Readmissions in Australian Patients with Cardiovascular Disease

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“There is no part of my life, upon which I can look back without pain”.

“I attribute my success to this – I never gave or took any excuse”.

- Florence Nightingale.

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Abstract

Background and objectives:

The overall objective of this thesis is to investigate readmissions in Australian hospitals in patients previously admitted with heart failure (HF) or an acute myocardial infarction (AMI).

The **specific aims** of this thesis are:

1. To conduct a scoping review of the contemporary Australian literature regarding readmissions with an index admission of any cardiovascular disease (CVD).
2. To determine the rates of readmission and mortality in Australian and New Zealand HF patients between 2010-15.
3. To determine the accuracy of the LACE index score (a prediction tool) for predicting 30-day all-cause mortality and readmission rates (independently and combined) in South Australian AMI patients who had an angiogram between 2015-6.
4. To conduct a pilot clinical study to determine whether an association exists between a) the quantity and b) the quality of sleep time in hospital and 30-day all-cause unplanned readmission in a South Australian cohort of cardiovascular inpatients.

Methods:

The thesis employs multiple methodological approaches including a scoping review (Chapter II), 'big data' techniques (Chapter III), registry data analysis (Chapter IV) and a prospective clinical observational cohort study (Chapter V).

Summary of major findings:

Chapter II: The scoping review of contemporary Australian literature found limited literature on the topic of readmissions following hospitalisation for a CVD or condition. Furthermore, it

found that the methods used in prior studies lacked uniformity and standardisation which was reflected in the large range of readmission rates observed (from 6.3% to 27%, median 13%).

Chapter III: The hospital-level analysis of administrative data found that Australian and New Zealand HF inpatients had a 30-day all-cause mortality rate of 10.7% across 392 hospitals and a 30-day all-cause readmission rate of 22.3% across 391 hospitals. Additionally, readmission rates remained stable whilst an overall improvement in the mortality rates were seen over the study period.

Chapter IV: Analysis of registry patients found a 30-day unplanned readmission rate of 11.8% and mortality rate of 0.7%. Moreover, the LACE index was a moderate predictor (C-statistic=0.62) of readmissions in this cohort and a score ≥10 indicated moderate discriminatory capacity to predict 30-day readmissions. The two variables with the best predictive variables were length of stay and admissions to the emergency department in the prior six months.

Chapter V: The clinical study found an association between the quality of sleep in hospital and 30-day all-cause unplanned readmissions as measured by the Pittsburgh Sleep Quality Index. This study also found trends but no statistically significant association between any objective measure of sleep quantity and 30-day all-cause unplanned readmissions.

Conclusions

This thesis has contributed to the literature by determining the rate of readmission in HF patients, incorporating predictive models into medicine and exploring a hypothesised variable (disrupted sleep) in clinical practice to help reduce the burden of readmissions. It supports the importance of measuring 30-day all-cause unplanned readmissions as an objective, broad, generic measure of hospital care quality and safety, and promotes efforts to improve this outcome.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Signed: Dated: 21/06/2019

Clementine Labrosciano.

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Abbreviations

ACA = Affordable Care Act

ACC = American College of Cardiology

ACE = Angiotensin Converting Enzyme

ACS = Acute Coronary Syndrome

ABS = Australian Bureau of Statistics

AICD = Automatic Implantable Cardiac Defibrillator

AIHW = Australian Institute of Health and Welfare

AHA = American Heart Association

AHRQ = Agency for Health care Research and Quality

AMI = Acute Myocardial Infarction

AUC = Area Under the Curve

BMS = Bare Metal Stent

BP = Blood Pressure

CABG = Coronary Artery Bypass Graft

CAD = Coronary Artery Disease

CADOSA = Coronary Angiogram Database Of South Australia

CC = Condition Category

CHD = Coronary Heart Disease

CK-MB = Creatinine Kinase-Myoglobin Binding

CMS = Centre for Medicare and Medicaid Services

CRT = Cardiac Resynchronisation Therapy

CVD = Cardiovascular Disease

DES = Drug Eluding Stent

ECG = Electrocardiogram

ED = Emergency Department

EF = Ejection Fraction

EQ-5D-3L = Euro Quality of life questionnaire – 5 Dimensions – 3 Levels

ESC = European Society of Cardiology

ESS = Epworth Sleepiness Scale

GRACE = Global Registry of Acute Coronary Events

GTN = Glyceryl TriNitrate

HF = Heart Failure

HGLM = Hierarchical Generalised Linear Model

HFmrEF = Heart Failure with midrange Ejection Fraction

HFpEF = Heart Failure with preserved Ejection Fraction

HFrEF = Heart Failure with reduced Ejection Fraction

HR = Hazard Ratio

HRRP = Hospital Readmissions Reduction Program

ICC = Intraclass Correlation Coefficient

ICD = International Classification of Diseases

LVEF = Left Ventricular Ejection Fraction

STEMI = ST-segment Elevated Myocardial Infarction

STOP BANG = Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference and Gender

NREM = Non-Rapid Eye Movement

NSTEACS = Non-ST-segment-elevation acute coronary syndrome

NSTEMI = Non-ST segment Elevated Myocardial Infarction

NYHA = New York Heart Association

OSA = Obstructive Sleep Apnea

PCI = Percutaneous Coronary Intervention

PSG = Polysomnography

PSQI = Pittsburgh Sleep Quality Index

REM = Rapid Eye Movement

ROC = Receiver Operating Characteristic

RSMR = Risk Standardised Mortality Rate

RSRR = Risk Standardised Readmission Rate

TST = Total Sleep Time

WHO = World Health Organization

Achievements and Recognition

Published Manuscript from this Thesis

Labrosciano C, Air T, Beltrame JF, Tavella R and Ranasinghe I. (2019) Readmissions following hospitalisations for cardiovascular disease: a scoping review of the Australian literature". *Australian Health Review*. DOI:10.1071/AH18028.

Other Published Manuscripts During the Candidature

Smolderen KG, Gosch K, Patel M, Jones S, Hirsch AT, Beltrame JF, Fitridge R, Shishehbor M, Denollet J, Vriens P, Heyligers J, Stone N, Aronow H, Abbott D, **Labrosciano C**, Tutein-Nolthenius R and Spertus J. (2018) Patient-centered Outcomes Related to Treatment practices in peripheral Arterial disease: Investigating Trajectories (PORTRAIT): Overview of Design and Rationale of an International Prospective Peripheral Arterial Disease Study. *Circulation: Cardiovascular Quality and Outcomes.* DOI: 10.1161/CIRCOUTCOMES.117.003860

Moore K, Ganesan A, **Labrosciano C**, Heddle W, McGavigan A, Hossain S, Horton D, Hariharaputhiran S and Ranasinghe I. (2019) Sex Differences in Acute Complications of Cardiac Implantable Electronic Devices (CIED): Implications for Patient Safety. *Journal of the American Heart Association*. Volume 8, Issue 2. DOI: 10.1161/JAHA. 118.010869

Ranasinghe I, **Labrosciano C**, Horton D, Ganesan A, Curtis JP, Krumholz HM, McGavigan A, Hossain S, Air T and Hariharaputhiran S. (2019) Institutional Variation in Quality of Cardiovascular Implantable Electronic Device Implantation: A Cohort Study. *Annals of Internal Medicine.* DOI: 10.7326/m18-2810 10.7326/m18-2810

Submitted Manuscripts

Thomas M, Patel KK, Gosch K, **Labrosciano C**, Spertus JA and Smolderen KG. (2019) Mental Health Concerns in Patients with Symptomatic Peripheral Artery Disease: Insights from the PORTRAIT Registry. Submitted to *Journal of General Internal Medicine.*

Labrosciano C, Tavella R, Reynolds A, Air T, Beltrame JF, Ranasinghe I and Adams RJT. (2019) The Association between Sleep Quality and Quantity with Readmissions: An Exploratory Study among Cardiology Inpatients. *Submitted to the Journal of Clinical Sleep Medicine.*

Labrosciano C, Horton D, Air T, Tavella R, Beltrame JF, Zeitz CJ, Krumholz HM, Adams RJT, Scott IA, Gallagher M, Hossain S, Hariharaputhiran S and Ranasinghe I. (2019) Frequency, Trends and Institutional Variation in 30-Day All-Cause Mortality and Unplanned Readmissions Following Hospitalization for Heart Failure in Australia and New Zealand. *Submitted to JAMA Cardiology.*

Published Abstracts from this Thesis

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Labrosciano C*, Air T, Tavella R, Beltrame JF, Zeitz C, Horton D and Ranasinghe I. (2017) Rates of 30-Day Readmission and Mortality After Heart Failure Hospitalisation in Australia and New Zealand: A Population Study. *Heart, Lung and Circulation*, Volume 26, S145 - S146.

Labrosciano C*, Air T, Tavella R, Beltrame JF and Ranasinghe I. (2017) Readmissions After Hospitalisation for Cardiovascular disease in Australia and New Zealand. *Heart, Lung and Circulation*, Volume 26, S300.

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Labrosciano C*, Air T, Tavella R, Beltrame JF and Ranasinghe I. (2017) Readmissions After Hospitalisation for Cardiovascular disease in Australia and New Zealand. *Heart, Lung and Circulation,* Volume 26, S300.

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Labrosciano, C*, Cowled P, Fitridge R and Beltrame J. (2016) Does a Relationship Between Ankle Brachial Index and Health Status in Patients With Peripheral Artery Disease Exist? A Pilot Study. *Heart, Lung and Circulation*, Volume 25, S318. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017, poster.*

Ranasinghe I*, Horton D, **Labrosciano C,** Air T, Beltrame JF, Zeitz C and Tavella R. (2017) Early Mortality after Isolated Coronary Artery Bypass Graft (CABG) Surgery Among Hospitals in Australia and New Zealand. *Heart, Lung and Circulation,* Volume 26, S317. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017, poster.*

Ranasinghe I*, **Labrosciano C,** Horton D, Air T, Beltrame JF, Zeitz C and Tavella R. (2017) Early Complications of Cardiac Pacemaker and Defibrillator Implantation Among Hospitals in Australia and New Zealand. *Heart, Lung and Circulation,* Volume 26, S179-S180. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017, poster.*

Smolderen K*, Shore S, Wang J, **Labrosciano C**, Beltrame J and Spertus J. (2017) Abstract 19317: Defining Clinically Meaningful 12-Month Health Status Changes in Patients With Peripheral Arterial Disease as Perceived by Patients. *Circulation,* 136:A19317. *American Heart Association Annual Scientific Meeting 2017, poster.*

Labrosciano C*, Air T, Tavella R, Beltrame JF, Zeitz C, Horton D and Ranasinghe I. (2017) Post-Discharge Readmissions and Mortality Following Hospitalisation for Acute Myocardial Infarction in Australia and New Zealand. Heart, Lung and Circulation, Volume 26, S89. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017, poster.*

Labrosciano C*, Air T, Beltrame JF, Tavella R, Horton D, Zeitz C and Ranasinghe I. (2017) Variation in Early Death and Readmission Following an Acute Myocardial Infarction Hospitalization in Australia and New Zealand. Circulation, Volume 136, Supp 1, A18866. *American Heart Association Annual Scientific Meeting 2017, poster.*

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Ganesan A*, Hossain S, McGavigan A, Heddle W, Hortan D, **Labrosciano C**, Hariharaputhiran S, Air T and Ranasinghe I. (2018) Differences in Acute Complications of Cardiac Implantable Electronic Devices (CIED) in Public Versus Private Hospitals in New South Wales and Queensland. *Heart, Lung and Circulation*. 27:S160. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2018,* poster.

Nadlacki B*, Horton D, **Labrosciano C**, Hossain S, Hariharaputhiran S, Aliprandi-Costa B, Adams R, Visvanathan R and Ranasinghe I. (2018) Long-Term Mortality Following Acute Myocardial Infarction in Australia and New Zealand: a Population-Wide Study. *Heart, Lung and Circulation*. 27:S54-S55. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2018,* poster.

Hariharaputhiran S*, Horton D, Hossain S, **Labrosciano C**, Nadlacki B, Adams R, Visvanathan R and Ranasinghe I. (2018) Long-Term Mortality Following Hospitalisation for Heart Failure in Australia and New Zealand: a Population-Wide Study. *Heart, Lung and Circulation*. 27:S55-S56. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2018*, oral presentation.

Ganesan A*, Hossain S, McGavigan A, Heddle W, Hortan D, **Labrosciano C**, Hariharaputhiran S, Air T and Ranasinghe I. (2018) Population-Level Gender Differences in Acute Complications of Cardiac Implantable Electronic Devices: Implications for Patient Safety. *Heart, Lung and Circulation*, 27:S182. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2018,* poster.

Decker C*, Gosch K, Thomas M, **Labrosciano C** and Smolderen K. (2018) Medication adherence profiles in peripheral arterial disease: insights from the international PORTRAIT Registry. *European Journal of Cardiovascular Nursing,* 17, 9-10. *EuroHeart conference 2018*, oral presentation.

