\bar{x} = 4.38 \pm .14$, p=0.01). Also the probability the patient may have significant CAD

increased as the level of TIMI risk increased (low TIMI risk: $\bar{x} = 4.25 \pm .18$, moderate TIMI risk: $\bar{x} = 4.43 \pm .18$, high TIMI risk: $\bar{x} = 4.89 \pm .16$, p<0.01) (Table 4). Differences in the probability of the patient having significant CAD were not detected among patients of different ages (Table 4).

Among women who did not want a CC procedure, physicians were less likely to suspect significant CAD compared to women who were agreeable or who had no opinion for the procedure ('refused' women $\bar{x} = 3.85 \pm .27$ versus 'agreeable' women $\bar{x} = 4.62 \pm .26$ and 'no opinion' women $\bar{x} = 4.66 \pm 0.2$, p<0.01).

3.19 Influence of patient opinion for referral for CC

Physicians were asked to rate the degree to which a patient's opinion influences their decision to refer a patient for CC on a 5-point Likert scale (1, not very much to 5, very much). Physicians reported that they are not swayed by the patient's opinion according to gender, age or their expressed preference for a CC procedure, rather, the level of TIMI risk was a statistically significant influential factor when a physician considers the patient's opinion in deciding to refer a patient to catheterization (low TIMI risk: $\bar{x} = 2.64 \pm .29$, moderate TIMI risk: $\bar{x} = 2.97 \pm .33$ versus high TIMI risk: $\bar{x} = 3.23 \pm .33$, p<0.01) (Table 4).

3.20 Discussion

Our study indicates that among Canadian specialists, women are perceived to benefit less from cardiac catheterization than men of equal age, risk and expressed preference for catheterization. In addition, specialists perceive younger patients more likely to benefit from cardiac catheterization than older patients, high risk patients to benefit more than low risk patients and patients agreeable for cardiac catheterization more likely to benefit than patients who refuse or express no opinion at all.

The results from our study support those in the literature that women are less often referred for cardiac procedures than men (4;10-12;23;29;30;35;36). Although post-hoc hypotheses have alluded to sex/gender differences in the past, our study is unique in that physician decision-making was prospectively assessed, unlike past studies that depended on retrospective data collection, database analysis or post-hoc analyses of larger trials with insufficient power to detect sex/gender differences. The sex/gender difference in catheterization benefit we detected was consistent across all models, which were controlled for age, risk and patient preference. We were able to explain some of the sex/gender difference due to risk. The interaction between TIMI risk and gender suggests that among patients that are truly low risk, women are evaluated appropriately as so, whereas low risk men were perceived to gain more benefit from cardiac catheterization. Previous literature has suggested that perhaps women are being appropriately treated, and that men may undergo excess cardiac catheterizations (16;35) and our results lend

support to this. It is possible that symptoms and risk factors in men may be overestimated, while symptoms and risk factors in women may be appropriately estimated. Our results support this, because cardiac chest pain and significant stenotic disease were perceived more likely among men than women, across scenarios controlled for gender, age, TIMI risk and patient preference. Although this perspective may seem somewhat confusing, it is not contradictory. Cardiac catheterization is the gold standard in coronary artery disease diagnosis. Evidence shows that high risk patients have the most to gain from cardiac catheterization; by identifying these patients, treatment options to improve prognosis can be offered including surgical revascularization. However, beyond risk factor modification, much debate surrounds treatment options for low and moderate risk patients, implying that "benefit" from cardiac catheterization is unknown. Currently, we do not know what the 'catheterization-benefit' threshold is for lower risk patients. We have demonstrated that there is a perception by physicians that women are at "lower risk" for CAD and therefore will not "benefit" from cardiac catheterization. We are not suggesting that this perception is inappropriate, as it may in fact be a more reasonable approach to determining who will benefit from cardiac catheterization. There is no evidence in the literature to suggest why a low risk patient would benefit from cardiac catheterization at all, irrespective of sex/gender. Evidence of survival benefit from revascularization has only been demonstrated among high risk patient groups (45, 46).

Our study also revealed that physicians perceive younger patients more likely to benefit more from cardiac catheterization than older patients. This finding was reinforced in that physicians identified chest pain among younger patients as more likely cardiac than such pain in older patients. It may also reflect the belief that younger patients benefit more from early diagnosis of CAD in terms of potential years of life lost than older patients, despite trends of actual risk (1). For this reason, physicians may be more driven to make a diagnosis among younger patients. In our study, a 75 year old low risk patient was perceived to be significantly less likely to benefit from a cardiac catheterization than a 55 year old patient of equal risk. This contradicts the epidemiology of CAD which demonstrates a greater probability of CAD among older patients. Interestingly, other studies have also reported that younger patients, and not necessarily higher risk patients, are more likely to be referred for invasive procedures (31;37).

When we evaluated risk, both as a main effect and as an interaction term, high risk patients were identified appropriately and seen to benefit the most from cardiac catheterization. Our assessment of risk was internally valid as physicians identified increasing risk for MI as we increased the TIMI risk in the scenario. This finding was particularly evident among high risk scenarios, where patient factors such as sex, age or expressed patient preference did not influence the physician's decision to refer. However, the same was not true among low and moderate risk patients. Low and moderate risk patients that expressed a desire for cardiac catheterization were more likely to receive a cardiac catheterization than patients

that refused or expressed no opinion at all. This suggests that while high risk patients are being appropriately referred for cardiac catheterization, greater standardization of catheterization referral in low and moderate risk patient groups is needed because cardiac catheterization is not a procedure without risk, and these risks may not outweigh the benefit, particularly among low risk patients.

3.21 Limitations

To recruit physicians for our study, we used non-random sampling of Canadian cardiologists and internal medicine specialists and the response rate to our invitation was low, thus some respondent bias likely exists. At the same time, we invited specialists to participate in our study via an e-mail invitation only as this was a web-based instrument and in today's internet world of increasing firewalls. spam, junk and other protective e-mail filters, we are uncertain how many physicians we actually reached and therefore our true denominator remains unknown. However, despite a small sample size, physicians sampled in our study are representative of the actual distribution of physicians across Canada. Furthermore the characteristics of the physicians who responded to our survey reflect the current characteristics of cardiac specialists in Canada, where most specialists are male, practicing for at least 10 years (38), with women representing less than half of their patient population. It is important to note that the responders were blinded to the intent of the study which was to identify gender differences in Scenarios were randomly allocated to each cardiac catheterization referral.

physician so it is unlikely that there is any internal bias. Also, the subtleties and complexities of human interaction cannot be fully captured in paper scenarios, although previous studies have shown that response to hypothetical case scenarios parallels real world decision-making (39;40). Lastly, to represent risk, we used the TIMI risk score because this is the most popular, validated ACS risk score (41-44) and this was reflected by our sample where almost 75% of the physicians surveyed who used a risk score, reported using TIMI risk. Also, the use of the TIMI risk score is internally valid as physicians correctly assessed increasing risk according to the TIMI risk score (p<0.001).

3.22 Conclusion

Canadian specialists' decisions to refer patients for CC appear to be influenced by gender, age and patient preference in clinical scenarios where cardiac risk is held constant. Future investigation of possible age and gender biases as well as better understanding of how physicians use these factors as proxies for risk is warranted.

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Table 1: Participating Physician Demographics and Hospital Factors

Table 1

Physician Characteristics	Number of Physicians (N=79)
-	(%)
Male Physician	69 (87.3)
Speciality	
Cardiology	72 (91.1)
Internal Medicine	7 (8.9)
Years practicing	
<10 years	21 (26.6)
10<20 years	31 (39.2)
20<30 years	22 (27.8)
<u>≥</u> 30 years	5 (6.3)
Female patients seen in practice	(N=76)
<35%	10 (13.2)
35% <50%	45 (59.2)
<u>>50%</u>	21 (27.6)
Non-white patients seen in practice	(N=72)
<10%	14 (19.4)
10% <25%	33 (45.8)
25% <40%	16 (22.2)
>40%	9 (12.5)
Risk score used	(N=72)
No	37 (51.4)
Yes	35 (48.6)
TIMI Risk Score	26 (74.3)
Other	3 (8.6)
Hospital Characteristics	
Presence of catheterization facilities	49 (64.5)
Academic Centre	58 (73.4)
Region of Canada	
West	18 (22.8)
Ontario & Quebec	56 (70.9)
Atlantic	5 (6.3)

Main Effect Results of RACE CAR Study

Table 2: Benefit from Cardiac Catheterization Controlled for Gender, Age, TIMI RiskScore and Patient Preference

What is the likelihood this patient would benefit from a cardiac catheterization procedure? 1=Very unlikely to 5=Very likely

Variable	Mean Value <u>+</u> 95% CI	Significance Level
Gender	Male 4.44 <u>+</u> .14	0.03
	Female 4.25 <u>+</u> .14	
Age	55 years 4.55 <u>+</u> .18	0.01
	75 years 4.14 <u>+</u> .18	
Level of Risk	Low 3.87 <u>+</u> .2	<0.01
	Mod 4.25 <u>+</u> .2	
	High 4.93 <u>+</u> .16	
Expressed	Agreeable for $CC = 4.65 \pm 25$	0.01
Preference		0.01
	Disagreeable for CC 4.17 <u>+</u> .24	
	No opinion 4.21 <u>+</u> .16	
Table 3: Interaction of Patient Benefit From Cardiac Catheterization (CC) ReferralBetween TIMI Risk Score and Gender, Age and Patient Preference

What is the likelihood this patient would benefit from a cardiac catheterization procedure? 1=Very unlikely to 5=Very likely

	Low TIMI Risk Mean <u>+</u> 95% CI	Moderate TIMI Risk	High TIMI Risk Mean <u>+</u> 95% CI	
		Mean <u>+</u> 95% CI		
Gender				
Male	4.20 <u>+</u> .25*	4.16 <u>+</u> .24	4.97 <u>+</u> .22	
Female	3.54 <u>+</u> .27*	4.33 <u>+</u> .25	4.88 <u>+</u> .22	
Age				
55 years	4.52 <u>+</u> .33*	4.13 <u>+</u> .29	4.98 <u>+</u> .25	
75 years	3.22 <u>+</u> .31*	4.36 <u>+</u> .33	4.85 <u>+</u> .27	
Patient Preference				
Agreeable for CC	5.00 <u>+</u> .45*	4.06 <u>+</u> .47*	4.88 <u>+</u> .33*	
Disagreeable for	3.67 <u>+</u> .41*	3.93 <u>+</u> .39*	4.92 <u>+</u> .39*	
CC				
No opinion	2.95 <u>+</u> .27*	4.74 <u>+</u> .25*	4.94 <u>+</u> .24*	

*p<0.001

Controlled	Estimate	d Risk	Chest	Pain	Probabi	lity of	Influen	ce of
Patient	of Myoc	ardial	Characterization ⁺		Significant		Patient	
Variable	Infarct	tion*			CAD‡		Opinion [§]	
	Mean <u>+</u>	P-	Mean <u>+</u>	Р-	Mean <u>+</u>	P-	Mean <u>+</u>	Р-
	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value
Gender		0.12		0.02		0.01		0.39
Male	2.47 <u>+</u> .12		2.66 <u>+</u> .08		4.67 <u>+</u> .14		2.90 <u>+</u> .27	
Female	2.34 <u>+</u> .12		2.53 <u>+</u> .08		4.38 <u>+</u> .14		2.99 <u>+</u> .27	
Age		0.26		<0.01		0.53		0.43
55 years	2.47 <u>+</u> .14		2.77 <u>+</u> .1		4.57 <u>+</u> .16		3.03 <u>+</u> .31	
75 years	2.34 <u>+</u> .16		2.43 <u>+</u> .1		4.48 <u>+</u> .18		2.87 <u>+</u> .33	
TIMI Risk		<0.01		<0.01		<0.01		< 0.01
Low	1.95 <u>+</u> .16		2.36 <u>+</u> .1		4.25 <u>+</u> .18		3.23 <u>+</u> .33	
Moderate	2.36 <u>+</u> .16		2.48 <u>+</u> .1		4.43 <u>+</u> .18		2.97 <u>+</u> .33	
High	2.90 <u>+</u> .12		2.95 <u>+</u> .1		4.89 <u>+</u> .16		2.64 <u>+</u> .29	
Patient		0.43		0.10		<0.01		0.28
Preference								
Agree for CC	2.47 <u>+</u> .16		2.58 <u>+</u> .14		4.71 <u>+</u> .18		2.69 <u>+</u> .41	
Disagreeable	2.39 <u>+</u> .18		2.69 <u>+</u> .14		4.29 <u>+</u> .2		3.12 <u>+</u> .41	
for CC								
No opinion	2.35 <u>+</u> .12		2.53 <u>+</u> .08		4.57 <u>+</u> .14		3.03 <u>+</u> .29	

Table 4:	Influence	of Secondary	Objectives	Controlled	for	Gender,	Age,	TIMI	Risk
Score and	Patient Pr	eference							

*How would you characterize this patient's level of risk of suffering a fatal or non-fatal MI in the next 14 days? 1= Low risk, 2=Moderate risk, 3=High risk

[†]How would you characterize this patient's chest pain? 1=Non-cardiac, 2=Possibly cardiac, 3=Definitely cardiac

‡Estimate the probability that this patient has significant CAD (stenosis >70%). 1=Very unlikely to 5=Very likely

 $^{\$}$ How much does the patient's opinion influence your decision to refer them for cardiac catheterization? 1=Not very much to 5=Very much

CHAPTER 4

4.0 Identifying Women with Severe Angiographic Coronary Disease

The second study of my thesis entitled, "Identifying women with severe angiographic disease" sought to examine the characteristics including the distribution of risk factors according to age, severity of functional angina symptoms (CCS classification) and pattern of angiographic disease of over 23,000 men and women referred for their first cardiac catheterization. The methodology of this study consisted some stratification and univariable and multivariable logistic regression modelling. This paper was published in the Journal of Internal Medicine and is presented in Appendix C.

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Identifying Women with Severe Angiographic Coronary Disease

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4.1 Abstract

Background: Sex/gender differences in risk factors and symptoms of coronary artery disease (CAD) have been characterized however there is little information if variation in symptom severity between men and women is associated with differences in CAD severity and age.

Methods: 23,771 patients referred for first coronary angiogram from 2000 to 2006 were analysed according to angiographic disease severity, stratified by age. Univariate and multivariate logistic regression assessed association between risk factors and angina symptoms with severe CAD.

Results: Women are significantly older (69.8 \pm 10.6 vs. 66.3 \pm 10.7 years), have higher rates of diabetes (35.0% vs. 26.6%) and hypertension (74.8% vs. 63.3%). Men are more likely to be smokers (56.9% vs. 37.9%). Although women are less likely to have severe CAD than men (22.3% vs. 36.5%), among those with severe CAD, CCS class IV angina was more prevalent among women than men (56.7% vs. 47.8%). Factors independently associated with severe CAD include age (OR=1.05, p<0.01), male sex (OR=2.43, p<0.01), diabetes (OR=2.00, p<0.01), hyperlipidemia (OR=1.50, p<0.01), smoking (OR=1.10, p<0.01) and CCS class IV symptoms (OR=1.43, p<0.01). CCS Class IV angina is a stronger predictor of severe CAD among women compared to men (OR= 1.82, vs. men OR= 1.28, p<0.01).

Conclusions: Women referred for first diagnostic angiography have lower rates of severe CAD compared to men. While conventional risk factors are primary determinants of CAD, CCS Class IV angina is more strongly associated with severe CAD in women than in men. These findings can assist physicians to identify women at risk.

Keywords: coronary artery disease; gender; angiography; risk factors; angina

4.2 Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity of both men and women in westernized countries accounting for over one third of total deaths (1:2). In women, the annual mortality rate from CAD is greater than that of breast cancer, even among the younger groups (i.e. 35-55 years) (1-6). Despite this importance of CAD for women, there is a persistent perception that CAD is a "man's disease". Contributing to this notion is the observation of differences in incidence rates according to age; the incidence of CAD in women is lower than men, but rises steadily after the fifth decade and nearly equalises between the sexes by the seventh decade of life (5:6). Correspondingly, the distribution of CAD risk factors varies between men and women across age ranges and failure to consider these differences may have contributed to the belief that women are at lower risk of CAD compared to men (7;8). In addition, gender differences in the symptoms of CAD exist between women and men, as women are more likely to have symptoms considered atypical compared to men (3;5;11;13;16-20). All of these factors likely contribute to the lower referral rates for coronary angiography among women compared to men, even in patients who have severe CAD and acute coronary syndromes (ACS) (3;7;13). Younger women with ACS are at three times higher risk for mortality than their young male counterparts (30;31). The higher risk of mortality in these young women may be due in part to the *perception* that younger women are at very low risk of CAD and therefore diagnostic and therapeutic

management is minimal. On the other hand, a lower rate of angiography may be appropriate because when women do undergo coronary angiography, they are more often reported to have "normal" coronary anatomy and are less likely to have severe CAD (i.e. three vessel and left main disease) compared to men (9-15). Although sexrelated differences in risk factors for CAD and the presentation of CAD symptoms are well-known, there is little information on whether the variation in the degree of symptom severity between men and women is associated with differences in CAD severity and whether the relationships vary by age. There is an urgent need to better understand the presentation of cardiac symptoms in women in order to facilitate diagnosis and treatment, initiate aggressive risk factor intervention, and to improve the quality of life.

The objective of our investigation is to examine the distribution of risk factors and coronary angiographic patterns of CAD in women and men who are referred for first diagnostic angiogram and to identify factors associated with severe CAD. Specifically we aimed (i) to investigate sex differences in the distribution of conventional risk factors and the angiographic pattern of CAD in young patients \leq 60 years of age compared to older patients >60 years of age (ii) to examine the factors associated with the presence of severe CAD defined as left main stenosis \geq 50%, 3 vessel disease with \geq 70% stenosis or 2 vessel disease including proximal left anterior descending stenosis of \geq 70% and (iii) to evaluate the utility of Canadian Cardiovascular Society (CCS) class angina scoring system in predicting severe CAD

among a cohort of women and men referred for first diagnostic coronary angiography at a tertiary care institution in Canada.

4.3 METHODS

The study sample included 23,771 consecutive men and women who underwent diagnostic coronary angiography between April 1, 2000 to November 15, 2006. Data used were part of the Hamilton Health Sciences Angiography Registry. Details of the database are described elsewhere (21). Briefly, the purpose of this prospective registry was to document the characteristics of patients waiting for coronary angiography and to document their subsequent angiographic outcomes. The Hamilton Health Sciences is the sole provider of tertiary cardiac care services including coronary angiography, percutaneous coronary intervention and cardiac surgery for most patients, covering the geographic region of Central-South Ontario, Canada, a population of over 2.2 million people. Eligible patients were suspected of having CAD and only those without a prior diagnosis of CAD were included in this analysis. This inclusion criterion was intended to capture patients only with suspected CAD that have not been previously diagnosed with CAD as confirmed by the gold standard, cardiac catheterization. Patients were excluded if they were undergoing coronary angiography for reasons other than diagnosing coronary artery disease such as valvular disease, or if they had a prior or recent evidence of an MI, previous coronary artery bypass graft surgery (CABGS) or

percutaneous coronary intervention (PCI). The Hamilton Health Sciences Angiography Registry has been approved by the Research Ethics Board.

4.3 Data Collection

Patient information was prospectively collected at the time of coronary standardised Hamilton-Wentworth angiography referral using Regional Cardiovascular Program Coronary Angiography Consult Forms distributed to all referring physicians in the region. Information was recorded by the referring physician, electronically entered and edited into a computerised database. The Coronary Angiography Consult forms include patient demographic characteristics, reason for referral (coronary disease, cardiomyopathy, valvular disease. other). state of urgency for coronary angiography, anginal symptom class graded according to the Canadian Cardiovascular Society (CCS) Class Grading system 0-IV and patient risk factor profile; history of smoking, diabetes (insulin dependent or oral medication), hyperlipidemia and hypertension requiring medical treatment, including a comprehensive list of current medications (21). Coronary anatomy was graded by the angiographer immediately following the procedure using a standardised diagram (22). In this analysis, we categorised patients according to severity of disease; severe CAD was defined as left main stenosis >50%, 3-vessel disease with >70% stenosis in at least one vessel, or 2-vessel disease, including a proximal left anterior descending (LAD) stenosis >70%; moderate risk CAD

included 2-vessel disease (excluding proximal LAD) with \geq 70% lesion, 1-vessel disease with \geq 70% lesion; low risk CAD was defined as lesions with \leq 50% stenosis or normal coronary anatomy. The criterion for "severe CAD" was chosen to characterise those that have prognostically significant CAD in terms of surgical revascularisation compared to medical therapy (23).

4.4 Statistical Analysis

All analyses were performed using SAS, version 9.1 software (Cary, N.C.) and SPSS, version 16.0 (Chicago, IL). Baseline characteristics including age, risk factors, coronary anatomy and CCS symptom class were compared between women and men. Continuous variables were expressed as means with standard deviations and probability estimates were obtained using analysis of variance. Dichotomous variables were expressed as percentages with 95% confidence intervals (CI) and probability values were estimated using logistic regression. To present proportions in risk factor prevalence rates, the data were stratified by sex and age. Patients were categorised and analysed according to CAD risk group; patients with angiographically documented severe CAD were compared to patients with low risk CAD (consisting of moderate and low risk groups). Univariate and multivariate logistic regression were used to determine which of the proposed risk factors (independent variables) were significantly associated with severe CAD. The dependent variable was binary and defined as the presence or absence of severe CAD (1 versus 0, respectively). Independent variables included age, sex, medically

treated risk factors, past or present smoking and severe (CCS Class IV) angina. Logistic models employed a backwards elimination process. Interactions were tested and adjusted for the other risk factors in model. Odds ratios and their accompanying 95% confidence intervals (CI) were calculated. All tests employed 2tailed significance testing.

4.5 RESULTS

Baseline Characteristics of Study Population

During the study period, April 2000 to November 2006, 31,758 patients were enrolled in the Hamilton Health Sciences Angiography Registry. For this study, 23,771 are included in the analysis, excluding elective patients with prior MI (n=1,405), prior CABGS (n=3,221) and prior PCI (n=3,361). Of 23,771 study patients, 9,112 (38.4%) are women and 14,645 (61.6%) are men. The baseline characteristics are presented in Table 1. Briefly, compared to men, women are significantly older (65.2 + 12.0 vs. 62.3 + 12.3, p<0.01), less likely to be past/present smokers (37.3% versus 57.2%, p<0.01) and more likely to be hypertensive (65.9% versus 57.9%, p<0.01) (Table 1).

Among young patients referred to coronary angiography, women are slightly older (51.4 + 6.1 years versus 50.9 + 7.2 years, respectively), are more likely to be diabetic (20.7% versus 16.4%), and hypertensive (53.4% versus 49.5%), less likely to be

past/present smokers (49.9% versus 62.9%), and to have considerable hyperlipidemia (57.3% versus 60.1%) compared to men (Table 1).

Angiographically, we found women are more likely to have normal/ mild CAD (39.7% versus 21.3%, p<0.01) and less likely to have severe CAD (36.5% versus 22.3%, p<0.01) compared to men (Table 2).

Some differences in symptom severity in CCS angina classification between the sexes was observed; men are more likely to have CCS Class 0 to II angina (31.2% versus 29.3%, p<0.01) and CCS Class IV angina (44.0% versus 42.9%, p<0.01) compared to women (Table 3).

4.6 Patients Identified with Angiographically Severe CAD

Risk Factors in Patients with Angiographically Severe CAD Stratified by Age Risk Factors Among Young Women versus Young Men

When stratified by age (\leq 60 years versus >60 years) differences in risk factor distribution by the presence of severe angiographic CAD are observed. Consistent with the overall observations, younger women are less likely to have severe CAD than younger men (19.9% versus 30.0%, p<0.01). Young women are more likely however to have diabetes (45.7% versus 24.7%, p<0.01) and have hypertension (65.1% versus 55.7%, p<0.01) compared to young men. Young men on the other hand, are more likely to past/present smokers compared to young women (64.7% versus 58.8%, p=0.04). There are no statistically significant differences in the proportion of women and men with hyperlipidemia (72.2% women versus 71.3% men, p=0.74) (Table 4).

4.7 Risk Factors Among Young Women Versus Older Women

As expected, older women referred for first diagnostic angiogram are more likely to have severe CAD (80.1% versus 19.9%, p<0.01) compared to younger women. However, younger women with severe CAD are more likely to be diabetic (45.7% versus 32.2%, p<0.01) and more likely to be past/present smokers (58.8% versus 32.7%, p<0.01), compared to older women. On the other hand, older women are more likely to be hypertensive (77.1% versus 65.1%, p<0.01) compared to younger women. There are no statistically significant differences in the proportion of women with hyperlipidemia between the two age strata (p=0.73) (Table 4).

4.8 Angina Severity in Patients with Severe CAD Stratified by Age

Overall, women with angiographically severe CAD are more likely to have severe angina than men. Specifically, women are more likely to have CCS Class IV angina (56.7% versus 47.8%, p<0.01), whereas men are more likely to have CCS Class 0 to II symptoms compared to women (23.5% versus 17.8%, p<0.01) (Table 3).

4.9 Angina Severity Among Young Women versus Young Men

Younger men are more likely to have less severe symptoms or CCS 0 to II angina compared than women (23.0% versus 18.7%). On the other hand, young women <60 years of age with severe CAD are more likely to have CCS Class IV angina than their young male counterparts (54.5% versus 49.1%) (Table 3).

4.10 Angina Severity Among Young Women versus Older Women

Older women with severe CAD are more likely to have CCS Class IV angina than their younger female counterparts (57.2% versus 54.5%). However there are no differences between CCS Class 0 to II angina and CCS Class III angina between younger and older women (Table 3).

4.11 Risk Factors Associated with Severe Angiographic CAD

Factors independently associated with the presence of severe angiographic CAD include age (OR=1.04, 95% CI 1.04-1.05, p<0.01), male sex (OR=2.01, 95% CI 1.88-2.14, p<0.01), diabetes (OR=2.09, 95% CI 1.94-2.24, p<0.01), hyperlipidemia (OR=1.69, 95% CI 1.58-1.80, p<0.01), hypertension (OR=1.43, 95% CI 1.35-1.53, p<0.01), smoking (OR= 1.13, 95% CI 1.06-1.20, p<0.01) and CCS class IV anginal symptoms (OR=1.43, 95% CI 1.34-1.52, p<0.01) (Table 5). In an adjusted multivariate logistic regression model, the factors independently associated with severe CAD include age (OR=1.05, 95% CI 1.05-1.05, p<0.01), male sex (OR=2.43,

95% CI 2.26-2.62, p<0.0001), diabetes (OR=2.00, 95% CI 1.86-2.18, p<0.01), hyperlipidemia (OR=1.50, 95% CI 1.39-1.61, p<0.01), smoking (OR=1.10, 95% CI 1.03-1.18, p=0.006) and CCS class IV symptoms (OR=1.43, 95% CI 1.34-1.53, p<0.01) (Table 5). An interaction between CCS Class IV angina and sex was identified (p<0.01) and indicates that women with CCS class IV angina are more likely to have severe CAD compared to men with CCS class IV angina, (OR= 1.82, 95% CI 1.61-2.04 versus OR= 1.28, 95% CI 1.18-1.39, p<0.01, respectively) (refer to Figure 1).

4.12 Discussion

In this prospective registry of over 23,000 individuals referred for first diagnostic coronary angiography for CAD, women were found to be older, have more diabetes and hypertension and are less likely to smoke compared to men. Furthermore, the coronary angiography profile of women indicates that women are more likely to have normal/ mild CAD and less likely to have severe angiographic CAD. Conventional risk factors and CCS Class IV symptoms are all strong predictors of severe angiographic CAD. The presence of CCS Class IV angina appears to be more predictive of severe angiographic CAD in women compared to men. This information should be used by clinicians when deciding which patients to refer to coronary angiography.

Sex differences in the distribution of risk factors between women and men have been previously reported by several investigators and in prospective studies (3-5;7;9;13-15;17;19;24-31). Despite differences between studies, our findings are consistent with previous reports. Our observation that women are older at time of first referral lends supports to the observation that women develop CAD later in life than men. Moreover, the risk factor profile among women within this cohort is also consistent with prior literature supporting women at time of referral are more often hypertensive whereas men are more likely to smoke.

The proportion of patients with severe angiographic CAD is greater in men than women. A 20% excess in the prevalence of severe CAD remains even after adjustment for age and other risk factors. It is possible that other sex differences may make men more prone to develop obstructive CAD. While the proportion of women with severe angiographic CAD is lower than men, among young patients <60 years of age with suspected CAD, there is no difference attributed to age. In particular, within this subgroup of young women with severe angiographic CAD, the proportion with diabetes is almost 2 fold times higher than among men, and the prevalence of hypertension, smoking and elevated lipids is particularly high, over 50%. Prior studies note that the protective "female advantage" of lower CAD prevalence is essentially eliminated among diabetic women (5;32;33), and that the 10 years of delayed onset in CAD between women and men is largely explained by more frequent risk factors among men at younger ages (38). Unfortunately, diabetic women may receive less treatment and CAD risk factor modification than diabetic

men, because of the perception that women are at lower risk of CAD (33). Despite the perception that younger women are less likely to have severe CAD compared to men, our data emphasizes that women with diabetes and other proven cardiovascular risk factors should be considered carefully for diagnostic coronary angiography particularly if they have symptoms suggestive of CAD, regardless of their age and sex.

While women with risk factors have a greater probability of having severe CAD compared to women without risk factors, we and others have observed that women referred for diagnostic coronary angiography, in the outpatient as well as in the ACS setting, are more likely to have normal coronary arteries (39). Existing evidence suggests that women may indeed experience typical symptoms of angina in the presence of normal coronaries because they suffer vasospasm, excessive plaque/non-obstructive disease and/ or endothelial dysfunction (34:35:39); the question of the utility of typical symptoms of angina in predicting the presence of severe CAD has been raised (13:24:36). In our study we observed that the presence of severe anginal (CCS Class IV) symptoms using a standardised symptom classification is a useful predictor, despite the prior controversies reported in the literature (3;9-13). In fact, despite a slightly higher and statistically significant proportion of men presenting with CCS Class IV symptoms, the association of CCS class IV symptoms and severe CAD was stronger in women than in men in our study. This finding is of particular interest, since women are often reported to have more atypical symptoms with less severe obstructive CAD. This has been identified as a

'paradox', where the prevalence of angina in women is similar to that of men, although men are more often found to have angiographically demonstrated CAD (37). Our data confirms that women with severe angina and risk factors are very likely to have angiographically documented severe disease. Further, this finding is particularly robust since the definition of "severe CAD" used reflects standard criterion and has prognostic significance (23). Researchers in women's cardiac health have called for the "imminent need" for better clinical classification to predict the presence or absence of severe CAD in women with suspected CAD (39). Our data should aid clinicians in determining who should be referred for diagnostic angiography among at risk women with suspected CAD.

It is important to note that although there are limitations inherent to all database analyses our prospective registry represents "real world" clinical practice. While referral bias may limit the external validity, our results are internally valid. Despite the fact that women are referred less often for catheterization, within the ones who were referred, we demonstrate that more women are likely to have normal/ mild CAD, and less likely to have severe CAD. In this analysis, patient referrals are dependent on "real world" physician decision making rather than protocol driven angiograms. Consequently, we relied on the summarised reporting of the risk factors by the referring physician and did not have actual laboratory values for diabetes and hyperlipidemia, or blood pressure readings for hypertensive patients. However we cross-checked the reported risk factors with medical treatment to minimise this potential bias, and as such our prevalence estimates may

be underestimates. Also, much like real world practice, the severity of angiographic stenosis was solely determined by the angiographer performing the procedure. Lastly, the primary purpose of the registry was to document adverse events while patients were waiting for their angiogram, and follow-up data was not collected. Despite this, it is important to note that this study represents one of the largest series of women analysed alongside men.

