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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Discipline of Medicine

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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

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***Dreyer R**, Arstall M, Tavella R, Weekes A, Morgan C, Beltrame J. Gender Differences in Patients with Stable Angina attending Primary Care Practices. Heart, Lung and Circulation 2011; 20:452–459.

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 Kaplin 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...Jan 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.....15/1/2013.....

Publications and Presentations Derived from this Thesis

Refereed Journal Articles & Book Chapters

1. **Dreyer R**, Arstall M, Tavella R, Weekes A, Morgan C, Beltrame J. Gender Differences in Patients with Stable Angina attending Primary Care Practices. Heart, Lung and Circulation 2011; 20:452–459.

2. Beltrame J, **Dreyer R,** and Tavella R. (2012). Epidemiology of Coronary Artery Disease, Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment, Dr. David Gaze (Ed.), ISBN: 978-953-51-0262-5, InTech, Available from: http://www.intechopen.com/books/coronary-artery-disease-current-concepts-in-epidemiology-pathophysiology-diagnostics-and-treatment/epidemiology-of-coronary-artery-disease

3. **Dreyer, R.** Beltrame, J. Air, T. Tavella, R. Hoffmann, B. Pati, P. Di Fiore, D. Arstall, M and Zeitz, C. Evaluation of Gender Differences in Door-to-Balloon Time in ST-Elevation Myocardial Infarction *(Submitted, Circulation: Cardiovascular Quality and Outcomes)*.

4. **Dreyer, R**. Beltrame, J. Neil, C. Air, T. Tavella, R. Hoffmann, B. Pati, P. Di Fiore, D. Arstall, M and Zeitz, C. Sex Differences in Cardiac Haemodynamics during Acute ST-Elevation Myocardial Infarction *(Submitted, Circulation: Cardiovascular Quality and Outcomes)*.

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

1. **Dreyer R,** Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. Do Cardiac Haemodynamic Differences in Patients with Acute ST-Elevation Myocardial Infarction Contribute to Gender Differences in Outcomes? Circulation: Cardiovascular Quality and Outcomes 2011; 108: P202.

2. **Dreyer R,** Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. Women Experience significant time delays when presenting with Myocardial infarction. Circulation: Cardiovascular Quality and Outcomes 2011; 132: P256.

3. **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. Circulation: Cardiovascular Quality and Outcomes 2012; 5: A250.

Conference Proceedings: International

1. **Dreyer R,** Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. "Women Experience significant time delays when presenting with Myocardial infarction". Quality of Care and Outcomes in Cardiovascular Disease and Stroke (QCOR) Conference, Washington D.C, USA. **Poster presentation**. May 2011.

2. **Dreyer R,** Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. "Do Cardiac Hemodynamic Differences in Patients with Acute ST-Elevation Myocardial Infarction Contribute to Gender Differences in Outcomes?" Quality of Care and Outcomes in Cardiovascular Disease and Stroke (QCOR) Conference, Washington D.C, USA. **Poster presentation**. May 2011.

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.

Conference Proceedings: Local

1. **Dreyer R.** "Cardiovascular Disease and Depression: Understanding the Links". Basil Hetzel Institute (BHI) Cardiology Lab Meeting, Discipline of Medicine, The University of Adelaide. **Oral presentation**. May 2009.

2. **Dreyer R.** "Gender Disparities in Cardiovascular Disease". Medical Grand Round Lecture, The Lyell McEwin Hospital, Adelaide, Australia. **Invited speaker**. June 2009.

3. **Dreyer R**, Arstall M, Tavella R, Weekes A, Morgan C, Beltrame J. "Do Men and Women with Chronic Stable Angina have similar Clinical characteristics and Treatments?" The Queen Elizabeth Hospital (TQEH) Annual Research Day, Adelaide, Australia. **Poster presentation**. October 2009.

4. **Dreyer R**, Arstall M, Tavella R, Weekes A, Morgan C, Beltrame J. "Gender Differences in Patients with Stable Angina attending Primary Care Practices". South Australian Cardiovascular Research Forum, Adelaide, Australia. **Poster presentation**. April 2010.

5. **Dreyer R**, Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. "Gender Differencs in Patients with ST-Elevation Myocardial Infarction (STEMI) Outcomes". The Queen Elizabeth Hospital (TQEH) Annual Research Day, Adelaide, Australia. **Invited seminar.** October 2010.

6. **Dreyer R**, Tavella R, Schrader G, Beltrame J. "Health Status in Depressed Patients following Acute Myocardial Infarction". National Heart Foundation Conference, Melbourne, Australia. **Moderated Poster**. March 2011.

