Gender Disparities in Vascular Disease

A Thesis Submitted to The University of Adelaide as the requirement for the degree of Doctor of Philosophy

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Faculty of Health Sciences
Discipline of Medicine
The University of Adelaide
South Australia

January 2013
“We should acknowledge differences, we should greet differences, until difference makes no difference anymore”.

-Adela Allen
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Thesis Declaration

For a thesis that contains publications

NAME:......................................................PROGRAM:..................................

This work contains no material, which has been accepted for the award of any other
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SIGNATURE:............................................DATE..................................

*Dreyer R, Arstall M, Tavella R, Weekes A, Morgan C, Beltrame J. Gender
Differences in Patients with Stable Angina attending Primary Care Practices. Heart,
Acknowledgements

First and foremost I’d like to thank my primary PhD supervisor, Professor John Beltrame for his ongoing support, encouragement and patience over the course of my doctorate. It has been an absolute pleasure to work along side such a talented cardiologist and researcher.

I’d also like to offer my sincere gratitude to my supervisory panel. To Dr Margaret Arstall, A/Prof Chistopher Zeitz and Dr Geoffery Schrader, for their time, support and assistance during this research. In particular, I’d like to thank Dr Arstall for being such an iconic and strong female figure in my immediate academic circle, one of which I greatly admire. To my mentor, Dr David Wilson, thank you for your brilliance, wisdom and sense of clarity in trying times.

To the nursing staff at the coronary care units of the Queen Elizabeth, the Lyell McEwin and the Royal Adelaide Hospitals, for their patience and support during patient recruitment. Of course, I also wish to acknowledge the time and willingness of those patients who participated in this research and did so without expectation or personal benefit.

I also owe thanks to several individuals who contributed towards specific projects. For the CADENCE study I’d like to thank Claire Morgan and Andrew Weekes for their statistical support and guidance.

In regards to the STEMI registry I’d like to thank the registrar’s from 2005-2010 as well as Dr Purenda Pati and Bernadette Hoffmann for their crucial role in assistance
in data collection. In addition, I am grateful to Thomas Sullivan, Tracy Air and Dr Rosanna Tavella for their statistical support.

For the VIRGO study *(see Ancillary projects coordinated)*, I’d sincerely like to thank Gabrielle Douglas for her professionalism, knowledge, support and friendship over the last 3 years. Additionally, I’d like to extend my gratitude to the VIRGO team at Yale University for they’re on-going support and assistance. At the Basil Hetzel Institute I’d like to specifically thank Melanie Wittwer and Yang Timothy Du for their help in patient recruitment and data collation.

In regards to the PORTRAIT registry and the Dutch Peripheral artery disease database *(see Ancillary projects coordinated)* I’d like to thank Drs Kim Smolderen and Moniek Van Zitteren for their guidance and mentorship. I’d also like to acknowledge my colleagues at the Mid America Heart Institute in Kansas City and Tilburg University in Holland.

I am eternally obliged to my lab colleagues and close friends, whose patience and humor have rescued me from peril more times than I can recall. In particular I’d like to thank my dear friend and colleague, Amenah Jaghoori, for her companionship, encouragement and honesty throughout this long journey.

Last but not least I am deeply thankful to my family. To my parents Jon and Shelley for their constant love, encouragement, understanding and financial support, it is to you that this thesis is dedicated.
Abstract

**Background and Objectives:** This thesis investigates sex/gender disparities in a range of vascular disorders. Specific aims include, (1) To evaluate gender differences in chronic stable angina patients attending general practitioner clinics in relation to (a) health status, and (b) potential contributing clinical factors. (2) To investigate gender differences in Door-to-Balloon (DTB) time amongst patients with ST-Elevation myocardial infarction (STEMI) receiving percutaneous coronary intervention (PCI) in relation to (a) the components of DTB time in women, and (b) the independent effect of gender on DTB time. (3) To examine sex differences in cardiac haemodynamic parameters in patients with STEMI, especially if (a) female sex is an independent determinant of pulmonary capillary wedge pressure (PCWP), and (b) whether elevated PCWP is a determinant in all-cause 30-day mortality/re-infarction. (4) To evaluate gender differences in peripheral artery disease (PAD) patients attending Dutch vascular clinics in relation to (a) long term mortality/major adverse cardiovascular events, and (b) self reported symptomatic health status.

**Methods:** Each chapter of this thesis employs different quantitative methods to evaluate clinical outcomes and health status in arrange of coronary and peripheral disorders. Specifically, chapters 3 and 6 employ patient-reported health status measures derived from both generic and disease specific instruments. Chapters 4 and 5 employ clinical outcome measures such as hospital performance metrics and haemodynamic endpoints. For cross sectional data, analyses have been adjusted for age and conventional clinical risk factors in order to compare genders. In terms of multivariate statistics, linear or logistic regression has been employed relevant to the
analyzed outcome. For longitudinal data, Cox proportional hazards models and Kaplan Meier curves were conducted as well as imputation for missing data.

Summary of major findings: (1) Compared with men, women with stable angina have worse angina-related health outcomes. Despite this, women were less likely to (a) undergo revascularisation therapies, (b) receive cardio-protective agents or (c) be referred for any specialist cardiology review (Chapter 3). (2) Analysis of the DTB time components in patients with STEMI confirmed a delay in both diagnosis and the initiation of PCI therapy in women. Furthermore, gender was found to be an independent determinant of DTB (Chapter 4). (3) Women with STEMI undergoing PCI have an elevated PCWP compared with men. In addition, female sex, hypertension and creatine kinase estimated infarct size were the independent predictors of an elevated PCWP. The effect of female sex on 30-Day mortality/re-infarction was partially mediated through PCWP, which had its own direct effect on 30-day outcomes. (4) In patients with PAD, there was found to be no significant effect of gender on mortality/major adverse cardiovascular events, however, women had poorer physical/mental health status scores at baseline and 12 months compared with men.

Conclusion: Gender disparities in relation to poorer health status and poor clinical outcomes are evident in both coronary and peripheral artery disease. These findings confirm that the gender disparity conundrum in contemporary cardiovascular health is ‘alive and well’ in 2012. Future gender specific research into women’s cardiovascular health is essential in bridging this gap in knowledge.
Statements of Authorship of Jointly Authored Papers Presented within this Thesis

STATEMENT OF AUTHORSHIP

Gender Differences in Patients with Stable Angina attending Primary Care Practices

Heart, Lung and Circulation 2011; 20:452-459.

Dreyer, R.
Study conception and design, management and interpretation of the data, manuscript revisions and preparation for critical review.

I hereby certify that the statement of the contribution is accurate
Signed... ......Date...January 15, 2013

Arstall, M.
Interpretation of the data, preparation for critical review.

I hereby certify that the statement of the contribution is accurate

Signed... .Date: January 15, 2013

Tavella, R.
Study conception and design, interpretation of the data.

I hereby certify that the statement of the contribution is accurate
Signed... ......Date...January 15, 2013

Weekes, A.
Data collation, study conception and design and manuscript revisions.

I hereby certify that the statement of the contribution is accurate
Signed... ......Date...January 15, 2013
Morgan, C.
Data collation, study conception and design, and statistical analysis.

I hereby certify that the statement of the contribution is accurate
Signed.. ............Date.. ...............

Beltrame, J.
Supervised development of the work, study conception and design, interpretation of
the data, preparation and critical review.

I hereby certify that the statement of the contribution is accurate
Signed.............. ............Date.. ...............

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Publications and Presentations Derived from this Thesis

Refereed Journal Articles & Book Chapters


5. **Dreyer R.** Van Zitteren, M. Beltrame, J. Fitridge, R. Denollet, J.Vriens, P. Spertus, JA & Smolderen, K. Gender Differences in Outcomes and Health Status of Patients with Peripheral Artery Disease (Submitted, Circulation: Cardiovascular Quality and Outcomes)

Published Abstracts


**Conference Proceedings: International**


3. **Dreyer R.** “Gender Differences in ST-Elevation Myocardial Infarction: An Australian Experience”. The Mid America Heart Institute, Kansas City & Yale University, New Haven Connecticut, USA. Post Doctoral Lab visit & guest speaker. May 2011.

Conference Proceedings: Local


# Awards and Honours Received over Course of Doctorate

## PRIZES

<table>
<thead>
<tr>
<th>Year</th>
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<tr>
<td>2012</td>
<td>First prize for the TQEH “Clinical Higher Degrees Research” Oral Presentation</td>
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<td>2011</td>
<td>First prize for best poster presentation, Health Science Post Graduate Conference</td>
</tr>
<tr>
<td>2010</td>
<td>First Prize for the TQEH “Clinical Higher Degrees and Registrars” Oral Presentation</td>
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## AWARDS

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<tr>
<td>2012</td>
<td>Awarded the American Australian Association Fellowship, Sir Keith Murdoch Fellow</td>
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<td>2012</td>
<td>Awarded the National Heart Foundation (NHF) Travel Fellowship</td>
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<td>2011</td>
<td>Awarded the 2011 Barbara Crase Bursary, The Australian Federation of University Women</td>
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<tr>
<td>2011</td>
<td>Awarded the De la Lande Travel Fellowship, Clinical Pharmacology &amp; Cardiology award</td>
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<tr>
<td>2011</td>
<td>Awarded the EO Myers Trust Fund Travel Grant, National Heart Foundation</td>
</tr>
<tr>
<td>2011</td>
<td>Awarded the Faculty of Health Science Travel Fellowship, University of Adelaide</td>
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<tr>
<td>2011</td>
<td>Awarded the South Australian Heart Research Achievement Award</td>
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## HONOURS

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<th>Year</th>
<th>Description</th>
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<tr>
<td>2013</td>
<td>Nominated for the SA Young Achiever Awards, Science &amp; Technology category</td>
</tr>
<tr>
<td>2012</td>
<td>Young Australian of the Year National Finalist, National Australia Day Council</td>
</tr>
<tr>
<td>2011</td>
<td>Plenary lecture guest speaker, National Heart Foundation Conference, Melbourne, Australia</td>
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<td>2011</td>
<td>Invited guest speaker at National Heart Week, National Heart Foundation</td>
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<tr>
<td>2011</td>
<td>Invited guest speaker at the SA Cardiovascular Health &amp; Rehabilitation Conference</td>
</tr>
<tr>
<td>2011</td>
<td>Invited speaker at the Early Career Researcher Program, National Heart Foundation</td>
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<td>2011</td>
<td>Selected for Oral Presentation at the National Heart Foundation Conference</td>
</tr>
<tr>
<td>2011</td>
<td>Nominated for the SA Young Achiever Awards, Science &amp; Technology category</td>
</tr>
<tr>
<td>2009</td>
<td>Medical Grand Round ‘Invited’ Guest Speaker, The Lyell McEwin Hospital</td>
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## EXTRA CURRICULAR ACTIVITIES

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<tr>
<td>2012</td>
<td>Awarded Certificate IV in telephone counseling, Lifeline Australia</td>
</tr>
<tr>
<td>2012</td>
<td>Participated in the 100km fundraising bike ride for the ‘Go the Distance’ campaign</td>
</tr>
<tr>
<td>2012</td>
<td>Official Ambassador for the National Heart Foundation’s ‘Go the Distance’ Campaign</td>
</tr>
<tr>
<td>2011</td>
<td>Highest fundraising award for the NHF ‘Go Red for Women’ campaign, 50km bike ride</td>
</tr>
<tr>
<td>2011</td>
<td>Early Career Researcher group member, National Heart Foundation</td>
</tr>
<tr>
<td>2011</td>
<td>Lifeline Australia Training Supervisor</td>
</tr>
<tr>
<td>2009</td>
<td>National Heart Foundation ‘Go Red for Women’ Active Volunteer</td>
</tr>
<tr>
<td>2009</td>
<td>Lifeline Australia telephone counselor</td>
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</table>
Ancillary Projects Coordinated

In addition to the work presented in this thesis I have also played pivotal roles as the Australian coordinator for two major international studies that originally formed part of my thesis. These included VIRGO (Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients), HOPIC and the PORTRAIT (Patient centered Outcomes Related to Treatment practices in Peripheral Arterial disease: an International Trajectory) studies.

The VIRGO study is a Yale University based project, designed to explore why women under the age of 55 years who experience an acute myocardial infarction have a three-fold higher in-hospital mortality than their male counterparts. This project has been the first large prospective study to examine the underlying mechanisms responsible for this gender disparity. The study was originally exclusive to the United States, however with the support of my primary supervisor, I initiated VIRGO-Australia, a parallel collaborative study. Over the course of my doctorate, I have regularly liaised with the Yale University investigators via early morning teleconferences to ensure that VIRGO Australia was conducted in close alignment with the American parent study. I originally initiated the study at the Queen Elizabeth Hospital but subsequently extended the study to the Lyell McEwin and the Royal Adelaide Hospitals. When recruitment accelerated and additional staff were required, I successfully coordinated and managed the data-Collectors at the three participating institutions, including supervision of undergraduate and Honours’ students. My important, ongoing contributions to VIRGO Australia have been formally acknowledged in newsletters of the Yale Coordinating Center (See Appendix 4). Earlier this year the US VIRGO sites completed enrollment with a total of 2000
women between 18 - 55 years of age and a comparison group of 1000 men from approximately 120 hospitals. A smaller comparison group was collected for VIRGO Australia [163 patients in total (n=49 women, n=114 men)]. At the time of writing this thesis data audits were still underway therefore the decision was made to exclude this project from my thesis. However, my Postdoctoral term at Yale University, supported by the Sir Keith Murdoch Fellowship (American Australian Association), will involve my input in the analysis of the VIRGO study in the United States as well as involvement with the 12-month follow up data.

The HOPIC Study, was established to evaluate health outcomes in patients with intermittent claudication attending the Queen Elizabeth Hospital PAD Clinics. After designing the study protocol, obtaining ethics permission and recruiting patients over a 3-month period, we learned that our US colleagues were planning to conduct a similar study. Thus the HOPIC study was merged into the international PORTRAIT study and provided the first recruited patients into this international study that spans three continents.

The PORTRAIT Study is coordinated at the Mid-America Heart Institute in Kansas USA and involves Tilburg University in the Netherlands as well as The Queen Elizabeth Hospital. I was responsible for the development of the case report forms and the database specific to our site, patient recruitment and follow-up as well as the training of new personnel into the study. Towards the end of 2011, it was appreciated that the data from PORTRAIT would not be completed in time to include in my PhD thesis. As an alternative, our Dutch colleagues made available their local PAD registry data to assess gender differences in PAD. I therefore formulated a research
proposal and analysis plan, thereby investigating the original objective of the HOPIC study. This manuscript can be seen in chapter 6 and has been submitted for publication.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<tr>
<td>IHD</td>
<td>Ischaemic Heart Disease</td>
</tr>
<tr>
<td>CVB</td>
<td>Cerebrovascular Disease</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral artery Disease</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute Myocardial infarction</td>
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<tr>
<td>UA</td>
<td>Unstable angina</td>
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<tr>
<td>CSA</td>
<td>Chronic stable angina</td>
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<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-Elevation myocardial infarction</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non-ST-Elevation myocardial infarction</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischaemic attack</td>
</tr>
<tr>
<td>IC</td>
<td>Intermittent Claudication</td>
</tr>
<tr>
<td>CLI</td>
<td>Critical Limb Ischaemia</td>
</tr>
<tr>
<td>ABI</td>
<td>Ankle Brachial Index</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>MCD</td>
<td>Microvascular Coronary Dysfunction</td>
</tr>
<tr>
<td>SES</td>
<td>Socio-economic Status</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
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<tr>
<td>PCOS</td>
<td>Polycystic ovarian syndrome</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>HRQOL</td>
<td>Health related quality of life</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>CK</td>
<td>Creatine Kinase</td>
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<td>LDL</td>
<td>Low density lipoprotein</td>
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<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>FHS</td>
<td>Framingham Heart Study</td>
</tr>
<tr>
<td>FRS</td>
<td>Framingham risk score</td>
</tr>
<tr>
<td>RSC</td>
<td>Reynolds risk score</td>
</tr>
<tr>
<td>CDM</td>
<td>Clinical Data Management</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>CADENCE</td>
<td>Coronary Artery Disease in General Practice</td>
</tr>
<tr>
<td>CCSC</td>
<td>Canadian Cardiovascular Society Classification</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association Assessment</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>CCU</td>
<td>Coronary care unit</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Airways Disease</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiac event</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>TVR</td>
<td>Target vessel revascularisation</td>
</tr>
<tr>
<td>ARS</td>
<td>Angiographic restenosis</td>
</tr>
<tr>
<td>DES</td>
<td>Drug Eluting stent</td>
</tr>
<tr>
<td>BMS</td>
<td>Bare metal stent</td>
</tr>
<tr>
<td>PTD</td>
<td>Pain-to-Door</td>
</tr>
<tr>
<td>DT-ECG</td>
<td>Door-to-ECG</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DTC</td>
<td>Door-to-Code</td>
</tr>
<tr>
<td>CTL</td>
<td>Code-to-Lab</td>
</tr>
<tr>
<td>LTB</td>
<td>Lab-to-Balloon</td>
</tr>
<tr>
<td>CTB</td>
<td>Code-to-Balloon</td>
</tr>
<tr>
<td>DTB</td>
<td>Door-to-Balloon</td>
</tr>
<tr>
<td>DTN</td>
<td>Door-to-Needle</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>LVH</td>
<td>Left Ventricular Hypertrophy</td>
</tr>
<tr>
<td>MSS</td>
<td>Mental Summary score</td>
</tr>
<tr>
<td>PSS</td>
<td>Physical Summary Score</td>
</tr>
<tr>
<td>SF-12</td>
<td>Short form-12</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>SAQ</td>
<td>Seattle Angina Questionnaire</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in Myocardial infarction (TIMI Frame Count)</td>
</tr>
<tr>
<td>WISE</td>
<td>Women’s Ischaemia Syndrome Evaluation Study</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart Lung and Blood Institute</td>
</tr>
</tbody>
</table>
Historically, women’s health has focused on breast cancer and menopause, leading women to believe that Heart disease is a ‘man’s disorder’ and therefore not an important health concern. This lack of education has resulted in many women not being appropriately informed of their cardiovascular risks and consequently in health care providers underestimating this threat as compared with men. Recognition of gender disparities in cardiovascular disease (CVD) have been slow to gain acceptance and have only been highlighted in the past 15 years with the first women-specific clinical recommendations for the prevention of CVD published by the American Heart Association (AHA) in 1999. Previously, the higher morbidity and mortality observed in women with CVD had been appreciated however guidelines had been primarily targeted at men. As a result, much of the research in the past has been stratified from predominately male populations and thus the gender gap in coronary and peripheral disorders has not been well documented until recently. In 2012, the female enrollment rate in cardiovascular clinical trials is 30% with only a third of trials publishing sex specific results, even though US regulations require sex stratification. The gender phenomenon in CVD is multi-factorial and far-reaching with the cause of poor prognosis in women still under speculation. There exist clear disparities in presentation, diagnosis and management of women with CVD, leaving many questions unanswered.

The work presented in this thesis aims to improve the insights into gender specific issues in CVD and the cause of the poorer outcomes of women. This thesis contains four main studies within both coronary and peripheral artery disease, each employing different quantitative methods. The first study focuses on patients with chronic stable
angina attending general practitioner practices, assessing gender differences in health status (Chapter 3). The second and third experimental studies focus on sex/gender differences in patients with ST-elevation myocardial infarction (STEMI), assessing both differences in clinical outcomes (Chapter 4) as well as cardiac haemodynamics (Chapter 5). The final experimental study focuses on gender differences in outcomes and health status amongst patients with PAD (Chapter 6).
CHAPTER 1: Introduction
1.1 The Spectrum of Vascular Disorders

1.1.1 Definition of Cardiovascular Disease

Cardiovascular disease (CVD) includes any disorder of the heart and blood vessels. For the purposes of this thesis, CVD will be considered to constitute coronary heart disease (CHD), cerebrovascular disease (CVB) and peripheral artery disease (PAD), all of which have atherosclerosis as a major underlying factor. This is a condition where abnormal deposits of fat, cholesterol and other substances build up in the inner lining of the arteries to form plaque\(^5\). The atherosclerotic process is slow and multifaceted, often starting in childhood and progressing with age. Clinical symptoms usually only appear when the atherosclerotic plaques impair blood flow to vital organs, either due to a slowly progressing obstructive lesion (e.g. stable angina, intermittent claudication) or a sudden occlusive lesion from plaque rupture (e.g. acute coronary syndrome).

1.1.2 Epidemiology of Vascular Disorders

Within the epidemiology field, prevalence is the proportion of a population or the number of patients found to have a condition at any particular time. Conversely, incidence is a measure of the risk of developing a new condition over a specified period of time.

Cardiovascular disease is the leading cause of morbidity and mortality worldwide, responsible for over 17.3 million deaths each year\(^6\). The World Health Organisation (WHO) estimates that CVD caused almost 32% of all deaths in women in 2004 as
well as a corresponding 27% of deaths in men. Although the rate of cardiovascular
deaths in men has declined over the last decade, the number of cardiovascular
deaths in women remains unchanged or may even be increasing. Cardiovascular
diseases are also the leading cause of death in Australia, resulting in 48,456 (34%)
for all deaths in 2007-08. Coronary heart disease is the leading cause of death
(49%) followed by stroke (18%) and PAD in both genders respectively.

In terms of prevalence it is estimated that over 3.5 million Australians suffered
from CVD in 2008, corresponding to 17% of the population. Furthermore, a slightly
higher prevalence of females (16%) were estimated to have CVD compared with
their male counterparts (15%). Heart, stroke and vascular conditions occur mainly
among older Australians with a higher prevalence amongst the elderly, namely,
62% of those aged ≥75 years were estimated to have this condition. Among those
aged 45–54 years, 19% had CVD and the estimate was 5% for those aged less than
45 years.

In terms of incidence, CVD was the main cause for 475,000 hospitalisations in
2007–08 and played a secondary role in a further 797,000 cases. Vascular diseases
remain as the most expensive disease group in Australia costing the healthcare
system around $5.9 billion annually and contributing to significant illness,
premature death, disability and poor quality of life.
1.1.3 Atherosclerotic Risk Factors

The concept of modifiable biological ‘risk factors’ in CVD was first proposed in 1948 following the initiation of the Framingham Heart Study (FHS)\textsuperscript{10}. This landmark project was established to investigate the epidemiology of atherosclerotic CVD and hypertension in the progression towards acute myocardial infarction (AMI), as at the time the causes of heart disease were predominately unknown. Thus, the main objective of the study was to identify the characteristics that contribute to CVD by following its development over a longitudinal period within a large group of healthy participants. The contribution to the field of cardiology has been far reaching as it precipitated a paradigm shift in the approach to CVD. From its findings, the FHS transformed the known belief that atherosclerotic CAD was a normal ageing process and accordingly laid the foundations for the use of the term ‘risk factors’, which included new lifestyle modifications to prevent CVD\textsuperscript{11}.

Over the years, careful monitoring of the FHS population has led to the identification of the major CVD risk factors including advancing age, smoking, hypercholesterolaemia, hypertension and physical inactivity/obesity. As a result the Framingham investigators pioneered the ‘Framingham Risk Score’ (FRS) which enables physicians to predict a 10 year risk of patients developing CAD based upon age, cholesterol profile, blood pressure levels, diabetes and smoking status\textsuperscript{12}. The investigators concluded that by the age of 40 years the lifetime risk of CAD is 33% for women and 50% for men. The FHS continues to unfold with new investigations into the role of gender, psychosocial issues as well as socio-economic factors.
Although groundbreaking, the results from the FHS have several important limitations. Namely, results have been generated from a select east coast USA community and may not necessarily be ‘representative’ of the global population. In light of this, a recent large multinational trial of 151,52 patients, the INTERHEART study has been conducted to evaluate the association between the known modifiable risk factors in progression towards AMI\textsuperscript{13}.

The INTERHEART study enrolled patients from 52 countries and reported that the traditional risk factors described in the FHS accounted for most of the risk of AMI (independent of country). Table 1 below demonstrates the importance of these major risk factors and in particular the odds ratios and exponential risks when these factors are combined. Other factors which also increased the risk of AMI included reduced exercise, alcohol consumption and daily fruit/vegetable intake\textsuperscript{14}. 
<table>
<thead>
<tr>
<th>Risk Factor (RF)</th>
<th>Odds Ratio (99% CI)</th>
<th>Population attributable risk (PAR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (1)</td>
<td>2.9 (2.6-3.2)</td>
<td>35.7%</td>
</tr>
<tr>
<td>Diabetes (2)</td>
<td>2.4 (2.1-2.7)</td>
<td>9.9%</td>
</tr>
<tr>
<td>Hypertension (3)</td>
<td>1.9 (1.7-2.1)</td>
<td>17.9%</td>
</tr>
<tr>
<td>Dyslipidaemia* (4)</td>
<td>3.3 (2.8-3.8)</td>
<td>49.2%</td>
</tr>
<tr>
<td>1+2+3</td>
<td>13.0 (10.7-15.8)</td>
<td>-</td>
</tr>
<tr>
<td>All 4</td>
<td>42.3 (33.2-54.0)</td>
<td>-</td>
</tr>
<tr>
<td>+ Abdominal Obesity</td>
<td>68.5 (53.0-88.6)</td>
<td>20.1%</td>
</tr>
<tr>
<td>+Psychosocial</td>
<td>182.9 (132.6-252.2)</td>
<td>32.5%</td>
</tr>
<tr>
<td>All RF’s</td>
<td>333.7 (230.2-483.9)</td>
<td>-</td>
</tr>
<tr>
<td>Daily fruits/vegetables</td>
<td>0.70 (0.62-0.79)</td>
<td>13.7%</td>
</tr>
<tr>
<td>Regular alcohol consumption</td>
<td>0.91 (0.82-1.02)</td>
<td>6.7%</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>0.86 (0.76-0.97)</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

Table 1: Risk of Acute Myocardial Infarction Associated with Exposure to Multiple Risk Factors (P<0.001 for all risk factors and p=0.03 for alcohol consumption). *As defined by apolipoprotein B/A1 ratio. Adapted from Yusuf et al, Lancet, 2004\textsuperscript{13}. 
1.1.4 Scope of Thesis

This thesis will focus on two of the above atherosclerotic CVDs, namely coronary and peripheral artery disease. In particular it will investigate sex/gender differences within these disorders, evaluating the clinical outcomes and health status in patients with chronic stable angina (CSA), ST-elevation myocardial infarction (STEMI) and PAD. In order to provide background information to these investigations, this introductory chapter will examine the underling principles for the studies including:

(a) The clinical syndromes in CHD & PAD
(b) Fundamental principles of understanding the pathophysiology behind CHD and PAD.
(c) Basic pathophysiological concepts relating to coronary heart disease (CHD) and PAD.
(d) In depth discussion of current gender disparities in CHD and PAD.

Finally the specific objectives of the thesis will be defined.
1.2 Coronary Heart Disease

1.2.1 Definition of Coronary Heart Disease

Coronary heart disease (CHD) is a generic term used to describe a spectrum of closely related coronary disorders and syndromes. This disorder can involve any portion of the coronary circulation, including the coronary arteries, arterioles, veins and/or capillaries but generally involves the arterial circulation with dysfunction occurring in the large conduit and microscopic resistance vessels. When these vessels are dysfunctional, they may reduce blood flow to the myocardium thereby impairing the supply of oxygen and nutrients to the myocardial cells so that myocardial ischaemia ensues. The importance of this blood supply is exemplified by the fact that a 50% or more reduction in this blood supply to the myocardium is incompatible with life. Thus, not surprisingly, dysfunction of the coronary circulation may result in significant morbidity and mortality.

1.2.2 Epidemiology of Coronary Heart Disease

For a detailed discussion of the epidemiological concepts regarding CHD please refer to Appendix 3 (Epidemiology of CAD Book Chapter). In brief, CHD is the most common cause of cardiovascular deaths (45% of all CVD deaths) accounting for 7.2 million deaths per year, or 12% of all deaths worldwide\textsuperscript{15}. In Australia CHD is also the leading single cause of mortality, accounting for over 22,729 deaths (17%) in 2007-08 with approximately half due to AMI\textsuperscript{8}.

In terms of prevalence, self reported data from the National Health survey indicate that around 3% of the Australian population suffered from CHD in 2008 (~685,000
people) and of these 449,000 were burdened with ischaemic heart disease. The prevalence of CHD as well as its components of angina and AMI are higher among males than females in all age groups older than 35 years. In 2007–08, around 7% of Australians aged 55–64 years were estimated to have CHD, increasing to 24% among those aged 85 years and over.

The yearly incidence of CHD in Australia during 2007-08 was reported to include 49,391 major coronary events among 40–90 year olds (31,036 men and 18,355 women), which equates to about 135 per day. Between 1987 and 2007, the age-standardised CHD death rate more than halved in Australia falling from 251 deaths per 100,000 population to 98 per 100,000. This decline in deaths from CHD is most likely due to improvements in modifiable lifestyle risk factors and the medical care of acute coronary syndromes and preventative therapies.

1.2.3 Pathophysiological Manifestations of CHD

The two main pathological consequences of CHD include myocardial infarction and myocardial ischaemia\textsuperscript{16}. Myocardial infarction is a pathological condition where inadequate coronary blood flow results in myocardial necrosis. This is most commonly due to an occlusion of a coronary artery following the rupture of a vulnerable atherosclerotic plaque and is manifest by the leakage of troponin from the myocardial cells into the circulation.

Conversely myocardial ischaemia is a pathophysiological condition where a transient coronary blood flow insufficiency results in inadequate oxygen supply and
the accumulation of wastes products in the myocardium, typically manifesting as angina. The delineation between myocardial infarction and ischaemia is dependent upon the extent and duration of disrupted blood supply and whether it is sufficient to result in myocardial necrosis.

1.2.4 Pathophysiological Mechanisms of CHD

The pathophysiological mechanisms underlying CHD include the triad of atheroma, thrombosis and vasospasm. Atherosclerosis involves an inflammatory process including the accumulation of macrophage cells containing lipids and a variable amount of fibrous connective tissue in the walls of coronary arteries. The atheromatous plaques can restrict blood flow to the myocardium (resulting in ischaemia) when the vessel lumen is obstructed ≥ 70% of its cross sectional area by the plaque. An obstruction greater than 90% can result in necrosis or infarction due to the complete deprivation of oxygen to the myocardium. Coronary blood flow can also be obstructed by thrombus formation, typically at a site of an unstable atheromatous plaque.

Thrombus generation is typically initiated by platelet activation in response to endothelial injury. The activated platelets adhere to the vessel wall thereby stimulating a cascade of reactions resulting in thrombus formation with the addition of fibrin. Atherosclerotic plaque rupture frequently underlies acute coronary syndromes and involves the rupture of a thin walled, lipid-laden atherosclerotic plaque, exposing the thrombogenic lipid contents to circulating platelets thereby resulting in thrombus formation. The intricacies of this complex process is beyond the scope of this thesis and more closely detailed in other literature.
Although the above atherothrombotic process has received considerable attention in the literature, the role of coronary vasospasm has received little consideration. It is known that activated platelets release vaso-active substances (i.e. serotonin, thromboxane), which in turn cause vasoconstriction (vasospasm). However vasospasm may also occur in the absence of thrombus formation but is difficult to quantify given its frequent transient nature\textsuperscript{19}.

1.2.5 Clinical Syndromes

1.2.5.1 Acute Coronary Syndromes

Depending on the underlying pathophysiologic process (as described above), and the severity and timing of a potential myocardial ischaemic insult, a spectrum of distinctive clinical syndromes may result into either an acute or chronic coronary syndrome. Acute coronary syndromes encompass a range of biological processes which can progress from plaque instability to plaque rupture, thrombosis, reduced coronary blood flow, myocardial ischaemia as well as myocardial necrosis. These particular syndromes include a spectrum of clinical disorders caused by acute ischaemic disease including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). Rarely, other mechanisms can precipitate an ACS and are listed in Table 2 below\textsuperscript{20}. 

11
Causes of Acute Coronary Syndromes

- Atherosclerotic plaque instability/rupture
- Vasculitic syndromes
- Coronary emboli (i.e. from endocarditis, artificial valves)
- Congenital anomalies of the coronary arteries
- Coronary trauma or aneurysm
- Coronary artery spasm (primary or cocaine induced)
- Increased blood viscosity
- Markedly increased myocardial oxygen demand

Table 2: Causes of Acute Coronary Syndromes (ACS). Adapted from Naik (in Lilly) Pathophysiology of Heart Disease, 2007\textsuperscript{20}.

Acute Myocardial Infarction

At the beginning of the 20\textsuperscript{th} century James Herrick was the first to describe the causes of AMI as we know it today\textsuperscript{21}. In his classic paper entitled “Clinical Features of Sudden Obstruction of the Coronary Arteries” he provided a definitive description of coronary thrombosis and emphasized the important observation that sudden obstruction of a coronary artery is not necessarily fatal.

The clinical diagnosis of AMI has evolved over the past 10-15 years with the need to make an early diagnosis so that prompt therapy can be instituted. As shown in Table 3, the most recent guidelines recommend that the clinical diagnosis of AMI be made primarily on the basis of an abnormal troponin with at least one other feature; alternatively the diagnosis may be made on autopsy pathological examination\textsuperscript{22}. In
addition to detecting myocardial infarction in the acute setting, a number of the above techniques may detect a previous myocardial infarct as mentioned in Table 3 relating to ‘healed myocardial infarction’. Each of these methods has their advantages and disadvantages in relation to availability, cost and accuracy.

It is important to note that myocardial cell necrosis (i.e. from STEMI) results in leakage of intracellular proteins into the blood. Early on, creatine kinase (CK) was used as a marker of AMI as this was found in large amounts within myocardial cells\(^23\). Despite this, as a marker it was not specific, as CK was also known to be prevalent in skeletal muscle and in the brain. Conversely, the CK-MB sub type was found to be more specific. Troponin is also an intracellular peptide but is found almost exclusively in myocardial cells. Troponin I and T have since been developed with the later being the most frequently used\(^24,25\). Recently, a high sensitivity TnT assay has been developed, however, its clinical utility is under investigation\(^26\).

Previously, AMI was classified on the presence or absence of Q waves on the ECG following myocardial infarction. The presence of Q waves is a marker of transmural myocardial infarction, as compared with non-Q wave MI where the myocardial necrosis is principally sub-endocardial. The evolution of Q waves typically begins after 24 hours of the myocardial infarct process and thus of limited value in the initial diagnosis of AMI.
In recent years the focus in AMI has been on ST segment changes rather than Q waves, particularly with the advent of early treatments for AMI. Thus in contemporary cardiology practice, AMI has been sub-classified on the basis of the presenting ECG as either STEMI or NSTEMI. The hallmark of STEMI is ST segment elevation, which may also be associated with T wave abnormalities and may evolve to the development of Q waves. On the contrary, NSTEMI is characterised by the absence of ST elevation and may include ST depression as well as T wave changes. As above, STEMI usually reflects threatened transmural myocardial injury whereas NSTEMI often reflects sub-endocardial damage\textsuperscript{20}.

The amount of tissue that ultimately succumbs to a myocardial infarction relates to (a) the mass of myocardium perfused by the occluded vessel, (b) the extent and duration of impaired coronary blood flow, (c) the oxygen requirement of the affected area, (d) the sufficiency of collateral vessels and (e) the degree of tissue response that modifies the ischaemic process\textsuperscript{20}. In addition, the pathophysiologic alterations that occur during AMI occur in two main stages including early changes at the time of acute infarction and delayed alternations during myocardial healing and remodeling\textsuperscript{20}. Differentiating these two forms of AMI is essential as the immediate clinical management differs.

In STEMI, immediate coronary reperfusion strategies (either percutaneous coronary interventions or thrombolysis) on arrival to hospital are mandated in order to reduce the risk of death. In contrast, NSTEMI does not require immediate intervention although early invasive therapy (at least within days) is preferred. However, it is
important to note that NSTEMI is equally associated with a high 30-day mortality. Although immediate reperfusion strategies have not been shown to be of benefit, early PCI (i.e. within a few days) does reduce the risk of re-infarction/death at 30 days.
Criteria for acute, evolving or recent Myocardial Infarction

Either one of the following satisfies the diagnosis for acute, evolving or recent AMI:

1. Typical rise and/or fall or cardiac biomarkers (preferably troponin) with at least one of the following:
   • Ischaemic symptoms
   • Development of pathological Q waves in the ECG
   • Electrocardiographic changes indicative of ischaemia (ST-segment elevation or depression)
   • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

2. Pathologic findings of an acute myocardial infarction

Criteria for healing or healed Myocardial Infarction

Any one of the following criteria satisfies the diagnosis for healing or healed myocardial infarction:

1. Development of new pathological Q waves with or without symptoms. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a non-ischaemic cause.

2. Pathological findings of a healed or healing myocardial infarction.

Table 3: Revised Definition of Myocardial Infarction Adapted from Thygesen et al, J Am Coll Cardiol 2012²²:
Unstable Angina

Unstable angina (UA) constitutes a clinical syndrome subset of the ACS that most often caused by atherosclerotic CAD and is associated with an increased risk of cardiac death and subsequent AMI (Table 4). Unstable angina is essentially angina pectoris precipitated by disruption of an atherosclerotic plaque with partial thrombosis and potentially embolisation or vasospasm. It is manifest as one of the following clinical scenario’s: (1) angina at rest persisting >20 minutes; (2) new onset (i.e., within 1 month) angina; (3) crescendo pattern angina (more increasing frequency of angina), or (4) post-infarct angina. The mechanisms responsible for UA are usually similar to those of myocardial infarction but the severe ischaemia does not progress on to infarction (and thus is not associated with a troponin rise).

<table>
<thead>
<tr>
<th>Causes of UA/NSTEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus or thromboembolism, usually arising on disrupted or eroded plaque</td>
</tr>
<tr>
<td>• Occlusive thrombus, usually with collateral vessels</td>
</tr>
<tr>
<td>• Sub totally occlusive thrombus on per-existing plaque</td>
</tr>
<tr>
<td>• Distal micro vascular thromboembolism form plaque-associated thrombus</td>
</tr>
<tr>
<td>Thromboembolism from plaque erosion</td>
</tr>
<tr>
<td>• Non-plaque associated coronary thromboembolism</td>
</tr>
<tr>
<td>-Dynamic obstruction (coronary spasm or vasoconstriction) of epicardial and/or micro vascular vessels</td>
</tr>
<tr>
<td>-Progressive mechanical obstruction to coronary flow</td>
</tr>
<tr>
<td>-Coronary arterial inflammation</td>
</tr>
<tr>
<td>-Coronary artery dissection</td>
</tr>
</tbody>
</table>

Table 4: Causes of Unstable Angina/ Non ST-Elevation Myocardial Infarction.

Adapted from Braunwald, Circulation 1998.
1.2.6 Clinical Management of ACS

Therapeutic decisions are required before patients with ACS can be categorized into AMI or UA based on both serum cardiac markers and ECG changes. Patients can be classified into either STEMI or NSTEMI ACS based on the presence or absence of ST-elevation ≥1mm in two or more contiguous leads on initial ECG. Clinical features and management of ACS are summarized in Table 5 below. For a detailed discussion of current STEMI and UA/NSTEMI therapies and treatment modalities please refer to the latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines\textsuperscript{30, 31}. The current controversies and indications for therapy in STEMI and UA/NSTEMI will be discussed in brief below.

1.2.6.1 Current Controversies & Indications for Therapy in STEMI

In STEMI, 90% of patients have an occluded coronary vessel, thus restoring flow is paramount. To limit damage to the myocardium, acute and rapid reperfusion therapy with either thrombolytic therapy or PCI is recommended for all STEMI patients within 12 hours of symptom onset. Primary stenting is preferred over balloon angioplasty (percutaneous transluminal coronary angioplasty, PTCA), however both approaches reduce the extent of myocardial necrosis and greatly improve survival. Pre-hospital thrombolysis has been shown to reduce treatment delay by approximately 1 hour compared to in-hospital thrombolysis and is associated with improved survival and less progression to AMI. Transfer to a PCI center may be preferred to onsite thrombolysis therapy if the total DTB can be achieved in less than 90 minutes. Coronary artery bypass grafting is not routinely utilized in patients with STEMI as a primary indication for reperfusion due to lengthy delays and
difficulty in establishing perfusion of the infarct vessel with bypass grafts as well as the general success of PCI as a therapy.
### Presentation
- Typical chest/neck/jaw discomfort lasting >30 mins.
- Atypical symptoms in women, diabetics, and elderly.
- Same as STEMI
- Early risk stratification important for prognosis & therapy.

### ECG Findings
- Persistent ST elevation ≥1mm in at least two consecutive leads
- LBBB & posterior AMI treated the same as STEMI
- Q waves develop in 80% without reperfusion.
- ST depression > 0.5mm and/or T wave inversion > 2.0mm indicate high risk.
- Non-specific ST-T changes or normal ECG present.
- Complete coronary occlusion with persistent ST-elevation develop in some patients.
- Q waves develop in 20%.

### Pathophysiology
- Plaque rupture with occlusive thrombus.
- Most ruptures develop in moderate stenoses with soft, lipid rich cores/thin fibrous caps.
- Complete coronary occlusion develops in 90% patients.
- Plaque rupture with microvascular embolization of platelet aggregates from non-occlusive thrombus.
- Complete coronary occlusion develops in 10-40% patients.
- Intermittent thrombosis/dynamic vasoconstriction causes symptoms of UA.

### Initial Therapy
- PCI with primary stents
- Thrombolytic therapy if interventional team not available in timely fashion.
- Pre-hospital thrombolysis reduces treatment delay by ~1 hour compared to in-hospital thrombolysis & associated with survival.
- PCI with stents plus antithrombin therapy, clopidogel & GP IIb/IIIa inhibitor for high/immediate risk patients. *(Note: Thrombolytics are detrimental in NSTEMI)*
- Antithrombin therapy for all other hospitalized patients followed by PCI for re-current ischemia.

### Prognosis
- In-hospital survival depends on the speed/ adequacy of reperfusion.
- In-hospital AMI or death in UA varies from 1-5% (depending on risk class).
- NSTEMI has lower hospital mortality than STEMI but higher 1-year mortality due to more late events.

Table 5: Clinical features of Acute Coronary Syndromes. Adapted from Califf & Roe (ACS Essentials), 2010.
STEMI Reperfusion Therapies

Thrombolytic Therapy

Thrombolytic therapy is the most common reperfusion strategy in patients with STEMI and has evolved greatly over the years. To date, five major studies have confirmed the efficacy of intravenous thrombolytic therapy in AMI, and have laid the groundwork for current therapeutic practice. Of particular note, the ISIS-2 trial (Second International Study of Infarct Survival) was the first to demonstrate improved clinical efficacy of aspirin and streptokinase in reducing mortality in AMI. Further studies which support the use of thrombolytic therapy (by demonstrating an overall decrease in hospital mortality), include the GISSI-I, ISIS-3 and GUSTO-I randomized trials.

Primary PTCA

Primary PTCA, when rapidly available, is the preferred strategy for reperfusion in patients with STEMI owing to a lower risk of re-infarction and improved survival compared with thrombolysis. In 1986, PTCA was initially compared with thrombolytic therapy (i.e. streptokinase) and was shown to produce similar rates of early coronary reperfusion during evolving transmural infarctions. Over the next decade, a plethora of clinical trials compared the use of PTCA with intravenous thrombolytic therapy for STEMI. Since this time, PTCA has been proven to be more effective than thrombolytic therapy in patients with STEMI. Keeley and colleagues demonstrated that primary PTCA is better than thrombolytic therapy in reducing
overall short-term death, non-fatal re-infarction and stroke as well as the combined composite endpoint (Table 6)\textsuperscript{40}.

<table>
<thead>
<tr>
<th>30-Day outcomes (%)</th>
<th>Primary PTCA ( (n=3872) )</th>
<th>Lytic Therapy ( (n=3867) )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>7.0</td>
<td>9.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Re-infarction</td>
<td>3.0</td>
<td>7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0</td>
<td>2.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.05</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death, re-infarction or stroke</td>
<td>8.0</td>
<td>14.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 6: Meta analysis of 23 Randomized Trials of Primary PTCA vs. Thrombolytic Therapy or STEMI. Adapted from Keeley et al, Lancet, 2003\textsuperscript{40}.

\textit{Stenting versus PTCA}

Previous research suggests that the use of stents is superior over PTCA in patients with STEMI and thus should be considered as the routine reperfusion strategy for acute AMI. The controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLIAC) trial was the largest study of its kind to demonstrate that stenting was associated with a better outcome than angioplasty alone in acute AMI patients\textsuperscript{41,42}. Namely, it was revealed that stents reduced the rate of clinical and angiographic stenosis by \(~50\%\) and led to the lowest event rates of any AMI trial to date (i.e. 30-day mortality, re-infarction, ischaemic target vessel revascularization (TVR), stroke). The main randomized trials evaluating the efficacy of PTCA versus stents are summarized in Table 7 below.
<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Results (Stents relative to PCTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADILLAC&lt;sup&gt;42&lt;/sup&gt;</td>
<td>2082</td>
<td>Less clinical/angiographic stenosis but no effect on death/AMI.</td>
</tr>
<tr>
<td>STOPAMI-2&lt;sup&gt;43&lt;/sup&gt;</td>
<td>162</td>
<td>Smaller infarct size, better myocardial salvage &amp; trend towards less death/AMI at 6 months.</td>
</tr>
<tr>
<td>STENTIM-2&lt;sup&gt;44&lt;/sup&gt;</td>
<td>211</td>
<td>Less angiographic re-stenosis (ARS) but no difference in procedural success, event free survival or TVR at 6 months.</td>
</tr>
<tr>
<td>FRESCO&lt;sup&gt;45&lt;/sup&gt;</td>
<td>150</td>
<td>Less major adverse cardiac events (MACE) &amp; ARS at 6 months.</td>
</tr>
<tr>
<td>STENT-PAMI&lt;sup&gt;46&lt;/sup&gt;</td>
<td>900</td>
<td>Less TIMI-3 flow, ischaemic TVR at 6-months/1 year, less ARS/MACE at 6 months but higher mortality at 1 year.</td>
</tr>
<tr>
<td>GRAMI&lt;sup&gt;47&lt;/sup&gt;</td>
<td>104</td>
<td>Less MACE</td>
</tr>
<tr>
<td>ZWOLLE&lt;sup&gt;48&lt;/sup&gt;</td>
<td>227</td>
<td>Less TVR &amp; MACE</td>
</tr>
<tr>
<td>PSAMMI&lt;sup&gt;49&lt;/sup&gt;</td>
<td>44</td>
<td>Reduction in MACE</td>
</tr>
<tr>
<td>PRISAM&lt;sup&gt;50&lt;/sup&gt;</td>
<td>110</td>
<td>Trend towards less TVR &amp; re-infarction</td>
</tr>
<tr>
<td>PASTA&lt;sup&gt;51&lt;/sup&gt;</td>
<td>136</td>
<td>Similar success rate reduced MACE &amp; less ARS at 6 months.</td>
</tr>
</tbody>
</table>

Table 7: Randomized Trials of Stenting vs. PTCA for STEMI. Adapted from Califf & Roe (ACS Essentials), 2010<sup>32</sup>. Results presented as stents relative to PCTA.
**Bare Metal versus Drug Eluting Stents**

Numerous randomized trials have highlighted that drug-eluting stents (DES), in comparison with bare metal stents (BMS), reduce recurrent ischaemia and re-intervention in patients with STEMI for PCI\textsuperscript{52, 53} (Table 8). However, there is still considerable controversy as to the relative benefits of BMS versus DES with some authors confirming a benefit of DES over BMS and not others. Sirolimus (SES) and paclitaxel drug eluting stents (PES) have led to dramatic reductions in restenosis compared with standard stents (<5% versus 20-30%). In a recent meta-analysis of both small and large clinical trials, DES proved superior to BMS in the treatment of STEMI patients\textsuperscript{54}. The role of these stents (i.e. BMS, DES) in comparison to PTCA for culprit lesions in relatively small (i.e.<2.5mm) diameter vessels as well as saphenous vein grafts requires further investigation and/or definition.
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Results (DES vs. BMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone GW et al</td>
<td>3006</td>
<td>PES vs. BMS</td>
<td>4.5% vs. 7.5%; TVR 5.8% vs. 8.7%</td>
</tr>
<tr>
<td>MULTISTRATEGY</td>
<td>745</td>
<td>SES vs. BMS</td>
<td>7.0% vs. 14.5% at 8 month follow up</td>
</tr>
<tr>
<td>BASKET-AMI</td>
<td>-</td>
<td>PES/SES vs. BMS</td>
<td>7.2% vs. 12.1%; driven by TVR 4.6% vs. 7.8%</td>
</tr>
<tr>
<td>HAAUMU-STENT</td>
<td>164</td>
<td>PES vs. BMS</td>
<td>0.26mm vs. 0.73mm; stenosis 24% vs. 34%</td>
</tr>
<tr>
<td>MISSION</td>
<td>310</td>
<td>SES vs. BMS</td>
<td>0.12mm vs. 0.68mm; TVR 5.1% vs. 13.3%</td>
</tr>
<tr>
<td>PASSION</td>
<td>619</td>
<td>PES vs. BMS</td>
<td>8.8% vs. 12.8%</td>
</tr>
<tr>
<td>SESAMI</td>
<td>320</td>
<td>SES vs. BMS</td>
<td>9.3% vs. 21.3%; TVR 5% vs. 13.1%; MACE 6.8% vs. 16.8%</td>
</tr>
<tr>
<td>TYPHOON</td>
<td>712</td>
<td>SES vs. BMS</td>
<td>7.3% vs., 14.3% due to TVR (5.6% vs. 13.4%)</td>
</tr>
</tbody>
</table>

Table 8: Drug Eluting Stents Versus Bare Metal Stents for STEMI. Adapted from Califf & Roe (ACS Essentials), 2010. *Results presented as DES relative to BMS.*
Door-to-Needle Time

A shorter time from symptom onset to treatment with thrombolytic therapy (Door-to-Needle or Door-to-Lytic) time has been repeatedly shown to reduce mortality in STEMI patients\textsuperscript{34, 36, 63}. The ACC/AHA recommends a timely Door-to-Needle (DTN) time of 30 minutes or less for the administration of thrombolytic therapy in patients with STEMI\textsuperscript{64}. Meeting this target is vital for patient’s outcomes, as it has been shown that mortality rates increase with further delays in DTN time\textsuperscript{65-67}. As a direct result of this, DTN has since been utilized as a quality of care indicator\textsuperscript{68}.

Pre-Hospital Thrombolysis

Early clinical trials in the administration of thrombolytic therapy proposed the concept that ‘time is muscle’ based on the fact that benefit from lytic therapy became less significant with time. Specifically, the greatest reduction in mortality appears to occur when the thrombolytic treatment is administered within the first 1-2 hours from initial pain onset. The myocardial infarction triage and intervention trial (MITI), clearly demonstrated that initiating treatment prior to arrival at hospital reduced the period from onset of symptoms to thrombolytic treatment on average by 33 minutes\textsuperscript{69}. 
Rescue PCI - ‘Drip & Ship’

The evidence base suggests that inpatient angiography represents the best management for the majority of thrombolised STEMI patients. If thrombolysis is unsuccessful, it is generally accepted that immediate rescue PCI is beneficial\textsuperscript{70}, ideally within 24 hours (‘drip and ship’). There have been four major randomized trials (2003-2005) that have showed reductions in primary endpoints of combined death, AMI and recurrent ischaemia as well as infarct size (SIAM-III\textsuperscript{71}, GRACIA-1\textsuperscript{72}, CAPITAL-AMI\textsuperscript{73} and LPLS\textsuperscript{74}). As a direct result of this evidence, the European Society of Cardiology (ESC) issued guidelines in 2005 which recommend routine coronary angiography within 24 hours and PCI, if available, in patients following successful thrombolysis\textsuperscript{75}.

Door-to-Balloon Time

Similarly to DTN described above, DTB is another time measurement in emergency cardiac care specifically in the treatment of STEMI. This time interval is initiated with the patient’s arrival to the hospital emergency department and ends when the catheter guide wire crosses the culprit lesion in the cardiac catheterisation laboratory. It has been shown to be an extremely important factor in the outcome STEMI patients receiving PCI\textsuperscript{76, 77}. Specifically, increased DTB times are associated with increased mortality, irrespective of the presentation being high risk or low risk.