4.13 Conclusion

Women referred for first diagnostic angiography are more likely to have normal/ mild CAD and to have lower rates of severe CAD compared to men across all ages. While conventional risk factors including age, sex, diabetes, smoking and hyperlipidemia are primary determinants of CAD, CCS Class IV angina is more strongly associated with severe CAD among women than in men. These findings have implications for physicians to better identify women at risk and to target diagnostic and treatment strategies accordingly.

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Table 4-1

Table 1: Baseline Characteristics of Patients in the Hamilton Health ScienceCoronary Angiography Registry

	MEN		WOMEN		P-Value
	Total	Men	Total	Women	Total Men
	Men	<u><</u> 60 years	Women	<u><</u> 60 years	vs. Total
	N (%)		N (%)		Women
Total N	14645	6421	9112 (38.4)	3091	< 0.01
	(61.6)	(67.5)		(32.5)	
Mean Age	62.3	50.9 <u>+</u> 7.2	65.2 <u>+</u> 12.0	51.4 <u>+</u> 6.8	< 0.01
	<u>+</u> 12.3				
Diabetes	2832	1055	1832 (20.7)	621 (20.7)	0.15
	(20.0)	(16.4)			
Smoking	8238	3986	3351 (37.3)	1525	< 0.01
	(57.2)	(62.9)		(49.9)	
Hypertension	8395	3147	5946 (65.9)	1634	< 0.01
	(57.9)	(49.5)		(53.4)	
Hyperlipidemia	9019	3806	5530 (61.5)	1750	0.14
	(62.4)	(60.1)		(57.3)	

	Total Men	Total Women	P-Value
	N (%)	N (%)	
Normal coronaries	1437 (9.8)	2154 (23.6)	<0.01
Mild CAD	1677 (11.5)	1466 (16.1)	<0.01
1 vessel disease	4092 (27.9)	2010 (22.1)	<0.01
2 vessel disease	722 (4.9)	293 (3.2)	<0.01
All other 2 vessel	1553 (10.6)	640 (7.0)	<0.01
3 vessel disease	3291 (22.5)	1176 (12.9)	<0.01
Left main disease	519 (3.5)	235 (2.6)	<0.01
Low Risk CAD	7873 (63.5)	5941 (77.7)	<0.01
Severe CAD	4532 (36.5)	1704 (22.3)	<0.01

Table 4-2: Coronary Anatomy Differences Between Men and Women

CCS Angina Class	Total P	atients		Severe CAD			
			Μ	ale	Female		
	All Male	All	<60	>60	<60	>60	
	N (%)	Female	Years	Years	Years	Years	
		N (%)	N (%)	N (%)	N (%)	N (%)	
CCS Class 0-II	4341	2528	305	730	62	223	
Angina	(31.2%)	(29.3%)	(23.0)	(23.8%)	(18.7)	(17.7)	
CCS Class III	3457	2396	370	889	89	331	
Angina	(24.8%)	(27.8%)	(27.9)	(29.0)	(26.8)	(25.1)	
CCS Class IV	6135	3697	651	1447	181	755	
Angina	(44.0%)	(42.9%)	(49.1)	(47.2%)	(54.5)	(57.2)	

Table 4-3: Frequency of CCS Class* Angina Symptoms According to Sex andAge

*CCS Class 0 –Asymptomatic

CCS Class I –Ordinary physical activity such as walking or climbing stairs does not cause angina; angina with strenuous, rapid or prolonged exertion at work or recreation.

CCS Class II -Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind or under emotional stress, or during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.

CCS Class III – Marked limitation of ordinary physical activity. Walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

CCS Class IV –Inability to carry out any physical activity without discomfort –anginal syndrome may be present at rest.

	M	EN	P-Value	WO	MEN	P-Value
	<u><</u> 60	>60	<u><</u> 60 years	<u><</u> 60	>60	Women
	years	years	Women vs.	years	years	<u><</u> 60 yrs
	N (%)	N (%)	Men	N (%)	N (%)	vs. >60
						yrs
Severe CAD	1357	3162	< 0.01	339	1362	< 0.01
	(30.0)	(70.0)		(19.9)	(80.1)	
Mean Age	53.1 <u>+</u>	72.0 <u>+</u>	0.93	53.1 <u>+</u>	73.9 <u>+</u>	< 0.01
	6.0	6.5		6.1	6.1	
Diabetes	325	841	< 0.01	149	427	< 0.01
	(24.7)	(27.4)		(45.7)	(32.2)	
Smoking	867	1667	0.04	197	439	< 0.01
	(64.7)	(53.5)		(58.8)	(32.7)	
Hypertension	746	2087	< 0.01	218	1040	< 0.01
	(55.7)	(66.5)		(65.1)	(77.1)	
Hyperlipidemia	955	2185	0.74	242	960	0.73
	(71.3)	(69.9)		(72.2)	(71.3)	

Table 4-4: Proportion of Risk Factors in Younger Patients Versus OlderPatients with Severe CAD

VARIABLES	UNIVARIABLE ANALYSIS		MULTIVARIAB	LE ANALYSIS				
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value				
Diabetes	2.09	< 0.01	2.00	< 0.01				
	(1.94-2.24)		(1.86-2.18)					
Sex (Men vs. Women)	2.01	< 0.01	2.43	< 0.01				
	(1.88-2.14)		(2.26-2.62)					
Hyperlipidemia	1.69	< 0.01	1.50	< 0.01				
	(1.58 - 1.80)		(1.39-1.61)					
Hypertension	1.43	< 0.01	1.01	0.73				
	(1.35-1.53)		(0.94-1.09)					
CCS Class IV Angina	1.43	< 0.01	1.43	< 0.01				
	(1.34-1.52)		(1.34-1.53)					
Smoke	1.13	< 0.01	1.10	0.05				
	(1.06 - 1.20)		(1.03-1.18)					
Age	1.04	< 0.01	1.05	< 0.01				
-	(1.04-1.05)		(1.05-1.05)					
Interaction of CCS Class IV Angina and Sex*								
Male x CCS Class IV Angina			1.28 (1.18-1.39)	<0.01				

Table 4-5: Univariable and Adjusted Multivariable Logistic Regression Model ofVariables Associated with Severe CAD

 Female x CCS Class IV Angina
 1.82
 <0.01</td>

 (1.61-2.04)
 *Interaction terms are adjusted for diabetes, hyperlipidemia, hypertension, smoke

and age. Odds ratio values did not change from presented model.

Figure 4-1



CHAPTER 5:

Understanding Cardiac-Related Symptoms According to Sex/Gender:

Re-constructing Angina in Men and Women

A qualitative exploration of symptoms

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Chapter 5: Understanding Cardiac-Related Symptoms According to Sex/Gender

5.0 Introduction

5.1 Sex and Gender Differences

A PubMed search, of the number of papers published within one calendar year, 30 years apart, using the medical subject headings (MeSH) "sex" versus "gender" and cardiovascular disease was conducted. During the year 1980, 476 articles were identified using the terms ["cardiovascular disease" AND "sex"] versus no articles using the terms ["cardiovascular disease" AND "gender"]. In the year 2010, almost 4000 articles were identified using ["cardiovascular disease" AND "sex"] compared to just over 2000 articles using the terms ["cardiovascular disease" AND "gender"]. This finding prompts several questions: *What is the difference between "sex" and "gender"*? Why was the term "gender" introduced as a new construct? Is the distinction between "*sex"* and "gender" important in the study of CVD? And most importantly, can we measure "gender"?

The term *sex* is defined as "the biological differences between females and males, which includes reproductive differences as well as anatomical and physiological differences"; whereas the term '*gender*' refers to the array of socially constructed roles and relationships, personality traits, attitudes, behaviours, values, relative power and influence that society ascribes to two sexes on a differential basis (Canada, 2011). The World Health Organization (WHO) further describes that

"aspects of sex will not vary substantially between different human societies, while aspects of gender may vary greatly" (World Health Organization, 2011). The term 'gender' was introduced as a medical subject heading (MeSH) term in the year 1975, during a time of remarkable societal change related to the ideological construct of the sexes, particularly the changing role and voice of women in western society (de Beauvoir, 1949). The new construct of 'gender' was introduced as a means to incorporate this "shift" into medicine while simultaneously trying to advance the distinction between the terms 'sex' and 'gender'. However, since gender has been introduced in medicine, this has been met with little overall success as the two terms continue to be incorrectly used interchangeably (Krieger, 2003).

The term '*sex*' was traditionally used to refer to the biological differences between men and women, varying only in chromosomes and in systems related to the reproductive system, including the reproductive organs, glands and hormones related to reproduction (National Library of Medicine, 2011). This perspective of sex differences has long prevailed in medicine as even the most popular anatomy and medical textbooks illustrate predominantly men and illustrations of women are almost exclusively reserved for depicting reproductive systems (M. Giacomini, Rozée-Koker, & Pepitone-Arreola-Rockwell; Mendelsohn, Nieman, Isaacs, Lee, & Levison, 1994). As a result, women are grossly underrepresented in anatomy/medical textbooks and the implication of the absence of women in illustrations of non-reproductive anatomy may perpetuate the image of the male body depicted as the "normal adult" (M. Giacomini et al.; M. Giacomini, Rozée-Koker,

& Pepitone-Arreola-Rockwell, 1986; Mendelsohn et al., 1994). This controversial hypothesis was challenged at the time (Arja, 1995; Brunemeier, 1995; Gale, 1995; Passaretti, 1995; Wright, 1995; Yeakel, 1995; Zahniser, 1995) however supporters (Denman, 1995; M. Giacomini et al.; Hubel, 1995; Mendelsohn et al., 1994; Willms & Schneiderman, 1995) were quick to acknowledge the *gender gap* in medicine, calling out for the greater inclusion of women, equal gender representation and a shift for change.

Not surprisingly, the focus and research about women's health was also largely centred around reproductive health (Miller, 2002; Thomas & Braus, 1998) such that, until recently, the primary health care for a woman was provided by an obstetrician-gynaecologist in many western countries including Canada and the United States. As a result, the provocative term, "bikini medicine" was proposed to capture the areas of a woman's body that receive the most medical attention. Thus, the systematic reproduction-focused isolation of women likely played a role in the development of the middle-aged white male as the normative frame for all nonreproduction/ hormone related diseases.

At the same time, there has been a well-documented overrepresentation of middle-aged white men enrolled in research studies and clinical trials. A call to curb the overrepresentation of white men in clinical trials was initiated by the National Institute of Health (NIH) in the United States in the early 1990's. At that time a policy requiring researchers to submit an explanation as to why women were not included in studies was implemented (Baird, 1999; Palca, 1990). Historically,

women have been excluded from studies and/or publications (Baird, 1999; O'Donnell, Condell, & Begley, 2004), even among large landmark clinical trials, such as the British Regional Heart Study, the Lipid Research Clinics Coronary Primary Prevention Trial and the Multiple Risk Factor Intervention Trial that collectively enrolled over 15,000 men and no women (Gordon et al., 1989; "Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group," 1982; Pocock, Shaper, Phillips, Walker, & Whitehead, 1986). In particular, pregnant women and women of childbearing age have been largely excluded from all non-pregnancy related medical research. Even today, this age group of women has been overwhelmingly omitted from clinical trials and very little information exists in the efficacy of various therapies in this population (Baird, 1999; Goldberg et al., 1998). The most common reasons cited for the exclusion of women from clinical trials include reasons relating to the possible confounding effects of the menstrual cycle of women, the added difficulty in patient recruitment strategies resulting in increased sample size and costs, and the unknown risks that may be imparted to the foetus (Baird, 1999; O'Donnell et al., 2004). Although all of these reasons may contain some truth, they remain untested and unknown. Further, women who develop cardiovascular disease are typically older and post-menopausal, further reducing the strength of traditional arguments (O'Donnell et al., 2004). The systematic exclusion of women due to biologically weak arguments and potential challenges in the recruitment of study patients is ethically unacceptable and statistically flawed (O'Donnell et al., 2004). As a result of
PhD Thesis

the overrepresentation of men in research studies, much of our current medical knowledge, including knowledge of cardiovascular disease, has been established on the study of middle-aged white men. This may also help to explain why heart disease is perceived to be a "man's disease" even while claiming more lives among women.

To help promote and ensure more equal representation and knowledge accumulation in the health of women, the policy of the NIH formally implemented legislation in the 1993 NIH Revitalization Act, requiring potential sex/gender differences to be explored in all NIH funded research (Miller, 2002). Despite enhancements to improve the knowledge of heart disease progression in women, women are still represented in smaller numbers compared to men and studies are rarely adequately powered to determine if sex/gender differences do in fact exist. As a result, the persistent sex/gender imbalances and biases in cardiovascular research, reinforce the perception that cardiac disease is a "man's disease", and contribute to the "male gendering" of cardiovascular disease, which is reinforced through media, health education, research and medical press (O'Donnell et al., 2004). The "add women and stir approach" to cardiac research has resulted in a knowledge gap of the disease course among women (O'Donnell et al., 2004).

5.1. Sex Differences in Angina

5.1.1 A Brief History of Angina

William Heberden in his 1768 address to the Royal College of Physicians of London has been credited as providing the first known description of 'angina pectoris':

"Those who are afflicted with it are seized, while they are walking and more particularly when they walk soon after eating with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away if it were to increase or to continue; the moment they stand still, all this uneasiness vanishes... the os sterni is usually pointed to as the seat of the malady..." (Comeau, Jensen, & Burton, 2006; Michaels, 2001)

Amazingly this description has been conceptualized into even illustrative material and remains unchanged some 250 years later (Gibbons et al., 1999; Netter, 1969). The importance of angina pectoris as a clinical manifestation of CAD was echoed by the Framingham investigators where they identified angina pectoris as a "better indicator of coronary arteriosclerosis (the etiologic cause of CAD) than other manifestations of CHD," (Dawber & Kannel, 1963). The initial results of Framingham revealed that angina, the cardinal manifestation of CAD, represented one-third of all new cases of CAD in men, and almost all the new cases in women (Dawber, Moore, & Mann, 1957). They claim that the

"The most notable fact is the predominance of the diagnosis of angina pectoris in women in proportion to the total number of women with atherosclerotic heart disease (CAD). Conversely, myocardial infarction was an uncommon disease in these women." (Dawber et al., 1957)

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This finding has been repeatedly supported since the Framingham Heart Study first published their study results over 60 years ago, perplexing researchers today while perpetuating the perception that CAD is a "man's disease". The Framingham investigators acknowledged the dissimilarity of CAD between the sexes and felt that the "the predominance of angina pectoris in women may be due to a faulty diagnosis or the manifestations of CAD in women may be different than in men" (Dawber et al., 1957). In the same report, the Framingham investigators refer to angina in women as "definite but uncomplicated angina" and it is likely this was the antecedent term to "atypical angina". The Framingham investigators published follow-up data at frequent time intervals and in several subsequent publications Framingham provided very minimal follow-up data in women or did not report cardiac findings in women at all, claiming that it was a "benign and uncomplicated condition in women because the incidence of MI was too low" (Dawber & Kannel, 1963). At the same time, they also justified the reporting of male data because "the male predominance has long been recognized as characteristic of CHD" (Dawber & Kannel, 1963).

During the same time period, the promising new diagnostic procedure known as cardiac catheterization/ coronary angiography/ cine coronary arteriography was developed. This ground-breaking procedure entails the insertion of a catheter through the femoral or radial artery and is inserted into the coronary conduit system of the heart where images are captured through x-ray radiology.

"The development of selective cine coronary arteriography has made possible the correlation of clinical syndromes and evidence of arterial obstruction during life. If this method of study is valid, there should be a close relationship between the typical clinical syndromes (angina pectoris and MI) and the presence of significant arteriographic abnormality." (Proudfit, Shirey, & Sones, 1966)

Despite being an invasive procedure with an associated risk of bleeding, stroke, MI

and death, it became firmly established as the gold standard procedure to diagnose

CAD. Proudfit et al (Proudfit et al., 1966) conducted the first large study seeking to

angiographically correlate CAD with angina and/or myocardial infarction on 1,000

patients. Although the investigators selected all patients into the study, they

declared a "striking predominance of men to women (786 to 214, respectively)"

with angiographic CAD concluding that women have more "atypical angina"

(Proudfit et al., 1966). The study investigators further define "atypical angina" as,

"Atypical angina pectoris is pain that was thought to be due to angina pectoris but the precipitating factors were unusual or inconstant. It is a vague term and it has a different meaning for each clinician.... Patients with atypical angina were referred to us because of confusion of clinical features... difficult therapeutic problems presented... no objective clinical evidence of the disease... emotional colouring... neurotic with convulsion... conversion neurosis was a common problem among those in whom the arteriographic findings proved to be normal..." (Proudfit et al., 1966).

In 1968, Campeau and colleagues conducted a study to "confirm the reliability" of the correlation between angina symptoms and angiographic CAD. In this study, Campeau is credited as being among the first to characterize and categorize the "types of angina", including a definition for "atypical angina", alongside angiographic study findings. Women were found to have more "Class I, no angina, and Class II, atypical angina" than men, while men had more "Class III angina

and myocardial infarction" than women (Campeau et al., 1968). The results of the study are summarized in Table 1 further supporting the higher prevalence of "atypical angina" among women.

Table 5: From the Study entitled, Clinical significance of selective coronarycinearteriography

	No. Of Cases	Mean	Age	Male to Female
		(years)		ratio
Diagnosis				
Without associated disease				
Class I (No angina)	50	42.5		1:2
Class II (Atypical angina)	26	46.1		1:1.5
Class III (Typical angina)	55	48.2		3.5:1
Myocardial Infarction	55	47.3		All males
				except two
Hyportonsion	12	170		2.1
Tryper tension	15	47.2		2.1
Valvular Disease	35	52.1		1.5:1
Source (Compose at al 10	2681			

Material: Clinical Diagnosis, Mean Age and Sex Distribution

Source: (Campeau et al., 1968)

Although the original Framingham Heart Study predated angiographic technology, the Framingham investigators felt that the results of the angiographic studies supported their earlier clinical findings and published a paper entitled, "The Framingham Study of Coronary Disease in Women." The abstract states: "Male chauvinists that we are (or at least are accused of being), we have too long concentrated our study of the evolution of CHD on male subjects. This is, and has been, unjustified on two counts: First, because explanation for the relative immunity of the pre-menopausal woman has implication for retarding the disease in the male. Second, because the disease while far less common in the female, nevertheless kills more women than other single cause." (Kannel & Castelli, 1972)

Despite the strong tone of the abstract, interestingly there is no mention of the term "angina" when describing the disease in women throughout the entire paper.

The internationally recognized and widely used tool to quantify angina severity today is credited to Dr. Campeau who submitted a "Letter to the Editor" to the journal *Circulation* in 1976, expanding his original categorization from the angiography study to include four categories (from three) entitled, the "Canadian Cardiovascular Society Angina Classification" (Campeau, 1976). The exact number of men and women enrolled in the study remains unknown however through some deductive calculations it is determined that women comprised less than half of the study population.

5.1.2 Defining Typical versus Atypical Angina Today

The American College of Cardiology/ American Heart Association (ACC/AHA) Task Force on Practice Guidelines formed an expert panel in 1999 to make recommendations on the diagnosis and treatment of patients with known or suspected angina. As a baseline starting point the guidelines panel defined angina: "Angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back or arm. It is typically aggravated by exertion or emotional stress and relieved by nitroglycerin." (Gibbons et al., 1999)

The classification scheme of angina is further grouped into the following:

Typical Angina (definite)
(1) Substernal chest discomfort with a characteristic quality and duration that is
(2) Provoked by exertion or emotional stress and
(3) Relieved by rest or nitroglycerin

Atypical Angina (probable) Meets two of the above characteristics

Noncardiac chest pain Meets <10f the typical angina characteristics

(Gibbons et al., 1999)

Inspired by the quest to study disease prevalence, the WHO also defined angina and

this definition was later expanded on by the Joint European Society of Cardiology

/American College of Cardiology Committee for the Redefinition of Myocardial

Infarction (Antman et al., 2000). Possible typical symptoms are defined as,

"Possible ischemic symptoms include chest, epigastric, arm, wrist or jaw discomfort with exertion or at rest. The discomfort may develop in the central or left chest and then radiate to the arm, jaw, back or shoulder. The discomfort is usually not sharp or highly localized and may be associated with dyspnea, diaphoresis, nausea, vomiting or light-headedness." Alternatively,

"The discomfort can develop in the epigastrium (often confused with indigestion), arm, shoulder, wrist, jaw or back without occurring in the chest but such a pattern is atypical."

(Antman et al., 2000)

As is evident from these two expert panels, there is no current consensus on the specific symptoms that constitute "typical" and "atypical" angina. The implication of this lack of agreement and standardization of terms has had detrimental consequences in the field of cardiovascular research. Currently it is virtually impossible to compare study findings between studies that use the terms "typical" versus "atypical". The variation in the symptoms that constitute "typical angina" in one study may compose the symptoms for "atypical angina" in another study. For example, Ryan et al (Ryan, DeVon, & Zerwic, 2005) define "typical" symptoms as,

"...substernal or left-sided chest pain or discomfort that the patients often describes as pressure or heaviness. This chest pain may radiate to the neck, jaw, shoulder or arms and is often accompanied by shortness of breath, nausea and diaphoresis."

"...is atypical if its location is other than substernal or left-sided or if it's described as numbness, tingling, pricking, stabbing or burning."

(Ryan et al., 2005)

In a study that analysed patients that presented with atypical angina, Canto et al define "typical" angina as,

"Typical presentation was defined as (1) chest pain located substernally in the left or right chest; and (2) chest pain characterized as squeezing, tightness, aching, crushing, arm discomfort, dullness, fullness, heaviness or pressure aggravated by exercise or relieved with rest of nitroglycerin. Atypical presentation was defined as the absence of typical presentation." (Canto et al., 2002)

It is important to note these definitions from Ryan et al (Ryan et al., 2005) and Canto et al (Canto et al., 2002) were generated after both expert panel definitions were published. Worse, the vast majority of published papers do not even define what symptoms they consider to be "typical" or "atypical" angina, assuming that the reading audience would know these definitions.

5.2 Clinical implications of sex differences in angina

Collectively the impact of no universal definition of the specific symptoms that constitute 'typical' and 'atypical' angina, coupled with the systematic underrepresentation of women in cardiovascular research, the focus on the reproductive-related health of women, and perception that CAD is a "man's disease," it is not surprising that there is confusion in both the patient population and professional medical community regarding heart disease in women. Even though women have a one in two lifetime risk of dying from CAD, women and health care providers alike do not realize that CAD is the greatest health risk for women

("Assessing the odds," 1998; Herrmann, 2008; Lori Mosca et al., 2000; The Lancet, 1998). The American National Council on Aging reported that middle- aged women are more concerned with developing breast cancer than CAD (61% vs. 9%, respectively) (The Lancet, 1998). These results have been echoed in other surveys of women's attitudes, fears and beliefs (Caldwell, Arthur, Natarajan, & Anand, 2007; J. D. Cameron et al., 1997; Griffiths, 1995; Lori Mosca et al., 2000; Pilote & Hlatky, 1995). On the one hand, women who experience cardiac-related symptoms, for a variety of reasons do not immediately identify them as potentially cardiac related and thus delay seeking medical treatment (Dempsey, Dracup, & Moser, 1995; Gallagher, Marshall, & Fisher, 2010; Lefler & Bondy, 2004). Similarly when women, particularly younger women (under age 50), present with acute myocardial infarction (AMI) for medical attention, they have up to three times higher risk of mortality compared to their young male counterparts (Vaccarino et al., 1998; Vaccarino, Krumholz, Yarzebski, Gore, & Goldberg, 2001). Furthermore, women are referred less for angiography than men, and receive less medical therapy and fewer invasive procedures (Bell et al., 1995; King et al., 2004; Lagerquist et al., 2001; Malenka et al., 2002; Roger et al., 2000; Vaccarino et al., 2005; Weintraub, Kosinski, & Wenger, 1996) even among women with acute coronary syndromes (Anand et al., 2005; Ayanian, 2001; Ayanian & Epstein, 1991; Roger et al., 2000). The suboptimal care of women is likely due to a combined confusion in the cardiovascular symptomology of women including the identification and interpretation of symptoms among patients and health professionals alike.

PhD Thesis

Much of our current cardiology knowledge has been established on the disease presentation using the male construct. Symptomology has been almost exclusively based on the male presentation of the disease where ill-defined terms such as "typical angina" have come to reflect the symptoms most common among men, and "atypical angina" has come to describe symptoms most common among women (Arslanian-Engoren et al., 2006; Comeau et al., 2006; DeVon, Hogan, Ochs, & Shapiro, 2010; DeVon & Zerwic, 2002; Granot, Goldstein-Ferber, & Azzam, 2004; Lefler & Bondy, 2004; Leuzzi & Modena, 2010; Lovlien, Schei, & Hole, 2006, 2007; Patel, Rosengren, & Ekman, 2004). The Canadian Cardiovascular Society Classification angina grading system was initially adopted to characterize patients undergoing bypass graft surgery recruited from Veteran Affairs hospitals, consisting almost exclusively of men (Campeau, 1976; Coronary artery surgery study (CASS) Investigators, 1983). This grading system, considered the gold standard, remains virtually unchanged today. And so, it is not surprising that so much confusion exists with the cardiac disease process as it occurs in women since the current framework was built through the study of men.

5.3 Study Rationale

When examining the trends of heart disease in women contradictory messages emerge: On the one hand, there is a prevailing perception that CAD is a "man's disease" yet CAD is the leading cause of death among women in the

developed world (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; Pilote et al., 2007). Further, among the exploration of various aspects of sex/gender differences in cardiovascular disease, it is essential that the underlying assumptions contributing to these differences be revisited. First, CAD was defined on a white male construct, which has come to represent the "normal adult". Those who did not present symptomatically as a white male or "normal adult" construct, including women, were described as "atypical". There are several issues embedded even within the "atypical" label. The word "atypical" itself has a connotation of "abnormal, uncharacteristic, unusual and uncommon" to name a few. Further, there are likely definable characteristics within this term however historically it was poorly defined and continues to be so. It is important to determine what constitutes common symptoms within an "atypical" group, including female-specific characteristics. Second, the term "gender" was first introduced in the medical literature in the 1970's to include "the array of socially constructed roles and relationships, personality traits, attitudes, behaviours, values, relative power and influence that society ascribes to two sexes on a differential basis" (Canada, 2011). Unfortunately, the distinction between the terms "sex" and "gender" have been poorly understood and incorrectly used, particularly in a cardiovascular setting, and this may be due to the earlier "established" angina constructs, prior to the introduction of "gender" into medicine.

To understand heart disease and the role of angina in women, it is necessary to redefine angina in women, developed on a construct established on women. It is

important to understand the symptoms most commonly experienced by women, in gender-centered language informed specifically by situated women (Stanford Encyclopedia, last updated March 16, 2011;). Qualitative methodology, including the use of semi-structured interviews will allow women and men to individually express their symptoms and perceptions in a *gender-centered language*. Further, the gold standard to diagnose CAD is coronary angiography, however it is an invasive procedure with associated risks. Only patients where the benefit outweighs the risks are recommended to be referred for coronary angiography. Since symptoms in women are not well defined and true risk assessment remains unknown, women are often not appropriately selected for angiography (Alter, Naylor, Austin, & Tu, 2002; Hochman et al., 1999; Roger et al., 2000; Schulman et al., 1999: Sharaf et al., 2001). As a result, the underlying assumptions of sources of sex and gender differences remained unexplored, hindering the advancement of scientific knowledge of CVD among women (O'Donnell et al., 2004). In order to progress the knowledge of CVD in women it is important to establish the "typical angina" symptomatic presentation on a construct informed by women.

5.4 Research Study Objective

1) To qualitatively explore angina and associated symptoms in women and men referred for coronary angiography, using a gender-centred approach rooted in feminist epistemology and 2) to develop a new construct of angina for women and men using gender-centred language informed from our qualitative exploration.

5.5 Study Design

A qualitative approach (modified grounded theory) was used to capture the interplay between the symptoms and perceptions of cardiac-related pain that patients experience, along with their understanding of disease (Charmaz, 2006; Russell Bernard & Ryan, 2010; Strauss, 1987). A modified grounded theory approach was selected to explore relationships and interrelationships between symptoms, perception of symptoms and the role of gender, while capturing these perspectives from the patient's individual "voice." The incorporation of a *gender-centered perspective* was guided using from concepts borrowed from feminist epistemology. Further, modified grounded theory approach was considered the optimal methodology to discover relationships, incorporate concepts from feminist epistemology with the goal of constructing a new theory that encompasses any discoveries made. The goal was to qualitatively explore angina symptoms in men and women referred for coronary angiography using concepts from feminist epistemology including:

Situated-knower: "Knowers" are situated in relation to what is known and the way it is known (Stanford Encyclopedia, last updated March 16, 2011;). Women and men who are symptomatic, are perceived by themselves/ a loved one/ their physician and referred for coronary angiography, are *situated to know* what angina symptoms feel like. Women in particular will be able to express their symptoms from their own situated experiences to better inform a new construct of "typical female" angina.

Gender norms: Women and men are expected to comply with different norms of behaviour and bodily demeanour (Haslanger, 2000; Stanford Encyclopedia, last updated March 16, 2011;). If CAD is perceived to be a "man's disease" even by the general public, individuals experiencing symptoms may perceive and express them differently according to gender.

Gendered first-personal knowledge: A woman experiencing something (i.e. angina) is in a "first personal knowledge" position to provide insight on the condition. It is useful to other women who are able to see the generalizable value of another woman's experience to determine if they do or do not share the same predicament (Stanford Encyclopedia, last updated March 16, 2011;).

5.6 Selection of Patients

5.6.1 Patient Screening and Study Site

This is a single-centre study, where all patients were referred for coronary angiography to the Hamilton Health Sciences, Hamilton General Hospital. The Hamilton Health Sciences is the sole provider of tertiary cardiac care services including coronary angiography, percutaneous coronary intervention and cardiac surgery for most patients, covering the geographic region of Central-South Ontario, Canada, a population of over 2.2 million people. Theoretical purposeful sampling was used to screen for elective or in-hospital patients referred for their first diagnostic angiogram (Charmaz, 2006). This theoretical sampling frame of (approximately) equally represented men and women was selected to explore chest-related symptoms suspected to be CAD. We interviewed patients immediately prior to undergoing their first coronary angiography, to prospectively capture their symptoms while not being influenced by the results of their coronary angiogram.

Patients were screened for eligibility into the study based on their cardiac catheterization referral form, a mandatory form for all incoming patients into this regional catheterization laboratory. The patient eligibility criteria were broad enough to comprise a diverse group of patients, while ensuring equal representation of women and men, thus allowing for maximum variation in sampling. The study was reviewed and received ethical approval by the McMaster University/ Hamilton Health Sciences Research Ethics Board.

5.6.2 Inclusion Criteria

 Patients considered eligible for this study must be referred for cardiac catheterization for a primary diagnosis of suspected CAD and/or a primary diagnosis for angina/cardiac ischemia. This inclusion criterion is intended to only capture patients with suspected CAD to determine risk factor, symptom

prevalence and predictability as confirmed by the currently accepted gold standard, cardiac catheterization.