7. **Dreyer R**, Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. "Do Haemodynamics in Patients with Acute Anterior and Non-Anterior ST-Elevation Myocardial Infarction (STEMI) Explain Gender Differences in Outcome?". National Heart Foundation Conference, Melbourne, Australia. **Poster presentation**. March 2011.

8. **Dreyer R**, Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. "Possible Mechanisms for Gender Differences in ST-Elevation Myocardial Infarction (STEMI) Outcomes". National Heart Foundation Conference, Melbourne, Australia. **Invited Plenary Lecture speaker**. March 2011.

9. **Dreyer R**. "Gender Differences in Acute Myocardial Infarction". National Heart Foundation, Heart Week Health Professionals Forum, Adelaide, Australia. **Invited guest speaker**. May 2011.

10. **Dreyer R**. "Gender Disparities in Cardiovascular Disease". National Heart Foundation Early Career Researcher Forum, Adelaide, Australia. **Invited guest speaker**. May 2011.

11. **Dreyer R**. "Gender Differences in ST-Elevation Myocardial Infarction: An Australian Experience". Cardiology lab meeting, Adelaide, Australia. **Invited guest speaker**. June 2011.

12. **Dreyer R,** Tavella R, Hoffmann B, Pati P, Beltrame J, Arstall M, Zeitz C. "Women Experience Significant Treatment Delays when Presenting with Acute Myocardial Infarction". Health Science Post graduate Research Conference, Adelaide, Australia. **Poster presentation.** August 2011

13. **Dreyer R.** "Gender Differences in Acute Myocardial Infarction". South Australian Cardiovascular Health Network Conference, Adelaide, Australia. **Invited guest speaker**. September 2011.

14. **Dreyer R**. "Sex Differences in Cardiac Haemodynamics during Acute ST-Elevation Myocardial Infarction (STEMI)". The Queen Elizabeth Hospital Research Day, Adelaide, Australia. **Invited guest speaker**. October 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 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

CVD	Cardiovascular Disease
CHD	Coronary Heart Disease
IHD	Ischaemic Heart Disease
CVB	Cerebrovascular Disease
PAD	Peripheral artery Disease
AMI	Acute Myocardial infarction
UA	Unstable angina
CSA	Chronic stable angina
ACS	Acute coronary syndrome
STEMI	ST-Elevation myocardial infarction
NSTEMI	Non-ST-Elevation myocardial infarction
TIA	Transient Ischaemic attack
IC	Intermittent Claudication
CLI	Critical Limb Ischaemia
ABI	Ankle Brachial Index
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting
MCD	Microvascular Coronary Dysfunction
SES	Socio-economic Status
US	United States
HRT	Hormone replacement therapy
PCOS	Polycystic ovarian syndrome
WHO	World Health Organisation
HRQOL	Health related quality of life

CK	Creatine Kinase
LDL	Low density lipoprotein
HDL	High density lipoprotein
FHS	Framingham Heart Study
FRS	Framingham risk score
RSC	Reynolds risk score
CDM	Clinical Data Management
GCP	Good clinical practice
CADENCE	Coronary Artery Disease in General Practice
CCSC	Canadian Cardiovascular Society Classification
NYHA	New York Heart Association Assessment
AHA	American Heart Association
ACC	American College of Cardiology
ESC	European Society of Cardiology
CCU	Coronary care unit
COPD	Chronic Obstructive Airways Disease
MACE	Major adverse cardiac event
ECG	Electrocardiogram
LOS	Length of stay
TVR	Target vessel revascularisation
ARS	Angiographic restenosis
DES	Drug Eluting stent
BMS	Bare metal stent
PTD	Pain-to-Door
DT-ECG	Door-to-ECG

DTC	Door-to-Code
CTL	Code-to-Lab
LTB	Lab-to-Balloon
CTB	Code-to-Balloon
DTB	Door-to-Balloon
DTN	Door-to-Needle
HR	Heart rate
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MSS	Mental Summary score
PSS	Physical Summary Score
SF-12	Short form-12
HADS	Hospital Anxiety and Depression Scale
SAQ	Seattle Angina Questionnaire
SPSS	Statistical Package for the Social Sciences
TIMI	Thrombolysis in Myocardial infarction (TIMI Frame Count)
WISE	Women's Ischaemia Syndrome Evaluation Study
NHLBI	National Heart lung and Blood Institute

Preface

Historically, women's health has focused on breast cancer and menopause, leading women to believe that Heart disease is a 'man's disorder'[1] and therefore not an important health concern. This lack of education has resulted in many women not being appropriately informed of their cardiovascular risks[2] and consequently in health care providers underestimating this threat as compared with men[3]. 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[4]. 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).