Malik AO*, Peri-Okonny P, Provance J, Gosch K, Thomas M, **Labrosciano C**, Spertus JA and Smolderen K. (2019) The association of perceived stress with health status outcomes in patients with peripheral artery disease. *Journal of the American College of Cardiology,* 73(9):2081. DOI: 10.1016/S0735-1097(19)32687-7. *American College of Cardiology conference 2019*, poster.

Smolderen K*, Safley D, Jones P, Patel M, Jones S, Shishehbor M, Aronow H, **Labrosciano C**, Fuss C, Scott K, Stone N and Spertus JA. One-year major adverse limb events and planned revascularizations following invasive versus optimal medical therapy for new or worsening of claudication symptoms: insights from the PORTRAIT Registry. *Journal of the American College of Cardiology* 73 (9) Supplement 1: 2115. DOI: 10.1016/S0735-1097(19)32721-4. *American College of Cardiology conference 2019*, poster.

Stretton B, Tavella R, Zeitz C, Arstall M, Sinhal A, Worthley M, Beltrame J and **Labrosciano C***. (2019) Antithrombotic Therapy and Bleeding Outcomes in Atrial Fibrillation Patients after PCI: Insights from the CADOSA Registry. *Heart, Lung and Circulation* 28, S284-S285. DOI: 10.1016/j.hlc.2019.06.350. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2019*, mini-oral presentation.

Presentations Arising from this Thesis

*denotes the presenter

Labrosciano C* Beltrame JF, Tavella R and Ranasinghe I. Readmissions following cardiovascular diagnosis in Australia: A Systematic Review. *10th Florey Postgraduate Research Conference 2016,* poster.

Labrosciano C*, Beltrame JF, Tavella R and Ranasinghe I. Readmissions following Cardiovascular Hospitalisations: A Systematic Review of the Contemporary Australian Literature." *Finalist in The Queen Elizabeth Hospital Research Day 2016,* oral presentation.

Labrosciano C*, Air T, Beltrame JF, Tavella R, Horton D and Ranasinghe I. Australian and New Zealand Rates of Readmissions and Mortality following Hospitalisation for Heart Failure. *Australian Society of Medical Research Adelaide meeting 2017,* oral presentation.

Labrosciano C*, Air T, Beltrame JF, Tavella R, Horton D, Zeitz C and Ranasinghe I. Readmission and Mortality Rates following Heart Failure Hospitalisations across Australia and New Zealand. *10th Health Services & Policy Research of Australia and New Zealand Conference 2017,* poster.

Labrosciano C*, Air T, Beltrame JF, Tavella R, Horton D, Zeitz C and Ranasinghe I. Rates of 30-day Readmission and Mortality Following an Acute Myocardial Infarction across Australia and New Zealand. *10th Health Services & Policy Research of Australia and New Zealand Conference 2017,* poster.

Labrosciano C*, Tavella R, Reynolds A, Air T, Adams R, Beltrame JF and Ranasinghe I. Does poor sleep in hospital lead to cardiology patients returning? *The Queen Elizabeth Hospital Research Day 2018,* clinical oral session finalist.

Labrosciano C*, Tavella R, Reynolds A, Air T, Adams R, Beltrame JF and Ranasinghe I. The Association between the Quality and Quantity of Sleep and 30-day Readmissions in Cardiology Patients: A Pilot Study. *SAHMRI/ The Heart Foundation Cardiovascular Research Showcase 2018,* poster.

Labrosciano C*, Tavella R, Reynolds A, Air T, Adams R, Beltrame JF, Ranasinghe I. The Relationship between Sleep Characteristics and 30-day Readmission: A Pilot Study of Cardiology Patients. *Adelaide Sleep Retreat 2018,* young investigator oral presentation.

Other Presentations During the Candidature

* Denotes the presenter

Ranasinghe I, Horton D, **Labrosciano C*,** Air T, Zeitz C, Beltrame JF and Tavella R. Variation in Risk Standardised Mortality following Isolated Coronary Artery Bypass Grafting Surgery Among Hospitals in Australia and New Zealand. *10th Health Services & Policy Research of Australia and New Zealand Conference 2017*, oral presentation.

Ranasinghe I, **Labrosciano C*,** Air T, Horton D and Hossain S for the ORION Study Investigators. The Observing Recurrent Incidence of Adverse Outcomes following HospitalisatioNs (ORION) Study: Towards Nationwide Reporting of Outcomes of Hospital-Based Cardiovascular Care Using Existing National Data Infrastructure. *10th Health Services & Policy Research of Australia and New Zealand Conference 2017*, poster.

Ranasinghe I*, Horton D, **Labrosciano C**, Air T, Zeitz C, Beltrame JF and Tavella R. Early Mortality after Isolated Coronary Artery Bypass Grafting (CABG) Surgery Among Hospitals in Australia and New Zealand. *Cardiac Society of Australia Annual Scientific Meeting 2017*, poster.

Ranasinghe I*, **Labrosciano C**, Air T, Horton D, Zeitz C, Beltrame JF and Tavella R. Early Complications of Cardiac Pacemaker and Defibrillator Implantation Among Hospitals in Australia and New Zealand. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017*, mini-oral presentation.

Smolderen K*, Shore S, Wang J, **Labrosciano C**, Beltrame JF and Spertus J. (2017) Defining Clinically Meaningful 12-Month Health Status Changes in Patients With Peripheral Arterial Disease as Perceived by Patients. *American Heart Association Annual Scientific Meeting 2017*, poster.

Smolderen KG*, Wang J, Jones P, **Labrosciano C** and Spertus J. (2017) Developing a Clinical Prediction Model for 1-Year Health Status Outcomes in Peripheral Arterial Disease: Insights From the PORTRAIT Registry. *American Heart Association Annual Scientific Meeting 2017*, poster.

Ranasinghe I*, **Labrosciano C,** Horton D, Air T, Beltrame JF, Zeitz C and Tavella R. (2017) Early Complications of Cardiac Pacemaker and Defibrillator Implantation Among Hospitals in Australia and New Zealand. *Cardiac Society of Australia and New Zealand Annual Scientific Meeting 2017*, mini-oral presentation.

Nadlacki B*, Horton D, **Labrosciano C**, Hossain S, Hariharaputhiran S, Aliprandi-Costa B, Adams R, Visvanathan R and Ranasinghe I. Long-term Mortality Following Acute Myocardial Infarction (AMI) in Australia and New Zealand (ANZ): A population-wide study. *SAHMRI/The Heart Foundation Cardiovascular Research Showcase 2018*, poster.

Awards and Recognition

Faculty of Health Sciences Divisional Scholarship, University of Adelaide (2016-2019).

Joanna Briggs Institute Certificate – Systematic Review Course (2016).

Non-Award Study in the University of Adelaide Faculty of Health Sciences Introduction to Biostatistics and Biostatistics (2016).

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Science in Public Media & Communications Training Workshop, won competition supported by The Hospital Research Foundation (2017).

The Hospital Research Foundation Travel Grant (2017).

Cardiac Society of Australia and New Zealand Annual Scientific Meeting Travel Fellowship (2017).

Adelaide Medical School Research Travel Awards - Round 2 (2017).

Heart Failure work featured in the Cardiology Update of the Medical Observer: "https://www.medicalobserver.com.au/medical-news/cardiology/acs-treatment-differs-for-men-and-women" (August 2017).

The Hospital Research Foundation coordinated Community Awareness Program to U3A (University of the Third Age) Flinders. Talk titled "Returning to hospital after a heart attack" (4th May 2017).

Nominated for the Channel 9 Young Achiever of the Year Award in 2018.

Invitation from The Hospital Research Foundation to be interview on Coast FM 88.7 (February 2018).

Basil Hetzel Institute Management Committee member and student representative (2018-19).

St. John's First Aid, basic emergency life support and CPR course (26/07/2018).

Peer reviewer for *JBI Database of Systematic Reviews and Implementation Reports and Annals of Internal Medicine* (2018-19).

Judging Panel for the University of Adelaide First Florey Undergraduate Conference (2018).

Ivan de la Lande Award (2018).

Nominated for The University of Adelaide STEM Award in the 2019 Seven News Young Achiever of the Year Awards.

CALHN Good Clinical Practice (GCP) Awareness Training on 4th December 2018.

Community talk for The Hospital Research Foundation on 15th May 2019, titled "Returning to hospital after a heart attack".

Women in STEMM Australia. Dr Jane Goodall's Australian tour on 14th May 2019.

PRAXIS Monitoring Approved Research Workshop, Adelaide on 25th June 2019.

Volunteer at Science Alive SA on 3rd August 2019.

Mental First Aid Training at the University of Adelaide on 23rd and 24th September 2019.

Chapter I: Background

1.1.0 Cardiovascular Disease

Cardiovascular disease (CVD) encompasses diseases and disorders of the blood vessels and heart, and is the greatest disease epidemic in the world. In 2012, the Australian Bureau of Statistics (ABS) estimated that 4.2 million Australians were living with CVD[1]. Acute CVD hospitalisations in Australia have increased by 20% over a 10 year period (2005-06 to 2015-16)[2]. Moreover, admissions to hospital for any CVD accounted for 11% of all Australian hospitalisations between 2015 and 2016[2]. In 2008, global figures found that CVD was the underlying cause of death in 17.3 million people[3] and nationally, one Australian dies from CVD every 12 minutes[4]. In 2017, 43,000 Australian deaths were attributed to CVD[5] costing 11% of the Australia's hospital expenditure[6].

1.1.1 Cardiovascular-related Mortality

Over the last few centuries there have been drastic changes in the causes of mortality[7]. Prior to and during the World Wars, mortality was most commonly caused by famine, infectious diseases and pandemics. After the Great Wars ended, lifestyle factors such as obesity, sedentary routines, in addition to chronic/degenerative diseases and increases in stress have led to a greater proportion of cardiovascular-related deaths. The Australian Institute of Health and Welfare (AIHW) report that CVD is the underlying cause of death in approximately one third of all Australians (45,400 deaths in 2015), where 44% are due to coronary heart disease (CHD) and 10% are due to heart failure (HF) and cardiomyopathy[2]. Despite the significant mortality associated with CVD, both the number and rate of cardiovascular-related deaths have declined substantially over the last three decades. In Australia, the number of cardiovascular-related deaths has declined by 21% (from around 57,500 to 45,400) between 1985 and 2015[2]. However, there are a significant number of people living with CVD - approximately 4.2 million Australian adults (18.3%)[8]. As such, the

broader burden of CVD has critical significance, including the impact on functional capacity, quality of life, hospital resources and the economy.

1.1.2 The Burden of Cardiovascular Diseases

CVD has a detrimental effect on the Australian health care system, reflected as a financial burden to Australia's economy[9]. Between 2008 and 2009 Australia spent $7,605 million on CVD, equating to 12% of the nation's health-care expenditure[10].

Further to the financial damages, hospitalised patients with CVD are known to have poorer early health outcomes such as higher rates of 30-day mortality and readmission. The landmark *New England Journal of Medicine* paper by Jencks and colleagues reported that one in every five patients hospitalised for any reason is readmitted within 30 days of discharge[11]. Although readmission rates can vary dramatically between conditions and diseases, the two cardiovascular conditions that have consistently been reported as having the highest international rates of readmission are HF and acute myocardial infarction (AMI). Internationally, amongst patients admitted with a primary diagnosis of HF, approximately one in four (23.6%[12], 24.56%[13]) patients are readmitted and just over one in ten (12.1%[14], 11.17%[13]) patients die within 30 days. Similarly, of the patients admitted with a primary diagnosis of AMI approximately one in every five (18.9%[15], 19.94%[13]) are readmitted and 16.60%[13] die within 30 days. Moreover, both HF and AMI were diseases targeted by policy reforms in the United States and are further discussed in section 1.4.6.

1.2.0 Angina Pectoris

The classical symptom of chest pain or discomfort referred to as ***angina pectoris***[16] is a commonly associated with CHD. The term ***angina pectoris*** is derived from the Greek

ankhone, meaning a strangling sensation and the Latin *pectoris* meaning chest[17]. This descriptive term is often simplified to 'angina' and refers the characteristic chest tightness attributable to myocardial ischaemia. Leonardo Da Vinci first detailed the coronary artery anatomy in his landmark diagrams, also documenting the presence of coronary artery disease (CAD) in 1511. This pioneering work was followed by William Harvey's documentation of the definition of coronary circulation[18]. Subsequently, in 1772 William Heberden gave the first infamous elegant description of angina:

> "*there is a disorder of the breast marked with strong and peculiar symptoms, considerable to the kind of danger belonging to it, and not extremely rate, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris"*[19].