- Referred patients must also have at least one prior abnormal test such as an abnormal exercise stress test, nuclear imaging, electrocardiogram changes, elevated troponin or creatine-kinase rise PRIOR to cardiac catheterization referral.
- Patients must agree to provide their angiographic results as routinely captured on the Hamilton-Wentworth Regional Cardiovascular Program Coronary Angiography Consult Form. (This information is currently captured on all patients undergoing cardiac catheterization at the Hamilton Health Sciences and does not require any additional information provided directly from the patient.)
- Patient must agree to possible long-term telephone follow-up up to three-years post-angiogram. (Although three- year follow-up is not an endpoint for this study, we would like to leave the possibility open for a future outcomes study).
- Patient must provide written informed consent.

5.6.3 Exclusion Criteria

- Patients referred for coronary angiography for reasons other than diagnosing coronary artery disease such as valvular disease, arrhythmia or pre-operation.
- Elective patients with prior or recent evidence of an MI
- Patients unable to communicate their own symptoms (i.e. severe dementia)

• Patients that have undergone a previous coronary artery bypass graft surgery (CABGS) or percutaneous coronary intervention (PCI).

5.7 Data collection

In-depth semi-structured interviews were used to enable the interviewer to explore symptoms, perceptions and patient impressions, while providing the interviewee the freedom to express their account of the topic. We initially estimated a sample size of 8 to12 male and 8 to 12 female patient-informants however saturation was reached at 14 male and 17 female patients. Interviews were held at the patient's bedside in the Heart Investigation Unit at the Hamilton General Hospital prior to undergoing coronary angiography. The purpose of the study was reviewed with each patient and written informed consent was obtained prior to enrolling the patient into the study. Interviews were tape-recorded with permission of the participant, and subsequently transcribed. The length of the interviews varied, ranging from 12 minutes to 50 minutes with most interviews lasting between 25-35 minutes. The interview questions were designed to focus and promote discussion on the patients' description of symptoms, discomfort, feelings, their interpretation of events, duration of symptoms, impressions of their pain, access to medical care, relationship with family physician, their health knowledge and literacy, using a gender-centered language from a feminist approach. Probing occurred throughout the interviews to permit the researcher to search for detail and

clarification (Charmaz, 2006). Please refer to Appendix A for the interview guide. All patients were debriefed and had the opportunity to ask any questions upon completion of the interview. Following each interview, the interviewer documented their impressions of each interview in memo form, to keep a record of their thoughts and observations to review later (during the analysis stage). Memo writing is considered to be a pivotal step in grounded theory, prompting the researcher to analyse the data and codes by documenting their thoughts, comparing the connections you make, formulating questions and directions to pursue throughout the research process (Charmaz, 2006).

5.8 Qualitative Data Analysis

All interviews were audio-recorded, transcribed verbatim into MS Word documents and imported into NVivo-8 software for coding. Principles from grounded theory approached were used (discussed below). Emerging themes that appeared to be related or associated with each other within each transcript were grouped together.

5.8.1 Analysis of data

Data analysis of the textual interviews was guided by coding practices centred on ground theory (Charmaz, 2006). The coding process involved multiple stages. In the first stage, initial open coding was undertaken, fragmenting the data into conceptual components. This initial step in coding was the first step in PhD Thesis

selecting, separating and sorting the data to begin the analytic account of the data, with the intention of trying to stay close to the data (Charmaz, 2006). An example of an initial category from the data is, "*Experiencing physical symptoms*" a term used to describe the sensations that the patient qualified as symptoms. Every effort was made to "remain open and close to the data, using simple and precise short codes, preserving actions while comparing data with data" (Charmaz, 2006). A second researcher coded ten interviews to ensure credibility of the initial codes. The data were recoded, using a line-by-line and incident-by-incident coding approach. After re-examining the first stages of coding and some discussion, new concepts and categories for coding began to emerge, including *in vivo* codes, where the exact words from the participants were used to capture concepts directly as "situatedknower", "gender norms" and "gendered first-personal knowledge". An example of an "in vivo" code is, "The big incident" which was a term several patients used to describe the (symptomatically significant) event that immediately preceded medical attention. The textual data was all re-coded using more focused and axial coding. A third coder, a qualitative expert, was also invited to code some interviews to determine if any new codes or concepts would emerge. Focused coding was used to code, synthesize and explain larger amounts of data. The constant comparison method was used to check each coded data with the rest of the data to establish analytic categories (Glaser & Strauss, 1967). During axial coding, categories were linked together to subcategories to define the properties and dimensions of a category, so as to "build a dense texture of relationships around the 'axis' of a

category" (Charmaz, 2006). An example of an axial code is, *"tipping point for medical care"*. Theoretical coding was the last stage of coding and this process linked together the focused codes, relating them to each other as hypotheses to be integrated into a theory (Charmaz, 2006). When considering the categories and subcategories, along with the focused and axial codes to collectively address, *"What seems to be going on here"*, the theory emerged (Strauss, 1987). From this point onwards, the analysis was restricted to the modifying and integrating the core theme. Categories were considered "saturated" when gathering new data no longer contributed to additional theoretical insights.

During the interview stage, field and journaling notes were taken documenting a record of chronological events and development of research, including the researchers' own reactions to, feelings about and opinions of the research process (i.e. reflexivity). This process was implemented so that the study investigator could later reflect during the analysis stage of any possible biases or ideas. Throughout the coding stages, memo-writing occurred in parallel documenting analytic insights and ideas. Memo-writing was instrumental throughout the process to help bring awareness to the abstraction of ideas, as the properties of each category developed and to generate hypotheses about the interrelationships between the categories (Charmaz, 2006). Many of the subcategories were formed from ideas originating from the memos.

Trustworthiness and Credibility

The aim of trustworthiness in a qualitative study is a qualitative measure of validity to support the argument that the inquiry's findings are "worth paying attention to" (Lincoln & Guba, 1985). Credibility or truth value, seeks to establish if the researcher has confidence in the truth value of the study participants, within the context which study was conducted (Lincoln & Guba, 1985). While the goal of the data collection is to produce detailed data as representative of the experience as possible and to leave a trail of data and analysis that another investigator could potentially follow or audit (M. K. Giacomini & Cook, 2000). For this study, several different sources were collated for the analysis. First, a demographic and risk factor sheet was collected on each patient documenting their age, sex, presence of any traditional cardiac risk factors, and if they were medically treated. In-depth semistructured interviews were transcribed verbatim including pauses, "ums" and any laughter in speech. Although a written record of nonverbal communication has inherent limitations, effort was made to include these in the transcription as it was felt that they might be important to the interpretation of gender in the analysis (D. Cameron, 2007). Also, the interviewer's impressions were immediately recorded after each interview and captured as field notes. In the field notes, impressions of the patient's interpretation of symptoms from the standpoint of the interviewer, the nurses and/or angiographer physician were recorded as a means of peer-debriefing. Lastly, the results of the patients' angiogram were also incorporated into the

analysis of the study results. Collectively, these sources of data formed the raw data for analysis.

As a further measure of triangulation, two data coders were invited at different stages of the analysis. The first double-coder was invited to independently code the interviews using the initial coding. Focus codes and axial codes emerged after reaching a consensus between the two coders from the initial findings. Both the second and third coders are qualitative research experts who are not experts in cardiology. Since much of the cardiology literature, both historical and current have been studied from a clinical lens, in support of the underlying hypothesis for this qualitative study we sought a more objective perspective so that any disciplinary biases would not excessively influence the study findings. As our theory emerged, a sociolinguist was invited to provide further expertise and deeper insights, helping us to modify the theory. These experts were consulted to ensure researcher credibility. Another measure of triangulation, a form of member-checking was also undertaken. Due to feasibility issues with appointment times, member-checking did not occur with same the patient that provided the interview, rather towards the end of our patient recruitment (after some of our initial analysis was undertaken), at the end of the interview (once all the questions on the interview guide were addressed), we discussed some of our preliminary study findings with patients to "check" if our study findings were similar and consistent with their perspectives to ensure credibility of our study findings. Collectively, the convergence of the multiple data sources including in-depth semi-structured interviews, the information on risk

factors, the angiographic results, the incorporation of field notes, peer-debriefing, multiple expert involvement for research credibility, triangulation and the modified member-checking ensured that our topic area was thoroughly covered from a variety of perspectives.

As measures of dependability (most similar to reliability in quantitative methodology), we have provided a dense description of our study methods. Along with triangulation methods described above, a few randomly selected interviews were coded and then re-coded approximately one month post initial coding as a measure of the code-recode procedure. We also hope that the peer-debriefing and modified member-checking also support the dependability of our study findings.

5.9 Study Results

5.9.1 Description of Study Population

The primary study population consisted of 17 women and 14 men. Of the study participants, the mean age was 66 years old (range 44 years to 84 years) for women and 60 years old for men (range 38-71 years). Patients were asked about the presence of the following risk factors: diabetes, smoking (past or present), hypertension, dyslipidemia, family history (<65 female, \leq 55 male, first degree relative), congestive heart failure, stroke and menopausal status. Women reported a slightly higher risk factor load, where all women described at least 3 risk factors present and all men reported the presence of at least one risk factor.

5.9.2 Main Study Findings

The primary focus of our study is to gain a deeper understanding of the symptoms that patients experience prior to undergoing coronary angiography, according to gender. From our qualitative exploration of symptoms using concepts from feminist epistemology, including *situated knower, gender norms* and *gendered first-personal knowledge*, emerged a new theory presenting cardiac-related symptoms along a gender continuum (refer to Figure 1). Represented and anchored on the one end of the continuum are experiences reported most commonly by men, and anchored on the opposite end of the continuum are experience" is situated in the centre of the continuum to represent the symptoms commonly expressed by both men and women (refer to Figure 5-1).

Figure 5-:1Gender Continuum of Symptoms

Men

Shared experience

Women

5.9.3 Symptoms parameters on the gender continuum

The symptomatic themes that emerged from the descriptions that men and women provided of their possibly cardiac-related symptoms established the following symptom parameters: chest location of pain/discomfort, non-chest localized areas of pain/discomfort, descriptors of pain/discomfort, other associated symptoms, attributed conditions of chest pain/discomfort, and physical limitations associated with symptoms.

Chest location of pain/discomfort

Men and women commonly reported a chest "pain". Some patients preferred to describe the sensation they experienced as "pain" whereas others insisted it was not a "pain". The descriptive terminology of their "pain-type" sensations are described in a later section however, for our purposes we will refer to the term "pain/discomfort" to represent a commonly heard term of a non-pain sensation from the study patients.

Men and women commonly experienced a chest pain/discomfort, however this was not always the principal complaint of patients. When "pain" or discomfort in the chest region was experienced, both men and women described it as being localized in the central chest area or off to the right of centre. One man described this as,

"I was confused because I had a previous impression that heart symptoms were located exclusively on left side, and pain was on right side of chest; checked the internet which said, pain in the chest (not on a specific side) and decided to check it out."

There were no differences described in the location of chest pain between

the sexes (refer to Figure 2).

Figure 5-2: Location of Chest Pain/Discomfort Described by Patients on Gender Continuum

-Centre of chest -Right side of chest

Men

Shared experience

Women

Non-chest localized areas of pain/discomfort

Both men and women experienced localized pain/discomfort beyond the chest region. Men and women reported pain/discomfort in the shoulders, top of the arms, tingling sensation in the left arm, right arm weakness and pain in both arms until the elbows/bicep area. Women additionally reported localized pain/discomfort in the upper back, spanning across from shoulder to shoulder, a backache in the upper-mid back, neck pain and tightness in the throat. One woman

(age 48) described it as,

"The main issue was, uh, the shortness of breath due to the chest pains but I could feel it go from my chest, basically the centre, and across my shoulders to the other side, across my upper back. It was like an elastic. That's what it felt like. And then if I stopped doing what I'm doing, then it would be like, like letting go of the elastic. It felt like at the same time they were squeezing towards the middle, right across the upper back."

Men in our study sample did not report any additional localized areas of pain/discomfort (refer to Figure 5-3).

Figure 5-3: Non-Chest Localized Areas of Pain/Discomfort

-Top of arm until elbow/bicep	-High back pain
- Tingling of left arm shoulders	spanning across
- Right arm weakness	shoulders
-Shoulders	-Backache
- Jaw pain	-Tightness in throat
	-Neck pain

Men

Shared experience

Women

Descriptors of pain/discomfort

There were gender differences in the way patients described their pain/discomfort. Overall, men used succinct language emphasizing that the pain/discomfort they experienced was not a severe type pain. Men most often used terms such as "not severe, uncomfortable" and "not a huge pain". One male, age 49, described it this way,

"It wasn't... it wasn't a pain though... well you wouldn't think it was a heart pain of any type... No real symptoms, but over the past few years I feel a bit of tightness with work" (Male, Age 49).

Another man, age 66, describes the sensation as follows,

"When pain comes it's not really a pain, it's a soreness right here in the centre of the chest. It's not a real sharp pain, it's just an annoying thing. I can't describe it, it's not a sharp pain that goes and comes, it's just persistent." (Male, Age 66)

The shared experience between women and men also emphasized that it was, "Not a sharp pain," "it was more of a tightness", "discomfort", "a very funny pain". There is an element of unwillingness to commit to the "pain" label to describe the sensation. Specifically, several men and women sought to correct their health professionals' use of the term, "pain", opting for more preferred terms such as "discomfort", "pressure", "tightness", and "weakness". One woman, age 84, sought to correct the "pain" label;

"I felt weak. Very weak. So weak, I couldn't go... But no! No! I had no pain to speak of! I cannot say that I had any pain! I had a little bit of pressure on my chest sometimes and my breathing was not perfect..." (Female, Age 84)

Another woman, age, 44, also corrected the "pain" label;

"I woke up with a really bad pressure, really bad pressure. It wasn't a pain, it was a pressure. It was annoying, but it wasn't a pain. They ask me all the time, "How's your pain?" but it's not really a pain, I don't know how to compare it but it's not severe." (Female, Age 44)

Yet another women, also questioned the use of the term "pain",

"Ah the chest pains? I found that it was like something pressing against my chest and part of my job is doing a lot of heaving lifting. I went to lift something and there was no way I could do it, it just felt like something was crushing my ribcage." (Female, Age 58).

Along the gender continuum, women use a more diverse spectrum of terms

to describe their pain/discomfort. Women described the sensation in their chest

most often as a "pressure". This women differentiates between "pain in her arms"

with "painful pressure" in her chest,

"I have very severe pain down both arms, it was very bad, bad, bad pain. It was the worst thing I ever had. It was very painful pressure, like my chest was going to explode." (Female, Age 75). The expansiveness of chest "pain" descriptions increase along the gender continuum, where women use the more descriptive terms to describe their pain (depicted in Figure 5-4).

Figure 5-2: Description of Pain/Discomfort

Men	Shared experience	Women
-Not a huge pain -Just a bit hurting -Burning in chest, not pain	-No chest pain! -Tightness -Discomfort -Not severe -Annoying pain -Strange pain -Very funny pain -Soreness - Weakness, not pain	-Heaviness -Really bad ache -Bad pain -Chest exploding -Severe chest pain, crushing but not stabbing -Vague pain, not crushing and travels -Pressing
-Uncomfortable	-Not a sharp pain	-Pressure

Other Associated Symptoms

Symptoms patients felt were associated with their chest pain/discomfort and/or other localized areas of pain/discomfort differed between men and women. Men experienced unique symptoms from women, which include headache, nausea, vomiting, paleness and feelings of aggravation. One man, age 69 describes a "pain" associated with vomiting and sweating, "The pain wasn't exactly in my tummy, like right in my stomach, it was right here [pointing to the centre of his chest]. I threw up, I thought it seems funny but I wanted to throw up. And then I started to sweat. After I threw up, the pain didn't go away, it started to get worse." (Male, Age 69)

Another man, age 64, describes developing feelings of aggravation when unable to go up a flight of stairs;

"I had such shortness of breath. And I couldn't go up a flight of stairs and I felt aggravated. (Male, Age 64)

Almost all women and men reported shortness of breath with some difficulty breathing or taking a breath. Men and women also reported periods of profuse sweating followed by coldness/clamminess with their chest pain/discomfort. For example, when asking one man about the difficulty breathing he reported earlier, he states:

"Even now, when I take a deep breath I can feel the pain in my chest." (Male, Age 69)

Both men and women commonly reported sweating and one woman reported surprise with the degree of her sweating,

"I couldn't take it anymore, I was having difficulty breathing and I sat down in a bus shelter. I just saw that I was sweating and by the time I decided I better get on home it was 9:30 at night promptly. The walls [of the bus shelter], the glass walls were just dripping and running from my wet perspiration. Unbelievable! (Female, Age 71) One man, age 39, describes sweating, followed by coldness,

"I was playing hockey but I couldn't finish the game and it took me to the point where I broke out in an instant sweat. The sweat lasted 3-5 minutes and then I went from instant sweating to dry and shivering cold." (Male, Age 39)

However, women reported additional symptoms including dizziness, weakness, sweating at night, feeling faint/fainting, fatigue, dry mouth, confusion, anxiety and panic. One woman describes feeling a panic attack and dizziness,

"At first I thought I was having a panic attack because I could feel this pressure. I felt this pressure before when I was flying, so I thought it was related to my nerves when flying. But then I felt so dizzy, it hurt a lot to inhale and it scared me. I couldn't even put my slippers on." (Female, Age 56)

Other symptoms associated with chest pain/discomfort along the gender continuum are illustrated in Figure 5-5:

Figure 5-3: Other Associated Symptoms

-Headache	-Shortness of breath	-Dizziness
-Nausea	-Difficulty breathing/inhaling	-Felt faint/fainted
-Vomiting	-Profuse sweating	- Sweating at night
-Pale	-Clamminess	- Weakness
- Aggravation		- Confusion
		-Panic
		-Anxiety
		- Dry mouth
		- Fatigue

Men

Shared experience

Women

Attributed conditions of chest pain/discomfort

The interviews were purposefully scheduled to take place immediately prior to angiography, to qualitatively explore symptoms prospectively, prior to being possibly influenced by the angiographic results. We asked patients what condition(s)/explanation they initially attributed their chest pain/discomfort symptoms and both men and women echoed that they initially felt their symptoms were related to stomach ailments including indigestion and heartburn or muscle strain. Examples of the commonness of suspecting the stomach ailments and muscle soreness include, "You wouldn't think it was heart pain of any type, it was more like indigestion." (Male, Age 49)

"At first it was really just uncomfortable and I thought well I just strained something or I pulled a muscle. I also thought I maybe had heartburn because it just felt wrong. So I you know, took some eno and that didn't help much with anything; I burped a few times but nothing much, pain was still there." (Female, Age 58)

"It feels like an acid, a burning in your chest, especially when walking around. I went to the doctor and he gave me these little stomach pills but they didn't do anything." (Female, Age 83)

"On Saturday evening, 11pm, I went to bed, I thought I was suffering from really bad indigestion. Then I thought, it is probably stuff from work, just sore muscles. I always thought it was something I ate, something else, I never thought..." (Female, Age 44)

In addition, several men thought their symptoms may be attributed to a hiatus

hernia and several women felt it may be a panic attack (refer to Figure 5-6).

Figure 5-4: Originally Attributed Chest Pain/Discomfort

on -Panic attack n nuscle

Physical Limitations

Almost all men and women in our study population complained of shortness of breath, especially on exertion. This was often accompanied by chest pain/discomfort on exertion. Most patients reported experiencing shortness of breath for some time prior. One women, age 48, describes,

"I have had shortness of breath on exertion for a long time. I have shortness of breath when I'm going up and down the stairs too many times, if I'm walking or going a certain distance." (Female, Age 48)

Often, patients would slow down, limit or avoid physical activity when experiencing "shortness of breath".

"I had very bad breathing, very short, very short and I was struggling to breathe. The breathing problems come when I try to walk; I can't walk anymore." (Female, Age 83)

As a result, patients often de-condition themselves gradually when experiencing shortness of breath to avoid this symptom.

"The chest pain, or rather the slight pain, or uncomfortable feeling in the chest, especially on the treadmill. It feels tight with difficulty breathing. The difficulty breathing results in not wanting to carry on doing walking/activity." (Male, Age 68)
"At my home there's two stories and there is 14 stairs from, from the rec room to the main floor. And then there's 14 stairs from there to go up to the bedroom. And that's when I used to notice, when I leave my rec room to go upstairs to bed at night. If I climb the 14 stairs twice, without stopping, by the time I get upstairs I would have the pain in my chest. I just sold my house and I'm moving in a month to a house with no stairs!" (Male, Age 66)

In addition, men reported experiencing limitations to their physical activity with

feelings of stress (refer to Figure 5-7).

Figure 5:5: Physical Limitations

Men	Shared experience	Women
-Experience shortness of breath and/or chest pain/discomfort with stress	-Shortness of breath on exertion -Chest pain/discomfort on exertion -Limit/avoid physical exertion due to shortness of breath	I

5.9.4 Symptomatic Tipping Point

We sought to gain a deeper understanding of the common underlying mechanism that prompts an individual to qualify their symptoms as requiring medical attention and the process of seeking medical care. When asking patients to describe their symptoms and the process in which they were referred for coronary angiography, it was apparent that symptoms alone did not prompt medical care. Interestingly, all patients in our study experienced many of these symptoms prior to seeking medical attention. Patients went through a process between experiencing symptoms at some point prior to the incident that lead them to seeking medical attention. We constructed the term *"symptomatic tipping point"* to capture the transitional period between experiencing a change in the symptom(s) and developing the concern to seek medical attention.

To reach the *symptomatic tipping point*, each patient went through a series of stages. From our qualitative inquiry, the stages that emerged were common to both men and women varying only in time duration between and within stages. We were not interested in determining the time scale per se, but rather to establish the common stages that each patient transitions through. The following section will describe the stages of the process we identified.

5.9.4 Model of the Symptomatic Tipping Point Process

A model representing the stages of the symptomatic tipping point is presented in Figure 8. From our analysis emerged eight symptomatic tipping point stages. The stages progress in the same order for both men and women with an arrow depicting the direction of time (along the left margin). Each stage is labelled with a brief description in the centre column of our model. Specific sex/gender characterizations or differences of each stage are depicted according to stage in the sex/gender specific columns labelled "Men" and "Women" (refer to Figure 8).

Men	Stage of Symptomatic Tipping Point	Women	
	Background personal experience	-can trace symptoms back further than men	
	-felt symptoms for some time prior		
	-may have risk factor modification		
-could not continue with	"Big" (Critical) Incident	-more dramatic incident	
	-dramatic change in symptoms	ionger watchig period	
-consulted with a loved one/friend over health state	Uncertainty period –Attribution to other health condition	-uncertainty period longer in women	
state	-experienced a period of symptom		
	-uncertainty associated with the		
	assessment of change of symptoms		
	-symptoms affecting functionality		
-denial period short	Denial/ Dismissal of symptom	-denial period long	
	-sometimes optimistic bias (symptoms will improve or pass on their own -more often –DENIAL		
-sought second opinion	Assistance/second opinion	-others commented on	
	-someone close (emotionally or	-reacted to others	
	proximally) played a role in recognition of	comments regarding their	
	symptoms	symptoms	
-self-recognition in need	Recognition of severity of symptom	-others suggested patient	
of medical attention	with feelings of defeat	was "defeated" by	
	-recognition of change in symptoms	-it was "time" for	
	requiring medical attention	individual to get help	
Seeking medical attention			
-concerned for self	Acceptance	-"knew" something was	
		wrong	

Figure 5-6: Symptomatic Tipping Point

Background personal experience

Each patient reported previously experiencing (at least some) of the symptoms sometime prior. For example, almost all patients with angiographic disease reported shortness of breath on exertion prior to the "big incident". Many of the patients experienced chest pain/discomfort/pressure in the chest area also for some time prior to seeking medical attention. Further, patients that had previously visited their family doctors/cardiologist were on some "treatment" for risk factor modification and many had some background knowledge about possible cardiac symptoms. One man states,

"I've been feeling these symptoms pretty infrequently for quite some time but now I carry my nitroglycerin with me all the time. I told this to my doctor and that's the reason why I am here today." (Male, Age 64)

There were many similarities in the background personal experience of symptoms between men and women. When analyzing the differences between men and women, both women and men experienced symptoms for varying amounts of time prior to "big"/critical incident, however upon probing, women could trace their symptoms further back than men. One woman describes living with symptoms for years,

"I had some chest discomfort and my doctor sent me for some stress testing. I've been feeling these symptoms for a couple of years but they weren't anything awful to report. And then I just had enough of them, I thought it was time to mention them." (Female, Age 71) A male, age 39 describes previously experiencing symptoms, however just 6-7 days prior,

"I had this pain 6-7 days before but I took the Zantac, burp, burp I felt better. This time it wasn't letting up and this time was worse and worse." (Male, Age 39)

The "Big" (Critical) Incident

To varying degrees, each patient reported a critical or "big" incident representing a significant change in symptoms. For some patients the change in symptoms was signified by an increase in the frequency of the symptoms, for others it signified a dramatic change in symptoms. All patients described a "big" (critical) incident however men sought help quicker than women, because they "could not continue with the current pain state" (Male, Age 39). Women overall had a longer waiting period than men. Regardless if they sought care through their family doctor's office or the emergency room, the women in our study reported enduring the symptoms longer. One woman describes experiencing severe pain at a prior incident that did not prompt medical attention,

"The pain was getting worse, it was reaching a 10 [out of ten], and some other times it goes to 10 but not always. The day before I came to hospital I was cutting a branch off a tree and my arm is up here trying to cut and it and it just hit me really, really hard, really sharp, really bad. That same night I sat down to read my book and I had another one." (Female, age 79) One man, age 64, describes waiting for five minutes before asking his wife to look up his symptoms on the internet and deciding to come to hospital.

"I felt chest pain in the middle of the chest and a little to the right side and was accompanied with sweating. I waited for 5 minutes for pain to go away but it was the wife who made me come to the hospital." (Male, Age 64)

Uncertainty period -Attribution to other health condition/physical activities

Once patients had experienced a 'big' or critical incident, a period of uncertainty followed. Although each patient acknowledged a change in symptoms there was a period of uncertainty while evaluating whether the 'new' symptoms could be attributed to another health condition or prior physical activity. The uncertainty was a result of trying to understand their new symptoms from the big/critical incident in the context of previously experienced symptoms or in the context of another condition they may suspect.

"At first I thought it was a hiatus hernia but when the pains were getting more severe. I was washing the windows of my truck and was talking while washing. I felt tired and went inside to sit down and read the paper but pains were getting worse. I my told my wife I think I'm having a heart attack and that's when I went to hospital." (Male, Age 65)

Intertwined with their feelings of uncertainty is embedded an element of compromise in their ability to physically function in the presence of their new/changed symptom further fuelling the uncertainty. Men most often consulted

with a loved one or friend over their health state. Women did not always consult with someone and most often sustained a longer duration of uncertainty.

Denial/Dismissal of Symptom

Along with the uncertainty period is a period of denial or dismissal of the symptoms associated with the big/critical incident. Despite acknowledging a change in symptoms and some uncertainty regarding what may be causing these symptoms, there is a period of dismissing the symptom, sometimes accompanied with feelings of optimism that the symptom will improve or pass altogether. However uncertainty is most commonly accompanied with feelings of denial. The denial period in men seems to be of a shorter duration than in women.

"This couldn't be happening. I went home from work early and tried to convince myself to sleep it off. I have never been to hospital, this is my first time ever and in my head that's a major block to overcome, it's my stubbornness. I was in denial or something I guess." (Female, Age 58)

"I showered quick, I got my equipment packed, I got out [from hockey arena]. Now here's the dumbest mistake: I should have said "guys, I'm going to the hospital, forget the beers, next week". No, I just stood there. I tried to get rid of it [the pain] while the guys were having beers. I'd say a good forty minutes I was standing there." (Male, Age 39)

Assistance/second opinion

As patients tried to grapple with the big/critical incident while assessing the change in symptoms (uncertainty period) and overcome a period of symptom

dismissal, patients commonly sought assistance and/or a second opinion from someone close to them (either proximally and/or emotionally close, i.e. someone physically close by or a loved one). Patients first tried to review their symptoms with another person, for a second opinion, provided there was someone available. Interestingly, when seeking assistance/second opinion gender differences were observed; men often sought a second opinion/assistance from a loved one or a friend. One man describes,

"It was around seven o'clock at night, I was watching my son play soccer and all of a sudden I felt a pain in my right side of my chest and nausea, and going home it wasn't getting any better. So at about eight o'clock I said to my wife, uhm, can you go on the Internet and look up the signs and symptoms of a heart attack? (Male, Age 50)

Women on the other hand, rather than seeking an opinion, only responded when someone (either proximally close or a loved one) commented on their symptomatic state.

"I felt like life was leaving me so my husband took my blood pressure and it's like a carousel, up and down and my pulse went down to 37 and then to 33, so what could he do with me? He brought me to hospital!" (Female, Age 84)

Recognition of severity of symptom with feelings of defeat

Following the evaluation of the big/critical incident, feelings of uncertainty, while moving beyond the denial/dismissal stage and asking a friend/loved one for their opinion regarding their health state, all patients began to acknowledge the PhD Thesis

severity of their symptoms. They also exhibited feelings of "defeat" that this big/critical incident will in fact require medical attention. Men and women differ significantly in how they approached this recognition of severity; while men sought a second opinion from a loved one/friend, their feelings of defeat were facilitated through self-recognition in the need of medical attention. Women on the other hand, consistent with waiting for others to comment on their symptomatic state, would often also wait for "suggestions" by their loved one/friend that they were defeated by the symptom(s) and that it was "time" for the individual to seek medical attention.

"Everyone was looking at me, "Are you ok?" and I said, "I'm fine, I'm fine" and kept working but it was not so good. I couldn't work the way I usually do and everybody knew it. I had to throw in the towel." (Female, Age 58)

"I went home and got some Zantac (stomach anti-acid) and started to head back to the rink; I didn't make it half way when I said, "What am I doing? This is killing me!" when I turned back home and that that's when it clicked, "what are you doing?" I looked at my wife... my mother and wife drove me in [to emergency]. (Male, Age 39)

Seeking Medical Attention

Soon after the patient acknowledged the severity in the change of their symptoms, patients sought medical attention. Both men and women sought medical attention at the hospital emergency room or through their family doctor. In our study population only a few men were referred for cardiac catheterization through their family doctor/cardiologist's office. Instead the majority of men sought medical attention urgently through the emergency room. Interestingly, the men that sought medical attention through the emergency room reported that they did not have good relationships with their family doctors.

Women also sought medical attention through their family doctor's office and the emergency room. Almost all women were referred for cardiac catheterization urgently through the emergency room despite reporting that they had good relationships with their family practitioners.

Acceptance

Once patients sought medical attention, they each accepted that the change in the severity of symptoms they experienced during the big/critical incident were real and were not going to improve without medical attention. Once patients reached the acceptance stage, there were no differences between men and women in the acceptance of requiring medical attention for the change in their symptoms.

"...I was only there probably seven or eight minutes until they got me in and then they did all the tests and stuff and he came back out. He says 'yeah, you had a heart attack'. He goes – and he quotes, "small heart attack." I'm like, explain "small one", he says, just small. And I just, I just was devastated." (Male, Age 39)

5.10 Discussion

The primary focus of our study was to gain a deeper understanding of the cardiac-related angina symptoms that patients experience according to gender. Over the past half century, the term "typical angina" has come to represent the cardiac-related symptoms most common in men, while "atypical angina" has come to represent the symptoms most common among women. At the same time, CVD is the largest cause of mortality in both men and women in the western world, yet despite this, there is a prevailing perception that CAD is a "man's disease." It is likely that this perception is intricately related to the "typical" angina label most associated with men.