Due to the known adage that ‘time is muscle’, delays in treating patients with STEMI should be immediate so as to reduce the likelihood and amount of muscle damage due to localized hypoxia. The ACC/AHA guidelines recommend a DTB
time of no more than 90 minutes. However, despite this recommendation, currently fewer than half of STEMI patients receive reperfusion with primary PCI within the guideline timeframe. In light of this, the DTB alliance advocated six key evidence-based strategies to reduce DTB times including early catheterisation laboratory activation and a pre-hospital 12 lead ECG. The concept of DTB in regards to gender differences is further explored in chapter four of this thesis.

*Adjunct Pharmacotherapies*

In addition to improved thrombolytic agents and regimens, several adjunctive antithrombotic therapies for STEMI have been developed that have the potential to improve patency, decrease re-occlusion rates, recurrent ischaemia, and ultimately improve safety. Such drugs include routine anti-platelet agents (aspirin, adenosine diphosphate (ADP) inhibitors, heparin, beta-blockers, ACE inhibitors, statins and nitrates) as well as platelet receptor antagonists such as glycoprotein IIb/IIIa inhibitors. The effect of administering these inhibitors, given as an adjunct to therapy with a thrombolytic agent, have been associated with more rapid and complete reperfusion in patients with AMI.
1.2.6.2 Current Controversies & Indications for Therapy in UA/NSTEMI

In both management strategies for UA and NSTEMI, the goal is to reduce the risk for future adverse cardiac events such as short-term death and non-fatal AMI. Accordingly, initial therapy for patients with UA/NSTEMI depends on the risk category on presentation to hospital. High-risk patients are best treated with an early invasive strategy, which can include coronary angiography and revascularisation (PCI or CABG) within 48 hours of initial presentation, in addition to a GP IIb/IIIa inhibitor. CABG is the preferred method of revascularisation, however efforts should be made to stabilize patients pharmacologically and if needed the insertion of an intra-aortic balloon pump. In addition, patients at intermediate risk are typically treated with antithrombin therapy with/without a GP IIb/IIIa inhibitor with either an early conservative or early invasive strategy. Lastly, low risk patients are treated medically with an early conservative approach, usually in the outpatient area or chest pain clinic (similar to patients with stable angina). Validated risk prediction scores in UA/NSTEMI include the TIMI risk score, which is useful in guiding management strategies in this patient cohort.

*TIMI Risk Score*

The Thrombolysis in Myocardial Infarction or TIMI risk score is a validated risk prediction measure, which assesses the risk of death and ischaemic events in patients experiencing UA/NSTEMI. This risk score integrates past coronary history, the frequency of symptoms, ECG findings as well as biomarker levels. Higher scores are linked with an increased risk of adverse events such as death, re-infarction or recurrent ischaemia. Patients with higher TIMI risk scores have previously been
shown to gain greater benefit from specific pharmalogic therapies (i.e. enoxaparin), platelet glycoprotein IIb/IIIa inhibitors as well as an early cardiac catherterisation\textsuperscript{84}.

\textit{Contraindication of Thrombolytic Therapy in UA/NSTEMI}

In patients with UA/NSTEMI, plaque stabilization to prevent progression of the disease is required. While thrombolytics like streptokinase benefit patients with STEMI, they have been shown to increase the risk of bleeding complications for those with UA/NSTEMI and thus are contraindicated in this subset of patients. The TIMI IIIA and IIIB trials were amongst the most all-inclusive clinical trials to evaluate the role of thrombolytic therapy in non-Q wave myocardial infarction and UA to date\textsuperscript{85, 86}. Within these trials, administration of tissue plasminogen activators (tPA) was associated with fatal and nonfatal AMI and severe intra-cerebral hemorrhagic events, thus available data strongly argue against the use of thrombolytic therapy in this sub-set of patients.

\textit{Early Invasive versus Early Conservative Approach}

Four major randomized trials of patients with UA/NSTEMI have compared the early invasive management versus early conservative approach and are summarized in Table 9. In brief, early trials such as TIMI-3B\textsuperscript{86} and VANQWISH\textsuperscript{87} showed no difference of increased risk or death or AMI with early invasive management, however these trials were performed prior to the availability of coronary stents and GP IIB/IIIa inhibitors which limits their relevance to clinical practice. In the FRISC-2 trial\textsuperscript{88}, at 1-2 years randomized patients assigned to the early invasive strategy had a lower incidence of death or AMI as well as less need for revascularization.
procedures. In the TACTICS-TIMI 18\textsuperscript{89} trial, it was shown that the primary endpoint for death, AMI or rehospitalisation at 6 months was reduced by 18% in the invasive group with the greatest benefit among high and intermediate risk patients (Table 9).

Thus, from the above evidence the ACC/AHA and ESC guidelines recommend an early invasive strategy for patients presenting with UA/NSTEMI without life-threatening symptoms but with high-risk features. Invasive management such as PCI significantly reduces the risk of 30-day re-infarction and death and should be employed in this patient subgroup. Conversely, the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial\textsuperscript{90} compared an early invasive with a selective invasive strategy in patients with UA/NSTEMI and positive troponin T and showed no benefit of an invasive approach for composite of death, AMI or rehospitalization for anginal symptoms at 1 and 3 year follow up\textsuperscript{90, 91}. For those patients stabilized on medical treatment, a Class IIb recommendation was included in the ACC/AHA guidelines.
<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Invasive vs. Conservative Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI-3B&lt;sup&gt;86&lt;/sup&gt;</td>
<td>1473</td>
<td>Hospital death (2.4% vs. 2.5%), AMI (5.1% vs. 5.7%), length of stay (LOS) (10.2 days vs. 10.9 days) 6-week death (2.5% vs. 2.4%) 6 week AMI (5.7% vs. 5.1%)</td>
</tr>
<tr>
<td>VANQWISH&lt;sup&gt;87&lt;/sup&gt;</td>
<td>920</td>
<td>Hospital death (4.5% vs. 1.3%), Death/AMI (7.8% vs. 3.3%) 1-year death (12.6% vs. 7.9%) 1-year death/AMI (24% vs. 18.6%)</td>
</tr>
<tr>
<td>FRISC-II&lt;sup&gt;88&lt;/sup&gt;</td>
<td>2457</td>
<td>1-year death (2.2% vs. 3.9%) AMI (8.6% vs. 11.6%) Death/AMI (10.4% vs. 14.1%) 2-year death (3.7% vs. 5.4%) 2-year AMI (9.2% vs. 12.7%) 2-year death/AMI (12.1% vs. 16.3%)</td>
</tr>
<tr>
<td>TACTICS-TIMI&lt;sup&gt;18&lt;/sup&gt;</td>
<td>2220</td>
<td>6-month death/AMI or re-admission for ACS (15.9% vs. 19.4%) 6-month death/AMI (7.3% vs. 9.5%)</td>
</tr>
<tr>
<td>ISAR-COOL&lt;sup&gt;92&lt;/sup&gt;</td>
<td>410</td>
<td>Large AMI or death at 30-days (5.9% vs. 11.6%)</td>
</tr>
<tr>
<td>RITA-3&lt;sup&gt;93&lt;/sup&gt;</td>
<td>1810</td>
<td>Death/AMI or refractory angina at 4 months (9.6% vs. 14.5%)</td>
</tr>
</tbody>
</table>

Table 9: Early Invasive versus Early Conservative Approach to UA/NSTEMI

Adapted from Califf & Roe (ACS Essentials), 2010<sup>32</sup>. Results presented as stents relative to PCTA.
Anti-Platelet Therapy

The ‘cornerstone’ medical therapy for patients with UA/NSTEMI is primarily the use of anti-platelet drugs which aim at stabilising the underlying partially occlusive coronary thrombus\textsuperscript{20}. Three classes of antiplatelet agents have significant roles in the management of UA/NSTEMI including: aspirin, thienopyridines, and platelet glycoprotein IIb/IIIa inhibitors.

\textit{Aspirin & Clopidogrel}

Aspirin is one of the most important interventions to reduce mortality in patients with UA/NSTEMI. This drug inhibits platelet synthesis of thromboxane A\textsubscript{2} and is a potent mediator of platelet inactivation. Aspirin has been shown to reduce cardiovascular events by 50-70\%\textsuperscript{94}. This is administered immediately on presentation and continued indefinitely in patients without contraindication.

The combination of aspirin plus thienopyridines (i.e. clopidogrel) significantly reduces cardiac events or stroke in patients with UA/NSTEMI. The role of dual anti-platelet therapy (i.e. aspirin and clopidogrel) was evaluated in the CURE trial\textsuperscript{95}. As shown in Table 10, clopidogrel resulted in a highly significant 20% reduction in the primary composite endpoint of cardiovascular death, AMI or stroke. These benefits were observed for patients treated by medical therapy alone or revascularisation (PCI or CABG)\textsuperscript{95}. Based on the above CURE trial, clopidogrel should be added to aspirin on admission and continued for at least 9-12 months for patients with UA/NSTEMI for whom a ‘non-interventional’ approach is planned.
<table>
<thead>
<tr>
<th>Endpoint (average 9 months)</th>
<th>Aspirin (n=6303)</th>
<th>Aspirin + Clopidogrel (n=6259)</th>
<th>Risk ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, AMI or stroke</td>
<td>11.5%</td>
<td>9.3%</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, AMI, stroke, or refractory ischemia</td>
<td>19.0%</td>
<td>16.7%</td>
<td>0.88</td>
<td>0.004</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.7%</td>
<td>3.6%</td>
<td>1.34</td>
<td>0.003</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>8.6%</td>
<td>15.3%</td>
<td>1.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 10: Dual Anti-platelet Therapy for NSTE-ACS** Adapted from Califf & Roe (ACS Essentials), 2010\textsuperscript{32}.

**Prasugrel**

Prasugrel is a novel thienopyrdine ADP receptor antagonist that is utilized in treatment of moderate to high-risk ACS patients who are managed with PCI. Results from the TRITON-TIMI 38 study\textsuperscript{96}, comparing prasugrel and clopidogrel revealed that the primary composite endpoint (death, non-fatal AMI or stroke), TVR and stent thrombosis rates were significantly reduced in patients receiving prasugrel. Despite its advantages, this drug was also linked to higher rates of major bleeding. Sub-groups most affected by the bleeding included those with a prior TIA/stroke, older age (≥75 years) and lower body weight (<60 kg).

**Ticagrelor**

The PLATO-ACS trial is a large study, which evaluated the effect of Ticagrelor, an oral direct-acting P2Y\textsubscript{12} platelet aggregation inhibitor, on clinical outcomes in
patients with UA/NSTEMI⁹⁷. Results from this study indicated that treatment of ACS with ticagrelor as compared with clopidogrel, significantly reduced the rate of mortality from vascular causes and AMI. Specifically, the composite end point of death and vascular causes at 12 months was 9.8% in patients receiving ticagrelor and 11.7% in those receiving clopidogrel⁹⁷.

**GP IIb/IIIa Inhibitors**

Data available support the routine use of anti-platelet GP IIb/IIIa inhibitors (i.e. abciximab, tirofiban) in UA/NSTEMI patients being treated with PCI. These classes of drugs are administered prior to or during the PCI procedure with an infusion continuously monitored for 12-18 hours following PCI. As adjuncts to aspirin, heparin and beta-blockers, these type of inhibitors reduce the risk of major adverse cardiac events after PCI by 30-40%. More specifically, results from the PRISM-PLUS⁹⁸ and CAPTURE⁹⁹ trials comparing abciximab and tirofiban revealed that pre-interventional administration of GP IIb/IIIa inhibitors reduce the risk of AMI prior to PCI by up to 70%.

**Un-fractionated Heparin vs. Low Molecular Weight Heparin**

Enoxoparin, a low molecular weight heparin, is recommended in conjunction with aspirin, clopidogrel and GP IIb/IIIa inhibitors for primary medical management of patients with UA/NSTEMI. It has the clinical advantage over unfractionated heparin in producing reliable therapeutic anticoagulation so that coagulation monitoring is not required. Results from a meta-analysis of two randomized trials (ESSENCE, TIMI IIb) comparing Enoxoparin and unfractionated heparin (UFH) highlighted a
20% reduction in the composite endpoint of death or AMI at 30 days as well as at 12% at 1 year in favour of enoxoparin\textsuperscript{100}.

*Adjunct Pharmacotherapies*

As in the case for STEMI, adjunct AMI therapies available in UA/NSTEMI include the administration of routine anti-platelet agents as described above (aspirin, adenosine diphosphatase (ADP) inhibitors, heparin, beta-blockers, ACE inhibitors, statins and nitrates). Anti-ischaemia therapies available and commonly utilized include nitrates and non-dihydropyridine calcium channel blockers.

Again, for a more detailed discussion of the current STEMI and UA/NSTEMI therapies and treatment modalities please refer to the latest ACC/AHA guidelines\textsuperscript{30, 31}.
1.2.7 Chronic Coronary Syndromes

1.2.7.1 Angina Pectoris

Angina pectoris derives from the Latin word *angore*, meaning choking and suffocation and also anxiety, fear or terror. Angina was recognised in the Middle Ages, however the first clinical description by William Heberden is far better known. In his 1772 publication entitled ‘Some account of a disorder of the breast’\(^{101}\), it refers to a strangling sensation, which usually occurs on exertion, however patients may experience angina without physical activity whereupon it is referred to as rest angina\(^{102}\).

‘Angina’ may then be used in a more generic context, referring to any CHD syndrome that results in myocardial ischaemia without necrosis and is further qualified by its precipitating factors, time course to relief and clinical characteristics, such as radiation and quality. The clinical presentation of angina can be highly variable and forms a spectrum of syndromes, which are summarized in Table 11 below. Of these, Prinzmetal angina and syndrome X warrant further discussion and are summarized in section 1.2.8. Importantly, these angina syndromes may have different coronary pathophysiological mechanisms responsible for initiating the myocardial ischaemia, including coronary artery spasm and microvascular dysfunction. They may manifest as exertional or rest angina, depending upon the underlying mechanism.
1.2.7.2 Chronic Stable Angina

Despite these diverse implications for the term ‘angina’, it is most commonly used to refer to patients with CSA. Although the initial description of exertional angina by Heberden still holds true today, a more operational version has been detailed by the American College of Physicians\textsuperscript{103}. As summarised in Table 12, this definition describes angina as either ‘typical’ or ‘atypical’ on the foundation of how many of the clinical features are consistent with exertional angina. In those patients with features of typical angina, the sensitivity and specificity for detecting significant coronary artery disease on angiography is respectively 91\% and 87\% in males, and correspondingly 89\% and 63\% in females\textsuperscript{104}.

Pathophysiology of Stable Angina

Chronic stable angina is most often caused by fixed, obstructive atheromatous plaque in one or more coronary arteries (whereby obstructive lesions are defined as stenoses $\geq 50\%$ of the diameter of a major epicardial vessel). Although by convention an obstructive coronary artery lesion is typically defined as $\geq 50\%$ stenosis, coronary haemodynamic studies have verified that the lesion must be $\geq 70\%$ before maximal (hyperaemic) blood flow is impaired and $\geq 90\%$ before resting blood flow is impaired\textsuperscript{105}. Precipitating circumstances may remain analogous between anginal episodes and patients may predict thresholds with relief patterns known to occur.

The pattern of symptoms is usually related to the degree of stenosis with narrowing in a coronary artery lumen diameter by more than 70\% insufficient to compensate
for any significant increase in oxygen demand (i.e. during physical exertion). When oxygen demand exceeds available supply, myocardial ischaemia results in chest discomfort known as angina pectoris (as described above)\textsuperscript{106}. The ischaemia and chest symptoms persist until the increased demand is alleviated and oxygen balance is restored.

Stable angina may limit the patient’s physical capacity and thus quality of life, however they may have a lower risk of cardiac events when compared to those with ACS (i.e. STEMI, UA/NSTEMI). For the remainder of this thesis, the data presented concerning ‘angina’ will predominantly focus on patients with CSA (defined as a pattern of chronic, predictable, transient angina during exertion or emotional stress).
### Table 11. Clinical Forms of Angina

<table>
<thead>
<tr>
<th>Angina Syndrome</th>
<th>Clinical Features</th>
</tr>
</thead>
</table>
| **Unstable Angina**              | • Characterised by crescendo or rest angina  
• An acute coronary syndrome manifestation (may progress on to myocardial infarction)  
• Typically due to an unstable atherosclerotic plaque  |
| **Stable Angina**                | • Characterised by exertional angina  
• Typically due to a stable but tight obstructive coronary artery stenosis  |
| **Prinzmetal Variant Angina**    | • Characterised by rest or nocturnal angina  
• Typically due to coronary artery spasm  |
| **Decubitus Angina**             | • Characterised by angina when lying down  
• Typically due to left ventricular dysfunction resulting in redistribution of pulmonary fluids and thus increased cardiac workload.  |
| **Silent Ischaemia**             | • Absence of angina in the presence of documented ischaemia  
• May occur with coronary artery or microvascular dysfunction  |
| **Syndrome X**                   | • Includes classical syndrome X, microvascular angina, coronary slow flow phenomenon  
• Characterised by prolonged episodes of exertional or rest angina  
• Typically due to coronary microvascular dysfunction  |

### Chest Pain Features

1. **Substernal chest discomfort** – characteristic quality (tightness) & duration (minutes)  
2. **Provoking Factors** – exertion or emotional stress  
3. **Relieving Factors** – rest or sublingual nitrates

**ACP Classification:**  
- **Typical Angina** – all 3 of above criteria met.  
- **Atypical Angina** – only 2 of above criteria  
- **Non-cardiac Chest Pain** – only 1 of above criteria

### Table 12. American College of Physicians (ACP) Angina Pectoris Definition.

Adapted from Diamond et al, J Am Coll Cardiol, 1983.103
1.2.8 Clinical Mangement of CSA

1.2.8.1 Current Controversies & Indications for Therapy in CSA

The management of CSA includes eliminating and/or controlling coronary risk factors, implementing specific lifestyle changes to reduce the risk of atherosclerotic coronary disease as well as controlling precipitating factors or prescribing appropriate anti-ischaemic therapy\(^\text{106}\). Except for a minute subset of patients with angina whose survival is improved with CABG, stable angina patients can be appropriately managed with medical therapy with the goal of eliminating ischaemia, reducing the frequency of anginal attacks, preventing AMI and improving long term survival.

Treatment usually consists of aspirin, beta-adrenergic blockers, cholesterol-lowering agents and other anti-ischaemic drugs that can ameliorate angina and essentially improve the patient's quality of life, which is particularly important in this subset of patients. For a detailed discussion of current CSA therapies and treatment modalities please refer to the latest ACC/AHA\(^\text{107, 108}\) and ESC guidelines\(^\text{109}\). These therapies will be discussed in brief below.

*Medical Therapy for Stable Angina*

In order to prevent the onset of an acute episode of angina, pharmacological agents such as organic nitrates, beta-blockers and calcium channel blockers are utilized with the goal of increasing cardiac workload of the heart and to increase myocardial perfusion\(^\text{107, 110}\).
**Organic Nitrates**

These classes of drugs relieve ischaemia, primarily through vascular smooth muscle relaxation (vasodilatation) thereby augmenting coronary blood flow and thus helping to restore oxygen balance. Organic nitrates, particularly in its sublingual or intravenous form, are effective for immediate relief of angina or may be used as a prophylactic measure before the patient begins an activity that typically precipitates angina. Long-acting nitrates are used as maintenance medications for the prevention of angina.

**Beta-blockers**

Previous meta-analyses have highlighted that beta-blockers are in fact more effective in reducing angina burden compared to calcium channel blockers, however the effects of exercise tolerance and ischaemia are similar\(^\text{107, 111, 112}\). This class of drugs exerts their therapeutic benefit by blocking beta-1 receptors on myocardial cells. Inhibition of these beta-receptors on the myocardium decreases both the force of contraction and the heart rate, especially during exercise, leading to a decrease in myocardial oxygen demand. As the heart rate slows, the diastolic period is prolonged, enabling increased oxygen delivery by improving myocardial perfusion.

**Calcium Channel Blockers**

Calcium channel blockers belong to a diverse group of compounds that block calcium entry into the myocardial and smooth muscle cells, thereby causing relaxation and vascular dilatation. A select group of calcium channel blockers (i.e.
verapamil and diltiazem) also exert an inhibitory effect on the sinus and atrioventricular nodes, causing the heart rate to slow.

In addition to anti-ischaemic benefits, management with the above medications may aid in reducing the progression of atherosclerosis and stabilize plaques in patients with stable angina. The use of anti-platelet therapy, particularly the use of aspirin has been shown to reduce cardiovascular morbidity and mortality by up to 32%\textsuperscript{113}. Even if asymptomatic or not, beta-blockers and aspirin are recommended in patients with a previous AMI\textsuperscript{107}. Statins not only reduce pathogenetic lipid levels but have also been shown to reduce coronary events and mortality by up to 30% in a population of CSA patients\textsuperscript{114}.

Lifestyle Modifications

In patients with CSA, particular attention should be owed to the elements of lifestyle that may have previously contributed to the condition and may influence prognosis. This includes modifiable factors such as physical activity, smoking cessation and dietary habits. In terms of treatment, the recommendations of the 3\textsuperscript{rd} Joint European Societies Task Force on CVD prevention in Clinical Practice should be adhered to\textsuperscript{115}.

CSA Reperfusion Delivery Strategies

Revascularisation Therapies for CSA have come under considerable scrutiny in recent years. Results from the landmark CASS study (coronary artery surgery study registry) revealed that CABG acts better than medical therapy for patients with
combined proximal left anterior descending and proximal left circumflex or ‘left main equivalent’\textsuperscript{116}. Specifically, the five-year survival rates of patients who received surgical versus medical therapy were 85% and 55%, respectively, with improved survival remaining significant following adjustment of baseline variables known to influence prognosis. Despite its implications contemporary medical therapy was not employed in this early study.

The COURAGE trial\textsuperscript{117} has had a major influence on contemporary cardiology practice when it demonstrated no additional benefit in preventing myocardial infarction/death in patients with stable angina by the use of coronary stenting as compared with optimal medical therapy alone; this was evident in patients with multi-vessel disease.

1.2.9 Other Coronary Syndromes

1.2.9.1 Prinzmetal Angina

Prinzmetal or otherwise known as variant angina is a condition, which typically consists of angina at rest and occurs in cyclically, manifest as episodes of vasospasm in the absence of obstructive atherosclerotic lesions. This disorder was first pioneered in 1959 by Prinzmetal and colleagues\textsuperscript{118} who reported a subgroup of patients presenting with chest pain with no physical exertion. In addition, Maseri and colleagues\textsuperscript{119} undertook a study highlighting that coronary vasospasm was a cause of myocardial ischaemia in many coronary disorders.
In 1976, the underlying pathophysiology of Prinzmetal angina was shown to be coronary spasm\textsuperscript{120}. This can be visualized by catheterisation by provocation testing using endothelium dependent vasodilators (i.e. acetylcholine), which can induce coronary artery spasm and thus angiography, ECG as well as clinical responses can be observed. The clinical presentation with patients presenting with Prinzmetal angina includes transient ST elevation in association with transient acute myocardial ischaemia, which is initially indistinguishable from transmural myocardial ischaemia\textsuperscript{119}. The prognosis of patients with coronary spasm or near normal coronary arteries is favorable as calcium channel blockers diminish the effect of vasospasm. Prinzmetal angina is especially prevalent in non-Caucasian populations but particularly in the Japanese cohort\textsuperscript{121}. Specifically, only 2-3\% of Caucasian patients with chest pain undergoing angiography were diagnosed with Prinzmetal angina\textsuperscript{122}.

1.2.9.2 Cardiac Syndrome X

This disorder was first described in 1973 by Arbogast and colleagues\textsuperscript{123}, who performed atrial pacing in patients with obstructive CAD (control) and those with angina but normal angiography (group X). The group demonstrated that both groups had ECG and transmyocardial lactate evidence of myocardial ischaemia. Group X was then referred to as “cardiac syndrome X”, which is now a term used to refer to a particular cohort of patients with typical symptoms of angina pectoris with no evidence of obstructive atherosclerotic disease. Furthermore, some of these patients may show characteristic signs of ischaemia during exercise testing\textsuperscript{106}.
In this condition the pathogenesis of ischaemia may be due to inadequate vasodilator reserve of the coronary resistance vessels. These resistance vessels (too minute to be viewed in angiography) may not dilate appropriately during periods of increased myocardial oxygen demand. Other factors contributing to this syndrome include micro-vascular dysfunction, vasospasm and hypersensitive pain perception. Patients with cardiac syndrome X have a low risk of developing a cardiac event\textsuperscript{124}, however due to persistent chest pain this may induce adverse psychosocial effects and thus impair a patient’s quality of life\textsuperscript{125, 126}.

The discussion of the treatment of Prinzmetal angina and syndrome X are extensive and thus beyond the scope of this thesis. Readers should refer to the most recent ACC/AHA\textsuperscript{107, 108} and ESC guidelines\textsuperscript{109}. 

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1.3 Peripheral Artery Disease

1.3.1 Definition of Peripheral Artery Disease

Despite ongoing awareness campaigns to improve secondary prevention and optimization of treatment in vascular diseases\textsuperscript{127, 128}, PAD is still an unrecognized condition, which has not been prioritized by these programs\textsuperscript{129}. Peripheral artery disease generally refers to diseases of arteries outside the heart and brain. For the purposes of this thesis, it refers to atherosclerotic disease in the arteries of the lower limbs\textsuperscript{130, 131}. Peripheral artery disease results from processes that can be grouped into three categories including (a) structural alterations within the vessel wall (leading to dilation, aneurysm development, dissection/rupture of a conduit artery), (b) vascular lumen narrowing resulting from atherosclerosis, thrombosis or inflammation; and (c) vascular smooth muscle spasm\textsuperscript{132}. These latter processes may essentially lead to embolism, stenosis or thrombus formation that can cause acute or chronic ischaemia (similar to CHD).

The remainder of this thesis will focus strictly on occlusive arterial diseases rather than disease causing large arterial spasm (i.e. raynauds phenomenon), diseases of the aorta (i.e. aortic aneurysms/ dissection) and/or venous disease (i.e. varicose veins). Since PAD involves the same underlying pathological process as coronary and cerebral atherosclerosis, it is associated with the same cardiovascular risk factors and events\textsuperscript{133}. In fact, the major cause of death in people with PAD is CHD, reflecting the generalised nature of the disease process\textsuperscript{134}. 
1.3.2 Epidemiology of Peripheral Artery Disease

In the general population, the age-adjusted prevalence of patients with PAD is approximately 12% (based upon ABI screening) and may exceed 20% in those 70 years or older\textsuperscript{134-136}. Although there are no national data available on the number of Australian’s that have PAD, a study published in 2002 demonstrated an age-standardized prevalence of 16% among men between the ages of 65-83 years living in Western Australia\textsuperscript{137}.

In 2007 the mortality rate in Australia from PAD was responsible for 2,160 deaths (1.6% total deaths, 4.6% CVD deaths)\textsuperscript{8}. In the same year, the age-standardised death rate for PAD was higher among males (12 per 100,000 population) than females (7 per 100,000), particularly amongst those aged over 65 years. Of those individuals affected with PAD 70%-80% are asymptomatic with only a minority ever requiring revascularisation or amputation. In terms of symptomatic disease, 10%-30% of patients with PAD have intermittent claudication (IC). Overall, the estimated prevalence of claudication ranges from 1.0%-4.5% of a population older than 40 years\textsuperscript{134, 138}.

Both the prevalence and incidence of claudication increase with age and are greater in men than in women in most studies\textsuperscript{134, 136, 139}. Peripheral artery disease patients frequently have generalised atherosclerotic vascular disease since as many as 85% may be angiographic evidence of CHD and 60% have carotid artery disease\textsuperscript{135}.

As mentioned, since the underlying pathology of PAD is similar to that of CHD, these two conditions share the major atherosclerotic risk factors (e.g. hypertension, diabetes, dyslipidemia) as outlined in section 1.1.3 of this thesis. Thus not
surprisingly, PAD patients are at a high risk of cardiovascular events with 20-60% increase risk of AMI, 2-6 fold increase risk of CHD death and a 4-5 fold increase risk of stroke\textsuperscript{138}. The overall mortality rate for PAD is 4-6%\textsuperscript{138}. Furthermore, PAD prevalence is greater in certain minority groups such as African American and Hispanics\textsuperscript{140,141}.

1.3.3 Peripheral Artery Disease Classification

Peripheral artery disease ranges from asymptomatic disease, through pain on walking (intermittent claudication), to pain at rest and limb-threatening reduced blood supply that can lead to amputation. Peripheral artery disease is frequently divided in the Fontaine stages, introduced by the infamous René Fontaine in 1954 for ischaemia\textsuperscript{134}. These include (a) mild pain when walking/ incomplete blood vessel obstruction, (b) severe pain when walking short distances, (c) pain while resting (rest pain) and (d) biological tissue loss (gangrene). A more contemporary classification by Rutherford consists of three grades and six categories including the following: (1) mild claudication, (2) moderate claudication, (3) severe claudication, (4) ischaemic pain at rest, (5) minor tissue loss and (d) major tissue loss\textsuperscript{134}.

1.3.4 Pathophysiological Mechanisms of PAD

The pathophysiology of PAD is similar to that of atherosclerotic CHD. However, in patients with lower extremity vascular disease it is important to take into account both (a) the balance of circulatory supply of nutrients to the skeletal muscle and (b) the oxygen/nutrient demand of the skeletal muscle (Table 13)\textsuperscript{132}. Two of the main
clinical manifestations of PAD (claudication and critical limb ischemia) are discussed in brief below.

1.3.4.1 Intermittent Claudication

As mentioned above, the most common clinical manifestation of PAD is IC; this process is known to occur when the skeletal muscle oxygen demand during exercise exceeds blood oxygen supply. This typically results from the activation of local sensory receptors via a buildup of lactate and/or other metabolites. Patients suffering from IC may have single or multiple occlusive lesions in the arteries supplying the limb and therefore these obstructive lesions limit blood flow and oxygen delivery, fundamentally leading to ischaemia\textsuperscript{132}.

1.3.4.2 Critical Limb Ischaemia

Patients with critical limb ischemia (CLI) typically have multiple occlusive lesions that frequently affect proximal and distal limb arteries. As a result of this, the resting blood supply is diminished and cannot satisfy metabolic requirements of the limb. This may then progress to tissue necrosis and gangrene where amputation may be required\textsuperscript{132}.

In addition to haemodynamic changes associated in patients with PAD, alterations in muscle structure and function also contribute substantially to the dramatic reduction in exercise capacity. One likely change is the ‘dropout’ of muscle fibers (thought to occur as an adaptation to intermittent ischaemia). This loss of vital
muscle fibers can explain the reduced muscle strength and atrophy in this subset of patients. Taken together, these physical and biochemical changes result in weak lower limbs that suffer ischaemic discomfort during exercise\textsuperscript{142}.

### Factors Regulating Blood Supply to Limb

- Flow-limiting lesion (stenosis severity, inadequate collateral vessels)
- Impaired vasodilation (decreased nitric oxide and reduced responsiveness to vasodilators)
- Accentuated vasoconstriction (thromboxane, serotonin, angiotensin II, endothelin, norepinephrine)
- Abnormal rheology (reduced red blood cell deformability, increased leukocyte adhesivity, platelet aggregation, microthrombosis, increased fibrinogen)

### Altered Skeletal Muscle Structure and Function

- Axonal denervation of skeletal muscle
- Loss of type II, glycolytic fast-twitch fibers
- Impaired mitochondrial enzymatic activity

**Table 13: Pathophysiologic Considerations in Peripheral Artery Disease.**

Adapted from Creager and Libby (Braunwald’s Heart Disease), 2011\textsuperscript{132}.

#### 1.3.5 Clinical Diagnosis of Peripheral Artery Disease

Peripheral artery disease is a condition, which may affect the aorta, iliac, femoral, popliteal or tibioperoneal arteries. As a result patients may develop buttock, thigh or calf discomfort, which is generally precipitated by walking and relieved by rest. Many patients with PAD are indeed asymptomatic, however the most frequent clinical manifestation is leg pain, with IC (classic symptom of exertional limb fatigue) occurring in 35%, atypical leg pain in 40% and 10% experiencing CLI\textsuperscript{138} (as described in section 1.3.4.2). The chronically reduced blood flow in these patients predisposes their extremities to infection, ulceration and skin necrosis. Patients who
have diabetes or who smoke are at a higher risk of developing these complications\textsuperscript{142}.

1.3.5.1 Ankle Brachial Index

In the evaluation of PAD, it is common practice to measure the ratio of systolic blood pressure in the ankles to that of the arms using a blood pressure cuff and Doppler instrument, a technique known as the ankle-brachial index (ABI). A normal ABI is $\geq 1.0$ with an index of $\leq 0.9$ considered diagnostic of PAD\textsuperscript{134}. This may be associated with symptoms of claudication, whereas and index of $<0.5$ is often observed in patients with rest pain and severe arterial compromise of the affected extremity.

Considering the relationship between PAD and CHD described above, it is not surprising that ABI is a strong predictor of cardiovascular events\textsuperscript{143}. An ABI $\geq 1.4$ is also considered pathological, as it may be attributable to calcified non-compressible conduit vessels in the ABI assessment therefore producing the high ratio. This high ABI value has also been associated with increased cardiovascular events\textsuperscript{144} and impaired quality of life\textsuperscript{145}. Nevertheless, in the context of an individual patient and diagnosing the presence of obstructive PAD, an ABI $>1.4$ may not be diagnostic and thus alternative diagnostic modalities are required including toe perfusion pressure or arterial duplex ultrasound imaging\textsuperscript{134, 146}.
1.3.5.2 CT Angiography & Duplex Ultrasound

Other gold standard measures to assess PAD include CT angiography with a stenotic lesion >50% being diagnostic for the condition. In addition, bilateral arterial leg duplex ultrasound scans provide an accurate, non-invasive assessment of PAD without the use of x-ray radiation.

For further details on management of patients with PAD please refer to the Inter-society consensus for the management of PAD (TASC II) guidelines\textsuperscript{134} and the most recent ACC/AHA PAD guidelines\textsuperscript{138}.

1.3.6 Health Outcomes in PAD Patients

Asides from their increased cardiovascular risk burden, patients with PAD have a diminished health status\textsuperscript{147, 148}, even following revascularisation therapies\textsuperscript{149}. Unfortunately, information regarding PAD patient’s health status is under-documented as compared with other vascular disorders and despite recommendations in the latest guidelines there is currently no gold standard to measure PAD patient’s disease specific health status\textsuperscript{134, 150}.

Patient reported outcomes (i.e. involving the patient’s perspective of the disease, their health status/quality of life) are becoming increasingly important in evaluating treatment and care for patients, particularly in this vulnerable cohort (see section 2.1.4.1 on health status)\textsuperscript{147}. Since the majority of patients with PAD (>70%) survive greater than 5 years following initial presentation, surviving patients often have to
cope with the consequences of this chronic disease\textsuperscript{150} and thus it is imperative to measure their symptoms, daily functioning and quality of life.

A further important omission in the literature for PAD is the study of vulnerable subgroups such as those from different racial and gender groups, socio-economic differences and psychological backgrounds. In light of these disparities in care the PORTRAIT study was initiated (Patient-centered Outcomes Related to Treatment practices in peripheral Arterial disease: an International Trajectory) (See Ancillary projects coordinated). This is the first large prospective international multi-centre registry to focus on patients with PAD. Specifically, the study aims to (a) document treatment practices in the way care for PAD is organized, (b) identify high-risk subpopulations in terms of their PAD care and outcomes, (c) study the impact of identified differences in PAD care on health status, and (d) relate differences in PAD care practices with outcomes.

1.3.7 Prognosis and Risk of Cardiovascular events

As mentioned above, patients with PAD face substantial disparities in health outcomes in comparison to other cardiovascular risk groups\textsuperscript{133, 151}. Part of the ‘worse’ outcomes for PAD patients is partially explained by the fact that they do not achieve cardiovascular risk factor control as compared with other vascular diseases\textsuperscript{151}. As a result these PAD patients have high event rates and costs associated with this disease, which translates into a high economic and societal burden as compared with other atherosclerotic risk groups\textsuperscript{152}.  

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Patients with PAD have an increased risk for adverse cardiovascular events, risk of limb loss and impaired quality of life\textsuperscript{133, 139, 153}. In addition, patients with PAD often have related CHD and CVB\textsuperscript{134, 139}, which has been observed in several main clinical trials\textsuperscript{154, 155}. The relative prevalence of each of these disease states is dependent on the diagnostic criteria used to establish patient’s diagnosis. For example, patients with abnormal ABI’s are 2-4 times more likely than those with normal ABI’s to have a history of angina, AMI, congestive heart failure, or cerebrovascular ischaemia\textsuperscript{134, 139}.

Significant CAD on angiography occurs in approximately 60% to 80% of patients with PAD, and 15% to 25% of patients with PAD have significant carotid artery stenoses as detected by duplex ultrasonography. The specificity of an abnormal ABI to predict future cardiovascular events at 6-10 years is approximately 90\%\textsuperscript{156}. The risk of death from cardiovascular causes increases 2.5- to 6-fold in patients with PAD, and their annual mortality rate is 4.3\% to 4.9\%. Furthermore, the risk of death is greatest in those with the most severe PAD such as CLI. Approximately 25\% of patients with CLI die within 1 year, and the 1-year mortality rate among patients who have undergone amputation for PAD may be as high as 45\%\textsuperscript{134}. Both smoking and diabetes mellitus independently predict progression of disease. The risk of amputation in those with diabetes mellitus is at least 12-fold higher than in non-diabetic persons\textsuperscript{157}.

1.3.8 Clinical Management of PAD

The first line of treatment for all patients with PAD is to reduce cardiovascular morbidity and mortality as well as to improve quality of life\textsuperscript{134}. This is achieved by
(a) decreasing symptoms of IC, (b) eliminating pain at rest and (c) preserving limb viability.

Therapeutic considerations include risk factor modification (i.e. smoking cessation) and pharmacologic treatment (i.e. lipid lowering and control of diabetes and hypertension). Patients with PAD are prescribed anti-platelet therapy such as aspirin, which has been shown to reduce the likelihood of a cardiac event occurring (See section 1.2.6.2). In addition, a formal exercise program is considered first line therapy in the management of patients with PAD which has been shown to reduce symptoms of claudication by increasing metabolic efficiency in the skeletal muscle of the lower limbs\textsuperscript{146}.

Similarly to CHD, revascularisation strategies such as PCI or arterial bypass grafting are indicated if medical therapy has failed, such as in the case of CLI. Surgical procedures include bypass operations to circumvent the occluded arteries using saphenous vein or prosthetic graft. Amputation may be necessary if blood flow cannot be established to maintain limb viability\textsuperscript{142}.

For a full perspective on the current treatment modalities in the management of patients with PAD please refer to the most recent TASC-II\textsuperscript{134} and ACC/AHA guidelines\textsuperscript{138}.
1.4 Gender Disparities in Vascular Syndromes

1.4.1 Sex versus Gender Distinction

As this thesis is primarily based on assessing disparities between men and women it is important to first make distinctions between “sex” and “gender” and to define the use of the word ‘disparity’. In 2001, the Institute of Medicine endorsed this distinction and clarified the use of these terms:

“Sex is defined as the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement”\(^{158}\).

“Gender is defined as a person's self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual's gender presentation. Gender is rooted in biology and shaped by environment and experience”\(^{158}\).

In the context of this thesis, the term ‘gender’ will be referred to in chapter three, four and six as a more appropriate expression since we will be evaluating differences due to socialisation experiences (i.e. quality of life). Conversely, in chapter five the term ‘sex’ will be used as we will be referring to a biological endpoint (i.e. haemodynamics).

Furthermore, the Institute of Medicine defines the word disparity as “a difference in treatment provided to members of gender, ethnic or racial groups that is not justified by health condition differences or treatment preferences”\(^{159}\).
1.4.2 Definition of Female Pattern Heart Disease

In this thesis we refer to women having ‘female pattern ischaemic heart disease’ (IHD), which refers to their microvascular coronary dysfunction (MCD) (See sections 1.4.9.2 & 1.4.11.5). This is a novel phenotype hypothesised by Professor Bairey Merz and colleagues following the observation that women have an increased prevalence of angina yet have lower rates of obstructive CAD\textsuperscript{160-162}. In brief, symptomatic women undergoing coronary angiography have less extensive and severe obstructive CAD, despite being older and having a higher risk factor burden than men. Despite this less obstructive CAD, women have a more adverse prognosis compared with their male counterparts. This ‘female pattern disease’ is not easily recognised given that male pattern strategies are aimed at detection and treatment of obstructive CAD\textsuperscript{163}.

1.4.3 The Yentyl Syndrome: ‘Alive and Well in 2012’

Previous literature insinuates that when women share similar characteristics to men (i.e. with male-pattern obstructive CAD as described above), they are more likely to be diagnosed and treated like men\textsuperscript{164}. Yentyl was a 19\textsuperscript{th} century female character of Issac Bashevis Singer’s short story. In this narrative she had to disguise herself as a man to secure an education and study the Jewish Talmud. In light of this, the late Dr Bernadine Healy used the term the ‘Yentyl Syndrome\textsuperscript{164} to call attention to the concerning under treatment of women with IHD at the time as well as the adverse outcomes compared with men\textsuperscript{165,166}. In her 2001 article published in the New England Journal of Medicine, Healy wrote (noting that his was parallel to Yentyl in Issac Bashevis Singer’s short story):
“Once a woman showed that she was just like a man, by having severe coronary artery disease or a myocardial infarction, then she was treated as a man would be.”

More than ten years later, the Yentyl syndrome is ‘alive and well’ with the publication of numerous studies highlighting significant gender disparities. Specifically, Johnston and Bugiardini have recently confirmed the medical under treatment of women with ACS, including lower rates of prescribed cardio-protective agents and life saving revascularisation procedures (i.e. angiography, PCI, CABG) compared with men, findings which are consistent with the early literature.

In light of the above, the AHA/ACC have released specific guidelines, which now specify treatment strategies for women and have been particularly crucial in closing the gender gaps that have historically disadvantaged women. These include the (a) guidelines for the prevention of cardiovascular disease in women, (b) the management of patients with UA/NSTEMI Infarction and (c) the AHA ‘Get with the Guidelines’ and ACC ‘Guidelines Applied in Practice’ reports. Of particular concern, the gender disparity is not limited to coronary disease but extends to PAD. Consistent with the under recognition and treatment of PAD in women, the recent scientific statement from the AHA, issued a ‘call to action’ for more focused care and research that is sensitive to particular concerns women with PAD may be dealing with.

In light of the persistent gender gap in cardiovascular disease, this section will address the current gender based data available for women in regards to coronary (including
acute and chronic coronary syndromes) and peripheral artery disease. Specifically, it will address gender disparities in the main themes of (a) epidemiology, (b) risk factors, (c) clinical characteristics, (d) biological factors and (e) psychosocial characteristics.

### 1.4.4 Epidemiology of CHD in Women

Coronary heart disease is the most common cause of death amongst women in developed countries, responsible for nearly 250,000 deaths annually in the United States\(^{173}\). In 2008, CHD claimed the lives of 11,221 Australian women, corresponding to 31 deaths per day\(^{174}\). The manifestation of CHD in females is usually delayed by around 10 years compared with men due to the protection of circulating oestrogens, however, CHD is not solely a disease of the elderly. The adverse CHD gender gap is the widest in relatively young women, where AMI mortality is 2-3 fold higher in women under 55 years compared with age-matched men\(^{175, 176}\). This now places younger women (i.e. <55 years) as the new sub-group now impacted and has been the driving force behind the VIRGO study (See Ancillary projects coordinated & section 1.4.9.6)\(^{177}\). For a comprehensive discussion on the epidemiology including geographic variations of CHD (ACS, CCS) in women please refer to Appendix 3.

### 1.4.5 Awareness of CHD in Women

Contemporary research has yielded findings suggesting that Australian women are dangerously unaware of their risk of CHD, with population surveys demonstrating that a mere 31% recognize that heart disease is the leading cause of death\(^{178}\). The majority of women mistakenly believe that breast cancer represents the largest burden
(accounting for only 2,774 deaths in 2008), when in fact women are four times more likely to die of CHD\textsuperscript{179}. This may be a direct result of women still holding the view that heart disease is a middle aged ‘man’s problem’\textsuperscript{1}. This misconception may stem from the lack of CVD research conducted on women, less public education/awareness toward female specific risks\textsuperscript{2} or possibly an inherent bias against women within the health care system which has resulted in poor access to both diagnostic and therapeutic interventions.

Accordingly, much of the research in the past on the diagnosis and treatment of heart disease has either excluded women entirely or included only limited numbers of women\textsuperscript{180}. In 2004, the AHA launched their ‘Go Red for Women’ campaign to raise awareness about the risks of heart disease in women. This campaign has subsequently provided a framework for Australia’s response to this crucial health issue and thus the ‘Go red for women’ campaign has been run nationally since 2009. Through the education of cardiovascular risk in women through such campaigns, awareness has increased from 30\% in 1997 to 54\% in 2009\textsuperscript{181}. These ongoing education campaigns for women are vital in order to improve women’s awareness of signs and symptoms of CHD and ultimately a prompt presentation to emergency care settings when poised with a cardiac event.

\subsection{1.4.6 Atherosclerotic Coronary Syndromes}

Sex/gender differences exist in many aspects of ACS, including risk factors, clinical characteristics, biological factors and psychosocial characteristics. Table 14 summarises the main female differences in ACS within the current literature.
### Differences in ACS Features Compared with Men

#### Traditional Risk Factors
- **Age**: 7-10 years older on average (prevalence rapidly post menopause)
- **Diabetes**: >50%↑ CVD mortality in women, relative risk CHD 3-7 fold in women vs. 2-3 fold in men
- **Smoking**: Less likely to smoke but women <55 years↑ risk ACS
- **Hypertension**: ↑Prevalence at older age
- **Hyperlipidemia**: Low HDL (>1.6mmol/L) & TG 22mmol/L↑ potent risk factor (particularly following menopause)
- **Family history**: <65 years risk CHD events compared with men
- **Obesity**: Waist-hip ratio >0.9 predictive CHD
- **Ethnicity**: African American women have↑ prevalence ACS

#### Risk factor Assessment
- **Framingham risk score**: underestimates risk in women as >90% classified as low risk
- **Reynolds risk score**: Sex specific tool which classifies >40% of intermediate Framingham risk scores in women

#### Novel risk factors
- **C-reactive protein**: ↑risk factor for women (CRP levels higher in women beginning at puberty)
- **Estrogen deficiency/hypothalamic dysfunction**: ↑risk of ACS
- **Polycystic Ovarian Syndrome**: occurs in 10-13% women & ↑risk of ACS
- **Metabolic syndrome**: Post menopausal ↑dyslipidemia, weight & cluster of risk factors

#### Clinical factors
- **Presentation**: 
  - Women present with more NSTEMI & UA compared to men with STEMI
  - Atypical symptoms frequent- nausea/vomiting, neck/back pain, indigestion
  - More Associated symptoms (3.4±1.9 women vs. 2.5±1.4 men)
  - Increased pain threshold
- **Diagnosis**: 
  - ECG stress testing has lower sensitivity/specificity in women
  - Sequential approach (ECG & SPECT imaging) more effective in women
- **Treatment**: 
  - Prescribed less cardio-protective agents (i.e. aspirin, statins)
  - Receive less revascularisation procedures (PCI, CABG) & thrombolytic therapy
  - Delay in STEMI Therapies (longer pain-to-door time)
Poorer Outcomes:
- Higher short term (in-hospital, 30-day) and long term (12 month, 2-10 years post AMI) mortality
- Higher mortality when undergoing PCI following AMI
- Greater likelihood of re-infarction (particularly following thrombolysis)
- Long term disability (QOL/psychosocial adjustment following ACS event)
- More post procedural (PCI) complications (bleeding risks, stroke)
- More medication adverse effects

**Biological factors**
- **Coronary Biology:**
  - Plaque erosion & distal embolisation rather than plaque rupture
- **Micro-vascular dysfunction (MCD):**
  - Myocardial infarction with normal coronary arteries more prevalent
- **Smaller coronary arteries** even following adjustment for body surface area
- **Female specific hormones** - Hypoestrogenaemia of hypothalamic origin
- **Genetic influences** - Powerful predictor CHD death in women & polymorphisms associated with risk AMI postmenopausal women

**Psychosocial factors**
- **Socioeconomic Status** (low class, education & increased work load): Linked to poor post AMI outcomes in women
- **Social/Emotional support** - Powerful risk factor following AMI in women
- **Quality of life** - QOL following ACS event & procedure (i.e. PCI)
- **Depression** - Pre & post infarct depression

Table 14: Sex/Gender Differences in Acute Coronary Syndrome Features
1.4.7 Risk Factors

As described in section 1.1.3, the FHS originally identified the major coronary risk factors in the progression towards CVD\textsuperscript{12}. Although these risk factors are universal between sexes in the progression towards heart disease, gender specific differences in ACS are noted\textsuperscript{207, 268}. In the case control INTERHEART study (as previously described in section 1.1.3), nine potentially modifiable risk factors (smoking, hypertension, diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, plasma apoliproteins, psychosocial factors) accounted for 94\% of the population attributable risk of AMI in women and 90\% of the risk in men\textsuperscript{13}. In addition, prior studies have consistently shown that women presenting with an ACS are on average 7-10 years older than men. The prevalence of CVD in women increases rapidly in the postmenopausal years and is similar to that seen in men by the seventh decade\textsuperscript{182-184}. As per the INTERHEART study, on initial presentation, women carry a greater burden of traditional cardiovascular risk factors such as diabetes, hypertension and hyperlipidemia, but are less likely to smoke, even following adjustment for age\textsuperscript{175, 207, 218, 269}. The major gender differences in regards to cardiac risk factors, risk factor assessment and novel risk factors for ACS discussed in brief below.

\textit{Diabetes}

While the effect of diabetes poses an increased risk in both genders, the increase in CHD risk is greater in women than in men\textsuperscript{185, 270-273}. Diabetes eliminates the usual female advantage for coronary disease mortality\textsuperscript{274, 275}, a finding which was highlighted through the FHS. Several studies have shown that the relative risk of
CHD in diabetic women varies from 3-7 fold as compared with 2-3 fold in diabetic men^{185, 186}. Thus, diabetes provides greater prognostic information in women than any other of the traditional risk factors. Women may indeed have higher rates of diabetes due to a clustering of other various risk factors due to older age onset including obesity, hypertension and elevated hypercholesterolemia^{276}. The increase in cardiac event risk in women with diabetes, as well as adverse outcomes following AMI, have since been confirmed in various epidemiological studies^{277, 278}. 

**Hypertension**

In women, diabetes and hypertension appear to confer a higher risk of coronary events in comparison to men^{13} with the prevalence of hypertension in the general population >60 years of age reported to also be higher among women^{191}. It is known that premenopausal hypertension significantly increases the risk of CVD mortality in women as compared with postmenopausal women and may indeed be a marker for more aggressive medical intervention^{192}.

**Hypercholesterolemia**

Following menopause women are known to have higher concentrations of total cholesterol than men and therefore low high-density lipoprotein (HDL) cholesterol is a stronger coronary risk factor in women as compared with men^{193}. Elevated triglycerides are a powerful contributor to cardiovascular risk in women. For example, Low LDL and increased triglycerides appear to be the only factors that increase the risk of death from heart disease in women over 65 years of age^{279}. Following multivariate adjustment for conventional risk factors, a HDL cholesterol level less
than 1.6mmol/L was significantly associated with an increased CVD mortality. Furthermore, fasting triglycerides are a potent risk factor for women at levels greater than 22mmol/L. In addition, the ratio of HDL and total cholesterol is thought to be highly predictive of future cardiovascular events in women as compared with men\textsuperscript{194, 195}.

**Smoking Status**

Previous data has highlighted that in women who smoke one or more packs of cigarettes a day, their CHD risk is 2-4 times higher than that of non-smokers\textsuperscript{187}. Furthermore, even in women who smoke less than half a pack a day, their risk of heart disease is doubled compared with non-smoking women\textsuperscript{188}. Women who smoke also have a higher risk of AMI than men, which is associated to almost 50\% of all coronary events in this female cohort\textsuperscript{186, 189, 190}.

**Family History**

A family history of premature CHD is also observed more regularly in women as compared with men\textsuperscript{196}. For example, a first-degree male family member suffering from CHD before the age of 55 years or a female relative with CHD before the age of 65 years is now known to be an independent determinant of CHD risk in women\textsuperscript{197}. 
Obesity/Metabolic Syndrome

In addition to family history, women with obesity have an increased risk of CHD, independent of diabetes (waist to hip ratio >0.9 is predominantly predictive)\textsuperscript{198}. The metabolic syndrome, otherwise known as “insulin resistance syndrome” or “syndrome X” is known to predict cardiovascular risk better than obesity on its own in women as compared with men\textsuperscript{199}.