This illustrative definition of the symptoms experienced by patients is still clinically applicable today in describing *stable angina*, where the symptoms occur from a predictable, reliable amount of exertion or stress. This constitutes the hallmark of 'the chronic coronary syndromes' as recently described in the European Society of Cardiology Guidelines[20]. When the usual pattern of angina changes in the duration, frequency or intensity, or occurs at rest, the symptoms are referred to as unstable angina, which indicates an acute coronary syndrome (ACS). The term ACS is applied to patients in whom there is a suspicion or confirmation of acute myocardial ischemia or infarction.

1.2.1 Acute Myocardial Infarction

An ACS results from acute obstruction of a coronary artery causing disruption of blood supply to the myocardium and resulting in myocardial ischaemia. Depending on the degree and location of obstruction, the clinical consequences range from unstable angina to AMI. Myocardial infarction results from prolonged ***myocardial ischaemia*** causing necrosis[21].

In 2018, the *Universal Definition of AMI* was updated to clearly distinguish between myocardial infarction and myocardial injury[21]. The clinical diagnosis of AMI is based upon universally defined criteria[21], unlike HF. The diagnosis of AMI is based upon changes on electrocardiogram (ECG), elevated cardiac markers along with supportive evidence of clinical symptoms or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. The evaluation of the ECG allows for the distinction to be made between the two types of AMI: ST-segment Elevation MI (***STEMI***) and ST-segment depression or Non-ST-segment Elevation MI (***NSTEMI***), their distinguishing features are described in Table 1.0. A STEMI is typically associated with a complete obstruction of the artery and leads to damage across the entire heart wall. In contrast, a NSTEMI involves the partial obstruction of the artery and the resulting ischaemia does not affect the entire heart wall. Non-ST elevation acute coronary syndrome (NSTEACS) refers to patients presenting with NSTEMI or unstable angina[22]. The clinical presentation of these patients are similar, and the diagnosis can be separated following the results of a troponin assay, further discussed in section 1.2.4.

Table 1.0 Differences and similarities between STEMI and NSTEMI.

	STEMI	NSTEMI
Electrocardiogram (ECG)	ST-segment elevation, with or without T wave change Subsequent Q wave. *look for left bundle branch block as this can lead to rupture of the septum*	Absence of ST–segment elevation but may include ST depression and/or T wave changes.
Location of damage	Transmural (across the heart wall).	Subendocardial.

1.2.2 Acute Myocardial Infarction Epidemiology

Globally, over three million people suffer a STEMI and a further four million suffer a NSTEMI annually[23]. In 2008, the World Health Organization (WHO) attributed 7.3 million global deaths to AMIs[3]. The leading cause of Australian deaths in 2016 was CHD[24,25], whereby AMI accounted for 40% of CHD mortality[25].

AMI *incidence* refers to the number of new cases that are identified every year and *prevalence* refers to the proportion of the population with AMI. The Australian incidence of AMI hospitalisations between 1993 and 2010 was found to be over 700,000[26]. Moreover, approximately 55,000 Australians suffer an AMI every year, equating to one infarct every ten minutes[27]. The cost of an Australian AMI hospitalisation is variable, though a prospective, multicentre survey of Victorian hospitals found the average cost per AMI hospitalisation was $20,502[28].

1.2.3 Acute Myocardial Infarction Aetiology and Pathophysiology

The aetiology of AMI is prolonged myocardial ischaemia causing obstructed coronary blood flow to the myocardium. Myocardial cell death does not begin immediately after the onset of myocardial ischaemia. An acute coronary artery occlusion lasting for at least 20 minutes initiates myocardial necrosis. Decreased coronary blood flow can occur for various reasons and thus the pathophysiology of AMI reflects the cause/s of the occluded coronary artery. Gould and colleagues demonstrated that a coronary artery obstruction must be at least 70% to impede on coronary flow reserve, but more severe lesions of at least 90% could result in myocardial ischaemia at rest[29]. Atherosclerotic plaques causing coronary artery occlusion from plaque rupture or erosion are the most common underlying cause of AMI, accounting for at least 70% of events[30,31]. Other aetiologies of decreased coronary blood flow and prolonged myocardial ischaemia include coronary spasm, coronary embolism, and thrombosis in non-atherosclerotic arteries. Thus, the pathophysiological mechanisms of AMI are defined by the triad of the ruptured atherosclerotic plaques[30,31], or coronary spasm and/or thrombosis in non-atherosclerotic normal vessels[32].

1.2.4 Acute Myocardial Infarction Clinical Presentation and Diagnosis

In patients presenting with chest pain suspicious of ACS, the key objective of clinical testing is to determine the presence or absence of AMI. Symptoms are similar in each of the ACSs and are characterised by angina, described by patients as a heavy weight on the chest which can radiate to the jaw, neck or back. Aside from angina, patients may present with an array of other symptoms that may include dyspnoea, nausea, cold sweat, feeling faint and fatigue. Angina lasting longer than 20 minutes may be considered characteristic of AMI.

The ECG is the most common tool in the initial evaluation and triage of patients in whom AMI is suspected. Laboratory tests are used in the diagnosis of AMI. Creatinine kinase-

myoglobin binding (CK-MB) is a biomarker which is released following damage to cardiomyocytes, however its use has been replaced by the troponin assay. The introduction of the biomarker troponin (both subtypes troponin I and troponin T) has provided improved sensitivity in determining myocardial damage. Levels of troponin continue to rise for approximately the first three hours following an AMI, and in some cases can remain elevated for 14 days[33]. The characteristic rise and fall of troponin is consistent with the acute injury to the myocardial cells[21].

Clinical cardiac societies have identified the importance of obtaining a 12-lead ECG in a timely fashion for the management of ACS and AMI. If the ECG specifies an ST-segment elevation in conjunction with elevated troponin levels, the final diagnosis is a STEMI – whereby a thrombus is causing complete occlusion of the artery. The ECG of some STEMI patients may also display a Q wave[34].

If the ECG shows an ST-segment depression or an T wave inversion the working diagnosis is a NSTEMI. Following the ECG, if the biomarker confirms a serially elevated troponin, the final diagnosis is NSTEMI – whereby a thrombus causes subtotal occlusion of the artery. If there are no abnormalities in biomarkers (specifically no troponin rise) the final diagnosis is unstable angina.

1.2.5 Acute Myocardial Infarction Management

The treatment of AMI aims to revascularise the heart and additionally reduce the oxygen consumption by the heart muscle. The introduction of percutaneous coronary intervention (PCI) has transformed the treatment of CAD. Thrombolysis and PCI are the principal treatments for STEMI[35]. Keeley and colleagues[36] conducted a review of randomised trials in AMI patients, to compare PTCA to thrombolytic therapy. They found that patients treated

with primary PTCA had lower early mortality (7% vs. 9%, p=0.0002) and non-fatal reinfarction (3% vs. 7%, p=0.0003). More recently, the importance of patient health status (refer to section 1.4.4) has again shifted the focus of treatment in patients with CAD.

Acute ST Elevation Myocardial Infarction Management

A code STEMI is called and the patient urgently undergoes a primary PCI in order to re-establish coronary artery patency; consistent with the 'open artery hypothesis'[37]. It is vital that primary PCI is undertaken within 90 minutes of the STEMI being identified (known as door to balloon time). If a patient cannot be transferred to a catherisation laboratory for urgent PCI, thrombolytic therapy should be administered[38-40]. Thrombolytic therapy has been shown to be effective if administered within the first six hours of symptom onset and is most effective within the first hour[41]. If thrombolytic therapies fail to alleviate the occlusion, 'rescue PCI' may be undertaken when the patient arrives at a PCI-capable facility[34].

Acute Non-ST elevation Myocardial Infarction Management

In relation to the management of NSTEMI, the Australian National Heart Foundation guidelines[33] stratify patients into different risk categories according to their likelihood of mortality or recurrent events. Several risk assessment scores have been developed to help identify patients with NSTEACS, such as the Thrombolysis In Myocardial Infarction (TIMI) risk score. A patient is deemed to be at **very high risk** if they are hemodynamically unstable, have HF, cardiogenic shock or a mechanical complication arising from their AMI. For these patients the recommended treatment is angiography within two hours of symptom onset. Patients who are at **high risk** may present with the characteristic rise and fall in troponin that is consistent with AMI, dynamic ST-segment and or T wave changes with or without symptoms. It is recommended that these patients undergo angiography within 24 hours. Patients with an **intermediate risk** are those who present with diabetes mellitus, renal

insufficiency, left ventricular ejection fraction (LVEF) of ≦40%, prior PCI or CABG and a GRACE score between 109 and 140. It is recommended that these patients have a planned angiography within 72 hours. If a patient is **low risk**, they display none of the characteristics above, then angiography may be considered pending the results of non-invasive testing.

Acute Coronary Syndrome Pharmacological Therapy

Pharmacological treatment strategies include the administration of cardioprotective and antianginal medications. Cardioprotective drugs such as statins, aspirin and Angiotensin Converting Enzyme (ACE) inhibitors reduce the risk of major adverse events (such as stroke, a subsequent infarction or mortality). Anti-anginal medications such as nitroglycerin, aid in the managing the symptoms of angina. Following treatment of the acute incident, lifelong management to reduce the risk of adverse outcomes may include aspirin, ACE inhibitors, statins and possibly beta-blockers[38]. A comprehensive list of recommended medications is provided in Table 1.1.

Table 1.1: Commonly used pharmacological therapy for AMI patients.

Drug	Reason for use
Nitro-glycerine (also known as glyceryl trinitrate (GTN))	Dilate vessels.
Opiates (predominantly morphine)	Reduce chest pain.
Oral antiplatelet agents (aspirin, clopidogrel and ticagrelor) and glycoprotein IIA/IIB inhibitors	Inhibit the enzyme which causes platelet aggregation that leads to thrombus formation.
Anti-coagulants (e.g. heparin, warfarin)	Reduce clotting thereby reducing fibrin formation and prevents platelet aggregation that leads to thrombus formation.
Beta-blockers	Reduce oxygen demand of the heart.
Statins	Lower lipid levels and improve endothelial function.
ACE inhibitors	Cardioprotection.
Calcium antagonists	Reduce oxygen demand of heart, vasodilation, treat hypertension.

Acute Coronary Syndrome Procedures and Surgery

Invasive ***coronary angiography*** involves a catheter being inserted (either via the femoral, brachial or radial artery) into the coronary arteries and is the gold standard method allowing the interventional cardiologist to image the coronary arteries by the injection of contrast[42]. Following on from the pioneering work of Sones, who performed the first angiogram in 1959[43] there have been continuous improvements in the technique.

PCI is a non-surgical procedure to unblock the obstructed coronary artery, during which a catheter with a small deflated balloon attached to its tip is advanced on a previously placed guide wire. When the balloon arrives at the site of the atherosclerotic obstruction, the balloon is inflated, and the plaque is crushed against the walls of the artery. A bare metal stent (BMS) or drug eluting stent (DES) may also be placed inside of the artery so that it remains open. A suspected STEMI is treated with urgent angiography and PCI[44], within 12 hours of symptom onset[34], followed by the continuation of aspirin and clopidogrel[34].

Acute Coronary Syndrome Lifestyle Changes

Following AMI, patients are advised to make changes to their lifestyle to reduce the risk of a subsequent AMI or further CVD. It is recommended that the patient ceases smoking, reduces alcohol intake, eats a healthy diet, maintains a healthy weight and increases physical activity[45]. The attendance of cardiac rehabilitation is also highly recommended, as these programs encourage the patient to regain their strength, increase their physical activity and provide emotional support[46].

1.3.0 Heart Failure

HF is a complex clinical syndrome that lacks a clear universal definition[47,48], unlike AMI discussed in section 1.2.0 of this thesis. HF diagnosis is based on a clinical syndrome, dependent upon history, examination and the treating cardiologist's judgement. Despite a lack of global concurrence, HF has been defined as the:

> "*adequate ventricular filling, when the heart's output is decreased or in which the heart is unable to pump blood at an adequate rate to satisfy the requirements of the tissues with function parameters remaining within normal limits*"[47].

In addition to the conceptual definition outlined above, clinical guidelines have been developed. HF can manifest clinically as right-sided HF or left-sided HF (which is subdivided into systolic and diastolic HF). ***Systolic HF*** or ***HF with reduced EF (HFrEF)***, refers to the reduced capacity for the heart to contract and is the more common form. ***Diastolic HF*** or ***HF with preserved EF (HFpEF)***, refers to impaired filling capacity of the left ventricle in the presence of normal contraction.

As depicted in Table 1.3, the functional severity of HF can be classified in accordance with the patient's ejection fraction (EF), which is measured by left ventricular function and reported as New York Heart Association (NYHA) classes I to IV[49]. As indicated in Table 1.4, HFpEF refers to patients with HF and an EF over 40%. In contrast, patients with an EF lower than 40% are referred to has having HFrEF. In addition to the European Society of Cardiology (ESC) guidelines[50], the American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) Task Force guidelines[51] have further subdivided HF to include a mid-range EF (HFmrEF) category which is defined as an EF as being between 41% and 49%.