In our review of the literature review we sought to open the "black box" of how the angina construct was initially conceived. A historical exploration of the literature revealed that much of the current angina construct was initially developed on the symptoms that manifested into myocardial infarction in the white middleaged male (Dawber et al., 1957; Shapiro, Weinblatt, Frank, & Sager, 1965). The advent of the coronary angiography was monumental in diagnosing patients with suspected CAD. "Typical angina" symptoms could now be (visually) correlated with stenoses in the arterial conduit system of the heart (Proudfit et al., 1966) and as a result, coronary angiography was quickly established as the gold standard diagnostic test for CAD. In early angiographic studies, symptoms in women were poorly correlated with angiographic evidence of CAD, and the diagnosis of "atypical

angina" in women was advanced. Further, ideas of "CAD immunity" in women were proposed (Kannel & Castelli, 1972), entrenching the perception that CAD is a "man's disease". It is important to note that patients enrolled in the early landmark trials consisted almost exclusively of white middle-aged men. The criteria in the selection process of patients into the early studies are questionable, however the results of the early angiographic studies were so promising that they have rarely been a point of critique. Our current construct of angina today, although not always realized, contains an underlying element of comparison to the white middle-aged male.

We demonstrated in our literature review some of the historical shortcomings in the original construction of the terms "typical angina" and "atypical angina" and highlighted the current lack of standardization and discordant use of these terms that prevail even today. We sought to give women "a voice" and reconstruct these terms through a qualitative exploration of symptoms using concepts from feminist epistemology, including concepts of *situated knower, gender norms* and *gendered first-personal knowledge* to overcome previous limitations and to ensure a gender-centered perspective.

From our analysis emerged a new theory presenting cardiac-related symptoms along a gender continuum (Figure 1). We found considerable overlap in symptomology between men and women and felt that inflexible categorization of symptoms does not accurately reflect the diversity of human individuality. Further, if the underlying "gold-standard comparison group" of "typical" angina represents a white middle-aged male, it is not surprising that the angina-type symptoms

experienced among women and/or other ethnic groups are referred to as "atypical". However, it is possible that there are some common symptoms within these patients groups including sub-categorizations and nuances within the current "atvpical" label must exist. There are several issues embedded even within the "atypical" The word "atypical" itself has a connotation that implies "abnormal, label. uncharacteristic, unusual and uncommon" to name a few. Presumably one who symptomatically presents with "typical" angina symptoms should receive "typical" treatment. By the same token, would the label "atypical" allow a diversion from typical treatment, allowing "atypical" treatment? Could this in part explain why women are reported to be referred less than men for invasive procedures despite having severe symptoms (Alter et al., 2002; Hochman et al., 1999; Mikhail, 2006; Mosca, Appel, et al., 2004; Vaccarino, Krumholz, Berkman, & Horwitz, 1995)? Further, the label "atypical" has become a catchall phrase for anyone who does not present "typically". There is no current consensus as to what symptoms precisely comprise "atypical" as the definitions have changed across studies and time, resulting in a lack of conformity and standardized of terms. Lastly, the term "atypical" simply said, represents sloppy science. Unfortunately this term has already become embedded in the cardiovascular domain and we are challenging the continued use of this term.

We sought to shed the "sex" barriers and to reframe the issue considering *gender*; and from our analysis emerged a gender continuum where the term "atypical" theoretically can no longer exist! The gender continuum can capture

"shared experiences" along with symptoms more commonly experienced by men and/or women. An individual can be of a certain sex yet gendered along a continuum. This is a new way of approaching cardiac symptomology and we hope our theory can help to demystify the spectrum of angina symptoms.

Symptom Parameters on Gender Continuum

From our qualitative exploration of symptoms, we discovered that patients describe their symptoms along six common parameters; chest location of pain/discomfort, non-chest localized areas of pain/discomfort, descriptors of pain/discomfort, other associated symptoms, attributed conditions of chest pain/discomfort, and physical limitations associated with symptoms. We present the findings of each symptom parameter along a gender continuum. Overall, we found were more *shared experiences* between men and women than previously reported using traditional typical/atypical angina classifications. This finding further challenges the term "atypical" to describe cardiac symptoms common among women and may help to explain the inconsistencies in the literature when describing "atypical" symptoms. Previous research focused largely on describing symptoms, typical versus atypical symptoms according to sex (Arslanian-Engoren et al., 2006; Comeau et al., 2006; DeVon & Zerwic, 2002; Granot et al., 2004; Kerry A. Milner, Funk, Arnold, & Vaccarino, 2002; K. A. Milner et al., 1999; Patel et al., 2004). As was discussed earlier, there is no current consensus as to what symptoms

specifically constitute "typical" versus "atypical" angina and it is not surprising that that so many discrepancies in the literature currently exist.

In our study we found that both men and women described chest pain/discomfort to be localized in the same chest area and patients expressed surprised to feel pain radiate a little to the right side of their chest, claiming they *"knew the heart was located a little left of centre" (Male, Age 49).* When reporting other non-chest areas of localized pain, again there was significant overlap between men and women and women reported a few additional areas of pain. It is important to consider that both men and women reported pain/discomfort in the chest region and areas outside the chest region. Could the additional areas of pain reported by women be attributed to what was previously described as "atypical" pain?

When we asked women and men to describe the sensation(s) they felt in the chest region and men and women reported unique symptoms. Where men used words to de-emphasize the severity of the pain, women provided very detailed explanations of the pain they were experiencing. We believe that this may be a function of *gendered language*. There are several theories of gender and language, among them include the theory of "difference", whereby differentiating women as being socialised from a very young age to belong to different sub-cultures. Deborah Tannen compares gender differences in language comparing the conversational goals of men as being more "report-style" while women use often a "rapport style" which is more concerned about establishing relationships (Tannen, 1990).

More recent approaches including the 'social constructivist' perspective, view speech as falling into a natural gendered category, where many factors of an interaction determine the gender construct. In this perspective, language itself is "doing gender" rather than the components of speech. Deborah Cameron points out that men and women have the same gender speech abilities and differences in language or in the uses of language are actually displays of differential power (D. Cameron, 2007). It is possible that men and women, in their social roles, may express their cardiac-related pain differently and in our study these elements of speech differences are evident in the descriptions of chest pain (Figure 4) and in the description of other associated symptoms experienced (Figure 5) in men and women.

We found it difficult to fully grasp the extent of the relationship between shortness of breath which every patient experienced and chest pain. Upon more exploration of patients' description of shortness of breath, we found that both men and women de-conditioned themselves slowly over time, almost expecting this symptom to occur regardless of their heart condition, and more as a consequence of their age. Furthermore, as patients de-condition themselves, they gradually established new norms for physical function and it was difficult to determine the extent of impact this symptom posed on their physical functionality.

We also held an underlying assumption that patients would try to relate new symptoms to something relatively "familiar" to what they have previously experienced and we were interested in gender differences of familiar ailments of

similar pain/discomfort quality. We found all men and women initially thought the symptoms they were experiencing could be attributed to stomach-related ailments such as heartburn and indigestion, or muscle soreness/strain.

Symptomatic tipping point

During our in-depth qualitative exploration of symptoms, we realized symptoms alone did not prompt the patient to seek medical attention. Rather, there was a process that each patient underwent before qualifying the change in symptoms and seeking medical attention. This process was initiated among background knowledge or past experiences qualifying the new symptoms as being significantly different, often more frequent or severe in presentation. The process overall was similar between men and women and we would like to emphasize that we are not presenting a comparison between men and women. Rather we are presenting the stages of the *symptomatic tipping point* theory we discovered and describe the process as it occurs in men and women.

Overall, women transitioned through the *symptomatic tipping point* stages (often self-admittedly) slowly and we suspect this is likely due to a complex interplay of factors. Although men and women could trace their symptoms back in time (often in a milder form) they each recognized a dramatic (severe change) or increased frequency in their symptoms. This finding is important as estimates in the literature of silent ischemia, where the first manifestation of CAD is either sudden death or MI ranges widely from 25% to 70% (Greenland, Smith Jr, & Grundy,

2001; Gutterman, 2009; Myerburg, Kessler, & Castellanos, 1993; Oberman, Kouchoukos, Holt, & Russell, 1977). Our study population included stable and urgent in-hospital patients and all patients in our study reported feeling symptoms prior to the "big/critical incident" and we question the true proportion of asymptomatic patients and truly "silent" ischemic attacks. Are patients truly asymptomatic or are their symptoms "a-gendered"? Are patients aware of the full spectrum of possible angina symptoms? This finding is consistent with the literature as there is an increasing body of literature supporting the presence of prodromal symptoms particularly among women (Gallagher et al., 2010; Graham, Westerhout, Kaul, Norris, & Armstrong, 2008; Lovlien, Johansson, Hole, & Schei, 2009; McSweeney et al., 2003). Prodromal symptoms are considered especially important in women as they experience both higher morbidity and disability than men and are almost more likely to die from AMI than men within one year post AMI (American Heart, 2009; McSweeney et al., 2003). It has been reported that women are largely unaware of their risk for CAD, often ignore symptoms, symptoms do match their expectations, and women often do not anticipate the symptoms they experience to be indicative of heart problems (McSweeney, Cody, & Crane, 2001). In our study, all patients reported that they experienced some symptoms prior to the "big/critical incident" however they did not initially attribute the symptoms to their Patients attributed their symptoms largely to stomach ailments (i.e. heart. heartburn, indigestion) or muscle strain/soreness as these are conditions they previously experienced and were familiar with. However when probing patients

PhD Thesis

further, many patients reported that they felt their symptoms could be attributed to their older age, stress associated with aging and the natural aging process. This is an area that requires future research.

The stages of the *symptomatic tipping point* process are intricately tied to the perception that "CAD is man's disease". Several survey studies have found that women do not suspect CAD as being a serious health concern (McSweeney et al., 2001; Mosca, Ferris, Fabunmi, & Robertson, 2004; L. Mosca et al., 2000) although awareness of heart disease in women has been steadily improving (Mosca, Ferris, et al., 2004). We observed in our study that the women in particular would not act quickly on their symptoms, almost waiting for a more severe event to occur before they would qualify it as "possibly cardiac". This finding is consistent with the literature that women rate their cardiac disease as less severe than do men, even when controlling for other measures of cardiac disease severity (Nau et al., 2005). This is also in agreement with the long "denial/dismissal of symptom" stage among women. Women were in denial and/or dismissed their symptoms as "possibly cardiac", often waiting for their symptoms to improve or pass on their own, and as a result were in this stage for a long period of time. We asked patients why they delayed seeking medical attention when they first experienced the symptoms, and in addition to the other conditions they attributed their symptoms to (i.e. stomach and muscle ailments), women in particular cited that they, "didn't think it was anything serious" (Female Age 58), that they had family responsibilities, including spouses and dependants at home that 'relied on them" (Female Age 48).

Often people around women would comment on their (visually) distressed state and women reacted to their concern, only then recognizing the severity of their symptoms. Women were often encouraged by a friend/ loved one to seek medical attention, that it was *"time to seek some help."* This process may be due to the lack of perceived risk for CAD by women (Emslie, 2005; Mosca, Ferris, et al., 2004; L. Mosca et al., 2000), that the symptoms are not qualified as severe enough (Emslie, 2005; Lockyer & Thompson, 2009; Nau et al., 2005) or that women lack awareness of cardiac symptoms among women and are prompted to look for symptoms only among men (Mosca, Ferris, et al., 2004). These questions remain unanswered and require future exploration.

5.11 Limitations

Although our study sample is small, in order to achieve an in-depth exploration of CAD symptoms and to overcome some of the previous limitations encountered, we felt it was necessary to "start over", and begin re-constructing angina, informed through qualitative interviews. Some of our next steps include testing our theory quantitatively in a larger study sample. We also hope to conduct more qualitative interviews in other patient groups (i.e. different ethnicities, among people of different socioeconomic position, different education levels) to build on aspects that may interact with gender to further develop the gender continuum.

We commenced this study with knowledge of the previous limitations, including historical shortcomings in the underlying assumptions in the progression

of CAD and the consequential impact it has had in clinical practice. For this reason we intentionally wanted our interviewers to not have clinical training, as we sought a truly fresh perspective. This position proved a little more difficult than anticipated as we have all been patients in a clinical setting at some point in time and it was easy to "revert" into clinical history-taking type behaviour. During the memo-ing stage this conflict arose and we decided to consult a linguist, to help us rephrase some questions using all non-medical terminology. For example, initially we asked, "Can you please describe the symptom(s) that led you for this procedure?" This question was changed to, "Can you please describe what you have been feeling/experiencing in the time leading up to this test?" The word "symptom(s)" was changed to *"feeling/experiencing"* for two main purposes: first, we did not want to prompt the patient to speak in "medical-ese" (specialized medical terminology) and we realized that the word "symptom(s)" may have prompted the patient to repeat the medical history they gave their physician. Second, we wanted to change the noun to a gerund (a non-finite verb form) to keep in line and facilitate with initial coding as recommended by Charmaz (Charmaz, 2006).

All interviews with male and female patients were conducted by a female interviewer. A patient may be situated and respond differently to an interviewer of their own sex versus an interviewer of the opposite sex. We are aware that we are all gendered and our individual gender knowledge may have influenced the study results, however this is as an inherent limitation to most gender studies.

5.12 Conclusions and Future Directions

We sought to reconstruct angina symptoms according to gender, and we uncovered symptom parameters that we placed along a gender continuum of symptom expression. We recognize the large amount of overlap in *shared experiences* between men and women developed a new theory of angina expression, while seeking to abolish previous labels of "typical" and "atypical" angina. A *gendercentered* approached was utilized however we believe there are more gender parameters that can build upon and expand this theory. Among our next steps we hope to expand our theory to other ethnicities and non-white male patient groups. We have also developed a checklist of reported symptoms to test quantitatively in a larger study and quantitatively expand the gender continuum. We hope that our theory provides a fresh perspective in approaching CAD and that the concept of the gender continuum expands.

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Chapter 6: Understanding Cardiac-Related Symptoms According to Gender Using the McMaster University Symptom in Cardiac Assessment *MUSICA* Tool

1.0 Introduction

1.1 Early Angina Studies

Coronary artery disease (CAD) is the leading cause of mortality and morbidity of both men and women in the westernized world, accounting for over one third of total deaths (Statistics, 2007; Thom et al., 2006). Although not often realised, the total number of deaths from CAD is slightly higher in women than in men (Lerner & Kannel, 1986; Mosca et al., 2006; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Wise, 2006; Smith et al., 2001; Statistics, 2007; Thom et al., 2006), and specifically in 2007 in Canada, 30% of women succumbed to CAD, compared to 29% of men (Statistics, 2010).

Consistent with this finding is that chest pain/discomfort known as angina, the cardinal manifestation of CAD (Braunwald, 1992) occurs more often in women than in men. This finding was first reported in the early landmark studies, including the monumental Framingham Heart Study, observing that the prevalence of angina was higher among women than in men (Dawber, Moore, & Mann, 1957; Epstein, 1965; Shapiro, Weinblatt, Frank, & Sager, 1965). However, the study population of early landmark studies consisted mostly of European populations and it has recently been re-affirmed in a meta-analysis of over 24,000 patients from 31 countries over four decades (Hemingway et al., 2008). Despite this, there is a prevailing perception that 'CAD is a man's disease'.

There are several reasons why this perception exists, and arguably the main reason lies in some of the initial assumptions in the construct of angina. The early CAD studies consistently observed a higher prevalence of angina among women than in men, interestingly however, and against theoretical prediction, angina manifested as myocardial infarction in men more often than in women (Dawber et al., 1957; Shapiro et al., 1965). As a result, the severity of angina in women was dispelled as being a "faulty diagnosis" (Dawber et al., 1957; Kannel & Castelli, 1972).

The advent of coronary angiography allowed physicians to insert a catheter in the arterial conduit system, guided by x-ray fluoroscopy, to visually detect a stenosis impeding blood flow to the myocardium. Early investigators sought to "confirm the reliability" of angina symptoms by correlating angina and/or MI with angiographically diagnosed CAD (Proudfit, Shirey, & Sones, 1966). Despite some risks to the patient (i.e. 1/1000 risk of stroke), the diagnostic success of coronary angiography/catheterization led to its becoming the gold standard diagnostic test for CAD, even today. Proudfit et al (Campeau et al., 1968; Proudfit, Shirey, & Sones, 1966) carefully selected 1,000 non-consecutive patients (criteria for selection undisclosed) to investigate the relationship of angina-type symptoms with angiographic evidence of CAD and found a "striking predominance of men to women (786 versus 214, respectively) with angiographic evidence of CAD" (Proudfit et al., 1966) The authors of this landmark study concluded that the "typical angina"
symptoms most common in men were strongly correlated with angiographic CAD, while the "atypical angina" symptoms common in women were poorly correlated with angiographic results (Proudfit et al., 1966). The early CAD studies often described angina symptoms in women as "atypical symptoms" or "uncomplicated angina" since it did not manifest as myocardial infarction or angiographic CAD as often as it did in men (Campeau et al., 1968; Kannel & Feinleib, 1972; Proudfit et al., 1966). This contradictory finding led investigators to conclude that women "enjoy immunity from CAD" (Kannel & Castelli, 1972).

This concept became further entrenched with efforts to categorize angina severity. The introduction of an angina classification tool, known as the Canadian Cardiovascular Society (CCS) Angina Classification, graded the severity of angina symptoms based on a construct of the "typical" angina symptoms as they presented in men (Campeau, 1976). The impact of this tool was first realized in the screening process of patients undergoing coronary artery bypass graft surgery (CABGS). Patients in the Coronary Artery Surgery Study (CASS) were recruited from Veteran Affairs (VA) Hospitals which consisted of an almost exclusively male population ("Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data," 1983). Not surprisingly, CCS classification was useful in determining the severity of "typical angina" symptoms among surgical coronary bypass patients, since it was established and validated among patient populations that consisted almost exclusively of men. It is important to note that the majority of early studies investigating CAD studied predominately white,

middle-aged men and although not always realised, the current angina construct contains an underlying element of comparison to the angina symptoms in white middle-age men.

Further reinforcing the perception that 'CAD is a man's disease' is the observation of the confounding effects of incidence rates according to age; the incidence of CAD in women is lower than men, but rises steadily after the fifth decade and nearly equalises between the sexes by the seventh decade of life (Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006). The age relationship in women is important to note, particularly among the early CAD studies, as the age categories which CAD, angina and MI were first described consisted of much younger patient populations, such in the Framingham Heart Study where angina symptoms and MI were first described among 30-44 years old and 45-62 years of age (Dawber et al., 1957). Failure to consider these age-related differences may have contributed to the perception that women are less likely to suffer from CAD compared to men (Mosca et al., 2000).

1.3 The impact of early angina studies

Some 30 years later, the downstream implications of the "typical" and "atypical" constructs of angina and CAD presentation, may have had a negative

impact in the cardiac care of women. Although women are often reported to have "atypical" symptoms, women have a one in two lifetime risk of dying from CAD while women and health care providers alike do not realize that CAD is the greatest health risk for women (Herrmann, 2008; Mosca, Ferris, Fabunmi, & Robertson, 2004; The Lancet, 1998). The American National Council on Aging reported that middle- aged women are more concerned with developing breast cancer than CAD (61% vs. 9%, respectively) (The Lancet, 1998). These results have been echoed in other surveys of women's attitudes, fears and beliefs (Caldwell, Arthur, Natarajan, & Anand, 2007; Cameron et al., 1997; Griffiths, 1995; Mosca et al., 2004; Pilote & Hlatky, 1995). Furthermore, women are referred less for angiography than men, receive less medical therapy and fewer invasive procedures (Bell et al., 1995; King et al., 2004; Lagerqvist et al., 2001; Malenka et al., 2002; Roger et al., 2000; Vaccarino et al., 2005) even among women with acute coronary syndromes (Anand et al., 2005; Ayanian & Epstein, 1991; Roger et al., 2000). These trends have been particularly alarming among younger women with ACS who are reported to have up to three times higher mortality than their young male counterparts (Vaccarino, Abramson, Veledar, & Weintraub, 2002; Vaccarino et al., 1998).

Over the years, beyond the entrenchment of the term "typical angina" associated with symptoms in men and "atypical angina" associated with symptoms in women, there has been much confusion associated with which cluster of symptoms constitute "typical" and "atypical" angina symptoms. First, definitions of specific symptoms that constitute typical versus atypical angina vary greatly

between studies (Arslanian-Engoren et al., 2006; Comeau, Jensen, & Burton, 2006; DeVon & Zerwic, 2002; Granot, Goldstein-Ferber, & Azzam, 2004; Milner et al., 1999; Patel, Rosengren, & Ekman, 2004) and even between expert panels/practice guidelines (Gibbons et al., 1999; Thygesen et al., 2007). To pause for a moment, it is important to note that the label "atypical" itself carries a negative connotation implying "abnormal, unusual, uncommon, uncharacteristic, and unnatural" subtly reinforcing the perception that "CAD is a man's disease". And so, it is not surprising that so much confusion exists with the symptomatic presentation of the cardiac disease process in women since it was built on a framework established through the study of men. The current lack of consensus as to what symptoms specifically comprise "typical" or "atypical" has muddled the issue further and it is likely that the contradictory findings over the years are likely due to this "faulty construct".

1.4 Angina 'Re-Constructed'

The qualitative study entitled, *"Understanding cardiac-related symptoms according to sex/gender"* assessed some of the underlying assumptions into the development of the original angina construct and developed a new theory and construct of angina, by scaling symptoms parameters along a gender continuum. Rather than using the traditional approach of categorizing symptoms according to sex, the qualitative exploration revealed that men and women share many common symptoms that overlap, essentially abolishing the theoretical expression of "atypical

angina". As a result, the theory predicts that women and men have many *shared experiences,* along with some unique symptoms that are gendered in their expression and not necessarily *sexed.* Men and women reported symptoms along six *symptom parameters* which include: location of chest pain/discomfort, non-chest location of chest pain/discomfort, other associated symptoms, initial attribution of chest pain/discomfort and physical limitations. The vast majority of symptom parameter with the most variation in the gender continuum was *the description of chest pain/discomfort.* The authors hypothesize that the reporting of multiple descriptive terms among women may be attributed as a function of *gender language* (refer to Chapter 5), however this hypothesis has yet to be tested.

This qualitative reconstruction of angina study (Chapter 5) presented a fresh approach to conceptualizing angina symptoms according to gender, while providing some new insight in the process that patients undertake before seeking medical care. The development of this new construct of angina holds exciting possibilities in optimizing the prediction of CAD in both men and women.

2.0 Study Rationale

CAD is the leading cause of death among men and women in the western world. The prevalence of angina (chest pain/discomfort), the cardinal manifestation of CAD, has been repeatedly observed to be higher among women, from classic studies to present day meta-analyses studies spanning over four decades. Yet despite this there is a prevailing perception that 'CAD is a man's disease'.

The literature review highlighted some of the shortcomings in the early assumptions in the development of the angina construct, including discrepancies in the interpretation of early coronary angiography findings according to sex and assumptions in the development and validity of CCS angina classification. As a result, the term "typical angina" has come to represent the angina symptoms common in men while "atypical angina" has come to represent the angina symptoms among women (Canto et al., 2002; Canto et al., 2000; Charney, 2002; Comeau et al., 2006; DeVon & Zerwic, 2003; Goldberg et al., 1998; Granot et al., 2004; Lovlien, Schei, & Hole, 2006; O'Donnell, Condell, & Begley, 2004; Patel et al., 2004; Ryan, DeVon, & Zerwic, 2005). At the same time, there is no standardised definition that identifies and outlines the specific symptoms that constitute typical and/or atypical angina, even among expert panels, making the comparison of symptoms across studies nearly impossible (Antman et al., 2000; Gibbons et al., 1999). Furthermore, the term "atypical" itself is associated with a negative connotation, implying "abnormal or unnatural"; an ironic term to describe the symptoms of the disease

claiming the most lives among women. Perhaps not an unexpected term since the angina construct was established almost exclusively on the symptom presentation of white middle-aged men.

The gold standard to diagnose CAD is coronary angiography, however it is an invasive procedure with associated risks. Only patients for whom the benefit outweighs the risks should be referred for coronary angiography. Since symptoms are not well identified or defined among women as a result, women are not being appropriately selected for angiography (Alter, Naylor, Austin, & Tu, 2002; Hochman et al., 1999; Roger et al., 2000; Schulman et al., 1999; Sharaf et al., 2001).

To overcome some of the construct limitations associated with typical/atypical angina, the qualitative study entitled, "Understanding cardiacrelated symptoms according to sex/gender", concluded with a proposed new construct of angina, by conceptualising symptoms along a gender continuum. We would like to test this new construct of angina, by developing a tool to capture the symptom parameters identified in the qualitative study, with the ultimate goal of correlating the symptoms on the gender continuum with individual angiographic outcomes.

3.0 Study Objectives

The overarching goals of this study including to study the following objectives:

1) To develop a quantitative assessment tool, informed from the findings of the qualitative study, to capture risk factors, symptom parameters, symptomatic tipping point and patient perception/knowledge.

2) To assess the distribution of the symptom parameters according to sex.

3) To assess the distribution of the symptom parameters in men and women according to obstructive CAD.

4) To determine the distribution of the symptoms parameters along the gender continuum.

5) To determine if there is a difference between men and women in the correlation of CCS classification between patient rating and physician rating, and

6) To determine the strength of association of patient and physician ratings of CCS classification with obstructive CAD.

4.0 Methods

4.1 Brief overview of study design

Informed by the qualitative study entitled *"Understanding cardiac-related symptoms according to sex/gender",* an assessment tool was developed to

quantitatively capture study findings including symptom parameters, symptomatic tipping point and patient perspectives/knowledge. The assessment tool was administered only to patients who provided written informed consent, immediately prior to undergoing their *first* coronary angiogram. The assessment tool was administered to a sample of 210 patients (105 men and 105 women) in the pre-catheterization area, after written informed consent was obtained. A physician-angiographer read the individual angiograms of enrolled patients, approximately two months post –procedure to avoid any re-call bias.

4.2 Selection of Patients

4.2.1 Study Site

For this single-centre study, all patients were referred for cardiac catheterization to the Hamilton Health Sciences at the Hamilton General Hospital. The Hamilton Health Sciences is the sole provider of tertiary cardiac care services including coronary angiography, percutaneous coronary intervention and cardiac surgery for most patients, covering the geographic region of Central-South Ontario, Canada, a population of over 2.2 million people. Eligible patients for this study were approached to participate in the study, in the pre-catheterization clinic/Heart Investigation Unit area of the Hamilton General Hospital. Elective patients without previously documented CAD and/or in-hospital patients awaiting their *first* cardiac catheterization were approached for eligibility in this study.

4.2.2 Inclusion Criteria

- Patients considered eligible for this study were those referred for cardiac catheterization for a primary diagnosis of suspected CAD and/or a primary diagnosis for angina/cardiac ischemia. This inclusion criterion is intended to restrict the participants to patients with suspected CAD to determine risk factor, symptom prevalence and predictability as confirmed by the currently accepted gold standard, cardiac catheterization.
- Referred patients must also have had at least one prior abnormal test such as an abnormal exercise stress test, nuclear imaging or electrocardiogram PRIOR to cardiac catheterization referral.
- Patients must agree to provide their angiographic results as routinely captured on the Hamilton-Wentworth Regional Cardiovascular Program Coronary Angiography Consult Form. (This information is currently captured on every patient undergoing cardiac catheterization at the Hamilton Health Sciences and will not require any additional design of form(s) or information provided directly from the patient.)
- Patient must agree to possible long-term telephone follow-up up to three-years post angiogram. (Although three- year follow-up is not an endpoint for this study, we would like to leave the possibility open for a future outcomes study).
- Patient must provide written informed consent.

4.2.3 Exclusion Criteria

- Patients referred for coronary angiography for reasons other than diagnosing coronary artery disease such as valvular disease, arrhythmia or pre-operation.
- Elective patients with prior or recent evidence of an MI
- Patients unable to communicate their own symptoms (i.e. severe dementia)
- Patients who have undergone a previous coronary artery bypass graft surgery (CABGS) or percutaneous coronary intervention (PCI).

4.3 Assessment tool development and administration

4.3.1 Assessment tool development

Guided by the study findings from the qualitative study entitled, *"Understanding cardiac-related symptoms according to sex/gender"*, an assessment tool was developed highlighting six main domains:

1) Demographic information: Information including age and sex of the patient.

2) *Risk factor assessment:* To capture the presence/absence of traditional risk factors including diabetes, hypertension, dyslipidemia, family history, history of heart failure, previous stroke, menopausal status for women, smoking history and second-hand smoking history. Risk factor modification therapies were also noted.

3) Symptom parameter assessment: Symptom categories were grouped into:

• Pain/discomfort sensation in the chest region

- Words/ terms that describe the sensation experienced
- Non-chest areas of pain/discomfort
- Other associated symptoms
- Perceived patterns and timing onset of symptoms

4) *Functionality using CCS angina classification:* Assessed by the patient and the physician independently

5) Understanding the "Tipping Point": Understanding the time line of events leading to the decision to seek medical attention, timing of "big"/critical event, breakdown of uncertainty period and attribution to other health conditions/ physical activities at the time, denial/dismissal of symptoms along a 'time' continuum, who decided to come to hospital, recognition of severity of symptoms and acceptance.

6) *Patient perspectives/knowledge:* Patient knowledge of risk factors was assessed. Also, we asked patients what they thought a typical heart attack should feel like and how similar they felt their symptoms were to a typical heart attack.

The assessment tool entitled, *McMaster University Symptom in Cardiac Assessment* or MUSICA is illustrated in Appendix A.

4.3.2 Administration of assessment tool MUSICA

Once the study was explained to the patient and written informed consent was obtained, the assessment tool was administered by the study investigator and/or a research assistant at the patient's bedside, prior to the patient undergoing angiography. All data was collected by the lead study investigator and/or research assistant was well versed with the study. All efforts were made to follow the patient's terminology throughout the study. For example, if the patient referred to their chest sensation as "discomfort" the term "discomfort" was used during the interaction with the patient. The research assistant had a non-clinical background to help limit the possibility of introducing bias of clinical history-taking learned in nursing/medical school.

4.4 Collection of Coronary Angiography Results

After the assessment tool was administered to the patient, the patient underwent their scheduled coronary angiography, following the standard of care. The angiographic results of patients were obtained at a later date for interpretation for our study. An angiographer blinded to the name, sex and age of the patient, reported the angiographic results approximately two-months post-procedure to ensure no re-call or sex bias in the interpretation of the angiogram.

5.0 Statistical Considerations

5.1 Sample Size

The sample size of the study was determined on the primary outcome to assess the association of angina symptoms on angiographically diagnosed CAD.

To detect an odds ratio of 2.4 and assuming that approximately 70% of individuals will report having angina symptoms (dichotomous outcome), a sample size of 210 (147 with symptoms, 63 without symptoms) would be needed to reach a power of 80%, assuming a significance level of 0.05 (two-sided) (Dupont & Plummer).

To detect an odds ratio of 2.0 for a one standard deviation increase in pain severity, a sample size of 210 would produce 99% power, assuming a significance level of 0.05 (two-sided) (Figure 1) (Dupont & Plummer).

Figure 6-1



Odds ratio for one SD increase angina pain severity

5.2 Statistical Analysis Plan

Baseline characteristics including age, risk factors, coronary anatomy and CCS angina classification were compared between women and men. Continuous variables were expressed as means with standard deviations. Dichotomous variables were expressed as number (N) and percentages and probability values were estimated using chi square tests and logistic regression. Symptoms gathered from the questionnaire were analysed according to sex, among the total study population and according to obstructive CAD angiographic results. The binary variable *obstructive CAD* was defined as the presence or absence of obstructive CAD (1 versus 0, respectively). Agreement between physician and patient ratings were

estimated using weighted kappa values and the concordance/discordance between patient and physician ratings was estimated using Wilcoxon sign ranks test. All tests employed two-tailed significance testing. All analyses were performed using IBM SPSS version 19, (Armonk, NY).