Racial Background

The race of an individual is particularly important when referring to gender differences within ACS. For example, African American women not only pose a greater risk of developing heart disease\textsuperscript{197} but also have a higher in-hospital mortality, lower rates of reperfusion therapy following AMI and are less likely to be referred for cardiac testing compared with Caucasian women\textsuperscript{200, 201}.

In addition to the above co-morbidities on initial presentation, women are also more likely to have had prior angina, congestive heart failure and a higher Killip class (despite a more preserved LV function)\textsuperscript{280} but are less likely to have suffered from a previous AMI or received prior PCI or CABG.

In lieu of the data available, there is a strong need for both women and health care professionals to recognise the existence of CVD risk factors and the potential this has for developing future cardiac events. Ongoing cardiovascular risk assessment, according to available evidence based guidelines, should be integral to a female patient’s medical care\textsuperscript{281}. Lifestyle interventions in women such as smoking cessation
and dietary changes remain a top priority in reducing the chance of an ACS event\textsuperscript{170}, \textsuperscript{282}.

1.4.7.1 Risk Factor Assessment

Current guidelines emphasise the importance of recognising the full spectrum of CHD and thus classify women as being at high risk, lower risk and optimal risk\textsuperscript{203}, \textsuperscript{283} (Table 15). The original assessment of this cardiac risk was based on clinical criteria as well as the Framingham global risk score (FRS)\textsuperscript{12}. However, of particular concern, variables included in these risk algorithms for women have remained constant from the first recommendations over 40 years ago, despite the evolving view of pathophysiology over the past century. Accordingly, despite its implications, the FRS often underestimated the actual cardiovascular risk in women\textsuperscript{280}. In light of this, additional markers have been proposed (i.e. apolipoproteins A-1 & B-100, non high density lipoprotein cholesterol)\textsuperscript{284} yet negligible data is available in evaluating whether these improve cardiac risk\textsuperscript{285},\textsuperscript{286}, particularly within genders.

Conversely, the Reynolds risk score is a sex specific tool devised from large deviation and validation cohorts of women (approximately 24,558 participants), followed up for 10.2 years\textsuperscript{203}. The authors demonstrated the approval of two highly accurate clinical algorithms to assess global cardiovascular risk prediction. Specifically, when compared with the FRS, use of the Reynolds risk score resulted in risk reclassification in >40\% of intermediate FRS women\textsuperscript{203}. Accordingly, healthcare professionals should take several factors into account just beyond the FRS, including medical/lifestyle history, family history of CHD, markers of pre-clinical disease as well as any other
conditions as they make decisions about the intensity of preventive therapy for women\textsuperscript{287}.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Framingham global risk (10 yr absolute CHD risk)</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>&gt;20%</td>
<td>• Established CAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cerebrovascular or TIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peripheral artery disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Abdominal aortic aneurysm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chronic or end stage kidney disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10-20%</td>
<td>• Subclinical CVD (coronary calcification)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiple risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Elevated levels of a single risk factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• First degree relative with early onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Atherosclerotic CVD</td>
</tr>
<tr>
<td>Lower risk</td>
<td>&lt;10%</td>
<td>• Women with multiple risk factors, metabolic syndrome or \leq 1 risk factor</td>
</tr>
<tr>
<td>Optimal risk</td>
<td>&lt;10%</td>
<td>• Optimal levels of risk factors and healthy lifestyle</td>
</tr>
</tbody>
</table>

Table 15: Spectrum of CVD Risk in Women. Adapted from Mosca et al, Arterioscler Thromb Vasc Biol, 2004\textsuperscript{283}.

1.4.7.2 Novel & Female Specific Risk Factors

Contemporary data from the United States Preventative Services Task Force reviewed the evidence with reference to nine novel biomarkers, which may improve risk detection in women\textsuperscript{202}. These include inflammatory markers such as C-reactive protein \textit{(C reactive protein (hsCRP), interleukin (IL-6), fibrinogen/ acute phase protein)}\textsuperscript{204}, lipoprotein (a), homocysteine, leucocyte count, fasting blood glucose, periodontal disease, ABI, coronary artery calcification score as well as carotid intima-
media thickness\textsuperscript{202}. Although the review concluded that contemporary data fails to support the routine use of these novel biomarkers, high sensitive CRP was the strongest candidate for screening in women\textsuperscript{202}. Other female specific biomarkers which may be useful in women include estrogen deficiency/ hypothalamic dysfunction\textsuperscript{205} and polycystic ovary syndrome (PCOS)\textsuperscript{206}. A detailed discussion of these novel makers is beyond the scope of this thesis and thus readers are referred to review articles on this matter\textsuperscript{288, 289}.

1.4.8 Clinical Factors

The next section of this thesis will focus on the current gender disparities within ACS in relation to clinical factors including (a) presentation, (b) diagnosis, (c) treatment and (d) outcomes.

1.4.8.1 Presentation/Diagnosis

Apart from women presenting at an older age with more co-morbidities, there are also gender specific differences in the type of ischaemic event. According to major trials such as GUSTO IIb (Global Use of Strategies to Open Occluded Coronary arteries in acute Coronary syndromes)\textsuperscript{207}, TIMI IIIB (Thrombolysis in Myocardial Infarction)\textsuperscript{208} as well the Euro Heart survey\textsuperscript{209}, women present more frequently with UA and NSTEMI whereas men more frequently experience STEMI\textsuperscript{207, 220, 290-293}. The outcomes in NSTEMI appear to be equal between sexes, but STEMI mortality is higher in women. Women, who do experience a STEMI, have less ST-segment elevation and are less likely to have 3 vessel disease or left main disease\textsuperscript{291-293}. 
In terms of diagnosis women are known to have less obstructive coronary artery disease, which fits the picture of their ‘female pattern’ heart disease. For example, in women undergoing angiography for STEMI, NSTEMI and UA, 10%, 9% and 31% are known to have no significant or ‘obstructive’ CAD\(^\text{207}\). On the contrary, women who do present with obstructive CAD are just as likely than men to undergo revascularisation procedures, however they are more likely to suffer from adverse complications such as higher rates of bleeding\(^\text{207, 294}\).

1.4.8.2 Symptoms

In general, women with ACS more often present with atypical and non-specific symptoms compared with men\(^\text{210, 211}\). Specifically, women describe abnormal pain locations and associated symptoms including nausea, vomiting, fatigue and dyspnea and detail their pain as ‘intense, sharp or burning in nature’\(^\text{295}\).

Compared with men, women are also more likely to report a significantly greater number of associated symptoms (3.4±1.9 vs. 2.5±1.4 symptoms)\(^\text{210, 212, 213}\). Due to the multidimensional factors contributing to different symptoms observed between genders in ACS, previous authors have constructed a theoretical framework\(^\text{296}\). DeVon and colleagues have reported that type, severity, location and quality of symptoms may vary due to (a) psychosocial, (b) physiological, (c) anatomical and (d) biological differences between gender groups\(^\text{296}\). The atypical features predominately observed in women may explain to a degree, why they are to be less likely to present to the emergency department and also why they are prone to receiving less rigorous
cardiac evaluations as compared with men\textsuperscript{288, 297}, including a higher mortality rate\textsuperscript{298, 299}. This assertion that women fail to recognize their symptoms and thus delay acute presentation to hospital is not always true. Gender disparities in ACS may also be due to a significant bias in health care seeking behaviour for CHD related symptoms (this is akin to ‘blaming the victim’)\textsuperscript{300}. More importantly, women who actually interact with the health care system concerning their cardiac symptoms are less likely to be hospitalised, prescribed fewer medication or invasive treatment and are also less likely to be referred to a cardiologist. Therefore, gender disparities may be apparent in the way women are treated and not in how they utilise the health care system\textsuperscript{300}.

\textit{Pain Perception}

 Apart from experiencing different symptoms during an ACS, there is some clinical and experimental data to suggest that women may have a higher pain threshold compared with men, with or without coronary disorders\textsuperscript{301-303}. In terms of ACS, one study investigated gender disparities in self reported pain perception as characterised by pain symptoms diagnosed in patients with UA. The findings revealed that women not only described an atypical clinical picture but scored the intensity of their angina significantly higher than men and alarmingly related this less to heart disease\textsuperscript{214}. Secondly, in a study investigating angina pectoris, women reported a significantly greater intensity of pain than men for all pain descriptors. More importantly, female sex remained a significant predictor of pain scores even following adjustment for demographic and clinical variables\textsuperscript{215}. Although the mechanism responsible for the gender difference in pain perception is still under debate, it is hypothesised that
biological and psychosocial factors may contribute\textsuperscript{304-308}. Specifically, this may be due to sex differences at the level of endogenous pain modulatory systems\textsuperscript{309,310}.

In light of the above, new prospective research is warranted to not only measure the severity, type, location, quality and duration of pain but also the principal complaint and the total number of symptoms. In addition, evaluating the symptoms by diagnosis (STEMI, UA, NSTEMI) may provide a more definitive picture of gender disparities in ACS. Women seem to report a higher threshold of pain in ACS compared to men, however more research is required to support this hypothesis.

1.4.8.3 Treatment and Medical Therapy

Following an acute coronary event such as AMI it has been consistently shown that women receive fewer cardiac investigations as well as less intensive medical and interventional therapies. This includes less evaluation of cardiac symptoms\textsuperscript{165,311,312}, less thrombolytic therapy\textsuperscript{223,224,313}, and revascularisation procedures (coronary angiography, PCI or CABG)\textsuperscript{218-223,297,314}. In regards to these therapies, women have also been shown to receive time delays, which may contribute to their poorer outcomes\textsuperscript{247,315}. The cause for the under utilisation of cardiovascular procedures is unknown but may be due to referral bias\textsuperscript{316}, difference in older age and other comorbidities.

Women with ACS have been shown to receive less medical treatment, particularly following AMI. The cooperative cardiovascular project as well as the more recent CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of
Cardiology/American Heart Association Guidelines) trial indicate that women receive less aspirin, beta blockers and statins at discharge following AMI compared with men\textsuperscript{218, 219}. This difference in medical based therapies is not due to the fact that women have less significant coronary disease as studies such as the Global Registry of Acute Coronary Events have documented that both women with mild and advanced disease\textsuperscript{317} are still less likely to receive suboptimal treatment (i.e. receive less standard discharge medications\textsuperscript{318}).

In addition, women are known to respond differently to various medications as they differ to their male counterparts in terms of physiology, pharmacokinetics and pharmacodynamics\textsuperscript{319-322} including more adverse drug reactions\textsuperscript{248, 249}.

Although the reason for this concerning disparity in treatment is unclear, the sex bias in health care delivery within ACS may reflect (a) how women themselves respond to cardiac symptom onset and how women’s symptoms are diagnosed and treated, and (b) how health care providers perceive cardiac health threats in women.

*Invasive Versus Conservative Treatment in ACS*

The benefit of an invasive strategy in ACS for women remains unclear with diverse findings published from numerous clinical trials. However, an invasive strategy used in patients with UA/NSTEMI suggests that this may not benefit women. The (RITA)-3\textsuperscript{93} and Fragmin and Fast Revascularization During Instability in Coronary Artery Disease (FRISC-II)\textsuperscript{88} trials demonstrated that despite an overall benefit, invasive strategies were associated with and increased risk of death or AMI in women. In the
TACTICS-TIMI 18 trial\(^9\), an early invasive strategy was associated with improved outcomes in both gender groups with particular benefit observed in high-risk women (identified by an elevated troponin). In light of this controversy, O’Donoghue and colleagues conducted a meta-analysis of eight major trials in NSTEMI and revealed that women with positive biomarkers and an early invasive strategy showed a significant reduction in composite endpoints of death, AMI or ACS\(^292\). In conclusion, an invasive strategy seems to have a comparable benefit in high-risk women for reducing the composite end point for death, AMI or rehospitalisation with ACS. These results support the new guideline recommendation for a conservative strategy in low-risk women\(^292\).

1.4.8.4 Cardiac Outcomes

Over the last decade a plethora of studies have consistently highlighted gender related disparities in the treatment and outcomes of patients with ACS\(^169, 218, 219, 237, 323, 324\). In addition, there is also preliminary data which indicates that women with AMI are less likely than men to be admitted to hospitals with revascularisation capability\(^238\). Traditionally, women have less favourable short-term outcomes (i.e. in-hospital death) and a higher mortality following PCI than men\(^237-240, 325\). This may be due to smaller vessel size/procedural complication, bleeding risks and more baseline co-morbidities\(^246, 247, 291, 326, 327\). Importantly in women, in-hospital death persists even after adjustment for potential confounders\(^220\). Analyses of sex-based differences in outcomes after ACS have revealed conflicting results. In-hospital mortality rates in young women with ACS are significantly higher compared with similarly aged men\(^175, 328\) (see section 1.4.8.6). In 2009 Berger and colleagues published a meta-
analysis involving 11 randomized ACS trials, which examined sex-based differences in 30-day mortality. From this review they concluded that the sex differences observed could be largely explained by clinical differences at presentation as well as the severity of disease\(^{233}\). Specifically, sex differences in outcomes in STEMI persist following multivariate adjustment whereas NSTEMI and UA are largely explained by women’s advancing age and clustering of risk factors\(^{207, 233, 329, 330}\). Apart from a higher short-term mortality (in-hospital, 30-days), women have significantly greater long-term morbidity and morality rates ranging from 2-10 years post AMI as compared with men\(^{234-236}\). In addition, in STEMI patients receiving thrombolytic therapy, female sex is an independent predictor of re-infarction compared with men\(^{241, 242}\).

1.4.8.5 Gender Disparities in Women with STEMI

As previously discussed in section 1.2.6.1 of this thesis, time to treatment is a key predictive indicator of mortality and morbidity outcomes within STEMI patients receiving either medical or reperfusion therapy\(^{76, 331-338}\). Interestingly, previous studies have documented significant PCI reperfusion delays among women compared with men\(^{225-228, 339-342}\). More specifically, it has been highlighted that female sex is an independent predictor of a delayed DTB time\(^{220, 229, 231, 232}\). Disparities in DTB time have been addressed, however no study has (a) explored the components influencing this time interval difference, and (b) assessed gender differences in DTB within an Australian hospital setting. Gender differences in DTB time will be covered in chapter four (Evaluation of Gender Differences in Door-to Balloon Time in ST-Elevation Myocardial Infarction).
1.4.8.6 Young Women with Acute Myocardial Infarction

From the last decade of research it is now known that there is a complex interaction between sex and age contributing to differences in early mortality following AMI. In 1999, Vaccarino and colleagues published data from the National Registry of Myocardial Infarction 2 (NERMI 2) concluding that following AMI, younger women (i.e. those under 55 years), but not older women had twice the risk of dying in-hospital compared to men of the same age (Figure 1) (16.7% vs. 11.5%, OR 1.54, 95% CI 1.51-1.57)\textsuperscript{175,343}. Furthermore, of those who survived, their subsequent risk of death was about 50% higher than men. This mortality differences between the sexes decreased with mounting age and was no longer significant after the age of 74. Furthermore, even after adjusting for differences in medical history, clinical severity of infarction and early management, young women still had a higher risk of death for every five-year decrement in age\textsuperscript{175}.

In light of these findings, Berger et al (2006) conducted a more contemporary study to investigate this sex-age interaction in the era of treating AMI with primary PCI\textsuperscript{344}. Findings of this study revealed that although the in-hospital mortality rates were twice as high in women, after adjustment for age, risk factors, co-morbidities and haemodynamic status, there was no longer a mortality difference. However, among patients <75 years of age, women had a 37% increased adjusted risk of in-hospital mortality (adjusted OR 1.37, 95% CI 1.01-1.98, P=0.04). Asides from these groundbreaking studies, the lack of research in this area has led to a limited knowledge about CHD in young women and has resulted in frequent under diagnosis. In light of this, the VIRGO study was established in 2009 to focus on understanding this extreme phenotype of women\textsuperscript{177} (See Ancillary projects coordinated). For a
comprehensive discussion on young women with ACS the reader is referred to a recent review conducted by Levit and colleagues. Figure 1: Rates of Death during Hospitalisation for AMI Among Women and Men, According to Age. [Sample size of 384,878 patients (155,565 women and 229,313 men)]. The interaction between sex and age was significant ($P<0.001$). Adapted from Vaccarino et al, N Engl J Med, 1999.
1.4.9 Biological Factors

The next section of this thesis will review the current biological controversies in regards to gender and ACS including (a) platelet function/erosion, (b) Micro-vascular coronary dysfunction, (c) autonomic function, (d) vessel size, (e) genetic influences, (f) sex hormones, PCOS and pregnancy and (g) Hormone replacement therapy.

1.4.9.1 Platelet Function & Plaque Erosion

Previous research has highlighted that women have more platelet aggregability to adenosine disphosphate as well as less platelet inhibition to prostacyclin than their male counterparts following an AMI. In addition, thrombi discovered in women following autopsy studies, who died of sudden cardiac death, were shown to have an increased erosion of a proeoglycan-rich plaque rather than rupture of a lipid-rich plaque with a thin fibrous cap, which is more often observed in men. Further autopsy data published by Burke and colleagues highlighted that women have a greater frequency of plaque erosion and distal embolisation compared with men and older women, where plaque rupture is more prominent. This infamous study also highlighted that women who die from plaque erosion are in fact younger and more likely to smoke whereas those women who die from plaque rupture are more likely to be older and have hypercholesterolemia. Younger age and plaque erosion seem to be associated with a lesser degree of luminal narrowing within the plaque site, including a lower overall extent of CAD. These findings indicate an underestimation of risk by angiography, particularly in younger women.
1.4.9.2 Microvascular Coronary Dysfunction (MCD)

Although still controversial it has been proposed that the biology of a woman with CHD may be distinct from that of men and older patients. Namely, women may have a different type of coronary artery disease compared with men. Findings from the Women’s Ischaemia Syndrome and Evaluation (WISE) study led by Prof Bairey Merz have upended the decade long paradigm in which heart disease was thought to be ‘gender neutral’ or the same as men (i.e. ‘male pattern’ obstructive disease)\textsuperscript{160}. Data from the WISE study suggest that many women suffer from a form of heart disease called micro-vascular coronary dysfunction (MCD) compared with men who predominately present with macro-vascular disease\textsuperscript{160, 163}. This type of MCD in women is a concern as this condition is not detectable by gold standard diagnostic procedures and thus goes unrecognised and undertreated. As MCD relates more to myocardial ischaemia this important topic will be discussed in section 1.4.11.5. An in depth discussion of sex based physiology is beyond the scope of this thesis and thus readers are referred to a review conducted by Luczak and colleagues\textsuperscript{347}.

1.4.9.3 Autonomic Function

Compared with men, women have been shown to have a dominant parasympathetic autonomic cardiac tone\textsuperscript{348}. This is consistent with a higher female rate of hypotension, syncope and bradycardia following AMI and conversely with more malignant post AMI tachyarrhythmia’s and a higher occurrence of sudden cardiac death among men\textsuperscript{349, 350}. These differences in autonomic function may be the direct result of developmental variation and/or hormonal differences between the sexes\textsuperscript{348, 351}. Additional factors which may alter autonomic cardiac activity and influence
sex/gender differences include age\textsuperscript{352}, obesity\textsuperscript{351}, inflammation\textsuperscript{353} and psychological factors (i.e. depression)\textsuperscript{354}. Although women normally have a more favourable autonomic function than their male counterparts, specific syndromes that are more common among women include cardiac syndrome X (see section 1.2.9.2)\textsuperscript{355} and takotsubo cardiomyopathy\textsuperscript{356} which are paradoxically linked to adverse autonomic tone. Although relevant, more substantial data is required to support the role of an altered autonomic function in women with ACS.

1.4.9.4 Coronary Vessel size

Women have smaller coronary arteries than men (average diameter of 2.90mm versus 3.09mm in men\textsuperscript{252}), even following adjustment for body surface area\textsuperscript{253}. Stenting smaller vessels is associated with less favourable outcomes so that interventionalists are more reluctant to stent such vessels, which may contribute to the fewer PCI's performed in women\textsuperscript{288}. We can speculate that the smaller vessel size in women may present delays in DTB within the catheterisation laboratory. This paradigm is explored in chapter four (Evaluation of Gender Differences in Door-to Balloon Time in ST-Elevation Myocardial Infarction).

1.4.9.5 Genetic Influences

Heredity has been shown to play an important role in women with heart disease. Twin and family studies of CHD have revealed that genetic factors are of importance, particularly in young women\textsuperscript{357}. Further studies have indicated that genetic influence is a powerful predictor of CHD death in both sexes, but is disproportionately potent in
women\textsuperscript{256, 257}. In addition, limited progress has been made in the elucidation of specific genes involved in sex-specific risk of AMI. In a key study by Schuit et al it was found that the \textit{ESR1} haplotype created by the \textit{c.454-397T>C (Pvu II) and c.454-351A>G (Xba I) polymorphisms} is associated with AMI and IHD risk in postmenopausal women but not in men\textsuperscript{258}. Other studies have implicated only a few specific genetic variants- such as 6A variant of stomelysin-1 and 5G variant of plasminogen activator inhibitor 1 (PAI-1) as risk factors in women, but not in men\textsuperscript{358-360}. Additional positive genetic associations with AMI in women have included factor V Leiden in smokers\textsuperscript{361}, platelet glycoprotein IIb in smokers\textsuperscript{362} and prothrombin G20210A\textsuperscript{362}. These genetic variants may be potentiated by smoking, suggesting that thrombosis risk may be a key to the pathogenesis of AMI in women\textsuperscript{258}.

1.4.9.6 Sex Hormones, PCOS & Pregnancy

The lower incidence of CHD in premenopausal women as well as the menopause-associated increase in CVD has long been thought to involve the protective effect of oestrogen. Sex hormones such as oestrogens have multiple benefits on vascular function including improving coronary/peripheral endothelial dysfunction and preventing coronary artery spasm in the presence/absence of coronary atherosclerosis\textsuperscript{363-365}. The WISE study investigators highlighted the fact that premenopausal women undergoing coronary angiography (for evaluation of ischaemia) reported that hypoestrogenaemia of the hypothalamic origin was associated with CAD\textsuperscript{160}. This important observation supports the notion that female protection is lost when a woman's ovarian function is disrupted\textsuperscript{205}. In fact, premenopausal women have been shown to pose a greater risk of AMI during the
menstrual or follicular phase of their ovarian cycle during which their estradiol blood levels are the lowest\textsuperscript{205}. Further studies have discovered an association of low 17\textbeta-estradiol levels and increased risk of an acute coronary event\textsuperscript{254, 255}. Furthermore, when women of the Determinants of Myocardial Infarction Onset Study (ONSET Study) were followed, there was found to be a relative risk of 3.3 for having an AMI during the early follicular phase of menses\textsuperscript{254}.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder amongst women. Although this heterogeneous disorder has uncertain etiology, there is convincing evidence that it can be classified as a genetic disease\textsuperscript{366-368}. This female-based disorder has been shown to produce symptoms in approximately 5-10\% of women of reproductive age (i.e. 12-45 years). In addition, prior research has confirmed that hormonal dysfunction in women of reproductive age (particularly the androgen excess as present in women with PCOS), is associated with an increased risk of atherosclerosis and IHD events\textsuperscript{369, 370}. Specifically, a recent meta-analysis has highlighted a 2-fold increased risk of arterial disease for women with PCOS compared to women without PCOS (independent of BMI)\textsuperscript{371} as well as a 7-fold increased risk of AMI\textsuperscript{372}. Despite this preliminary evidence, it is still uncertain whether the PCOS is an independent risk factor for the development of atherosclerosis\textsuperscript{205, 373}.

In addition to PCOS, evidence is mounting that pregnancy may soon be considered as a ‘stress-test’ for future cardiovascular risk in women. Much of this evidence stems from hypertensive disorders during pregnancy, which have been shown to be
predictors for hypertension and CVD events. Women who present with complications in relation to their unborn fetus including poor fetal growth as well as a placental syndrome or intrauterine death are considered to be at the greatest risk.

Furthermore, an impaired glucose tolerance during pregnancy as well as gestational diabetes remain as female-specific risk factors for the development of diabetes and the metabolic syndrome in young women.

The effects of hormones, PCOS and pregnancy in relation to women and ACS should not be underestimated. Since there is a high rate of PCOS in the general population, and because CVD is the major cause of death in older women, the prevention of cardiovascular disease in women with PCOS should be a major public health priority. One of the major aims of the VIRGO study (See Ancillary projects coordinated) is to determine sex differences in the prevalence and prognostic importance of selected biochemical biomarkers following AMI, (which has not been previously investigated in a young cohort of women). Results from the VIRGO study will most likely drive the next 5-10 years of research in this area.

1.4.9.7 Hormone Replacement Therapy

As previously mentioned, the strong association of mortality and morbidity from CVD in postmenopausal women is thought to be due to a protective role for oestrogen in the heart. Prior observational studies of postmenopausal women receiving hormone replacement therapy (HRT) demonstrated a 40% reduction in cardiovascular events. However, this cardio-protective role of oestrogen was challenged in 2002 by findings from the Women’s Health Initiative (WHI) study. Alarmingly, in
In addition to the traditional and female specific risk factors, psychosocial factors including emotional status and chronic stress can influence the onset and clinical course of CHD in women\textsuperscript{385}. Findings from the INTERHEART study (See section 1.1.3) revealed that the joint exposure to depression, perceived stress and major life events was significantly associated with AMI (OR 2.6 in men vs. 3.5 in women)\textsuperscript{13}. The main psychosocial factors pertaining to gender are described in detail below, including differences in (a) socio-economics, (b) health related quality of life, (c) depression, (d) social support, (e) quality of care and (f) type D personality and (g) acute/chronic stress.

### 1.4.10 Psychosocial factors

In this study, HRT was shown to increase unfavorable events in postmenopausal women (i.e. blood clots, breast cancer and stroke) and thus was ceased immediately causing much havoc in the media. However, a major problem with this study was that HRT was not initiated in women until the average age of 63, thus corresponding to around 12 years post menopause. Since this time there has been intense debate about whether the risk of HRT outweighs the benefit of treatment. Ten years on, a new review has found that that sufficient evidence supports benefits over risks with the return to rational use of HRT generally with initiation near menopause (i.e. safe if women begin in their 50s)\textsuperscript{384}. However, further evidence is required to confirm these reported benefits in this population.
1.4.10.1 Socioeconomic Status

Socioeconomic status is a vital measure in relation to gender, which may encompass a person's work experience and a family’s economic and social standing in relation to others based on income, education and occupation. The incidence of AMI is related to both gender and social class\textsuperscript{259}. In particular, socioeconomic status, work and home roles may play an important prognostic role in women\textsuperscript{259-261}. A few earlier studies suggest that low educational attainment, low socioeconomic class, increased work loads of employment and family are more influential risk factors for post-AMI adverse outcomes in older women compared with older men\textsuperscript{259-261}. Women often work outside the home, in addition to their roles within the household as wives, mothers and caregivers to elderly parents. In addition to work and education, the type of relationship status is important when referring to women and differs by gender. For example, a single partner status (i.e. single, widowed) is associated with adverse outcomes and decreases the protective effect that marriage is equated with\textsuperscript{386-387}. This may be due to a lack of social/moral support in single women or a lack of motivation for personal care, which usually equates with having a spouse and marital responsibility. For a more detailed discussion on socio-demographic factors please refer to reviews on this topic\textsuperscript{388, 389}.

1.4.10.2 Health related Quality of Life

Across both genders and all age groups, health status has been shown to predict short- and long-term adverse cardiovascular events, such as death and rehospitalisation\textsuperscript{390-392}. Beyond their prognostic import, patient-reported health status measures have become increasingly valuable in quantifying patient’s perceptions of how their
disease affects them in terms of their symptoms, function and health-related quality of life (HRQOL)\textsuperscript{393} and thus have been advocated as a marker of healthcare quality\textsuperscript{391, 394} (See section 2.1.1.1). There is mounting evidence that age, gender, and social class affect HRQOL in the general population, with women reporting both a poorer HRQOL and psychosocial adjustment than men, particularly following a cardiac event such as AMI\textsuperscript{244, 233-235, 245}. Likewise, previous authors have suggested that women with coronary disease report significantly poorer physical functioning and mental health than men\textsuperscript{262-264}. Despite all considerations mentioned above, it is necessary to improve the knowledge of gender differences in HRQOL including the effect that socio-demographic, clinical and psychological variables have on the evolution of HRQOL following a cardiac event such as AMI.

1.4.10.3 Depression

For centuries long, Folklore claimed a prominent link between the mind and body (referred to as the heart-mind connection) in human moods and in the heart in particular\textsuperscript{395}. Over the past decade there have been a plethora of studies confirming the link between depression and CHD\textsuperscript{396}. In terms of gender, it is now known that depression is twice as prevalent in women than men and is evident in 40\% of young women with AMI\textsuperscript{266}. In fact, depression is an independent risk factor for adverse events in women such as cardiovascular death and all cause mortality, even following adjustment for important clinical covariates\textsuperscript{265, 397, 398}. In addition to cardiac outcomes, depression is related to a poorer HRQOL in women\textsuperscript{399} as well as poorer health status benefit following procedures such as CABG\textsuperscript{267}. In addition to increased depression at baseline, women also suffer from more post infarct depression, which has been shown
to be a significant predictor of 1-year cardiac mortality. The symptoms of depression also highlight gender differences. Specifically, women report greater somatic depressive symptoms (i.e. sleep and appetite disturbances) compared with men.

1.4.10.4 Type D Personality

Individuals with a type D personality have a joint tendency towards negative affectivity (e.g. worry, irritability) as well as social inhibition. The prevalence of type D personality ranges between 18-53% in cardiac patients. Previous research has highlighted that a type D personality is associated with a 4-fold increased risk of mortality, recurrent AMI or sudden cardiac death independently of clinical risk factors. In relation to gender, there is some preliminary data to suggest that women report higher incidences of type D personality compared to men. Further studies have shown that women suffer from more exhaustion prior to AMI, score higher on distress and exhaustion and have more difficulty with emotional adjustment compared with men. The extent to which a type D personality state has an effect on the development of adverse cardiac events in terms of gender requires further investigation.

1.4.10.5 Social Support

As a collective, depression and lack of social support are important and more powerful risk factors for post-AMI adverse outcomes in older women than in older men. Specifically, a lower social support in women has been associated with
a worse health status and more depressive symptoms in the first year following an AMI\textsuperscript{410}. Factors such as character traits (e.g. optimism), feelings of control, and social and emotional support play an important role in the outcomes of women following AMI\textsuperscript{411}. These findings of an interaction between social support and gender need to be confirmed in larger cohort studies.

1.4.10.6 Quality of Care & Rehabilitation

Gender differences in access to care and quality of care is a relatively important topic but remains understudied. Obstacles to high-quality care for women may relate to personal preferences or beliefs, baseline co-morbidity, differences in the perception and reporting of their symptoms, lack of coordination with diverse caregivers (e.g., internists, cardiologists, and gynecologists), and poor advice from lay consultants\textsuperscript{309}. Previous research has highlighted that women may be less likely to be referred by health care professionals for medical care and some procedures are performed less often for women with AMI\textsuperscript{166, 223} compared with men (as discussed in section 1.4.8.3). However, whether gender is independently associated with referral for an indicated procedure remains controversial. Following a cardiac event it has been found that women with AMI are more likely to be on sick or disability leave, are less likely to return to work and also both less likely to receive or to adhere to cardiac rehabilitation programs than men\textsuperscript{388, 412, 413}. More research is needed to understand how women recover after their AMI, particularly in the younger cohort (i.e. <55 years), where the largest in-hospital mortality gap is observed. The VIRGO study specifically addressed quality of care factors and thus will provide valuable information on future steps and will improve care for all women worldwide.
Stressful events, acute anger, sudden mood disturbances and extreme excitement have been implicated in triggering an AMI and/or sudden cardiac death in vulnerable individuals\textsuperscript{414}. Although it is unknown whether there are sex disparities in these effects, a stress-induced condition known as ‘tako-tsubo cardiomyopathy’ is almost exclusively prominent among post-menopausal women\textsuperscript{415}. Chronic stress factors such as anxiety, martial stress and exposure to early life adversities has been linked to cardiovascular risk in women. Anxiety in itself is a moderate but independent risk factor for IHD and cardiac death in both women and men\textsuperscript{416}. Furthermore, marital stress has been associated with subsequent cardiac events as well as with progression of CAD measured by angiography in Scandinavian women\textsuperscript{417}. Another study has linked marital satisfaction to reduced carotid artery atherosclerosis progression\textsuperscript{418-420}. Childhood psychological trauma is also an emerging risk factor for both IHD and depression, equally more common in women than men\textsuperscript{270}.

These surrogate markers of socioeconomics as described above (education, work status, relationship status) should, however, definitely remain the focus of future research as they have been able to explain many disparities in outcomes among cardiovascular populations.
1.4.11 Chronic Coronary Syndromes

1.4.11.1 Epidemiology of CSA in Women

Stable angina is the most prevalent manifestation of CHD. Although the exact prevalence in Australia is unknown, it is estimated that 2.1 million people suffered from angina in the United Kingdom in 2009, thus representing a prevalence of approximately 5% of men and 4% of women\textsuperscript{421}. Similarly in the US, 10.2 million Americans were reported to have angina in 2006 with 4.7% of Caucasian men and 4.5% of Caucasian women over the age of 20 affected\textsuperscript{422}. The prevalence of angina is affected by age with 17% amongst males and 12% amongst females over the age of 75 years, however this statistic is less than 1% for those under the age of 45. Despite a higher overall incidence and prevalence of CHD in men than in women, stable angina is more common as an initial presentation of coronary disease in women\textsuperscript{184, 423, 424}. Furthermore, population based surveys using the Rose questionnaire from the US\textsuperscript{425}, Northern\textsuperscript{426, 427} and Southern Europe\textsuperscript{428} report higher prevalence rates for angina in women than in men.

Past research has highlighted important differences in the clinical treatment and management of CHD by way of gender, with particular emphasis on ACS highlighting that women are investigated and treated less aggressively than men. However, despite the higher prevalence in women, there is comparatively few data on the investigation and treatment of CSA in this population, particularly within the primary care setting (please refer to Table 17: main studies generated within the primary care setting). Similarly to ACS, the next section of this thesis will focus on the main issues in relation to gender disparities in chronic stable angina.
<table>
<thead>
<tr>
<th>Author</th>
<th>No. Women</th>
<th>Study Inclusion</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carroll (2003)</td>
<td>2787</td>
<td>&gt;44 years of age</td>
<td>Age specific/standardised</td>
<td>Women received cardio-protective agents, confirmed diagnosis &amp; revascularisation procedures.</td>
</tr>
<tr>
<td></td>
<td>(41%)</td>
<td></td>
<td>prevalence rates &amp; age</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>adjusted RR</td>
<td></td>
</tr>
<tr>
<td>Owen-Smith (2003)</td>
<td>11797</td>
<td>Under GP observation &amp; ROSE</td>
<td>5 year mortality (rose angina)</td>
<td>Women with angina symptoms not documented by GP have increased risk of future mortality.</td>
</tr>
<tr>
<td></td>
<td>(100%)</td>
<td>survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(47%)</td>
<td>angina by GP</td>
<td>adjusted for age, angina</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>duration, and previous AMI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(51%)</td>
<td>angina by GP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(48%)</td>
<td>nitrates over previous 3</td>
<td>secondary prevention &amp; cardiac</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td>investigations)</td>
<td></td>
</tr>
<tr>
<td>Buckley (2009)</td>
<td>846</td>
<td>Clinical diagnosis of</td>
<td>Events (i.e. death) at 5 years</td>
<td>Sex differences in survival &amp; age &amp; sex differences in the provision of revascularisation after a diagnosis.</td>
</tr>
<tr>
<td></td>
<td>(47%)</td>
<td>angina</td>
<td>from date of the index episode of angina</td>
<td></td>
</tr>
</tbody>
</table>

Table 17: Summary of Gender Differences in CSA in Primary Care Practice.
1.4.11.2 Risk Factors & Assessment

The cardiovascular risk factors in patients with CSA as well as the type of risk factor assessment (Framingham versus Reynolds) are similar to ACS. It is important to classify women as being high, intermediate or low risk for CHD. For a complete review on management of risk factors please refer to the ACC/AHA guidelines for the management of patients with CSA.\textsuperscript{108}

1.4.11.3 Clinical Factors

\textit{Presentation}

Unlike ACS where there are multiple registries of patients available with this condition, there are few large registries of patients with CSA, particularly stratified by gender. Studies in the primary care setting, as well as Framingham,\textsuperscript{184} have speculated that CHD is a condition that afflicts primarily men and that women with angina have a better prognosis than men with the same condition. However, this remains controversial as despite women’s higher prevalence of CSA, there is little information regarding presentation, prognosis and response to treatment.

The CADENCE study (Coronary Artery Disease in general practice) is one of the largest cohorts of CSA patients, which recruited 2,031 participants with stable angina from general practices across Australia. This study particularly focused upon continuing angina symptoms in these patients and surprisingly found that almost 1 in 3 continued to experience angina at least once a week, despite contemporary
therapies. These findings mirrored data from the United States as well as another key international study. In terms of clinical characteristics, not surprisingly, the majority of CSA patients were elderly men with most having a clustering of conventional CVD risk factors. Most had experienced an episode of ACS with almost half reporting AMI. Most importantly, the CADENCE study reported that gender, the presence of heart failure or PAD were independent clinical predictors of ongoing weekly angina in patients with CSA.

The EURO Heart Survey stratified CSA patients by gender and included 1582 women (42%). In this study, cardiologists enrolled patients with a clinical diagnosis of stable angina on initial assessment and followed them up at 1 year. Baseline clinical characteristics of women and men are presented in Table 1. Similarly to ACS, women with stable angina are more likely to be older on average and present with a clustering of traditional cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia and heart failure. The majority of subjects (88%) in the Euro Heart survey had mild to moderate angina (CCS classes I or II). Women had proportionally more class II symptoms and fewer class I symptoms than men. Similarly, Crilly and colleagues identified 552 women with angina treated in primary care practice. Women were significantly older than men and less likely to receive a detailed risk factor assessment, cardio-protective agents (aspirin, beta-blockers, statins), ECG stress testing, angiography and coronary revascularisation.
Symptoms

Non-chest pain symptoms or atypical angina are more common in women and in older individuals. Women with angina have been known to report greater functional disability than men, however the underlying anatomic or pathophysiologic differences in presentation remain uncertain. Women with CSA rate their chest pain as more intense than men and more often describe their pain as throbbing, sharp, hot, burning, fearful and pressing. These atypical chest pain features may to some degree explain why women who present to an emergency hospital setting undergo less rigorous clinical assessment than men. In addition, diagnostic ECG’s are ordered less frequently in women as compared with men and females are also less likely to be admitted to a coronary care unit or to receive cardiology consultation as either an inpatient or outpatient.
<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Women (n=1582)</th>
<th>Men (n=2197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62±11**</td>
<td>60±11**</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66%**</td>
<td>59%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>59%</td>
<td>57%</td>
</tr>
<tr>
<td>Previous or current smoker</td>
<td>30%**</td>
<td>69%</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Prior AMI (&lt;1 year)</td>
<td>3%*</td>
<td>5%</td>
</tr>
<tr>
<td>Prior CVA or TIA</td>
<td>4%*</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Symptom severity (CCS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>35%**</td>
<td>41%</td>
</tr>
<tr>
<td>Class II</td>
<td>53%**</td>
<td>46%</td>
</tr>
<tr>
<td>Class III</td>
<td>12%**</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Duration of angina symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>1%**</td>
<td>2%</td>
</tr>
<tr>
<td>0-5 months</td>
<td>50%**</td>
<td>55%</td>
</tr>
<tr>
<td>6-11 months</td>
<td>21%**</td>
<td>21%</td>
</tr>
<tr>
<td>≥12 months</td>
<td>28%**</td>
<td>23%</td>
</tr>
</tbody>
</table>

Table 18. Baseline Clinical Characteristics of Female Stable Angina Patients.

Adapted from Daly et al, Euro Heart Journal; 2005. CCS= Canadian Cardiovascular Society Classification.
1.4.11.4 Treatment and Outcomes

Similar to ACS, women with CSA also receive suboptimal treatment. In the Euro Heart Survey as described above, Daly and colleagues explored the effects of gender on both the treatment and outcome of angina patients. Following initial cardiology consultation significantly more men than women were prescribed cardio-protective agents such as aspirin and statin therapy. Of importance, gender differences in drug prescription persisted even after a diagnosis of CAD had been confirmed angiographically (both at baseline and 1 year follow up). In addition, women received less revascularisation procedures such as PCI (29% of men versus 13% women), reported more angina and poorer outcomes such as AMI or death at 1-year follow up. Women were also twice as likely to experience AMI and/or death even after adjustment for conventional clinical covariates.

In a Finnish prospective ambulatory cohort of patients between 45-89 years of age women with test positive angina had a coronary standardised mortality ratio greater than men (9.9 per 100 per year for women vs. 9.3 for men). Following the publication of this Finnish paper by Hemingway and colleagues, there have been a myriad of studies supporting the underuse of cardio-protective agents and suboptimal use of appropriate revascularisation procedures in CSA for women. As with AMI, CABG surgery and heart failure, women with angina have more adverse outcomes than men, with a doubled morbidity rate from CSA and a mortality rate of 19% at 4.5 years. Authors have attempted different explanations for the reported inequalities between genders. These include the presence of higher risk factors in women due to older disease onset, a higher incidence of cardiac failure,
severe concomitant vascular disease and more complications due to smaller coronary arteries that are less amenable to revascularisation therapies$^{239, 448, 449}$. Furthermore, MCD is more prevalent in women and may be less responsive to conventional anti-anginals.

1.4.11.5 Biological Factors

*Micro-vascular Coronary Dysfunction (MCD)*

As briefly mentioned, the ongoing symptoms observed in women coupled with abnormal cardiovascular stress tests have prompted the recent hypothesis of an alternative, ‘female specific pattern of IHD’, which has been attributed to MCD$^{160-162}$. In contemporary medicine, male-pattern strategies are aimed at detecting obstructive CAD$^{163}$. However, in women with angina and atypical stress tests, this may occur without a significant flow-limiting lesion and thus has sparked debate in regards to the ‘gender paradox’ in IHD$^{268}$. Women have been shown to have a lower overall occurrence of obstructive CAD as well as a higher prevalence of angina compared to men. Evidence of this ‘gender paradox’ in biology stems from the WISE study, whereby ~60% of women presenting with angina undergoing angiography had a significant lesion (defined to be $>50\%$ luminal stenosis in a coronary artery)$^{160}$. Of particular concern, despite these women having non-obstructive coronary disease/luminal narrowing, they not only continued to experience ongoing symptoms but they suffered poorer outcomes compared to age matched controls during long term follow up (i.e. for a period of 4-5 years)$^{57, 279}$. From the WISE study we can conclude that women undergoing coronary angiography have less extensive and
severe obstructive CAD, despite an older age and a higher cardiovascular risk factor presentation compared with their male counterparts. Although an in depth discussion of the semi-quantitative categorisation of coronary flow and microcirculatory perfusion are beyond the scope of this thesis, perfusion may be measured invasively via intracoronary Doppler or by thrombolysis in AMI frame count or measured non-invasively via with positron emission tomography and magnetic resonanceimaging\textsuperscript{450-452}.

*Endothelial Dysfunction*

The endothelium plays an important role in vascular function, not only influencing vasomotor function but also adhesion of inflammatory cells and thrombosis. In addition to MCD, the ‘female pattern of IHD’ may also in part be due to endothelial dysfunction\textsuperscript{453}. Although the role of endothelial dysfunction in women is still largely controversial the WISE investigators have reviewed this topic in detail\textsuperscript{454}. Previous studies have demonstrated that impaired endothelium-dependent vasomotor function of the brachial and coronary arteries is associated with long term risk of cardiovascular events in women\textsuperscript{453, 455-457}. For a comprehensive review on stable angina in women please refer to a review conducted by women’s health pioneer Dr Wenger\textsuperscript{458}. 
A strong body of evidence supports the fact that individuals with CSA report a poorer HRQOL\textsuperscript{459,460}. Assessment of health status amongst 1000 patients following PCI and CABG showed uniformly that those free of angina had a better HRQOL than patients with residual angina\textsuperscript{460}. In the Australian CADENCE study, one in three reported angina occurring at least once a week, which was associated with a poorer HRQOL. Predictors of weekly angina in CADENCE included female gender, a history of heart failure and PAD\textsuperscript{435}. Although the CADENCE study utilised a threshold of angina of at least once week, the relationship is a continuum as shown in Figure 2. Thus the more frequent the angina, the greater the impairment in physical limitation and quality of life. Hence enquiring about angina frequency may provide useful clinical insights into the impact of the disorder on the patient’s quality of life\textsuperscript{435}. Among patients in the Trial of Invasive Versus Medical Therapy in Elderly (TIME) study, baseline angina severity correlated significantly with quality of life. At similar angina levels, women had significantly poorer quality of life scores than men. Anti-ischaemic treatment improved physical, mental and social HRQOL domains, concomitant with relief of angina. This occurred in both genders, but was more pronounced following revascularisation than with medical treatment\textsuperscript{461}. 
Figure 2. Relationship between Angina Frequency and Patient-assessed Quality of Life Indices. SAQ = Seattle Angina Questionnaire. Adapted from Beltrame et al Arch Intern Med, 2009. 
1.4.12 Peripheral Artery Disease

1.4.12.1 Epidemiology of PAD in Women

Although in previous years we have seen the emergence of awareness campaigns focused primarily on CHD in women, endorsed by professional organisations such as the AHA, less attention has been emphasized on other atherosclerotic arterial beds, particularly PAD. This gap in awareness and knowledge has been addressed by the recent Scientific Statement of the AHA: “A Call to Action: Women and Peripheral Artery Disease”

Unlike CHD, the population-based prevalence of PAD in women has been incompletely evaluated with few population surveys performed. In fact, ongoing PAD investigation is not currently conducted in any state or nation and many studies do not report prevalence for women separately.

Previous literature is miscellaneous but one PAD review published in 2003 reported that the prevalence of PAD in women aged between 45 to 93 years ranged from 3-29% over the span of 5 decades. Due to the lack of prevalence data available by gender in 2012, Hirsch and colleagues calculated the prevalence for both gender groups using individual participant data and meta-analytic methods. In this contemporary analysis, the prevalence of PAD increased with age for both men and women, in particular women aged 70 years had a PAD prevalence of up to 12% and 25% for those aged over 80. More concerning, as reflected by 2010 US census data, the burden of PAD appear to be more prevalent in women than in men (particularly those ≥40 years of age). In terms of mortality, few prior studies have reviewed gender specific differences. However, preliminary data suggest that the association between ABI values and total mortality, CVD mortality and major coronary events are similar.
in women compared with men. Specifically, in women, the risks for morbidity and mortality are increased with lower ABI values and with values $\geq 1.40^{463}$. Conversely to CHD, clinical research to evaluate gender-based differences that might underlie the delayed, postmenopausal presentation of PAD in women has not yet been conducted. As in CHD (ACS, CCS), the main female differences in PAD are summarised in Table 19 below.
<table>
<thead>
<tr>
<th>Category</th>
<th>Differences in PAD Features Compared with Men</th>
</tr>
</thead>
</table>
| **Traditional Risk Factors**   | • **Age, Hypertension** & **Hyperlipidemia**- similar to men (age ~65 years)\(^{464}\)  
  • **Diabetes**- ↑risk factor for women (however, preventative care for women poor)\(^{465-467}\)  
  • **Smoking**- ↑potent risk factor for symptomatic PAD in women\(^{468}\)  
  • **Ethnicity**- Minority women (African American, Hispanic) have ↑prevalence PAD\(^{469-473}\) |
| **Clinical factors**           | • **Presentation:**  
  - Women report ↑asymptomatic symptoms\(^{474-476}\)  
  - ↓walking distance, speed & leg strength\(^{475, 477, 478}\)  
  **Treatment:**  
  - Receive ↓aggressive therapy/risk factor management\(^{172, 479}\)  
  - ↓lower limb revascularisation (despite ↓functional impairment)\(^{469, 480}\)  
  - ↑graft stenosis (perhaps due to smaller artery size)\(^{481-483}\)  
  • **Poorer outcomes:**  
  - ↑Risk CVD morbidity/mortality (particularly in those women with low ABI values ≥1.40)\(^{463}\)  
  - ↑rates of amputation compared to men\(^{484}\)  
  - ↓lower extremity functional impairment compared to women without PAD\(^{474, 485}\) |
| **Biological factors**         | • *Not examined within the current literature* |
| **Psychosocial factors**       | • **Socio-economic status**- ↓leads to poorer preventative services for women\(^{486}\)  
  • **Quality of life**- ↓baseline/12 month function & ↓HRQOL in women with PAD\(^{487-490}\)  
  • **Depression**- ↑prevalence in women (specifically, women >65 years)\(^{491}\) |

Table 19: Sex/gender Differences in Peripheral Artery Disease
1.4.12.2 Risk Factors

PAD is traditionally associated with male sex and a smoking history presenting with IC. The risk factors for the development of PAD in women are similar to other atherosclerotic disease such as CHD, which are described in section 1.1.3. These include older age, diabetes, smoking, family history, hypertension and hyperlipidemia$^{464}$. Diabetes is well known risk factor for PAD however specific preventative care for women is poor$^{465}$. In minority groups (i.e. African American), the interaction of biology and environment leads to a greater prevalence of diabetes as well as a more advanced stage of PAD on initial presentation$^{466, 467}$. In addition to diabetes, smoking is now known to be a potent risk factor for symptomatic PAD in women (amongst relatively healthy patients), which has also been associated with subclinical inflammation$^{468}$. In light of the above, the disparity in risk factors for women is more likely to be strongly related to social determinants of disease$^{492}$.

Ethnicity/Racial background

Similarly to CHD, gender differences in regards to race have been documented in the prevalence and treatment of PAD$^{469-473}$. Specifically, minority women perform worse than Caucasian women in terms of health status as well as rates of disability and mortality. Graft failure rates are also the highest amongst African American women; with an increased risk of graft thrombosis and major amputation at 12 month follow up$^{471}$. In a post hoc analysis of the PREVENT III (Project of Ex vivo vein graft engineering via transfection III) trial,$^{471}$ it was revealed that graft failure rates were the highest among African American women (with an increased risk of graft
thrombosis) (HR 2.02 for secondary patency) as well as an increased risk of amputation (HR 2.3) at 12 month follow up. In addition, Hispanic origin has been reported to be an independent predictor of both limb loss and those undergoing lower extremity bypass surgery\textsuperscript{493}. In light of the above gender, racial background and ethnicity appear to be major determinants of vein graft and limb loss and thus more prospective research is warranted.

\textbf{Social Factors}

Previous research has highlighted that socio-economic status is a key factor that may determine access to preventative care in women with PAD\textsuperscript{486}. For example, there is pilot data to suggest that certain environmental exposures may influence socio-economic status and thus result in higher rates of diabetes and greater rates of obesity/physical inactivity in women\textsuperscript{492}. Specifically, in the Heinz Nixdorf Recall Study, both gender groups with PAD were been shown to have lower ABI values yet higher rates of PAD coupled with lower education levels\textsuperscript{486}. Importantly, PAD patients with a low (OR 2.58) or medium level (OR 1.90) education had higher odds of developing PAD compared to participants with a high level of education (even following adjustment for important clinical covariates)\textsuperscript{486}. Furthermore, independent determinants of lower education and higher PAD prevalence levels included smoking status, diabetes and a high BMI. Accordingly, it has been suggested that adequate risk factor management (i.e. smoking cessation, weight management) should be targeted in individuals from a low socio-economic background and amongst minority groups (i.e. women).
1.4.12.3 Clinical Factors

*Presentation: Leg symptoms*

Although IC is considered a characteristic manifestation of lower extremity PAD, it is well recognized that many patients with PAD do not actually present with classic symptoms. Compared with men, around 50% of women with PAD have been found to be more often asymptomatic (defined as absence of exertional leg symptoms in the presence of an ABI >0.90) or only mildly symptomatic. Non-specific symptoms in women include fatigue in the extremities as well as rest discomfort. In the Women’s Health and Ageing study (WHAS) of 933 disabled women ≥65 years of age, it was reported that 63% of patients had no exertional leg pain among those with walking pain. Furthermore, other lower extremity symptoms were present. The decline in function from PAD was also reported to be greater in women than men. These low level types of activities correspond with activities of daily living, which can ultimately lead to greater functional decline and dependency for care in women. The increased prevalence of asymptomatic disease in women with PAD may lead to delayed diagnosis and treatment (as per CHD).