Table 1.3: Classifications for HF, adapted from the American College of Cardiology (ACC)/ American Heart Association (AHA)[52] and the New York Heart Association (NYHA)[49].

Stage[52]	Symptoms and Characteristics[52]	Class[49]	Functional classification[49]
A	Patient at risk of developing HF (i.e. patients with diabetes or coronary disease without prior infarct).	I	Normal physical activity without fatigue, palpitations or dyspnoea.
B	Structural heart disease without symptoms (i.e. reduced ejection fraction, left ventricular hypertrophy or chamber enlargement).	II	Slight limitation of physical activity. Ordinary physical activity causes fatigue, palpitations or dyspnoea. No symptoms at rest.
C	Clinically defined HF.	III	Limited physical activity. Reduced physical activity that results in fatigue, palpitations or dyspnoea. No symptoms at rest.
D	Refractory HF requiring advanced intervention (i.e. biventricular pacemakers or transplantation).	IV	Unable to conduct physical activity. If physical activity is performed, discomfort occurs. HF symptoms at rest.

Table 1.4: Heart Failure classification via ejection fraction, adapted from the ESC guidelines[50].

Class	Definition
HFrEF	Left Ventricular Ejection Fraction (LVEF) <40%.
HFmrEF	LVEF 40-49%. Elevated natriuretic peptide and at least one of the following additional: 1. Structural heart disease. 2. Diastolic dysfunction.
HFpEF	LVEF ≥50%. Elevated natriuretic peptide and at least one of the following additional: 1. Structural heart disease. 2. Diastolic dysfunction.

1.3.2 Heart Failure Epidemiology

Evidently, the ageing population in combination with the prolonged lifespan has led to increased prevalence and mortality in HF patients, which remain unacceptably high[53]. However, due to the lack of consensus on HF definition, the true prevalence of HF remains unknown. Understandably, there is ambiguity in the literature surrounding the incidence of HF, which is further alluded to in Chapter III of this thesis.

Global figures estimate that there are currently 37.7 million patients suffering from HF[54], with this figure rising due to increased survival following AMI[55]. Australian figures estimate that 30,000 new cases of HF are diagnosed annually[56]. A systematic review[57] reported the Australian prevalence of HF between 1990 and 2015 to be 1-2%, however this reported prevalence is underestimated due to the unknown number of asymptomatic patients. The

rising number of HF admissions are causing financial hardship, with the average HF admission to an Australian public hospital estimated to cost $990 per patient per day[58]. HF is a fatal condition, with mortality occurring in 50% of patients within five years of diagnosis[58]. The AIHW has reported a decline in Australian mortality due to HF from 1980 to 2001[59].

1.3.3 Heart Failure Pathophysiology

In the normally functioning heart, the left ventricular output is responsible for supplying the systemic circulation with its cardiac output and thus fundamental to life. The right ventricle operates at a lower pressure and ensures adequate preload to the left ventricle via maintenance of the pulmonary circulation. This thesis focuses on HF, which may involve either or both the right/left ventricle, however the discussion relates primarily to failure of the left ventricle unless otherwise specified.

HF is a complex clinical syndrome manifesting as inadequate cardiac function to provide adequate tissue perfusion. The "typical" symptoms of patients with HF can manifest both upon exertion and at rest. Symptoms occur at rest due to inadequate cardiac function, that may be due to loss cardiac myocytes (for example myocardial infarction) but may equally arise from dysfunctional myocytes. Clinically, HF has been categorised on the basis of the left ventricular ejection fraction (LV-EF) and accordingly classified as HFrEF and HFpEF, using and LV-EF cut-off of 50%, these are discussed below.

HFrEF is defined as HF with an LV-EF <50%, and is typically due to damage to the cardiomyocytes caused by AMI, hypertension and cardiomyopathy all contribute to the weakening of the heart muscle, leading to decreased contractility and ultimately decreased

cardiac output[9]. There are both hemodynamic and remodelling aspects of the pathophysiology of HF. In HFrEF, global left ventricle systolic dysfunction predominates, usually with progressive chamber dilation and eccentric remodelling. Due to cardiomyocyte damage, haemodynamic and neurohormonal mechanisms (catecholamines, renin-angiotensin-aldosterone system, and others) are activated to compensate for the reduced function. However, these 'compensatory mechanisms' are potentially deleterious as they may increase the workload of the heart and thus further aggravate the HF.

Unlike the pathophysiology of patients with HFrEF, the underlying causes of HFpEF are multifactorial and less clearly understood[60]. By definition, the systolic contraction in HFpEF is not significantly impaired but there is inadequate functioning, resulting in increased left ventricular end-diastolic pressure at rest or during exertion. Although there is no major loss of cardiomyocytes, these cells may be enlarged and/or dysfunctional resulting in abnormal diastolic relaxation, filling or distention of the left ventricle and subsequently HF.

1.3.4 Heart Failure Clinical Presentation

Patients with HF have various symptoms which are dependent on the pathophysiology of the disease[61]. The most commonly associated symptom of HF is acute pulmonary oedema defined as the accumulation of fluid in the lungs, making it more difficult for oxygen to cross from the alveoli to the capillaries and resulting in hypoxia. HF manifests clinically as left-sided and right-sided HF, depending on the affected ventricle. Additionally, biventricular failure, or *congestive heart failure*, refers to both left and right HF. However, the term "*congestive heart failure*" is being used less frequently to describe these patients as congestion is not the sole cause of HF[61]. With the potential variation in the causes of HF, the symptoms are also quite diverse, but can be broadly classified as being due to volume overload and symptoms due to

low cardiac output. This alludes to the importance of cardiologists being meticulous when taking a patient's history, to cover the broad range of potential causes of HF. The underlying aetiology of HF is in most cases due to pre-existing cardiovascular disease (hypertensive, ischaemic, valvular), cardiomyopathy, cor pulmonale (alternated structure and function of right ventricle) and pulmonary hypertension (association between lung and heart disease). HF can be aggravated by factors including anaemia, arrythmias, viral infections such as human immunodeficiency virus (HIV) or Chagas disease, history of substance abuse or exposure to other cardiotoxic substances (including chemotherapy drugs) and fever[61].

The clinical presentation of a HF patient lies on a broad clinical syndrome, making diagnosis challenging[62]. Moreover, it is important to distinguish the clinical presentation of patients with acute HF compared to those with chronic HF. A comprehensive history of the patient is evaluated and corroborated by physical examination[63]. Clinical diagnosis of HF is derived following careful patient history and physical examination. Physical examination of the patient involves meticulous assessment of the patient's physical appearance, such as their posture, pallor, cyanosis or jaundice and emancipation, which can provide important clues for their diagnosis. Patients may present with fatigue which can be attributed to the decreased cardiac output. These symptoms may appear upon exertion, or at rest and despite the manner of presentation, all patients warrant further investigation[63]. Cardiac auscultations may also provide insight when diagnosing HF, the detection of the additional S_3 sound, often referred to as a gallop may be indicative of left ventricular failure[64].

Left-sided Heart Failure

Clinical presentation of pulmonary oedema is caused by failure of the left ventricle. This leads to increased left ventricular end diastolic pressure which increases pulmonary venous pressure. The intravascular pressure exceeds the onconic pressure, as described by Starling's

Law of Fluids, leading to fluid leaking from the pulmonary capillaries to the intra-alveolar tissues and then into the alveolar space. This accumulation of fluid, most commonly presents as increased dyspnoea (*shortness of breath*), which may be related to increased filling pressures or impeded cardiac output[61] which are consistent with left-sided HF. Orthopnoea (*dyspnoea when lying flat*) at night, may be alleviated by sleeping in an upright position.

Further physical examination may identify tachycardia, irregular cardiac rhythm or pulse and tachypnoea (*abnormally rapid breathing*), which can all be signs and symptoms of HF. The characteristic crackling sound heard, referred to as rales, is another common indicator of HF. As the disease progresses, an abnormal breathing pattern known as *Cheyne-Stokes respiration* may develop[65,66], indicative of a poor prognosis[67].

Right-sided Heart Failure

Similar to left ventricular failure described above, right-sided HF there is increased right ventricle end diastolic pressure. This increased pressure results in increased pressure of the superior vena cava and inferior vena cava, thus leading to increased pressure in the periphery. Swelling of the ankles and pitting oedema (in the ankles) are consistent with right-sided HF and may occur due to the fluid overload and increased hydrostatic pressure. Patients may also present with ascites (peritoneal fluid build-up) and hepatomegaly, observed upon physical examination. Jugular venous distention another symptom observed in patients with right sided HF and is observed via physical examination of the jugular venous pressure (JVP) indicates with good sensitivity and specificity (70% and 79% respectively)[68] of the patients central venous pressure[69]. The jugular veins communicate directly with the superior vena cava and then the right atrium[70]. JVP is an estimation of right atrial pressure. If there is increased pressure in the right atrium, blood flows backward into the jugular vein, observed as pulsing of the jugular vein when the patient lies at 45 degrees[71]. In contrast, to the above pulmonary

related symptoms. Patient's may also experience weight gain and loss of appetite or feeling full quickly (early satiety)[61].

1.3.5 Heart Failure Diagnosis

Echocardiography is a non-invasive diagnostic imaging technique for patients suspected of having HF[56]. Echocardiography can measure important markers of cardiac function including haemodynamic status, EF, cardiac volume and mass[72]. Moreover, echocardiography assists in the distinction between HFrEF and HFpEF and may provide further insight to whether AMI or valvular disease precipitated the HF presentation.

Chest x-rays provide a relatively safe, affordable and convenient initial investigation for patients presenting with suspected HF (or any cardiovascular condition)[73]. The chest x-ray provides the cardiologist with specific anatomical or physiological abnormalities of the heart, such as an enlarged left ventricle or atria (in the case of a HF patient)[63], cardiomegaly (enlarged heart) and/or pulmonary oedema.

An ECG is routinely conducted in all cardiovascular patients but help the cardiologist understand the cause of HF, which therefore aids in treatment[61]. An ECG may be helpful in identifying arrhythmias, the presence of conduction delay or abnormalities such as left bundle branch block amongst others. Biomarkers investigations may include analysis of plasma levels of B-type natriuretic peptide (BNP), a neurohormone that measures the overstretching of the cardiomyocytes, has shown to have good diagnostic accuracy for HF[74,75] and has been recommended by the ESC HF guidelines[76]. In Australian clinical practice, BNP is more commonly requested in the emergency department, compared to than inpatient wards. Furthermore, BNP may assist in determining whether dyspnoea is cardiac or non-cardiac related.

1.3.6 Heart Failure Management

The main goal of treatment and management of HF patients is to improve quality of life whilst reducing readmissions and mortality. As with AMI, there are various therapies and management options available to achieve these outcomes. Management of HF patients differs depending upon whether presentation is acute or chronic and have been described accordingly below.

Management of Acute Heart Failure

The goal of therapy for a patient presenting with acute HF is to stabilise the patient. For example, a patient who presents to the emergency department with shortness of breath will most commonly be treated with Continuous Positive Airway Pressure (CPAP) and frusemide. In the outpatients setting, a patient presenting with swelling of ankles may be prescribed frusemide.

In some cases of HF, the intubation and mechanical ventilation of a patient may be required, which may be a traumatic experience for the patient. Fortunately, non-invasive ventilation approaches and avoid endotracheal intubation, by using a mask or similar device to provide ventilatory support and aids in the gas exchange occurring in the alveoli, CPAP and Bi-level Positive Airway Pressure (BiPAP) are the two methods utilised in patients. CPAP provides continuous positive pressure (usually between 5 and 12cm of water) and aids oxygenation. In 1991, Bersten and colleagues[77] conducted a study of 39 patients with respiratory failure and acute pulmonary oedema. Patients were randomised to receive either high flow oxygen therapy or CPAP, and the results concluded that the patients on CPAP had better outcomes. In comparison BiPAP provides and expiratory airway pressure and an inspiratory airway pressure to help ventilation. A randomised study of three tertiary Australian hospitals found

no significant difference in the period of non-invasive ventilation between patients given CPAP compared to BiPAP therapy[78]. Both CPAP and BiPAP are advantageous compared to other HF treatments[79-81].

