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

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“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:..........................................

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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 21/1/13

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 18/1/13
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.

4. **Dreyer R.,** Van Zitteren, M. Beltrame, J. Fitridge, R. Denollet, J.Vriens, P. Spertus, JA & Smolderen, K. Gender Differences in Health Status of Patients with Peripheral Artery Disease. Quality of Care and Outcomes in Cardiovascular Disease and Stroke (QCOR) Conference, Atlanta, Georgia USA. **Poster presentation.** May 2012.


Awards and Honours Received over Course of Doctorate

PRIZES

2012  First prize for the TQEH “Clinical Higher Degrees Research” Oral Presentation
2011  First prize for best poster presentation, Health Science Post Graduate Conference
2010  First Prize for the TQEH “Clinical Higher Degrees and Registrars” Oral Presentation

AWARDS

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

HONOURS

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

EXTRA CURRICULAR ACTIVITIES

2012  Awarded Certificate IV in telephone counseling, Lifeline Australia
2012  Participated in the 100km fundraising bike ride for the ‘Go the Distance’ campaign
2012  Official Ambassador for the National Heart Foundation’s ‘Go the Distance’ Campaign
2011  Highest fundraising award for the NHF ‘Go Red for Women’ campaign, 50km bike ride
2011  Early Career Researcher group member, National Heart Foundation
2011  Lifeline Australia Training Supervisor
2009  National Heart Foundation ‘Go Red for Women’ Active Volunteer
2009  Lifeline Australia telephone counselor
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 PORTAIT 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 PORTAIT 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>Full Form</th>
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<tbody>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
</tr>
<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>
</tr>
<tr>
<td>UA</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>CSA</td>
<td>Chronic stable angina</td>
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<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<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>
</tr>
<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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<td>HRQOL</td>
<td>Health related quality of life</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>CK</td>
<td>Creatine Kinase</td>
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<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<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>
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<tr>
<td>RSC</td>
<td>Reynolds risk score</td>
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<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>
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<tr>
<td>MACE</td>
<td>Major adverse cardiac event</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>TVR</td>
<td>Target vessel revascularisation</td>
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<tr>
<td>ARS</td>
<td>Angiographic restenosis</td>
</tr>
<tr>
<td>DES</td>
<td>Drug Eluting stent</td>
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<tr>
<td>BMS</td>
<td>Bare metal stent</td>
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<tr>
<td>PTD</td>
<td>Pain-to-Door</td>
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<td>DT-ECG</td>
<td>Door-to-ECG</td>
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<td>Abbreviation</td>
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<tr>
<td>DTC</td>
<td>Door-to-Code</td>
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<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>
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Preface

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).