*Treatment*

Similarly to CHD, women with PAD who experience greater functional impairment are less likely to undergo lower extremity revascularisation compared to men. This is consistent with previous research, which suggest that graft stenosis is more common in women than men undergoing lower extremity revascularisation, perhaps due to smaller artery size in women. In addition, PAD is often undetected in...
women in general practice\textsuperscript{497} and thus no treatment is afforded to these patients\textsuperscript{498}. Consequently, women receive less aggressive therapy than their male counterparts including lack of awareness in access to screening, diagnosis and treatment of PAD\textsuperscript{479}.

\textit{Diagnosis}

As mentioned in section 1.3.5 of this introduction, the diagnosis of PAD is best established in both gender groups by a vascular history/physical examination, supported by the measurement of an ABI\textsuperscript{150}. In addition, duplex ultrasound and advanced imaging techniques may be utilised to evaluate the location and severity of the disease. Unfortunately, current data available does not support sex specific differences in these pathways for PAD therapy. For example, the ABI assessment is indicated for all individuals regardless of gender group as well as patients with diabetes, abnormal extremity pulses or exertional limb symptoms. Although the anterior and posterior systolic pressures in men and women vary somewhat, mainly due to gender based height differences), no current study to date has examined gender differences in the techniques used to measure ABI. In addition, there is no data available to support gender-based differences in the diagnostic sensitivity or accuracy of other classical imaging based PAD tests (i.e. toe-brachial indices) or anatomic imaging techniques (i.e. magnetic resonance angiography, computed tomographic angiography). Current literature also does not demonstrate a differential accuracy of stenosis assessment by gender, despite the observation that arterial diameters are smaller for women than men. In conclusion, the relative sensitivity and specificity of
diagnostic tests in PAD as well as pathways by gender remain unclear and should be the focus of future research.

1.4.12.4 Symptomatic Women with PAD

In symptomatic women with PAD, standard treatment includes risk factor modification, pharmacological therapy, a supervised exercise program, lower extremity revascularisation as well as pneumatic lower extremity compression\(^\text{172}\). As a detailed explanation of treatment practices in symptomatic women with PAD is beyond the scope of this thesis readers are referred to a recent review by Hirsch and colleagues\(^\text{172}\).

1.4.12.5 Peripheral Ischaemic Outcomes

Due to patient’s generalised disease burden, people with PAD have a greater functional decline and greater mobility loss than those without PAD. In fact, women with PAD have both a greater lower extremity functional impairment than those women without PAD\(^\text{474, 485, 487}\) and men with PAD\(^\text{475, 477, 478, 487}\). More specifically, women with PAD have an increased prevalence of leg pain on exertion and rest, poorer functioning and greater walking impairment from leg symptoms than men\(^\text{475, 477}\). In terms of ABI, lower scores predict greater mobility loss and decline in walking-related disability among women compared to men\(^\text{496, 499}\). Although the mechanism underscoring the poor outcomes in women is currently unknown several explanations have been hypothesised including lower gender based leg strength, poorer cardio-pulmonary fitness as well as reduced calf muscle hemoglobin oxygen saturation.
compared to men\textsuperscript{475, 477, 478}. In addition, women have been shown to have higher rates of limb amputation compared to their male counterparts\textsuperscript{484}. Women are underrepresented in all PAD randomized trials\textsuperscript{500} and thus efforts to enroll women must to be expanded, as future investigation is needed to determine why this subgroup has poorer outcomes.

1.4.12.6 Risk of Cardiovascular Events

Regardless of PAD presentation (i.e. symptomatic vs. non-symptomatic), the relative risk of all cause mortality has been shown to be three-times greater in women with an ABI <0.9 vs. those with an ABI >0.9 and for CHD the risk is four-times greater. Vogt and colleagues have reported the levels of risk are similar following the exclusion of symptoms or a history of other CVD’s at initial presentation\textsuperscript{501}. More specifically, in a cohort of primary care patients with PAD the risk of stroke doubled over a 5-year follow-up compared to those without PAD\textsuperscript{502}. No study thus far has focused on gender differences in reporting cardiovascular mortality and major adverse cardiovascular events in this vulnerable sub-population. This gap within the literature is further explored in chapter six of this thesis (Gender Differences in Outcomes and Health Status Amongst Patients with PAD)
1.4.12.7 Psychosocial factors

*Health related quality of life (HRQOL)*

Patients with PAD are faced with disability and reduced health status due to significant walking impairment. These manifestations include reduced walking speed, walking distance and stair climbing and appear to be greater in women with PAD\(^475\). Patient reported outcomes such as health status (see section 2.1.1.1) have gained increasing recognition in the literature as indicators of standard quality of care with disease specific measures utilised over generic assessments\(^393\). However, there is a paucity of data in regards to health status in PAD, particularly in terms of gender.

Previous research has reported that women have a poorer health status and HRQOL compared with men with PAD\(^487-490\) (Table 20). Conversely others have found the opposite result\(^503-505\). In their prospective longitudinal study evaluating HRQOL amongst patients with CLI and IC, Wann-Hansson and colleagues found that female gender adversely impacted durability of HRQOL following revascularisation\(^489\). Oka et al evaluated HRQOL in patients with claudication and reported that women had a decreased level of physical functioning, more bodily pain and a greater mood disturbances compared to men\(^488\). Furthermore, Collins et al reported that women had an impaired walking subscale as well as lower physical functioning and general health compared to men with PAD. More recently, Mastenbroek and colleagues demonstrated that women following endovascular repair experience worse physical health, greater disability and worse overall health status compared to men\(^490\). Due to their disability women with PAD may be less likely to leave their homes or community, making them less likely to travel for an examination or participate in a
study secondary to increased functional disability\textsuperscript{475}. Although these studies shed some light on important gender disparities in PAD, conclusions cannot be drawn in respect to the gender disparity in outcomes. Prospective research should target gender differences in self-reported health status at baseline (initial diagnosis) and 12 month follow up using PAD disease specific measures (See chapter six: Gender Differences in Outcomes and Health Status Amongst Patients with PAD)
<table>
<thead>
<tr>
<th>Author</th>
<th>No. Women</th>
<th>Study Inclusion</th>
<th>Outcome Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oka (2003)</td>
<td>26 (27%)</td>
<td>&gt;18 yrs with diagnosis of PAD based on ABI &lt;0.9</td>
<td>SF-36, WIQ</td>
<td>Women physical functioning &amp; bodily pain &amp; mood disturbances</td>
</tr>
<tr>
<td>Bloemenkamp (2003)</td>
<td>208 (30%)</td>
<td>Between 18-49 years with angiographically confirmed diagnosis of PAD</td>
<td>RAND-36</td>
<td>Quality of life in young women with PAD statistically diminished on all domains of RAND-36</td>
</tr>
<tr>
<td>Wann- Hanson (2005)</td>
<td>81 (57%)</td>
<td>Ischaemic claudicants &amp; critical limb ischemia</td>
<td>NHP score</td>
<td>Women associated with poorer HRQOL.</td>
</tr>
<tr>
<td>Collins (2006)</td>
<td>208 (52%)</td>
<td>&gt;50 yrs with diagnosis of PAD based on ABI &lt;0.9</td>
<td>SDCQ, SF-36, WIQ &amp; LCS</td>
<td>Women walking impairment, physical function, general health.</td>
</tr>
<tr>
<td>Mastenbroek (2012)</td>
<td>100 (28%)</td>
<td>Endovascular surgery patients</td>
<td>PAQ (Dutch version)</td>
<td>Women physical health, greater disability &amp; worse overall Health status.</td>
</tr>
</tbody>
</table>

Table 20: Summary of Previous Studies on Gender Differences in Health Status in PAD Patients.
**Depression**

In addition to traditional cardiovascular risk factors there is mounting data available to support the fact that psychological characteristics such as depression are crucial determinants of outcomes in patients with PAD. In fact, depression is common among PAD patients, affecting approximately one in five patients\(^{506-509}\). Depressive symptoms in this cohort are associated with a compromised functional status\(^{508}\) and poor prognosis such as an increased risk of CHD events\(^{510}\). The disability associated with PAD may induce depressive symptoms due to the loss of social functioning and also loss of independence in the community. The subsequent functional decline associated with depressive symptoms may be due to several psychologically and/or biologically mediated pathways. Similar to CHD\(^{266}\), younger women may be more prone to experiencing significant depressive symptoms in PAD\(^{191}\). Smolderen and colleagues demonstrated that young women with PAD (i.e. <65 years) have significantly greater depressive symptoms at baseline and 6 month follow up than men or any other age group.

**Mood States**

In addition to depressive symptoms, mood states such as anxiety and anhedonia (i.e. lack of positive affect- type D personality) have been recently investigated in PAD and are strong correlates of outcomes, even following adjustment for conventional PAD indices\(^{506, 509, 511}\). The type D personality profile identifies a subgroup of patients at risk of a broad range of adverse outcomes such as a range of negative feelings and poor social interaction which negatively impacts on patient’s HRQOL\(^{512}\). Smolderen and colleagues have demonstrated that anxiety; depression and anhedonia were
prevalent in 29%, 30% and 28% of PAD patients with atypical leg symptoms associated with co-morbid mood problems\textsuperscript{513}. No gender-based data on this topic is currently available. In conclusion, to eradicate gender based disparities in PAD, depression screening and monitoring in women may be an important direction for future research and intervention.
1.5 Thesis Objectives

The overall aim of this thesis is to examine sex/gender disparities in a range of cardiovascular disorders. The specific objectives of the experimental studies include the following:

A. In chronic stable angina patients attending general practitioner clinics (Chapter 3):
   1) To determine gender differences in health status outcomes using the Seattle angina questionnaire (SAQ).
   2) To evaluate potential contributing clinical factors that may explain any observed gender disparity in health outcomes.
   3) To examine gender disparities in (a) coronary risk factors, (b) angina characteristics and diagnostic investigations and (c) angina therapies.

B. Concerning gender differences in DTB time amongst patients with STEMI receiving PCI (Chapter 4):
   1) To evaluate the components responsible for the time delay in women.
   2) To evaluate the independent predictors of a delayed DTB time.

C. Regarding sex differences in cardiac haemodynamic measurements in patients with STEMI receiving PCI (Chapter 5):
   1) To examine if female sex is an independent predictor of PCWP.
   2) To evaluate whether PCWP contributes to all cause 30-day mortality/re-infarction in women.

D. In PAD patients attending Dutch vascular clinics (Chapter 6):
   1) If outcomes in women differ with regards to the occurrence of mortality and long-term major adverse cardiovascular events.
2) If there is a gender difference in self reported symptomatic health status using the short form SF-12 (SF-12) at baseline and 12 month follow up.
CHAPTER 2: METHODS
2.1 Thesis Methodology

The next section of this thesis details the methodology utilized in each chapter as well as a discussion of the attributes of the tools employed. In brief, this thesis explores different quantitative methods to evaluate clinical outcomes and health status in a range of coronary and peripheral disorders.

2.1.1 Epidemiology

The literal meaning of epidemiology is “the study of what is upon the people” which dates back to the Greek physician Hippocrates in 460-377 BC, the father of medicine and the first epidemiologist recorded in time. Today, the study of epidemiology involves the patterns, causes and effects of health and disease conditions in a defined population. Being the ‘pillar’ of public health practices, epidemiology informs policy decisions as well as evidence based medicine by classifying risk factors for disease and targets for preventative medicine.

Accordingly, this thesis utilises clinical epidemiological techniques associated with observational studies aiming to further examine known associations or hypothesised relationships using pre defined study design, data collection and statistical analysis as well as interpretation and dissemination of results. Specifically, this thesis employs measures of occurrence (i.e. incidence measures including hazard rates/survival analysis) and measures of association (i.e. relative measures including risk ratios, odds ratio and hazard ratios) with a particular focus on cardiovascular outcomes and HRQOL.
The broad principles described above have been utilized in this thesis to analyse three independent databases including (a) The Australia wide CADENCE study (Chapter 3), (b) a local South Australian hospital STEMI registry (Chapters 4-5) and (c) a Dutch PAD registry of outpatient participants (Chapter 6). The specific methods employed in these studies are described in this chapter and include a discussion of (a) clinical data management, (b) the case report form, (c) data dictionary, (d) data collection and entry, (e) data quality assurance and audit, and (f) data governance and ethics.

These methods for ‘good’ quality clinical epidemiological practice were not only gained from experience in conducting the above studies, but also in other databases I have established that have not been included in this thesis, as the studies are on-going. These include the VIRGO, PORTRAIT and HOPIC studies (See Ancillary projects coordinated), all of which I have established and coordinated. The processes of establishing a database within epidemiological research are listed in Figure 3 below.

2.1.2 Data Management and Design

2.1.2.1 Clinical Data Management

Clinical data management (CDM) is a crucial phase in clinical epidemiological research\(^{514}\), which ultimately leads to the ‘generation of high quality, reliable and statistically sound data’ in compliance with regulatory standards\(^{515}\). These standards are audited by government agencies such as the United States Food and Drug Administration (FDA) (See section 2.1.2.7). In turn, the database coordinator is
responsible for the collection, quality, recording, maintenance and retrieval of the data arising from the clinical study. The database coordinator may originate from a variety of backgrounds including science, nursing, statistics/computing or programming and generally work as part of team of primary investigators, researchers, data collection personnel, statisticians and analysts.

The processes involved in good CDM include the following: (a) study design and generation of the case report form (CRF), (b) development of the data dictionary, (c) design of the database, (d) patient enrollment and data collection, (e) data entry and auditing and (f) statistical analysis. Above all else, the database coordinator and study investigators should comply with ethical regulations and Good Clinical Practice (GCP) at all times. Study investigators may include both principal investigators (lead scientists or clinicians in a well defined science and/or research project such as a laboratory study or clinical trial) as well as study investigators (may include junior researchers as well as data coordinators).

A database in clinical research is intended to find answers to the research question by means of generating data for proving or disproving a scientific hypothesis, thus the quality of the data generated plays a crucial role in the outcome of the study. In clinical epidemiological research there are two main types of databases including relational databases or flat file databases which both provide a systematic way of accessing, managing and updating data.

A relational database is one that contains multiple tables of data that ultimately relate to each other through special key fields. In fact, relational databases are known to
be more flexible, (though more difficult to design and maintain) as compared with simple flat file databases, which contain a single table of data\textsuperscript{517}. In addition, within clinical research there are observational studies or clinical trials. This thesis deals with observational research projects within both cohort designs (observations made in a group of subjects followed over time) and cross sectional studies (observations made on a single occasion). Cohort studies can be further sub-classified into prospective studies (begin in the present and follow subjects into the future) and retrospective studies (examine information that have been collected in the past).

2.1.2.2 Study Design

As mentioned above, the database in clinical research is generated with the intent of finding answers to a specific research question for proving or disproving a hypothesis (Figure 3). The scientific hypothesis (from Ancient Greek- meaning to ‘put under’ or ‘suppose’) is a proposed explanation for a particular phenomenon. In accordance with GCP, the study investigators should have a pre-defined set of research questions/hypotheses based on previous observations and research. To generate a feasible research question it is crucial to conduct an extensive literature review of published research on the topic of interest, commonly referred to as a systematic review. The characteristics of a ‘good’ research question, assessed in the context of the intended study design, assume that is be (a) feasible, (b) interesting (c) novel (d) ethical and (e) relevant\textsuperscript{518}. The study findings are then used to raw inferences about the occurrence of the study sample (internal validity) and about events in the world outside (external validity).
1. Identify specific research question/hypothesis

2. Design appropriate study to address research question

3. Archiving of data & development of data dictionary/CRF

4. Clean data & audit

5. Enter data into statistical program (i.e. SPSS)

6. Explore data using descriptive statistics

**Conduct statistical analyses to compare groups:**
- T-tests
- Analysis of variance (ANOVA)
- Multivariate analysis of variance (MANOVA)
- Analysis of co-variance (ANCOVA)
- Non-parametric techniques

**Conduct statistical analyses to explore relationships:**
- Correlation
- Partial correlation
- Multiple regression
- Logistic regression
- Factor analysis

Figure 3: Process of Data Analysis and Cleaning in Clinical Epidemiological Research.
2.1.2.3 The Case Report Form

Once the data items, type of database, research question and study protocol have been identified the CRF is generated. This is a tool used to collect pre-defined data from a participant in a clinical or observational trial with emphasis based on (a) the importance of designing an appropriate CRF in terms of length (not too long that it impact on patient consent/data collection and not too short so that essential information be missed) and (b) the CRF should be easy to read and be cross referenced with the data dictionary. The international conference on harmonisation (ICH) define the CRF as “a printed or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject”. Although considerable advancements have been made in the study and production of electronic CRF’s, such as those with optical mark or character recognition, the majority of trial data are still collected on paper CRF’s with data responses then translated to the database by means of data entry performed in-house. A more detailed discussion of the case report form design and development process can be found in Avey and Wright. In brief, the CRF should be carefully reviewed referencing the protocol document to be sure that the questions and required fields on the CRF are clear.

2.1.2.4 Data Dictionary

In addition to the CRF a standard operating document should be prepared in the form of a data dictionary. This document provides detailed written instructions for the definitions of new variables, procedures and a general framework for the implementation of all the function and activities of each procedure. It contains a list of
all files in the database, the number of records in each file, and the names and types of each field. For a detailed discussion of the development and process of the data dictionary please refer to authors Hulley and Rondel.

2.1.2.5 Data Collection and Entry

In clinical research the transfer of data from the paper CRF to the online operating system or database is a critical step, and accuracy of data entry is essential. Although it is preferable that the CRF should be directly entered electronically, most contemporary clinical databases still rely on paper CRF’s. Professional data operators, database coordinators or other staff familiar with the trial or study can complete data entry. As errors in data entry process can lead to incorrect values entered into the database, it is extremely important that the data entry system be established with adequate quality control checks. There are several ways of carrying out data checks including (a) double entry data, (b) manual review of keyed data or (c) computerised consistency checks of the data after it has been entered, or a combination of the three. In addition, to supplement the continuous checking of each individual’s data during the study, descriptive statistics on each important variable in the database are useful in the detection of unusual data or outliers. In any later auditing of the study by an independent body, the documentation will allow them to perform a thorough retrospective assessment of the data and study performance. The database coordinator should retain the records and data from the study for safety reasons and for auditing and inspection subsequent to study completion. Access to data should be available only to authorized study personnel with confidentiality of the database protected by appropriate standard operating procedures. Transparency, authenticity
and accuracy are crucial in any epidemiological research. Thus, it is the responsibility of the investigators to ensure that the principles of GCP are adhered at all times.

2.1.2.6 Data Quality Assurance and Audit

The aim of data quality assurance in a clinical study is to primarily minimise the effects of missing and/or inaccurate data. Following the completion of the research project, the data editing process includes specified procedures for data confirmation and is necessary, modification of the data. The ideal procedure followed for data auditing should assure a rapid response to ensure that the process is efficient in bringing queries about validation to the attention of the database coordinator. The rationale for a data audit in clinical research is to (a) determine that the rights, safety and welfare of the study participants are upheld, (b) to evaluate the conduct of the research project, protocol compliance and the site’s operating procedures, (c) to validate the integrity and reliability of the data and (d) to determine that all local regulatory procedures are being followed which include standards set by institutional ethics committees and larger agencies such as the FDA.

Components of any clinical trial audit include assessing appropriate regulatory/ethics documents, informed consent and CRF data comparison to original source documents. Following a proper quality check and assurance, the final data validation is run. Once the approval for ‘locking’ is obtained the database is locked and clean data is extracted for statistical analysis. This ‘locking’ process refers to the completion of data collection, entry and audit by all study investigators as well as notification to institutional ethics committees that the study has been completed. Following a lock of
the data, the statistical analysis can be completed (Figure 3). The data is first explored using descriptive statistics and graphical techniques followed by modification of variables for further analysis. The main statistics used in clinical research are described in section 2.1.5 of this methods chapter. In short, statistical analyses are developed to explore relationships (i.e. correlation) or to compare groups (i.e. ANOVA).

2.1.2.7 Data Governance and Ethics

Data governance embodies a convergence of (a) data quality and management, (b) specific data policies and (c) business/risk process management surrounding the handling of data in a particular organisation. In CDM, guidelines and standards must be followed to ensure GCP. The main clinical trial regulatory agencies in the United States include the U.S. Food and Drug Administration (FDA) and the office for Human Research Protections (OHRP). The main regulatory body in Australia is the National Health and Medical Research Council (NHMRC), which promotes the development and maintenance of public and individual health standards. Through data governance, organisations such as the FDA and NHMRC are looking to exert positive control over the methods and processes utilized by their data stewards and/or data custodians to handle data. In light of these regulatory bodies, the database coordinator must ensure that adequate procedures and controls are put in place to ensure the integrity, authenticity and confidentiality of the data.
2.1.3 Study Endpoints

Within epidemiological clinical research, a clinical endpoint refers to the “incidence of a disease, symptom, sign or laboratory irregularity that constitutes one of the target outcomes of the trial, but may also refer to any such disease or sign that strongly motivates the withdrawal of that individual or entity from the trial”. A study endpoint is an objective morbid condition or cause of death linked to CVD, used as an indicator in a clinical trial or reportable event (e.g. quality of life). An endpoint in clinical research should be (a) relevant to the disease and the population under investigation, (b) acceptable to the scientific community and regulatory authorities, (c) responsive to change, (d) reproducible, (e) widely available (particularly when considering multicentre trials) and (f) reliable and acceptable to subjects. The three major types of endpoints include clinical (i.e. mortality, AMI, angina), patient-reported (i.e. response from questionnaire) and surrogate (i.e. laboratory measures) endpoints.

A study endpoint may be considered as a primary, secondary or safety endpoint. A primary endpoint of a study underlies the main objective of the study and thus determines the statistical design of the study from which sample size and power are based upon. Secondary endpoints are made up of combinations of outcome measures that provide useful information regarding the benefits and harms of the investigated treatment. On occasions, a safety endpoint may be required to alert a Data Safety and Monitoring Board. This is particularly relevant to medication/device registries in monitoring for adverse outcomes.
2.1.3.1 Clinical Outcome End Points

In cardiovascular outcomes research, a major clinical endpoint often utilised is the Major Adverse Cardiac Events (MACE) composite endpoint. This is comprised of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. It is often used as the primary endpoint in cardiovascular outcomes studies, for efficacy and safety purposes. Historically, the term MACE appears to have originated in the mid-1990s with its use restricted primarily to in-hospital complications related to PCI\textsuperscript{525,526}. Today, however, even though there is no standard definition of MACE, it is routinely used and reported for procedural, short-term, and long-term outcome evaluations, and may involve other cardiovascular treatments. Other important clinical endpoints of interest include mortality and complication rates (i.e. AMI, re-admission), which have been used to assess differences in treatment strategies, healthcare needs and costs for patients with CHD in randomised clinical trials, as well as symptoms such as angina which becomes relevant in chapter three in regards to the CADENCE study.

2.1.3.2 Physiologic and Biochemical End Points

Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured. They are employed because of their association with certain important clinical outcomes and are often used when observation of clinical outcomes is difficult to achieve. In chapter five of this thesis, the surrogate endpoint of interest is pulmonary capillary wedge pressure (PCWP). This is the pressure measured by wedging a pulmonary catheter with an
inflated balloon into a small pulmonary arterial branch. In addition, DTB is a hospital performance surrogate measure, which is employed in chapter four of this thesis and is discussed in section 2.1.3.1 of this methods section.

2.1.4 Study Instruments

2.1.4.1 Health Status

Epidemiology not only incorporates monitoring diseases within the wider community but also their impact on health. Accordingly, the focus should not only be on the disease manifestations of CHD (i.e. ACS and CCS) but also the patient’s perception of the impact of these disorders on their health. In patients with chronic disease the term ‘health status’ refers to: “The range of manifestation of disease in a given patient including symptoms, functional limitation and quality of life, in which quality of life is the discrepancy between actual and desired function”\textsuperscript{527}.

Therefore ‘health status’ (see Figure 4 below) is used to define the patient’s perception (rather than the clinician’s perception) of the disease process on their lifestyle, which is particularly important in everyday life. Conventionally, clinicians have focused on diagnosing the disease and evaluating the symptoms, whereas patients are focused on the complete range of health status. Patient reported health status measures have been shown to be significantly important when assessing the overall well being of a patient\textsuperscript{393, 528}. Thus, the most utilised framework for conceptualizing health status is to independently quantify the ways in which a chronic illness affects a patient’s life. The pathway of disease in CHD depicts the path to disability whereby clinical symptoms (i.e angina) caused
by CHD can lead to functional limitations and consequently an impaired quality of life\textsuperscript{391}.

\textbf{Figure 4. Summary of Patient-Centered Health Status.} Adapted from Spertus, Circulation, 2008\textsuperscript{393}.
2.1.4.2 Cardiovascular Health Outcomes

Within cardiovascular health outcomes research there are a range of subjective and objective endpoints, which are used to evaluate disease progression, and patient reported health status. Subjective outcomes (often referred to as ‘soft’ end-points) include measures such as quality of life, social health, pain perception, and patient satisfaction\(^529\). Conversely, objective measures (often referred to as ‘hard’ end-points) include measures such as cardiac events and mortality, and are frequently used in clinical research\(^530\). These objective outcomes are important clinical markers; however, they are often poor indicators of a patient's physical and emotional wellbeing.

Clinicians typically focus on hard end-point measures (i.e. mortality, AMI) or other adverse cardiovascular events when examining the effectiveness of a therapy. However, by doing so they have a propensity to underestimate a patient's disability\(^531\). Whilst objective measures such as mortality are central outcomes for measuring physical dimensions, they fail to reflect the functional limitations of the disease on a daily basis\(^532\). In light of this there has been much debate in the literature regarding the use of both measures with several studies showing that a combination between subjective and objective measures provide a more comprehensive evaluation\(^532-534\).

2.1.4.3 Health-Related Quality of Life in CHD

Health-related Quality of Life (HRQOL) characterises the functional effect of an
illness and its consequent treatment upon a patient, as perceived by the patient\textsuperscript{530}, which is assessed by the health dimensions relevant to a particular set of patients\textsuperscript{535}. These health dimensions can include the evaluation of clinical symptoms, bodily and emotional functions over a course of time\textsuperscript{536}. Although popular in the 1970’s as a multidimensional concept reflecting the overall subjective condition of the physical and mental welfare of the individual\textsuperscript{537}, HRQOL has since been replaced with ‘health status’, which has been defined in section 2.1.1.1. Furthermore, HRQOL has been used as a primary outcome measure in clinical trials for determining therapeutic benefit and improving quality of care.

2.1.4.4 Health-Related Quality of Life Assessments

Patient reported outcomes such as health status have gained increasing recognition in the medical literature as indicators of standard quality of care. Although both generic and disease specific measures are being used for this purpose, disease specific measures are sensitive to detect small but clinically meaningful differences in outcome as they evaluate patient limitations specific to the disease. Assessment of health status can be undertaken either by the patient or clinician. Validated instruments (i.e. questionnaires) quantify the impact of a patient’s health status and determine the extent of their symptoms, functional limitations and quality of life. The main validated instruments available for the assessment of HRQOL in patients with CHD are summarised in Table 21 below. The specific HRQOL tool utilised in clinical research should fulfill standard psychometric criteria including properties of validity, reliability or reproducibility and responsiveness.
Validity: In clinical research, this refers to the ability of a measure or instrument to quantify the item it is intended to measure. There are several specific types of validity, which have been described previously, including (a) criterion validity, (b) content validity, (c) face validity and (d) construct validity. Based on psychometric standards, criterion validity is a measure of how well one particular variable or set of variables is able to predict an outcome based on information from various other variables. In turn, content validity is defined as the extent to which a measure represents all facets of a given social construct. Face validity is often contrasted to content validity as a property of a test intended to measure something or ‘looks like’ it is measuring what it is purported to measure. Lastly, construct validity is defined as whether a scale correlates with the theorised psychological scientific construct that it purports to measure.

In addition to the above, the instrument should possess discriminative validity in its ability to detect changes in the observed variable without provoking a ‘floor ceiling’ effect that reflects an inability to detect clinically significant changes.

Reliability: This is usually assessed using either, (a) internal consistency and (b) test-retest reliability. These have been described previously, however in brief; internal consistency is an estimate of homogeneity of items measuring a specific health domain whilst test-re-test reliability is a measure of an instruments ability to produce data which are consistent over time. Thus, an instrument can be considered reliable when it measures what it truly intends to measure whereby reproducibility is defined as a high signal to noise ratio. If the variability in scores between patients (the signal) is much greater than the variability within patients (the noise), an instrument will be
considered reliable. Reproducible results are obtained when the measure is repeatedly given to stable patients.\textsuperscript{538}

**Responsiveness:** An instrument’s responsiveness is its ability to be sensitive in detecting any magnitude of clinical change.\textsuperscript{538, 539}

Overall, the measure employed in any clinical trial should be valid, reproducible and responsive to changes induced by treatment. In general there are two types of questionnaires that can be individually or equally used in population-based HRQOL studies:

**Generic instruments** address multiple aspects of quality of life across a range of different patient or disease groups. They are widely used to monitor a patient’s progress during an illness and give a broad assessment of that person’s health status.\textsuperscript{540} Thus they focus on general health issues rather than specific features of a particular disease, thereby allowing comparisons across different disease states. Many generic questionnaires have been developed for evaluating overall quality of life in relation to any chronic disease. However, because they are general, this sometimes limits their responsiveness to detecting change in a particular illness.\textsuperscript{541}

**Disease-specific instruments** comprise content specific to the disease in question and therefore tend to focus on areas of clinical relevance to clinicians. A disease-specific questionnaire is able to quantify the physical and emotional effects concerning a specific clinical condition.\textsuperscript{542} These disease specific tools are also more clinically sensitive and potentially more responsive to subtle improvements in health, especially
in patients with co-morbid conditions\textsuperscript{541}. In clinical trials, the combination of a generic and disease-specific questionnaire provides a more comprehensive assessment of health status.

2.1.4.5 CHD Instruments

Over the past 30 years there have been a plethora of health status instruments generated to specifically assess HRQOL\textsuperscript{543}. As previously mentioned, health status measures have become increasingly popular and important tools in assessing patient centered outcomes in CHD patients\textsuperscript{544}. The two main categories of instruments (as described above) include generic and disease specific assessments\textsuperscript{545} which are listed in Table 21 below

<table>
<thead>
<tr>
<th>Generic instruments</th>
<th>Disease Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickness impact profile (SIP)\textsuperscript{546}</td>
<td>Seattle angina questionnaire (SAQ)\textsuperscript{536}</td>
</tr>
<tr>
<td>Short Form health survey (SF-36)\textsuperscript{547}</td>
<td>Quality of life after Myocardial infarction questionnaire (QLMI MacNew)\textsuperscript{552}</td>
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<tr>
<td>Short Form health survey (SF-12)\textsuperscript{548}</td>
<td>The angina pectoris quality of life questionnaire (APQLQ)\textsuperscript{553}</td>
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<tr>
<td>Euro quality of life questionnaire (EQ-5D)\textsuperscript{549}</td>
<td>Myocardial Infarction Dimensional Assessment Scale (MIDAS)\textsuperscript{554}</td>
</tr>
<tr>
<td>Nottingham Health Profile (NHP)\textsuperscript{550}</td>
<td>Cardiovascular Limitations and Symptoms Profile (CLASP)\textsuperscript{555}</td>
</tr>
<tr>
<td>WHO quality of life questionnaire (WHOQOL)\textsuperscript{551}</td>
<td></td>
</tr>
</tbody>
</table>

Table 21: Validated Instruments Available for the Assessment of HRQOL in Patients with CHD.
**Generic Assessments in CHD**

There exist several generic measures, which are used to assess HRQOL in patients with CHD. In a review conducted by Donnelly and colleagues, it was highlighted that the most commonly utilised generic instruments in CHD setting include the Short-Form SF-36 (SF-36)\textsuperscript{547}, the Nottingham Health Profile (NHP)\textsuperscript{550} and the Sickness impact profile (SIP)\textsuperscript{546}.

**Short Form-36**

The Short form-36 (SF-36) is the most widely utilized generic health status measure, originally designed for use in population surveys and evaluative studies of health policy\textsuperscript{547}. Items on this questionnaire are grouped into eight main subscales including (a) physical functioning, (b) social functioning, (c) role limitations due to physical problems, (d) role limitations due to emotional problems, (e) mental health, (f) vitality, (g) bodily pain, (h) general health\textsuperscript{547}. The SF-36 has excellent psychometric properties as demonstrated in the general population\textsuperscript{556} and in CHD patients\textsuperscript{557-559}. The use of the SF-36 is an advantage to the researcher as it has the ability to create aggregated summary scores for both the physical and mental subscales with the added strength of an ability to distinguish a physical outcome from a mental outcome\textsuperscript{560}.
Short Form-12

The SF-12 has been condensed from the SF-36 in order to increase practicality and improve time application\textsuperscript{548}. The SF-12 has been demonstrated to be a valid and reliable instrument\textsuperscript{561} and similarly to the SF-36 it is the most widely used generic health status instrument in clinical trials\textsuperscript{560}. Instead of measuring the eight subscales as on the SF-36, the abbreviated SF-12 measures overall physical, and mental health status consisting of 12 items, which are answered along various Likert scales. The SF-12 is psychometrically comparable to the SF-36; however the SF-36 yields more information about health status as it can be divided into eight different scale scores whereas the SF-12 provides only two summary scores. Additionally, the SF-36 allows room for missing data so that scores can still be calculated, whereas the SF-12 is shorter and can be a limiting factor when dealing with small sample sizes\textsuperscript{562}. In this thesis within chapter six, a Dutch version of the SF-12 is utilised whereby physical component summary (PCS) and mental component summary (MCS) scores\textsuperscript{563} are generated through a standardised scoring algorithm and based on weights derived from Dutch population norms (score range between 0-100, mean score= 50, SD= 10) with higher scores indicating better functioning\textsuperscript{564}.

The Euro Quality of life questionnaire (EQ-5D)

The Euro quality of life questionnaire (EQ-5D) is a standardised measure of health status, which provides a simple and generic measure of health for clinical assessment\textsuperscript{549}. This questionnaire has two parts. The first is a descriptive section that classifies patients into one of 243 health states consisting of the following dimensions
(mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has three possible levels (i.e. 1-3) representing ‘no problems- extreme problems’. The second part is a 20cm visual analog scale (EQ-VAS) that ranges from ‘best imaginable state- worst state’ anchored at 100 and 0 respectively. This scale has been validated in both AMI patients and those with ACS undergoing cardiac rehabilitation.

**Nottingham Health Profile**

The Nottingham health profile (NHP) is a well-known generic quality of life instrument designed to measure subjective physical, emotional and social aspects of health. The questionnaire consists of two main parts. The first section requires yes/no responses to 38 statements grouped into eight scales (mobility, pain, energy, sleep, emotional reactions and social isolation) and the second section consists of questions related to the effect of health on work, looking after the home, social/home life, sex life, interests/hobbies and holidays. Although the NHP is useful in assessing the presence of severe health problems it does not provide the most comprehensive measure of HRQOL compared to other such measures. In addition it is controversial as to whether the NHP is able to distinguish between clinical cases of angina and also in its ability to discriminate between CHD patients and healthy controls. Reliability of the NHP has shown to be moderate-high, which have been evaluated using test/re-test methods as an indicator of subjective physical, emotional and social health status.
**Sickness Impact Profile**

The Sickness impact profile (SIP) is a generic measure of sickness related dysfunction\(^546\) which has a high internal consistency\(^574\) and is responsive to changes in health status following surgery\(^575\) but not AMI\(^576\). This instrument consists of 136 items grouped into 12 categories (sleep and rest, eating, work, home, management, recreation/pastimes, ambulation, mobility, body care/movement, social interaction, alertness behaviour, emotional behaviour as well as communication). Factor analysis has been used to scale down the categories into a physical dimension or a psychosocial dimension as well as an overall score of the SIP\(^577\).

**Disease Specific Instruments in CHD**

Over the past 20 years, a number of disease specific instruments\(^578\) have been designed to assess particular aspects of CHD including angina, AMI and other vascular disorders. The main measures employed include the Rose angina questionnaire, the Quality of Life after Myocardial infarction (QLM-1)\(^552\) now known as the MacNew\(^579\) and in more recent times the Seattle Angina Questionnaire (SAQ)\(^536\).

**The Rose Angina Questionnaire**

The Rose angina questionnaire has been widely used in epidemiological research as a standardised method for assessing angina\(^580\). Although this survey is a screening tool, rather than a diagnostic assessment tool, it has been shown to predict both major adverse coronary events in men\(^581\) as well as CHD mortality in men and women\(^582\). It
has also been known to predict morbidity and mortality in population-based studies. The Rose survey defines angina based on typical symptoms of chest pain caused by exertion. The complete questionnaire is extensive, however there is a current modified shorter version, which consists of a 3-item survey and is known to demonstrate more sensitivity than the longer version. Although the specificity and sensitivity of this survey has been tested, presently it does not fulfill the relevant psychometric criteria need to be properly validated.

**Quality of Life after Myocardial Infarction (MacNew)**

This questionnaire was originally designed to be utilised in patients with cardiac rehabilitation. The first version of this measure contained 26 items grouped into five domains including: symptoms, restrictions, confidence, self-esteem and emotion. Following the 1990’s this questionnaire was further refined through psychometric assessments and referred to as the “MacNew heart disease survey (QLM1-2)”. This more recent version consists of 27 items grouped into three main domains of emotional, physical and social function. The domains of the QLM1-2 show (a) high internal consistency estimates, (b) high property estimates of test-retest reliability and (c) moderate to high responsiveness.

**Seattle Angina Questionnaire**

The Seattle Angina Questionnaire (SAQ) is the leading HRQOL measure for patients with CAD. This tool is a 19-item self-administered questionnaire, which measures five dimensions of CAD including angina stability, angina frequency, physical
limitation, treatment satisfaction and disease perception. This SAQ disease-specific questionnaire has been shown to be valid, reliable, reproducible and sensitive in detecting clinical change, therefore making it a valuable functional health status measure. The SAQ tracks how patients are doing if they have angina, prior AMI, angioplasty, stent insertion or CABG and consequently measures how daily activities are limited by symptoms of CAD (particularly related to chest discomfort and angina). The advantage of administering this questionnaire in clinical practice is its ability to identify whether health status is improving, stable or deteriorating. Additionally, health status measures obtained from the SAQ have been shown to independently predict both mortality and hospitalisation in outpatients with CAD.

The SAQ is utilized in chapter three when focusing on gender differences in patients presenting with CSA.

In terms of comparisons between the HRQOL instruments in CHD mentioned above (generic versus disease specific), several authors have reviewed this topic in more detail and thus readers are referred to recent reviews on this matter. In brief, some aspects of a generic HRQOL instrument may not be sensitive or relevant to specific problems faced by CHD patients. Conversely, the disease specific measure is sometimes limited in its scope and therefore group comparisons are not available. In order to measure HRQOL more accurately in CHD patients it may be useful to utilize a combined measure of both generic and disease specific measurements.
2.1.4.6 Health related quality of life in PAD

PAD is associated with major limitations in mobility and physical functioning, and a decreased HRQOL. Many of the generic CHD instruments listed in Table 21 are also utilised in PAD research where health status is concerned. However, there are disease specific instruments, which assess claudication, symptoms of PAD and overall quality of life. The main instruments used within PAD care are listed below in Table 22. The most utilised measure, the peripheral artery disease questionnaire (PAQ) is described in brief below.

**Disease Specific**

- Peripheral artery disease questionnaire (PAQ)\(^{592}\)
- San Diego Claudication questionnaire (SDCQ)\(^{593}\)
- Walking impairment questionnaire (WIQ)\(^{594}\)
- Edinburgh Claudication Questionnaire\(^{595}\)
- Rose Claudication Questionnaire\(^{580}\)

**Table 22: Validated Disease Specific Instruments Available for the Assessment of HRQOL in Patients with PAD.**

*Peripheral artery disease Questionnaire (PAQ)*

The peripheral artery disease questionnaire (PAQ) is a 20-item survey, which was developed to assess health status in patients with PAD. Similarly to the SAQ, the PAQ quantifies patients’ physical limitations, symptoms, social function, treatment satisfaction and quality of life\(^{592}\). It has been demonstrated to be valid,
reliable and responsive and is useful in clinical trials and as a potential aid in disease management.

2.1.4.7 Depression Instruments

In assessing the HRQOL in patients with depression, both generic and disease specific measures are also available. Most depression specific measures are fairly short and relatively easy to score which makes them attractive instruments\textsuperscript{596}. Although there are several depression-specific questionnaires, the next section briefly reviews three well-established measures: the Hospital Anxiety and depression scale (HADS)\textsuperscript{597}, the patient health questionnaire (PHQ-9)\textsuperscript{598} and the Center for Epidemiologic Studies Depression Scale (CES-D)\textsuperscript{599}.

\textit{Hospital Anxiety and Depression Scale (HADS)}

The hospital anxiety and depression scale (HADS) was originally developed by Zigmond and Snaith\textsuperscript{597} and is commonly used by clinicians to determine the levels of anxiety and depression that a patient may be experiencing. The HADS is a 14-item scale with seven of the items related to anxiety and seven relating to depression. In chapter six, the HADS was used to detect the incidence of depression and anxiety in the PAD population\textsuperscript{513}. Criterion scores of $\geq 8$ for both subscales denoted clinically relevant symptoms of anxiety and depression\textsuperscript{513}. 
Patient Health Questionnaire (PHQ-9)

The PHQ-9 is the nine-item depression scale of the Patient Health Questionnaire. This survey is a powerful tool for assisting primary care clinicians in diagnosing depression as well as selecting and monitoring treatment. The main two components of the PHQ-9 include (a) assessment of symptoms and functional impairment in order to make a tentative depression diagnosis, and (b) deriving of a severity score to help select and monitor treatment. The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV)\(^598,600\).

Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D survey is a short self-report scale designed to measure depressive symptomatology in the general population. In this questionnaire, the focus is on the affective component, the depressive mood. The CES-D is widely used and easy to administer, especially in older populations. The items of the scale are symptoms associated with depression, which have been used, in previously validated longer scales\(^599\). The CES-D has a good reliability and shows an excellent sensitivity to detect major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Criteria.

2.1.5 Functional Outcome Assessment in CHD

The following section focuses on measures assessed and/or categorized by an observer rather than patient self-report. Two commonly used assessments utilized by
health care providers include the Canadian Cardiovascular Society Classification system (CCSC) and the New York Heart Association Classification system (NYHA).

2.1.5.1 Canadian Cardiovascular Society Classification System (CCSC)

Physicians may assess the severity of angina using the Canadian Cardiovascular Society Classification (CCSC) system\(^{601}\). This scale ranges from Class I (mild) to IV (severe)\(^{602}\). This scale for angina has been used as a reliable outcome measure in studies where severity is correlated with the extent of disease\(^{603}\). Although this scale assesses the physical limitations experienced by patients due to their angina, it has been known to have limited reproducibility and sensitivity which has been attributed to health status measured by the physicians perspective and not patient self report\(^{604-606}\).

2.1.5.2 The New York Heart Association (NYHA) Classification System

The New York Heart Association functional classification (NYHA)\(^{607}\) is similar to the CCSC system in that it quantifies the patient’s activity, quality of life (from the clinicians’ point of view), thus health status, is not directly reported by the patient. The NYHA classification system is frequently used in clinical practice and research; however it also has limited reproducibility and sensitivity\(^{604}\).
Performance measures identify aspects of care from clinical guidelines that improve patient outcomes and for which data can be feasibly collected and acted upon.\textsuperscript{608, 609} These measures afford healthcare professionals and clinicians with specific "tools" to assess the quality of care provided by defining specific and measurable elements. Through assessing performance on such elements, clinicians can identify opportunities for improvement. In the United States, the Centers for Medicare and Medicaid services (CMS) has been publicly reporting hospital specific quality alliance (HQA) performance measures since 2005. These measures evaluate whether available care processes recommended in current clinical guidelines are appropriately administered. These include the administration of aspirin within 24 hours, receiving PCI or achieving a DTB time within 90 minutes of hospital arrival (Table 23).\textsuperscript{610}

### Acute myocardial infarction

- Aspirin on arrival
- Aspirin at discharge
- ACE inhibitor or Angiotensin receptor blocker for left ventricular systolic dysfunction
- Beta blocker on arrival
- Beta blocker at discharge
- Fibrinolytic medication within 30 minutes of arrival
- PCI received within 90 minutes of hospital arrival
- Smoking cessation advice/counseling

| Table 23: Current Hospital Quality Alliance Process measures for AMI. Adapted from Shih et al\textsuperscript{610}. |
2.1.6.1 Door-to-Balloon time

Door-to-balloon (DTB) is a common performance measure or time measurement in emergency cardiac care, specifically in the treatment of STEMI. This time interval starts with the patient’s arrival to the emergency apartment and ends when the catheter guide wire crosses the culprit lesion within the catheterization laboratory. This interval is commonly linked with the common adage “time is muscle”\(^{611}\), meaning that delays in treating an infarct increase the likelihood and amount of myocardial muscle damage due to hypoxia. Accordingly, the ACC/AHA guidelines recommend a Door-to-balloon interval of no more than 90 minutes\(^78\). Currently fewer than half of STEMI patients receive reperfusion with PCI intervention within the guideline-recommended timeframe.

2.1.7 Appropriateness Measures in PCI

Appropriateness measures in CHD have only come to light in the past few years, especially in PCI where cost and invasiveness is particularly important\(^612\). Due to a lack of national standards for defining PCI procedures, appropriate and inappropriate indications have been developed to aid in identifying procedural overuse as well as to highlight areas for quality improvement and/or cost savings\(^612\). In light of this, appropriate use criteria for coronary revasculariation have been developed by six key professional organizations in the US to support the rational use of PCI\(^613\). The inclusion of the appropriate criteria in the most recent 2012 update provides an opportunity to examine the appropriateness of PCI in modern day practice in the United States\(^614\).
2.1.8 Data analysis

The process of data analysis involves inspecting, cleaning, transforming and modeling data with the objective of highlighting useful information, which can propose conclusions or decision-making. Data analysis has multiple facets and approaches, however in epidemiological clinical research this involves conducting statistical analyses to compare groups (i.e. association analysis) or to explore relationships (i.e. comparative group statistics), which should be defined in the first instance (i.e. established methodology should be established before the project starts) (Figure 3). Before arriving at this point the data dictionary should be well defined, the data itself ‘cleaned’ and appropriately entered into the preferred statistical program. From here baseline descriptive statistics and graphical procedures can be run as well as modification of variables for further analysis. The next section will review the different aspects of data analysis in epidemiological research.

2.1.8.1 Descriptive statistics

Once the data file is clean it is possible to begin the descriptive phase of the analysis. The main steps in this process include (a) describing the baseline characteristics of the sample, (b) checking variables for any violation of the assumptions underlying the statistical technique used in later stages, and (c) addressing specific research questions. When assessing the characteristics of the sample it is important to check both categorical and continuous data points as well as any required background information (i.e. % of male and female). Graphical techniques such as histograms, bar graphs and box plots can be used to describe the sample. In terms of examining the violation of assumptions one should verify the
range of scores, skewness and kurtosis of the sample as well as the impact of outliers and missing data. Once the descriptive statistics have been finalised and checked for accuracy, the next step involves manipulating the raw data into a form that can be used to conduct analyses (i.e. transforming skewed variables, collapsing continuous variables).

2.1.8.2 Association Analysis

In epidemiological research one may be interested in the strength of the relationship between variables. The techniques below involve exploration of the relationship between continuous variables\(^\text{615}\). However, in the case of categorical variables one can use the Chi Square test for relatedness or independence to explore their relationship.

**Correlation:** Pearson or Spearman correlation is often used to explore the strength of the relationship between two continuous variables. This gives one an indication of both the direction (+/-) and the strength of the relationship. A positive correlation indicates that as one variable increases so does the other and vice versa.

**Partial correlation:** Partial correlation is an extension of Pearson correlation, however this technique allows one to control for the possible effects of another confounding variable. Partial correlation removes the confounding variable, which allows a more accurate picture of the relationship between the two variables of interest.
**Multiple Regression:** Multiple regression is a more complicated extension of correlation and is used when one wants to explore the predictive ability of a set of independent variables on one continuous variable. There are many different types of multiple regressions (i.e. exploratory, step-wise), which allow one to compare the predictive ability of particular independent variables and to find the best set of variables to predict a dependent variable. In this thesis linear, logistic and cox proportional hazards regression are employed in chapter three-six.

**Factor analysis:** This technique allows one to condense a large set of variables or scale items down to a smaller, more manageable number of dimensions or factors. It does this by summarising the underlying patterns of correlation and looking for groups of closely related items. Factor analysis is often used when developing scales and measures to identify the underlying structure.

Other more advanced techniques to explore relationships include discriminant function analysis, canonical correlation and structural equation modeling. These techniques are beyond the scope of this thesis and thus are described in depth in Tabachnick et al\textsuperscript{616}.

2.1.8.3 Comparative group statistics

There is another family of statistics, which can be used to assess if there is a statistically significant difference among a number of groups. The main parametric versions of these tests are presented below, along with non-parametric alternatives.
**T-tests:** This type of technique is used when two main groups are present (i.e. males & females) or within two sets of data where a researcher may wish to compare the mean score on a continuous variable. The two main types of t-tests include (a) paired sample t-tests (repeated measures) and (b) independent samples t-tests. The non-parametric alternatives include Mann-Whitney U Test and Wilcoxon Signed Rank Test.

**One-way ANOVA:** This technique is similar to the simple t-test, however it is used when one has two or more groups with the aim to compare their mean score on a continuous variable (impact of one independent variable on dependent variable). Post hoc analyses can be conducted to find out which groups are statistically different from one another. There are two types of ANOVAs, which include repeated measures, and between groups ANOVA. The non-parametric alternatives include the Kruskal-Wallis Test and the Friedman Test.

**Two-way ANOVA:** The two-way ANOVA allows an investigator to test the impact of two independent variables on one dependent variable. The main advantages of using this technique are that it allows one to test for an interaction effect as well as a main effect (overall effect of each independent variable). The two different types of ANOVA include between groups ANOVA and repeated measure ANOVA.

**MANOVA:** The MANOVA technique is used when a researcher wants to compare groups on a number of different, but related, dependent variables. Multivariate ANOVA can be used with one-way, two-way and higher factorial designs involving one or more independent variables.
ANCOVA: This statistical method is used when a researcher wants to statistically control for the possible effects of an additional confounding variable (covariate). Therefore, this technique is used when one suspects that the groups differ on some variable (may include the effect that the independent variable has on the dependent variable). Analysis of covariance can be used as part of a one-way, two-way or multivariate design.

2.1.8.4 Survival Analysis

The major outcome variable in some clinical studies is the time measured from patient entry into a study until a pre-specified ‘critical event’ has occurred (i.e. death, AMI). A key feature of ‘survival time’ data is the presence of ‘censored’ observations. Censored observations arise in participants that are included in the study but for whom the critical event of interest has not yet been observed. Thus, the length of time from study entry to when the critical event occurs is referred to as survival time (time from diagnosis or death). Even when the final outcome is not actual survival time, the techniques employed with such data are conventionally termed ‘survival’ analysis methods. Survival analysis is employed in chapter six in relation to gender differences in patients with PAD.

2.1.8.5 Kaplan Meier Curves & Log-rank test

One method of analysis of survival data is to specify in advance a fixed time point at which comparisons are to be made and then compare proportions of patients whose survival times exceed this time period. The Kaplan-Meier survival curve technique
was developed to deal with survival data that can take account of the information provided by censored observations and can estimate the survival function from lifetime data\textsuperscript{617}. In medical research it is often used to measure the fraction of patients living for a certain amount of time following treatment. The plot of the Kaplan–Meier estimate of the survival function is a series of horizontal steps of declining magnitude which, when a large enough sample is taken, approaches the true survival function for that population. An important advantage of the Kaplan–Meier curve is that the method can take into account some types of censored data (particularly right censoring), which occurs if a patient withdraws from a study. In comparing the survival time for two groups, the Kaplan–Meier survival curves are first calculated and then formally compared using the Log-rank test. This is essentially a non-parametric test, which is appropriate to use when the data are right skewed, or censored. The Log-rank test compares estimates of the hazard functions of the two groups at each observed event time\textsuperscript{617}.