6.0 Study Results

6.1 Baseline characteristics of study population

During the study period from June 2010 until November 2010, there were 237 patients enrolled into our study, of which 128 were men and 109 women. All patients enrolled in the study were never previously diagnosed with CAD and were referred for their first coronary angiogram. The baseline characteristics are presented in Table 1. Briefly, the women are slightly older than the men (67.5 ± 10.8 years versus 64.5 ± 11.5 , respectively, p=0.06) and within the women, 89 (82%) were post-menopausal. Among this study population, men were more likely to be past smokers compared to women (69% men versus 46% women, p<0.01). And although the prevalence of hypertension (69% men, 70% women, p=0.87), dyslipidemia (54% men, 62% women, p=0.24) and exposure to second hand smoke (83% men, 78% women, p=0.32), was present in over 50% of study population, there were no significant differences between men and women in the presence of the traditional risk factors, including diabetes mellitus, family history, heart failure and stroke, between men and women (Table 1).

Angiographically, we found women were more likely to have normal coronaries (20% women compared to 8% men, p<0.01) and less likely to have severe CAD (17% women compared to 34% men, p<0.01) compared to men. Overall, men were more likely to have *obstructive CAD* (69% men versus 46% women, p<0.01) compared to women (Table 2).

6.2 Symptom Parameters

6.2.1 Descriptive Terms of Sensations in the Chest-Region Among All Patients

Of the terms used to describe the sensations in the chest region, many of the descriptive terms used were common to both men and women. The most common descriptor was 'chest pain' where 83% of men and 81% of women (p=0.68) used this term to describe the sensation they were experiencing. Other common terms expressed by both men and women to describe their experience include 'pressure' (55% men, 63% women, p=0.18), 'tightness' (45% men, 53% women, p=0.18) and 'heaviness' (39% men, 49% women, p=0.14). Descriptive terms used more commonly among women include 'discomfort' (42% women compared to 23% men, p<0.01), 'crushing' (18% women compared to 8% of men, p=0.02), 'not a sharp pain' (34% women compared to 19% men, p<0.01) and 'pressing' (28% women compared to 14% in men, p<0.01). Other less common descriptive terms but equally likely to be used by both men and women include 'no chest pain', 'bad ache', 'soreness', 'annoying', 'smothering', 'funny pain', 'vague pain', 'stabbing' and 'burning' (Table 3).

6.2.2 Descriptive Terms of Sensations in the Chest-Region Among Patients with Obstructive CAD

The descriptive terms used among patients with obstructive CAD were strikingly similar (in proportion) to the descriptive terms used by all patients referred for coronary angiography, where most of the terms used to describe the symptoms/sensations in the chest region were similar between men and women. The most common descriptor among patients with obstructive CAD was 'chest pain' where 82% of men and 84% of women (p=0.72) followed by 'pressure' (54% men versus 58% women, p=0.65), 'tightness' (43% men and 58% women, p=0.08) and *'heaviness'* (44% men and 42% women, p=0.85). There were some descriptive terms that were more commonly expressed among women with obstructive CAD than men which include 'discomfort' (46% women compared to 28% men, p=0.03), 'crushing' (24% women compared to 9% of men, p=0.02), 'pressing' (28% women compared to 14% in men, p=0.04) and 'bad ache' (30% women compared to 15% men, p=0.04). Other less common descriptive terms but ones equally likely to be used by both men and women include 'not a sharp pain, 'no chest pain', 'burning', 'soreness', 'funny pain', 'annoying', 'stabbing', 'vague pain', and 'smothering'. Men did not use any descriptive terms more commonly than women to describe their sensations/symptoms (Table 4).

6.2.3 The Gender Continuum

Using the gender continuum (from the qualitative study), the findings from this study are mapped onto the gender continuum, illustrating the sensations/symptoms experienced by men and women (Figure 1). The descriptive terms expressed by men and women represent more *shared experiences* than experiences for either sex individually. Women expressed terms such as *'discomfort', 'crushing', 'pressing'* and *'not* a *sharp* pain' more commonly than men, while men did not express any terms more commonly than women (Figure 1).

When analyzing the descriptive terms of the sensations/symptoms that men and women with obstructive CAD used, the results proportionally are strikingly similar to all patients referred for coronary angiography (refer to Figure 2). Men and women expressed more *shared experiences*, while women referred to their chest sensation/symptoms as '*discomfort'*, '*crushing'*, '*pressing'* and '*bad* ache' more often than men used these terms. Women with obstructive CAD differed only from all women being referred for angiography in their use of the descriptive term '*bad* ache' (Figure 2).

6.2.4 Non-Chest Region Pain/Discomfort Among All Patients

Among all patients referred for coronary angiography, approximately 50% of patients described a non-chest region of pain/discomfort that was associated with their *'chest pain'*. Men and women most commonly reported additional and associated pain/discomfort in their arms (37% of men and 45% of women, p=0.20),

shoulders (28% of men and 33% of women, p=0.41), neck (20% of men compared to 30% of women, p=0.07) and in their throat (16% of men and 19% of women, p=0.46). Women were more likely than men to report left arm pain in particular (42% compared to 26%, p<0.01, respectively), back pain (40% women compared to 26% men, p=0.02) and jaw pain (20% of women compared to 10% of men, p=0.03) (Table 5).

6.2.5 Non-Chest Region Pain/Discomfort Among Patients with Obstructive CAD

Among patients with angiographically determined obstructive CAD, both men and women were equally likely to report arm pain (left and right), shoulder pain, back pain, neck pain, jaw pain and throat pain (all p=not significant) (Table 6). There were no differences of pain/discomfort in the non-chest region among women and men with obstructive CAD.

6.2.6 Gender Continuum of Pain/Discomfort in the Non-Chest Region

Among all patients referred for coronary angiography in our study, when illustrating the symptoms of non-chest pain/discomfort along the gender continuum, although left arm pain, back pain and jaw pain were more commonly expressed by women than men, these symptoms were not more commonly associated with obstructive CAD in women (refer to Figure 3 and Figure 4).

6.2.7 Other Symptoms Associated with Chest-Related Sensations/Symptoms Among All Patients

Over 80% of patients reported other symptoms that were associated with their chest-related symptoms. Other symptoms commonly expressed by both men and women include *faint/light-headedness* (40% men and 51% of women, p=0.08), *weakness* (34% men, 45% of women, p=0.10), *sweating* (47% men, 52% women, p=0.41), *clamminess* (23% men and 31% women, p=0.14), *nausea, vomiting* and *confusion* (Table 7). Women frequently reported more often than men *shortness of breath* (82% women compared to 67% men, p<0.01), *fatigue* (71% of women compared to 56% of men, p=0.02), along with *dry mouth, headache, anxiety* and *panic* (Table 7).

6.2.8 Other Symptoms Associated with Chest-Related Sensations/Symptoms Patients with Obstructive CAD

Among patients with obstructive CAD, *shortness of breath* was the most commonly expressed non-chest pain symptom (67% of men and 76% of women, p=0.25), followed by *fatigue* (56% of men and 62% of women, p=0.52) *sweating* (48% of men and 46% of women, p=0.80), *weakness* (32% of men and 46% of women, p=0.11), *nausea, vomiting, headache, anxiety, panic* and *confusion* (Table 8). Women with obstructive CAD were more likely to report dry mouth than men (34% of women, compared to 18% of men, p=0.04). Men did not express any symptoms more frequently than women (Table 8).

6.2.9 Gender Continuum of Other Symptoms Associated with Chest-Related Symptoms

When illustrating the symptoms of non-chest pain/discomfort along the gender continuum, although shortness of breath, fatigue, dry mouth, headache, anxiety and panic were more commonly expressed by women than men, these symptoms were not more commonly associated with women who had obstructive CAD, with the exception of dry mouth, which was associated more commonly in women (refer to Figure 5 and Figure 6).

6.3 Severity of Symptoms According to CCS Angina Classification

6.3.1 Patient and Physician CCS Angina Classification Rating Among Men

We asked patients to rate the severity of their angina-type symptoms according to the CCS angina grading classification scheme. The patient's assessment of their angina is compared to the physician assessment of the patient's angina. Among the total study population, men were more likely to underestimate their angina compared to physician assessment (Table 9). For example, 16% of patients evaluated their angina to be CCS Class 0 angina versus 6% of physicians who rated their angina to be CCS Class 0 angina. Physicians on the other hand, were more likely to rate the angina symptoms in men more severely than the male patients themselves. For example, 44% of male patients rated their angina as CCS IV angina. The

discrepancy in the overall CCS angina classification rating between physicians is illustrated in Figure 7. We found the agreement in the individual ratings between physician and patient to be moderate (weighted kappa=0.36).

6.3.2 Patient and Physician CCS Angina Classification Rating Among Women

At first glance, it appears that women assessed the severity of their angina similarly to physician assessment among all CCS angina classification categories. For example, 4% of patients rated their angina as CCS Classification 0 compared to 5% of physicians and on the other end of the spectrum, 61% of patients rated their angina as CCS Class IV compared to 62% of physicians (Table 9). An illustration of the CCS angina classification between female patients and physicians is presented in Figure 8. However, there was almost no agreement of CCS classification between individual female patients and physician assessment (weighted kappa=0.03) (Table 9).

We sought to explore the discordance between patient and physician ratings a little further by conducting a Wilcoxon Signed Ranks test to determine the direction of discordance among men and women. Of total patients 36% of men underestimated their CCS angina class (as established by a physician) while 17% overestimated their CCS angina class (p=0.02). On the other hand, 27% of women underestimated their CCS classification compared to 17% which overestimated their CCS angina class (p=0.82). Men and women often were aligned in their CCS

angina classification with their physician (47% and 43%, respectively) (Table 10, Figure 9).

6.3.3 The Association of CCS Angina Classification with Obstructive CAD According to Patient and Physician Ratings

Lastly we sought to determine the association of physician and patient CCS angina classification ratings with obstructive CAD. CCS angina classification was associated with obstructive CAD when physicians rated angina severity according to CCS Class (CCS Class III angina Odds Ratio $OR_{physician}=2.8$ (95% CI 1.0-7.5), p=0.05 and CCS Class IV angina $OR_{physician}=2.1$ (95% CI 1.1- 4.0), p=0.03). However, patient assessment of CCS Class was not predictive of obstructive CAD (CCS Class III $OR_{patient}=1.5$ (95% CI 0.7-3.4), p=0.27 and CCS Class IV $OR_{patient}=0.9$ (95% CI 0.4-1.6), p=0.67).

7.0 Discussion

In this prospective study of 237 patients referred for their first diagnostic coronary angiogram, the risk factor profiles of men and women were very similar with the exception that women tended to be older than men, while men were more likely to have a history of smoking. The coronary angiographic profile of women in our study indicates that women were more likely to have normal coronary arteries and less likely to have severe and obstructive CAD than men. Among all patients referred for coronary angiography, women reported additional symptoms to men, however among patients with obstructive CAD, women and men have more *shared symptoms/experiences* than previously reported, debunking the "atypical angina" myth in women. This information should be strongly considered by clinicians, while targeting the eradication of the term "atypical angina".

The sex distribution in the risk factors between men and women we observed is consistent with the literature where women develop CAD later in life and men are more likely to be smokers (Granot et al., 2004; Hochman et al., 1999; Catherine Kreatsoulas, Natarajan, Khatun, Velianou, & Anand, 2009; C. Kreatsoulas, Natarajan, Khatun, Velianou, & Anand, 2010; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006). The angiographic profile of women is also consistent with the literature, where women are observed to have a lower prevalence of obstructive CAD compared to men (Alter et al., 2002; Anand et al., 2005; Hochman et al., 1999; King et al., 2004; C. Kreatsoulas et al., 2010; Roger et al., 2000; Sharaf et al., 2001; Shaw, Bairey Merz, Pepine, Reis, Bittner, Kelsey, Olson, Johnson, Mankad, Sharaf, Rogers, Wessel, Arant, Pohost, Lerman, Quyyumi, Sopko, & Investigators, 2006).

We sought to test the hypothesis informed from the qualitative study entitled, "Understanding chest-related symptoms according to sex/gender" and instead of trying to categorize sex-specific symptoms and fit symptoms into the label of "typical" versus "atypical" angina we sought to present symptoms along a gender continuum. The theory of the gender continuum emerged from the findings of the qualitative study, which consisted of 31 total patients, 14 men and 17 women. We have been able to substantiate this new theory with the findings from 237 patients.

By mapping reported symptoms of patients referred for coronary angiography onto the gender continuum, we found that the symptoms shared by women and men were remarkable similar in the total study population and among patients with obstructive CAD. Over 84% of all men and women referred for coronary angiography used the term '*chest pain*', '*pressure*', '*heaviness*', or '*tightness*' to describe their chest sensation. Interestingly, these same four terms, '*chest pain*', '*pressure*', '*heaviness*', or '*tightness*' were also the most commonly reported terms to describe the chest sensations among 83% of men and 90% of women with obstructive CAD (not presented in table).

We found that women used the terms 'discomfort', 'not a sharp pain', 'crushing' and 'pressing' to describe their chest sensations/symptoms more often than men. Almost the same terms were associated more often with obstructive CAD in women (with the exception of 'not a sharp pain' and the addition of 'bad ache', Figures 1 and 2). However it is important to note that these terms were not exclusively used by women, and that some men expressed these terms also. The increased expression of these terms may be a function of gendered language however we did not have the opportunity to explore this postulation further in this study.

Moreover, when we analysed seemingly 'biological' symptoms (as opposed to descriptive terminology of symptoms) such as non-chest localisation of pain/discomfort, we found that arm pain (right arm in particular), shoulder, neck and throat pain were commonly expressed by all women and men referred for coronary angiography. Among all women referred for coronary angiography, women expressed left arm pain, back pain and jaw pain more often than men. However when we analysed the non-chest region of pain/discomfort among patients with obstructive CAD, we found that men and women *shared* the same experiences of non-chest related symptoms.

Similarly, patients reported other symptoms associated with their chestrelated sensation/symptoms and among all patients referred for coronary angiography, half of the symptoms expressed were *shared experiences* between men and women (faint/light-headedness, weakness, sweating, clamminess, nausea, vomiting, confusion) while other symptoms were more commonly expressed by women (shortness of breath, fatigue, dry mouth, headache, anxiety, panic). However, when analysing these symptoms according to the presence of obstructive CAD, all 'other symptoms' associated with chest-related sensations/symptoms (with the exception of dry mouth which may be a confounding effect due to drug sideeffects or fight-or-flight response) were equally expressed by men and women.

In the past, most studies focused on the categorizing the *differences* in symptoms according to men or women, typical or atypical angina. We have taken a different approach and the unusual stance to present our *non-significant* p-values

and findings, recognizing the importance of the overwhelming similarities of symptoms between men and women. Rather than presenting a masculine-feminine or typical-atypical angina binary, we feel by presenting these terms on the gender continuum, we capture the commonness of the *shared experience* of the symptoms/sensations by men and women, while allowing for the gender expression Others have also recognized the inflexibility and ceiling of of certain traits. knowledge-progress which previous symptom categorization have been limited (Arslanian-Engoren, 2002; Galdas, Johnson, Percy, & Ratner, 2010; Lockyer & Bury, As result of various categorizations schemes, and perhaps not always 2002). realised, researchers have bought into gender stereotypes associated with health behaviour, which have likely commenced from the early construct of CVD and angina, and continue to influence current frameworks. For example, in a study that examined patient-actors' portraval of "businesslike" symptoms versus a "histrionic" portraval of symptoms, for the same exact symptoms, physicians, rated 50% of the businesslike portrayal of symptoms due to a cardiac cause, compared to 13% of the histrionic presentation style of symptoms (Birdwell, Herbers, & Kroenke, 1993). A more recent study developed a 'femininity score' and found that men who identified themselves with more 'feminine' characteristics had a lower risk of CVD death but women with feminine characteristics had no benefit (Hunt, Lewars, Emslie, & Batty, 2007). Such findings continue to fuel the perception that 'CAD is a man's disease' and the gender stereotypes continue to influence how clinicians treat patients and researchers seek to explain health behaviours.

A study by Galdas et al (Galdas et al., 2010), found that cardiac symptoms, presentation and behaviour stereotypically considered to be 'masculine' or 'feminine' gender practice, were shared by both male and female participants, rejecting the binary gender distinction. The overdependence of research findings to date, have focused on presenting the dissimilarities of symptoms between men and women rather than the similarities, reinforcing stereotypes (Arslanian-Engoren, 2002; Galdas et al., 2010). Although Galdas (Galdas et al., 2010) rejects the notion of masculine and feminine being on opposing ends of the gender continuum, we emphasize that the gender continuum we are proposing does not seek to explain character typology of isolated symptoms, but rather to present symptoms as a fluid configuration of more 'commonness' rather than of 'differentiation'.

As another measure of symptom expression, we sought to ask patients to assess their angina and compare it to the physician's rating of their angina using the CCS angina classification tool, which is considered the gold-standard measure of angina severity. The agreement of patient and physician ratings was slightly better among men than in women however, men tended to underestimate their angina symptoms more often than overestimate while women equally over and underestimated their angina severity according to CCS classification. Further, our regression model revealed that physicians were accurately assessing CCS class angina to predict obstructive CAD whereas patients were not. Patients may not understand the CCS categories as well as physicians who have experience and understand the groupings better. We demonstrated that there is no advantage in

having a self-reported CCS classification by the patient. We suspect that communication, *gendered language* and *gender norms* (a concept from feminist epistemology where men and women are expected to comply with different norms of behaviour and bodily comportment) (Stanford Encyclopedia, last updated March 16, 2011;) may influence the presentation of symptoms. However we are not aware of any other studies that may have found a similar finding, but feel that this is an area for further exploration.

It is important to note that our study population consisted of patients referred for their first coronary angiogram, and that referred patients in our study represent the 'real world' clinical decision making, including any referral biases that may have occurred prior to referral to coronary angiography. Despite the fact that women are referred less often for coronary angiography, we demonstrated that women are more likely to have normal coronary arteries and less likely to have obstructive CAD. This finding which has been reported by others (King et al., 2004; C. Kreatsoulas et al., 2010; Lagerqvist et al., 2001; Malenka et al., 2002; Roger et al., 2000; Vaccarino, Berkman, & Krumholz, 2000) may be in part explained by confusion in the symptomology and we hope our findings help to better inform Often when we asked patients if they had a CVD risk factor such as clinicians. 'hypertension' they would respond, "no" even when they were on risk factor modification medical therapy, believing that they were 'cured' of the risk factor since their levels were perceived to be 'under control'. As a result we cross-checked all risk factors with their medication and reported medically treated risk factors.

The severity of angiographic stenosis was determined by an angiographer who was blinded to the name, sex and age of the patient. Although we conducted multiple statistical analyses, since our analyses relied heavily on non-significant p-values, we felt a post-hoc correction was not necessary. Despite having a moderately sized study sample, our study represents one of the few prospective cardiac symptomology studies.

Our study was internally valid as we consulted with cardiologists and cardiovascular nurses to determine if the measures on the tool reflected measures of cardiovascular disease and symptom presentation as they understood (face validity). We also consulted with and medical experts patients (cardiologists/internists/ cardiovascular nurse specialists) to ensure that important concepts and behaviours related to angina and cardiac catheterization referral were captured in MUSICA. Further, as a measure of criterion validity, domains represented in MUSICA were validated against the gold standard test for coronary artery disease diagnosis, cardiac catheterization.

8.0 Conclusions

We developed a tool to test the presentation of cardiac-related symptoms using a new framework. The gender continuum revealed that symptoms in men and women represent more *shared experiences* rather than sex-specific symptoms, particularly among patients with obstructive CAD. This information is useful to clinicians to better contextualise symptoms associated with obstructive CAD. The

gender continuum proposes a new framework for clinicians and researchers and we hope that this framework is tested and validated in more study populations.

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Table 6-1: Baseline Demographic Characteristics of Study Population

Risk Factor	Total Men N (%)	Total Women N (%)	<i>P-value</i> Total men vs Total women
Total N	128 (54)	109 (46)	
Age	64.7 <u>+</u> 11.5	67.5 <u>+</u> 10.8	0.06
*Current smoker	24 (18)	13 (12)	0.84
*Past smoker	77 (69)	45 (46)	0.84
Exposed to second hand smoke	84 (83)	76 (78)	0.32
Diabetes	31 (24)	24 (22)	0.69
Hypertension	88 (69)	76 (70)	0.87
Dyslipidemia	69 (54)	67 (62)	0.24
Family History	51 (40)	52 (48)	0.22
Heart failure	13 (10)	6 (6)	0.19
Stroke	13 (10)	13 (12)	0.66

 χ^2 =0.04, p=0.84 for current smoker versus past smoker

Table 6-2: Morphological Differences Between Men and Women of Coronary Anatomy

Anatomy	Total Men N=130 (%)	Total Women N=105 (%)
*Normal coronaries	10 (8)	22 (20)
Mild CAD ^a	31 (24)	33 (30)
Obstructive CAD ^b	89 (69)	50 (46)
Moderate CAD ^c	45 (35)	31 (28)
*Severe CAD ^d	44 (34)	19 (17)

 χ^2 =14.57, p<0.01 for normal coronaries versus mild CAD versus moderate CAD versus severe CAD

^aMild CAD includes a lesion of <50% in at least one epicardial vessel

^bObstructive CAD includes moderate and severe CAD as defined above

^cModerate CAD includes two-vessel disease (excluding a proximal left anterior descending) with a stenosis of at least \geq 70% or one-vessel disease with 70% lesion ^dSevere CAD includes a left main stenosis \geq 50%, three-vessel disease with at least one lesion with \geq 70% stenosis, or two-vessel disease including proximal left anterior descending stenosis of \geq 70%

Descriptive term	Men	Women	P-Value
•	N=128	N=109	Men vs. Women
	N (%)	N (%)	
Chest pain	106 (83)	88 (81)	0.68
Pressure	70 (55)	69 (63)	0.18
Tightness	57 (45)	58 (53)	0.18
Heaviness	50 (39)	53 (49)	0.14
Discomfort	29 (23)	46 (42)	< 0.01
Not a sharp pain	24 (19)	37 (34)	< 0.01
Crushing	10 (8)	20 (18)	0.02
Pressing	18 (14)	30 (28)	0.01
Burning	19 (15)	23 (21)	0.21
Bad ache	16 (13)	21 (19)	0.15
No chest pain	13 (10)	20 (18)	0.07
Soreness	16 (13)	15 (14)	0.77
Funny pain	2 (2)	4 (4)	0.30
Annoying	4 (3)	4(4)	0.82
Stabbing	6 (5)	8 (7)	0.39
Vague pain	4 (3)	5 (5)	0.56
Smothering	4 (3)	6 (6)	0.36

Table 6-3: Descriptive Terms of Sensations/Symptoms In The Chest-Region Among All Patients

Descriptive term	Men	Women	P-Value
	N=87	N=50	Men vs. Women
	N (%)	N (%)	
Chest pain	71 (82)	42 (84)	0.72
Pressure	47 (54)	29 (58)	0.65
Tightness	37 (43)	29 (58)	0.08
Heaviness	38 (44)	21 (42)	0.85
Not a sharp pain	18 (21)	15 (30)	0.22
Discomfort	24 (28)	23 (46)	0.03
Crushing	8 (9)	12 (24)	0.02
Pressing	12 (14)	14 (28)	0.04
Bad ache	13 (15)	15 (30)	0.04
Burning	14 (16)	12 (24)	0.26
No chest pain	7 (8)	9 (18)	0.08
Soreness	10 (12)	7 (14)	0.67
Funny pain	1(1)	2 (4)	0.27
Annoying	3 (3)	2 (4)	0.87
Stabbing	3 (3)	5 (10)	0.12
Vague pain	3 (3)	2 (4)	0.87
Smothering	4 (5)	3 (6)	0.72

Table 6-4: Descriptive terms of sensations/symptoms in the chest-region among
patients with obstructive CAD

Men

Figure 6-2: Gender Continuum of Descriptive Terms of Sensations/Symptoms in the Chest-Region Among All Patients

Chest pain Pressure Tightness Heaviness Bad ache Burning No chest pain Soreness	Discomfort Crushing Pressing Not a sharp pain
Soreness Shared Experience	Women

Figure 6-3: Gender Continuum of Descriptive Terms of Sensations/Symptoms in the Chest-Region Patients with Obstructive CAD

Men	Shared Experience	Women	
	Chest pain Pressure Tightness Heaviness Not a sharp pain Burning No chest pain Soreness	Discomfort Crushing Pressing Bad ache	
	Chastnain	Discomfort	

Location of Pain	Men	Women	P-value
	N= 128	N=109	Men vs Women
	(%)	(%)	
Arm	47 (37)	49 (45)	0.20
Right arm	23 (18)	19 (17)	0.91
Left arm	33 (26)	46 (42)	<0.01
Back	33 (26)	44 (40)	0.02
Shoulder	36 (28)	36 (33)	0.41
Neck	26 (20)	33 (30)	0.07
Jaw	13 (10)	22 (20)	0.03
Throat	20 (16)	21 (19)	0.46

Table 6-5: Non-Chest Region Pain/Discomfort Among All Patients

Table 6: Non-Chest Region Pain/Discomfort Among Patients With Obstructive CAD

Location of Pain	Men	Women	P-value
	N= 87	N=50	Men vs Women
	(%)	(%)	
Arm	37 (43)	25 (50	0.40
Right arm	19 (22)	10 (20)	0.80
Left arm	25 (29)	21 (42)	0.11
Back	23 (26)	15 (30)	0.65
Shoulder	28 (32)	13 (26)	0.45
Neck	15 (17)	14 (28)	0.14
Jaw	9 (10)	10 (20)	0.12
Throat	13(15)	11 (22)	0.30

Figure 6-4: Gender Continuum of Pain/Discomfort in the Non-Chest Region Among All Patients

Men	Shared Experience	Women	
	Arm Right arm Shoulder Neck Throat	Left arm Back Jaw	

Figure 6-5: Gender Continuum of Pain/Discomfort in the Non-Chest Region Among Patients with Obstructive CAD

Mon	Shared Experience	Women	
	Throat		
	Jaw		
	Neck		
	Shoulder		
	Back		
	Left arm		
	Right arm		
	Arm		

Symptom	Men	Women	P-value
	N= 127	N=109	Men vs. Women
	(%)	(%)	
Shortness of breath	86 (67)	89 (82)	0.01
Fatigue	72 (56)	77 (71)	0.02
Faint/lightheadness	51 (40)	56 (51)	0.08
Weakness	44 (34)	49 (45)	0.10
Sweating	60 (47)	57 (52)	0.41
Clamminess	29 (23)	34 (31)	0.14
Nausea	27 (21)	26 (24)	0.61
Vomiting	10 (8)	12 (11)	0.40
Dry mouth	27 (21)	38 (35)	0.02
Headache	25 (20)	36 (33)	0.02
Anxiety	26 (20)	38 (35)	0.01
Panic	17 (13)	26 (24)	0.04
Confusion	13 (10)	15 (14)	0.39

Table 6-7: Other symptoms associated with chest-related sensation/symptoms among all patients

Table 6-8: Other Symptoms Associated With Chest-Related Sensation/SymptomsAmong Patients With Obstructive CAD

Symptom	Men	Women	P-value
	(%)	N=30 (%)	men vs. women
Shortness of breath	58 (67)	38 (76)	0.25
Faint/light-headedness	33 (38)	20 (40)	0.81
Fatigue	49 (56)	31(62)	0.52
Weakness	28 (32)	23 (46)	0.11
Sweating	42 (48)	23 (46)	0.80
Clamminess	21 (24)	12 (24)	0.99
Nausea	20 (23)	10 (20)	0.68
Vomiting	7 (8)	5 (10)	0.70
Dry mouth	16 (18)	17 (34)	0.04
Headache	18 (21)	17 (34)	0.09
Anxiety	19 (22)	14 (28)	0.42
Panic	12 (14)	7 (14)	0.97
Confusion	11 (13)	5 (10)	0.64

Men

Men

Figure 6-6: Gender Continuum of Other Associated Symptoms with Chest-Related Sensations/ Symptoms Among all Patients

Shared Experience	Women
Faint/lightheadedness Weakness Sweating Clamminess Nausea Vomiting Confusion	Shortness of breath Fatigue Dry mouth Headache Anxiety Panic
Estat /lishthandadaaa	Charter and of here ath

Figure 6-7: Gender Continuum of Other Associated Symptoms with Chest-Related Sensations/ Symptoms Among Patients with Obstructive CAD

Shortness of breath Fatigue Sweating Faint/lightheadedness Weakness Headache Anxiety Clamminess Nausea Panic Confusion Vomiting	Dry mouth
Shared Experience	Women

Table 6-9: CCS Angina Classification According to Physician and PatientAssessment

	Total Patients			
	Men N= 128 (%)		Women N=107 (%)	
	Physician	Patient	Physician	Patient
CCS Class 0	6 (6)	20 (16)	5 (5)	4 (4)
CCS Class I	7 (6)	9 (7)	5 (5)	4 (4)
CCS Class II	15 (14)	11 (9)	15 (15)	16 (15)
CCS Class III	12 (11)	32 (25)	13 (13)	18 (17)
CCS Class IV	70 (64)	56 (44)	63 (62)	65 (61)
Weighted				
Карра	κ_{weighted} =0.36		$\kappa_{\text{weighted}}=0.03$	
Value				

CCS Class 0 –Asymptomatic

CCS Class I –Ordinary physical activity such as walking or climbing stairs does not cause angina; angina with strenuous, rapid or prolonged exertion at work or recreation.

CCS Class II -Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind or under emotional stress, or during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.

CCS Class III – Marked limitation of ordinary physical activity. Walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

CCS Class IV –Inability to carry out any physical activity without discomfort –anginal syndrome may be present at rest.

Figure 6-8



Figure 6-9



Ranks	Men N=109 (%)	Women N=98 (%)
Underestimated by	39 (36)	26 (27)
Patient		
Same rating	51 (47)	42 (43)
Overestimated by Patient	19 (17)	30 (31)
P-value	0.02	0.82

Table 6-10:Comparison of Patient Ratings to Physician Rating of CCS Angina
Classification using Wilcoxon Signed Ranks Test

Figure 6-10



Table 6-11: Regression Model of CCS Angina Classification Physician and PatientRatings Associated with Obstructive CAD

Variables	Odds Ratio (95% CI) Physician Rating	P-value	Odds Ratio (95% CI) Patient Rating	P-value
CCS Class 0-II Angina	1.0 (reference)	0.04	1.0 (reference)	0.27
CCS Class III Angina	2.8 (1.0-7.5)	0.05	1.5 (0.7-3.4)	0.27
CCS Class IV Angina	2.1 (1.1-4.0)	0.03	0.9 (0.4-1.6)	0.67

Chapter 7: Conclusions and Epilogue

Introduction

Since the mid-twentieth century, CVD has been the leading cause of mortality and morbidity among women and men in the western world. Researchers set out to gain a deeper understanding by systematically studying disease pathways, clinical presentation and possible causes of heart disease (Dawber & Kannel, 1963; Thomas R. Dawber, Gilcin F. Meadors, & Felix E. Moore, Jr., 1951; Epstein, 1965; Proudfit, Shirey, & Sones, 1966; Shapiro, Weinblatt, Frank, & Sager, 1965). As a result of this huge effort to reduce mortality and morbidity, the knowledge base of CVD /CAD has been steadily increasing with impactful advances in diagnostic testing, treatments, interventions and therapies, with improvements ranging from preventative therapy to acute care.