Management of Chronic Heart Failure

The majority of therapeutic recommendations for patients presenting with HF have been conducted through randomised controlled trials in patients with HFrEF. Medications are prescribed with the intention of alleviating the most common symptom of HF such as exertional dyspnoea and orthopnoea. Different pharmacological agents have been shown to benefit patients with HF, by improving survival and reducing morbidity in the form of readmissions (refer to Table 1.5). Patients presenting with chronic HFrEF may be treated with beta-blockers and ACE inhibitors, with the more recent addition of aldosterone antagonists such as spironolactone. These pharmacological agents antagonise the detrimental neurohormonal systems that are activated in HF, as described in section 1.3.3. Furthermore, the guidelines recommend that a patient with stabilised systolic HF that is still symptomatic be administered beta blockers. A trial of over 15,000 patients who were prescribed a beta blocker in addition to an ACE inhibitor improved all-cause mortality by 30-65% and reduced the number of deaths and hospitalisations by 35-40%[82]. Beta blockers prevent the detrimental tachycardia that is aggravated by the sympathetic systems response which results in a surge of catecholamines. ACE inhibitors and spironolactone antagonise the activated renin-aldosterone system, thereby reducing the detrimental effects of fluid retention and increased afterload. Loop diuretics, digoxin and nitrates may also be considered to improve patient symptoms. The addition of Ivabradine may be considered, although it has been shown to have no effect on mortality, but significantly decreases morbidity[83]. Devices such as cardiac resynchronisation therapy (CRT), permanent pacemakers and automatic implantable cardiac defibrillations (AICD) may be beneficial in controlling the electrical rhythms. CRT has been

shown to be to be of particular benefit to patients with an EF <35% with left and right ventricle dys-synchronisation, which is reported as a broad QRS[84]. HF is a fatal disease thus, the only lifesaving option (available in rare cases) is heart transplantation[85].

Table 1.5: Pharmacological Medical Therapy for Heart Failure.

Agent	Survival	Morbidity
ACE inhibitors e.g. Enalapril[86,87].	Improved.	Decreased.
Angiotensin II receptor blockers[88-92] e.g. losartan, valsartan and candesartan.	Improved.	Decreased.
Beta blockers[93-101] e.g. bisoprolol, metoprolol and carvedilol.	Improved.	Decreased.
Loop diuretics e.g. furosemide.	Improved.	Decreased.
Digoxin[102].	No effect.	Decreased.
Nitrates.	Improved.	Decreased.
RAAS inhibitors e.g. spironolactone.	Improved.	Decreased.
Ivabradine[83].	No effect.	Decreased.
Eplerenone[103].	Improved.	No effect.

Non-pharmacological Management

Lifestyle modifications such physical activity programs, fluid management and weight loss are all essential in the management of HF. HF specific programs, either clinic or home-based interventions provide the patient with psychosocial support, education and support to modify risk factors, including ceasing smoking and reducing alcohol intake. Moreover, by designing HF programs that specifically focus on the individual patient, the programs result in optimising function, reducing symptoms and improving self-management.

Palliative care

Finally, as HF is a chronic and terminal illness, the objective of care may shift from prolongation of life to improving the patient's quality of life. At this point, hospice care may be an appropriate option for patients. Although hospice care has long been thought of as a facility for terminal cancer patients, the second most common (18.7%) admitting diagnosis was cardiovascular or circulatory diseases[104]. Moreover, as HF progresses, the associated symptoms have been reported to be a greater burden than the symptoms of advanced cancer patients[105]. Palliative care exemplifies the principles of shared decision making by providing the patient with evidence based information and working ***with*** the patient (and their family/relatives) to deliver holistic care[106]. For example, a patient in advanced or final stages of HF may wish to have their implantable cardioverter defibrillator deactivated[107].

1.4.0 Evaluation of Health Care and Health Outcomes

Health care quality is defined by the Institute of Medicine as:

> "*the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge[108]".*

The quality of health care refers to how well the care provided coincides with the predefined benchmarks[108] and the extent to which the clinician portrays this[109]. Six domains have been suggested by the Institute of Medicine (IOM) to define the quality of health care, they are*: effectiveness, safety, equity, timeliness, efficiency, and patient-centeredness*[108]. These six domains have been promoted by the IOM as a core focus when measuring health outcomes and health care quality. The quality of health care should be measured and defined by how care effects the health of individual patients and <u>not</u> by health care efficacy[110]. It is imperative that health care quality is monitored for continuous improvement[111-113]. Health care quality is

assessed by measuring the health care structures, processes and outcomes[114]. As health cannot be directly measured, it is quantified by a single indicator, surrogate marker[115]. Readmission rates are an example of a surrogate marker for avoidable adverse events. Moreover, the validity and reliability of readmission rates as a measure of health care quality have also been recently debated in the literature[116].

The Donabedian model offers a conceptual framework allowing the measurement of health care quality by measuring structure, process and outcomes[117]. An example of measuring structure is assessed by the number of procedures or admissions that an institution may perform. An example of measuring process is by evaluating how and which medications are prescribed. Furthermore, performance can be specifically measured in a disease or condition, for example the rate readmissions and/or mortality that occurs in a cohort of HF patients.

1.4.1 The Evolution of Health Outcomes

Health can be measured in two distinct approaches: quantity and quality[118], which are each measured using diverse methods. Health outcomes have been measured and reported since the mid to late nineteenth century, as seen in the novel research conducted by Florence Nightingale[119,120], where she improved the health outcomes of British soldiers fighting in the Crimean War. Nightingale investigated the potential causes of the rising number of deaths in military hospitals despite her best efforts to make the environment safe and clean[121]. She published her findings that infections were the major cause of these deaths and reduced mortality rates from 42.7% to 2.2%[122]. Today, health evaluation continues to be increasingly important. Policymakers, health care providers and health researchers have become more concerned with the rigorous assessment of health care policies, health interventions and health research. Solid evaluation of health care requires reliable data on care processes and health outcome indicators.

1.4.2 Health Data Sources

Review and abstraction of medical records for the purposes of medical research have well documented methods. With the introduction of electronic health records in clinical practice, the use of administrative data for the purposes of research has also evolved. Additionally, the notion of *big data* is ill-defined[123]. Administrative data, a type of big data, that is not collected for research purposes and most commonly originates from government or large agency records for financial purposes and thus can be thought of as transaction data[124]. Due to the ambiguity in the aims of this data collection, the data is usually complex and requires "cleaning" and organisation before it can be used for research purposes[125]. The involvement of administrative data in health care and outcomes research is continuously evolving. The introduction of administrative data into health care research began in 1970, when administrative data was used to examine the patterns and variation of health care practice between different areas in Vermont in the United States[126]. In 1990, administrative data was used to analyse the potential issues surrounding the safety and quality of health care provided to patients, with the proposal of using administrative data as a screening tool[127]. The progression of uses of screening continued when the United Health care Corporation developed a screening tool to determine outcomes rates, adverse events and other outcome measures[128]. The assistance of administrative data in screening for potential complications following hospital procedures and the potentially preventable readmissions began in to early 1990s[129-131]. The identification of readmissions for complications following medical procedures using Medicare claims data (using the International Classification of Diseases (ICD)-9-CM coding) was first utilised by Riley and colleagues in 1993[132]. In 1994, further analysis of administrative data found that patients who suffered complications were older, had more comorbidities, endured a longer length of stay and experienced poorer outcomes[131]. In 2002, the Agency for Health care Research and Quality (AHRQ) employed administrative

data in the development of screening tools for the reduction of medical error and consequently improvement of patient's safety[133].

The source and type of health care data used for monitoring and research depends on the question which is being investigated[134]. Australia uses a universal health care system, making these services accessible to all Australians[135] and is comprised of both public and private sectors funded at both state and federal levels[136]. Medical data is collected in various ways. Administrative records are routinely collected by hospitals to keep track of patients, admissions and costs. With the analogy of administrative data being much like bank transactions, this data source contains key information such as date, time, primary and up to 50 subsequent diagnoses and procedures that a patient has during that encounter. In comparison, clinical registry data is collected for a specific reason to improve the outcomes of patients, using observational study methods[137]. Registry data that is collected for the purpose of improving quality of health care collect data used to benchmark, analyse and improve specific health outcomes[138]. In Australia, the Australian Commission for Safety and Quality in Health Care developed principles[139] and a framework[140] for the operation of clinical registries. Although clinical registries are useful and credible tools in measuring and monitoring improvements in health care, in recent years, registries have facilitated clinical research and even randomised clinical trials[141].

1.4.3 Administrative Data Coding

The WHO classifies diagnoses into the universally accepted coding structure known as the *International Classification of Diseases* (ICD). Several editions of the ICD coding exist, the eleventh edition was announced by the WHO in 2018. However, the ninth edition is used in American practice and an Australian modified tenth edition is currently used in Australian

practice. The ICD system has been adapted and refined for different countries or health care systems[142,143]. In Australia, the coding standards were developed by the Australian National Centre for Classification in health. Similarly, procedure codes have been developed by the institute known as Australian Classification of Health Interventions (ACHI) codes. For international studies where different editions or coding versions exist, mapping codes are available which enable the cross referencing of these codes. A comparison of the quality of ICD-10-AM to the original ICD-10 coding found 85% accuracy[144]. Comorbidities are grouped into clinically meaningful groups known as Condition Categories (CC)[145,146], further explored in Chapter III of this thesis.

Data linkage refers to the linkage of data from different sources/datasets via a unique common identifier[147,148]. For example, Chapter III of this thesis links hospital administrative records to mortality registry records, for the reporting of mortality rates using a statistical technique known as probabilistic matching[149]. Probabilistic matching is a technique which has been shown to have over 99% accuracy in this context[150]. Gaining access to administrative data and the subsequent data linkage can be complex and tedious for the purposes of research[125,151].

1.4.4 Health Status

Health status is a holistic concept taken from the patient's perspective incorporating their symptoms, functional limitation and quality of life (discrepancy between actual and desired function)[152]. To put this into context, a patient with CHD may present with angina. This patient suffers from functional limitations in daily life which may impede their physical function such as taking daily walks. The physical symptoms of angina may also impact the patient's emotional wellbeing, which may manifest as feelings of depression and limited the

patient's ability to function socially. All these limitations impact the patient's quality of life. Health status aims to determine the impact of disease on a patient's life[153], thus it is a subjective measure unique to every individual patient[154-156]. Health status is conceptualised in Figure 1.0.

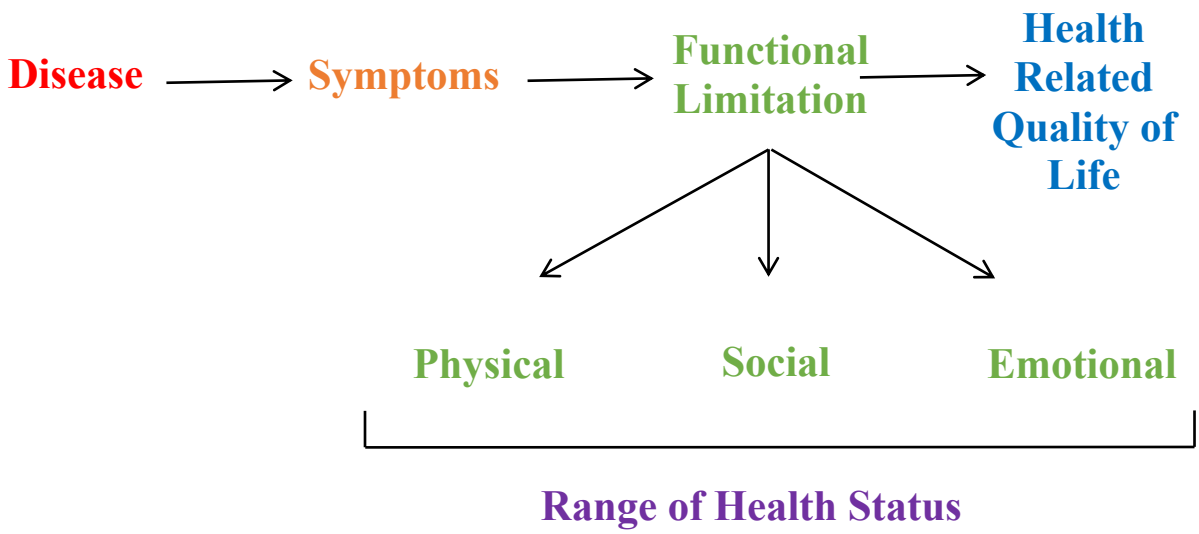

Figure 1.0 An overview of Health Status adapted from Spertus, 2008[157].

Health status is most commonly measured using self-administered questionnaires, which can either be generic or disease-specific and the combination of both instruments is most appropriate to measure changes in health status[158]. The measurement of health status has permitted the clinician to work with the patient to make shared decisions for their treatment[159]. The importance of understanding what the patient values most (such as treatment of symptoms) results in improving health status and has been reinforced by a scientific statement from the American Heart Association[160]. The advances in shared decision making in clinical practice are increasingly important, following concerning evidence that clinicians do not accurately estimate patients' health status[161].