2.1.8.6 Cox Proportional Hazards Regression Model

The Cox proportional hazards models are a class of survival models in statistics whereby survival models relate the time that passes before some event occurs to one or more covariates that may be associated with that quantity. In the proportional hazards model, the unique effect of a unit increase in a covariate is multiplicative with respect to the hazards rate (HR)\textsuperscript{617}. Both Cox proportional hazards regression and Kaplan Meier curves were also utilized in chapter six in regards to gender differences in patients with PAD.
2.1.8.7 Cost Benefit Analysis

Cost–benefit analysis is a statistical technique that sets out to define all the costs and benefits associated with a given project in money terms in order to weigh up whether a project brings a net gain to society\textsuperscript{619}. It allows the researcher to calculate and compare the benefits and costs of a particular project or government policy. In this technique, the benefits and costs are expressed in terms of money and can be adjusted for the time value of money or expressed on a common basis in terms of their present value. Cost benefit analysis has two main purposes, (a) to determine if it is a sound investment/decision and (b) to provide a basis for comparing projects\textsuperscript{619}. In clinical research, cost benefit analysis is often used to evaluate the desirability of a given policy. The main analysis is of the expected balance of benefits and costs that help to predict whether the benefits of a policy outweigh its costs and by how much.

The two main alternatives to cost benefit analysis include cost-effectiveness analysis and cost utility analysis. Cost effectiveness analysis is a type of economic evaluation that examines both the costs and health outcomes of alternative intervention strategies (e.g. deciding between the best treatments for AMI patients). Conversely, cost utility analysis the purpose is to estimate the ratio between the cost of a health related intervention and the benefit that this produces in terms of the number of years lived in health by the beneficiaries (e.g. used mainly in health economics whereby the benefits are measured in terms of quality-adjusted life years)\textsuperscript{619}. Although not employed in this thesis, this technique is important in epidemiological research.
2.1.9 Summary of Important Methodological Principles

As described in this methods section, this thesis employs current epidemiological principles in relation to observational research studies in three independent databases with a focus on cardiovascular outcomes and HRQOL. The importance of good clinical database management in epidemiological research should not be taken lightly. Specifically, the generation of a sound research question/hypothesis should be generated prior to the study design and implementation. Once this is established the processes of initiation of a clinical database include (a) generation of study design (including generation of the CRF and data dictionary), (b) database design, (c) data collection and entry, (d) data quality assurance and audit and (e) statistical analysis/dissemination of results.

This dissertation is focused towards patient oriented research practices in the way of health status and HRQOL. Accordingly, appropriate generic and disease-specific health status instruments are administered as in chapter three (SAQ) and chapter six (SF-12, HADS) with demonstrated validity, reliability and responsiveness. Apart from health status measures this work also concentrates on performance measures as in chapter four with a spotlight on DTB time and its components as well as clinical and physiologic endpoints (i.e. PCWP as therein chapter five). In terms of statistical analysis this thesis employs measures of association (i.e. general linear modeling, linear/logistic regression analysis), comparative group statistics (i.e. t-tests, ANOVA) and more complicated measures including survival analysis, Kaplan Meir curves and Cox proportional regression analysis.
CHAPTER 3: Gender Differences in Patients with Stable Angina attending Primary Care Practices

This results chapter is reproduced in the exact form as it appears in the article “Gender Differences in Patients with Stable Angina attending Primary Care Practices” authored by Rachel Dreyer, Margaret Arstall, Rosanna Tavella, Andrew Weekes, Claire Morgon and John Beltrame, and published in Heart, Lung and Circulation, Volume 20, pages 452-459, 2011. (Please refer to Appendix 1 for published manuscript)

In keeping with the style of this thesis the figures and tables have been modified, references incorporated into the thesis’s master reference list and the manuscript repaginated.
Study Overview

This manuscript demonstrates important gender differences amongst stable angina patients in the coronary artery disease in general practice (CADENCE) study. Although gender differences in patients with coronary artery disease admitted to hospital and/or attending tertiary hospital outpatient clinics have been extensively investigated, the CADENCE study provides new insights in a stable angina population that complements the previous findings.

The CADENCE study has several important design features including, (i) a large nation-wide representative cohort of consecutive stable angina patients attending general practitioners, irrespective of the purpose of the consultation, (ii) detailed evaluation of the health outcomes using the Seattle Angina Questionnaire, (iii) a comprehensive documentation of patient risk factors, investigations, medications and revascularisation therapies, and (iv) evaluation of guideline treatment gaps and the perspective of the treating general practitioner in the achievement of these targets.

The principal findings of the study is that women with chronic stable angina have poorer health outcomes compared with their male counterparts in relation to angina frequency, physical limitation associated with the angina and thus quality of life. This complements previous studies that have either focused on gender differences in patients with ACS, stable angina patients attending hospital clinics, or cardiac event outcomes (death/myocardial infarction) in stable angina patients attending primary care practices. The study also speculates on potential reasons for the gender disparity in health outcomes including differences in (a) risk factors and their management, (b)
clinical aspects including presentation, diagnostic work-up and therapies, (c) potential underlying biological mechanisms, and (d) psychosocial factors.
ABSTRACT

Objective: The primary objective of this study was to assess gender differences in the health status of patients with chronic stable angina using the Seattle Angina Questionnaire (SAQ). Potential contributing clinical factors were also examined.

Methods: Gender disparities in 2005 stable angina patients (712 females) were determined from general practitioner clinical evaluations and patient-completed questionnaire (SAQ). As there were significant age differences between genders, all subsequent analyses were adjusted for age.

Results: Compared with men, women with angina had poorer angina-related health outcomes as assessed by the SAQ, including more frequent angina (81±22 vs. 85±22, respectively, p < 0.001) with greater associated physical limitations (65±27 vs. 73±26, respectively, p < 0.001) and a poorer quality of life (68±24 vs. 71±24, respectively, p = 0.0026).

Conclusion: Women with stable angina have poorer angina-related health outcomes compared with their male counterparts. Multiple factors may contribute to this disparity including differences in clinical factors, underlying biological mechanisms and psychosocial factors.
INTRODUCTION

Although it is well recognised that coronary artery disease (CAD) is more prevalent in males, it remains the leading cause of death among women in most developed countries\(^\text{620}\). The misperception that CAD is less frequent in women is in part due to its earlier manifestation in males with first-time acute myocardial infarction occurring in males approximately 9 years earlier than females\(^\text{621}\). Despite this, many studies have demonstrated an increased age-adjusted mortality in women with acute coronary syndromes relative to men\(^\text{175, 201, 233, 622}\). This is particularly evident in young women (i.e. < 55 years of age) with a myocardial infarct\(^\text{175}\). The mechanism/s responsible for these gender differences remain uncertain and the subject of on-going studies\(^\text{234, 243, 343, 623}\).

This increased mortality in women is not limited to acute coronary syndromes but has also been reported in stable angina patients. In the Euro Heart Survey\(^\text{442}\), cardiologists recruited consecutive patients with newly diagnosed stable angina and followed them for at least a 12-month period. In those with angiographically-documented CAD, women had a higher risk of death or non-fatal myocardial infarction; furthermore female gender was an independent predictor of these cardiac events in a multivariate model\(^\text{442}\). Also, Hemingway et al identified newly-diagnosed “test-positive angina” patients from linked Finish national registries and found that women below the age of 75 years had a higher standardised coronary mortality ratio compared with men\(^\text{443}\).

Although many studies have documented increased cardiac mortality in women with CAD, few have focused on health-related quality of life outcomes in these patients. Several have examined this in patients with a recent myocardial infarction\(^\text{243, 624}\).
but there is negligible data on patients with chronic stable angina. This is not surprising considering the difficulty in investigating the later population since they seldom attend hospital for their condition and thus not easily assessable. However patients with chronic stable angina perhaps require even greater scrutiny of their health outcomes considering the chronic nature of their condition.

The CAD in General Practice (CADENCE) study was a prospective, cross-sectional study that examined symptomatic angina status and its impact on health-related quality of life in men and women with chronic stable angina attending Australian primary care practices. This unique study cohort provides an opportunity to examine gender differences in patients with chronic stable angina particularly in relation to health outcomes but also evaluating potential contributory factors such as coronary risk factors, clinical presentation, diagnostic investigations, and coronary heart disease therapies. Thus the primary objective of this study is to assess gender differences in health outcomes using the Seattle Angina Questionnaire (SAQ), in patients with chronic stable angina attending primary care practices. Secondary objectives will include evaluating potential contributing clinical factors to any gender disparity in health outcomes.
METHODS

Study Procedures

The CADENCE study was a cluster-stratified, cross-sectional survey of chronic stable angina patients attending Australian General Practices. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12608000347369) and was approved by the Royal Australian College of General Practitioners (GPs) National Research and Evaluation Ethics Committee, with all participating patients providing informed consent. The methods have been previously published and summarised in brief, below.

A representative cohort of consecutive patients with a history of chronic stable angina who attended Australian GP practices were recruited by the following method: (i) expressions of interest were sought from all practicing Australian GPs by mail-out; (ii) of those responding, GPs were selected to participate on the basis of practice location, stratified by state population and urban/rural distribution; (iii) invited GPs were considered to be active participants if they recruited 10-15 consecutive patients with a clinical diagnosis of angina, irrespective of the purpose for the consultation; finally, (iv) a second round of GPs invitations were conducted in stratified areas that were under-represented. Participating GPs completed a case report form detailing the clinical history of the patient with the aid of pre-defined clinical criteria and quantified the extent of the patient’s disability using the Canadian Cardiovascular Society Classification (CCSC) for Angina, as well as commenting upon whether the angina was optimally controlled. Independently, the patients completed the Seattle Angina Questionnaire (SAQ) which is a well established, validated, health outcomes questionnaire specifically designed for chronic stable angina.
Data Analysis

The primary analyses conducted in this study were prospectively developed before initiating the CADENCE study. The primary endpoints for this study were the angina-related health outcomes as assessed by the SAQ; in particular, the angina frequency, physical limitation and quality of life domains. Secondary endpoints included the (a) coronary risk factors and co-morbidities, (b) angina characteristics and diagnostic investigations, and (c) the angina therapies.

Comparisons between male and female characteristics were undertaken using a general linear model with gender used as a categorised predictor variable and the clinical characteristics or SAQ variables being either binary or continuous. For all analyses, the complete available dataset was used with no imputation for missing variables. Continuous variables were expressed as Mean±SD and discrete variables as confidence intervals. Confidence intervals were produced using SAS v9.1 software (SAS Institute, Cary North Carolina, USA), accounting for the stratified (i.e., 16 state and urban/rural strata), clustered (i.e., 207 GP clusters) survey design. Comparisons between genders were adjusted for by age.
RESULTS

From October 2006 to March 2007, the 207 participating GPs recruited 2005 consecutive chronic stable angina patients who attended their clinics, irrespective of the purpose of the consultation. The distribution of the participating GPs has been previously described and is representative of Australian GPs based upon geographic distribution. Of the 1284 males and 721 females recruited, ages were available on most patients (1275 and 713 respectively) with the female chronic stable angina patients being considerably older than the males (69±12 vs 73±11 years respectively, p < 0.0001). Accordingly all subsequent gender comparisons in this study were adjusted for age.

Angina-related Clinical Features

Health outcomes may be influenced by coronary risk factors, co-morbidities and patient management. Accordingly, gender differences in these clinical features will be examined before considering differences in health outcomes.

Even with adjustment for age, there were important gender differences in relation to (a) the prevalence of the coronary risk factors, (b) measured values for these risk factors, and (c) the extent of achieving risk factor targets as per guideline recommendations as well as those perceived by the GP’s. As shown in Table 1, although the prevalence of diabetes does not differ between genders, hypertension and obesity is more prevalent amongst women whereas smoking and alcohol consumption is less common. Moreover, women are less likely to achieve guideline targets for blood pressure, lipids, and weight, although the GP’s only appeared to be cognisant of this in relation to lipid status (Table 1).
The study cohort had an established history of angina, although males had a slightly longer history of angina compared to females (Table 2); possibly reflecting the earlier disease onset in men. Interestingly, the angina characteristics differed between genders with females less likely to experience exertional angina but more likely to describe anginal episodes occurring in the context of emotional stress. Women with chronic stable angina were less likely to have a remote history of an acute coronary syndrome compared with males (Table 2). There were no differences between male and female chronic stable angina patients in the frequency of heart failure (Table 2), peripheral arterial disease (18% vs 17% respectively, $p > 0.1$) and chronic obstructive airways disease (21% vs 25% respectively, $p > 0.1$).

In relation to diagnostic investigations for CAD, women were less likely to undergo exercise stress testing or invasive coronary angiography. When these investigations were performed, they were less likely to demonstrate significant coronary artery disease or evidence of myocardial ischaemia (Table 2).

There were several gender disparities in the therapeutic management of angina in the study cohort (Figure 1). Women were less likely to (a) be reviewed by a cardiologist, (b) receive cardio-protective medications (anti-platelet agents, statins and ACE inhibitors), and (c) undergo coronary revascularisation procedures (percutaneous coronary interventions and/or coronary artery bypass grafting). However they were more likely to be prescribed long acting nitrate therapy and calcium channel blockers (Figure 1).

**Angina-related Health Outcomes**

In this chronic stable angina cohort, women had more angina than men, as reflected by a lower SAQ angina frequency score (i.e. $81\pm22$ vs. $85\pm22$, respectively, $p <$
0.001). Consistent with this finding, more women experienced anginal episodes at least once a week and were prescribed more anti-anginal agents (Table 2). As documented by the SAQ scores (Figure 2), women were also more physically limited by their angina compared with men (65±27 vs. 73±26, respectively, p < 0.001) and had a poorer quality of life (68±24 vs. 71±24, respectively, p = 0.0026). As well as these patient derived indices, the GP’s perceived the women to be more disabled by their angina, ranking almost half of them as CCSC II-IV angina (Table 2).
DISCUSSION

This prospective, observational, cluster-stratified, cross-sectional survey with a representative cohort of chronic stable angina patients attending Australian general practices, demonstrated significant gender disparities in angina-related health outcomes as well as differences in coronary risk factors, clinical features/investigations and management. In this study women were several years older, which would potentially impact on the assessed parameters, thus age-adjusted analyses were undertaken. Despite adjusting for age, females had poorer health outcomes including increased angina frequency, more physical impairment from their angina and a reduced quality of life. Clinical observations that may be associated with this gender health outcome disparity includes, females being more likely to (a) have a history of hypertension, (b) experience emotionally provoked angina, (c) prescribed long-acting nitrates or calcium channel blockers, although less likely to (d) achieve guideline lipid or weight targets, (e) undergo exercise stress testing or angiography, (f) be prescribed cardioprotective agents, and (g) undergo revascularisation therapies. These concerning observations warrant further discussion.

Gender Differences in Health Outcomes Amongst Patients with Chronic Stable Angina

The spectrum of angina-related health outcomes span from cardiac events (death or myocardial infarction), to symptomatic angina status, it’s associated physical limitations, and its impact on health-related quality of life. As described above, previous studies have documented an increased mortality in female chronic stable angina patients\(^{442, 443}\). This study has extended the health outcome continuum and
demonstrated that women with chronic stable angina experience more angina, are more physically limited, and have a greater impairment in their quality of life compared to their male counterparts. The reason for these gender differences is multifactorial and requires further evaluation.

**Potential Mechanisms of Gender Differences in Patients with CAD**

The mechanisms contributing to the observed gender disparity in health outcomes may include differences in atherosclerotic risk factors, biological factors, clinical factors and psychosocial factors. Women had a higher prevalence and poorer control of coronary risk factors, which may have contributed to their poorer outcomes\(^{628}\). This finding is supported by previous research which has shown that quality of life impairment (as indicated by lower scores on SF-36 dimensions) increases as the number of cardiovascular risk factors\(^{629}\) and age of an individual increases\(^{630}\).

Clinical factors also play a role in the observed gender differences, since it is well described that women have atypical symptoms for coronary artery disease\(^{631}\) and also have less reliable exercise test findings\(^{429, 433, 444}\). Consistent with these previous observations, women in this study more often had atypical angina features and were less likely to undergo exercise stress testing or angiography. Thus it is possible that at least some women who did not undergo angiography, may have been denied revascularisation therapy which may have improved their health outcomes. However, as shown in this study and by other investigators\(^{176, 632}\), women are less likely to show significant coronary artery disease on angiography and thus less likely to undergo revascularisation therapies\(^{429, 433, 442, 633}\). Furthermore, those women that do undergo percutaneous coronary intervention\(^{634}\) or surgical revascularisation\(^{635}\), are less to be free
of angina at 4-year follow-up, compared with men. Consistent with this limited benefit of revascularisation therapies in women, this study found that women were more likely to be prescribed anti-anginal agents including long acting nitrates, calcium channel blockers and other agents such as nicorandil. The higher prevalence of insignificant coronary artery disease on angiography amongst women and the limited benefit of revascularisation therapies in those that do have significant coronary artery disease, raises the possibility that epicardial coronary artery disease plays less of role in the pathogenesis of angina in women and that other biological mechanisms such as microvascular dysfunction may play a greater role.

Biological differences in women with angina have been extensively studied by the National Heart, Lung and Blood Institute-sponsored Women’s Ischemia Syndrome Evaluation (WISE) study. These investigators have highlighted that women tend to have smaller epicardial coronary arteries\(^\text{636}\) that are often diffusely diseased and thus potentially less suitable for revascularisation therapies\(^\text{637}\). However, they have also emphasized that coronary microvascular disorders such as cardiological syndrome X are more prevalent amongst women\(^\text{637}\). Microvascular dysfunction presents a significant management problem and thus potentially more anginal symptoms and poorer health outcomes since revascularisation therapies are not only ineffective in targeting this angina mechanism but also conventional anti-anginal agents may be of limited benefit. Long-acting nitrates have been shown to have limited benefit in alleviating angina amongst patients with coronary microvascular dysfunction\(^\text{638}\). Moreover, we have recently shown that conventional calcium L-channel blockers are not as effective as those that also target the calcium T-channel due to the higher prevalence of T-channels in microvessels\(^\text{639}\).
Psychosocial factors may also contribute to the observed gender differences in angina-related health outcomes. Previous studies suggest that low socioeconomic class and educational standing\textsuperscript{261, 409} as well as increased work loads of employment and family obligations are prevailing risk factors for post infarct adverse outcomes in women as compared with men\textsuperscript{261, 388}. Social issues such as the impact of ill health on family dynamics need to also be considered in this population. Depression\textsuperscript{408}, which is especially prevalent amongst women, is not only a major determinant of quality of life but also a predictor of mortality following myocardial infarction\textsuperscript{400}. Hence, future therapeutic efforts for stable angina patients needs to focus on depression screening.

\textbf{Study Limitations}

As with all observational surveys, there are limitations in the interpretation of the data. Although the study has clearly documented poorer health outcomes in women with chronic stable angina, inferences about relationships with other observed clinical phenomena in these patients are only plausible associations without substantiating evidence for causation. This study is also limited by a potential selection bias since a history of ‘angina’ was the key inclusion criteria yet women often experience atypical symptoms and thus may not have been recruited. Finally, statistical adjustment has been made for age however many other factors (as eluded to above) may influence health outcomes and have not been adjusted for in the analysis.

\textbf{Conclusion}

This study has extended previous observations of gender differences in health outcomes amongst patients with chronic stable angina. In addition to previously
documented increased cardiac events in women with stable angina, this study has shown that they experience angina more frequently with associated greater physical limitations and a poorer quality of life. Although differences in atherosclerotic risk factors, clinical presentation, diagnosis and management may contribute to these gender differences, the underlying biological mechanisms and the influence of psychosocial factors requires further investigation.
TABLE 1. Age Adjusted Coronary Risk Factor Status.

<table>
<thead>
<tr>
<th>Diabetic Status</th>
<th>Males (N=1284)</th>
<th>Females (N=721)</th>
<th>Age Adjusted P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>388 (1265)</td>
<td>206 (711)</td>
<td>0.4303</td>
<td>0.4287</td>
</tr>
<tr>
<td>HbA1c [1]</td>
<td>375 (388)</td>
<td>200 (206)</td>
<td>0.7707</td>
<td>0.3697</td>
</tr>
<tr>
<td>Achieved Guideline HbA1c Targets</td>
<td>196 (362)</td>
<td>103 (194)</td>
<td>0.8031</td>
<td>0.6005</td>
</tr>
<tr>
<td>GP Perceived HbA1c Controlled</td>
<td>211 (348)</td>
<td>108 (185)</td>
<td>0.6219</td>
<td>0.4282</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Pressure Status</th>
<th>Males</th>
<th>Females</th>
<th>Age Adjusted P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension [2]</td>
<td>836 (1220)</td>
<td>540 (692)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0011</td>
</tr>
<tr>
<td>Systolic BP [3]</td>
<td>1277 (1284)</td>
<td>709 (721)</td>
<td>&lt;0.0001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diastolic BP [4]</td>
<td>1277 (1284)</td>
<td>710 (721)</td>
<td>0.0756</td>
<td>0.4458</td>
</tr>
<tr>
<td>Achieved Guideline BP Targets</td>
<td>764 (1265)</td>
<td>412 (702)</td>
<td>0.4493</td>
<td>0.2093</td>
</tr>
<tr>
<td>GP Perceived BP Controlled</td>
<td>1076 (1254)</td>
<td>596 (700)</td>
<td>0.6926</td>
<td>0.5868</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipid Status</th>
<th>Males</th>
<th>Females</th>
<th>Age Adjusted P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol [5]</td>
<td>1239 (1284)</td>
<td>695 (721)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL Cholesterol [6]</td>
<td>1195 (1284)</td>
<td>678 (721)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL Cholesterol [7]</td>
<td>1170 (1284)</td>
<td>673 (721)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1227 (1284)</td>
<td>690 (721)</td>
<td>0.1168</td>
<td>0.5822</td>
</tr>
<tr>
<td>Achieved Guideline Lipid Targets</td>
<td>281 (1221)</td>
<td>109 (690)</td>
<td>0.1566</td>
<td>0.0003</td>
</tr>
<tr>
<td>GP Perceived Lipids Controlled</td>
<td>874 (1212)</td>
<td>434 (668)</td>
<td>0.0021</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking &amp; Alcohol Status</th>
<th>Males</th>
<th>Females</th>
<th>Age Adjusted P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex-smoker [8]</td>
<td>745 (1266)</td>
<td>208 (707)</td>
<td>0.0369</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current Smoker [**]</td>
<td>135 (1266)</td>
<td>59 (707)</td>
<td>0.0369</td>
<td>0.0063</td>
</tr>
<tr>
<td>Alcoholic beverages/week [8]</td>
<td>1118 (1284)</td>
<td>582 (721)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight Status</th>
<th>Males</th>
<th>Females</th>
<th>Age Adjusted P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity [9]</td>
<td>1059 (1255)</td>
<td>606 (695)</td>
<td>0.1112</td>
<td>0.0198</td>
</tr>
<tr>
<td>BMI [10]</td>
<td>1262 (1284)</td>
<td>705 (721)</td>
<td>0.8614</td>
<td>0.0604</td>
</tr>
<tr>
<td>Waist Circumference [**]</td>
<td>1237 (1284)</td>
<td>675 (721)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Achieved Guideline Wgt Target</td>
<td>198 (1257)</td>
<td>89 (695)</td>
<td>0.0964</td>
<td>0.016</td>
</tr>
<tr>
<td>GP Perceived Wgt Controlled</td>
<td>527 (1225)</td>
<td>308 (681)</td>
<td>0.3859</td>
<td>0.6741</td>
</tr>
</tbody>
</table>

[1] HbA1c < 7%. Diabetic patients only.

[2] Hypertension is defined as the initiation of pharmacological antihypertensive therapy.
[3] Heart Foundation Guidelines\textsuperscript{12}: Systolic BP targets for age $\geq 65$ years and/or not diabetic is $<140$ mmHg, otherwise $<130$ mmHg.

[4] Heart Foundation Guidelines\textsuperscript{12}: Diastolic BP targets for age $\geq 65$ years and/or not diabetic is $<90$ mmHg, otherwise $<85$ mmHg.

[5] Heart Foundation Guidelines\textsuperscript{12}: Treated with a statin and HDL $>1$ mmol/L, LDL $<2.0$ mmol/L and TG $<1.5$ mmol/L.

[6] Heart Foundation Guidelines\textsuperscript{12}: HDL cholesterol target $>1.0$ mmol/L.

[7] Heart Foundation Guidelines\textsuperscript{12}: LDL cholesterol target $<2.0$ mmol/L.

[8] $<7$ standard drinks/week for females or $<14$ standard drinks/week for males.

[9] Obese defined as BMI $\geq 25$ and/or waist circumference $>94$ cm males (90 cm if Asian) $>80$ cm females.

[10] BMI = weight (kg)/height (metres)$^2$
TABLE 2. Age Adjusted Angina Characteristics.

<table>
<thead>
<tr>
<th>Angina Characteristics</th>
<th>Males</th>
<th>Females</th>
<th>P value</th>
<th>Age Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Adjusted</td>
<td>% or Mean±SD</td>
<td>% or Mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina duration (years)</td>
<td>1259 (1284)</td>
<td>708 (721)</td>
<td>0.347</td>
<td>0.0028</td>
</tr>
<tr>
<td>Substernal chest discomfort</td>
<td>1070 (1284)</td>
<td>591 (721)</td>
<td>0.394</td>
<td>0.4304</td>
</tr>
<tr>
<td>Pain provoked by exertion**</td>
<td>870 (1284)</td>
<td>446 (721)</td>
<td>0.008</td>
<td>0.0027</td>
</tr>
<tr>
<td>Pain provoked by emotional stress**</td>
<td>269 (1284)</td>
<td>193 (721)</td>
<td>0.004</td>
<td>0.0012</td>
</tr>
<tr>
<td>Pain relieved by rest</td>
<td>638 (1284)</td>
<td>336 (721)</td>
<td>0.230</td>
<td>0.1305</td>
</tr>
<tr>
<td>Pain relieved by sublingual nitrates</td>
<td>562 (1284)</td>
<td>349 (721)</td>
<td>0.054</td>
<td>0.154</td>
</tr>
<tr>
<td>CHD Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary Syndrome***</td>
<td>964 (1284)</td>
<td>452 (721)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable Angina*</td>
<td>610 (1246)</td>
<td>298 (693)</td>
<td>0.0862</td>
<td>0.0110</td>
</tr>
<tr>
<td>Myocardial Infarction***</td>
<td>668 (1265)</td>
<td>271 (706)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>276 (1249)</td>
<td>189 (696)</td>
<td>0.0204</td>
<td>0.4929</td>
</tr>
<tr>
<td>Angina Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex Stress Test</td>
<td>824 (1261)</td>
<td>402 (703)</td>
<td>0.0014</td>
<td>0.0176</td>
</tr>
<tr>
<td>Coronal Angiogram - Undertaken**</td>
<td>681 (802)</td>
<td>317 (392)</td>
<td>0.059</td>
<td>0.0096</td>
</tr>
<tr>
<td>Coronary Angiogram - CAD detected***</td>
<td>1044 (1251)</td>
<td>471 (700)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary Angiogram -CAD detected***</td>
<td>1004 (1029)</td>
<td>431 (464)</td>
<td>&lt;0.0006</td>
<td>0.0003</td>
</tr>
<tr>
<td>Stress Scintigraphy - Undertaken</td>
<td>349 (1239)</td>
<td>189 (691)</td>
<td>0.7215</td>
<td>0.8510</td>
</tr>
<tr>
<td>Stress Scintigraphy - CAD detected*</td>
<td>291 (335)</td>
<td>142 (180)</td>
<td>0.0360</td>
<td>0.0333</td>
</tr>
<tr>
<td>Stress Echo</td>
<td>319 (1221)</td>
<td>184 (679)</td>
<td>0.6448</td>
<td>0.4969</td>
</tr>
<tr>
<td>Angina Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent Angina*** [1]</td>
<td>334(1284)</td>
<td>238 (721)</td>
<td>0.0002</td>
<td>0.0551</td>
</tr>
<tr>
<td>GP Optimal Angina Control</td>
<td>970 (1191)</td>
<td>513 (661)</td>
<td>0.0690</td>
<td>0.0551</td>
</tr>
<tr>
<td>CCSC – Class I ***</td>
<td>803 (1284)</td>
<td>373 (721)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Class II**</td>
<td>328 (1284)</td>
<td>229 (721)</td>
<td>&lt;0.0017</td>
<td>&lt;0.0066</td>
</tr>
<tr>
<td>- Class III</td>
<td>94 (1284)</td>
<td>70 (721)</td>
<td>0.0970</td>
<td>0.2949</td>
</tr>
<tr>
<td>- Class IV*</td>
<td>15(1284)</td>
<td>18 (721)</td>
<td>0.0529</td>
<td>0.0388</td>
</tr>
</tbody>
</table>

[1] Persistent angina ≥ 1 episode/week
LEGENDS

FIGURE 1. Gender Comparisons in the Clinical Management of Stable Angina Patients.
Age adjusted frequency data for (a) cardiology review, (b) pharmacological therapy and (c) revascularisation therapy, in 2005 stable angina patients categorised by gender. (male [blue] vs female [red]: *p < 0.05, **p < 0.01, ***p < 0.001).

FIGURE 2. Gender Comparisons in Health Outcomes of Stable Angina Patients.
Age adjusted Seattle Angina Questionnaire scores in 2,005 stable angina patients categorised by gender. (male [blue] vs female [red]: *p < 0.05, **p < 0.01, ***p < 0.001).
FIGURE 1.

![Graph showing clinical management with percentage (%) for male and female patients.](image)
FIGURE 2.
CHAPTER 4: Evaluation of Gender Differences in Door-to Balloon Time in ST-Elevation Myocardial Infarction

This results chapter is reproduced in the exact form as it appears in the article “Evaluation of Gender Differences in Door-to Balloon Time in ST-Elevation Myocardial Infarction” authored by Rachel Dreyer, John Beltrame, Tracy air, Rosanna Tavella, Bernadette Hoffmann, Purendra Pati, David di Fiore, Margaret Arstall and Christopher Zetiz (Submitted and under review in Circulation: Cardiovascular Quality and Outcomes).

In keeping with the style of this thesis, the figures and tables have been modified, the references incorporated into the thesis’s master reference list and the manuscript repaginated.
Study Overview

This manuscript demonstrates important gender differences in patients presenting with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI). Although female gender has been shown to be an independent predictor of a delayed Door-to-Balloon (DTB) time following STEMI, no previous study has explored the components contributing to the DTB time. In addition, although performance measures such as DTB have been extensively studies in the United States and Europe, no study thus far has focused on gender differences in DTB within an Australian hospital setting.

In light of the above, this study provides new insights into the components responsible for the delayed DTB time in women, demonstrating that the delay occurs throughout the continuum of the DTB time components. Specifically, women experience significant time delays in identification of the STEMI diagnosis (i.e. emergency department) and also in the PCI process (i.e. catheterisation laboratory).

In addition, female gender is a significant predictor of a delayed DTB time following adjustment for clinical covariates. Other important predictors of delay included presentation during out of office hours, a history of hypertension, degree of ST-elevation on initial ECG and low priority triage category.
ABSTRACT

**Background:** A delayed Door-to-Balloon (DTB) time in women with ST-elevation myocardial infarction (STEMI) has been associated with an increased mortality. Understanding the components of the delayed DTB time may identify strategies for improving this gender gap. The objectives of this study were to (a) quantify the components of the delayed DTB time in women and (b) assess the independent effect of gender on DTB time in patients undergoing percutaneous coronary intervention (PCI) for STEMI.

**Methods and Results:** Clinical parameters were prospectively collected for 735 STEMI patients undergoing primary PCI from 2006-2010, with particular attention to the components of DTB time, including the onset of chest pain and the ‘code’ notification of the STEMI team by the Emergency Department. Women were significantly older, had more co-morbidities, and a longer median Pain-to-Door time (147 vs. 97 minutes, \( P = 0.011 \)). Upon hospital arrival they also experienced delays in Door-to-Code (23. vs. 17 minutes, \( P = 0.012 \)), Code-to-Balloon time (63. vs. 57 minutes, \( P = 0.001 \)) and thus DTB time (88 vs. 72 minutes, \( P = 0.001 \)). After multivariate adjustment, independent determinants of DTB time included female gender (ratio of geometric means \([RGM]=1.13;\) 95% CI 1.02-1.26; \( P = 0.022 \)), hypertension (\( RGM=1.12,\) 95%CI 1.02-1.23, \( P = 0.014 \)), maximum ST-elevation (\( RGM=0.97,\) 95%CI 0.94-0.98, \( P < 0.001 \)), office hours (\( RGM=0.84,\) 95%CI 0.78-0.92, \( P < 0.001 \)) and triage category (\( RGM=1.23,\) 95%CI 1.09-1.40, \( P = 0.001 \)).

**Conclusions:** Women experience delays in identification of the STEMI diagnosis and also in the PCI process. Thus a multifaceted approach addressing both the diagnosis and management of STEMI in women is required.
INTRODUCTION

Primary percutaneous coronary intervention (PCI), when rapidly available, is the preferred strategy for reperfusion in patients with ST-elevation myocardial infarction (STEMI)\textsuperscript{40, 640}. Time to treatment is a key prognostic indicator of morbidity and mortality outcomes in STEMI patients either receiving pharmacologic or mechanical reperfusion therapy\textsuperscript{76, 331-338, 641}. Specifically, increased Door-to-Balloon (DTB) times are associated with increased mortality, irrespective of the presentation\textsuperscript{76}.

The delay between symptom onset and opening the occluded vessel is longer in female STEMI patients than males\textsuperscript{225, 227, 228, 339-342, 642, 643} and may be attributable to patient and health system factors. Patient factors include women delaying seeking medical attention for their myocardial infarct because of the false perception that they are at low risk\textsuperscript{342, 644-647}. Health system delays are reflected in the DTB time, with some studies highlighting that female sex is an independent predictor of a delayed DTB time\textsuperscript{77, 220, 229-231, 648, 649}, while others have not observed such a relationship\textsuperscript{650}. To date, no study has explored the components contributing to the DTB time.

The primary objective of this study was to quantify the components of the delayed DTB time in women, and to assess the independent effect of gender on DTB time whilst adjusting for conventional clinical covariates. We hypothesize that the components of DTB time in women are significantly delayed compared to men (Hypothesis A) and that female gender is an independent predictor of DTB following covariate adjustment (Hypothesis B).
METHODS

To address the above objectives, a prospectively designed STEMI registry was established at two STEMI PCI centers based in tertiary care hospitals.

PCI Centers

Adelaide has a population of approximately 1 million, which is serviced by 4 STEMI PCI centers that provide 24-hour cardiac catheterization facilities. The Queen Elizabeth and Lyell McEwin Hospitals are two of these centers, providing this service since 1999. When first established, primary PCI was initiated by emergency department staff consultation with the on-call cardiology fellows but in April 2006, the ‘Code STEMI’ protocol was introduced to optimize DTB times. The ‘Code STEMI’ protocol is initiated when a provisional diagnosis of STEMI is made in the Emergency Department and involves the central emergency activation (via dedicated pagers from the hospital switchboard) of the on-call PCI team.

STEMI Registry

From April 2006, consecutive patients presenting to the emergency departments of the participating PCI centers were enrolled into the STEMI registry. The comprehensive registry included (a) all patients who underwent emergency angiography with the intent for primary PCI (i.e. those for whom a code STEMI was activated), irrespective if subsequent clinical evaluation revealed an alternative diagnosis, (b) out-of-hospital cardiac arrest who had features of acute STEMI upon return of spontaneous rhythm, (c) patients who died prior to the emergency PCI, (d) patients transferred from non-PCI hospitals with acute STEMI, without prior
thrombolysis, and (e) in-patients who subsequently developed acute STEMI. For the purpose of this study, only STEMI registry patients who presented to the emergency department and underwent primary PCI were included. Accordingly, those who did not undergo PCI, were transferred from non-PCI hospitals or were in-patient STEMI’s (including those with re-infarction), were excluded from this study. The study was approved by the institutional human ethics committee with all subjects providing informed consent.

The prospectively designed STEMI registry collected the following details on each STEMI admission to the PCI centers: (a) cardiovascular risk factors, (b) maintenance medications, (c) admission electrocardiograph (ECG) details, (d) pre-catheterization laboratory clinical status, (e) hospital management logistics, (f) PCI treatment details, and (g) myocardial infarct outcomes. An audit of 22% of the patient entries by case-note abstraction undertaken by an independent observer, demonstrated 90% agreement with the original data, confirming the reproducibility of the registry.

**Study Definitions and Outcome Variables**

The primary outcome measure is the DTB time and its components including (a) time from first medical contact to emergency STEMI code call (Door-to-Code; DTC), (b) time from STEMI code to arrival at the catheterization laboratory (Code-to-Lab; CTL), (c) time from catheterization laboratory arrival to first balloon inflation (Lab-to-Balloon; LTB), and (d) the overall time from hospital arrival to first balloon inflation (DTB) (see Figure 1). Secondary outcomes of interest included 30-day and 12 month all cause mortality/re-infarction, peak creatine kinase (CK), TIMI-3 post angiography and length of stay. Diagnosis of recurrent infarction was based on typical chest pain,
new ST-segment changes and an increase in CK of at least 50% over the previous
trough level in at least 2 samples reaching 240 U/L or higher. During the hospital stay,
CK or its isoenzyme were determined immediately after admission and at least daily
thereafter. Following discharge, follow-up information was obtained from case note
abstraction and administrative datasets. Patients re-presenting with another STEMI
(involving the index lesion or a different lesion or vessel) ≤30 days or ≤12 months after
the initial PCI were recorded as having a 30-day or 12-month mortality/re-infarction
episode.

**Statistical Analysis**

For the descriptive baseline analyses, patients’ pre-hospital clinical characteristics,
STEMI management and outcomes were compared between men and women.
Categorical variables are presented as frequencies with percentages and comparisons
made using Pearson Chi Squared tests or Fisher exact. Means and standard deviations
or medians and inter quartile ranges (IQR: 25th, 75th) are presented for Gaussian or non-
Gaussian data respectively with comparisons made using student’s independent t-tests
or non-parametric Mann-Whitney U tests where appropriate. Median values are
reported for all pain-to-door (PTD) and DTB time points. Myocardial infarction
outcomes (30-day, 12 month mortality, 30-day re-infarction & composite end point)
were compared between men and women using logistic regression models, with
adjustment for age.

A multiple linear regression model was constructed to examine the effect of gender on
Door-to-Balloon time (DTB) whilst adjusting for clinical covariates. As DTB was not
linear, a log transformation was utilized to correct for skewness and non-linearity\textsuperscript{651}. 
The DTB model was sequentially built including the following variables in blocks (ENTER method): age, cardiovascular risk factors [hypercholesterolemia, hypertension, diabetes, family history, history of smoking, previous coronary artery disease (CAD)], infarct characteristics (extent of ST-elevation on ECG), haemodynamics [initial heart rate (HR), initial systolic blood pressure (SBP), acute pulmonary edema (APO), ventricular fibrillation (VF) arrest and logistics (office hours, arrival status (self arrival vs. non self arrival) and triage category (low priority vs. high priority). After arriving at a final multivariate model, regression coefficients and 95% confidence intervals were back transformed for ease of interpretation with reported percentage increase and/or decrease in median DTB time. For all analyses, the complete available dataset was used with no imputation for missing variables (assumed to be missing completely at random). A two tailed p value of <0.05 was considered statistically significant. All analyses were performed using SPSS 18.0 for Macintosh (SPSS Inc., Chicago Ill).
RESULTS

Between 2006-2010, 912 consecutive STEMI patients were admitted to the PCI centers of which 234 were women and 678 men. Of these, a total of 735 STEMI patients with PCI were included in this study.

Patient Characteristics & Cardiovascular Risk Profile

Baseline characteristics of 735 consecutive STEMI patients are presented in Table 1. Compared with males, females were significantly older (67±14 vs. 60±13, P=.001) with a greater proportion over 75 years of age (15% vs. 39%, P=.001). In relation to cardiovascular risk factors, females had higher rates of hypertension (45% vs. 60%, P=.001) and were less likely to smoke (63% vs. 44%, P=.001) compared with their male counterparts. Females were more likely to present to hospital on aspirin (16% vs. 26%, P=.024) and beta-blocker therapy (6% vs. 13%, P=.008).

ST-Elevation Myocardial Infarction (STEMI) Management

Mode of hospital arrival (ambulance and/or self arrival), patient triage, inter-hospital transfers and time of presentation (office hours) were similar between genders (Table 2). Females had a significantly longer PTD time with a median delay of 147 minutes (IQR: 62, 349) compared to males with a delay of only 97 minutes (IQR: 55, 225, P=.011). Males and females met the criteria for reperfusion therapy and had comparable arrival heart rates and initial systolic blood pressures. On arrival to the catheterization laboratory males and females had a similar frequency of anterior infarction as well as pre lab complications such as APO and VF arrest (Table 2).
**Door to Balloon Time & Logistical Components (Hypothesis A)**

As detailed in Figure 1, the median Door-to-ECG [6 (IQR: 3, 11) vs. 8 (IQR: 5, 13) minutes, \(P=0.001\)] and DTC [17(IQR: 8, 38) vs. 23(IQR: 10, 48) minutes, \(P=0.012\)] were significantly delayed in females versus males, however CTL was similar between genders. Females were also more likely to have a significantly delayed LTB [19 (IQR: 13, 28) vs. 23 (IQR: 14, 31) minutes, \(P=0.008\)], CTB [57 (IQR: 45, 68) vs. 63 (IQR: 51, 76) minutes, \(P=0.001\)] and conventional DTB [72 (IQR: 55, 101) vs. 88 (IQR: 67, 120) minutes, \(P=0.001\)] time compared with males. The overall median DTB time difference between genders was 16 minutes. As a result, 65% of males, versus 49% of females \((P=0.001)\) received balloon inflation under the recommended guideline of 90 minutes.

**Percutaneous Coronary Intervention Management and Outcomes**

There were no significant gender differences in the prevalence of triple vessel disease, TIMI-3 flow Pre- or Post-PCI, admission blood urea nitrogen/Creatinine ratios, peak CK, stent type (bare metal vs. drug eluting), the use of IIb/IIIa antagonist/thrombectomy catheter, or intra-aortic balloon pump (Table 3). In-hospital length of stay was similar between genders but 30-day re-infarction (2% vs. 5%, \(P=0.009\)), unadjusted 30-day all-cause mortality (6% vs. 10%, \(P=0.034\)) and 12-month mortality (7% vs. 12%, \(P=0.035\)) were all significantly higher in females in the STEMI cohort. However, after adjusting for age utilizing logistic regression analyses, the risk of 30-day/12-month mortality and the composite endpoint of all cause mortality/re-infarction did not significantly differ from that of males; although the 30-day re-infarction rate in women persisted even after adjustment for age (adjusted OR=0.374; 95% CI, 0.150-0.931, \(P=0.034\)) (Table 3).
Model for Door to Balloon Time (Hypothesis B)

To assess the effect of gender on DTB time whilst adjusting for clinical confounders (Hypothesis B), a multivariable linear regression analysis was undertaken. The unadjusted and adjusted association between gender and DTB is summarized in Table 4 and final model results are reported in Table 5 (Appendix 1). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Overall the final regression model was statistically significant, ($F (16, 496)=4.52, P<0.001, R^2= 0.13$, adjusted $R^2= 0.10$), with the covariates in the model explaining 10% of the variance in DTB time.

In the final model female gender remained a significant predictor of a delayed DTB, even following adjustment for important clinical covariates (Table 4). Other independent predictors of DTB included hypertension, peak ST-elevation on ECG, office hours and triage category. Female gender was associated with a 13% increase (16 minute difference) in median DTB time (ratio of geometric means [RGM]=1.13; 95% CI 1.02-1.26, $P=.022$). Secondly, a history of hypertension was associated with a 12% increase in median DTB time (RGM=1.12; 95% CI 1.02-1.23, $P=.014$). For every 1mm increase in ST-elevation on ECG there was found to be a 3% decrease in DTB time (RGM=0.97; 95% CI 0.94-0.98, $P<0.001$). In addition, arrival within office hours was related to a 16% decrease in median DTB time (RGM=0.84; 95% CI 0.94-0.98, $P<0.001$). Lastly, being assigned to low priority triage (non emergent categories 3-5) was associated with a 23% increase in median DTB time (RGM=1.23 95% CI 1.09-1.40, $P=.001$).
DISCUSSION

Previous studies have demonstrated a delay in both presentation to hospital (reflected by an increased pain-to-door\textsuperscript{225, 227, 228, 652}) and in the hospital management (as assessed by an increased DTB time\textsuperscript{77, 229-231, 648}) amongst women with STEMI. Any delay in restoring reperfusion results in a larger infarct and thus may contribute to the poorer outcomes experienced by women with STEMI. The delay in presentation to hospital has been attributed to atypical symptoms and the limited understanding within the community of the prevalence of coronary heart disease amongst women. This insight has prompted the ‘women in red’ campaign to address this erroneous perception.

A delayed DTB time for women has been reported in several studies with some reporting delays of \textsuperscript{8}\textsuperscript{220} and \textsuperscript{13}\textsuperscript{231} minutes compared to men (similar to the 16 minutes observed in this study), whilst others reported > 120 minute difference\textsuperscript{229}. The present study has confirmed that gender is an independent determinant of DTB time, along with presentation during office hours, triage category, a history of hypertension, and the extent of peak ST-elevation on the initial ECG. Moreover, it provides insights into the components responsible for the delayed DTB time in women, demonstrating that the delay occurs throughout the continuum of the DTB time components. By using the ‘code call’ to delineate the time interval for when a diagnosis of STEMI was established, this study demonstrates a delay for female patients in both (a) the time to diagnosis (as evidenced by a delay in Door-to-Code time), and (b) the interventional treatment time interval (as reflected by the delayed Lab-to-Balloon time). These insights provide directions for addressing these gender disparities.
Mechanisms of Delayed Diagnosis and Therapy

As shown in Figure 1, a delay in diagnosis amongst women with STEMI occurs due to delays in both the (a) Door-to-ECG and (b) ECG-to-Code times. The delay in Door-to-ECG time may be attributable to several factors. Firstly, women more often experience atypical symptoms during acute myocardial infarction (such as nausea\textsuperscript{653, 654}, back pain\textsuperscript{654} and shortness of breath\textsuperscript{653}) and thus may not be appropriately triaged on arrival to the emergency department thereby delaying the Door-to-ECG time. Secondly, women usually have a longer time interval from the onset of chest pain to presenting to the hospital, thus the ‘sense of urgency’ may be lost by the triage personnel resulting in a less urgent triage classification and subsequent delay in Door-to-ECG time. A third potential factor that may contribute to the delay in performing the ECG is the presence of breasts in women. Accordingly, closer attention may be required in placing the ECG electrodes in the correct anatomical position to ensure an adequate tracing.

The factors responsible for a delay in the ECG-to-Code time would include delays in the physician sighting the ECG and their interpretation of the recording. As discussed above, women more often have atypical symptoms and thus the physician may delay reviewing the ECG. Another potential explanation is the extent of peak ST elevation, which is an independent determinant of DTB time (Table 5). Thus more subtle ST elevation may delay ECG interpretation and recognition of the STEMI. Although not statistically different, women tended to have less peak ST elevation than men in this study (Table 2), and this may contribute to the delayed ECG interpretation.
In addition to this delay in the diagnosis of STEMI, this investigation has identified that women experience a further delay in instituting effective reperfusion therapy (i.e. successful first balloon inflation). Although there appears to be no gender difference in Code-to-Lab time (in the transfer of patients from the emergency department to the catheterization laboratory), the Lab-to-Balloon time was significantly delayed in women (Figure 1), which may indicate that unrecognized technical factors contribute to the delayed DBT time. These may include difficulty in establishing arterial access, catheter engagement of the infarct-related artery, passage of the guidewire/balloon through the coronary occlusion or even balloon inflation itself. Further studies are required to identify which of these potential technical factors may contribute to women experiencing a delay in Lab-to-Balloon time. Previous studies have noted that women have smaller coronary arteries (average diameter of 2.90mm versus 3.09mm in men)\textsuperscript{252}, even after adjusting for body surface area\textsuperscript{253}, which may contribute to the technical difficulties in performing the PCI.

**Multivariate Model: Predictors of Door-to-Balloon Time**

As described above, female gender is a recognised predictor of a delayed DTB time, which has been supported by previous study findings\textsuperscript{77, 220, 229-231, 648, 649}. The observation of office hours as an independent predictor of DTB time has been previously described with multiple studies demonstrating that fewer patients presenting after-hours achieve DTB time guideline recommendations\textsuperscript{229, 655-658}. Previous studies have also demonstrated that hypertension\textsuperscript{77, 230, 659} and triage category\textsuperscript{660} are important determinants of DTB time. The extent of ST elevation as a contributing factor to DTB time has also been previously described\textsuperscript{77} and is worthy of further discussion. Although an independent factor to gender in determining DTB
time, it is noteworthy that women tended to have less peak ST elevation (Table 2). Further studies are required to examine if the total amount of ST elevation in all leads may contribute to DTB time and whether this differs in women thereby resulting in a delay in diagnosis.

**Limitations**

The study has several limitations that should be considered in interpreting the findings. Firstly, although a comprehensive set of variables were examined, they were not exhaustive and thus it is possible that important determinants of DTB were not considered. Thus we have limited data on demographic/socioeconomic factors, ejection fraction, body mass index and further information on diseased vessels, all of which may have explained more of the variance in our multivariate model. Furthermore, as this was an observational dataset we have several missing data points that may impact on our results, although subgroup analyses were conducted for missing data versus no missing data and both groups had similar clinical characteristics.