From the onset of studying CAD, it was observed that although angina, the cardinal presentation of CAD, was more prevalent among women, the prevalence of myocardial infarction was higher among men, prompting two main assumptions: first, women have an "uncomplicated" course of CAD (Dawber, Moore, & Mann, 1957), resulting in "immunity" among women (Kannel & Castelli, 1972), and second, the concept of sex differences in CAD emerged. Since the progression of CAD in men followed the theoretical expected course of disease (Dawber & Kannel, 1963; T. R. Dawber, G. F. Meadors, & F. E. Moore, Jr., 1951; Dawber, et al., 1957), many subsequent landmark studies enrolled men almost exclusively, further propagating the notion that "CAD is a man's disease". As a result, much of the knowledge we

have acquired today has been established on the male construct of the disease and it is not surprising that discrepant findings have been repeatedly reported among women, further perpetuating the sex/gender controversy in CVD/CAD research.

The aim of this thesis was not to resolve the controversy of whether there is in fact a sex/gender bias in the diagnosis and treatment of CVD, but rather to assess and critique potential sex/gender differences from a variety of perspectives, explored through various methodologies. In the introduction of this thesis, an overarching framework, entitled *"Framework of Patient Cardiac Care"*, was developed to illustrate the pathway that a cardiac patient transitions through to receive cardiac care. Each study in this thesis was developed to explore a sex/gender difference along a specific "avenue" of care.

Chapter 1: Framework of Patient Cardiac Care

Chapter one introduced the "Framework of Patient Cardiac Care" (Figure 1-1). This framework contextualises how each study of this thesis relates to one another while including advances in cardiovascular disease literature such as the concept "risk factor" (described in Chapter 2) and advent of cardiac catheterization (described in Chapters 5 and 6), in addition to incorporating the findings from this thesis (chapters 3 to 6). The relationship of the CVD advancements and thesis study findings, in the backdrop of the *framework of patient cardiac care* are summarized below.

Chapter 2: Literature Review

In chapter two, the traditional CVD risk factors are examined, including sex/gender differences within specific risk factors and their impact in clinical care. Sex/gender differences in the presentation of myocardial infarction, outcomes in cardiac catheterization and physician recommendations are also explored. When collectively considering and assessing the sex/gender differences outlined in the literature review in Chapter 2, it is not unreasonable to suspect that physicians may be influenced by the mixed array (and confusing at times) results, prompting the subsequent studies of this thesis.

Chapter 3: Referrals in Acute Coronary Events for CARdiac Catheterization: The *RACE CAR* Trial

The Referrals in Acute Coronary Events for CARdiac catheterization: The *RACE CAR* Trial is a conceptual experiment, presenting clinical vignettes to physicians to decide whether the patient would benefit from a referral for cardiac catheterization. Clinical vignettes were controlled for sex, age (55 years old versus 75 years old), TIMI risk (low, moderate, high) and patient preference for cardiac catheterization (agreeable/not agreeable/ no opinion) randomly allocating sex to the vignette, to determine if physicians perceived a difference in benefit of cardiac catheterization according to sex/gender. Physicians were blinded to the primary objective of the study. We found that for scenarios of equal age, risk and preference

PhD Thesis

for cardiac catheterization, Canadian physicians were more likely to rate men to benefit from cardiac catheterization compared to women (Kreatsoulas, Sloane, Pogue, Velianou, & Anand, 2010). In addition, we observed that physicians perceive younger patients to benefit more from cardiac catheterization than older patients, high risk patients to benefit more than low risk patients and patients agreeable for cardiac catheterization to benefit more than patients who were not agreeable for the procedure or expressed no opinion at all (Kreatsoulas, Sloane, et al., 2010). Our study findings indicate that the decision to refer a patient for cardiac catheterization is influenced by a complex interplay of factors including sex/gender, age, risk and patient preference for cardiac catheterization. There were several unique features to this study including the design which was a conceptual experiment seeking to assess physician opinion *prospectively* and the analysis, which employed multi-level modeling representing an innovative way to assess multiple opinions of physicians.

Chapter 4: Identifying women with severe angiographic coronary disease

While the *RACE CAR* study (Chapter 3) *prospectively* assessed physician opinion, the next study in this thesis was designed to characterize and analyse the risk profile of the patients who have *already* been referred for cardiac catheterization/coronary angiography. In this study we analysed over 23,000 men and women referred to the Hamilton Health Sciences Heart Investigations Unit for their first coronary angiography. Patients in our study represented a consecutive

PhD Thesis

sample of 'real world' clinical practice representing a referral catchment area of 2.2 million people in the Central-South Ontario geographic region. Relating this back to the framework presented in chapter 1 (Figure 1-1), we examined the risk factor profile, stratified according to sex and age, along with their symptoms and functionality as assessed through Canadian Cardiovascular Society (CCS) angina classification (gold standard) to determine the strength of association with the severity of their angiographic CAD. Using univariate and multivariate logistic modeling, we found that overall, women were more likely to be older, have diabetes and hypertension, while men are more likely to smoke. Women were also more likely to have normal/mild CAD and less likely to have severe CAD (Kreatsoulas, Natarajan, Khatun, Velianou, & Anand, 2010). Among patients with severe CAD, the traditional risk factors and CCS Class IV angina were predictive of severe CAD in both men and women; however CCS Class IV angina was a stronger predictor of severe CAD in women compared to men (Kreatsoulas, Natarajan, et al., 2010). This finding is interesting as most data in the literature suggest that men present more often with "typical" angina symptoms, while women present with "atypical" angina symptoms (Canto et al., 2002; Canto et al., 2000; Comeau, Jensen, & Burton, 2006; DeVon & Zerwic, 2003; Goldberg et al., 1998; Granot, Goldstein-Ferber, & Azzam, 2004; Hochman et al., 1999; Patel, Rosengren, & Ekman, 2004; Roger et al., 2000).

Independent Study from Comprehensive Exams

Although not a part of this thesis, the research paper requirement composed for the independent study of the comprehensive exam process, entitled, *"Deconstructing Angina in Women"* opened the "black box" of angina and historically de-constructed the early construct of angina, revealing the underlying assumptions that led to the perception that "CAD is a man's disease". The findings from this study inspired the next two chapters of this thesis by bringing forth the need to reconstruct angina using a *gender-centered* approach.

Chapter 5: Understanding Cardiac-Related Symptoms According to Sex/Gender

After a historical exploration of the underlying assumptions that informed the terms "typical angina" to represent the symptoms most common among men and "atypical angina" to represent the symptoms most common among women, it was apparent that a qualitative study design would yield the most informative insights to reconstruct angina symptoms in men and women. Bt conducting semistructured interviews, and guided by grounded theory approach and concepts from feminist epistemology, we sought to capture symptoms using *gender-centered language* from a *situated-knower* perspective, by asking the patients to describe their experiences in their own words. After intense coding procedures, and multiple attempts at categorization, a theory of understanding symptoms according to sex/gender along a *gender continuum* emerged. Men and women have more *shared experiences* in symptom presentation and the *gender continuum* allows patients of a certain sex to be *gendered* in their expression of the symptom. This is an important finding as we are proposing a shift in the current thinking and understanding of angina since men and women have more *shared experiences* than previously reported using traditional "typical-atypical" binary classifications.

At the same time we observed that symptoms alone did not prompt a patient to seek medical care, rather most patients reported previously experiencing their symptoms (to varying degrees). However, patients described a "big"/critical incident that represented a significant change in their symptoms urging them to seek medical attention. We constructed the term "symptomatic tipping point" to capture the transitional period between experiencing the change in symptom(s) and developing the concern to seek medical care. The symptomatic tipping point was a process that both men and women transitioned through varying only in the duration within each stage. The symptomatic tipping point is also represented in the framework of patient cardiac care (Figure 1-1) occurring against the backdrop of previous personal experience including risk factor modification.

Chapter 6: Understanding Cardiac-Related Symptoms According to Gender Using the McMaster University Symptoms in Cardiac Assessment *(MUSICA)* Tool

Recognizing the limitations in continuing with the inaccurate and inflexible labels of "typical/atypical" angina, particularly as they related to men/ women respectively, this study sought to test the new construct of angina proposed in Chapter 5 entitled, "Understanding cardiac-related symptoms according to sex/gender" by developing a quantitative assessment tool (MUSICA) to capture the risk factors symptom parameters, 'symptomatic tipping point' and patient perception/knowledge as they correlate with angiographic outcomes. In other words, this final thesis study encompasses the entire framework proposed in chapter 1, Framework of patient cardiac care (Figure 1-1). Specifically the distribution of the symptom parameters were analysed in men and women according to obstructive CAD and the findings were illustrated along the *gender* continuum, among all patients referred for coronary angiography, and among the patients that had obstructive CAD. When initially analysing the data, I was dismayed by the lack of significant p-values and then it hit me! I suddenly realised how powerful it was to not have significant differences between men and women, how the 'elegance' of the study findings was in the *similarities*. This is a very untraditional approach in reporting statistical findings and by the same token, it is one of the strengths of this study. When analysing the figures of symptom

parameters along the *gender continuum* it is readily apparent that men and women have far more common *shared experiences* than sex-specific symptoms, particularly among patients with obstructive CAD. We feel that this study substantiates the theory of the *gender continuum* and hope that we re-shape the way clinicians and patients understand angina.

Epilogue

This thesis has truly been a journey! As this thesis comes to a close, ironically I am left with more study questions to explore, and this "end" feels rather arbitrary. I have had so many impactful experiences during this journey, commencing from Dr. Mita Giacomini's course in the Philosophy of Science which has forever changed the way I view and think about scientific problems. Although not explicitly mentioned throughout the thesis, I was guided by several philosophical theories including Imre Lakatos, Bruno Latour, Kathy Charmaz and feminist epistemology, each of whose theories laid the foundation and scaffolding for the scientific discoveries represented in this thesis.

When I first embarked in this subject area of sex controversies in the cardiovascular disease literature, I felt that I would struggle as a non-clinician. Reflecting back, I now feel that this ironically was one of my greatest strengths. In deconstructing and reconstructing angina, I did not bring clinical judgement to my investigation and exploration of the topic area. I was not influenced with what was

taught in medical/nursing school; one could say I was blinded to the clinical teachings that many have influenced my results.

I am particularly grateful to all the skills and mentoring I received during this journey, including the statistical skills and thoughtful use of English language conveyed by Dr. Harry Shannon. His depth and understanding of context are so valuable amidst his statistical expertise. And lastly, I am so grateful for the mentorship, guidance, support and scientific curiosity that was fostered during this journey by my supervisor Dr. Sonia Anand, I will be forever grateful! Thank you "Dream Team", I have had the more extraordinary journey!

Catherine Kreatsoulas

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CJC SYMPOSIUM 2009

The impact of social determinants on cardiovascular disease

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C Kreatsoulas, SS Anand. The impact of social determinants on cardiovascular disease. Can J Cardiol 2010;26(Suppl C):8C-13C.

Cardiovascular disease is the leading cause of death among high-income countries and is projected to be the leading cause of death worldwide by 2030. Much of the current research efforts have been aimed toward the identification, modification and treatment of individual-level risk factors. Despite significant advancements, gross inequalities continue to persist over space and time. Although increasing at different rates worldwide, the magnitude of increase in the prevalence of various cardiovascular risk factors has shifted research efforts to study the causes of the risk factors (ie, the 'causes of the causes'), which include the social determinants of health. The social determinants of health reflect the impact of the social environment on health among people sharing a particular community. Imbalances in the social determinants of health have been attributed to the inequities in health observed between and within countries. The present article reviews the role of the social determinants of health on a global level, describing the epidemiological transition and the persistent trend known as the 'inverse social gradient'. The impact of social determinants in Canada will also be examined, including data from ethnic and Aboriginal communities. Possible solutions and future directions to reduce the impact of social factors on cardiovascular health are proposed.

Key Words: Cardiovascular disease; Global health; Health inequity; Social determinants; Social gradient

Nardiovascular disease (CVD) is the leading cause of morbidity ⊿and mortality among high-income countries of the industrialized world, accounting for more than one-third of total deaths (1,2). CVD is the leading cause of noncommunicable morbidity and mortality among low- and middle-income countries, accounting for almost 25% of total deaths (3) and, by the year 2030, is projected to be the leading cause of death worldwide (1,2). One of the most important advances in cardiovascular research of the 20th century was the identification of risk factors associated with CVD, with subsequent treatments developed and rigorously tested to modify these risk factors with the goal of preventing CVD. The INTERHEART study (4) examined more than 27,000 cases and controls from 52 countries and found that more than 90% of the population-attributable risk for myocardial infarction can be explained by nine potentially modifiable risk factors: apolipoprotein B/apolipoprotein A ratio, smoking, diabetes, hypertension, abdominal obesity, psychosocial factors, fruit/ vegetable consumption, physical activity and alcohol consumption; thus, it is reasonable to believe that modification of these individual risk factors will significantly improve cardiovascular health. However, despite advances in the primary and secondary prevention of CVD, there are still gross inequalities in cardiovascular health care across space and time (5-7). To date, epidemiological studies have focused on identifying, modifying and treating individual risk factors; however,

Impact des déterminants sociaux sur la maladie cardiovasculaire

La maladie cardiovasculaire est la principale cause de mortalité dans les pays à revenus élevés et on s'attend à ce qu'elle devienne la principale cause de mortalité dans le monde d'ici 2030. Une bonne part de la recherche actuelle s'est attardée à la reconnaissance, à la modification et au traitement des facteurs de risque à l'échelon individuel. Or, malgré des progrès significatifs, d'importantes disparités persistent dans l'espace et le temps. Même si elle croît à un rythme différent selon les régions du monde, la prévalence de divers facteurs de risque cardiovasculaires force maintenant les chercheurs à étudier désormais l'origine des facteurs de risque eux-mêmes (c.à-d., « la cause des causes »), ce qui inclut les déterminants sociaux de la santé. Les déterminants sociaux de la santé témoignent de l'impact de l'environnement social sur la santé des personnes d'une communauté donnée. Les disparités quant aux déterminants sociaux de la santé ont été attribuées aux inégalités en matière de santé observées à l'intérieur des pays et entre eux. Le présent article fait le point sur le rôle des déterminants sociaux de la santé d'un point de vue mondial en décrivant l'évolution de l'épidémiologie et la tendance persistante connue sous le nom de « gradient social inverse ». L'impact des déterminants sociaux au Canada fera l'objet d'une analyse qui portera entre autres sur les données provenant des communautés ethniques et autochtones. On propose des solutions et des orientations qui pourraient éventuellement réduire l'impact des déterminants sociaux sur la santé cardiovasculaire.

many cardiovascular risk factors have been increasing at different rates worldwide. Efforts to narrow the persistent health gap has spurred recent interest in developing approaches to study the causes of risk factors (ie, the 'causes of the causes'), which include the social determinants of health.

The term 'social determinants of health' is used to describe the health impact of the social environment on people living in a particular community (8). Specifically, they include the conditions in which people are born, grow, live, work and age, and are shaped by the distribution of money, power and resources at global, national and local levels (9). The social determinants of health (including the health care system) are mostly responsible for health inequities between and within countries (9). Historical research has significantly established the impact of economic development and social organization on health (10). Because the prevalence of some cardiovascular risk factors (eg, obesity, hypertension and diabetes) is rising worldwide (2,10,11), it is necessary to focus efforts on understanding the role of the 'causes of the causes' (ie, the social determinants of health) to help bridge the current gap in equality. For the purpose of the present article, the social determinants of health as they pertain to CVD will first be explored on a global level and, second, within Canada, including data from ethnic and Aboriginal communities. Possible solutions to reduce the impact of social factors on CVD are also proposed.

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THE GLOBAL BURDEN OF DISEASE

The World Bank and the WHO commissioned the Global Burden of Disease study (1,2) to quantify mortality, morbidity and the health effects of selected diseases, injuries and risk factors for the world as a whole and within specific regions. Among worldwide noncommunicable causes of death, CVD accounts for more than one-half (1); this finding has been consistently projected to remain unchanged across multiple models for at least the next 20 years in countries of both the developed and developing world (1,2,11). This finding is at odds with the popular perception that noncommunicable disease, such as CVD, are 'diseases of affluence' whereby related risk factors are perceived to be more prevalent in high-income countries and not present among low-income countries (12). However, this apparent paradox of substantial noncommunicable death in adults of the developing world has insidiously been established without attracting global attention or local action (12,13). The magnitude of this problem has been greatly overlooked because more than 80% of CVD deaths worldwide currently occur in low- and middle-income countries (13). By the year 2020, CVD is expected to surpass infectious disease as the world's leading cause of death and disability (3), increasing from 25% in 1990 to 40% in 2020, illustrating the scale of this epidemic (13). Several factors are likely driving the worldwide increase in CVD, including the projected increase of 60% in the global population between 1990 and 2020, the increasing average life expectancy (due to a multitude of factors including improvements in nutrition, public health and medical care, while decreasing the rates of communicable diseases) and the economic, social and cultural changes that have led to increases in CVD risk factors including tobacco use, obesity, hypertension and diabetes (3). To put this into perspective, smoking, for example, is projected to kill 50% more people in 2015 than HIV/AIDS, and will be responsible for 10% of all deaths globally (11).

The epidemiological transition

Global patterns of death and disability have been observed over time. As societies become increasingly urban and industrialized, infant mortality declines, and the major causes of death and disability shift from nutritional deficiencies and infectious disease to degenerative or noncommunicable diseases such as CVD, resulting in an increasing average life expectancy. This shift has come to be known as the 'epidemiological transition' (3,14). Originally, three main transition states were identified (15); however, recently, up to five transition states have been described and characterize the total rates of CVD change (3,10,16) as illustrated in Figure 1. Briefly, the first stage, known as 'the age of pestilence and famine', is indicative of countries in the earliest stage of development, in which death from CVD accounts for less than 10%, predominantly as rheumatic heart disease and cardiomyopathies due to infection and malnutrition (3,10). Geographical regions currently experiencing this transition state include sub-Saharan Africa and rural areas of South America and Asia. During the second stage, known as 'the age of receding pandemics', infectious disease burdens are reduced, nutrition improves and, correspondingly, deaths attributed to CVD increase to up to 35%, manifesting mostly as rheumatic heart disease, hypertension, coronary artery disease and stroke (3,10,16). Geographical regions currently experiencing this transition state include China and other Asian countries. In the third stage -'the age of degenerative and man-made diseases' - life expectancy continues to improve, diets include higher fat content, cigarette smoking becomes more prevalent and sedentary lifestyles become more common (10). Not surprisingly, deaths attributed to CVD continue to rise, accounting for 35% to 65% of total deaths, primarily manifesting as atherosclerosis, coronary artery disease and stroke, often at ages younger than 50 years (10). Regions currently experiencing this stage include urban India, Latin America and former socialist European eastern block countries. In the developed world, most countries are in the fourth stage of transition referred to as 'the age of delayed degenerative diseases', in which up to 50% of deaths are attributed to CVD and typically present as coronary artery disease, stroke or congestive



Figure 1) The epidemiological transition states of cardiovascular disease (CVD). CHD Coronary heart disease. Reproduced with permission from reference 10

heart failure at more advanced ages (3,10,16). More recently, a fifth stage has been identified – 'the age of health regression and social upheaval' – which is used to describe conditions of social upheaval or war, resulting in a breakdown of the health system in which there is a resurgence of diseases seen in transition states one and two (eg, rheumatic heart disease), while the CVD diseases common in the third and fourth stage (eg, atherosclerosis) continue to persist (10). In total, approximately 35% to 55% of deaths are attributed to CVD, with a lower average life expectancy similar to what is currently experienced in Russia (10).

Epidemiological transition states occur on a macro level, affecting specific countries or regions; however, they may also occur on a micro level within a country, including affluent countries. A country or a region can enter an epidemiological transition state at any time, with the progression from one state to another closely associated with parallel economic, demographic and nutritional 'transitions'. From an economic perspective, progression through the transition states is often accompanied by an increase in per capita income: a social transition to industrialization, shifting from predominately rural to urban life; and the establishment of a public health infrastructure including wider access to health care (3). At the same time, a demographic transition occurs in which fertility and age-adjusted mortality decline, leading to an increase in average life expectancy and an aging population (3). As life expectancy increases, a shift in nutrition also occurs and populations are exposed to more cardiovascular risk factors including 'Westernized' diets (higher animal products and fat), sedentary behaviours and low physical activity, which lead to an elevation in blood pressure, body weight, blood sugar levels and lipid concentrations (13). This pattern has been repeatedly observed in many developing countries. For example, body mass index and blood cholesterol levels have dramatically increased in the Chinese population, likely due to a sharp increase in fat consumption; it is expected that China will soon experience a rapid escalation of coronary artery disease, surpassing the current one-third of total lives that it claims each year (13,17). Even with China's booming economic growth, health care costs are currently unsustainable - the impact of which has been detrimental to the poor. Health care is less accessible while the health care system is inundated, having to cope with the double burden of infectious and chronic disease in an excessively large population (13,17).

The epidemiological transition has been observed to occur within countries. Affluent regions are typically affected first and, as the epidemic matures, the socioeconomically disadvantaged groups become increasingly more vulnerable, widening the health inequality gap in a phenomenon widely known as 'the inverse social gradient' (13). The socioeconomically disadvantaged groups have a greater exposure to cardiovascular risk factors such as smoking, increasing incidence of atherosclerotic risk factors (eg, obesity, diabetes, dyslipidemia and hypertension), poor working and living conditions, stress, lower rates



Figure 2) Socioeconomic influences on cardiovascular disease (CVD) from a lifecourse perspective. Reproduced with permission from reference 18

of formal education, and reduced access to health care and health education (3,5,13,17). As research continues to emerge, evidence is mounting, indicating that epidemiological transition is a poor and incomplete model to understand how the social determinants of health interact with cardiovascular health because education, occupation, social norms, culture, geography, policy, economic factors and environment are considered to be independent individual risk factors. A comprehensive understanding of the social determinants of health must consider their dynamic nature, which inevitably includes a temporal component of early life and childhood exposures impacting adult health. The life course perspective is a methodological approach that takes into account the cross-sectional relationship of social circumstances from the early stages of life that may later be accompanied by similar social advantage/disadvantage in other spheres of adult life (5,18) (Figure 2). For example, a longitudinal study (19) from Scotland found that social disadvantage, defined by a father's occupation and neighbourhood (postal code of residence), contributed to CVD even after controlling for CVD risk factors. An increasing number of longitudinal epidemiological studies have demonstrated the importance of early-life socioeconomic circumstances with respect to future development of cardiovascular risk factors and CVD in later life (20).

CARDIOVASCULAR RISK FACTORS AND SOCIAL DETERMINANTS IN CANADA

CVD is the leading cause of death in Canada, accounting for one-third of total deaths (21,22). Despite the decline in CVD-related deaths over time in Canada, there are wide regional variations in death rates and risk factors (22). For example, the overall Canadian age-standardized CVD mortality rate (ASMR) from 1995 to 1997 was 245.8 per 100,000 population (22). Within Canada, there are significant differences in the ASMR from CVD, with Newfoundland and Labrador having the highest CVD mortality rate at 320.6 per 100,000 population, and the Northwest Territories having the lowest at 196.9 per 100,000. An east to west gradient in CVD mortality has been described, in which provinces in eastern Canada have higher CVDrelated ASMR, with mortality rates generally decreasing westward, where the province of British Columbia has the lowest ASMR from CVD. However, the Territories have the lowest CVD ASMR in the country (22). In addition to between province/territory variation, variability within provinces has been observed. In a study using crosssectional data from the National Population Health Survey of 1994, in combination with the Canadian Community Health Survey of 2005, Lee et al (21) compared temporal trends in the prevalence of cardiovascular risk factors across Canada. Over a 10-year study period, the prevalence of diabetes and obesity significantly increased, the prevalence of hypertension nearly doubled while smoking rates significantly declined (21). The prevalence of risk factors, when analyzed according to age and sex, indicates that they are increasing in both sexes and in



Figure 3) Canadian poverty rates over time, 1984 to 2004. Reproduced with permission from reference 28

all age groups among Canadians, particularly among the younger population groups (21). Such trends have important short- and long-term implications because the early presence of risk factors predisposes people to earlier onset of CVD, incurring greater health resource consumption and a greater potential for life-years lost (21,23,24).

Evidence of the inverse social gradient in Canada

When analyzing CVD mortality and risk factor prevalence rates according to income group, it is alarming to realize that despite affluence in Canada, individuals of lower socioeconomic status are more vulnerable to CVD than those of higher socioeconomic status (3,25). Evidence of the inverse social gradient and inequity gap reveals that mortality is highest among those in the poorest income group and, as income increases, the mortality rate decreases (3,25). Not surprisingly, these trends are also consistent with CVD risk factor prevalence rates in which individuals in a lower income group, especially in urban areas, have a greater exposure to risk factors (such as smoking and atherosclerosis) that manifest as obesity, diabetes, dyslipidemia and hypertension (21,22). Alarmingly, the inverse social gradient and inequity gap not only persisted but grew when the prevalence of cardiovascular risk factors according to income category over time were considered. Specifically, heart disease, hypertension, diabetes, smoking and obesity increased as income decreased in 1994. This trend was exaggerated when individual risk factors were compared between decades and within income group, with the exception of smoking (21). What is remarkable about these trends in a country such as Canada, is that they are persisting despite the availability and universality of health care. The presence and persistence of an inverse social gradient related to CVD mortality and associated risk factors is especially concerning because the inequity gap is widening between the highest and lowest income groups, and this trend is worsening with time (21).

It is likely that multiple factors contribute to the persistence of the inverse social gradient. Consistent with trends observed in the epidemiological transition state, the concurrent decline in malnutrition and communicable disease while CVD risk factors increase typically occur in privileged groups first, soon followed by higher rates of CVD including ischemic heart disease and stroke. This trend is likely responsible for the popular perception that CVD is a 'disease of affluence' (1,13). However, as the middle class expands and the epidemiological transition spreads to a broader population, individuals with the lowest socioeconomic status tend to acquire the harmful risk factors last, mostly due to their financial situation and the heavy physical activity usually associated with their work (3,17). At the same time, the socioeconomically disadvantaged are also less likely to have access to advanced health services, treatments and information for risk factor modification and, as a result, CVD mortality rates are slower to decline in this group (3,17). For example, of the percentage of the population living in poverty in Canada, two-parent families comprise the highest income group whereas female lone-parent families comprise the lowest-income group - a trend that has remained consistent over time (Figure 3). Socioeconomic status has been widely acknowledged as the



Figure 4) Socioeconomic gradient and cardiovascular disease (CVD) among Aboriginal Peoples and European descendants in Canada. Reproduced with permission from reference 27

most powerful social determinant of health; however, there are a multitude of factors that intersect with socioeconomic status, including systematic inequalities due to ethnicity and sex.

The inverse social gradient and Aboriginals in Canada

Ethnicity is a construct that embodies both genetic and cultural differences including language, religion and diet, to name a few. The construct of ethnicity is intertwined with variations in lifestyle, geography, socioeconomic position and education. Differences in morbidity and mortality among various ethnic groups are well documented within Canada. The Study of Health Assessment and Risk in Ethnic groups (SHARE) (26) used a population-based approach and confirmed differences in risk factor prevalence rates among three ethnic groups in Canada (26). This is an important finding because the overall prevalence of CVD is declining in Canada; however, CVD was observed to be rising within some ethnic groups. There are a number of explanations proposed for these differences including the concept of social exclusion, differences in risk factor frequency, access to screening/prevention, differences in treatment and adherence to treatment (26). Specifically, Aboriginals in Canada have been identified as the population group with the shortest life expectancy (25,27), averaging five to 14 years less than their fellow Canadians (28) despite a decline in infectious disease deaths. Aboriginal infant mortality rates that are 1.5 to four times greater than the Canadian rate contributed to the shorter life expectancy (29).

Not surprisingly, CVD health among Aboriginals is also poor. It has been demonstrated that Aboriginals have a higher prevalence of CVD and a greater burden of atherosclerosis than Canadians of European ancestry (27). Correspondingly, they also have a higher prevalence of conventional risk factors including higher rates of smoking, diabetes, obesity, abdominal obesity, hypertension, cholesterol and family history, which likely account for observed ethnic group differences (27). However, Aboriginals have also been identified to have an excess of social disparities including environmental dispossession - a term used to refer to the processes through which Aboriginal Peoples' access to the resources of their traditional environments are greatly reduced (30) – and high levels of poverty (27). Consistent with trends among other disadvantaged groups, there is evidence of an inverse social gradient; however, the social gradient is strikingly pronounced among Aboriginals when compared with their European-Canadian counterparts of similar income. In The Study of Health Assessment and Risk Evaluation in Aboriginal Peoples (SHARE-AP) (27), both Aboriginals and European-Canadians had the highest prevalence of CVD; however, even among individuals in the lowest income group (less than \$20,000 household income), the absolute rate of CVD was significantly higher among Aboriginals than among European-Canadians of all income



Figure 5) Cardiovascular disease (CVD) risk factor prevalence and income among Aboriginal Peoples and European descendants in Canada. Reproduced with permission from reference 27

ranges (27), as illustrated in Figure 4. Consistent with this trend (and equally as shocking!), the burden of CVD risk factors (more than three CVD risk factors) was greatest among people in the lowest income group in both Aboriginals and European-Canadians; however, the absolute rate of CVD risk factor burden was at least twice as high in Aboriginals compared with European-Canadians within each income level group (27) (Figure 5). The social disadvantage index score was developed to incorporate social and economic exposures into a single continuous measure, and found that increased social disadvantage is associated with an increased burden of some – but not all – cardiovascular risk factors independently associated with CVD (31). Specifically, social disadvantage was found to increase with age, was higher among women than men and varied greatly according to ethnic group, in which the highest risk for CVD was among Aboriginal men (Figure 6) (31).

THE TREATMENT GAP

In addition to the health inequities examined, both on a global and national level, the '10/90 gap' has been recognized as a serious limitation to the improvement of health care, citing that less than 10% of global health research spending is devoted to diseases that account for 90% of the global disease burden (32). Globalization may negatively affect countries in a lower epidemiological transition state by accelerating the transition of Western products and behaviours to non-Western cultures (13). At the same time, globalization can also offer opportunities to facilitate the prevention of CVD through risk factor modification, applying evidence of effective interventions and promoting health behaviour through mass media (13). Despite this, current effective therapies for secondary prevention, such as treatment with acetylsalicylic acid, blood pressure-lowering drugs and statins, are highly undersused. For example, a study conducted in rural India (13), where CVD is the leading cause of death, reported that less than onesixth of the patients who experienced a previous CVD event acknowledged taking antiplatelet therapy.

The reasons for the treatment gap are complex. Several proposed explanations include the following: incomplete guidelines for physicians, health care systems and policy; the cost of therapy relative to wages; cultural barriers such as the stigma of taking long-term medication; urban versus rural accessibility to health care; and international neglect, for which low- and middle-income countries account for onethird of the world's population but only receive 2% of global health resources (17). Even within affluent countries such as Canada and the United States, a '5/95 gap' is used to describe the ratio of resources devoted to prevention versus treatment (33).

To help address issues related to health inequities occurring at both a global and local level, the Centre for Urban Health – commissioned


Figure 6) Risk of cardiovascular disease and social disadvantage. Reproduced with permission from reference 31

TABLE 1 The traditional 10 tips for better health

- 1. Do not smoke. If you can, stop. If you cannot, cut down
- 2. Follow a balanced diet with plenty of fruit and vegetables
- 3. Keep physically active
- 4. Manage stress by, for example, talking things through and making time to relax
- 5. If you drink alcohol, do so in moderation
- 6. Cover up in the sun, and protect children from sunburn
- 7. Practice safer sex
- 8. Take up cancer screening opportunities
- 9. Be safe on the roads: follow the Highway Code
- 10. Learn the first-aid ABC's: airways, breathing, circulation (Donaldson, 1999)

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by the WHO - created a document titled 'The Solid Facts' to "promote awareness, informed debate and above all, action...a valuable tool for broadening the understanding of stimulating debate and action on the social determinants of health" (8). The Solid Facts document identifies 10 social determinants of health: social gradient, stress, early life, social exclusion, work, unemployment, social support, addiction, food and transport (8). This document is widely available, and every member state of the European Union (EU) has currently made efforts to integrate it into their health care agendas. Among the objectives for generating this document was to encourage other countries outside the EU to use it as a model/template for their health care agendas (8). However, current health models and dissemination of health information to the public from various government and health bodies have been strongly and individually oriented, and take the position that individuals can control the factors that determine their health, as exemplified in the 'Traditional 10 tips for better health' (29) depicted in Table 1. However, these conceptualizations have been recently refined to incorporate the information established from research on the social determinants of health using a socially oriented perspective, which assumes that the most important determinants of health are beyond the control of most individuals. The traditional 10 tips can be contrasted with the 'Social determinants 10 tips for better health' presented in Table 2 (29).