1.4.5 Measuring Health Outcomes

Health outcomes can be assessed using both objective and subjective methods. Objective outcomes are important clinical markers such as readmissions or mortality. Subjective endpoints allow for the assessment of patient's health status and can be measured using patient reported outcome measures to determine quality of life, social health, pain and patient satisfaction[162]. The effectiveness of outcome measures is optimal when a combination of objective and subjective measures are used. ***Surrogate outcomes*** are not the direct measure but are useful in reflecting values that are difficult to measure directly[109]. For example, readmissions are a surrogate marker of hospital performance and quality[116,163-172] and indicative of health care costs[173,174]. In contrast, a meta-analysis of 16 studies of inpatients found no relationship between quality of care and readmissions that occurred within 31 days of discharge[173]. Furthermore, Butala et al[175] has stated that the use of hospital-wide readmission measures are not good surrogates for hospital quality. This was further supported by a recent editorial that referred to the complexity of hospitals and that readmissions cannot possibly reflect hospital performance[176].There are various health outcomes that can be measured, this thesis focuses on readmissions and mortality.

A ***readmission*** is defined as a return to hospital following an index admission within a certain timeframe[173,177,178]. Readmissions can be measured at various time points, including seven days, 15 days, and 30 days after discharge of an index admission. The 30-day time frame is commonly assessed and has clinical relevance[13] as it is believed that if optimal care is provided during the index admission, a poor outcome should not ensue within a month. Moreover, the methods used to measure readmission rates differ between studies, a topic which is further explored in Chapter II of this thesis. Readmissions can either be measured as all-cause or same-cause (for readmissions that have the same diagnosis as that of the index admission). Readmissions have been previously measured and reported as those returns to the

same hospital or to any hospital. Readmission can be further considered as planned or unplanned, defined as related or unrelated to the index hospitalisation. Unplanned readmissions are more commonly reported in the literature because they are thought to reflect the safety and quality of the index hospitalisation[179]. Determining whether a readmission relates to the index hospitalisation is not clearly defined. The distinction between planned or unplanned readmission has been made evident through the Planned Readmissions Algorithm (PRA)[180] created by the Centres for Medicare and Medicaid Services. The algorithm removes planned readmissions as they are not believed to reflect quality of care[180]. Chapter III of this thesis utilises a modified PRA, to accommodate for the Australian modification of the ICD coding.

Additionally, patients who returns to the emergency department without being admitted into the hospital (***"treat and release")*** form a separate outcome. There is debate in the literature as to whether this outcome should form separate outcome to readmissions or whether they should be categorised into the same group as readmissions.

The outcome of ***mortality*** is an objective measure which can also be a surrogate marker of hospital safety and quality. For this purpose, mortality can be measured either in-hospital or at 30 days from the date of admission (unlike readmissions which are measured from the date of discharge). Although the fact of death is a hard outcome, the *cause* of death is not always accurate, due to the decreased number of autopsies performed.

Composite outcomes combine more than one measure of safety and quality and may be favourable because they can measure various aspects in a given cohort[181]. The development of

such measures is complicated because although they provide a broader perspective, they can take away from the impact of specific areas[182].

Avoidable or preventable readmissions are poorly defined in the literature and the classification is usually left to the physician's discretion. A meta-analysis reported that 23.1% of readmissions were preventable, however the definition of preventable readmissions were non-existent in the studies reported[183].

1.4.5.2 Health Outcomes in Acute Myocardial Infarction

Readmission following an index hospitalisation for AMI occurs for approximately one in four patients at one month. Additionally, approximately one in every ten patients will die within one month. These rates are quite variable depending on the study cohort and the methodology implemented. Selected studies and their associated rates have been presented in Table 1.6.

Table 1.6: Reported rates of readmission and mortality following an index hospitalisation for acute myocardial infarction (AMI).

Publication	Cohort/ data source	Year	Outcome definition	Rate (%)
Barbageleta et al.[184]	AMI patients from the GUSTO trial[185] from 15 countries.	1990-93	30-day all-cause readmission.	11.4
Cafagna and Seghieri[186]	Tuscany, Italy retrospective cohort study.	2011-14	30-day mortality.	7.0
Dodson et al.[187]	SILVER-AMI prospective cohort study from the United States.	2013-16	30-day readmission.	18.2
Kim et al.[188]	United States STEMI national readmission database analysis.	2010-14	30-day readmission.	12.3
Krumholz et al.[13]	United States Medicare patients.	2005-08	30-day all-cause readmission. 30-day mortality.	19.94 16.6
Krumholz et al.[15]	United States Medicare patients.	2006	30-day readmission.	12.3
Kwok et al.[189]	United Kingdom AMI registry / retrospective audit.	2012-14	30-day unplanned readmission.	9.1

Li et al.[190]	China PEACE prospective study.	2012-14	30-day all-cause unplanned readmission 30-day mortality.	6.3 0.7
Pinaire et al.[191]	France AMI/PCI.	2009-14	1-month readmission.	27
Rodriguez-Padial et al.[192]	Spanish administrative data.	2012	1-month readmission.	5.4
			3-month readmission.	9.3
			1-year readmission.	20.2
Saczynski et al.[193]	New England population-based sample.	2003-05	12-month readmission.	46
Shah et al.[194]	United States observational study.	2015-16	1-year unplanned readmission.	34
			1-year mortality.	5.4
Tran et al.[195]	Canada AMI + PCI	2004-14	30-day mortality.	0.7

	AMI + CABG			11
	STEMI + PCI			9.2
	NSTEMI + PCI			8.4

1.4.5.3 Health Outcomes in Heart Failure Patients

Compared to AMI readmissions, the readmission of HF patients is well-known to be quite high, particularly within the 30 days following discharge[163,196-202]. Akin to the outcomes of AMI patients, there is variability in the rates of readmission and mortality of HF patients. Table 1.7 outlines the range of readmission and mortality rates of patients hospitalised with HF, although roughly one in every five patients is readmitted to hospital and approximately one in ten patients die within one month of their index admission.

Table 1.7: Reported rates of readmission and mortality following an index hospitalisation for heart failure.

Publication	Cohort/ data source	Year	Outcome definition	Rate (%)
Amarasingham et al.[203]	United States single centre.	2007-2008	30-day mortality. 30-day readmission.	3.1 24.1
Aranda et al.[197]	United States Medicare data in patients hospitalised for HF for the first time.	2002-2004	6-9 months all-cause readmission. 6-9 months all-cause mortality.	24 8
Duflos et al.[204]	Administrative data from French region, median 22-month follow-up.	2012	All-cause mortality. HF readmission.	18 30
Eapen et al.[205]	Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) multinational, double-blind, placebo-controlled trial.	2007-2010	30-day all cause readmission. 30-day all-cause mortality.	11.4 1.2
Krumholz et al.[13]	United States Medicare administrative claims data.	2005-2008	30-day all-cause mortality.	11.17
Krumholz et al.[14]	United States Medicare administrative claims data.	1999-2001	30-day all-cause mortality.	12.1
Santos et al.[206]	Spanish National Health System retrospective analysis.	2012	Mortality in hospital and up to 1-year post-discharge. 1-year cardiovascular readmission.	14.5 32.6

Publication	Cohort/ data source	Year	Outcome definition	Rate (%)
Schaufelberger et al.[207]	Swedish Hospital Discharge Registry.	1988-2000	30-day mortality.	20 to 20 in men. 0 to 17 in women.
Robertson et al.[208]	New South Wales linked data.	2000-2007	28-day all-cause readmission. 1-year all-cause readmission. 28-day all-cause mortality. 1-year all-cause mortality.	27 73 10 28
Vader et al.[209]	Post hoc analysis of three acute HF trials.		30-day all-cause readmission/death. 60-day all-cause readmission/death.	26 38

1.4.6 Readmissions as a Marker of Health Care Safety and Quality

The relevance of readmission rates as a surrogate marker for hospital quality is a contemporary and controversial topic in the literature has been heavily influenced by the pioneering work undertaken in the United States. Standardised mortality rates for individual hospitals became the first outcome measure to be made publicly available in 2007 by the Centre for Medicare and Medicaid Services (CMS)[210]. In 2010, the Affordable Care Act (ACA) implemented the Hospital Readmissions Reduction Program (HRRP) aiming to reduce readmissions and thus health care costs for three targeted conditions: HF, AMI and pneumonia[211]. Following its implementation, the HRRP issued hospitals with higher than expected readmission rates with financial penalties[212]. Between 2007 and 2015, the risk standardised 30-day readmission rates declined from 21.5% to 17.8% among targeted conditions and from 15.3% to 13.1% in non-targeted conditions[213].

Despite the reduction in readmission rates following the introduction of the HRRP, post-discharge mortality rates appear to have risen[214]. This topic is further explored in the Australian and New Zealand context in Chapter III of this thesis. It has been suggested that the observed reduction in readmission rates could be attributed to changes in diagnosis coding resulting in the drastic overestimation of readmission, due to the lack of control groups and standardisation of rates[214]. Additionally, gravely ill patients contribute only to the mortality and not the readmission rate[215], once again contributing to the observed surge of mortality rates.

Patient factors, as opposed to hospital factors, have also been argued to drive readmission rates. One article suggests that focusing purely on readmission reduction due to hospital factors would result in neglecting quality improvement[216]. Moreover, the lack of concordance shown for the three targeted conditions indicates a greater decline compared to other

conditions following the introduction of the HRRP[217]. Accounting for both the combination of hospital and patient factors allows for optimal hospital quality and performance. Following case-mix adjustment of AMI and HF Medicare patients, the variation remained consistent implying the observed variation may be due to hospital quality in addition to other factors[218]. Moreover, analysis of Medicare data between 2014 and 2015 suggested that hospital quality formed a component of the readmission measure, in addition to patient factors[219].

1.4.8 Readmission Risk Prediction Models

Risk prediction models in health aim to predict which patients are most at risk for a certain outcome. By prospectively applying risk prediction models, patients at high risk for adverse outcomes could be identified and targeted for prevention of events. Different tools can be implemented to help predict which patients are at higher risk, as it been acknowledged that clinical providers are unable to accurately predict which patients will require readmission[220]. There are various proposed and potential risk factors for readmission such as demographic, socioeconomic and disease severity factors. Although there have been several prediction tools devised to help clinicians determine which patients are most at risk of readmission, they have been found to be poor predictors in general medical patients[221]. Two commonly used screening tools are the LACE index[222] and HOSPITAL score[223]. Although both have been validated in general and surgical patients, the LACE index uses more readily available variables and was developed in a Canadian setting (whose health care system is universal and more comparable with an Australian setting). The development of risk models and risk stratification allow for the identification of patients at higher risk of a certain outcome. There are multiple models available to predict readmission and mortality risk which have shown variable performance (refer to Table 1.8).

Table 1.8: Different models for predicting readmission and/or mortality. The C statistic is a measure of model discrimination, it measures the function (both the sensitivity and specificity) of the model. The C statistic values lie on a range of 0.0 to 1.0 (perfect prediction). A C-statistic scores of 0.5 is a random chance, C statistic scores of <0.7 are inadequate, C statistic scores of 0.7-0.8 are acceptable and C statistic scores of 0.8-0.9 are excellent[224].

Risk Model	Original Validation Population	What does it measure? Or Outcome measure?	Model discrimination / performance
Amarasingham et al.[203]	United States single centre HF patients 2007-2008 using electronic health records.	30-day readmission. 30-day mortality.	C statistic = 0.72 C statistic = 0.86
Bottle et al.[225]	English general medical inpatients (2000-2001) derived using administrative data.	Future emergency admissions.	ROC score = 0.72
Centres for Medicare and Medicaid Services AMI model[226]	United States Medicare patients (aged ≥65 years) 2005-2006 derived using administrative data.	30-day all-cause unplanned readmission.	C statistic = 0.63

Centres for Medicare and Medicaid Services HF model[227]	United States Medicare patients (aged ≥65 years) 2005-2006 derived using administrative data.	30-day all-cause unplanned readmission.	C statistic = 0.60
Risk Model	**Original Validation Population**	**What does it measure? Or Outcome measure?**	**Model discrimination / performance**
Global Registry if Acute Coronary Events (GRACE)[228]	Europe, Australia, New Zealand, North and South America registry of ACS patients between 1999-2005.	6-month mortality. 6-month mortality or myocardial infarction.	C statistic = 0.81 C statistic = 0.73
Hammill et al.[134]	United States linked data from the *Get With The Guidelines–Heart Failure* Registry with Medicare claims data between 2004-2006.	30-day mortality. 30-day readmission.	Administrative data only AUC=0.718 Administrative + registry AUC =0.761 Administrative data only AUC = 0.587 Administrative + registry AUC =0.599

HOSPITAL[223]	United States general medical patients using administrative and clinical data between 2009-2010.	Potentially avoidable 30-day readmission.	C statistic = 0.71
Risk Model	**Original Validation Population**	**What does it measure? Or Outcome measure?**	**Model discrimination / performance**
LACE index[222]	Canadian general medical and surgical patients using administrative data between 2004-2008.	30-day readmission and/or mortality.	C statistic = 0.684.
LACE+ index[229]	Canadian medical and surgical patients using administrative data between 2003-2009.	30-day readmission and/or mortality.	C statistic = 0.771.
QRISK[230]	United Kingdom aged 35-74 who did not have diabetes and existing cardiovascular disease at time of recruitment between 1995-2007.	10-year risk of a cardiovascular event.	Women ROC = 0.7879. Men ROC = 0.7674.