**Conclusion**

In conclusion, gender is an independent determinant of DTB time, being significantly delayed in women. Analysis of the DTB time components confirm a delay in both diagnosis and instituting PCI therapy in women. Strategies to rectify these important gender discrepancies should focus on educational campaigns within the emergency department, highlighting the potential pitfalls in diagnosing women with STEMI and considering technical factors in performing primary PCI.
FIGURE 1: Pain-to-Door and Components of Door-to-Balloon Stratified by Gender. Gender differences in Pain-to-Door and Door-to-Balloon in 735 STEMI patients undergoing primary percutaenous coronary intervention [female (red) vs. male (blue): p*<0.05, **P<0.001.
Table 1: Pre Hospital Clinical Characteristics Stratified by Gender

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<th>Men (N=562)</th>
<th>Women (N=173)</th>
<th>P value</th>
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<td></td>
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<tr>
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<td>Statin</td>
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<td>102 (22%)</td>
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<td>25 (21%)</td>
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<td></td>
<td>20 (4%)</td>
<td>9 (8%)</td>
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*Cardiovascular risk factors and maintenance medications are defined by the National Cholesterol Education Program criteria: Available from NCDR ACS coder’s dictionary

(NCDR: [http://www.ncdr.com/WebNCDR/Action/default.aspx](http://www.ncdr.com/WebNCDR/Action/default.aspx)\textsuperscript{661}  

195
<table>
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<th>Table 2: STEMI Management Stratified by Gender</th>
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<tr>
<td><strong>ECG and Pre-lab Clinical Status</strong></td>
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<tr>
<td><strong>No. of patients with ST-elevation</strong></td>
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<tr>
<td>(N=562) Available data points</td>
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<tr>
<td><strong>Peak ST elevation on ECG (mm)</strong></td>
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<tr>
<td><strong>Anterior STEMI</strong></td>
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<td><strong>Initial heart rate (BPM)</strong></td>
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<td><strong>Initial systolic blood pressure (mmHg)</strong></td>
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<td><strong>Acute pulmonary edema</strong></td>
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<td><strong>Hospital Management Logistics</strong></td>
</tr>
<tr>
<td><strong>Office hours presentation</strong></td>
</tr>
<tr>
<td>(N=562) Available data points</td>
</tr>
<tr>
<td><strong>Patient self arrival</strong></td>
</tr>
<tr>
<td><strong>Ambulance arrival</strong></td>
</tr>
<tr>
<td><strong>Triage 1-2 (high priority)</strong></td>
</tr>
<tr>
<td><strong>Triage 3-5 (low priority)</strong></td>
</tr>
<tr>
<td><strong>Patient transfers</strong></td>
</tr>
<tr>
<td><strong>Pain-to-Door (IQR: 25-75th)</strong></td>
</tr>
<tr>
<td><strong>Door-to-ECG (IQR: 25-75th)</strong></td>
</tr>
<tr>
<td><strong>Door-to-Code (IQR: 25-75th)</strong></td>
</tr>
<tr>
<td><strong>Code-to-Lab (IQR: 25-75th)</strong></td>
</tr>
<tr>
<td><strong>Lab-to-Balloon (IQR: 25-75th)</strong></td>
</tr>
<tr>
<td><strong>Code-to-Balloon (IQR: 25-75th)</strong></td>
</tr>
<tr>
<td><strong>Door-to-Balloon (IQR: 25-75th)</strong></td>
</tr>
<tr>
<td><strong>Door to balloon time under 90 mins</strong></td>
</tr>
</tbody>
</table>

*Defined by NCDR criteria


†Office hour’s presentation includes 0830-1700 hours, Monday to Friday.
Table 3: PCI Management Stratified by Gender

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=562)</td>
<td>(N=173)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Available</td>
<td>Available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>data points</td>
<td>data points</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% or Mean±SD</td>
<td>% or Mean±SD</td>
<td></td>
</tr>
<tr>
<td>PCI Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Creatine kinase (U/L)</td>
<td>537</td>
<td>166</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>2075±2711</td>
<td>1684±2007</td>
<td></td>
</tr>
<tr>
<td>BUN/Creatinine ratio (umol/L)*</td>
<td>541</td>
<td>166</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>91±39</td>
<td>84±48</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/L)‡</td>
<td><strong>552</strong></td>
<td><strong>159</strong></td>
<td><strong>.001</strong></td>
</tr>
<tr>
<td></td>
<td>146±19</td>
<td>130±18</td>
<td></td>
</tr>
<tr>
<td>TIMI-3 Pre-PCI‡</td>
<td>562</td>
<td>173</td>
<td>.57</td>
</tr>
<tr>
<td></td>
<td>57 (10%)</td>
<td>20 (12%)</td>
<td></td>
</tr>
<tr>
<td>TIMI-3 Post-PCI§</td>
<td>562</td>
<td>173</td>
<td>.57</td>
</tr>
<tr>
<td></td>
<td>508 (90%)</td>
<td>154 (89%)</td>
<td></td>
</tr>
<tr>
<td>Bare metal stent (BMS)</td>
<td>562</td>
<td>173</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>449 (80%)</td>
<td>129 (75%)</td>
<td></td>
</tr>
<tr>
<td>Drug eluting stent (DES)</td>
<td>562</td>
<td>173</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>38 (7%)</td>
<td>12 (7%)</td>
<td></td>
</tr>
<tr>
<td>Balloon therapy (PoBA)</td>
<td>562</td>
<td>173</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>24 (4%)</td>
<td>7 (4%)</td>
<td></td>
</tr>
<tr>
<td>Gp IIb/IIIa Antagonist*/‡</td>
<td>560</td>
<td>173</td>
<td>.15</td>
</tr>
<tr>
<td></td>
<td>176 (31%)</td>
<td>44 (25%)</td>
<td></td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>560</td>
<td>173</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>39 (7%)</td>
<td>12 (7%)</td>
<td></td>
</tr>
<tr>
<td>Export catheter</td>
<td>549</td>
<td>165</td>
<td>.15</td>
</tr>
<tr>
<td></td>
<td>51 (9%)</td>
<td>9 (6%)</td>
<td></td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>544</td>
<td>162</td>
<td>.79</td>
</tr>
<tr>
<td></td>
<td>290 (53%)</td>
<td>84 (52%)</td>
<td></td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>529</td>
<td>164</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>4±3</td>
<td>4±5</td>
<td></td>
</tr>
<tr>
<td>STEMI code cancelled/false call</td>
<td><strong>562</strong></td>
<td><strong>173</strong></td>
<td><strong>.002</strong></td>
</tr>
<tr>
<td></td>
<td>16 (3%)</td>
<td>15 (9%)</td>
<td></td>
</tr>
<tr>
<td>Normal angiography</td>
<td>552</td>
<td>163</td>
<td>.62</td>
</tr>
<tr>
<td></td>
<td>4 (1%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Slow flow</td>
<td>548</td>
<td>162</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>8 (2%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>493</td>
<td>136</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>15 (3%)</td>
<td>9 (7%)</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td><strong>489</strong></td>
<td><strong>136</strong></td>
<td><strong>.009</strong></td>
</tr>
<tr>
<td></td>
<td>13 (3%)</td>
<td>11 (8%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>493</td>
<td>136</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>2 (1%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarct outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>562</td>
<td>173</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>32 (6%)</td>
<td>18 (10%)</td>
<td></td>
</tr>
<tr>
<td>12-month mortality</td>
<td>562</td>
<td>173</td>
<td>.56</td>
</tr>
<tr>
<td></td>
<td>37 (7%)</td>
<td>20 (12%)</td>
<td></td>
</tr>
<tr>
<td>Re-MI 30 day</td>
<td><strong>562</strong></td>
<td><strong>173</strong></td>
<td><strong>.034</strong></td>
</tr>
<tr>
<td></td>
<td>12 (2%)</td>
<td>9 (5%)</td>
<td></td>
</tr>
<tr>
<td>All cause 30 Day mortality/re-MI</td>
<td>562</td>
<td>173</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>44 (8%)</td>
<td>27 (16%)</td>
<td></td>
</tr>
<tr>
<td>Morality prior to catheterization lab</td>
<td>562</td>
<td>173</td>
<td>.47</td>
</tr>
<tr>
<td></td>
<td>7 (22%)</td>
<td>1 (11%)</td>
<td></td>
</tr>
</tbody>
</table>

*BUN/Creatinine ratio= Blood urea nitrogen/ serum creatinine ratio (umol/L).
Normal reference ranges for Hemoglobin level in women (123-157 g/L) & men (140-174 g/L).

TIMI 3-Pre-PCI= Thrombolysis in myocardial infarction grade-3 flow pre-PCI.

TIMI-3-POST= Thrombolysis in myocardial infarction grade-3 flow post-PCI.

GpIIb/IIIa antagonist= Glycoprotein IIb/IIIa antagonist.
Table 4: The Unadjusted and Adjusted Association between Gender and DTB. Unstandardized regression Coefficients, p values, ratio of geometric means and 95% Confidence Intervals (CI) are presented.

<table>
<thead>
<tr>
<th></th>
<th>Estimate (B)</th>
<th>P value</th>
<th>Ratio of geometric means</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardized Coefficient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>.151</td>
<td>.005</td>
<td>1.16</td>
<td>1.05-1.29</td>
</tr>
<tr>
<td><strong>Adjusted 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>.163</td>
<td>.003</td>
<td>1.18</td>
<td>1.06-1.31</td>
</tr>
<tr>
<td><strong>Adjusted 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>.150</td>
<td>.007</td>
<td>1.16</td>
<td>1.04-1.29</td>
</tr>
<tr>
<td><strong>Adjusted step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>.138</td>
<td>.011</td>
<td>1.15</td>
<td>1.03-1.28</td>
</tr>
<tr>
<td><strong>Adjusted step 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>.140</td>
<td>.010</td>
<td>1.15</td>
<td>1.03-1.28</td>
</tr>
<tr>
<td><strong>Adjusted step 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>.122</td>
<td>.022</td>
<td>1.13</td>
<td>1.02-1.26</td>
</tr>
</tbody>
</table>

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and cardiovascular risk factors (hypercholesterolemia, hypertension, diabetes, family history, current smoking, previous CAD; ‡adjusted model 3 = model 2 and infarct characteristics (peak ST-elevation on ECG); §adjusted model 4 = model 3 and hemodynamics (initial HR, initial SBP, APO, VF arrest); ¶adjusted model 5 = model 4 and logistics (office hours, self arrival, SAAS arrival and triage category).

See Appendix 1 for full model.
Table 5: Multivariate Linear Regression Determinants of DTB Time.
Unstandardized regression Coefficients, p values, ratio of geometric means and 95% Confidence Intervals (CI) are presented.

<table>
<thead>
<tr>
<th></th>
<th>Estimate (B)</th>
<th>P value</th>
<th>Ratio of geometric means</th>
<th>95% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>.122</td>
<td>.022</td>
<td>1.13</td>
<td>1.02-1.26</td>
</tr>
<tr>
<td>Age</td>
<td>-.002</td>
<td>.23</td>
<td>0.99</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>-.048</td>
<td>.28</td>
<td>0.95</td>
<td>0.88-1.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>.116</td>
<td>.014</td>
<td>1.12</td>
<td>1.02-1.23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-.014</td>
<td>.77</td>
<td>0.99</td>
<td>0.89-1.08</td>
</tr>
<tr>
<td>Family history</td>
<td>-.058</td>
<td>.28</td>
<td>0.94</td>
<td>0.85-1.05</td>
</tr>
<tr>
<td>History of smoking</td>
<td>-.005</td>
<td>.92</td>
<td>0.99</td>
<td>0.91-1.09</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>-.015</td>
<td>.78</td>
<td>.783</td>
<td>0.88-1.09</td>
</tr>
<tr>
<td>Peak ST-elevation</td>
<td>-.036</td>
<td>.001</td>
<td>0.97</td>
<td>0.94-0.98</td>
</tr>
<tr>
<td>Arrival HR</td>
<td>.001</td>
<td>.29</td>
<td>1.00</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>Arrival SBP</td>
<td>.000</td>
<td>.35</td>
<td>1.00</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>APO</td>
<td>.081</td>
<td>.44</td>
<td>1.09</td>
<td>0.88-1.33</td>
</tr>
<tr>
<td>VF arrest</td>
<td>.081</td>
<td>.42</td>
<td>1.08</td>
<td>0.89-1.32</td>
</tr>
<tr>
<td>Office hours</td>
<td>-.172</td>
<td>.000</td>
<td>0.84</td>
<td>0.78-0.92</td>
</tr>
<tr>
<td>Arrival status</td>
<td>-.068</td>
<td>.16</td>
<td>1.07</td>
<td>0.9701.18</td>
</tr>
<tr>
<td>Triage category</td>
<td>.211</td>
<td>.001</td>
<td>1.23</td>
<td>1.09-1.40</td>
</tr>
</tbody>
</table>

See Appendix 1 for full-adjusted model.
FIGURE 1: Pain-to-Door and Components of Door-to-Balloon Stratified by Gender

![Bar chart showing median times for various components of Door-to-Balloon process stratified by gender.](image)

- **PTD**
- **DTE**
- **DTC**
- **CTL**
- **LTB**
- **CTB**

Median time (minutes)
CHAPTER 5: Sex Differences in Cardiac Haemodynamics during Acute ST-Elevation Myocardial Infarction

This results chapter is reproduced in the exact form as it appears in the article “Sex Differences in Cardiac Haemodynamics during Acute ST-Elevation Myocardial Infarction” authored by Rachel Dreyer, John Beltrame, Christopher Neil, Tracy air, Rosanna Tavella, Bernadette Hoffmann, Purendra Pati, David di Fiore, Margaret Arstall and Christopher Zetiz (submitted and under review in Circulation: Cardiovascular Quality and Outcomes).

In keeping with the style of this thesis, the figures and tables have been modified, the references incorporated into the thesis’s master reference list and the manuscript repaginated.
**Study Overview**

This manuscript demonstrates important sex differences in cardiac haemodynamics following acute STEMI. Although sex differences in 30-day outcomes following STEMI have been extensively investigated, no previous study has examined sex differences in cardiac haemodynamic parameters such as pulmonary capillary wedge pressure (PCWP) following STEMI. Thus, this study provides new insights into potential mechanisms for the higher in-hospital mortality and poor recovery following acute myocardial infarction in women.

The principal findings of the study are that women have an elevated PCWP and reduced mixed venous oxygen saturation during acute STEMI, compared with their male counterparts. This was found to be independent of age, hypertension and infarct size. Thus, PCWP may represent a marker for potential poor outcomes in women. Furthermore, female sex was an independent predictor of 30-day mortality/re-infarction but PCWP had only a minor impact on this outcome, underscoring the influence of the former.
ABSTRACT

Aims: Several biological and clinical factors contribute to the increased 30-day mortality/re-infarction in women with ST-elevation myocardial infarction (STEMI). Sex differences in cardiac haemodynamic parameters such as pulmonary capillary wedge pressure (PCWP) have not been examined and may play an important role. The objectives of this study were to (a) examine if female sex is an independent determinant of PCWP during acute STEMI and (b) whether elevated PCWP contributes to all cause 30-day mortality/re-infarction, in women.

Methods and Results: Clinical, angiographic and haemodynamic features of 470 consecutive STEMI patients (n=135 women) undergoing emergency coronary angiography with right heart catheterisation were evaluated with respect to sex. Women had an elevated PCWP (20±8 vs. 16±7 mmHg, P<0.001) and reduced mixed venous oxygen saturation (67±11% vs. 71±9%, P<0.001). On multivariate analysis, female sex (B=4.04; 95% CI 2.04-6.04, P<0.001), hypertension (B=2.07; 95% CI 0.32-3.83; P=0.021) and creatine kinase estimated infarct size (B=0.001, 95% CI 0.001-0.002, P=<0.001) were independent predictors of an elevated PCWP. Although female sex was also an independent predictor of 30-Day mortality/re-infarction (OR=2.36, 95% CI 1.25-4.46, P=0.008), this was partially mediated through PCWP, which in turn had its own direct effect on 30-day outcomes (OR=1.07, 95% CI 1.02-1.12, P=0.011).

Conclusion: During acute STEMI, women have higher left ventricular filling pressures compared with men, independent of age, hypertension and infarct size. The biologic explanation for this difference requires further investigation although it does not appear to contribute to the increased 30-day mortality/re-infarction observed in women.
INTRODUCTION

Contemporary management of acute ST-elevation myocardial infarction (STEMI) has resulted in a marked decrease in mortality\textsuperscript{662, 663}. Despite this, age-adjusted 30-day mortality and re-infarction rates remain higher for women than men\textsuperscript{175, 207, 220, 233, 234, 329, 343, 622}. The factors that contribute to this sex disparity include increased co-morbidities\textsuperscript{664, 665}, delays in initiating reperfusion therapies and less intensive treatment\textsuperscript{236, 329, 664, 666-668}, however other unknown factors are likely to contribute\textsuperscript{243, 664, 669}. To date, no previous study has examined sex differences in cardiac haemodynamics during acute STEMI.

Since its introduction by Swan and Ganz in 1970, the pulmonary arterial catheter has enabled direct measurement of right heart pressures and cardiac output\textsuperscript{670-672}. Although its routine use for monitoring haemodynamic status during acute myocardial infarction (AMI) has declined\textsuperscript{673}, it remains a significant adjunct to clinical assessment and acute management. Of particular use is the assessment of pulmonary capillary wedge pressure (PCWP) as a marker of left ventricular filling pressure. Accordingly, it is a marker of pulmonary congestion, with PCWP $\geq 18$mmHg typically associated with clinical evidence of pulmonary congestion in AMI\textsuperscript{674}. Furthermore, PCWP is a haemodynamic marker of poor prognosis\textsuperscript{675, 676}, a strong independent predictor of short and long term mortality following AMI\textsuperscript{677} and directly varies with AMI size. Mixed venous oxygen saturation (MV$O_2$) is another haemodynamic measure that can be obtained via pulmonary artery catheterisation and is a direct correlate of cardiac output. It may also have prognostic potential although weaker than PCWP.
In light of the above, the primary objective of this study was to examine the relationship between sex and haemodynamic status during acute STEMI, and determine if this influenced subsequent cardiac events. We therefore tested the hypotheses that (A) female sex is an independent predictor of an elevated PCWP measurement at the time of primary percutaneous coronary intervention (PCI) for acute STEMI and (B) that female sex and PCWP both influence 30-day all-cause mortality/re-infarction.
METHODS

This observational cohort study utilised data from a STEMI clinical registry, which was collected from two South Australian teaching hospitals (The Queen Elizabeth and Lyell McEwin hospitals). These university teaching hospitals service the North-Western suburbs of Adelaide. Between October 2005 and October 2010, 912 consecutive STEMI patients (234 women, 26%) presented to the two hospitals and had extensive clinical elements collected, including cardiovascular risk factors, medications, and STEMI details. This registry has been independently audited with over 90% agreement reported with case-note abstraction.

Study cohort

Patients included in this study had: (1) a diagnosis of acute STEMI as defined by the presence of ischaemic chest pain, and ST-segment elevation, or new left bundle branch block, and (2) performance of right heart catheterisation during acute STEMI. Consistent with the formal definition of AMI, patients were included if they had a troponin rise. The performance and timing of right heart catheterisation was at the discretion of the interventional cardiologist but all were performed immediately prior/following PCI. Patients were excluded if PCWP was not obtained during the primary PCI procedure. Institutional ethics committee approval was obtained to access the STEMI registry data and follow up details (30-day outcomes).
Acute STEMI Management

The patients were urgently transferred to the catheterisation laboratory for emergency coronary angiography and, if indicated, primary PCI. All patients received loading doses of heparin, aspirin ± clopidogrel before or during primary PCI. Use of glycoprotein IIb/IIIa inhibitors, thrombus aspiration device or intra-aortic balloon pump (IABP), were at the discretion of the treating cardiologist. All patients were subsequently monitored in the coronary or intensive care units for at least 48 hours.

Cardiac Catheterisation Haemodynamic Measurements

Sequential right atrial (RA), right ventricular (RV), pulmonary artery (PA), and pulmonary capillary wedge (PCWP) pressures were recorded via a Swan-Ganz catheter, with continuous recording of systolic femoral artery (FA) pressure via a femoral artery sheath. Arterial and mixed venous blood samples were taken for determination of arterial and MV0₂ saturations by a blood gas analyzer (Radiometer Copenhagen NPT 7 Series blood gas analyzer). Heart rate (HR, beats min⁻¹) was continuously monitored via a three-lead ECG recording.

Clinical Parameters Assessed

Detailed clinical data including patient demographics, cardiovascular risk factors, past medical history, maintenance medications, infarct characteristics/logistics, hospital arrival haemodynamic status, post-PCI outcomes (including peak creatine kinase (CK) estimated infarct size), and the above cardiac catheterisation haemodynamic measurements were abstracted from case notes and recorded in a prospectively maintained registry. An audit of 22% of the registry records was undertaken to assess
for data entry reliability. Clinical outcome measures were determined from administrative datasets and included 30-day mortality and 30-day re-infarction. Diagnosis of recurrent infarction was based on typical chest pain, new ST-segment changes and an increase in CK of at least 50% above the previous trough level in at least 2 samples with a minimum increase of twice the upper CK reference limit.

**Data and Statistical Analysis**

Clinical and outcome variables were compared between sexes. Categorical variables are presented as frequencies and compared using Pearson Chi Squared or Fisher exact tests. Continuous variables are expressed as mean ± standard deviation or medians with inter quartile ranges (25th, 75th), with comparisons made using Student’s independent t-tests or non-parametric Mann-Whitney U tests where appropriate. Myocardial infarction outcomes (composite end point of 30-day mortality/re-infarction) were compared between men and women using logistic regression models, with adjustment for age.

A multivariate linear regression model was fitted to identify independent predictors of PCWP whilst adjusting for conventional covariates (Hypothesis A)677. These included: age, cardiovascular risk factors (hypertension, diabetes, cholesterol, history of smoking), peak CK, acute pulmonary oedema and localisation of infarction (anterior vs. non-anterior). In addition, clinically-relevant determinants of cardiac mortality were incorporated into the model, including: sex, office hours presentation, arrival by the ambulance service, door-to-balloon time, blood urea nitrogen/creatinine ratio, Hemoglobin, Thrombolysis in myocardial infarction (TIMI) grade-3 before (Pre
TIMI-3) and after PCI (Post TIMI-3), use of IABP, stroke, ventricular fibrillation arrest, arrival heart rate and arrival systolic blood pressure.

To assess the relationship between sex, PCWP and early adverse outcomes (Hypothesis B), two logistic regression models were performed. The first assessed the total effect of sex on 30-day mortality/re-infarction and the second the direct/indirect effect of sex, whilst adjusting for PCWP\textsuperscript{678}. For all analyses, the complete available dataset was used with no imputation for missing variables. A p value of P<0.05 was considered statistically significant. All analyses were performed using SPSS 18.0 for Macintosh (SPSS Inc., Chicago Ill).
RESULTS

From the 912 consecutive cases in the STEMI registry, haemodynamic data was available for 470 patients (135 women, 15%). A quarter of the hospital interventional cardiologists routinely performed right heart catheterisation during acute STEMI and contributed to 90% of the patients included in this study. These interventionalists each performed right heart catheterisations in over 90% of the acute STEMI patients they attended. Thus the study cohort essentially represents consecutive patients treated by these interventional cardiologists. Moreover, compared with the overall cohort (n=912), the hemodynamic subset evaluated in this investigation was similar in regards to sex, cardiovascular risk factors, door-balloon time, heart rate, systolic blood pressure and 30-day all-cause mortality/re-infarction (Appendix-1). Accordingly, except for age (which has been adjusted for in subsequent analyses), there was no evidence of a systematic selection bias thereby suggesting that the study hemodynamic cohort is representative of the total STEMI population.

Baseline Patient Characteristics and Clinical Status

Pre-hospital clinical characteristics of the 470 consecutive STEMI patients are presented in Table 1. Women were significantly older than men with many over the age of 75 years (Table 1). Furthermore, women were more likely to have hypertension and be treated with beta-blockers whereas men were more likely to be smokers and heavier. Although women had prolonged pain-to-door and door-to-balloon times compared with men, they were similar in relation to other infarct characteristics, admission clinical haemodynamic status, and post-PCI outcomes; including infarct site and size (Table-2).
**Haemodynamic Measurements and Cardiac Events**

Despite similar right atrial and ventricular pressures to men, women had higher pulmonary artery pressures and PCWP; almost two-thirds having a PCWP ≥ 18mmHg as compared with a third of men (Table-3, Figure-1). Furthermore as illustrated in Figure-1, this appears to be independent of hypertension since 22 (36%) of women with PCWP ≥ 18mmHg did not have a history of hypertension. Also noteworthy, women with AMI had significantly lower MVO₂ despite preserved arterial oxygen saturation (Table 3). Thus compared with men, more women with acute STEMI had hemodynamic markers consistent with increased left ventricular filling pressure and/or a reduced cardiac output.

Unadjusted comparisons of cardiac events between men and women with acute STEMI demonstrated a non-significant trend in 30-day mortality (5% vs 10%, respectively, P=0.050) and 30-day re-infarction (2% vs. 5%, P=0.146) but did show increased events in women with respect to the composite endpoint of all-cause 30-day mortality/re-infarction (15% vs. 7%, P=0.012). Moreover, age-adjusted regression analyses showed no difference in the individual component endpoints (30-day mortality or 30-day re-infarction) and confirmed the increased composite endpoint of 30-day all-cause mortality/re-infarction in women (adjusted OR=2.05; 95% CI 1.05-4.00, P=0.034).
Clinical Determinants of PCWP: Effect of Sex

To assess the clinical determinants of PCWP and determine if female sex was an independent predictor (Hypothesis A), a multivariable linear regression analysis was undertaken with the results summarised in Table-4. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Overall the final regression model was statistically significant, \( F(20, 257)=4.49, \ P<0.001, \ R^2= 0.26, \) adjusted \( R^2= 0.20 \), with the covariates in the model explaining 26% of the variance in mean PCWP.

In the model, sex, hypertension and peak CK were found to be statistically significant independent predictors of PCWP. Female sex was associated with a 4.04mmHg increase in mean wedge pressure \( (B=4.04; \ 95\% \ CI \ 2.04-6.04; \ P<0.001) \). In addition, hypertension was related to a 2.07mmHg increase in PCWP \( (B=2.07; \ 95\% \ CI \ 0.31-3.83; \ P=0.021) \). Lastly, a 1000-unit increase in peak CK was associated with a 1.00mmHg increase in mean wedge pressure \( (B=0.001; \ 95\% \ CI \ 0.001-0.002; \ P<0.001) \).

Effect of PCWP and Sex-related 30-day cardiac events

Examination of the relationship between sex and composite 30-day all-cause mortality/re-infarction confirmed that female sex was a significant predictor of 30-day cardiac events \( (OR=2.36, \ 95\% \ CI \ 1.25-4.46, \ P=0.008) \). However, once PCWP was entered into the model, sex was no longer significant \( (OR=1.85, \ 95\% \ CI \ 0.79-4.33, \ P=0.155) \), suggesting that while PCWP may have its own direct effect of 30 day
events (OR=1.07, 95% CI 1.02-1.12, P=0.011), sex may be partially mediated by PCWP as the direct effect for sex reduced once PCWP was included.
DISCUSSION

This study has provided important insights into sex differences in clinical outcomes following acute STEMI, demonstrating that women have a higher PCWP compared to men. This was evident despite similar infarct site/size, extent of coronary artery disease, and hospital-arrival clinical haemodynamic status. Although women with acute STEMI were more likely to be older and have hypertension, multivariable regression analysis confirmed that female sex was an independent predictor of PCWP along with a history of hypertension and larger infarct size. Moreover, in logistic regression models, sex was an independent determinant of 30-day cardiac events (all-cause mortality and re-infarction), which was partially mediated through PCWP, which had its own direct effect on 30-day outcomes.

Previous Studies Supporting Study Findings

Although this study is unique in reporting a large dataset of STEMI patients with right heart catheter findings during emergency cardiac catheterisation, the findings are consistent with previous data published in the literature. Firstly, similar to other STEMI studies, women were older, more often had hypertension and had a higher early mortality.679 Secondly, as observed in this study, there was no difference in infarct size between men and women as determined by contrast-enhanced cardiac magnetic resonance imaging680; the benchmark for infarct size estimation. Surprisingly, a recent study has suggested that women have smaller infarcts on cardiac magnetic resonance imaging681. Thirdly, consistent with the documented increased left ventricular filling pressures amongst women in this study, Wiviott et al (2004)682 reported increased brain natriuretic peptide in women with AMI. Fourthly
and most importantly, several studies have reported adverse clinical outcomes that would be expected with an elevated PCWP in women. Valente et al (2012)\(^{679}\) examined sex-related differences in 1,127 STEMI patients undergoing PCI and reported that women had (a) a higher Killip class, and (b) increased requirements for inotropes and non-invasive ventilation. In addition, Akhter et al (2012)\(^{683}\) utilised the American College of Cardiology National Cardiovascular Data Registry and noted that women with AMI had higher rates of cardiogenic shock and congestive heart failure.

**Mechanisms for Higher PCWP in Women**

This and previous studies suggest that women have increased filling pressures during an acute STEMI\(^{684}\). The mechanism responsible for this haemodynamic difference is unclear but may relate to their pre-morbid cardiac status or the pathophysiological mechanisms responsible for the acute STEMI. In patients presenting with acute pulmonary edema, women are more likely to have normal left ventricular systolic function as compared with men\(^{685-687}\). Thus similar to the current study, there is a sex disparity in the underlying pathophysiological haemodynamic mechanisms within the same clinical syndrome. These sex differences have also been observed in relation to coronary heart disease with women more often experiencing myocardial infarction and angina, in the absence of obstructive coronary artery disease\(^{176, 688, 689}\). Thus it is evident that women’s heart disease often differs from ‘men’s heart disease’\(^{288, 690}\).

Accordingly, a plausible explanation for the observed differences in this study is a different response from the myocardium to the same ischaemic insult during STEMI. Whether this is due to pre-existing diastolic stiffness in women’s heart’s\(^{691}\), more
prevalent microvascular dysfunction, or other underlying differences, requires further investigation. Alternatively, whether pre-morbid coronary/myocardial function is similar in men and women is unknown. Alternatively whether the STEMI process in women involves a greater extent of de-novo microvascular dysfunction, myocardial inflammation\textsuperscript{692}, or ischemic-reperfusion injury\textsuperscript{693, 694}, also warrants further consideration.

**Limitations**

Several important limitations need to be considered when interpreting our results. Firstly, potential sample selection bias has been examined by comparing the clinical attributes of the consecutive acute STEMI cases included and excluded from the study (Appendix-1). Except for age (accounted for in subsequent analyses), female sex and hypercholesterolemia, there were no clinical differences between the cohorts suggesting the study sample was representative. However, sub-clinical differences between the groups cannot be excluded.

A second limitation relates to the pre-morbid cardiac status of the study patients. Although there were no differences in relation to previous coronary artery disease, there is no data in relation to the pre-morbid left ventricular function or the presence of left ventricular hypertrophy. Thus we cannot exclude that women had poorer baseline left ventricular function (systolic or diastolic), prior to the acute STEMI. The increased prevalence of hypertension in women may imply increased diastolic dysfunction amongst the women in the cohort, however sex was independent of hypertension as a determinant of PCWP. Closer evaluation of the increased use of
beta-blockers amongst women (Table-1) revealed that these were primarily prescribed for hypertension rather than cardiac failure.

**Conclusion**

This large study has demonstrated that women with acute STEMI have a higher PCWP than their male counterparts, independent of age, hypertension and infarct size. In keeping with other reports, acute PCWP exerted only a minor independent effect on 30-day mortality/re-infarction with the effect of sex on post-STEMI outcomes potentially mediated though PCWP. Thus, further studies are required in women with acute STEMI in order to (a) examine the mechanism/s involved in the increased PCWP, and (b) to define the clinical determinants for the increased 30-day cardiac events.
FIGURE LEGENDS

Figure 1. Pulmonary Capillary Wedge Pressure (PCWP) in Relation to Sex, Hypertension and Age in Acute ST-elevation myocardial infarction (STEMI) patients.

(a) Sex differences in PCWP tertile distribution in patient’s with/without hypertension (cross- hatched section). [Men (blue) vs. women (red): *p <0.05, **p < 0.001].

(b) Sex Differences in PCWP with Respect to Age groups (Mean±SD). [Men (blue) vs. women (red): *p <0.05, **p < 0.001].
Table 1: Pre Hospital Clinical Characteristics Stratified by Sex

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=335)</td>
<td>(N=135)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available data points</td>
<td>Available data points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>335</td>
<td>61±13</td>
<td>135</td>
</tr>
<tr>
<td>&lt;55</td>
<td>335</td>
<td>128 (38%)</td>
<td>135</td>
</tr>
<tr>
<td>56-64</td>
<td>335</td>
<td>75 (22%)</td>
<td>135</td>
</tr>
<tr>
<td>65-74</td>
<td>335</td>
<td>73 (21%)</td>
<td>135</td>
</tr>
<tr>
<td>≥75</td>
<td>335</td>
<td>59 (18%)</td>
<td>135</td>
</tr>
</tbody>
</table>

Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>307</td>
<td>159 (52%)</td>
<td>120</td>
</tr>
<tr>
<td>Hypertension</td>
<td>309</td>
<td>143 (46%)</td>
<td>120</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>311</td>
<td>83 (27%)</td>
<td>124</td>
</tr>
<tr>
<td>Family history CAD†</td>
<td>307</td>
<td>59 (19%)</td>
<td>119</td>
</tr>
<tr>
<td>History of smoking</td>
<td>307</td>
<td>195 (64%)</td>
<td>120</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>305</td>
<td>72 (24%)</td>
<td>119</td>
</tr>
</tbody>
</table>

Maintenance medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>269</td>
<td>43 (16%)</td>
<td>92</td>
</tr>
<tr>
<td>Statin</td>
<td>269</td>
<td>67 (25%)</td>
<td>92</td>
</tr>
<tr>
<td>ACE inhibitor†</td>
<td>269</td>
<td>49 (18%)</td>
<td>91</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>270</td>
<td>12 (4%)</td>
<td>92</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>270</td>
<td>8 (3%)</td>
<td>92</td>
</tr>
</tbody>
</table>

*As defined by the American College of Cardiology Foundation: Get with the Guidelines

NCDR ACS  Coder’s dictionary<sup>661</sup>.

†CAD=Coronary artery disease

‡ACE Inhibitor= Angiotensin converting enzyme inhibitor
Table 2: Acute STEMI Clinical Status Stratified by Sex

<table>
<thead>
<tr>
<th></th>
<th>Men (N=335) Available data points</th>
<th>N (%) or Mean±SD</th>
<th>Women (N=135) Available data points</th>
<th>N (%) or Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infarct Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTD [median (IQR: 25-75th)]*</td>
<td>230</td>
<td>101 (55, 218)</td>
<td>82</td>
<td>141 (60, 307)</td>
<td>0.040</td>
</tr>
<tr>
<td>DTB [median (IQR: 25-75th)]†</td>
<td>294</td>
<td>73 (54, 101)</td>
<td>106</td>
<td>85 (67, 115)</td>
<td>0.004</td>
</tr>
<tr>
<td>Office hours presentation‡</td>
<td>331</td>
<td>143 (43%)</td>
<td>134</td>
<td>51 (38%)</td>
<td>0.350</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>325</td>
<td>125 (38%)</td>
<td>129</td>
<td>45 (35%)</td>
<td>0.520</td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>326</td>
<td>170 (52%)</td>
<td>126</td>
<td>61 (48%)</td>
<td>0.529</td>
</tr>
<tr>
<td>Pre-PCI TIMI-3 Flow</td>
<td>335</td>
<td>44 (13%)</td>
<td>135</td>
<td>27 (20%)</td>
<td>0.065</td>
</tr>
<tr>
<td>BUN/Creatinine ratio (umol/L)‡</td>
<td>322</td>
<td>94±34</td>
<td>125</td>
<td>90±58</td>
<td>0.529</td>
</tr>
<tr>
<td>% Patients with eGFR ≤60 ml/min</td>
<td>316</td>
<td>51 (16%)</td>
<td>121</td>
<td>44 (36%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Arrival Anemia (Hb g/dL)ǁ</td>
<td>335</td>
<td>48 (14%)</td>
<td>103</td>
<td>32 (24%)</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>Clinical Haemodynamic Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival heart rate (BPM)</td>
<td>297</td>
<td>79±21</td>
<td>106</td>
<td>79±24</td>
<td>0.696</td>
</tr>
<tr>
<td>Arrival SBP (mmHg)</td>
<td>296</td>
<td>137±29</td>
<td>107</td>
<td>136±30</td>
<td>0.879</td>
</tr>
<tr>
<td>Acute pulmonary oedema#</td>
<td>335</td>
<td>16 (5%)</td>
<td>135</td>
<td>6 (4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Stroke</td>
<td>293</td>
<td>1 (1%)</td>
<td>108</td>
<td>2 (2%)</td>
<td>0.178</td>
</tr>
<tr>
<td>Ventricular fibrillation arrest</td>
<td>335</td>
<td>21 (6%)</td>
<td>135</td>
<td>7 (5%)</td>
<td>0.830</td>
</tr>
<tr>
<td>Intra-aortic balloon pump use</td>
<td>335</td>
<td>25 (8%)</td>
<td>135</td>
<td>10 (7%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Post-PCI Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-PCI TIMI-3 Flow achieved</td>
<td>335</td>
<td>289 (86%)</td>
<td>135</td>
<td>117 (87%)</td>
<td>1.000</td>
</tr>
<tr>
<td>No re-flow phenomenon</td>
<td>328</td>
<td>9 (3%)</td>
<td>126</td>
<td>7 (6%)</td>
<td>0.160</td>
</tr>
<tr>
<td>Peak creatine kinase (IU/L)</td>
<td>319</td>
<td>2100±5541</td>
<td>121</td>
<td>1320±1416</td>
<td>0.127</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>312</td>
<td>4±3</td>
<td>128</td>
<td>4±4</td>
<td>0.568</td>
</tr>
</tbody>
</table>

* PTD= Pain-to-Door Time (mins)
† DTB=Door-to-Balloon Time (mins)
‡ Office hours presentation = normal catheterization office hours (8:30-1700, Monday t Friday)
§ Arrival BUN/Creatinine ratio = Blood urea nitrogen/ serum creatinine ratio (umol/L)

// Normal reference ranges for Hemoglobin level in men (<13.0 g/dL) & women (<12.0 g/dL) ⁶⁹⁵

# APO Defined by NCDR

(NCDR: http://www.ncdr.com/WebNCDR/Action/default.aspx) ⁶⁶¹
Table 3: Haemodynamic Parameters and Outcomes of STEMI patients stratified by Sex

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=335)</td>
<td>(N=135)</td>
<td></td>
</tr>
<tr>
<td>Available data points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodynamic measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>293 10±11</td>
<td>108 10±5</td>
<td>0.876</td>
</tr>
<tr>
<td>Systolic RV pressure (mmHg)*</td>
<td>286 39±12</td>
<td>98 41±9</td>
<td>0.095</td>
</tr>
<tr>
<td>Mean PA pressure (mmHg)†</td>
<td>312 22±8</td>
<td>113 26±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean PCWP (mmHg)</td>
<td>310 16±7</td>
<td>112 20±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients with PCWP ≥18mmHg</td>
<td>310 111 (36%)</td>
<td>112 68 (61%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean femoral artery pressure (mmHg)</td>
<td>324 95±19</td>
<td>128 95±20</td>
<td>0.838</td>
</tr>
<tr>
<td>MV0₂†</td>
<td>309 71±9%</td>
<td>112 67±11%</td>
<td>0.004</td>
</tr>
<tr>
<td>Femoral artery saturation</td>
<td>310 98±3%</td>
<td>113 97±3%</td>
<td>0.364</td>
</tr>
<tr>
<td>Cardiac Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
<td>335 15 (5%)</td>
<td>135 13 (10%)</td>
<td>0.242</td>
</tr>
<tr>
<td>30-day re-infarction</td>
<td>335 8 (2%)</td>
<td>135 7 (5%)</td>
<td>0.069</td>
</tr>
<tr>
<td>30-day all-cause mortality/re-infarct</td>
<td>335 23 (7%)</td>
<td>135 20 (15%)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*Systolic RV pressure = Systolic right ventricular pressure

†Mean PA pressure = Mean pulmonary artery pressure

‡MV0₂= Mixed venous oxygen saturation
Table 4: Linear Regression Analysis (Predictors of PCWP)

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Unstandardized Coefficients</th>
<th>95% Confidence Interval for B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>7.89</td>
<td>5.45</td>
<td>-2.83</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.02</td>
<td>0.04</td>
<td>-0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.07</td>
<td>0.89</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.54</td>
<td>0.91</td>
<td>-1.25</td>
</tr>
<tr>
<td>Previous coronary disease</td>
<td>0.66</td>
<td>0.97</td>
<td>-1.25</td>
</tr>
<tr>
<td>History of smoking</td>
<td>0.33</td>
<td>0.86</td>
<td>-1.36</td>
</tr>
<tr>
<td>Peak CK (IU)</td>
<td><strong>0.001</strong></td>
<td><strong>0.000</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>1.04</td>
<td>2.06</td>
<td>-3.01</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>1.33</td>
<td>0.81</td>
<td>-0.26</td>
</tr>
<tr>
<td>Sex</td>
<td>4.04</td>
<td>1.02</td>
<td>2.04</td>
</tr>
<tr>
<td>Office hours</td>
<td>-0.80</td>
<td>0.79</td>
<td>-2.37</td>
</tr>
<tr>
<td>Arrival via ambulance</td>
<td>1.57</td>
<td>0.90</td>
<td>-0.21</td>
</tr>
<tr>
<td>Door to Balloon time (mins)</td>
<td>0.004</td>
<td>0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>BUN/Creatinine ratio (umol/L)</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>-0.02</td>
<td>0.02</td>
<td>-0.06</td>
</tr>
<tr>
<td>Pre-PCI TIMI-3 Flow</td>
<td>-2.35</td>
<td>1.47</td>
<td>-5.24</td>
</tr>
<tr>
<td>Post-PCI TIMI-3 Flow</td>
<td>-0.85</td>
<td>1.46</td>
<td>-3.72</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.54</td>
<td>3.87</td>
<td>-5.08</td>
</tr>
<tr>
<td>Ventricular fibrillationarrest</td>
<td>0.81</td>
<td>1.48</td>
<td>-2.09</td>
</tr>
<tr>
<td>Arrival heart rate (bpm)</td>
<td>0.01</td>
<td>0.02</td>
<td>-0.03</td>
</tr>
<tr>
<td>Arrival systolic BP (mmHg)</td>
<td>-0.003</td>
<td>0.02</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

*Number of complete cases for multivariate analysis n=278
FIGURE (1B)
APPENDIX 1: Characteristics of those with Right Heart Catheterisation vs. No Right Heart Catheterisation

<table>
<thead>
<tr>
<th></th>
<th>Right Heart Cath (N=470)</th>
<th>No Right Heart Cath (N=442)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Available data points</td>
<td>N (%) or Mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>470</td>
<td>63±13</td>
<td>0.001</td>
</tr>
<tr>
<td>Female Sex</td>
<td>470</td>
<td>135 (29%) or 99 (23%)</td>
<td>0.034</td>
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</tbody>
</table>

**Cardiovascular risk factors**

<table>
<thead>
<tr>
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<th>N (%) or Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>226 (53%) 191 (48%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>217 (51%) 191 (48%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>123 (28%) 110 (48%)</td>
</tr>
<tr>
<td>Family history CAD*</td>
<td>82 (19%) 79 (20%)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>246 (58%) 231 (58%)</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>103 (24%) 84 (22%)</td>
</tr>
</tbody>
</table>

**Maintenance medications**

<table>
<thead>
<tr>
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<th>N (%) or Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>65 (18%) 65 (20%)</td>
</tr>
<tr>
<td>Statin</td>
<td>94 (26%) 69 (22%)</td>
</tr>
<tr>
<td>ACE inhibitor†</td>
<td>68 (19%) 54 (17%)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>28 (8%) 20 (6%)</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>14 (4%) 16 (5%)</td>
</tr>
</tbody>
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**Clinical factors**

<table>
<thead>
<tr>
<th></th>
<th>N (%) or Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CK†</td>
<td>1886±4787 1943±2846</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>170 (37%) 152 (40%)</td>
</tr>
<tr>
<td>Acute pulmonary oedema</td>
<td>22 (5%) 20 (5%)</td>
</tr>
<tr>
<td>Door-to-balloon time (mins)</td>
<td>76 (56, 104) 74 (58, 106)</td>
</tr>
<tr>
<td>Arrival heart rate (BPM)</td>
<td>79±22 80±23</td>
</tr>
<tr>
<td>Arrival SBP (mmHg)§</td>
<td>137±30 141±59</td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
<td>28 (6%) 37 (8%)</td>
</tr>
<tr>
<td>30-day re-infarction</td>
<td>15 (3%) 8 (2%)</td>
</tr>
<tr>
<td>30-day all-cause mortality/re-infarct</td>
<td>43 (9%) 25 (10%)</td>
</tr>
</tbody>
</table>

*CAD= Coronary artery disease
†ACE inhibitor= Angiotensin converting enzyme inhibitor
‡Peak CK= Peak Creatine Kinase
§Arrival SBP= Arrival systolic blood pressure
CHAPTER 6: Gender Differences in Outcomes and Health Status
Amongst Patients with Peripheral Artery Disease

This results chapter is reproduced in the exact form as it appears in the article “Gender Differences in Outcomes and Health Status Amongst Patients with Peripheral Artery Disease” authored by Rachel Dreyer, Moniek Van Zitteren, John Beltrame, Robert Fitridge, Johan Denollet, Patrick Vriens, John Spertus and Kim Smolderen (submitted and under review in Circulation: Cardiovascular Quality and Outcomes).

In keeping with the style of this thesis, the figures and tables have been modified, the references incorporated into the thesis’s master reference list and the manuscript repaginated.
Study Overview

This manuscript demonstrates important gender differences in patients presenting with newly diagnosed peripheral arterial disease (PAD) or with an exacerbation of existing PAD symptoms. Compared with other atherothrombotic disorders, PAD has received little attention, particularly in regards to the gender conundrum, which has been evident in coronary disease for the past 15 years. As a result of this gap within the literature the AHA has recently issued ‘a call to action’ for more focused research specific to women with PAD, particularly in regards to mortality/cardiovascular outcomes and health status.

In light of the above, this is the first study to prospectively compare women and men’s outcomes following their diagnosis of PAD in a ‘real-world setting’. Specifically, we assessed whether outcomes in women with PAD differ with regards to long-term major adverse cardiovascular events, and self-reported symptomatic health status at initial diagnosis (baseline) and 12 month follow up.

The main findings of this study revealed that although there was no gender difference in survival or cardiovascular outcomes 3 years following initial PAD diagnosis, women reported lower scores for self reported physical and mental health status at baseline and 12 month follow up. These differences were largely confirmed in multivariable regression results and a trend was visible even following adjustment for important covariates.
Accordingly, our study has extended the literature on health status outcomes in a large PAD population demonstrating that women with PAD have a compromised health status. The mechanisms for the poorer health status in women with PAD are not clearly understood but may include differences in socio-demographics, clinical characteristics, psychosocial factors, and functional limitations.
ABSTRACT

**Background:** Few studies have examined gender differences in health status and cardiovascular outcomes in patients with peripheral artery disease (PAD). This study assessed (a) whether outcomes in women with PAD differ with regards to long-term major adverse cardiovascular events, and (b) self-reported symptomatic health status at both diagnosis and 12-month follow up.

**Methods:** A total of 816 patients (531 men, 285 women) with PAD were consecutively enrolled from 2 vascular clinics in the Netherlands. Clinical details/cardiovascular events were recorded and patients completed the Short Form 12 (SF-12) at baseline and 12-months later. Cox proportional hazards models were used to assess the association between gender and all-cause mortality/major adverse cardiovascular events and median regression models were used to examine the relationship between gender and health status.

**Results:** Women and men had similar ages and clinical characteristics, but women had a poorer socio-economic background and suffered from more depressive symptoms at initial diagnosis. Although there was no significant differences by gender on either mortality (P=.74) or major adverse cardiovascular events (P=.57) women had poorer physical (PCS: 37±10 vs. 40±10, P=.004) and mental (MCS: 47±12 vs. 49±11, P=.005) health status at the time of presentation, as compared with their male counterparts. At 12-months, women still reported a poorer overall PCS score (41±12 vs. 46±11, P=.006) and MCS score (42±14 vs. 49±12, P=.002). In multivariable analysis, female gender was an independent determinant of a poorer baseline PCS and poorer MCS at 12-month follow up.
**Conclusions:** In a real-world setting, female PAD patients have similar prognostic expectations as compared with men. However, women’s physical and mental health status is compromised both at initial diagnosis and 12-month follow-up, despite a similar magnitude of change in their health scores throughout the first 12-months after diagnosis.
INTRODUCTION

Peripheral arterial disease (PAD), along with coronary and cerebrovascular disease, constitutes the leading cause of morbidity and mortality worldwide\(^{133,696}\). While PAD affects up to 20% of the population aged 65 years or older, the disease has received less attention as compared with other atherothrombotic disorders in terms of its recognition and treatment of cardiovascular risk factors.\(^{138,697-699}\) Furthermore PAD may be even more disabling than other vascular diseases,\(^{147,700}\) not only because of its high event rate, but also due to its impact on patients’ health status (their symptoms, function and quality of life).\(^{147,701,702}\)

Gender-based disparities in the outcomes of PAD patients with have also not been as extensively investigated in PAD, as compared with coronary artery disease (CAD) where such differences have been documented in great detail. For example, women with CAD have worse in-hospital and long-term mortality,\(^{175,220,234}\) and increased mortality following cardiac revascularization procedures.\(^{240,703}\) In contrast, major knowledge gaps exist in terms of gender-specific cardiovascular mortality rates and differences in the health status of PAD.

Preliminary data available suggest that women with PAD have an increased risk for morbidity and mortality,\(^{463}\) however; no study has explicitly focused on differences between men and women. Beyond mortality, women also suffer from more depression,\(^{491}\) experience more atypical lower-extremity symptoms, and have a poorer overall health status as compared with men.\(^{475,149,474,485,487,488,490,704,705}\) With these factors in mind, the current study was designed to assess potential explanatory factors for gender-based differences in outcomes, including the potential influence of
depression. Most prior work examining PAD and gender-based differences were cross-sectional studies or were not explicitly addressing gender differences in their primary objectives and analyses. More prospective research is needed to illuminate potential gender differences in PAD. Consistent with these observations, the recent scientific statement from the American Heart Association (AHA) issued a ‘call to action’ for more focused care and research that is sensitive to the specific concerns of women with PAD.

Since potential gender disparities in cardiovascular outcomes and self-reported health status following PAD diagnosis have not been prospectively quantified, the current study aimed to prospectively evaluate whether outcomes in women with PAD differ with regards to the occurrence of long-term, major adverse cardiovascular events and their self-reported symptomatic health status outcomes. The underlying hypothesis was that women would have poorer outcomes, including increased mortality and an increased cardiovascular event burden, as well as a poorer self-reported health status as compared with men.
METHODS

Participants

Participants with newly diagnosed symptomatic PAD or with an exacerbation of existing PAD symptoms were consecutively enrolled from 2 vascular outpatient clinics of the St. Elisabeth Hospital (March 2006-November 2011) and TweeSteden Hospital (March 2006-October 2008) in Tilburg, the Netherlands. Study entry criteria for PAD patients included having symptomatic PAD and an abnormal resting ankle-brachial index (ABI) ($\leq 0.90$) or an abnormal post exercise ABI (ABI decrease of 15% following exercise). Exclusion criteria included patients with critical leg ischemia, significant cognitive impairment, severe psychiatric co-morbidities (e.g. psychosis), life threatening or debilitating conditions that prevented participation (e.g. undergoing active cancer treatment), and insufficient knowledge of Dutch language and/or illiteracy. Patients with a non-compressible ABI ($\geq 1.30$) were also excluded. The protocol was designed according to the Helsinki declaration and approved by the local ethics committees of the participating hospitals. All participants provided written informed consent. Patients were invited to participate in the study by their treating vascular surgeon during their visit at one of the outpatient clinics, following a vascular diagnostic work-up that confirmed the presence of PAD. All patients within the study completed a set of specific questionnaires collected by mail following recruitment at baseline as well as at 12-month follow up. Demographic, risk factor, medication, and therapeutic information were obtained by abstracting patients’ medical records.
Measures

All-Cause Mortality and Cardiovascular Events

The major adverse events studied included (1) all-cause mortality (i.e., in-hospital mortality as well as mortality events outside the hospital were documented as patients’ medical records are linked to the regional social security death index of the Tilburg community. Deaths occurring outside the Tilburg community were passed on by patients’ general practitioners); and major cardiovascular events including (2) acute myocardial infarction (AMI) that was diagnosed by a cardiologist and required hospitalization, (3) stroke that was diagnosed by a neurologist and required hospitalization, and (4) any PAD related lower-extremity amputation (e.g., amputation of toes or part of the foot, below or above knee amputation, and through knee amputation due to PAD, excluding traumatic amputations). Mortality was used both as a separate outcome of interest and also as a combined endpoint with the other major adverse cardiovascular events. Information on cardiovascular events were documented from patients’ medical records by a surgical fellow under supervision of two vascular surgeons, since diagnosis of PAD until January 1st 2012.

Health Status

The Dutch version of the Short Form 12 (SF-12) was administered to assess health status, both at baseline and 12-months later. This generic tool measures overall physical and mental health status and consists of 12 items with standard Likert scales. Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores are generated through a standardized scoring algorithm and were based on weights derived from Dutch population norms (score ranges between 0-100, mean
score=50, SD=10), with higher scores indicating better functioning. The SF-12 has been demonstrated to be a valid and reliable instrument and has been successfully used before in PAD populations.

**Depression**

The 14-item self report Hospital Anxiety and Depression Scale (HADS) was used to measure depressive symptoms in the PAD population. Criterion scores of ≥8 for the depression subscale denoted clinically relevant symptoms of depression.

**Ankle Brachial Index**

The vascular laboratory assessment procedures have been described previously. In brief, a handheld Doppler ultrasonic instrument was used to obtain systolic blood pressure readings in the right and left brachial arteries, right and left dorsalis pedis arteries, and right and left posterior tibial arteries. The ABI at rest and after walking on a treadmill (distance limited 1000 meters) was obtained with the lower resting ABI used in all analyses. In all patients, the pain-free walking distance, maximum treadmill walking distance and the ABI index were measured as indices of severity of PAD, whereby the ABI is defined as the ratio of the ankle systolic blood pressure to the brachial artery systolic blood pressure and has a normal resting value of approximately 1.0. A value of <0.90 has been shown to be highly sensitive to detect PAD.
Socio-Demographics and Clinical Variables

Age and gender were abstracted from medical records and information on socio-demographics was self-reported by the patients. These included marital status (having a partner vs. not having a partner), high school education or more (high school education or more vs. less than high school education) and work status (active vs. non-active working status). Clinical variables for patients were obtained from medical records at baseline and included: cardiovascular risk factors (current smoking, hypercholesterolemia, hypertension, diabetes mellitus, chronic heart failure), cardiovascular history (previous AMI, angina, coronary artery bypass grafting, percutaneous coronary intervention, stroke, and transient ischemic attack), co-morbidities (renal dysfunction, chronic obstructive pulmonary disease [COPD], body mass index [BMI, kg/m²], prior documented back pain, prior documented knee or hip pain, and depression) and PAD clinical factors (resting and post-exercise ABI, pain free walking distance, and maximum walking distance). Medications that patients were taking upon enrollment were abstracted from their medical charts and included aspirin, statins, anticoagulants, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, nitrates and antiarrhythmics (including digoxin), antidepressants, anxiolytics and hypnotics.