SUMMARY

Because CVD is increasing globally, it is crucial that we understand the social and economic forces that promote the development of risk factors affecting who is screened and who is treated. The dissemination of knowledge and the application of effective strategies are essential. The social determinants of health are tools to help illuminate how social processes interact with CVD health on a global, national and

TABLE 2 The social determinants 10 tips for better health

- 1. Do not be poor. If you can, stop. If you cannot, try not to be poor for long
- 2. Do not have poor parents
- 3. Own a car
- 4. Do not work in a stressful, low-paying manual job
- 5. Do not live in damp, low-quality housing
- 6. Be able to afford to go on a foreign holiday and sunbathe
- 7. Practice not losing your job and do not become unemployed
- Take up all benefits you are entitled to if you are unemployed, retired, or sick or disabled
- 9. Do not live next to a busy major road or near a polluting factory
- Learn how to fill in the complex housing benefit/asylum applications before you become homeless or destitute (Gordon, 1999)

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individual level. Specifically, if disadvantaged groups can be identified, intervention strategies can then be tailored at an early age before the individual exhibits the conventional risk factors thereby improving population health and reducing the burden placed on health care resources. It is critical that people – including the scientific community – advocate, educate, organize, lobby and convince policy makers that minimizing social and economic inequities will diminish the social gradients of cardiovascular risk factors and CVD.

Improvements to implement change must be made on many levels. Currently, there is an international plea to improve national health monitoring and surveillance systems (34,35). Advances in statistical linkage techniques (eg, geocoding and area-based socioeconomic measures), in addition to multilevel hierarchical analysis frameworks, have contributed to assessing public health outcomes to identify disadvantaged groups (35). In particular, these techniques have aided researchers and policy makers to study risk factors such as smoking (36) and physical activity level (37) at the neighbourhood-of-residence level so that new approaches to develop community-level interventions can be targeted (36). For example, clean indoor air legislation prohibiting smoking in the workplace has aided in reducing overall cigarette consumption (38,39). Similarly, a study (40) using hierarchical regression analysis techniques suggested that greater social cohesion, which seeks to capture the presence of strong social bonds and the absence of latent social conflict, was found to be directly associated with more general physical activity in Chicago (United States) neighbourhoods, independent of previous participation in recreational programs and other neighbourhood- and individual-level covariates. To increase the promotion of physical activity in this urban population, the authors recommended that efforts should target neighbourhood-level social and psychosocial processes that influence social cohesion (37). These examples highlight that an understanding of the community and household determinants of the major cardiovascular risk factors, which may vary by geographical region and cultural background, is required to develop prevention strategies. Finally, such context-dependent strategies must be evaluated to ensure that they are efficacious.

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Appendix B

HEALTH OUTCOMES/PUBLIC POLICY

Referrals in Acute Coronary Events for CARdiac Catheterization: The RACE CAR trial

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C Kreatsoulas, D Sloane, J Pogue, JL Velianou, SS Anand. Referrals in Acute Coronary Events for CARdiac Catheterization: The RACE CAR Trial. Can J Cardiol 2010;26(8):e290-e296.

BACKGROUND: Women with acute coronary syndromes have lower rates of cardiac catheterization (CC) than men.

OBJECTIVE: To determine whether sex/gender, age, risk level and patient preference influence physician decision making to refer patients for CC.

METHODS: Twelve clinical scenarios controlling for sex/gender, age (55 or 75 years of age), Thrombolysis in Myocardial Infarction risk score (low, moderate or high) and patient preference for CC (agreeable or refused/no preference expressed) were designed. Scenarios were administered to specialists across Canada using a web-based computerized survey instrument. Questions were standardized using a five-point Likert scale ranging from 1 (very unlikely to benefit from CC) to 5 (very likely to benefit from CC). Outcomes were assessed using a two-tailed mixed linear regression model.

RESULTS: Of 237 scenarios, physicians rated men as more likely to benefit from CC than women (mean [\pm SE] 4.44 \pm 0.07 versus 4.25 \pm 0.07, P=0.03), adjusted for age, risk and patient preference. Low-risk men were perceived to benefit more than low-risk women (4.20 \pm 0.13 versus 3.54 \pm 0.14, P<0.01), and low-risk younger patients were perceived to benefit more than low-risk older patients (4.52 \pm 0.17 versus 3.22 \pm 0.16, P<0.01). Regardless of risk, patients who agreed to CC were perceived as more likely to benefit from CC than patients who were disagreeable or made no comment at all (5.0 \pm 0.23, 3.67 \pm 0.21, 2.95 \pm 0.14, respectively, P<0.01).

CONCLUSION: Canadian specialists' decisions to refer patients for CC appear to be influenced by sex/gender, age and patient preference in clinical scenarios in which cardiac risk is held constant. Future investigation of possible age and sex/gender biases as proxies for risk is warranted.

Key Words: Acute coronary syndromes; Cardiac catheterization; Gender; Decision making

I thas been widely reported that coronary artery disease (CAD) is the leading cause of morbidity and mortality of both men and women in westernized countries, accounting for over one-third of total deaths (1). Furthermore, CAD accounts for the greatest proportion of deaths among women of all ages, yet despite this, it has often been viewed as a 'man's disease'. Although there are similarities, differences do exist, particularly in symptom presentation and risk profile, because women characteristically present with CAD at older ages than men (2-23), and more often with atypical symptoms (2,8,10,13,17,18). However, women generally have less severe CAD as determined by angiography (4,8,10-12,16,22,23,24-28), contributing to the perception that they are at lower risk. Differences in physicians' interpretations of symptoms, risk assessment and patient preferences may contribute to sex differences in

L'essai RACE CAR sur les aiguillages de cathétérisme cardiaque en cas d'événements coronariens aigus

HISTORIQUE : Les femmes ayant un syndrome coronarien aigu présentent un taux de cathétérisme cardiaque (CC) plus faible que les hommes.

OBJECTIF: Déterminer si le sexe, l'âge, le niveau de risque et la préférence du patient influent sur la décision du médecin à aiguiller les patients vers un CC.

MÉTHODOLOGIE : Les chercheurs ont conçu 12 scénarios cliniques tenant compte du sexe, de l'âge (de 55 à 75 ans), de l'indice de risque de thrombolyse en cas d'infarctus du myocarde (faible, modéré ou élevé) et de la préférence du patient à subir un CC (en accord, refus ou aucune préférence exprimée). Ils ont administré les scénarios à des spécialistes du Canada au moyen d'un sondage informatisé rempli par Internet. Ils ont normalisé les questions au moyen d'une échelle Likert de cinq points variant de 1 (très peu susceptible de profiter du CC) à 5 (très susceptible de profiter du CC). Ils ont évalué les résultats au moyen d'un modèle de régression linéaire bilatéral mixte.

RÉSULTATS : Dans les 237 scénarios, les médecins ont classé les hommes comme plus susceptibles que les femmes de profiter du CC (moyenne \pm ÉT 4,44 \pm 0,07 par rapport à 4,25 \pm 0,07, P=0,03), après rajustement selon l'âge, le risque et la préférence du patient. Les hommes à faible risque étaient perçus comme en profitant davantage que les femmes à faible risque (4,20 \pm 0,13 par rapport à 3,54 \pm 0,14, P<0,01), et les patients plus jeunes à faible risque, davantage que les patients plus âgés à faible risque (4,52 \pm 0,17 par rapport à 3,22 \pm 0,16, P<0,01). Quel que soit le risque, les patients qui acceptaient de subir le CC étaient perçus comme plus susceptibles d'en profiter que ceux qui y étaient réfractaires ou qui n'exprimaient pas de préférence (5,0 \pm 0,23, 3,67 \pm 0,21, 2,95 \pm 0,14, respectivement, P<0,01).

CONCLUSION : La décision des spécialistes canadiens d'aiguiller les patients vers un CC semble être influencée par le sexe, l'âge et la préférence des patients dans les scénarios clinique où le risque cardiaque est maintenu constant. De futures explorations sur les biais éventuels relativement à l'âge et au sexe comme indications du risque s'imposent.

the diagnosis and treatment of CAD (29). Women generally receive less medical therapy, and are referred less frequently for angiography, percutaneous coronary interventions and bypass graft surgery than men (4,10-12,16,23,30). Even among women with acute coronary syndrome (ACS), studies have reported that women are referred less often for invasive procedures than men (16,31,32). The implications of these findings have been controversial, suggesting higher mortality and poorer long-term survival among women (2,10,16,21,31,32). Interestingly, a growing body of literature cautions that age may be an important confounder in the sex/gender literature. Studies (21,22) have found that among patients postmyocardial infarction (MI) and postbypass graft surgery, mortality was up to three times higher among younger women compared with their young male counterparts, even after adjusting for

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possible comorbidities. The higher risk of mortality in these young women may be due, in part, to the perception that women, especially younger women, are at very low risk for CAD. At the same time, previous studies (33) consisting mostly of retrospective analyses of administrative databases or subgroup analyses of clinical trials, have generally suffered from methodological limitations including the lack of statistical power to determine whether true differences exist.

The proposed study is an effort to prospectively assess whether sex/ gender independently influences physician decision making among various profiles of patients with ACS, with the following primary objectives: to determine whether there is a difference among Canadian cardiologists' and internal medicine specialists' decisions to refer male and female patients of equal risk for cardiac catheterization (CC); and to determine patient factors that influence referral decisions including age, sex/gender, risk level and expressed preference for catheterization. Secondary objectives include the following: to determine factors that influence the perceived risk a patient will suffer from an MI within the next 14 days; the characterization of chest pain; the probability a patient has significant CAD; and patient opinion in physician decision making for referral for CC.

METHODS

For the purpose of the present paper, the term 'sex' refers to the biological and physiological determinants of disease, and 'gender' refers to a person's social roles as expressed through their values and beliefs, psychosocial characteristics and behaviours (24).

Design of survey instrument

Twelve clinical vignette scenarios describing patients presenting to the emergency room with chest pain were designed, controlling for all combinations of patient factors, including two age categories (55 or 75 years of age), three Thrombolysis in Myocardial Infarction (TIMI) risk levels (low, moderate and high) and two patient preferences (patient expressed preference and no preference expressed) for catheterization. Due to sample size concerns, the scenarios were designed with blank fields in place of 'gender', and a computer program was designed to randomly allocate sex/gender and sex/gender-specific pronouns to each scenario. In addition, gender-specific terms were matched and tagged to the randomly assigned sex, to deliberately tap into physician perceptions that may be associated with gender. Each physician was required to review and assess three randomly allocated vignette scenarios: one each of male, female and sex/gender neutral. After reading each clinical vignette scenario, physicians were required to answer a series of standardized questions about the patient. Physicians were blinded to the primary objective of the study. Physicians also provided demographic information about their practices. The scenarios were pretested for face validity using the American College of Cardiology/American Heart Association criteria for referral for catheterization (34). Before initiation of the study, pilot testing was administered, appropriately modifying the scenarios and computer program to work out any issues such as the design of 'limits' to ensure that there were no missing data fields. The design of the present study was inspired by and modelled after a study by Schulman et al (29). An example of a clinical vignette scenario is provided in Appendix A.

Survey administration

To recruit physicians for the present study, an e-mail with a link to the study's website was sent to cardiologists and internal medicine specialists from across Canada using the following sources: Canadian Cardiovascular Society (CCS) list of internal medicine and cardiology specialist regular members; a Canada-wide list of cardiologists in the Canadian Medical Association (CMA) directory (excluding previous CCS respondents); and colleagues and collaborators from across Canada, in addition to referring physicians at McMaster University (Hamilton, Ontario) who were not represented by the CCS or the CMA list.

Up to three e-mails describing the study, with a link to the website, were sent, each two weeks apart. Follow-up telephone calls were made to physicians on the CMA list, and the collaborators and colleagues list, which were subsequently followed with personally addressed e-mails as friendly reminders. There was no financial compensation for participation in the study; however, as an incentive, a draw for a gift certificate to a bookstore was proposed.

Controlled patient factors

The scenarios contained patient factors representing all possible combinations of variables of interest. The scenarios were controlled for sex/gender of the patient (male, female or sex/gender neutral), age (55 versus 75 years of age), level of TIMI risk score (low, moderate or high) and the patient's preference for CC (no preference expressed or preference expressed [which was further subdivided into agreeable toward or refused CC]).

Description of physician and hospital characteristics

Physician information was collected to understand and contextualize the sample population's demography and practice patterns including physician sex, type of specialty (internal medicine, cardiology or subspecialities within cardiology), years since graduation from medical school, an estimate of the percentage of female patients seen in practice, and if the physician used any type of risk assessment score in deciding whether to refer a patient for catheterization. Hospital factors included geographical region, the presence or absence of on-site catheterization facilities and type of practice (academic centre, communitybased, outpatient clinic only or other). The full list of physician demographics and hospital characteristics is available in Appendix B.

Survey questions

Physicians were blinded to the primary objective of the study, namely to detect a sex/gender bias for CC. Physicians were asked to assess the likelihood that a patient would benefit from CC on a five-point Likert scale ranging from 1 (very unlikely to benefit from CC) to 5 (very likely to benefit from CC). Physicians were also asked to characterize the patient's chest pain (noncardiac, possibly cardiac or definitely cardiac), the risk level of suffering a fatal or nonfatal MI in the next 14 days (low risk, moderate risk or high risk) and the probability that the patient has significant CAD (defined as a stenosis of 70% or greater of at least one major epicardial vessel) on a five-point Likert scale ranging from 1 (very unlikely) to 5 (very likely). Physicians who decided not to refer the patient for CC were asked if they would order any further tests and, if so, which tests. Physicians were also asked to report how much patient opinion influences their decision to refer a patient for CC, ranging from 1 (not much at all) to 5 (to a great extent). Finally, physicians were requested to report if they required any other information to make their decision for catheterization referral. The full list of vignette questions and scaling is available in Appendix C.

Statistical considerations

Statistical power: It was predetermined that 68 physicians completing three scenarios each, for a total of 204 scenario assessments, would be required to provide 90% power to detect a minimum difference of 10% in CC rate between men and women. The sample size calculation included the clustering effect of physicians, assuming an intracluster correlation coefficient of 0.5.

Analysis: To assess the differences in physician decision making to refer a patient for CC, a mixed linear model was used. Patient factors were represented as covariates and analyzed as fixed effects, which included the controlled patient factors of sex/gender, age, TIMI risk level and the patient's preference for catheterization. Interactions of all combinations of patient factors were also tested in the mixed effects model. Design variables were created for categorical variables. Because each physician answered standardized questions for three scenarios, scores for each physician rater were clustered and analyzed as a random effect. Sidak's correction was used to adjust for multiple testing. Significance testing was evaluated using two-tailed testing, with data presented as mean ± SE. All analyses were performed using SPSS 16.0 statistical software (SPSS Inc, USA).

TABLE 1

Participating physician demographics and hospital factors

Characteristics	Physicians (n=79), n (%)
Physicians	
Male physician	69 (87.3)
Speciality	
Cardiology	72 (91.1)
Internal medicine	7 (8.9)
Years practicing	
<10	21 (26.6)
10 to <20	31 (39.2)
20 to <30	22 (27.8)
≥30	5 (6.3)
Female patients seen in practice (n=76), %	
<35	10 (13.2)
35 to <50	45 (59.2)
≥50	21 (27.6)
Nonwhite patients seen in practice (n=72), %	
<10	14 (19.4)
10 to <25	33 (45.8)
25 to <40	16 (22.2)
≥40	9 (12.5)
Risk score used (n=72)	
No	37 (51.4)
Yes	35 (48.6)
TIMI risk score	26 (74.3)
Hospitals	
Presence of catheterization facilities	49 (62.0)
Academic centre	58 (73.4)
Region of Canada	
West	18 (22.8)
Ontario or Quebec	56 (70.9)
Atlantic	5 (6.3)

TIMI Thrombolysis in Myocardial Infarctior

RESULTS

Baseline demographics of physicians and their institutions

After sampling almost 700 physician specialists across Canada at multiple time intervals, a total of 79 physicians (11%) each completed three randomly assigned scenarios, for a total of 237 scenarios, between July and August 2006.

Physician characteristics

The baseline demographic information of the participating physicians is outlined in Table 1. Briefly, physicians participating in the present study were mostly men (87%) and specialized in cardiology (91%). The sample of physicians were experienced, with the majority of participating physicians practising for over 10 years; only one-quarter of physicians reported having less than 10 years of cardiology work experience. The percentage of female patients seen in practice varied, with 72% of physicians reporting that female patients comprised 50% or less of their practice, and only one-quarter of physicians reported that women comprised more than 50% of their practice. Similarly, the ethnic makeup of cardiology practices across Canada revealed that nonwhite patients comprise less than 25% of physician practices in the majority of practices. In addition, when physicians were asked if they used a risk score when assessing their patients, approximately one-half reported that they used a risk score. Of the number of physicians who used a risk score, 74% reported the TIMI risk score as their risk assessment score of choice (Table 1).

Hospital factors

Geographically, 70% of physicians practised in Ontario or Quebec, 23% practised in the western provinces and 6% of participating

TABLE 2

Benefit from cardiac catheterization controlled for sex/gender, age, Thrombolysis in Myocardial Infarction risk score and patient preference about cardiac catheterization (CC)

Variable	Benefit likelihood, mean ± SE	Р
Sex/gender		
Male	4.44±0.07	0.03
Female	4.25±0.07	
Age, years		
55	4.55±0.09	0.01
75	4.14±0.09	
Level of risk		
Low	3.87±0.1	<0.01
Moderate	4.25±0.1	
High	4.93±0.08	
Expressed preference		
Agreeable for CC	4.65±0.13	0.01
Disagreeable for CC	4.17±0.12	
No opinion	4.21±0.08	

What is the likelihood this patient would benefit from a CC procedure? Score: 1 = very unlikely to 5 = very likely

physicians practised in Atlantic Canada. Also, two-thirds of physicians reported the presence of catheterization laboratories at their institutions, and 73% worked at academic centres (Table 1).

Referral decisions based on sex/gender, age, patient preference and risk

Physicians rated men as more likely to benefit from CC than women $(\text{mean} [\pm SE] \text{ score} = 4.44 \pm 0.07 \text{ versus} 4.25 \pm 0.07, P=0.03), \text{ control}$ ling for age, risk level and expressed preference for a catheterization procedure (Table 2). Younger patients (55 years of age) were rated as more likely to benefit from catheterization than older patients (75 years of age) controlled for all patient factors (4.55±0.09 versus 4.14±0.09, P=0.01). Benefit from catheterization increased as the level of risk increased (low TIMI risk = 3.87±0.1, moderate TIMI risk = 4.25±0.1, high TIMI risk = 4.93±0.08, P<0.01). Patients who agreed to undergo CC were rated as more likely to benefit from the procedure than patients who would not or expressed no opinion, even after controlling for sex/gender, age and risk ('agreeable' = 4.65±0.13 versus 'refused' = 4.17±0.12 versus 'no opinion = 4.21±0.08, P=0.01) (Table 2).

Interactions between patient factors influencing referral decisions

Physicians rated low TIMI risk men as more likely to benefit from CC than low TIMI risk women (4.20±0.13 versus 3.54±0.14, respectively, P<0.01), controlling for all other patient factors. No significant differences were detected among moderate and high TIMI risk men and women (Table 3).

Physicians rated younger, low TIMI risk patients as more likely to benefit from CC than older, low-risk patients (4.52±0.17 compared with 3.22±0.16, respectively, P<0.01). No significant differences were detected between moderate-risk and high-risk, or 55-year-old and 75-year-old patients (Table 3).

When analyzing physician perceptions of CC benefit according to risk, patient preference influenced physician decision making. Low TIMI risk patients who agreed to undergo CC were perceived as more likely to benefit than low TIMI risk patients who would not undergo the procedure or made no comment at all (all low-risk patients: 'agreeable' = 5.0 ± 0.23 compared with 'refused' = 3.67 ± 0.21 and 'no opinion' = 2.95 ± 0.14 , P<0.01). No significant differences were detected among high-risk patients, regardless of the patient's expressed preference for the procedure, because physicians rated all high-risk patients to significantly benefit from CC (Table 3).

When considering physician perception of benefit from CC according to patient preference, TIMI risk level did not seem to influence physician decision making. Among patients who agreed to CC, low-risk patients were shown to benefit more than moderate-risk patients and equally as much as high-risk patients (all patients agreeable for CC: low risk = 5.0 ± 0.23 versus moderate risk = 4.06 ± 0.24 and high-risk = 4.88 ± 0.17 , P<0.01). Among patients who did not want CC or who did not express an opinion about the procedure, the benefit of catheterization reflected the main effects observed, where benefit from catheterization increased according to increasing risk (Table 3).

Secondary objectives

Risk of suffering an MI within the next 14 days: As an internal measure of validity of the TIMI risk score used to determine controlled risk in the present study's scenarios, physicians were asked to rate the level of risk (according to the TIMI risk criteria) that the described patient would suffer a fatal or nonfatal MI in the next 14 days. It was found that physicians in the present study appropriately identified low-, moderate- and high-risk patients according to TIMI risk criteria (P<0.01) (Table 4). There were no statistically significant differences detected in the risk of suffering an MI according to sex/gender, age or patient preference. However, an interaction was detected between age and sex/gender; physicians rated 55-year-old men as more likely to be at risk for an MI than 55-year-old women controlled for all other patient factors (2.62±0.09 versus 2.32±0.09, respectively, P<0.01 [interaction not presented in table]).

Characterization of chest pain: Physicians were asked to characterize patient chest pain on a three-point Likert scale (1 = noncardiac, to 3 = definitely cardiac). Physicians rated chest pain among men as more likely to be cardiac compared with the same pain among women, even when data analysis was controlled for all other patient factors (men = 2.66 ± 0.04 versus women = 2.53 ± 0.04 , P=0.02). Patients were rated as more likely to be experiencing cardiac pain if they were younger (55 years of age = 2.77 ± 0.05 versus 75 years of age = 2.43 ± 0.05 , P<0.01) or had higher TIMI risk (low TIMI risk = 2.36 ± 0.05 , moderate TIMI risk = 2.48 ± 0.05 and high TIMI risk = 2.95 ± 0.05 , P<0.01). Physicians were more likely to characterize chest pain in an older low-risk patient as more cardiac in nature than in a young low-risk patient, even after controlling for all other patient factors (1.93 ± 0.07 versus 2.79 ± 0.09 , respectively, P<0.01 [interaction not presented in table]). No differences were found between younger

TABLE 3

Interaction of patient benefit from cardiac catheterization (CC) referral between Thrombolysis in Myocardial Infarction (TIMI) risk score, and gender, age and patient preference

Benefit likelihood, mean ± SE					
Low TIMI risk	Moderate TIMI risk	High TIMI risk			
4.20±0.13*	4.16±0.12	4.97±0.11			
3.54±0.14*	4.33±0.13	4.88±0.11			
4.52±0.17*	4.13±0.15	4.98±0.13			
3.22±0.16*	4.36±0.17	4.85±0.14			
5.00±0.23*	4.06±0.24*	4.88±0.17*			
3.67±0.21*	3.93±0.2*	4.92±0.2*			
2.95±0.14*	4.74±0.13*	4.94±0.12*			
	Ben Low TIMI risk 4.20±0.13* 3.54±0.14* 4.52±0.17* 3.22±0.16* 5.00±0.23* 3.67±0.21* 2.95±0.14*	Benefit likelinood, mean Low TIMI risk Moderate TIMI risk 4.20±0.13* 4.16±0.12 3.54±0.14* 4.33±0.13 4.52±0.17* 4.13±0.15 3.22±0.16* 4.36±0.17 5.00±0.23* 4.06±0.24* 3.67±0.21* 3.93±0.2* 2.95±0.14* 4.74±0.13*			

What is the likelihood this patient would benefit from a CC procedure? Score: 1 = very unlikely to 5 = very likely. *P<0.01

and older patients of moderate or high-risk. Physicians were not influenced by the patient's preference for CC (P=0.10) (Table 4).

Estimated probability that patient has significant obstructive CAD: When physicians were asked to estimate the probability that the described patient has significant CAD on a five-point Likert scale (1 = very unlikely, to 5 = very likely), physicians rated men as more likely to have significant CAD than women, controlling for all other patient factors (men = 4.67 ± 0.07 versus women = 4.38 ± 0.07 , P=0.01). Also, the probability that the patient may have significant CAD increased as the level of TIMI risk increased (low TIMI risk = 4.25 ± 0.09 , moderate TIMI risk = 4.43 ± 0.09 and high TIMI risk = 4.89 ± 0.08 , P<0.01). Differences in the probability of the patient having significant CAD were not detected among patients of different ages (Table 4).

Among women who did not want a CC procedure, physicians were less likely to suspect significant CAD, compared with women who were agreeable or who had no opinion about the procedure ('refused' = 3.85 ± 0.14 versus 'agreeable' = 4.62 ± 0.13 and 'no opinion' = 4.66 ± 0.1 , P<0.01).

TABLE 4

Influence of secondary objectives controlled for sex/gender, age, Thrombolysis in Myocardial Infarction (TIMI) risk score and patient preference

	Estimated risk of myocardial infarction*		Chest pain characterization [†]		Probability of significant CAD [‡]		Influence of patient opinion [§]	
Controlled patient variable	Mean ± SE	Р	Mean ± SE	Р	Mean ± SE	Р	Mean ± SE	Р
Sex/gender		0.12		0.02		0.01		0.39
Male	2.47±0.06		2.66±0.04		4.67±0.07		2.90±0.14	
Female	2.34±0.06		2.53±0.04		4.38±0.07		2.99±0.14	
Age, years		0.26		<0.01		0.53		0.43
55	2.47±0.07		2.77±0.05		4.57±0.08		3.03±0.16	
75	2.34±0.08		2.43±0.05		4.48±0.09		2.87±0.17	
TIMI risk		<0.01		<0.01		<0.01		<0.01
Low	1.95±0.08		2.36±0.05		4.25±0.09		3.23±0.17	
Moderate	2.36±0.08		2.48±0.05		4.43±0.09		2.97±0.17	
High	2.90±0.06		2.95±0.05		4.89±0.08		2.64±0.15	
Patient preference		0.43		0.10		<0.01		0.28
Agreeable for CC	2.47±0.08		2.58±0.07		4.71±0.09		2.69±0.21	
Disagreeable for CC	2.39±0.09		2.69±0.07		4.29±0.1		3.12±0.21	
No opinion	2.35±0.06		2.53±0.04		4.57±0.07		3.03±0.15	

*How would you characterize this patient's level of risk of suffering a fatal or nonfatal myocardial infarction in the next 14 days? Score: 1 = low risk, 2 = moderate risk, 3 = high risk; [†]How would you characterize this patient's chest pain? Score: 1 = noncardiac, 2 = possibly cardiac, 3 = definitely cardiac; [‡]Estimate the probability that this patient has significant coronary artery disease (CAD) (stenosis greater than 70%). Score: 1 = very unlikely to 5 = very likely; [§]How much does the patient's opinion influence your decision to refer them for cardiac catheterization (CC)? Score: 1 = not very much to 5 = very much

Influence of patient opinion for referral for CC: Physicians were asked to rate the degree to which a patient's opinion influences their decision to refer a patient for CC on a five-point Likert scale (1 = not very much, to 5 = very much). Physicians reported that they are not swayed by the patient's opinion according to sex/gender, age or their expressed preference for a CC procedure; rather, the level of TIMI risk was a statistically significant influential factor when a physician considered the patient's opinion in deciding to refer a patient for catheterization (low TIMI risk = 3.23 ± 0.17 , moderate TIMI risk = 2.97 ± 0.17 , high TIMI risk = 2.64 ± 0.15 , P<0.01) (Table 4).

DISCUSSION

Our study indicates that among Canadian specialists, women are perceived to benefit less from CC than men of equal age, risk and expressed preference for catheterization. In addition, specialists perceive younger patients as more likely to benefit from CC than older patients, high-risk patients to benefit more than low-risk patients, and patients agreeable for CC as more likely to benefit than patients who refuse or express no opinion at all.

The results from our study support those in the literature that indicate women are less often referred for cardiac procedures than men (4,10-12,23,29,30,35,36). Although post hoc hypotheses have alluded to sex/gender differences in the past, our study is unique in that physician decision making was prospectively assessed, unlike previous studies that depended on retrospective data collection, database analysis or post hoc analyses of larger trials with insufficient power to detect sex/gender differences. The sex/gender difference in catheterization benefit that we detected was consistent across all models, which were controlled for age, risk and patient preference. We were able to explain some of the sex/gender difference due to risk. The interaction between TIMI risk and sex/gender suggests that among patients who were truly at low risk, women were evaluated appropriately as such, whereas low-risk men were perceived to gain more benefit from CC. Previously published literature (16,35) has suggested that, perhaps, women are being appropriately treated, and men undergo an excessive number of CCs, and our results lend support to this. It is possible that symptoms and risk factors in men may be over estimated, while symptoms and risk factors in women may be appropriately estimated. Our results support this because cardiac chest pain and significant stenotic disease were perceived to be more likely among men than women across scenarios controlled for sex/gender, age, TIMI risk and patient preference. Although this perspective may seem somewhat confusing, it is not contradictory. CC is the gold standard in CAD diagnosis. Evidence shows that high-risk patients have the most to gain from CC; by identifying these patients, treatment options to improve prognosis can be offered including surgical revascularization. However, beyond risk factor modification, much debate surrounds treatment options for low- and moderate-risk patients, implying that 'benefit' from CC is unknown. Currently, we do not know what the 'catheterization-benefit' threshold is for lower risk patients. We have demonstrated that there is a perception by physicians that women are at 'lower risk' for CAD and, therefore, will not 'benefit' from CC. We are not suggesting that this perception is inappropriate, because it may in fact be a more reasonable approach to determining who will benefit from CC. There is no evidence in the literature to suggest why a low-risk patient would benefit from CC at all, irrespective of sex/gender. Evidence of survival benefit from revascularization has only been demonstrated among high-risk patient groups (37,38).

Our study also revealed that physicians perceive younger patients as more likely to benefit from CC than older patients. This finding was reinforced in that physicians identified chest pain among younger patients as more likely to be cardiac than such chest pain in older patients. It may also reflect the belief that younger patients benefit more from early diagnosis of CAD in terms of potential years of life lost than older patients, despite trends of actual risk (1). For this

When we evaluated risk, both as a main effect and as an interaction term, high-risk patients were identified appropriately and seen to benefit the most from CC. Our assessment of risk was internally valid because physicians identified increasing risk for MI as the TIMI risk was increased in the scenario. This finding was particularly evident among high-risk scenarios, in which patient factors such as sex/ gender, age or expressed patient preference did not influence the physician's decision to refer. However, the same was not true among low- and moderate-risk patients. Low- and moderate-risk patients who expressed a desire for CC were more likely to receive a CC than patients who refused or expressed no opinion at all. This suggests that while high-risk patients are being appropriately referred for CC, greater standardization of catheterization referral in low- and moderate-risk patient groups is needed because CC is not a procedure without risk, and these risks may not outweigh the benefit, particularly among low-risk patients.