QRISK2[231]	England and Wales using QResearch database between 1994-2010.	10-year risk of developing cardiovascular disease.	Women ROC = 0.842. Men ROC = 0.828.
Systematic COronary Risk Evaluation (SCORE)[232]	Model was derived from 12 European countries using general population between 2003-2015.	10-year cardiovascular-related mortality.	ROC reported for individual countries = 0.71 to 0.84.
The Reynolds Risk Score[233]	United States women aged over 45 years using 35 risk factors between 1992-2004.	10-year cardiovascular event.	Best fitting model C statistic = 0.809.

1.4.8.1 LACE Index

The LACE index was developed in Canada as a simple, easy to use tool to predict a patient's risk of readmission or mortality in the 30 days post discharge[222]. The LACE index is comprised of four sections (length of stay, acuity of admission, comorbidity as per the Charlson comorbidity index[234] and emergency department visits in the prior six months) that can be answered retrospectively from case notes[222]. Internal validation of the LACE index in a cohort of medical and surgical patients found good accuracy (C statistic of 0.684)[222].

The LACE index has been further validated in various international disease cohorts resulting in varying degrees of accuracy. Among cardiovascular cohorts, patients with HF have been the most widely assessed cohort and have reported mixed accuracy of this tool. Two separate studies in different Canadian provinces reported a C statistic of 0.59 in patients with HF[235,236]. In contrast, a study of HF patients in the United States found that the LACE index was not a reliable measure to predict readmission[237]. Additionally, an abstract presented at the 2016 Cardiac Society of Australia and New Zealand reported that the LACE index was a strong predictor (C statistic = 0.82) of 30-day readmissions in 246 patients with ACS[238]. The use of the LACE index as a predictor of readmissions and mortality in a local cohort of patients hospitalised with an AMI and undergoing angiography is explored in chapter IV of this thesis. Despite best efforts, risk prediction models are still evolving and have poor performance, this may be due to the theory of post hospital syndrome.

1.4.9 Post Hospital Syndrome

As described in section 1.4.8.1, the risk prediction models are poor and thus this is an evolving field due to the uncertainty surrounding the potential causes of readmission. A hypothesised cause of readmission is post hospital syndrome, proposed by Professor Krumholz as an 'acquired, transient period of vulnerability' that occurs during the patients

index hospitalisation[239]. Professor Krumholz suggests that a readmission that occurs within 30 days of discharge and is rarely related to the index diagnosis[239]. During the inpatient admission patients suffer from a range of psychological and physiological stressors, which are beginning to be explored in the literature. Physiological stressors include the loss of muscle mass and strength due to the decreased mobility in hospital stay[240], which can manifest as newly developed disability which continues when the patient returns home and has impaired functioning in performing daily activities[241-243]. In addition, inpatients may experience decreased appetite or dietary restriction, such as sodium restriction for HF patients, which may lead to malnutrition of patients[244]. The index hospitalisation may also cause patients to experience delirium or altered cognition due to administration of medications, which has been shown to continue post discharge[245]. Psychological stressors may be exacerbated due to the pain and discomfort experienced by the patient. More recently, the concept of sleep disruption during the index hospitalisation has been hypothesised as a potential contributor to the observed patient readmission, a concept further explored in Chapter V of this thesis.

1.5.0 Sleep

Sleep has been defined throughout the ages in various ways. Scientifically, sleep is described as an altered state with an impaired level of consciousness to the external world[246]. Sleep is divided into two alternating stages, Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM), where REM sleep is composed of four stages. Table 1.9 compares the physiological properties of REM and NREM sleep.

Table 1.9: Physiological components of normal sleep, comparing REM to NREM sleep.

	REM	**NREM**
Heart rate and BP	Increased, makes myocardial infarction more likely in the morning[247].	Reduced BP[248].
Respiratory rate	Increased[249,250] and increased airway resistance[251].	Reduced respiratory rate[248].
Cardiac		Decreased cardiac output[252,253] and reduced heart rate[248].
Body Temperature		Decreased[248,254].
Muscle tone	Atonia with rapid eye movements[248].	Reduced vasomotor tone and motor activity[248].
Metabolism	Reduced[255].	Reduced[248].
Cognition	Promotes emotional healing, brain restoration and growth[254]. Emotional contents of dreams[248].	
Others		Decreased/concentrated urine and sympathetic nerve activity, increased endocrine, promotes healing and growth[254] and intestinal motility[248].

Sleep is beneficial for restoration[256], particularly of the heart[257]. Poor sleep has been associated as a risk factor for CVD[258]. Sleep also restores energy and well-being, [259] encourages memory consolidation [260] and strengthens immunity[261].

1.5.1 Fragmented Sleep

Sleep fragmentation is defined as the interruption of an entire 90 minute sleep cycle or the lack of normal order of sleep stages[254]. Logically, it is anticipated that the unfamiliar hospital environment may cause disrupted sleep in addition to pain, noise, other patients, emergencies and being woken to take medication[262]. As expected, a British study comparing sources of sleep disturbance in hospital from the perception of nurses and patients[262] found that 65% of patients had good sleep at home and 22% of these patients felt they had poorer sleep in hospital[262]. Similarly, other studies[262,263] have reported poorer sleep during the index hospitalisation compared to sleep at home. Moreover, various studies have shown that sleep disruption in hospital is associated with negative patient outcomes[264-269].

As opposed to the 'normal' physiology of REM and NREM sleep described in Table 1.7, deprivation of either stage of sleep results in pathophysiology with different symptoms. Deprivation of NREM sleep has been associated with fatigue, restlessness, decreased pain tolerance, anxiety, increased illness, increased secretions of cortisol, increased immunosuppression, delayed healing, nausea, diarrhea, constipation, headache, vertigo, discoordination and neck muscle weakness[254]. Deprivation of REM sleep has been associated with alertness, apathy, irritably, confusion, disorientation, combative, delusions, hallucination and decreased steroid secretions[254].

Sleep deprivation and fragmentation of sleep has been shown to negatively interfere with the healing process of patients[270]. A study of 42 healthy adults found a significantly lower total

sleep time (TST) after one night of sleep deprivation (0.74±1.39 hours vs. 7.33±0.52 hours, $p<0.001$) and that increased arterial stiffness was associated with the sleep deprivation[271]. CVD resulting from either short duration or poor sleep has been associated with inflammation[272], immunosuppression, disorientation[254], hypertension[273] and rapid heart rate[274].

1.5.2 Sleep and Mortality

Overall sleep duration is associated with mortality in a U-shaped curve with the highest risk found for short and long sleepers and the lowest risk in individuals who reported sleeping for an average of seven to eight hours[275-278]. A 12-year prospective study in the Netherlands of patients without a history of CVD was conducted to investigate the association between sleep duration and CVD incidence[279]. Compared to participants who had seven to eight hours of sleep, those with less than six hours of sleep had a 15% higher risk of CVD incidence. However, no association was found between those who slept for more than nine hours and CVD incidence.

1.5.3 Measuring Sleep

Similar to health outcomes, sleep can be measured both quantitatively and qualitatively. TST is defined as the duration (usually reported in minutes) of sleep within a 24-hour period[280,281]. The amount of sleep varies depending on several factors (including age and amount of daytime activity) and is unique to every individual, however there is general consensus that an average adult requires between seven and nine hours of sleep[248,282]. TST has been shown to be associated with health outcomes in CHD patients[279,283-285]. Both long and short[279,284-289] TST are associated with adverse CVD outcomes (including AMI, angina and stroke)[290].

Poor sleep quality can lead to mood disturbance, cognitive inefficiency, motor impairment, social discomfort, nonspecific physical ailments, reduced productivity, health related quality of life[291-295] and has been related to CVD[279,287-289,296,297]. Moreover, resulting difficulties in cognition have been shown to impair patient's self-care[260,298].

1.5.3.1 Polysomnography

Polysomnography (PSG) was introduced in 1974[299] and is the gold standard measure for examining sleep patterns. PSG can detect and measure the different stages of sleep by using electrodes that measure brainwaves muscles and eye movement. Although it is the gold standard measure, PSG is expensive and is an intrusive method, hence it can be difficult to use in clinical research.

1.5.3.2 Actigraphy

Actigraphy uses a piezoelectric transducer, worn on a wristband to measure sleep[300] and has been validated against PSG[301]. Actigraphy was first used to measure activity in the 1950's to evaluate for psychological disorders in children[302]. Although the use of actigraphy was deemed useful as a research instrument by the American Academy of Sleep Medicine, in 1995, its use clinically remained uncertain[303].

A Danish study validated the Phillips ActiGraph against PSG in 37 schizophrenic and five bipolar patients and found good agreement for TST (intraclass correlation coefficient (ICC)=0.78) but low for wake after sleep onset (WASO) (ICC at, or close to zero)[304]. The same model of ActiGraph used in an 8.5 hour sleep study in a laboratory found high sensitivity (0.9565), low specificity (0.329) and high accuracy (86%) between the two techniques[305]. Similarly, another validation study of 108 healthy subjects found ActiGraph

and PSG had a sensitivity of 90% and accuracy of 84%, but had low specificity (46%)[306]. The method of actigraphy will be utilised in chapter V of this thesis.

1.5.3.2.1 Total Sleep Time

As referred to in section 1.5.3, TST is defined as the amount of sleep within a 24-hour period[280]. Studies have shown that TST may be underestimated depending on the method used, for example wrist actigraphy may underestimate TST when compared to PSG[306,307]. However, a review reported that TST measured by actigraphy compared to PSG found good to very good correlation (between 0.7 and 0.98)[308]. Interestingly, some studies have found that TST is related to health outcomes[309].

1.5.3.2.2 Wake After Sleep Onset

WASO is defined as the number of minutes that the patient stays awake beginning from the time the patient falls asleep until they wake up[280]. A validation study compared WASO measured by actigraphy as opposed to PSG and found that actigraphy overestimated WASO by 32% on average [306].

1.5.4 Sleep Quality

In addition to measuring the objective quality of sleep as described above, subjective measures of sleep quality can also be analysed using validated questionnaires.

1.5.4.1 Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) was first introduced in 1988 and aims to determine a patient's perception of their own sleep quality over the past month[310]. The PSQI

is comprised of seven components: sleep quality, sleep latency, sleep disturbance, sleep duration, sleep efficiency, sleep medication use and daytime dysfunction, which provide an overall global score from zero to 21. Higher scores indicate poorer sleep and scores greater than five are used to distinguish between good and poor sleep with 89.6% sensitivity and 86.5% specificity[310,311]. Validation of the seven components of the PSQI have found high overall internal consistency (Cronbach's alpha coefficient = 0.83)[310]. Test-retest correlation coefficients for each component ranged from 0.65 (medication use) to 0.84 (sleep latency)[310]. The PSQI correctly distinguished between 88.5% of good and poor sleepers (kappa = 0.75, $p<0.001$) with sensitivity of 89.6% and specificity of 86.5%[310].

A study of 152 thoracic surgery patients in the intensive care unit were asked the PSQI and 46.1% reported poor sleep quality in hospital (pain was a major factor significantly related to their poor sleep quality)[312]. A systematic review of 22 studies that used the PSQI found disturbed sleep for up to one-year post-discharge[313].

1.5.4.2 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) was first introduced in 1991 to measure the patients likelihood of falling asleep during the day[314]. The ESS is scored from zero to 24, with higher values indicating greater excessive daytime sleepiness. The ESS has been validated in populations with both sleep and neurological disorders[311,314,315].

1.5.4.3 STOP BANG Questionnaire

The Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference and Gender (STOP BANG) questionnaire is an eight-item questionnaire that screens a patient for obstructive sleep apnea (OSA). Scores greater than or equal to three have

been shown to have high (93% for moderate OSA and 100% for severe OSA) sensitivity in the detection of OSA[316]. Moreover, two independent studies[317,318] of patients in sleep clinics have validated the STOP-BANG questionnaire. A study of 6369 patients screened for OSA using the STOP-BANG questionnaire found that a score lower than three do not have OSA and scores between five and eight can identify patients with a greater probability of moderate to severe OSA[319]. The STOP BANG questionnaire has been successfully used clinically, to screen for OSA in preoperative patients[320,321].

Summary

This summary of the literature identifies explicit gaps regarding Australian readmissions. For example, the Australian rates of readmission for cardiovascular disease are unknown and thus their impact on the Australian health care system is also unknown. This thesis aims to address these gaps in the literature by conducting a thorough review of all Australian literature followed by an evaluation of the readmission and mortality rates following admission to hospital for heart failure in Australia and New Zealand. Moreover, as indicated above, although readmission prediction models have been derived, their accuracy in Australian cardiovascular cohorts have not been reported. This thesis assesses the accuracy of the LACE index to predict readmissions and mortality in a cohort of patients undergoing angiography. There is also a need to determine which factors may play a role in readmissions, thus sleep quality and quantity will be explored as a potential cause of readmissions. To evaluate the proposed aims, the integration of various methods will be applied including a scoping review, big data techniques including the use of administrative and registry data and a clinical pilot study.