Statistical Analysis

Baseline characteristics were examined for the total sample and compared between genders. In addition, baseline and 12-month follow up health status scores were examined for the total population and stratified by gender. The Student’s t-tests and
Wilcoxon tests were used for continuous variables and Chi-square tests or Fisher’s Exact tests were used for categorical variables, as appropriate.

Two sets of Cox proportional hazards models were constructed to examine the relationship between demographics, cardiovascular risk factors and cardiovascular history, and (1) all-cause mortality and (2) major adverse cardiac events outcomes (i.e., all-cause mortality, AMI, stroke, and lower-extremity amputation). Both models were sequentially built including the following variables: demographics (gender, age), cardiovascular risk factors and cardiovascular history (diabetes mellitus, current smoking, prior stroke, prior AMI, heart failure, and renal dysfunction). In order to maintain adequate power in our models, socio-economic factors (marital status, educational level) and depression were only added as an exploratory last step. We assessed an interaction term between gender and age for all-cause mortality and major adverse cardiac event outcomes, but in both analyses the interaction term were not significant (P=.72, P=.49, respectively) and thus were excluded from the final multivariable model.

For the health status analyses, 6 sets of median regression models examined the relationship between gender, and (1) baseline health status scores (baseline PCS-12 and MCS-12), (2) 12-month health status scores (12-month PCS-12 and MCS-12), and (3) health status change scores (12-month PCS-12/MCS-12 scores minus baseline PCS-12/MCS-12 scores). Median regression was performed due to non-linear distribution of the health status scores. The following variables were sequentially entered into the models: demographics (gender, age), socio-demographics (marital status, educational level), cardiovascular risk factors and cardiovascular history
(diabetes, current smoking, prior stroke, prior AMI, heart failure, and renal dysfunction). As an exploratory step, obesity (BMI ≥30 vs. <30), COPD, back pain, knee/hip osteoarthritis, as well as depression were included into the model. Missing SF-12 items were assumed to be missing at random and handled by multiple imputation (mean of 5 iterations) if ≥75% of all items were complete at baseline and 12-months. The pooled estimates and 95% confidence intervals (CI) for the 5 imputed datasets were used. A comparison of baseline characteristics was conducted for those who were included in the SF-12 analyses (0-25% missing) vs. those who were eligible for inclusion but who were not in the SF-12 analyses (>25% missing). Baseline characteristics were similar between these groups, however patients not in the analyses were more likely to be women, smokers or to have a higher maximum walking distance as compared with those who were included in the SF-12 analyses. All tests were two-tailed and a P-value <.05 was considered statistically significant. All analyses were performed using SPSS 17.0 for Windows (PASW Inc., Chicago III) and SAS Software version 9.2. (SAS Institute Inc, Cary, North Carolina).
RESULTS

Patient Characteristics

Baseline characteristics of the total sample (N=816) are stratified by gender and listed in Table 1. The mean age of the total cohort was 65 years and 285 (35%) were women. Both men and women were similar in terms of age, cardiovascular risk factors, medical history and ABI values (resting and post exercise), however women were less likely to be partnered, have high school education or more, or suffer from renal dysfunction as compared with men. In addition, women had both a significant shorter pain-free walking distance and maximal walking distance. Women also had higher rates of depression and were more likely to be on antidepressants, anxiolytics, and hypnotics as compared with men (Table 1).

Cardiovascular Event Analyses

The study cohort had a median follow-up time of 3.2 years (IQR=1.7-4.5 years). During follow-up, a total of 92 (11%) deaths were documented [30 women (11%) vs. 62 men (12%)] and 138 patients (17%) experienced a first cardiovascular event (mortality, AMI, stroke, lower-extremity amputation) [45 women (16%) vs. 93 men (18%)]. The Kaplan Meier curves for all-cause mortality revealed no significant gender differences in survival time (P=.74, Figure 1). Similarly, for the onset of a first cardiovascular event (mortality, AMI, stroke, lower-extremity amputation) there was no difference between men and women (P=.57, Figure 2).

No difference in all-cause mortality was observed between men and women in the unadjusted (unadjusted hazard ratio (HR) for women, reported for all analyses) =0.93,
95% confidence interval (CI) 0.60-1.44, P=.74) and the final adjusted model (HR=0.86, 95%CI 0.55-1.34, P=.50) (Table 2). Older age (HR=1.05, 95%CI 1.02-1.08, P<.001), current smoking (HR=1.57, 95%CI 1.00-2.45, P=.048), heart failure (HR=3.27, 95%CI 1.80-5.92, P<.001), and renal dysfunction (HR=1.90 95%CI 1.07-3.39, P=.030) were independently associated with mortality in the final adjusted model (Full Model Results Presented in Appendix 1).

Similar results were found for the association with adverse cardiovascular events whereby men and women did not differ in both the unadjusted (HR for women=0.90, 95%CI 0.63-1.29, P=.57) and final adjusted (HR=0.85, 95%CI 0.59-1.23, P=.39) model. Again, older age (HR=1.06, 95%CI 1.04-1.08, P=<.001), current smoking (HR=1.59, 95%CI 1.10-2.30, P=.013), prior AMI (HR=1.72, 95%CI 1.18-2.52, P=.005), and heart failure (HR=2.04, 95%CI 1.19-3.49, P=.010) were independently associated with experiencing a first adverse cardiovascular event in the final adjusted model (Appendix 1).

As for the exploratory analyses, the all-cause mortality model and adverse cardiovascular event model were additionally adjusted for marital status, educational level, and depression (Appendix 2). In the full-adjusted mortality model, gender was not an independent determinant of mortality (HR for women=0.72, 95%CI 0.41-1.25, P=.24), however, age (HR=1.04, 95%CI 1.01-1.07, P=.004), heart failure (HR=2.76, 95%CI 1.36-5.58, P=.005), and renal dysfunction (HR=2.03, 95%CI 1.06-3.88, P=.034) were independent predictors of mortality. Although, female gender was also not statistically significantly associated with experiencing a first cardiovascular event, a trend emerged towards a lower risk for women (HR for women=0.70, 95%CI 0.45-
Age (HR=1.06, 95% CI 1.03-1.08, P<.001), current smoking (HR=1.54, 95% CI 1.02-2.33, P=.041), and prior AMI (HR=1.56, 95% CI 1.01-2.43, P=.047) were covariates that were independently associated with an increased risk of experiencing a first cardiovascular event in the final adjusted model (Appendix 2).

Health Status Analyses

In the total sample, median physical health status (PCS) improved from 39±10 at baseline to 43±11, at 12-month follow up (median difference 2.6±10, [mean difference] 3.5±10, P<.0001). Conversely, mental health scores (MCS) did not improve over 12-months (48±11 at baseline and 47±13 at 12-months, median difference -0.6±10, [mean difference -1.1±10, P=.12]). Women, as compared with men, had poorer physical (PCS: 37±10 vs. 40±10, P=.004) and mental (MCS: 47±12 vs. 49±11, P=.005) baseline health status scores upon being diagnosed with PAD (Figure 3). At 12-month follow up; women still reported a poorer overall PCS score (41±12 vs. 46±11, P=.006) and MCS score (42±14 vs. 49±12, P=.002). Women and men had similar improvement in their physical function over 12-months (3.2±11 vs. 2.4±10) and neither group experienced an improvement in their mental (-1.2±12 vs. -0.6±8.8) health status.

Table 3 presents the SF-12 baseline health status unadjusted and adjusted estimates and 95% CI for gender. Full model and exploratory results are reported in Appendix 3. In terms of PCS-12, there was no significant effect of female gender in the unadjusted model (B=2.74, 95% CI 0.11-5.63, P=.06) or sequentially adjusted models. However, when adjusting for clinical factors (Female B=2.70; 95% CI 0.14-5.25, P=.039) (adjusted step 4), exploratory factors (obesity [BMI ≥30 vs. <30], COPD, back pain,
knee/hip osteoarthritis) (adjusted step 5) (Female B=2.88; 95%CI 0.86-4.90, P=.005) and depression (adjusted step 6) (Female B=2.13; 95%CI 0.28-3.97, P=.024), a significant association between female gender and lower physical health status appeared.

In terms of MCS-12 at baseline, there was a trend towards women reporting a poorer mental health status at initial PAD diagnosis as observed in the unadjusted model (B=2.29, 95%CI 0.24-5.65, P=.08), which became significant after adjustment for age (B=2.95 95%CI 0.24-5.65, P=.033). In terms of all other adjusted steps there was no statistically significant effect of female gender in this model (Table 3).

Similarly, Table 4 presents the cross-sectional 12-month follow up unadjusted and adjusted regression estimates and 95%CI for female gender. Full model and exploratory results are presented in Appendix 4. In terms of PCS-12 at 12-month follow up, there was a trend towards women reporting a poorer physical health status (B=3.89, 95%CI -0.13-7.91, P=.06) in the unadjusted model. However, when adjusting for age (B=3.90; 95%CI 0.58-7.23, P=.022) and exploratory variables (obesity [BMI ≥30 vs. <30], COPD, back pain, knee/hip osteoarthritis) (adjusted step 5) (B=3.72; 95%CI 0.37-7.06, P=.030) both became significant. There was no effect of gender within the intermediate adjusted steps for PCS-12 at 12-month follow up.

With regards to the MCS scores at 12-month follow up, women reported a poorer mental health status which was observed in the unadjusted model (B=4.66; 95%CI 1.07-8.24, P=.011) and also following adjustment for age (B=4.99, CI 0.80-9.18, P=.020), clinical factors (B=4.10; 95% CI0.46-7.73, P=.027) (adjusted step 4) and
exploratory variables (obesity [BMI ≥30 vs. <30], COPD, back pain, knee/hip osteoarthritis) (adjusted step 5) (B=3.53; 95%CI 0.13-6.93, P=.043).

Lastly, Table 5 presents the unadjusted and adjusted regression estimates and 95% CI for the SF-12 12-month change scores with the beta coefficients reported for female gender for all analyses. Full model and exploratory results are reported in Appendix 5. Specifically, women’s 12-month change scores for physical and mental health status did not differ significantly from that of men’s, neither in the unadjusted models for PCS (B=-0.44, 95%CI -2.54-1.66, P=.68) and MCS (B=-0.35, 95%CI -2.15-1.45, P=.70), nor in the full-adjusted models for PCS (B=0.53, 95%CI -2.14-3.20, P=.70) and MCS (B=-0.30, 95%CI -2.53-1.93, P=.80).
DISCUSSION

This study was the first to prospectively compare women’s and men’s outcomes following their diagnosis of PAD in a real-world setting. Since little is known about the existence of potential gender disparities in PAD, the AHA issued a scientific statement prioritizing a research agenda for this important topic.172 Our group had data available to show that while survival and cardiovascular morbidity outcomes 3 years following initial PAD diagnosis did not seem to differ between men and women, there were differences at both presentation and follow up in terms of health status, although the lower scores for women failed to reach the threshold for what is defined as a clinically relevant difference (score of ≥10)149, 548, 564 for the SF-12. These differences were largely confirmed in the multivariable regression results and a trend was visible even after extensive adjustment for relevant covariates. The magnitude of change in women’s health status scores over 12-months was not different from the change men reported, but failed to reach the threshold for clinically relevant change as defined by the SF-12 instrument (score of ≥10)149, 548, 564 in both groups.

Mortality & Cardiovascular Events

Cardiovascular mortality, all-cause mortality and major adverse coronary event rates by gender have not been well examined in PAD population-based studies. The few data available suggest that the relationship between ABI values, mortality (total, cardiovascular) and major coronary events are in fact similar between genders.463 In the recent AHA statement, 16 population-based studies were pooled to examine these associations which revealed that the relationship between ABI values and total mortality, cardiovascular mortality, and major cardiovascular events are similar in
women and men. Furthermore, the gender effects on survival following lower extremity PAD revascularization have been inconsistent with some authors reporting a poorer long term survival in women and others demonstrating improved survival as compared with men. In our study, with real-world patients diagnosed with PAD, we observed no significant gender differences in survival or experiencing a first cardiovascular event over time, which seems to be in line with the indirect evidence that was derived from pooled population-based studies as described above. However, this appears to be counterintuitive with prior findings in CAD that provide clear evidence for poorer prognostic outcomes in women. Namely, women have a poorer 2-10 year long term survival rate following AMI compared with men. Although not an independent predictor of mortality and cardiovascular events, there was a trend observed for better outcomes in women (i.e. lower hazard ratios for women) following multivariable adjustment. Whether these trends are meaningful, needs to be confirmed in larger future studies. From the present findings we can conclude that there were no clear differences between women’s and men’s prognosis 3 years following their PAD diagnosis and evaluation.

**Symptomatic Health Status**

Women with PAD were found to have both a poorer physical and mental health status at initial diagnosis and 12-month follow up as compared with men. More specifically, women seem to present with poor physical and mental health at baseline, with both genders equally improving in physical health over 12-months. Multivariable analyses largely confirmed that female gender was an independent predictor of a poorer physical health status at initial diagnosis as well as a determinant of a poorer mental health status at 12-months (or showed a clear trend even after extensive adjustment
for confounders). These results are in line with previous studies suggesting that women with PAD have a worse health status and health-related quality of life (HRQOL) as compared with men, while others have found conflicting results. Importantly, these absolute differences in health status scores did not exceed the threshold for a minimal clinically important difference (which is defined as a score equal or greater than 10 in the SF-12), and as such, future studies need to further examine whether these differences are clinically meaningful to both patients and clinicians, ideally using a disease-specific instrument that is more sensitive to capturing relevant PAD-specific health status information.

Using the SF-36 in a cross-sectional study in primary care patients, Collins et al (2008) reported that physical functioning and general health were both significantly lower for women when compared with men. Similarly, Oka and colleagues utilized the same questionnaire in another smaller cross-sectional study and highlighted that despite a similar disease severity, women reported decreased physical functioning, more bodily pain and greater mood disturbance than men with PAD. In their smaller prospective longitudinal study, Wann-Hansson demonstrated that female gender adversely impacted durability or quality of life following revascularization for claudication or critical limb ischemia. Furthermore, Bloemenkamp and colleagues highlighted in a cross-sectional, population-based study that young women (<50 years) with PAD scored lower than age matched healthy controls on all HRQOL domains on the RAND-36. Finally, a mixed cohort of patients with PAD at various disease stages confirmed that women experience worse physical health, greater disability as well as poorer overall health status many years after diagnosis, however this study was limited by the lack of baseline health status data. Although these
preliminary studies contributed to the body of research in this field they were limited either in terms of their small sample size, their (cross sectional) design or did not explicitly focus on gender in their main objectives. Accordingly, our study has extended the literature on health status outcomes in a large PAD population demonstrating that women with PAD have a compromised health status. The reason for this gender disparity is likely to be multi-factorial and requires further evaluation.

**Mechanisms for Poorer Health Status in Women**

The potential mechanisms contributing to the observed gender disparity in health outcomes may include differences in socio-demographics, clinical characteristics, psychosocial factors, and functional limitations. As age and cardiovascular risk profiles were similar between genders in this specific cohort, we can rule out the potential effect this may have had on quality of life. Furthermore, although there was no disparity noted in disease severity with which these patients presented at diagnosis (as assessed by the ABI), others have proposed that differences in disease severity may explain poorer health-related quality of life for women.

In terms of socio-demographic factors, women reported a lower educational attainment compared with men, which may make them more vulnerable in dealing with the many challenges that a diagnosis and management of PAD brings forth, translating in poorer health status scores. Secondly, women were less likely to have a partner in our cohort which may have decreased the protective effect that marriage is equated with due to a lack of social/moral support or a lack of motivation for personal care, which usually equates with having a spouse and marital responsibility and thus detrimental to their health status. In addition, social support is also a potent
risk factor for women with CAD\textsuperscript{388, 713} and also may have had a major impact on women’s health status due to associated social isolation and lack of social support that comes hand in hand with unmarried states and increases the propensity to unhealthy behaviors\textsuperscript{714}. While we did notice the presence of a more vulnerable socio-economic profile in women, we were not able to confirm that these socio-demographics were responsible for the observed health status differences. These surrogate markers of socioeconomics (education, relationship status) should, however, definitely remain the focus of future research, as they have been able to explain many disparities in outcomes among cardiovascular populations.

At initial diagnosis, women were also more likely than men to present with depression, thus severely impacting their well-being. This finding has been previously demonstrated at diagnosis and long-term follow up, specifically, younger women that are known to be at a higher risk of depression than other gender-age groups\textsuperscript{491}. Depressive symptoms or ‘mood states’ as well as a greater degree of bodily pain may be associated with substantially compromised functional status\textsuperscript{507} as well as a poorer prognosis\textsuperscript{510}, which ultimately has adverse effects on patients’ health status\textsuperscript{148, 715}. We were only able to adjust for depression scores in the last step of our analyses, after including the most relevant demographic, socio-economic, and clinical factors, and have not completed a formal mediation analysis, and as such, its explanatory role needs to be further explored in future work. At this time, we did not observe a dramatic change in the interpretation of the estimates for the association between female gender and health status after adjusting for patients’ baseline depressive symptoms.
The adverse functional limitations experienced by women in this study are supported by the fact that women had a poorer pain free walking distance and maximum walking distance PFWD and MWD and thus may have greater walking impairment from leg symptoms than men with PAD.\textsuperscript{475,487, 488} Thus, the lower quality of life scores observed in women are not surprising given this greater compromise in walking ability. A poorer health status in women may then be directly affected due to restrictions in performing daily activities including grocery shopping and visiting family and friends.\textsuperscript{475, 485}

**Limitations**

Some limitations of this study are apparent. Firstly, only two institutions were included in this study and therefore results may only be applicable to a Dutch PAD population. Secondly, although we adjusted for clinically important confounders in both the Cox regression and SF-12 regression models, the possibility of residual confounding remains. Furthermore, due to sample size constraints we could not adjust for any other variables in the multivariable models such as pain free walking distance and maximum walking distance. Lastly, we did not utilize a disease-specific instrument and thus this should be the focus of future research.

**Conclusion**

In conclusion, this study has demonstrated for the first time in a prospective cohort of patients that were evaluated for their PAD in a specialty clinic that women have a similar prognosis as examined for all-cause mortality or the experience of a first cardiovascular event as compared with men. This is also the largest study to date that has documented in a prospective way how women’s health status scores differ with
scores from their male counterparts 1 year following the initial diagnosis of their PAD. We extended findings from earlier studies demonstrating that women suffer from more depression and report a poorer physical and mental health status both at initial diagnosis (baseline) and 12-month follow up. Future studies should focus on re-examining these effects using more sensitive disease-specific health status instruments and further exploring the role for socioeconomic, clinical, and psychological factors that may help explain these differences.
LEGENDS

FIGURE 1: Kaplan Meier survival curve for all-cause mortality stratified by gender. Log rank test for women (red) versus men (blue).

FIGURE 2: Kaplan Meier survival curve for experiencing a first cardiovascular event (all-cause mortality, AMI, stroke, and lower-extremity amputation) stratified by gender. Log rank test for women (red) versus men (blue).

FIGURE 3: Median physical (PCS) and mental (MCS) SF-12 summary scores at baseline and 12-Month follow-up stratified by gender [women (red), men (blue)].
<table>
<thead>
<tr>
<th>Demographic/Health Indicator</th>
<th>Total Sample (n=816)</th>
<th>Men (n=531)</th>
<th>Women (n=285)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean years, SD, range)</td>
<td>65.3 (9.8, 37-92)</td>
<td>65.3 (9.6)</td>
<td>65.2 (10.2)</td>
<td>.91</td>
</tr>
<tr>
<td>Partner (n, %)</td>
<td>523 (74.9)</td>
<td>371 (83.2)</td>
<td>152 (60.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>High school education or more (n, %)</td>
<td>515 (74.4)</td>
<td>350 (78.5)</td>
<td>165 (67.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Active work status (n, %)</td>
<td>172 (25.6)</td>
<td>116 (26.1)</td>
<td>56 (24.5)</td>
<td>.64</td>
</tr>
<tr>
<td><strong>Cardiovascular Risk factors</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker (n, %)</td>
<td>406 (49.8)</td>
<td>259 (48.8)</td>
<td>147 (51.6)</td>
<td>.45</td>
</tr>
<tr>
<td>Hypercholesterolemia (n, %)</td>
<td>548 (67.2)</td>
<td>358 (67.4)</td>
<td>190 (66.7)</td>
<td>.83</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>488 (59.8)</td>
<td>306 (57.6)</td>
<td>182 (63.9)</td>
<td>.08</td>
</tr>
<tr>
<td>Diabetes Mellitus (n, %)</td>
<td>196 (24.0)</td>
<td>128 (24.1)</td>
<td>68 (23.9)</td>
<td>.94</td>
</tr>
<tr>
<td>Chronic heart failure (n, %)</td>
<td>41 (5.0)</td>
<td>27 (5.1)</td>
<td>14 (4.9)</td>
<td>.91</td>
</tr>
<tr>
<td><strong>Cardiovascular History</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Myocardial infarction (n, %)</td>
<td>151 (18.5)</td>
<td>103 (19.4)</td>
<td>48 (16.8)</td>
<td>.37</td>
</tr>
<tr>
<td>Angina (n, %)</td>
<td>124 (15.2)</td>
<td>86 (16.2)</td>
<td>38 (13.3)</td>
<td>.28</td>
</tr>
<tr>
<td>Coronary artery bypass graft (n, %)</td>
<td>90 (11.0)</td>
<td>66 (12.4)</td>
<td>24 (8.4)</td>
<td>.08</td>
</tr>
<tr>
<td>Percutaneous coronary intervention (n, %)</td>
<td>74 (9.1)</td>
<td>50 (9.4)</td>
<td>24 (8.4)</td>
<td>.64</td>
</tr>
<tr>
<td>Stroke (n, %)</td>
<td>66 (8.1)</td>
<td>49 (9.2)</td>
<td>17 (6.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Transient ischemic attack (n, %)</td>
<td>76 (9.3)</td>
<td>53 (10.0)</td>
<td>23 (8.1)</td>
<td>.37</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Renal dysfunction (n, %)</td>
<td>73 (8.9)</td>
<td>56 (10.5)</td>
<td>17 (6.0)</td>
<td>.029</td>
</tr>
<tr>
<td>COPD (n, %)</td>
<td>142 (17.4)</td>
<td>91 (17.1)</td>
<td>51 (17.9)</td>
<td>.79</td>
</tr>
<tr>
<td>Body mass index (mean, SD)</td>
<td>26.8 (5.0)</td>
<td>26.8 (4.4)</td>
<td>26.7 (6.0)</td>
<td>.82</td>
</tr>
<tr>
<td>Back pain (n, %)</td>
<td>126 (15.4)</td>
<td>76 (14.3)</td>
<td>50 (17.5)</td>
<td>.22</td>
</tr>
<tr>
<td>Knee or hip pain (n, %)</td>
<td>169 (20.7)</td>
<td>116 (21.8)</td>
<td>53 (18.6)</td>
<td>.28</td>
</tr>
<tr>
<td>Depression (n, %)</td>
<td>186 (27.0)</td>
<td>103 (23.4)</td>
<td>83 (33.2)</td>
<td>.005</td>
</tr>
<tr>
<td><strong>PAD Clinical factors</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Resting ABI (mean, SD)</td>
<td>65.7 (16.9)</td>
<td>66.1 (17.1)</td>
<td>65.0 (16.5)</td>
<td>.35</td>
</tr>
<tr>
<td>Post-exercise ABI (median, SD)</td>
<td>36.0 (19.5)</td>
<td>35.0 (19.4)</td>
<td>36.5 (19.8)</td>
<td>.17</td>
</tr>
<tr>
<td>Pain-free walking distance (meters,</td>
<td>80.0 (140.5)</td>
<td>80.0 (143.4)</td>
<td>70.0 (133.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Measurement</td>
<td>Median (SD)</td>
<td>280.0 (316.8)</td>
<td>235.0 (306.4)</td>
<td>p</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-------</td>
</tr>
<tr>
<td>Maximum walking distance (meters, median, SD)</td>
<td>260.0 (313.8)</td>
<td>(316.8)</td>
<td>(306.4)</td>
<td>.005</td>
</tr>
</tbody>
</table>

**Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count (%)</th>
<th>280 (80.4)</th>
<th>235 (84.6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (n, %)</td>
<td>647 (79.3)</td>
<td>427 (80.4)</td>
<td>220 (77.2)</td>
<td>.28</td>
</tr>
<tr>
<td>Statin (n, %)</td>
<td>672 (82.4)</td>
<td>431 (81.2)</td>
<td>241 (84.6)</td>
<td>.23</td>
</tr>
<tr>
<td>Anticoagulants (n, %)</td>
<td>139 (17.0)</td>
<td>86 (16.2)</td>
<td>53 (18.6)</td>
<td>.38</td>
</tr>
<tr>
<td>Beta blocker (n, %)</td>
<td>345 (42.3)</td>
<td>222 (41.8)</td>
<td>123 (43.2)</td>
<td>.71</td>
</tr>
<tr>
<td>Calcium channel blocker (n, %)</td>
<td>186 (22.8)</td>
<td>128 (24.1)</td>
<td>58 (20.4)</td>
<td>.22</td>
</tr>
<tr>
<td>Angiotensin converting enzyme (n, %)</td>
<td>257 (31.5)</td>
<td>179 (33.7)</td>
<td>78 (27.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Diuretics (n, %)</td>
<td>206 (25.2)</td>
<td>128 (24.1)</td>
<td>78 (27.4)</td>
<td>.31</td>
</tr>
<tr>
<td>Nitrate (n, %)</td>
<td>77 (9.4)</td>
<td>48 (9.0)</td>
<td>29 (10.2)</td>
<td>.60</td>
</tr>
<tr>
<td>Antiarrhythmics (n, %)</td>
<td>21 (2.6)</td>
<td>12 (2.3)</td>
<td>9 (3.2)</td>
<td>.44</td>
</tr>
<tr>
<td>Antidepressants (n, %)</td>
<td>48 (5.9)</td>
<td>23 (4.3)</td>
<td>25 (8.8)</td>
<td>.010</td>
</tr>
<tr>
<td>Anxiolytics (n, %)</td>
<td>34 (4.2)</td>
<td>12 (2.3)</td>
<td>22 (7.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypnotics (n, %)</td>
<td>37 (4.5)</td>
<td>18 (3.4)</td>
<td>19 (6.7)</td>
<td>.032</td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation, COPD = chronic obstructive pulmonary disease, ABI = ankle-brachial index.
Table 2: The Unadjusted and Adjusted Cox Proportional Regression Model between Gender for Mortality and all Cause Cardiovascular Events (Mortality, AMI, Stroke, and Lower-Extremity Amputation). Hazard ratios (HR) and 95% Confidence Intervals (CI) are presented.

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th></th>
<th>Cardiovascular events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P value</td>
<td>HR</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>0.93</td>
<td>0.60-1.44</td>
<td>.74</td>
<td>0.90</td>
</tr>
<tr>
<td>Adjusted 1*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>0.90</td>
<td>0.58-1.39</td>
<td>.63</td>
<td>0.87</td>
</tr>
<tr>
<td>Adjusted 2†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>0.86</td>
<td>0.55-1.34</td>
<td>.50</td>
<td>0.85</td>
</tr>
</tbody>
</table>

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and clinical factors (diabetes, current smoking, prior stroke, prior acute myocardial infarction, heart failure, and renal dysfunction). See Appendix 1 for full model.
Table 3: The Unadjusted and Adjusted Association between Gender and Baseline Health Status. Regression Coefficients and 95% Confidence Intervals are presented.

<table>
<thead>
<tr>
<th></th>
<th>PCS-12</th>
<th></th>
<th></th>
<th>MCS-12</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>P value</td>
<td>Estimate</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>2.74</td>
<td>-0.11-5.63</td>
<td>.06</td>
<td>2.29</td>
<td>-0.24-4.82</td>
<td>.08</td>
</tr>
<tr>
<td><strong>Adjusted step 1</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Female gender</td>
<td>2.25</td>
<td>-0.57-5.07</td>
<td>.12</td>
<td>2.95</td>
<td>0.24-5.65</td>
<td>.033</td>
</tr>
<tr>
<td><strong>Adjusted step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjusted step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>1.51</td>
<td>-1.14-4.16</td>
<td>.26</td>
<td>0.40</td>
<td>-2.27-3.07</td>
<td>.77</td>
</tr>
<tr>
<td><strong>Adjusted step 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td><strong>2.70</strong></td>
<td><strong>0.14-5.25</strong></td>
<td><strong>.039</strong></td>
<td>1.08</td>
<td>-1.45-3.60</td>
<td>.40</td>
</tr>
<tr>
<td><strong>Adjusted step 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td><strong>2.88</strong></td>
<td><strong>0.86-4.90</strong></td>
<td><strong>.005</strong></td>
<td>2.28</td>
<td>-0.23-4.78</td>
<td>.08</td>
</tr>
<tr>
<td><strong>Adjusted step 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td><strong>2.13</strong></td>
<td><strong>0.28-3.97</strong></td>
<td><strong>.024</strong></td>
<td>1.78</td>
<td>-0.13-3.68</td>
<td>.07</td>
</tr>
</tbody>
</table>

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and gender x age; ‡adjusted model 3 = model 1 and socio-demographics (no partner and <high school education); §adjusted model 4 = model 3 and clinical factors (diabetes, current smoking, prior stroke, prior myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5 = model 4 and co-morbidities (body mass index ≥30 kg/m², chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis); ‼exploratory adjusted model 6 = model 5 and depression. See Appendix 3 for full model.
Table 4: The Unadjusted and Adjusted Association between Gender and 12-Month Health Status. Regression Coefficients and 95% Confidence Intervals are presented.

<table>
<thead>
<tr>
<th></th>
<th>PCS-12 at 12-months</th>
<th></th>
<th></th>
<th></th>
<th>MCS-12 at 12-months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>P value</td>
<td>Estimate</td>
<td>95% CI</td>
<td>P value</td>
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</tr>
<tr>
<td><strong>Unadjusted</strong></td>
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<td></td>
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<tr>
<td>Female gender</td>
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<td>.06</td>
<td>4.66</td>
<td>1.07-8.24</td>
<td>.011</td>
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<tr>
<td><strong>Adjusted step 1</strong></td>
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<tr>
<td>Female gender</td>
<td><strong>3.90</strong></td>
<td><strong>0.58-7.23</strong></td>
<td><strong>.022</strong></td>
<td><strong>4.99</strong></td>
<td><strong>0.80-9.18</strong></td>
<td><strong>.020</strong></td>
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<td>Female gender</td>
<td>9.53</td>
<td>-13.42-32.49</td>
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<td>17.30</td>
<td>-12.15-46.75</td>
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<tr>
<td>Female gender</td>
<td>2.32</td>
<td>-1.27-5.91</td>
<td>.22</td>
<td>2.82</td>
<td>-1.52-7.17</td>
<td>.20</td>
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<tr>
<td><strong>Adjusted step 4</strong></td>
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<td>Female gender</td>
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<td><strong>4.10</strong></td>
<td><strong>0.46-7.73</strong></td>
<td><strong>.027</strong></td>
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<tr>
<td>Female gender</td>
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<td><strong>.030</strong></td>
<td><strong>3.53</strong></td>
<td><strong>0.13-6.93</strong></td>
<td><strong>.043</strong></td>
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</tr>
<tr>
<td>Female gender</td>
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<td>-0.42-4.93</td>
<td>.10</td>
<td>2.44</td>
<td>-0.62-5.49</td>
<td>.12</td>
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</tbody>
</table>

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and gender x age; ‡adjusted model 3 = model 1 and socio-demographics (no partner and <high school education); §adjusted model 4 = model 3 and clinical factors (diabetes, current smoking, prior stroke, prior myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ||exploratory adjusted model 5 = model 4 and co-morbidities (body mass index $\geq 30$ kg/m$^2$, chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis); ‡exploratory adjusted model 6 = model 5 and depression. See Appendix 4 for full model.
Table 5: The Unadjusted and Adjusted Association between Gender and Health Status Change Scores. Regression Coefficients and 95% Confidence Intervals are presented.

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The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and gender x age; ‡adjusted model 3 = model 1 and socio-demographics (no partner and <high school education); §adjusted model 4 = model 3 and clinical factors (diabetes, current smoking, prior stroke, prior myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5 = model 4 and co-morbidities (body mass index ≥30 kg/m², chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis); ‡exploratory adjusted model 6 = model 5 and depression. See Appendix 5 for full model.
FIGURE 1: Kaplan Meier survival curve for death stratified by gender.
FIGURE 2: Kaplan Meier survival curve for first cardiovascular event (death, AMI, stroke, amputation) stratified by gender.
FIGURE 3: Median physical (PCS) and mental (MCS) SF-12 summary scores at baseline and 12-Month follow-up stratified by gender.
Appendix 1: Full Unadjusted and Adjusted Multivariate Cox Proportional Regression Model for Mortality and all Cause Cardiovascular Events (Mortality, AMI, Stroke, and Lower-Extremity Amputation). Hazard ratios and 95% Confidence Intervals are presented.

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Appendix 2: Exploratory Multivariable Cox Proportional Model for Mortality and All Cause Cardiovascular Events (Death, AMI, Stroke & Amputation). Hazard ratios and 95% Confidence Intervals are presented.

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<tr>
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<td>0.60-1.44</td>
<td>.74</td>
<td>0.90</td>
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<tr>
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<tr>
<td>Female Gender</td>
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<td>0.58-1.39</td>
<td>.63</td>
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<tr>
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<td>1.03-1.08</td>
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<td>.50</td>
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<tr>
<td>Age</td>
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<td>1.02-1.08</td>
<td>&lt;.001</td>
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APPENDIX 3: The Full Adjusted Model and Exploratory Models for the Association
between Gender and Baseline Health Status. Regression Coefficients (B) and 95% Confidence Intervals are presented.

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**Exploratory model 2**

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Abbreviations: MI = myocardial infarction, BMI = body mass index, COPD = chronic obstructive pulmonary disease. *Not significant.
**APPENDIX 4: The Full Adjusted Model and Exploratory Models for the Association**

**between Gender and 12-Month Health Status.** Regression Coefficients (B) and 95% Confidence Intervals are presented.

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Abbreviations: MI = myocardial infarction, BMI = body mass index, COPD = chronic obstructive pulmonary disease. *Not significant.
APPENDIX 5: The Full Adjusted Model and Exploratory Models for the Association between Gender and Health Status Change Scores. Regression Coefficients (B) and 95% Confidence Intervals are presented.

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Abbreviations: MI = myocardial infarction, BMI = body mass index, COPD = chronic obstructive pulmonary disease. *Not significant.
7.1 Thesis Overview

This thesis has demonstrated that the sex/gender disparity in CVD is omnipresent and remains a major health issue. Specifically, sex/gender differences were observed to be independent of the CVD process (CHD vs. PAD), acuity (acute vs. chronic syndromes) and geography (Adelaide vs. Australia vs. Holland). Results have revealed that in most aspects of CVD, particularly, CHD and PAD, women are substantially worse off in terms of diagnosis, management and prognosis. This thesis has advanced our understanding of sex and gender differences in cardiovascular disorders by:

(a) Characterising gender differences in chronic stable angina patients attending Australian general practitioner clinics (Chapter 3).

(b) Illustrating gender differences in patients with STEMI within a local South Australian hospital setting. In particular, focusing on gender differences in performance measures such as DTB time and its components (Chapter 4) as well as highlighting sex differences in cardiac haemodynamics during AMI (Chapter 5).

(c) Examining gender differences in cardiovascular outcomes and health status in patients with PAD attending Dutch outpatient clinics (Chapter 6).

The extent of the problem in women with CVD is multifaceted and includes differences in (a) risk factors, (b) clinical characteristics, (c) biological mechanisms and (d) psychosocial factors.

The first study, as detailed in chapter three, explored gender differences in regards to CSA patients enrolled in the Australian Coronary Artery Disease in General Practice (CADENCE) study. The objective of this manuscript was to assess gender
differences in health status of patients with CSA attending Australian GP practices using the disease specific Seattle Angina questionnaire (SAQ). Secondary objectives included evaluating potential contributing factors to any gender disparity in health outcomes. The principal findings of this study revealed that women with CSA were more likely to report more persistent angina with more physical limitations and a poorer quality of life (as assessed by the SAQ), however they were (a) less likely to have had specialist cardiology review, (b) less extensively investigated, (c) prescribed fewer cardio-protective agents and (d) less likely to undergo coronary revascularisation procedures. The underlying mechanisms in regards to gender disparities in health outcomes have been speculated to include differences in risk factors and their management, clinical aspects (including presentation, diagnostic work up/therapies), underlying biological mechanisms as well as psychosocial factors.

The second study, as detailed in chapter four, examined gender differences in DTB time in patients with STEMI undergoing PCI in a local South Australian hospital registry. The main objectives of this study were to firstly quantify the individual components of DTB time in women and secondly to assess the independent effect of gender on DTB time (whilst adjusting for conventional clinical covariates). This study has highlighted that the delay in women with STEMI occurs across the continuum of DTB time components. Specifically, women have a delayed STEMI diagnosis highlighted through a delayed Door-to-Code time (i.e. Emergency department) as well as a significant delay in instituting therapy for PCI as highlighted in a delay in Lab-to-Balloon time (i.e. Catheterisation laboratory). Secondly, female gender was found to be a significant predictor of a delayed DTB time even following adjustment for important clinical covariates. Additional key predictors of delay included
presentation within out of office hours, a history of hypertension, the degree of ST-elevation on initial ECG and low priority triage category. The cause of the delay in DTB and its components in women is still unknown but it has been speculated to include a delay in presentation to hospital due to lack of awareness of CHD in women and their associated atypical symptomology. In addition this delay may be due to diagnosing the STEMI in the emergency department as well as unrecognised technical factors in the catheterisation laboratory.

The third study, as detailed in chapter five, investigated sex differences in cardiac haemodynamics in patients presenting with STEMI in a local South Australian hospital registry. The primary objective of this study was to examine if female sex was an independent determinant of pulmonary capillary wedge pressure (PCWP) during acute STEMI. Secondly, to investigate whether an elevated PCWP contributed to all cause 30-day mortality/re-infarction in women. For the first time, results from this study revealed that women have an elevated PCWP and reduced mixed venous oxygen saturation during acute STEMI as compared with their male counterparts. Furthermore, female sex was found to be an independent predictor of PCWP along with hypertension and creatine kinase estimated infarct size. Although female sex was also an independent predictor of 30-day mortality/re-infarction, this was partially mediated through PCWP, which in turn had its own direct effect on 30-day outcomes. The mechanisms for this gender disparity in haemodynamics remain unclear but may include differences in women’s pre-morbid cardiac status or the pathophysiological mechanisms responsible for the acute STEMI.
The final study, detailed in chapter six, demonstrated significant gender disparities in cardiovascular outcomes and health status in patients presenting with PAD to a Dutch outpatient clinic setting. The main objectives of this study were to firstly assess whether outcomes in women with PAD differ in regards to their long-term adverse cardiovascular events and secondly to evaluate women’s self reported health status using the generic short form-12 (SF-12) at initial diagnosis and at 12 months follow up. The main findings of this study highlighted that although there was no significant effect of gender on mortality and major adverse cardiovascular events, women suffered from a poorer physical and mental health status at both baseline and 12 months follow up. Furthermore, female gender was an independent predictor of a poorer baseline physical health status and poorer mental health status at 12 month follow up. The underlying mechanisms for the poorer health status in women with PAD are still unknown but may likely involve differences in socio-demographics, clinical characteristics, psychosocial factors, and functional limitations.

7.1.1 How Chronic Disease can be understood through a ‘Sex/Gender Lens’

Stepping back and examining the ‘big picture’ of the role of sex and gender in other chronic disease states may provide us with clues on the gender disparity in CVD, including avenues for future research. As previously mentioned, sex differences are based on biological variations amongst men and women including differences in sex hormones, chromosomes or sex specific gene expression from autosomes. These sex differences lead to variations in metabolism, physiology and pathophysiology of diseases. In turn, gender differences are mainly the result of socio-cultural processes involving behaviour and lifestyle associated factors and diseases. This may
involves access to health care; help-seekin behaviour and individual use of the health care system.

The ubiquitous nature of the gender disparity is underscored as this bias is not isolated to cardiovascular disease and is more widespread than one may assume. Ironically, it seems that women develop many prominent disorders (asides from prostate cancer), which we know is specific to men. A recent systematic review conducted by members of the Institute of Gender in Medicine718 have revealed that sex and gender differences exist not only in CVD but also in autoimmune disorders, pulmonary disease, gastroenterology and hepatology, nephrology, endocrinology, hematology and neurology719 (to name a few). Authors from this review identified over 10,000 articles pertaining to sex and gender differences in modern day medicine and classified these according to major disease entities, epidemiology, pathophysiology, clinical factors as well as outcomes and management718. A more detailed discussion of sex/gender disparities in these various disease states is found in “Sex and Gender aspects of clinical Medicine” by Oertelt-Prigione718 as well as in a review by Arain and colleagues720. These considerations of gender differences in CVD and other chronic disorders raises the prompt and eternal question ‘why are men and women different?’

As previously mentioned, the underlying cause/s of these gender disparities may be due to (a) risk factors, (b) clinical characteristics, (c) biological mechanisms and/or (d) psychosocial factors. However, considering the ubiquitous nature of this gender disparity within medical disorders, it suggests that the differences are likely to fundamentally be biological in nature since differences in psychosocial aspects or clinical practice would vary geographically and between disorders, and thus so would
the gender disparity. From first principles in biology, males and females differ genetically based upon their XY or XX genotype. This genetic difference results in the well-described X-linked medical disorders however they may also contribute to the more complex polygenetic disorders. The difference in genotype results in different expressions in hormones (oestrogens/progestins vs androgens), which may exert different effects on pathological processes. For example, oestrogens influence vascular reactivity and inflammation, particularly with their loss in menopause (see section 1.4.9.6).

The potential relationship between sex hormones and inflammation warrants further consideration, especially as the importance of inflammation in disease processes becomes more apparent. For example, women are more susceptible to autoimmune disorders such as rheumatoid arthritis, systemic lupus and multiple sclerosis, which are characterised by periodic episodes of inflammation. This increased susceptibility has also been observed in female animal models such as systemic lupus erythematosus in (NZBxNZW)F1 and NZM.2328 mice, thyroiditis, Sjogren's syndrome in MRL/Mp-lpr/lpr mice and diabetes in non-obese diabetic mice. The two major clinical observations in autoimmune disorders are firstly that females seem to be more susceptible than their male counterparts and secondly that pregnancy reduces relapses in this female cohort. Interestingly, inflammation may also play a significant role in the development of psychiatric disorders such as depression and various neurological disease states such as stroke and Alzheimer's which again are more prevalent in women. In light of the above, inflammation not only underlies CVD but also many rheumatic and neurological disorders. Thus an abnormal inflammatory response in women due to sex hormones may be a fundamental underlying cause for the observed differences. The notion that inflammation
plays a central role in CHD is relatively novel, although it’s been known for some
time that increases in inflammatory markers such as CRP signal any type of
inflammation and perhaps more so in women than men\textsuperscript{201}.

Besides autoimmune disorders other disease related conditions, which are more
frequent in women, include reynaud’s phenomena, vasculitis, pulmonary
hypertension, migraines and coronary micro-vascular disease\textsuperscript{727-730}. Sex hormones
may again explain the difference between sexes in developing these disorders. For
example, there is sufficient evidence pointing to a connection between migraines and
fluctuations in oestrogen levels in women. Interestingly, the lifetime prevalence of
migraine is increased in females compared to males (female/male ratio ranging from
2:1 to 4:1) in several populations\textsuperscript{731, 732}. Several hypotheses have been alluded to in
regards to this female predominance including neurobiological factors, increased
sensitivity to environmental stressors or a greater genetic loading for migraine\textsuperscript{733, 734}.

Recent research has also highlighted that retinal microvascular abnormalities can
predict clinical and subclinical stroke as well as other cardiovascular outcomes\textsuperscript{735}.

Thus, studying sex differences in neurovascular dysfunction, associated with vascular
headaches, may in turn provide important insights into micro-vascular dysfunction,
which is predominately, observed in women with CHD. In terms of micro-vascular
disease our laboratory is currently investigating vasomotor reactivity of the
microvasculature in women as compared with men using subcutaneous tissue from
patients with no CAD. Thus far we have shown that small arteries of women are
hypersensitive to various agonists including catecholamine (noradrenalin and
phenylephrine) and thromboxane (Jaghoori et al 2012, unpublished).
In addition to the above disorders, there are a number of common vascular disease-related conditions that are unique to women including hypertensive disorders of pregnancy, gestational diabetes, peripartum dissection as well as PCOS (see section 1.4.9.6). As outlined in this thesis, there also appears to be substantial biological differences within vascular structure, function and atherosclerotic plaque between men and women. For example, the underling mechanism for AMI seems to differ between the genders with more women having a higher prevalence of subendocardial myocardial infarctions (i.e. NSTEMI), ‘emotionally provoked’ Takosubo infarctions, spontaneous dissection as well as more plaque erosion versus plaque rupture compared with men.736-738

These results suggest that by studying sex differences in inflammation, sex hormones and micro-vascular dysfunction may indicate the biological basis and scope of the gender disparity in CVD. Furthermore, based on the observations from this thesis and my reading of the literature, I propose the hypothesis of inflammation as the underlying cause of the gender disparity in CVD. However, patient bias, psychosocial differences and physician bias may also contribute to the disparity. While further studies are required to elicit the underlying mechanisms of this gender disparity, the question is what can we do about it, today?

7.1.2 What is needed to Bridge the Gender Gap in CVD?

While we need to continue the investigation for the underlying cause of the gender disparity, in the interim, we can address potentially reversible contributing factors including (a) patient education, (b) addressing clinical biases (c) improving gender
inclusion in clinical trials and (d) advancing gender based research. The final section of this conclusion will focus on avenues for future research.

*Education: Reducing the Stigma*

In order to bridge the gender gaps in CVD it is essential to firstly make visible the impact of CVD in women. As previously mentioned, part of the problem in the perception and awareness of CVD is the fact that historically vascular disease has been considered a ‘male based disorder’\(^1\). Instead, women have been focused on their risk of developing breast cancer due to strident campaigning of breast cancer during the 1980’s which evolved from feminist and women’s health movements of the 20\(^{th}\) century\(^739\). The breast cancer lobby group has been successful due to a series of political and educational campaigns, which have resulted in widespread awareness of this disease in the general population, so much so that the majority of Australian women consider this the number one cause of death, when in fact, heart disease kills four times as many women than breast cancer\(^179\).

In light of this; perhaps we can take note of the success of this campaign in moving forward in educating women about cardiovascular disease and ultimately ‘reducing the stigma’. The ‘Go red for women’ campaign has been a great success since being introduced in 2004 within the United States and in 2009 in Australia resulting in a marked improvement in the awareness of the signs and symptoms of CHD\(^181\). However, unlike the breast cancer awareness campaigns, we still have a long way to go. Not only do we need to continue to educate women on their risks of CHD through such campaigns, we need to develop similar programs in PAD which are currently lacking or are non existent and have sparked the recent ‘Call to action’ for focused
research and awareness for women with this disabling disease. Of importance, the burden of stroke in women is also now emerging as a major public health problem, especially due to women’s longevity over men. However, similar to PAD, the data on women in this area is scarce to non-existent and controversies exist regarding differences in stroke incidence, mortality and post-stroke disability outcomes. The available data suggest that there are gender differences in stroke symptoms, diagnosis, peri-procedural risk, treatment and preventive interventions. In order to understand the full spectrum of gender disparities in vascular disease future research should involve a multifaceted approach within all three major arterial beds.

*Patient Education*

There appear to be two major hurdles in educating women on their risks of vascular disease including, (a) education prior to the event occurring and (b) education/rehabilitation following a cardiac event. Furthermore, as well as instructing women, perhaps we need to involve their families of the risks of vascular disease, encompassing more of a ‘social connectivity’ or ‘hegemonic’ medical health care approach involving psychological, physical and social aspects of care (from the point of view of gender). This holistic approach may be particularly important for women since many are primary caregivers to children, their partners and elderly parents. This is supported by contemporary research, which suggests that women require more social supports compared with men following a cardiac event and thus may be an important factor in their recovery. This also raises the question of whether we need to target female specific rehabilitation programs (i.e. following AMI), which encompass the community/family unit.
Educating Health Care Providers

Health care providers also need to be educated on the risks of vascular disease in women and the greater ‘gender disparity’ in particular. This may include more focused updates/training on current gender specific guidelines, treatment modalities and recognition of the ‘female pattern’ non-obstructive heart disease as compared with men. Medical-school curricula must change in the future, to improve physicians’ training, knowledge, and skills in monitoring and improving the quality of care for women and minorities worldwide. A recent review by McGregor and colleagues has highlighted this urgency for a multifaceted gender approach in emergency medicine to improve the delivery of high-quality clinical care for both men and women. Medical educators and persons responsible to the public for higher education should discuss these ‘gender barriers’ to reform in the clinical curriculum. These changes, although desirable from a rational perspective, involve basic changes in the culture of medical schools and teaching hospitals. If we can change cultural values and ‘re-wire’ the way in which the general public, physicians and health care providers think about sex and gender differences, this has strong implications for improving health care for all women with CVD.

Gender Specific Inclusion in Clinical Trials

Disturbingly, the 2012 female enrollment rate in cardiovascular clinical trials is a mere 30% with only a third of clinical trials publishing sex specific results. This is despite vociferous political involvement of the National Institutes of Health Revitalization Act in 1993, which aimed to increase enrollment of minorities in clinical research. Furthermore, a review of articles published between 1994 and
1999 found that 86% of 120 trials examined did not conduct gender specific analyses\textsuperscript{758}. Since this time, a number of reviews articles have concluded that the majority of major clinical trials to date have not conducted gender specific analyses\textsuperscript{759, 760}. In moving forward, a multi-disciplinary gender specific approach to cardiovascular research must be adopted including the inclusion of a sizeable number of women into all cardiovascular clinical trials and/or observational studies together with an improved understanding of women’s enrollment patterns in order to develop strategies for greater generalizability of clinical trial results. In addition, we need to incorporate the use of appropriate statistical techniques that facilitate testing for specific sex interactions, as well as providing information about sex-specific differences in treatment responses.

\textit{Gender Specific Research and Health Care}

In addition to the inclusion of more women in trials we also need more focused gender specific research. In particular, the landmark WISE study was the first female exclusive study which focused on symptom evaluation/diagnostic testing, mechanisms for symptoms and myocardial ischaemia in the absence of epicardial coronary artery stenoses, as well as the influence of reproductive hormones on symptoms and diagnostic test response\textsuperscript{160, 176, 268}. The results of this study have been groundbreaking, suggesting that women with angina not only respond less effectively to standard diagnostic procedures but are far more likely than men to appear ‘free’ of blockages on angiography, hence coining of the term ‘micro-vascular dysfunction’ and the ‘female pattern’ heart disease. Results from WISE suggest that perhaps it’s time for gender specific diagnostic testing and gender specific care. For example, traditional tests for obstructive coronary artery disease are less sensitive and specific
In light of this more novel techniques such as stress echocardiography, SPECT imaging and MRI may be important and necessary options for women. In addition, tests for atherosclerosis (i.e. coronary artery calcium screening) and testing of endothelial function may have some advantages over traditional risk assessment algorithms in women. Asides from the impact of the WISE study, the field of gender disparities in CVD will be further influenced by findings from the VIRGO and the PORTRAIT studies which are the first large multinational registries to focus on young women with AMI (<55 years) as well as women with PAD (See ancillary projects coordinated).