Limitations

To recruit physicians for our study, we used nonrandom sampling of Canadian cardiologists and internal medicine specialists, and the response rate to our invitation was low; thus, some respondent bias likely exists. At the same time, we invited specialists to participate in our study via an e-mail invitation only because the present study used a web-based instrument. In today's Internet world of increasing firewalls, spam, junk and other protective e-mail filters, we are uncertain how many physicians we actually reached; therefore, our true denominator remains unknown. However, despite a small sample size, physicians sampled in our study are representative of the actual distribution of physicians across Canada. Furthermore, the characteristics of the physicians who responded to our survey reflect the current characteristics of cardiac specialists in Canada, where most specialists are men who have been practicing for at least 10 years (40) and women represent less than one-half of their patient population. It is important to note that the responders were blinded to the intent of the study, which was to identify sex/gender differences in CC referral. Scenarios were randomly allocated to each physician, so it is unlikely that there was any internal bias. Also, the subtleties and complexities of human interaction cannot be fully captured in paper scenarios, although previous studies have shown that the response to hypothetical case scenarios parallels real-world decision making (41,42). Finally, to represent risk, we used the TIMI risk score because this is the most popular, validated ACS risk score (43-46) and this was reflected by our sample, in which almost 75% of the physicians surveyed who used a risk score reported using the TIMI risk score. Also, the use of the TIMI risk score is internally valid because physicians correctly assessed increasing risk according to the TIMI risk score (P<0.001).

CONCLUSION

Canadian specialists' decisions to refer patients for CC appear to be influenced by sex/gender, age and patient preference in clinical scenarios in which cardiac risk is held constant. Future investigations into possible age and sex/gender biases as well as a better understanding of how physicians use these factors as proxies for risk are warranted.

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APPENDIX A

Sample of a clinical vignette scenario

RM is a 75-year-old individual who presents to the ER with retrosternal chest pain radiating down both arms. RM is also experiencing dyspnea and nausea, and claims a history of heart problems but has been well controlled until this ER visit. RM took three nitrosprays to relieve the chest pain, but it did not completely resolve itself as it had in the past.

RM's medical history includes a myocardial infarction seven years ago and an angioplasty to the RCA during that hospital stay. Cardiovascular risk factors include type 2 diabetes, hypertension and half-pack/day smoking history. There is no history of hypercholesterolemia. RM also reports that a younger brother had bypass surgery at 54 years of age.

Current medications include EC ASA 325 mg o.d., metformin 500 mg b.i.d., ramipril 5 mg o.d. and nifedipine XL 60 mg o.d., with nitroglycerin spray as needed.

On examination, height is 166 cm and weight is 72 kg. Blood pressure is 110/85, and HR is 108 and regular. Chest sounds are clear. On precordial examination, heart sounds are normal with a II/VI pansystolic murmur heard loudest at the apex. JVP is mildly elevated and has mild peripheral edema.

ECG on arrival shows a 1.5 mm ST segment depression in V1 to V3. Troponin and CK are slightly elevated. CBC, electrolytes and creatinine are normal.

 RM is resting quietly while you try and locate old notes from the last hospital visit.

APPENDIX B

Physician questions

- 1. Physician name: First, middle initial, last name.
- 2. Work address: Number, street, city, province, postal code, telephone number.
- 3. Name of practising hospital.
- 4. E-mail address.
- 5. Sex: male/female.
- 6. Number of years practising medicine.
- 7. Specialty.
- 8. An estimate of the percentage of female patients seen in practice.
- 9. An estimate of the percentage of white Caucasian patients seen in practice.

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- 10. Presence of on-site catheterization laboratory at your hospital.
- 11. Do you use any risk assessment score in your decision to refer a patient for cardiac catheterization? ie, FRISC score, TIMI score, GRACE score, other _____.
- 12. Type of practice: Academic centre, community-based, outpatient clinic only, other ______.

APPENDIX C

Vignette questions

- Scenario questions:
- 1. How would you characterize this patient's risk of suffering a fatal or nonfatal MI in the next 14 days?
 - Low risk
 Moderate risk
 High risk
- How would you characterize this patient's chest pain?
 Noncardiac
 Possibly cardiac
 Definitely cardiac
- 3. What is the likelihood that this patient would benefit from a cardiac catheterization procedure?
 - Very unlikely
 Somewhat unlikely
 Unsure
 - □ Somewhat likely □ Very likely
- Estimate the probability that this patient has a significant CAD (or stenosis >70%).
 - Very unlikely
 Somewhat likely
 Very likely
- 5. If you decide to not refer this patient for catheterization, would you order any further tests?
 Yes
 - If so, which of the following?
 - □ Stress test □ Stress test and thallium
 - □ Cardiac function assessment □ Other
- 6. How much does the patient's preference influence your decision to refer them for catheterization?
- □ Not much at all □ Not a lot □ Unsure
- □ A fair amount □ To a great extent
- Do you need any more information to make your decision regarding further testing?

□ Yes □ No

If so, what information would you require? ____

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Kreatsoulas et al

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Appendix C

Original Article

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Identifying women with severe angiographic coronary disease

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Abstract. Kreatsoulas C, Natarajan MK, Khatun R, Velianou JL, Anand SS (McMaster University; CAR-ING Network, McMaster University; Population Health Research Institute, McMaster University and Hamilton Health Sciences; Interventional Cardiology, Hamilton Health Sciences; Eli Lilly Canada–May Cohen Chair in Women's Health, McMaster University; Michael G. DeGroote-Heart and Stroke Foundation of Ontario Chair in Population Health Research, McMaster University; Population Genomics Program, McMaster University; McMaster University, Hamilton, ON, Canada). Identifying women with severe angiographic coronary disease. *J Intern Med* 2010; doi: 10.1111/j.1365-2796.2009.02210.x.

Objectives. To determine sex/gender differences in the distribution of risk factors according to age and identify factors associated with the presence of severe coronary artery disease (CAD).

Design. We analysed 23 771 consecutive patients referred for coronary angiography from 2000 to 2006.

Subjects. Patients did not have previously diagnosed CAD and were referred for first diagnostic angiography.

Outcome measures. Patients were classified according to angiographic disease severity. Severe CAD was defined as left main stenosis \geq 50%, three-vessel disease with \geq 70% stenosis or two-vessel disease including proximal left anterior descending stenosis of \geq 70%. Univariate and multivariate logistic regression was used to assess the association between risk factors and angina symptoms with severe CAD.

Results. Women were less likely to have severe CAD (22.3% vs. 36.5%) compared with men. Women were also significantly older $(69.8 \pm 10.6 \text{ vs.})$ 66.3 ± 10.7 years), had higher rates of diabetes (35.0% vs. 26.6%), hypertension (74.8% vs. 63.3%) and Canadian Cardiovascular Society (CCS) class IV angina symptoms (56.7% vs. 47.8%). Men were more likely to be smokers (56.9% vs. 37.9%). Factors independently associated with severe CAD included age (OR = 1.05; 95% CI 1.05–1.05, P < 0.01), male sex (OR = 2.43; CI 2.26-2.62, P < 0.01), diabetes (OR = 2.00; CI 1.86–2.18, P < 0.01), hyperlipidaemia (OR = 1.50; CI 1.39–1.61, *P* < 0.01), smoking (OR = 1.10; CI 1.03–1.18, P = 0.06) and CCS class IV symptoms (OR = 1.43; CI 1.34-1.53, P < 0.01). CCS Class IV angina was a stronger predictor of severe CAD amongst women compared with men (women OR = 1.82; CI 1.61-2.04 vs. men OR = 1.28; CI 1.18-1.39, P < 0.01).

Conclusions. Women referred for first diagnostic angiography have lower rates of severe CAD compared with men across all ages. Whilst conventional risk factors, age, sex, diabetes, smoking and hyperlipidaemia are primary determinants of CAD amongst women and men, CCS Class IV angina is more likely to be associated with severe CAD in women than men.

Keywords: angina, angiography, coronary artery disease, gender, risk factors.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity of both men and women in westernized countries accounting for over onethird of total deaths [1, 2]. In women, the annual mortality rate from CAD is greater than that of breast cancer, even amongst the younger groups (i.e. 35–55 years) [1–6]. Despite this importance of CAD for women, there is a persistent perception that CAD is a 'man's disease'. Contributing to this notion is the observation of differences in incidence

rates according to age; the incidence of CAD in women is lower than men, but rises steadily after the fifth decade and nearly equalizes between the sexes by the seventh decade of life [5, 6]. Correspondingly, the distribution of CAD risk factors varies between men and women across age ranges and failure to consider these differences may have contributed to the belief that women are at lower risk of CAD compared with men [7-11]. In addition, gender differences in the symptoms of CAD exist between women and men, as women are more likely to have symptoms considered atypical compared with men [3, 5, 12-18]. All of these factors likely contribute to the lower referral rates for coronary angiography amongst women compared with men, even in patients who have severe CAD and acute coronary syndromes (ACS) [3, 7-11, 13]. Younger women with ACS have up to 50% higher risk for mortality than their young male counterparts [19, 20]. The higher risk of mortality in these young women may be due in part to the perception that younger women are at very low risk of CAD and therefore diagnostic and therapeutic management is minimal. On the other hand, a lower rate of angiography may be appropriate because when women do undergo coronary angiography, they are more often reported to have 'normal' coronary anatomy and are less likely to have severe CAD (i.e. three vessel and left main disease) compared with men [11-13, 21-25]. Although sex-related differences in risk factors for CAD and the presentation of CAD symptoms are well-known, there is little information on whether the variation in the degree of symptom severity between men and women is associated with differences in CAD severity or if these relationships vary by age. There is an urgent need to better understand the presentation of cardiac symptoms in women in order to facilitate diagnosis and treatment, to initiate aggressive risk factor intervention and to improve the quality of life.

The objectives of our investigation were to examine the distribution of risk factors and coronary angiographic patterns of CAD in women and men who were referred for first diagnostic angiogram and to identify factors associated with severe CAD. Specifically we aimed (i) to investigate sex differences in the distribution of conventional risk factors and the angiographic pattern of CAD in young patients \leq 60 years of age compared with older patients >60 years of age, (ii) to examine the factors associated with the presence of severe CAD defined as left main stenosis \geq 50%, threevessel disease with \geq 70% stenosis or two-vessel disease including proximal left anterior descending stenosis of ≥70%, and (iii) to evaluate the utility of Canadian Cardiovascular Society (CCS) class angina scoring system in predicting severe CAD amongst a cohort of women and men referred for first diagnostic coronary angiography at a tertiary care institution in Canada.

Methods

The study sample included 23 771 consecutive men and women who underwent diagnostic coronary angiography between April 1, 2000 and November 15, 2006. Data used were part of the Hamilton Health Sciences Angiography Registry. Details of the database are described elsewhere [26]. Briefly, the purpose of this prospective registry was to document the characteristics of patients waiting for coronary angiography and to document their subsequent angiographic outcomes. The Hamilton Health Sciences is the sole provider of tertiary cardiac care services including coronary angiography, percutaneous coronary intervention and cardiac surgery for most patients, covering the geographical region of Central-South Ontario, Canada, a population of over 2.2 million people. During the study period, year 2000 to 2006, the mean wait time for cardiac catheterization was 56.0 days for outpatients and 8.4 days for inpatients [27]. No difference in wait times was detected between the sexes [26]. Eligible patients were suspected of having CAD and only those without a prior diagnosis of CAD were included in this analysis. This inclusion criterion was intended to capture patients only with suspected CAD that have not been previously diagnosed with CAD as confirmed by the gold standard, cardiac catheterization. Patients were excluded if they were undergoing coronary angiography for reasons other than diagnosing coronary artery disease such as valvular disease, or if they had a prior or recent evidence of an MI (definition of MI included two out of three criteria, including symptoms, EKG changes and/or biomarkers including elevated troponin), previous coronary artery bypass graft surgery (CABGS) or percutaneous coronary intervention (PCI). The Hamilton Health Sciences Angiography Registry has been approved by the Research Ethics Board.

Data collection

Patient information was prospectively collected at the time of coronary angiography referral using standardized Hamilton-Wentworth Regional Cardiovascular Program Coronary Angiography Consult Forms distributed to all referring physicians in the region. Information was recorded by the referring physician, electronically entered and edited into a computerized database. The Coronary Angiography Consult forms include patient demographic characteristics, reason for referral (coronary disease, cardiomyopathy, valvular disease, other), state of urgency for coronary angiography, anginal symptom class graded according to the Canadian Cardiovascular Society (CCS) Class Grading system 0-IV and patient risk factor profile; history of smoking, diabetes (insulin dependent or oral medication), hyperlipidaemia and hypertension requiring medical treatment, including a comprehensive list of current medications [26]. Coronary anatomy was graded by the angiographer immediately following the procedure using a standardized diagram [28]. In this analysis, we categorized patients according to severity of disease; severe CAD was defined as left main stenosis ≥50%, three-vessel disease with ≥70% stenosis in at least one vessel, or two-vessel disease, including a proximal left anterior descending (LAD) stenosis ≥70%; moderate risk CAD included two-vessel disease (excluding proximal LAD) with \geq 70% lesion, one-vessel disease with \geq 70% lesion; low risk CAD was defined as lesions with ≤50% stenosis or normal coronary anatomy. The criterion for 'severe CAD' was chosen to characterize those that have prognostically significant CAD in terms of surgical revascularization compared with medical therapy [29].

Statistical analysis

All analyses were performed using sas, version 9.1 software (Cary, NC, USA) and spss, version 16.0 (Chicago, IL, USA). Baseline characteristics including age, risk factors, coronary anatomy and CCS symptom class were compared between women and men. Continuous variables were expressed as means with standard deviations and probability estimates were obtained using analysis of variance. Dichotomous variables were expressed as percentages with 95% confidence intervals (CI) and probability values were estimated using logistic regression. To present proportions in risk factor prevalence rates, the data were stratified by sex and age. Patients were categorized and analysed according to CAD risk group; patients with angiographically documented severe CAD were compared with patients with low risk CAD (consisting of moderate and low risk groups). Univariate and multivariate logistic regression were used to determine which of the proposed risk factors (independent variables) were significantly associated with severe CAD. The dependent variable was binary and defined as the presence or absence of severe CAD (1 vs. 0

respectively). Independent variables included age, sex, medically treated risk factors, past or present smoking and severe (CCS Class IV) angina. Logistic models employed a backwards elimination process. Interactions were tested and adjusted for the other risk factors in model. Odds ratios and their accompanying 95% confidence intervals (CI) were calculated. All tests employed two-tailed significance testing.

Results

Baseline characteristics of study population

During the study period, April 2000 to November 2006, 31 758 patients were enrolled in the Hamilton Health Sciences Angiography Registry. For this study, 23 771 are included in the analysis, excluding elective patients with prior MI (n = 1405), prior CAB-GS (*n* = 3221) and prior PCI (*n* = 3361). Of 23 771 study patients, 9112 (38.4%) were women and 14 645 (61.6%) were men. The baseline characteristics are presented in Table 1. Briefly, compared with men, women were significantly older ($65.2 \pm 12.0 \text{ vs.}$ 62.3 ± 12.3 , P < 0.01), less likely to be past/present smokers (37.3% vs. 57.2%, P < 0.01) and more likely to be hypertensive (65.9% vs. 57.9%, P < 0.01) (Table 1). Amongst young patients (≤ 60 years) referred to coronary angiography, women were slightly older $(51.4 \pm 6.1 \text{ years vs. } 50.9 \pm 7.2 \text{ years respectively}),$ were more likely to be diabetic (20.7% vs. 16.4%), and hypertensive (53.4% vs. 49.5%), less likely to be past/present smokers (49.9% vs. 62.9%), and to have considerable hyperlipidaemia (57.3% vs. 60.1%) compared with men (Table 1).

Angiographically, we found women were more likely to have normal/mild CAD (39.7% vs. 21.3%, P < 0.01) and less likely to have severe CAD (36.5% vs. 22.3%, P < 0.01) compared with men (Table 2).

Some differences in symptom severity in CCS angina classification between the sexes was observed; men were more likely to have CCS Class 0 to II angina (31.2% vs. 29.3%, P < 0.01) and CCS Class IV angina (44.0% vs. 42.9%, P < 0.01) compared with women (Table 3).

Risk factors among young women versus young men with angiographically severe CAD

When stratified by age (≤60 years vs. >60 years) differences in risk factor distribution by the presence of severe angiographic CAD were present. Consistent with the overall observations, younger women were

C. Kreatsoulas et al.

	Men		Women	P-value	
	Totalmen		Total women	Women	- Total men versus
	N(%)	Men \leq 60 years	N(%)	≤ 60 years	totalwomen
Total N	14 645 (61.6)	6421 (67.5)	9112 (38.4)	3091 (32.5)	< 0.01
Mean age	62.3 ± 12.3	50.9 ± 7.2	65.2 ± 12.0	51.4 ± 6.8	< 0.01
Diabetes	2832 (20.0)	1055(16.4)	1832 (20.7)	621 (20.7)	0.15
Smoking	8238 (57.2)	3986 (62.9)	3351 (37.3)	1525 (49.9)	< 0.01
Hypertension	8395 (57.9)	3147 (49.5)	5946 (65.9)	1634 (53.4)	< 0.01
Hyperlipidaemia	9019 (62.4)	3806 (60.1)	5530 (61.5)	1750 (57.3)	0.14

Table 1 Baseline characteristics of patients in the Hamilton Health Science Coronary Angiography Registry

less likely to have severe CAD than younger men (19.9% vs. 30.0%, P < 0.01). Young women were more likely, however, to have diabetes (45.7% vs. 24.7%, P < 0.01) and have hypertension (65.1% vs. 55.7%, P < 0.01) compared with young men. Young men, on the other hand, were more likely to past/present smokers compared with young women (64.7% vs. 58.8%, P = 0.04). There were no statistically significant differences in the proportion of women and men with hyperlipidaemia (72.2% women vs. 71.3% men, P = 0.74) (Table 4).

Risk factors among young women versus older women with severe CAD

As expected, older women referred for first diagnostic angiogram were more likely to have severe CAD

	Total men	Total women	
	N (%)	N (%)	P-value
Normal coronaries	1437 (9.8)	2154 (23.6)	< 0.01
Mild CAD	1677 (11.5)	1466(16.1)	< 0.01
1-vessel disease	4092 (27.9)	2010 (22.1)	< 0.01
2-vessel disease	722 (4.9)	293 (3.2)	< 0.01
(with prox LAD)			
All other 2-vessel disease	1553 (10.6)	640 (7.0)	< 0.01
3-vessel disease	3291 (22.5)	1176(12.9)	< 0.01
Left main disease	519 (3.5)	235 (2.6)	< 0.01
Low risk CAD	7873 (63.5)	5941 (77.7)	< 0.01
Severe CAD ^a	4532 (36.5)	1704 (22.3)	< 0.01

^aSevere CAD includes left main stenosis ≥50%, three-vessel disease with ≥70% stenosis or two-vessel disease including proximal left anterior descending stenosis of ≥70%.

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(80.1% vs. 19.9%, *P* < 0.01) compared with younger women. However, younger women with severe CAD were more likely to be diabetic (45.7% vs. 32.2%, *P* < 0.01) and more likely to be past/present smokers (58.8% vs. 32.7%, *P* < 0.01), compared with older women. On the other hand, older women were more likely to be hypertensive (77.1% vs. 65.1%, *P* < 0.01) compared with younger women. There were no statistically significant differences in the proportion of women with hyperlipidaemia between the two age strata (*P* = 0.73) (Table 4).

Angina severity in patients with angiographically severe CAD

Overall, women with angiographically severe CAD were more likely to have severe angina than men. Specifically, women were more likely to have CCS Class IV angina (56.7% vs. 47.8%, P < 0.01), whereas men were more likely to have CCS Class 0 to II symptoms compared with women (23.5% vs. 17.8%, P < 0.01) (Table 3).

Angina severity among young women versus young men with severe CAD

Younger men were more likely to have less severe symptoms or CCS 0 to II angina compared with women (23.0% vs. 18.7%). On the other hand, young women ≤ 60 years of age with severe CAD were more likely to have CCS Class IV angina than their young male counterparts (54.5% vs. 49.1%) (Table 3).

Angina severity among young women versus older women with severe CAD

Older women with severe CAD were more likely to have CCS Class IV angina than their younger female counterparts (57.2% vs. 54.5%). However there were no differences between CCS Class 0 to II angina and CCS Class III angina between younger and older women (Table 3).

Identifying women with severe angiographic coronary disease

			Severe CAD			
	Total patients		Male		Female	
	Allmale	Allfemale	<60 years	≥60 years	<60 years	≥60 years
CCS Angina class	N = 13 933 (%)	N = 8621 (%)	N = 1326 (%)	N = 3066 (%)	N = 332 (%)	N = 1319 (%)
CCS Class 0–II angina	4341 (31.2)	2528 (29.3)	305 (23.0)	730 (23.8)	62 (18.7)	233 (17.7)
CCS Class III angina	3457 (24.8)	2396 (27.8)	370 (27.9)	889 (29.0)	89 (26.8)	331 (25.1)
CCS Class IV angina	6135 (44.0)	3697 (42.9)	651 (49.1)	1447 (47.2)	181 (54.5)	755 (57.2)

Table 3 Frequency of CCS class^a angina symptoms according to sex and age

CCS Class I – ordinary physical activity such as walking or climbing stairs does not cause angina; angina with strenuous, rapid or prolonged exertion at work or recreation.

CCS Class II – slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind or under emotional stress or during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.

CCS Class III – marked limitation of ordinary physical activity. Walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

 $CCS \ Class \ IV-inability to \ carry out any physical activity without \ discomfort-anginal \ syndrome \ may \ be \ present \ at \ rest.$

Table 4	Proportion	of risk fa	ictors in young	jer patients versus ol	der patients wi	th severe CAD
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	Men		P-value	Women		P-value	
	≤60 years	>60 years	≤60 years women	≤60 years	>60 years	Women≤60 years	
	N(%)	N(%)	versus men	N(%)	N(%)	versus >60 years	
Severe CAD	1357 (30.0)	3162 (70.0)	< 0.01	339 (19.9)	1362 (80.1)	< 0.01	
Mean age	53.1 ± 6.0	72.0 ± 6.5	0.93	53.1 ± 6.1	73.9 ± 6.1	< 0.01	
Diabetes	325 (24.7)	841 (27.4)	< 0.01	149 (45.7)	427 (32.2)	< 0.01	
Smoking	867 (64.7)	1667 (53.5)	0.04	197 (58.8)	439 (32.7)	< 0.01	
Hypertension	746 (55.7)	2087 (66.5)	< 0.01	218 (65.1)	1040(77.1)	< 0.01	
Hyperlipidaemia	955 (71.3)	2185 (69.9)	0.74	242 (72.2)	960 (71.3)	0.73	

Risk factors associated with angiographically severe CAD

Factors independently associated with the presence of severe angiographic CAD include age (OR = 1.04, 95% CI 1.04-1.05, P < 0.01), male sex (OR = 2.01, 95% CI 1.88-2.14, P < 0.01), diabetes (OR = 2.09, 95% CI 1.94–2.24, P < 0.01), hyperlipidaemia (OR = 1.69, 95% CI 1.58–1.80, P < 0.01), hypertension (OR = 1.43, 95% CI 1.35–1.53, P < 0.01), smoking (OR = 1.13, 95% CI 1.06-1.20, P < 0.01) and CCS class IV anginal symptoms (OR = 1.43, 95% CI 1.34-1.52, P < 0.01) (Table 5). In an adjusted multivariate logistic regression model, the factors independently associated with severe CAD included age (OR = 1.05, 95% CI 1.05–1.05, P < 0.01), male sex (OR = 2.43, 95% CI 2.26–2.62, P < 0.01), diabetes (OR = 2.00, 95% CI 1.86–2.18, P < 0.01), hyperlipidaemia (OR = 1.50, 95% CI 1.39-1.61, P < 0.01), smoking (OR = 1.10, 95% CI 1.03–1.18, P < 0.01) and CCS class IV symptoms (OR = 1.43, 95% CI 1.34–1.53, P < 0.01) (Table 5). An interaction between CCS Class IV angina and sex was identified (P < 0.01) and indicates that women with CCS class IV angina were more likely to have severe CAD compared with men with CCS class IV angina, (OR = 1.82, 95% CI 1.61–2.04 vs. OR = 1.28, 95% CI 1.18–1.39, P < 0.01 respectively) (refer to Fig. 1).

Discussion

In this prospective registry of over 23 000 individuals referred for first diagnostic coronary angiography for CAD, women were found to be older, have more diabetes and hypertension and were less likely to smoke compared with men. Furthermore, the coronary angiography profile of women indicates that women were

Identifying women with severe angiographic coronary disease

	Univariate analysis		Multivariate analysis	Multivariate analysis	
Variables	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	
Diabetes	2.09 (1.94-2.24)	< 0.01	2.00 (1.86-2.18)	< 0.01	
Sex (men versus women)	2.01 (1.88-2.14)	< 0.01	2.43 (2.26-2.62)	< 0.01	
Hyperlipidaemia	1.69 (1.58-1.80)	< 0.01	1.50 (1.39-1.61)	< 0.01	
Hypertension	1.43 (1.35–1.53)	< 0.01	1.01 (0.94–1.09)	0.73	
CCS Class IV angina	1.43 (1.34–1.52)	< 0.01	1.43 (1.34–1.53)	< 0.01	
Smoke	1.13 (1.06–1.20)	< 0.01	1.10 (1.03–1.18)	0.05	
Age	1.04 (1.04–1.05)	< 0.01	1.05 (1.05–1.05)	< 0.01	
Interaction of CCS class IV ang	gina and sex ^a				
Male \times CCS class IV angina			1.28 (1.18–1.39)	< 0.01	
Female \times CCS class IV angin	la		1.82 (1.61–2.04)	< 0.01	

Table 5 Univariate and adjusted multivariate logistic regression model of variables associated with severe CAD

^aInteraction terms are adjusted for diabetes, hyperlipidaemia, hypertension, smoke and age. Odds ratio values did not change from presented model.

more likely to have normal/mild CAD and less likely to have severe angiographic CAD. Conventional risk factors and CCS Class IV symptoms were strong predictors of severe angiographic CAD. The presence of CCS Class IV angina appears to be more predictive of severe angiographic CAD in women compared with men. This information should be used by clinicians when deciding which patients to refer to coronary angiography.

Sex differences in the distribution of risk factors between women and men have been previously reported by several investigators and in prospective studies [3–5, 7, 13, 15, 17, 19–21, 24, 25, 30–35]. Despite differences between studies, our findings are consistent with previous reports. Our observation that women are older at time of first referral



Fig. 1 Adjusted sex \times CCS class IV interaction.

lends supports to the observation that women develop CAD later in life than men. Moreover, the risk factor profile amongst women within this cohort is also consistent with prior literature supporting women at time of referral are more often hypertensive, whereas men are more likely to smoke.

The proportion of patients with severe angiographic CAD is greater in men than women. A 20% excess in the prevalence of severe CAD remains even after adjustment for age and other risk factors. It is possible that other sex differences may make men more prone to develop obstructive CAD. Whilst the proportion of women with severe angiographic CAD is lower than men, amongst young patients ≤60 years of age with suspected CAD, there is no difference attributed to age. In particular, within this subgroup of young women with severe angiographic CAD, the proportion with diabetes is almost two-fold times higher than amongst men, and the prevalence of hypertension, smoking and elevated lipids is particularly high, over 50%. Prior studies note that the protective 'female advantage' of lower CAD prevalence is essentially eliminated amongst diabetic women [5, 36, 37], and that the 10 years of delayed onset in CAD between women and men is largely explained by more frequent risk factors amongst men at younger ages [38]. Unfortunately, diabetic women may receive less treatment and CAD risk factor modification than diabetic men, because of the perception that women are at lower risk of CAD [37]. Despite the perception that younger women are less likely to have severe CAD compared with men, our data emphasize that women with diabetes and other proven cardiovascular risk factors

should be considered carefully for diagnostic coronary angiography particularly if they have symptoms suggestive of CAD, regardless of their age and sex. This would allow the appropriate patients to undergo further revascularization that may alter symptoms and/or prognosis [29].

Whilst women with risk factors have a greater probability of having severe CAD compared with women without risk factors, we and others have observed that women referred for diagnostic coronary angiography, in the outpatient as well as in the ACS setting, are more likely to have normal coronary arteries [39]. Existing evidence suggests that women may indeed experience typical symptoms of angina in the presence of normal coronaries because thev suffer vasospasm, excessive plaque/nonobstructive disease and/or endothelial dysfunction [9, 10, 39-41]; the question of the utility of typical symptoms of angina in predicting the presence of severe CAD has been raised [9, 13, 30, 42]. In our study, we observed that the presence of severe anginal (CCS Class IV) symptoms using a standardized symptom classification is a useful predictor, despite the prior controversies reported in the literature [3, 12, 13, 21-23]. In fact, despite a slightly higher and statistically significant proportion of men presenting with CCS Class IV symptoms, the association of CCS class IV symptoms and severe CAD was stronger in women than in men in our study. This finding is of particular interest, as women are often reported to have more atypical symptoms with less severe obstructive CAD. This has been identified as a 'paradox', where the prevalence of angina in women is similar to that of men, although men are more often found to have angiographically demonstrated CAD [43]. Our data confirm that women with risk factors and severe angina, particularly CCS Class IV angina, are more likely to have angiographically documented severe CAD. Further, this finding is particularly important since the definition of 'severe CAD' used reflects standard criterion and has prognostic significance [29]. Researchers in women's cardiac health have called for the 'imminent need' for better clinical classification to predict the presence or absence of severe CAD in women with suspected CAD [39]. Our data should aid clinicians in determining who should be referred for diagnostic angiography amongst at-risk women with suspected CAD.

It is important to note that although there are limitations inherent to all database analyses our prospective registry represents 'real world' clinical practise. Whilst referral bias may limit the external validity, our results are internally valid. Despite the fact that women are referred less often for catheterization, within the ones who were referred, we demonstrate that more women are likely to have normal/mild CAD, and less likely to have severe CAD. In this analysis, patient referrals are dependent on 'real world' physician decision making rather than protocol driven angiograms. Consequently, we relied on the summarized reporting of the risk factors by the referring physician and did not have actual laboratory values for diabetes and hyperlipidaemia, or blood pressure readings for hypertensive patients. However, we cross-checked the reported risk factors with medical treatment to minimize this potential bias and as such, our prevalence estimates may be underestimates. Also, much like real world practise, the severity of angiographic stenosis was solely determined by the angiographer performing the procedure. However, it remains unknown if the implications of equal burden of CAD are similar in both men and women. Although the majority of our patients likely had pre-catheterization noninvasive testing, we did not have access to these data in order to determine if symptoms were strongly correlated with noninvasive testing results or if sex differences were present. However our data are internally valid and clearly demonstrate the predictive nature of CCS class IV symptoms. Lastly, the primary purpose of the registry was to document adverse events whilst patients were waiting for their angiogram and follow-up data were not collected. Despite this, it is important to note that this study represents one of the largest series of women analysed alongside men.

Conclusion

Women referred for first diagnostic angiography are more likely to have normal/mild CAD and to have lower rates of severe CAD compared with men across all ages. Whilst conventional risk factors including age, sex, diabetes, smoking and hyperlipidaemia are primary determinants of CAD, CCS Class IV angina is more strongly associated with severe CAD amongst women than in men. These findings have implications for physicians to better identify women at risk and to target diagnostic and treatment strategies accordingly.

Conflict of interest statement

There are no conflicts of interest to report from any of the authors.

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C. Kreatsoulas et al.

Identifying women with severe angiographic coronary disease

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