7.1.3 Future Directions for Research

Apart from the above suggestions for research into the role of inflammation, sex hormones and MCD, the work presented in this thesis indicates that further targeted prospective research is required to investigate the mechanism of the gender disparity in health outcomes within both CHD and PAD (Chapter 3 & 6). Specifically, we require more gender based research in primary care as women with angina and claudication are more likely to present to GP practices than out patient hospital settings. Secondly, we need to better understand the mechanism of the delayed diagnosis and treatment for women with STEMI (Chapter 4), incorporating more of a multifaceted approach, which addresses both the diagnosis, and management of these patients. We recognize that women have both a delayed DTB and component time intervals and in light of this wish to advance local practice by introducing the ‘STEMI clock’ which will help pinpoint specific delays in treatment. It would also be interesting to conduct a pilot study to assess how long it takes to consent a woman
compared to a man as any small differences in improving DTB are critical. In addition, future efforts are needed in collaboration with the South Australian Ambulance Service to approve and conduct pre-door ECG’s, which has been shown to improve overall DTB times.

In addition, we have demonstrated for the first time that women have a higher PCWP, which is indicative of a higher left ventricular pressure (Chapter 5). This may be a potential marker for the higher in-hospital mortality and poor recovery following AMI in women. Future studies should aim to replicate this finding and focus on the underlying mechanism, which may include sex differences in women’s pre-morbid cardiac status, or the patho-physiological mechanism responsible for the acute STEMI. It would be particularly interesting to monitor the PCWP in women over time, which may provide valuable haemodynamic information. Alternatively, whether the STEMI process in women involves a greater extent of MCD or inflammation warrants further consideration.

Last but not least future research in PAD should focus on gender specific mortality and reporting of cardiovascular events as well as health status (Chapter 6). Ours was the first study to focus on such outcomes in a large PAD population and thus it is crucial to confirm or dispute these findings. Important and interesting areas of interest in PAD include mood states such as depression and anhedonia, socio-economic effects on gender as well as personality traits (i.e. Type D traits).
7.1.4 Conclusion

In conclusion, sex/gender differences in medical disorders are a ubiquitous problem that still requires considerable research. In addition, sex and gender differences have significant consequences on the daily practice of medicine, on outcomes and effects of therapies. Still, the question remains, *do we have sufficient knowledge to close the enduring gender gap in CVD?* Whilst previous research (including this thesis) has advanced our understanding on this matter, the gender disparity in CVD is far-reaching and multi-factorial and involves clear differences in (a) risk factors, (b) clinical characteristics, (c) biological mechanisms and (d) psychosocial factors. Future prospective research should target these key areas of interest with a focus more on mechanism.
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Appendix 2: Published CADENCE Manuscript
Appendix 3: Health–Related Quality of Life Instruments

Seattle Angina Questionnaire, authored by J. A. Spertus
Instrument available from Cardiovascular Outcomes, Inc. (CV Outcomes), United States.
www.cvoutcomes.org

Short-Form 12 Version 2.0 (Dutch version), authored by J. E. Ware, Jr.
Instrument available from Quality Metric Incorporated, United States.
www.qualitymetric.com

Hospital Anxiety and Depression Scale (HADS), authored by A.S. Zigmond
The Dutch version of the HADS questionnaire was translated/validated by Spinhoven et al. Psychol Med. 1997 Mar;27(2):363-70.
Instrument licensed to the department of medical psychology, Tilburg University
Appendix 4: Epidemiology of Coronary Artery Disease: Book Chapter


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Epidemiology of Coronary Artery Disease

John F. Beltrame, Rachel Dreyer and Rosanna Tavella

Discipline of Medicine, University of Adelaide, The Queen Elizabeth Hospital, Australia

1. Introduction

Epidemiology involves the study of the frequency, distribution, and impact of diseases within a community in order to address potential prevention or treatment of these conditions. Accordingly, evaluating the epidemiology of coronary artery disease (CAD) constitutes a particularly wide spectrum that cannot be comprehensively covered in a solitary book chapter. Consequently this first section will provide an introductory broad overview of CAD including pathophysiological concepts, clinical manifestations, geographic variations and its impact on patient health. After defining the broader context of this large field, the specific scope of chapter will be outlined.

1.1 Defining coronary artery disease

The coronary circulation consists of coronary arteries, the microcirculation and the coronary veins. Its function is to supply oxygen and nutrients to the myocardium and remove carbon dioxide and waste products. The importance of this function is exemplified by the fact that a 50% or more reduction in this blood supply to the myocardium is incompatible with life. Thus, not surprisingly, dysfunction of the coronary circulation may result in significant morbidity and mortality.

Although beyond the scope of this chapter, it should be noted that disturbances of the coronary circulation may involve dysfunction within the microcirculation as well as the coronary arteries. Thus the all-encompassing term ‘coronary heart disease’ includes both CAD and microvascular dysfunction. The later may mimic the clinical manifestations of CAD and indeed may co-exist with CAD. However, defining the epidemiology of microvascular dysfunction is especially difficult since specialised investigations are required to confirm its presence, as it may occur in the absence of associated structural microvascular disease.

In contrast, CAD is more readily identifiable and the most common underlying pathophysiological process is coronary atherosclerotic disease. This may be identified by imaging techniques such as coronary angiography, or unequivocally at post-mortem autopsy. Accordingly, detailing the epidemiology of CAD is more readily achievable and the focus of this chapter.

1.2 Atherosclerotic coronary syndromes

Coronary atherosclerotic disease involves the epicardial coronary arteries and may manifest as an acute or chronic coronary syndrome. Acute coronary syndromes (ACS) typically arise
from atherosclerotic plaque rupture with subsequent coronary thrombosis and/or spasm. The resulting coronary artery occlusion gives rise to intense myocardial ischaemia or even myocardial necrosis thereby manifesting as unstable angina or myocardial infarction. On occasions, the ischaemia/infarction may manifest as sudden cardiac death from malignant arrhythmias or acute pulmonary oedema in the compromised left ventricle. Hence ACS may have a spectrum of clinical manifestations ranging from unstable angina, acute myocardial infarction, acute pulmonary oedema or even sudden death, all arising from the same underlying pathophysiological process.

Chronic coronary syndromes (CCS) may also arise from coronary atherosclerotic disease. This typically manifests as exertional angina arising from a coronary atherosclerotic lesion that has progressed to the extent that it compromises coronary blood flow to the myocardium during the increased oxygen demand associated with exercise. As this obstructive lesion is non-occlusive, adequate oxygen supply is restored once the excess myocardial oxygen demand is removed with the cessation of exercise and thus the resolution of the ischaemic chest pain. Hence the principal manifestation of CCS is angina pectoris, which can be monitored in epidemiologic studies.

1.3 Geographic variations in coronary artery disease

The global prevalence of these CAD-related clinical manifestations is increasing although there are regional variations that are influenced by the extent of economic development and social organisation. With industrialisation, there is a shift from nutritional and infectious disorders to the chronic diseases such as CAD. This ‘epidemiologic transition’ has been described as involving 4 stages (Omran, 1971), as detailed in Table 1, (Yusuf et al, 2001). In developing countries, infectious disease and nutritional deficiency are responsible for most deaths (Stage 1) and cardiovascular disease plays only a minor role. The cardiovascular disorders (CVD) that are prevalent in these communities include infectious disease such as rheumatic heart disease or nutritional disorders such as beriberi. With improvements in public health and nutrition, these conditions become less prevalent and disorders related to uncontrolled hypertension become more common (Stage 2). With further industrialisation, lifestyle diseases become more evident. Thus smoking, high fat diets and obesity result in the rapid development of atherosclerosis so that CAD mortality is a major cause of death in middle-aged individuals (Stage 3). With further improvements in public health measures to address these lifestyle risk factors and advances in medical care, atherosclerotic disease associated mortality is delayed so that it is a condition of the elderly (Stage 4). Progression through each of these transition stages is associated with a greater life expectancy. Moreover as shown in Table 1, cardiovascular disease (and especially CAD) contributes proportionally more to the total population mortality.

As evident from Table 1, CAD is present across the globe although its frequency varies with geographic region. Consequently there is a wide spectrum in the prevalence of CAD in developing and industrialised countries; thus discussions relevant to one country may not be necessarily be pertinent to others. Hence it is important to report on the context of the findings when describing the epidemiology of CAD.
<table>
<thead>
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<th>% Deaths*</th>
<th>Cardiovascular Conditions</th>
<th>Countries</th>
</tr>
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<tbody>
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<td>1. Infections &amp; Nutritional Deficiency</td>
<td>5-10%</td>
<td>• Rheumatic Heart Disease • Nutritional Cardiomyopathy</td>
<td>• Sub-Saharan Africa • Rural South America • Rural Southern Asia</td>
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<td>2. Hypertensive Diseases</td>
<td>10-35%</td>
<td>• Haemorrhagic Stroke • Hypertensive Heart Disease</td>
<td>• China • Urban Southern Asia</td>
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<tr>
<td>3. Atherosclerotic CVD in the Middle-aged</td>
<td>35-65%</td>
<td>• CAD • Atherothrombotic Stroke</td>
<td>• Urban India • Latin America • Former USSR</td>
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<tr>
<td>4. Atherosclerotic CVD in the Elderly</td>
<td>&lt; 50%</td>
<td>• CAD • Atherothrombotic Stroke • Heart Failure</td>
<td>• Western Europe • North America • Australia, New Zealand</td>
</tr>
</tbody>
</table>

*%Deaths from CVD, in relation to total deaths. CVD = Cardiovascular Disease.

Table 1. The Epidemiologic Transition of Cardiovascular Disease*

### 1.4 Health status in coronary artery disease

Epidemiology not only involves monitoring diseases within the community but also their impact on health. Thus the focus should not only be on the disease manifestations of CAD (such as acute and chronic coronary syndromes) but also the patient’s perception of the impact of these disorders on their health. The term ‘health status’ (see Figure 1) is used to define the patient’s perception (rather than the clinician’s perception) of the disease process on their lifestyle. This incorporates the symptoms experienced (e.g. angina), the functional limitation from the symptom (e.g. reduced exercise tolerance) and quality of life (i.e. the

![Diagram of health status]  


Fig. 1. Summary of Patient-centred Health Status.
discrepancy between actual and desired function) (Rumsfeld, 2002). Thus congruous with our evolving patient-centred health care, this chapter will not only focus on CAD in relation to the prevalence and incidence of disease processes but will also detail the impact of CAD on health status.

1.5 Scope of the chapter

Considering the wide spectrum encompassing CAD epidemiology, it is necessary to limit the topics covered in this chapter. Thus the chapter will evaluate overall CAD mortality, myocardial infarction as an example of an ACS and chronic stable angina as the example of a CCS. Within each of these areas, the discussion will focus on (1) the difficulty and limitations in defining the condition and thus its impact in interpreting the data, (2) the prevalence of the condition, (3) the incidence of the condition, where relevant, (4) and the impact of the condition on health status, when appropriate. This comprehensive approach will provide a detailed evaluation of the epidemiology of CAD.

Since the prevalence of CAD varies with geographic location, the discussion in this chapter will be largely focus on industrialised countries (i.e. Stage 4 countries, Table 1). Data from these countries are readily available, generally reliable and the prevalence of disease similar, although there are small differences even within these countries. Thus although the data presented in this chapter is comprehensive in relation to the industrialised countries, it is acknowledged that it is not globally inclusive.

2. Coronary artery disease mortality

2.1 Defining coronary artery disease mortality

Detailing mortality data may seem straightforward since the presence/absence of death is seldom a contentious issue, however whether the death can be attributed or indeed is associated with CAD is more problematic. Many epidemiologic studies derive mortality data from administrative death registries. In most of these registries, the cause of death is obtained from the death certificate completed by the treating doctor, who ascribes the cause of death based upon clinical impression. This contrasts to the more objective assignment of a cause of death from formally conducted autopsy studies. Since non-forensic national autopsy rates are about 5% in most industrialised countries, the cause of death derived from these registries may be unreliable and this should be considered when interpreting the mortality data detailed below.

2.2 Prevalence of coronary artery disease mortality

CVD encompasses not only CAD but also cerebrovascular disease, peripheral arterial disease as well as other cardiac disorders, and is currently the leading cause of death in the world, particularly amongst women. The World Health Organisation (WHO) estimates that such diseases caused almost 32% of all deaths in women and 27% in men in 2004 (World Health Organisation [WHO], 2008). CAD is the most common cause of CVD deaths (45% of all CVD deaths) accounting for 7.2 million deaths/year, or 12% of all deaths worldwide (Figure 2).

In many developed countries, CAD is the single leading cause of death. In the United Kingdom (UK) in 2008, CAD was responsible for about one in five male deaths and one in eight female deaths; a total of 88,000 CAD deaths (15% of total deaths) (British Heart
Fig. 2. Distribution of Cardiovascular Diseases Accounting for Deaths Worldwide in 2004

Foundation [BHF], 2010). Similarly in the United States in 2005, CAD was responsible for one of every five deaths, accounting for 445,687 deaths (18% of total deaths) (Lloyd-Jones et al, 2009). In Australia in 2006, CAD accounted for 22,983 deaths (17% of all deaths) and once more was the most common condition responsible for Australian deaths (Australian Institute of Health and Welfare [AIHW], 2010).

2.3 Temporal changes in coronary artery disease mortality

The ‘epidemiologic transition’ described above (Table 1), not only accounts for geographic variations in CAD but also temporal changes. Over the past 30 years, two epidemiological trends have been observed in relation to CAD mortality. In many developed countries there has been an initial rise followed by a fall, while in developing countries there has mainly been a rise in CAD mortality.

In developed countries, there was a peak in CAD mortality in the 1950’s with a progressive decline since the 1960’s. The WHO Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project identified an annual 4% decline in CAD mortality rate trends over 10 years from the 1980’s across 21 countries (Tunstall-Pedoe et al, 2000). For example, in 1996 Australia reported 29,637 deaths (23% of all deaths) due to CAD, and in 2006, the equivalent figure was 22,983 (17% of all deaths). This decline in CAD deaths rates over the past 2 decades has been the most remarkable in Denmark, Australia, Sweden, the Netherlands and Canada, with the rate of CAD death falling by more than 60% (Figure 3). These trends are consistent with an ‘epidemiologic transition’ from Stage 3 to Stage 4 in these countries and reflect an increased life expectancy with the onset of CAD manifestations at an older age.
Figure 3 also highlights the heterogeneity between the countries in the improved CAD mortality. Thus while many Western European countries have shown substantial improvements in CAD mortality as described above, the Eastern European countries (such as Hungary) generally showed less improvement. These trends typically parallel socio-economic differences with the decline in CAD mortality being sharper in countries with a more favoured socio-economic status.

In contrast, some developing countries have an increasing rate of CAD mortality. Indeed, the WHO estimates that 60% of the global burden of CAD occurs in developing countries. Although mortality estimates are difficult to obtain in some of these countries, broad assessments of overall CVD epidemiology report rising CVD mortality in urban China, Malaysia, Korea and Taiwan. In China, CVD mortality increased as a proportion of total deaths from 12.8% in 1957 to 35.8% in 1990 (Khor, 2001). Like many developing countries, it has experienced rapid urbanisation, socioeconomic and health changes, together with an increase in life expectancy - features consistent with stage 2 of the epidemiologic transition.

2.4 Factors influencing coronary artery disease mortality

The landmark Framingham Heart Study was established in 1948 by the US Public Health Service to investigate the epidemiology of atherosclerotic CVD and hypertension. Its contribution to this field was huge as it precipitated a paradigm shift in the approach to CVD. This study transformed the popular belief at the time, which regarded atherosclerotic coronary artery disease as a normal aging process, to the ground-breaking concept of ‘risk factors’ thereby proposing that lifestyle modification could prevent CVD. This iconic longitudinal study demonstrated that advancing age, smoking, hypercholesterolaemia, hypertension and obesity increased the risk of CVD. Subsequently, these investigators developed the ‘Framingham Risk Score’, which predicts the 10 year risk of developing CAD based upon age, cholesterol profile, blood pressure level, diabetic and smoking status. They conclude that at the age of 40 years, the lifetime risk of CAD is 50% for men and 33% for women. Further insights into CAD continue to evolve from the study including the role of gender, depression, and socioeconomic status.

2.4.1 Age

Ageing is an unmodifiable risk factor for CAD, with males clinically manifesting this condition at 50-65 years of age and females about 10 years later, following menopause (Lerner & Kannel, 1986). The WHO reports that the principal cause of death of people over 65 years is CAD, and as age increases, a substantial proportion of deaths are among females. In many developed countries, the number and proportion of older people (i.e over 65 years) is increasing, which is largely explained by declines in fertility and mortality. The ageing population of many countries has accelerated the contribution of CAD to total disease burden. It is predicted that the global ageing population will maintain CAD as a predominant cause of death worldwide (Mensah, 2004).

Among countries with high but declining CAD mortality, it is suggested that these trends are changing with respect to younger age subgroups (O’Flaherty et al, 2009). A slowing or
levelling of the decline in CAD mortality in young adults has now been reported in England and Wales, the US, France, Australia, and New Zealand. These findings are cause for concern, indicating that decades of progress in reducing deaths from CAD appear to be stalling. Changes in lifestyle factors in the young (increasing obesity and sedentary lifestyles) may account for this reduced improvement.


Source Organisation for Economic Co-operation and Development (OECD), 2009

Fig. 3. Age Standardised CAD Death Rates in Developed Countries in 1980 and 2004
2.4.2 Gender

CAD is the leading cause of mortality for both adult males and females alike worldwide. Although the initial manifestation of CAD is delayed in females by about ten years compared to males, there is not an abrupt increase in CAD mortality rates for females immediately following menopause but a progressive increase over subsequent years. Thus more elderly post-menopausal females succumb to CAD then men and have done so since 1984 (Castelli, 1988). Nonetheless, CAD is not solely a disease of elderly women.

In the US, among men aged 35 to 54, the average annual mortality rate from CAD fell by 6.2% in the 1980’s, and levelled off between 2000 and 2002, with an annual decline of just 0.5%. Among women in the same age group, the annual rate of death from CAD dropped by 5.4% in the 1980’s. Between 2000 and 2002, CAD mortality actually increased for females by an average of 1.5%. Furthermore, even in younger females (35 to 44 years), the CAD mortality increased by an average of 1.3% annually between 1997 and 2002. Overall within the transitional trends, the percentage decline in mortality rates has been far greater for men than women, particularly in the US, the UK, Australia and Sweden. The age-standardised mortality rate for males and females since 1978 for the UK is depicted in Figure 4. More alarming is the higher mortality rate observed for young females following myocardial infarction. Younger women, but not older women, have higher rates of death during hospitalisation for myocardial infarction than men of the same age (see Myocardial Infarction section below).

![Graph showing age-standardised CAD mortality in the UK for males and females from 1978 to 2008.](www.intechopen.com)
2.4.3 Geographic differences

It is common to categorise CAD epidemiology by geographic region, however the natural history of CAD epidemics varies substantially between countries. For example, in Europe, the changes in CAD mortality in France and Southern European countries were smaller than that observed in the UK and Finland. The differences in industrialised nations are clearly evident in Figure 3. In Asia, CAD mortality is similar in Hong Kong and China, but it is different to trends in Thailand and South Korea, which report lower CAD mortality rates. These differences may be attributed to a low prevalence of CVD risk factors in the South-east Asian countries. Favourable trends observed in the US, Australia, Argentina, Chile and Cuba, who rates of CAD death are traditionally and substantially lower than in most other areas of the world, may in part be explained by improved control of hypertension, as well as better management of patients with CAD. In Eastern European countries, including Bulgaria, Croatia, Romania, and especially the Russian Federation, there is a persisting upward trend in mortality from CAD. Russian CAD mortality rates in the late 1990’s were higher than those of Finland, the USA, or Australia three decades earlier.

Regional variation in Britain has been consistently reported for 25 years. In Scotland and Northern England, CAD death rates are the highest, Southern England the lowest and intermediate rates in Wales and Northern Ireland. The rate of sudden death for males in Scotland is 63% higher and for females it is 100% higher compared to the rates observed in South Western England. Furthermore, the highest mortality rates are concentrated in urban areas.

2.4.4 Socio-economic status

Socioeconomic status (SES) indicators, including education, income and occupation, are associated with CAD risk factors, morbidity, and mortality. Early studies beginning in the 1930’s generally showed increased CAD prevalence with industrialisation and affluence in developed nations. However, contemporary data demonstrate that low SES, i.e. less education, lower income, and blue-collar occupations are associated with increased rates of CAD and increased risk of CAD mortality. Correspondingly, lower SES groups also have the least favourable lifestyle characteristics, including obesity, smoking, high cholesterol, hypertension, and lack of physical activity. It is suggested by some that these SES-related differences are increasing even as age-adjusted CAD mortality declines.

The British Heart Foundation reports a clear gradient in CAD mortality across low to high SES group. The inequality is more striking in females than males, with the CAD death rate being five times higher in female blue-collar workers compared to females in professional occupations.

2.4.5 Depression

Additional risk factors are continually being evaluated in order to identify their contribution to CAD mortality and thus potentially develop further targeted therapies. Research has consistently shown that depression is a risk factor contributing to both the development and complications of CAD. Depressive symptoms, regardless of a formal clinical diagnosis have an unfavourable impact on mortality in CAD patients. Both major depression and elevated depressive symptoms are associated with at least a doubling in risk of subsequent death in
CAD patients. The negative prognostic effect also remains in the long-term and after adjustment for other risk factors.

2.5 Summary comments

Epidemiologic data on CAD mortality is limited by the data source since most are derived from administrative registries where the cause of death is obtained from subjectively completed medical certificates rather than objectively performed autopsies. Considering this limitation, CAD is reported as the world’s leading cause of mortality for men and women, being responsible for more than 7 million deaths each year. Although in developed nations CAD is the most common cause of death, globally over 60% of fatalities now occur in developing countries. It is clear that a wide spectrum in the prevalence of CAD mortality exits, and despite much effort to improve the disproportional mortality rates, a social gradient in CAD still remains. This is evident by the higher CAD death rates in lower SES areas within regions and even within countries, and also an apparent gender bias, particularly amongst younger women. With a slowing down of age-adjusted mortality, it is likely that social differences will increase. By 2030, it is projected that the number of CAD deaths will rise by up to 137% in developing nations, and by up to 48% in areas where CAD is in decline, as such CAD will remain the leading cause of death worldwide.

3. Myocardial infarction

3.1 Defining myocardial infarction

Acute myocardial infarction (AMI) remains a leading cause of worldwide mortality, being responsible for 12.6% of total deaths each year (Beaglehole, 2004). As described above, AMI and unstable angina constitute the CAD-related acute coronary syndromes. AMI differs to unstable angina as the former is associated with evidence of myocardial necrosis. A variety of methods are available to detect myocardial necrosis including changes on the electrocardiograph (ECG), plasma cardiac markers (creatinine kinase, troponin), imaging techniques (cardiac magnetic resonance imaging, myocardial scintigraphy) and ultimately autopsy gross pathology and histology. The availability of these techniques allow for the definitive diagnosis of AMI to be made. In contrast, the diagnosis of unstable angina is more subjective relying on clinical impression and the absence of evidence of myocardial necrosis. Accordingly, investigating unstable angina epidemiologic data is less reliable and so this chapter will focus upon AMI data only.

The clinical diagnosis of AMI has evolved over the past 10-15 years with the need to make an early diagnosis so that prompt therapy can be instituted. Traditionally the diagnosis is made on the basis of chest pain symptoms, ECG changes and an abnormal plasma cardiac marker. These plasma cardiac markers are particularly pertinent as they are intracellular proteins that are released into the plasma when myocardial cell necrosis occurs. Previously the routine cardiac marker used was creatine kinase, which had limited sensitivity and specificity. The development of the more sensitive and specific troponin assay resulted in myocardial necrosis being detected in patients with a normal creatine kinase. When these troponin leaks were found to have prognostic implications, the clinical diagnosis of AMI was redefined to focus upon the troponin findings. Thus as shown on Table 2, a clinical diagnosis of AMI is primarily made on the basis of an abnormal troponin with at least one other feature; alternatively the diagnosis may be made on autopsy pathological examination (Thygesen et al, 2007).
This change in the diagnostic criteria for AMI, particularly with reference to the plasma cardiac marker, has resulted in more AMI’s being detected. Hence any longitudinal study of AMI will be confounded by the change in the criteria and needs to be considered when interpreting the epidemiologic data. This problem will be further compounded in the future with the evolution of high-sensitivity troponin assays, which may potentially detect even more AMI’s.

In addition to detecting myocardial infarction in the acute setting, a number of the above techniques may detect a previous myocardial infarct. Thus epidemiological studies may survey a population to detect the frequency of myocardial infarction by techniques mentioned in Table 2 relating to ‘healed myocardial infarction’. Each of these methods has their advantages and disadvantages in relation to availability, cost and accuracy. These need to be considered when interpreting the epidemiologic data.

Clinically, AMI has been sub-classified on the basis of the presenting electrocardiograph (ECG) as either ST-elevation myocardial infarction (STEMI) or Non-ST elevation myocardial infarction (NSTEMI). Differentiating these two forms of AMI is important as the immediate clinical management differs. In STEMI, immediate coronary reperfusion strategies (either percutaneous coronary interventions or thrombolysis) on arrival to hospital are mandated in order to reduce the risk of death. In contrast, NSTEMI does not require immediate intervention although early invasive therapy (at least within days) is preferred. This nomenclature has replaced the previous classification of Q-wave and non-Q wave myocardial infarction since the later ECG findings do not occur until late in the course of AMI evolution and do not influence contemporary management strategies. However, as mentioned above, the Q wave can be used to diagnose the presence of a previous myocardial infarct.

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<td>Either one of the following satisfies the diagnosis for acute, evolving or recent MI:</td>
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<td>1. Typical rise and/or fall in cardiac biomarkers (preferably troponin) with at least one of the following:</td>
</tr>
<tr>
<td>• Ischaemia symptoms</td>
</tr>
<tr>
<td>• Development of pathological Q waves in the ECG</td>
</tr>
<tr>
<td>• Electrocardiographic changes indicative of ischaemia (ST-segment elevation or depression</td>
</tr>
<tr>
<td>• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.</td>
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<td>2. Pathologic findings of an acute myocardial infarction</td>
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<tbody>
<tr>
<td>Any one of the following criteria satisfies the diagnosis for healing or healed myocardial infarction:</td>
</tr>
<tr>
<td>1. Development of new pathological Q waves with or without symptoms. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a non-ischemic cause.</td>
</tr>
<tr>
<td>2. Pathological findings of a healed or healing myocardial infarction.</td>
</tr>
</tbody>
</table>

Adapted from Thygesen K et al. Universal definition of myocardial infarction. Eur Heart J 2007; 28: 2525. Copyright permission gained from Oxford University Press 01/08/2011

Table 2. Revised Definition of Myocardial Infarction
In the following sections, the prevalence and incidence of myocardial infarction are described. The *prevalence* of a condition refers to its frequency within a given population at a particular point in time. The *incidence* of a condition refers to the number of new cases within a given population over a specified period of time. The estimates detailed in these sections are derived from several data sources including hospital discharge data, general practice registries and patient self-report from national survey data. Accordingly, the reliability of the data is dependent on the data source.

### 3.2 Prevalence of myocardial infarction

Based upon self-reported myocardial infarction in a UK national survey, the prevalence of myocardial infarction was reported as approximately 4.1% of men and 1.7% of women in 2006 (BHF, 2010). This represents some 1.5 million people within the UK. As shown in Figure 5, the prevalence is age-dependent, extending from 1% of men < 45 years of age to 17% of those ≥ 75 years old. Furthermore, there is local geographic variation for all ages in the United Kingdom the highest prevalence is seen in men from Wales (9%) and women from Scotland (2.4%).

Similarly, in the USA, the prevalence of myocardial infarction was 3.6% in 2006 based upon national survey data available from the American Heart Association (Lloyd-Jones et al, 2009). The prevalence was slightly higher in African American males (5.1%) compared with Caucasian males (4.9%) but lower in African American (2.2%) females compared with their Caucasian counterparts (3%). As with the UK data, the prevalence of myocardial infarction was greater in the elderly compared with those < 50 years of age.

In contrast to these developed countries, South Asian countries (such as India, Pakistan, Bangladesh, Sri Lanka, and Nepal) the highest prevalence of myocardial infarction is seen in those younger than 40 years of age, whereas it is less marked in those older than 60 years. These observations are consistent with Stage 3 of the epidemiologic shift (Table 1) and reflect the development of risk factors at younger ages (Joshi et al, 2007).

### 3.3 Incidence of myocardial infarction

While the prevalence of myocardial infarction reflects both previous and new (acute) myocardial infarcts, the incidence of myocardial infarction only reflects the later. The incidence of AMI has decreased in a number of developed countries during the past three decades, including the UK and remains the lowest in China and Japanese populations. Age adjusted data has indicated that for men and women between the ages of 35-64 years there are only 90/100,000 new cases for AMI in China and 20/100,000 new cases in Japan (Ueshima et al, 2008).

The most recent estimates of incidence of AMI in the UK are based on national level data from associated hospital and/or mortality statistics and suggest that in Scotland the incidence of AMI has decreased by about 25% between 2000 and 2009 in both men and women. Thus considering all ages in Scotland in 2006, approximately 252/100,000 males were newly diagnosed MI cases and 118/100,000 females.

In relation to the clinical type of AMI, it has been estimated that more than 3 million suffer from STEMI and 4 million people suffer from NSTEMI worldwide each year (White & Chew,
2008). The 6-month mortality rate following infarction has been reported as 4.8% for STEMI and 6.2% for NSTEMI in an international registry involving 14 countries (Goldberg et al, 2004). Other studies have also shown an adverse prognosis for NSTEMI compared with STEMI patients at 12 months post-infarction (Terkelsen et al, 2005; Montalescot et al, 2007).

![Prevalence graph]

Adapted from the British Heart Foundation, 2010 report. Prevalence rates are weighted for non-response. Respondents were asked to recall whether they had ever been diagnosed with myocardial infarction by a doctor.

Fig. 5. Age specific prevalence of AMI in the United Kingdom, England, 2006

3.4 Factors influencing myocardial infarction

The prevalence and incidence of myocardial infarction can be influenced by demographic, biological and psychosocial factors, some of which are modifiable and thus potential therapeutic targets. These factors warrant further discussion.

3.4.1 Demographic factors

Acute myocardial infarction is rare in childhood and adolescent years but increases in prevalence in the middle decades, particularly in the developing countries. In developed countries it is increasingly becoming a disease of the elderly, which has important economic implications. For example, 70% of AMI admissions in Australia are for patient’s ≥ 65 years old. These patients often have a complicated course as they have existing co-morbidities that complicate the therapy of their AMI.

Considerable interest has evolved in gender differences in CAD and is the focus of another chapter within this book. Epidemiologic data concerning AMI amongst women is now being
revised as early data primarily focused on middle-aged males. It is well described that men experience myocardial infarction about 10 years younger than women (Figure 5) but in the post-menopausal years, women rapidly catch up to the men. Despite this, women have a larger in-hospital mortality from their AMI until about the age of 80 years when they are similar to men (Figure 6) (Vaccarino et al, 1999). Of particular concern is that the greatest disparity in this mortality is between young women and men (Figure 6). The cause for this gender difference is not apparent and the focus of ongoing investigations.

In addition to age and gender, geographic factors influence the incidence of AMI. These have been described above and are likely to be multifactorial in origin. Factors such as ethnicity, and following social economic class, industrialisation may all contribute to apparent geographic differences.

![Graph: Age & sex specific prevalence of AMI mortality](image)


Fig. 6. Age & sex specific prevalence of AMI mortality

### 3.4.2 Biological/lifestyle risk factors

The Framingham Heart Study was instrumental in establishing modifiable biological risk factors that were associated with AMI. A plethora of subsequent therapeutic studies have since demonstrated that modifying these risk factors can prevent AMI thereby confirming the importance of these risk factors and establishing the practice of preventative cardiology. These risk factors have since been incorporated into many risk scores for predicting the risk of AMI.

A potential limitation of the Framingham study is the select population studied; an east coast USA community. More recently a large multinational study has been conducted to evaluate the association between the conventional modifiable risk factors and AMI (Yusuf et al, 2004). The INTERHEART study recruited patients from 52 countries in a case-control study. They reported that the traditional risk factors described in the Framingham study
accounted for most of the risk of AMI, independent of the country (Yusuf et al, 2004). In particular, the risk of AMI increased with the following factors in descending order of their adjusted approximate odds ratio: dyslipidaemia (3.3-fold, as defined by apolipoprotein B/A1 ratio), smoking (2.9-fold), psychosocial factors (2.7-fold), diabetes (2.4-fold), hypertension (1.9-fold) and abdominal obesity (1.6-fold). Reduced exercise and daily fruit/vegetable intake also increased the risk. Figure 7 highlights the importance of these factors and in particular the exponential risks when these factors are combined.

The prevalence of these biological factors within the community varies with age and gender, as shown in Figure 8. In relation to smoking rates, the UK prevalence is around 20% with the prevalence having peaked for men and even begun to decline; however for women they continue to climb. In contrast, hypercholesterolaemia, hypertension and diabetes all remain prevalent (Figure 8). Whereas the prevalence of hypertension and diabetes increases with age, the prevalence of hypercholesterolaemia plateau’s/declines in the elderly.

### 3.4.3 Psychosocial factors

Both social and psychological factors are associated with AMI risk. Socioeconomic factors such as shorter education and lower income (particularly in women), and unmarried cohabitation have been shown to contribute towards the risk of AMI (Nyboe et al, 1989). In particular, socioeconomic status, work and home roles may play an important prognostic
role, particularly in young women (Lacey & Walters, 2003). Women often work outside the home, in addition to their roles within the household as wives, mothers and caregivers to elderly parents. There is also mounting evidence that age, gender, and social class affect health related quality of life (HRQoL) in the general population, with women reporting a poorer HRQoL than men, particularly following a cardiac event.

Depression is the leading cause of disability worldwide affecting more than 120 million people every year. It is known to be an independent risk factor for the onset and subsequent poor prognosis of CAD (Schrader et al, 2004; Schrader et al, 2006) and can be a precursor to AMI and even cardiac death. Following AMI, 65% of patients report experiencing symptoms of depression and major depression is present in 15-22% of these patients (Guck, 2001). Depressed patients, particularly women, are also at an increased risk of mortality, experience a greater likelihood of cardiac hospitalisation and suffer from poor HRQoL in the first year post AMI (Frasure-Smith et al, 1999).

Depression has a significant, negative impact on psychological and social functioning, as well as on work and leisure-related activities. Patients who are depressed are more likely to experience social problems over the first year of post-MI recovery, are slower in returning to work, experience more frequent episodes of angina, report more physical impairment and are less likely to attend cardiac rehabilitation than are non-depressed patients (Carney and Freedland, 2003).

### 3.5 Health status in myocardial infarction

Mortality associated with myocardial infarction is well described and reflected in the CAD mortality figures described in section 2. However the impact on this disorder also must be considered in relation to health status. In a recent study, Maddox et al (Maddox et al, 2008) reported that almost 1 in 5 patients with AMI experienced ongoing angina 12 months following an infarct. The clinical determinants of this ongoing chest pain included cardiac variables such as a prior history of angina, post-infarct angina during the index hospital admission and previous coronary bypass surgery. Additionally, non-cardiac variables such as younger age, female gender, continued smoking post-infarction, and depression were also important. Indeed depression is not only associated with ongoing symptoms following AMI but is also an important determinant of subsequent HRQoL (Rumsfeld et al, 2001).

### 3.6 Summary comments

The diagnostic methods and criteria for AMI have evolved in recent years so that more infarcts can be detected with the current technologies. This needs to be considered when interpreting data (especially longitudinal data) concerning myocardial infarction. Despite this, it is clear that AMI is a leading cause of morbidity and mortality worldwide and is responsible for over 12% of deaths each year, with a larger majority of the population suffering from NSTEMI than STEMI. The incidence of AMI has decreased in the industrialised world due to lifestyle changes and therapeutics; however, rates are rising in developing countries such as Asia, Eastern Europe and parts of Latin America. Although the prevalence of AMI is higher in men of all age groups, it is concerning and unexplained why the in-hospital myocardial infarct mortality is higher in women, particularly in the premenopausal era. The factors influencing the occurrence of myocardial infarction have
been well addressed over the past 4-5 decades however the management of factors that influence health status in patients with a recent myocardial infarct require further development.

Percentage of adults with blood cholesterol levels ≥ 5.0mmol/l.

Fig. 8A. Prevalence of major biological risk factors by age and sex, in England in 2008.

Hypertension - blood pressure > 140/80.

Fig. 8B. Prevalence of major biological risk factors by age and sex, in England in 2008.
Diabetes mellitus – both Type I and II. Source a, b & c - British Heart Foundation 2010 report.
Fig. 8C. Prevalence of major biological risk factors by age and sex, in England in 2008.

4. Chronic stable angina

4.1 Defining chronic stable angina

The evaluation of epidemiologic data concerning chronic stable angina is more challenging than assessing CAD mortality or myocardial infarction data. Unlike these other conditions, the diagnosis of chronic stable angina is largely based upon clinical criteria and can only be objectively assessed with specialised investigations such as invasive coronary angiography. As these techniques may not be performed in all individuals with chest pain or angina, the background frequency of the disease is difficult to quantitate. Accordingly, interpretation of data concerning chronic stable angina must be made in the context of the data collected, which may be merely on clinical impression in many studies. This limitation should be considered when reviewing this data.

There exists a certain ambiguity in defining the term ‘angina pectoris’ which has arisen from its use to describe a group of clinical disorders rather than a symptom. First clinical characterised by William Heberden in his 1772 publication entitled ‘Some account of a disorder of the breast’ (Heberden, 1772), it refers to a strangling sensation, which usually occurs on exertion, however patients may experience angina without physical activity whereupon it is referred to as rest angina (Maseri, 1995).

In contemporary medicine, ‘angina’ may be used in a more generic context, referring to any coronary heart disease syndrome that results in myocardial ischaemia. These angina syndromes may have different coronary pathophysiological mechanisms responsible for initiating the myocardial ischaemia, including coronary artery spasm and microvascular dysfunction. They may manifest as exertional or rest angina, depending upon the underlying mechanism. The clinical angina syndromes are summarised in Table 3 below.
<table>
<thead>
<tr>
<th>Angina Syndrome</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable Angina</td>
<td>• Characterised by crescendo or rest angina</td>
</tr>
<tr>
<td></td>
<td>• An acute coronary syndrome manifestation (may progress on to myocardial infarction)</td>
</tr>
<tr>
<td></td>
<td>• Typically due to an unstable atherosclerotic plaque</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>• Characterised by exertional angina</td>
</tr>
<tr>
<td></td>
<td>• Typically due to a stable but tight obstructive coronary artery stenosis</td>
</tr>
<tr>
<td>Prinzmetal Variant Angina</td>
<td>• Characterised by rest or nocturnal angina</td>
</tr>
<tr>
<td></td>
<td>• Typically due to coronary artery spasm</td>
</tr>
<tr>
<td>Decubitus Angina</td>
<td>• Characterised by angina when lying down</td>
</tr>
<tr>
<td></td>
<td>• Typically due to left ventricular dysfunction resulting in redistribution of pulmonary fluids and thus increased cardiac workload.</td>
</tr>
<tr>
<td>Silent Ischaemia</td>
<td>• Absence of angina in the presence of documented ischaemia</td>
</tr>
<tr>
<td></td>
<td>• May occur with coronary artery or microvascular dysfunction</td>
</tr>
<tr>
<td>&quot;Syndrome X&quot;</td>
<td>• Includes classical syndrome X, microvascular angina, coronary slow flow phenomenon</td>
</tr>
<tr>
<td></td>
<td>• Characterised by prolonged episodes of exertional or rest angina</td>
</tr>
<tr>
<td></td>
<td>• Typically due to coronary microvascular dysfunction</td>
</tr>
</tbody>
</table>

Table 3. Types of Angina. Source British Heart Foundation, Coronary Heart Disease Statistics, 2010

Despite these diverse implications for the term ‘angina’, it is most commonly used to refer to patients with chronic stable angina. Although the initial description of exertional angina by Heberden still holds true today, a more operational version has been detailed by the American College of Physicians (Diamond, 1983). As summarised in Table 4, this definition describes angina as either ‘typical’ or ‘atypical’ on the basis of how many of the clinical features are consistent with exertional angina. In those patients with features of typical angina, the sensitivity and specificity for detecting significant coronary artery disease on angiography is respectively 91% and 87% in males, and correspondingly 89% and 63% in females (Detry et al, 1977).

<table>
<thead>
<tr>
<th>Chest Pain Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Substernal chest discomfort – characteristic quality (tightness) &amp; duration (minutes)</td>
</tr>
<tr>
<td>2. Provoking Factors – exertion or emotional stress</td>
</tr>
<tr>
<td>3. Relieving Factors – rest or sublingual nitrates</td>
</tr>
<tr>
<td>ACP Classification:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Table 4. American College of Physicians (ACP) Angina Pectoris Definition
In this section, the data presented concerning ‘angina’ will predominantly focus on patients with chronic stable angina. It will concentrate on the prevalence, incidence, clinical profile, associated morbidity and mortality with this condition. Although the clinical features of the other forms of angina have been alluded to, their epidemiological aspects are less clearly described and unfortunately there are no studies that directly compare the prevalence or incidence of the various forms of angina.

4.2 Prevalence of chronic stable angina

Despite the declining incidence of myocardial infarction, the prevalence of angina remains high with direct costs in the United States in 2000 estimated at over $75 billion (Javitz et al, 2004). Although the exact prevalence of stable angina is unclear, in the UK in 2009, it is estimated that 2.1 million people suffered from angina thus representing a prevalence of approximately 5% of men and 4% of women (BHF, 2010). Coronary heart disease accounts for 1 in 4 deaths in the UK and the lifetime risk for those over 40 years is 49% in men and 32% in women.

Similarly, in the United States, approximately 10.2 million Americans were reported to have angina in 2006 with 4.7% of Caucasian men and 4.5% of Caucasian women over the age of 20 years affected (Lloyd-Jones et al, 2010). These data are primarily based upon patient self-report of a history of angina and thus subject to limited validity.

Although the prevalence of angina in the UK and USA are similar, it is affected by age, gender, ethnicity, and geographic region. As shown in (Figure 9), within the UK, the prevalence is almost 17% amongst males and 12% in females over the age of 75 years but is less than 1% of all those under 45 years of age. Furthermore for all ages, the prevalence of angina in men from Northern Ireland is approximately 6% whereas amongst Welshman it is 4% (BHF, 2010). Ethnic differences in angina occurrence are well illustrated in the United States where the prevalence in men over the age of 20 years is 3.8% in Caucasians, 3.3% in African Americans, and 3.6% in the Hispanic population. The equivalent prevalence amongst females is 3.7%, 5.6% and 3.7%.

4.3 Incidence of chronic stable angina

Based upon surveying general practitioner patient case records, the incidence of newly diagnosed angina in the UK was estimated at 28,000 new cases in 2009 (BHF, 2010). Thus overall, approximately 49/100,000 males were newly diagnosed angina cases and 28/100,000 females. Figure 10 illustrates the age-specific incidence of angina.

4.4 Factors influencing chronic angina

Several large prospective epidemiological studies have provided important insights into the characteristics of patients with chronic stable angina. One of these was the Coronary Artery Disease in gEneral practICE (CADENCE) study (Beltrame et al, 2009), which recruited 2,031 chronic stable angina patients from general practices across Australia. The sample was representative of this population based upon geographic location. It particularly focussed upon continuing angina symptoms in these patients and surprisingly found that almost 1 in 3 continued to experience angina at least once a week, despite contemporary therapies. This
Source British Heart Foundation, Coronary Heart Disease Statistics, 2010

Fig. 9. Age-specific Prevalence of Angina in the United Kingdom in 2009.

Source British Heart Foundation, Coronary Heart Disease Statistics, 2010

Fig. 10. Age-specific Incidence of Angina in the United Kingdom in 2009.
was similar to that reported in United States (Wiest et al, 2004) and in an international multicentre study (Kirwan et al, 2008).

The clinical characteristics of the chronic stable angina population in the CADENCE study, is summarised in Table 5. As would expected, these are predominantly elderly males with many having conventional cardiovascular risk factors. Their angina symptoms were consistent with ACP defined angina in 72% of the patients. Most had experienced an episode of ACS at some stage of their chronic illness with almost half having experienced an acute myocardial infarction.

Importantly, this study reported that gender or the presence of heart failure or peripheral arterial disease, were independent clinical determinants of ongoing weekly angina in patients with chronic stable angina (Beltrame et al, 2009).

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary Artery Disease Risk Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>71 ± 11 years</td>
</tr>
<tr>
<td>Male gender</td>
<td>64%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>78%</td>
</tr>
<tr>
<td>Previous or current smoker</td>
<td>59%</td>
</tr>
<tr>
<td>Obesity (BMI and/or waist circumference)</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Associated Cardiovascular Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Previous acute coronary syndrome</td>
<td>70%</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>22%</td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>17%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Angina Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Substernal chest discomfort</td>
<td>93%</td>
</tr>
<tr>
<td>Pain provoked by exertion</td>
<td>73%</td>
</tr>
<tr>
<td>Pain provoked by emotional stress</td>
<td>26%</td>
</tr>
<tr>
<td>Pain relieved by rest</td>
<td>54%</td>
</tr>
<tr>
<td>Pain relieved by sublingual nitrates</td>
<td>51%</td>
</tr>
</tbody>
</table>

Table 5. Clinical Characteristics in Stable Angina Patients. Data from (Beltrame, Weekes et al. 2009).

4.4.1 Gender

In a gender sub-analysis of the CADENCE study, significant gender disparities in coronary risk factors, clinical features, diagnostic investigations and management were observed as well as differences in angina-related health outcomes (Dreyer et al, 2011). Although women had more frequent angina which was associated with greater physical impairment and a poorer quality of life, they were less extensively investigated, prescribed fewer cardio-protective agents, less likely to achieve guideline lipid or weight targets and were less likely to receive
any specialist cardiology review (Figure 11). The predilection for women having more frequent angina is likely to be multi-factorial and may include biological, clinical presentation and assessment differences between genders (Bairey Merz et al, 2006). For example, women may have smaller coronary arteries that are less amenable to revascularisation therapies. Furthermore, coronary microvascular dysfunction is more prevalent in women and angina resulting from this is less responsive to conventional anti-anginals.

![Clinical Management Diagram](https://www.intechopen.com)

Fig. 11. Gender comparisons in the clinical management of stable angina patients. Age adjusted frequency data for (a) cardiology review, (b) pharmacological therapy and (c) revascularisation therapy, in 2005 stable angina patients categorised by gender. (male vs. female: *p < 0.05, **p < 0.01, ***p < 0.001). Data from Dreyer et al (2011). Copyright permission gained Elsevier 30/09/2011

### 4.4.2 Co-morbidities

As shown in Table 5, many chronic stable angina patients have a history of a previous MI and their cardiac prognosis will be influenced by this event. In chronic stable angina patients who have not previously experienced a myocardial infarct, the risk of myocardial infarct or all-cause death has been described as 1.7%/year and 1.9%/year, respectively (Lampe et al, 2000).

Co-existing heart failure and/or peripheral arterial disease have been shown to be important determinants of on-going angina symptoms in patients with chronic stable angina (Beltrame et al, 2009). This potentially reflects the more extensive disease in these patients. Certainly, patients with chronic stable angina and co-existing peripheral arterial disease were more physically limited and a poorer quality of life than those without co-existing peripheral arterial disease (Wilson et al, 2011).
4.5 Impact of chronic stable angina on health status

The CADENCE study not only demonstrated that many patients with chronic stable angina have frequent ongoing symptoms but also that frequent angina is associated with reduced physical limitations and a poorer quality of life (Beltrame et al, 2009). Although the CADENCE study utilised a threshold of angina of at least once week, the relationship is a continuum as shown in Figure 12. Thus the more frequent the angina, the greater the impairment in physical limitation and quality of life. Hence enquiring about angina frequency may provide useful clinical insights into the impact of the disorder on the patient’s quality of life.

While enquiring about the frequency of angina provides some insights into the disability associated with the disorder, it does not replace a detailed history and evaluation identifying the full impact of the condition on the patient. Unfortunately clinicians may not be completely aware of the angina burden experienced by their patients as alluded to in the CADENCE study. In this study, the clinicians reported that 80% of their patients had optimally controlled angina and that 61% had minimal impairment in their physical activity by the angina. In contrast, patient questionnaires demonstrated that only 52% of patients reported being angina-free and only 47% described their angina as not limiting their enjoyment in life. Hence further efforts are required to bridge this gap between the patient’s experience and the clinician’s perception of the disability associated with angina.

![Frequency of Anginal Episodes](image)

**SAQ = Seattle Angina Questionnaire. Adapted from (Beltrame et al, 2009). Copyright gained 30/09/2011.**

**Fig. 12. Relationship between Angina Frequency and Patient-assessed Quality of Life Indices.**

4.6 Summary comments

Although data concerning the epidemiology of chronic stable angina must be interpreted with caution considering the objectivity of the data source, substantial information is available primarily based upon patient self-report and general practitioner clinic surveys. In developed countries, the estimated prevalence of stable angina is 4-5% and the incidence of new cases approximately 46/100,000 population. The chronic nature of this condition results
in significant impairment in patient health status with a recent study reporting that almost a third of patients have angina once a week. Since there is an inverse relationship between symptom frequency and its related physical limitation and quality of life, these patients have substantial health status impairment that warrants more attention.

5. Key facts in the epidemiology of coronary artery disease

Coronary artery disease (CAD) is the global leading cause of death and may manifest clinically as an acute coronary syndrome such as AMI, or a chronic coronary syndrome such as chronic stable angina.

Concerning CAD Mortality:
- It is estimated that 7.2 million people died world-wide in 2004 from CAD (i.e. approximately 12% of all deaths).
- In developing countries the CAD mortality is rising but in developed countries it has been falling since the 1960’s.
- CAD mortality varies with age, gender, geographic region, socioeconomic status and depression.

Concerning Myocardial Infarction:
- The prevalence of myocardial infarction within developed countries is approximately 3-4%.
- The incidence of new myocardial infarction within developed countries is approximately 200/100,000 population.
- Factors influencing the frequency of myocardial infarction within the community include (a) demographic – age, gender, (b) lifestyle/biological – lipid profile, smoking status, blood pressure, diabetic status, obesity, fruit/vegetable intake, alcohol consumption, and (c) psychosocial factors.
- Approximately 1 in 5 patients continue to experience angina 12 months following an AMI. The frequency of these ongoing symptoms is not only influenced by cardiac factors (such as a pre-infarction history of angina) but also non-cardiac factors such as age, gender and depression.

Concerning Chronic Stable Angina:
- The prevalence of chronic stable angina within developed countries is approximately 4-5%.
- The incidence of newly diagnosed angina within developed countries is approximately 46/100,000 population.
- Factors that influence the frequency of angina symptoms in patients with chronic stable angina include female gender and co-existing heart failure or peripheral arterial disease.
- Despite contemporary therapies in developed countries, almost 1 in 3 patients with chronic stable angina continue to experience angina at least once a week. Since angina frequency is inversely related to physical limitation and quality of life, these patients have a considerably impaired health status.
6. Appendix: definitions

ANGINA PECTORIS – a strangling sensation in the chest resulting from myocardial ischaemia.

CORONARY HEART DISEASE – a group of clinical disorders involving coronary circulatory dysfunction resulting in impaired coronary blood flow and thus myocardial ischaemia. This includes coronary atherosclerosis, coronary artery spasm and/or microvascular dysfunction.

CRESCEMDO ANGINA – angina pectoris that is occurring more frequently or with greater intensity, or with less provocation. It is a form of unstable angina.

EXERTIONAL ANGINA – angina pectoris precipitated by exertion.

INCIDENCE – the number of new episodes of a disorder over a period of time (eg new myocardial infarcts in 2007)

MIXED PATTERN ANGINA – angina pectoris occurring during exertion but also on occasions at rest.

MYOCARDIAL INFARCT – a pathological condition where inadequate coronary blood flow results in myocardial necrosis.

MYOCARDIAL ISCHAEMIA – a pathological condition where an insufficient coronary blood flow results in inadequate oxygen supply and the accumulation of wastes products in the myocardium.

PREVALENCE – the number of patients with the disorder at any particular time (eg patients with a myocardial infarct in Britain).

REST ANGINA – angina pectoris occurring at rest.

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Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment
Edited by Dr. David Gaze

Hard cover, 272 pages
Publisher InTech
Published online 16, March, 2012
Published in print edition March, 2012

Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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Appendix 5: VIRGO Australia Newsletters
NOTE:
This appendix is included on pages 334-359 of the print copy of the thesis held in the University of Adelaide Library.
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