Chapter II

Readmissions following Hospitalisations for Cardiovascular Disease: A Scoping Review of the Australian Literature

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This results chapter is reproduced in the exact form as it appears in the manuscript "**Readmissions following Hospitalisations for Cardiovascular Disease: A Scoping Review of the Australian Literature**," authored by **Clementine Labrosciano**, Tracy Air, John F. Beltrame, Rosanna Tavella and Isuru Ranasinghe and published in *Australian Health Review* in February 2019. DOI: https://doi.org/10.1071/AH18028.

In keeping with the style of this thesis, the abstract has been removed, the table and figures renumbered, the references have been incorporated into the thesis's master reference list, the supplemental appendices appear in the thesis's Appendix B and the manuscript has been repaginated.

Statement of Authorship

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Principal Author

Name of principal author (candidate)	Clementine Labrosciano		
Contribution to the paper	Acquisition of data, analysis and data interpretation, draft manuscript, critical revision and study conception and design.		
Overall Percentage (%)	80		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	03/06/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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2.0 Introduction

Cardiovascular disorders are among the most common cause of hospitalisation in the Australian Health System with more than 500,000 hospitalisations occurring annually[9]. This care is expensive, consuming 40% of the total national health care expenditure on cardiovascular disease (CVD)[322]. International studies have suggested that many of these hospitalisations are due to readmissions. Selected populations in the United States have found that one in four patients with heart failure (HF) are readmitted within 30 days[12], rising to one in two at six months[323]. Similarly, 15% of stroke patients are readmitted by 30 days[324], rising to 20-40% by one year[325]. High rates of readmission are also reported in selected populations in the United States for common conditions and procedure such as acute myocardial infarction (AMI) (19% by 30 days), percutaneous coronary intervention (PCI) (15% by 30 days)[326] and peripheral artery revascularisation (17.6% by 30 days)[327]. A proportion of these readmissions are inevitably due to the underlying condition. Nevertheless, a large proportion may be avoidable. Readmissions occurring due to preventable reasons such as hospital acquired infection, thromboembolism and medication errors are frequent, with a systematic review suggesting that at least a quarter of all readmissions are preventable[183]. Thus, reducing hospital readmissions is highly desirable to improve patient care and minimise avoidable health care expenditure.

Driven by the international findings, clinicians and policymakers in Australia are also increasingly focusing on reducing readmissions with cardiovascular conditions frequently touted as a priority condition. For example, the New South Wales (NSW) government plans to reduce the rates of unplanned readmissions by the year 2021[328]. However, readmission may be driven by contextual factors and international data may have limited relevance to the Australian setting. For example, Australia's universal health care system allows equal access to health care services, compared to the fee-for-service model implemented in countries such

as the United States. More affordable and accessible health care in Australia may result in lower rates of readmission. Thus, efforts to reduce readmissions through clinical or policy intervention requires an understanding of readmissions in the Australia setting including the frequency of readmissions, potential contributing factors and the impact of readmissions on the health system.

Accordingly, we conducted a scoping review of the Australian literature to identify and synthesise available evidence regarding readmissions following a hospitalisation for cardiovascular conditions. Our primary objective was to systematically evaluate the Australian literature with the intention of determining the frequency of readmission. Secondary objectives included (a) identifying the patient, hospital and social factors that contribute to the risk of readmissions, (b) detailing the potential impact of readmissions on the health care system, and (c) describing interventions that have been assessed in the Australian setting to reduce readmissions.

2.1 Material and Methods

2.1.1 Search Strategy

We searched Medline (Medical Literature Analysis and Retrieval System Online), EMBASE and CINAHL (Cumulative Index to Nursing and Allied Health Literature) bibliographic databases, restricting the search to English-language human clinical research articles published between 1 January 2000 and 11 March 2016 to review contemporary cardiovascular practice. We conducted the search using Medical Subject Heading [MeSH] terms including patient readmission, cardiovascular disease, coronary disease, cardiac surgical procedures and Australia. The full search strategy can be found in Appendix B (S1-S3).

We also searched the grey (non-academically peer-reviewed) literature by examining the reference lists of retrieved papers and conducting a Google search to identify any additional articles and other policy documents. This included an exhaustive search of Australian government and non-government stakeholder websites for publications on the topic of readmission following cardiovascular hospitalisations. A complete list of the grey literature search is available in Appendix B (S4).

2.1.2 Study Selection

We included observational studies of cardiovascular readmissions and studies reporting outcomes of interventions to reduce cardiovascular readmissions. Cardiovascular readmissions were defined as (1) articles where the primary or secondary objective related to readmissions; or (2) where hospital readmission was the primary outcome or a substantive secondary outcome. Included studies were required to recruit at least 100 adult (aged over 18 years) cardiovascular patients from Australia and measure readmissions following an inpatient admission for a cardiovascular condition. We excluded (1) review articles without original data; (2) studies that included readmissions as a composite endpoint but failed to report readmission data separately; (3) multi-national studies that included data from Australia, without reporting Australian data separately; and (4) studies that reported more than 50% of the data collected prior to the year 2000.

2.1.3 Assessment of Methodological Quality

Abstracts were independently screened by two investigators (CL, IR). All potentially relevant articles were extracted and reviewed in full by the same two researchers for methodological

validity prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) Appendix B (S5). Disagreement on article selection was resolved by discussion between reviewers.

2.1.4 Data Extraction and Synthesis

Relevant data were extracted from each article and entered into a standardised database. Data extracted from all articles included sample size, study design, study period (years), number of centres, state(s), study aim, study hypothesis, primary outcome, time of readmission measurement, type of rehospitalisation (inpatient readmissions, emergency, or both), factors affecting readmission, findings, strengths and weakness. We assessed for data heterogeneity by evaluating study design, methodology and reporting. We performed a statistical test of heterogeneity, where appropriate, using the I^2 test[329]. We reported our findings using the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines[330].

2.2 Results

The search yielded 794 articles and two government reports of which 729 remained following exclusion of duplicates. Based on abstracts, 657 articles were removed, with 72 full texts articles remaining. We identified 25 observational studies that reported readmissions as an outcome (Table 2.1). Furthermore, we identified 10 studies that described the outcomes of interventions to reduce readmissions (Table 2.2).

Table 2.1: Characteristics of Observational Studies.

Study	Condition(s)	Number of hospitals	Number of patients	Setting	All cause vs. Disease specific readmissions counted	Readmitted to same vs any hospital	Method to measure readmission	Rate (%) unless indicated otherwise				
								≤30 days	1-6 months	6 months	12 months	≥12 months
Saito et al (2015)[331]	HF	2	468	Tas	All	Any	Linked	17				
Huynh et al (2015)[332]	HF	State-wide	1537	Tas	All	Any	Linked	21				
Robertson et al (2012)[208]	HF	State-wide	29161	NSW	All	Any	Linked	27				
					HF			11				
					All						73	
					HF						32	
Paul et al (2008)[333]	HF	1	133	SA	All	Same	Phone call	25		43		
Islam et al (2013)[334]	HF	Multicentre	6252	VIC	HF	Any	Not reported	10				
Betihavas et al (2015)[335]	HF	3	280	NSW, QLD, SA	Cardiac condition	Same	Not reported	13				66
Pathik et al (2016)[336]	HF	1	1704	SA	Cardiovascular	Same	Linked					74 treated by general cardiologist v. 77 subspecialists
	ACS		7763									57 treated by general cardiologist v. 50

												subspecialists
	Arrhythmia		4398									61 treated by general cardiologist v. 50 subspecialists
Oldland et al (2014)[337]	HF	Not reported	135	VIC	All	Same	Not reported				56	
Lefkovits et al (2015)[338]	HF	13	289	VIC	All	Any	Linked	26				
	PCI	23	9166					13				
Bureau of Health Information (2015)[339]	AMI	53	27325	NSW	All	Any	Linked	17				
	Stroke	47	12776					11				
	HF	72	29961					23				
Kilkenny et al (2013)[340]	Stroke	1	788	VIC	All	Any	Linked	15		36	42	
Kilkenny et al (2013)[341]	Stroke	35	3328	NSW	All	Same	Hospital records	7				
Cadilhac et al (2016)[342]	Stroke	40	3007	VIC	All	Any	Phone call		22 treated in stroke unit, 24 in other unit (p=NS)			
He et al (2015)[343]	Stroke	5 (state-wide)	2105	NT	Stroke	Same	Hospital records				8 Indigenous, 6 non-Indigenous	13 Indigenous 10, non-Indigenous

Yu et al (2016)[344]	Stroke	1	182	NSW	Stroke	Same	Hospital records and phone call			5		
Nguyen et al (2015)[345]	AF	1	302	NSW	All	Same	Hospital records and phone call			41		
Rana et al (2014)[346]	AMI	1	1660	VIC	IHD	Same	Hospital records	6	9	12	15	
					All			13	19	25	31	
Kociol et al (2012)[347]	AMI	296 (# from Australia not reported)	Total=5571, Australian=465	Not reported	All	Same	Not reported	13 (Australia), 11 (overall)				
Parker et al (2008)[348]	ACS	1	489	NSW	Cardiac-related	Same	Hospital records and phone call		13 (2-12 months)			
Worrall-Carter et al (2016)[349]	ACS	State-wide	28985	VIC	All	Any	Linked					10 female, 11 males
Dwyer et al (2008)[350]	ACS patients with and without significant CAD	1	180	NSW	All	Same	Hospital record and face to face assessment				7 NOCAD, 39 CAD	
					Cardiovascular						14 NOCAD, 11 CAD	
Murphy et al (2008)[351]	CABG	1	181	VIC	Not reported	Any	Phone call	14				
Tully et al (2008)[352]	CABG	1	222	SA	Related to the surgical procedure, cardiovascular or vascular disease.	Any	Hospital record and phone call			32		

Slamowicz et al (2008)[353]	CABG	State-wide	6627	VIC	All	Any	Linked	7 = 7 days 15 = 30 days	32	
Atkins et al (2014)[354]	ATD	1	6172	WA	ATD	Any	Linked			32

Abbreviations: ACS = acute coronary syndrome; AF atrial fibrillation; ATD = atherothrombotic disease; CABG = coronary artery bypass surgery; HF = heart failure; AMI = acute myocardial infarction; NOCAD = non-obstructive coronary artery disease; PCI = percutaneous coronary intervention; NOCAD = non-obstructive coronary artery disease; CAD = coronary artery disease; Linked = linked data to other hospitals within the same state.

Table 2.2: Characteristics of studies reporting interventions to reduce readmissions**.**

Study	Condition	Sample Size	Design	Setting	Number of centres	All cause or disease specific	Same vs any hospital	Method to assess readmission	Intervention	Control Group Rate of readmission (%)				Intervention Group Rate of readmission (%)				p value
										≤ 30 days	6 M	12 M	>12M	≤30 days	6 M	12 M	>12 M	
Davidson et al (2010)[355]	HF	105	RCT	NSW	1	All	Same	Not specified	Individualised multidisciplinary 12-week cardiac rehabilitation program			69				44		0.01*
Driscoll et al (2013)[356]	HF	573	Cross-sectional	Not reported	48	All	Same	Hospital records	Chronic heart failure management program		25				14			0.005*
Stewart et al (2014)[357]	HF	280	RCT	QLD, SA, NSW	3	All	Same	Hospital records and phone call	Home vs clinic-based management program.				69.3				67.1	0.887
Roughead et al (2009)[358]	HF	5717	Retrospective cohort	Not reported	Not reported	All	Any	Linked	General practitioner pharmacist collaborative home medication review			12				5.5		HR 0.55, (95%CI 0.39-0.77)*
Barker et al (2012)[359]	HF	120	RCT	VIC	1	All	Same	Hospital records	Pharmacist directed home medication reviews		39				53			0.417
Scott et al (2004)[360]	HF	1524	Before and after design	QLD	9	Same	Same	Hospital records	Policy	7.2				2.4				0.02*
	ACS									5.2				4.2				0.02* #
Mudge et al (2010)[361]	HF	416	Prospective cohort	QLD	3	All	Same	Hospital records	Quality improvement program				36				49	0.009*
Stewart et al (2012)[362]	HF	280	RCT	Not reported	3	All	Not reported	Not reported	Home vs clinic-based management plan				n=547				n=592	NS

Stewart et al (2015)[363]	AF	335	RCT	SA, VIC and ACT	3	All	Same	Hospital records	AF-specific management strategy		502 (3254) ^ days in hospital	485 (2276)^ days in hospital	NS
Martin et al (2016)[364]	MI	470	Before and After	VIC	1	Cardiac	Same	Hospital records	Strategy to reduce door to balloon time	12.8	11.1		0.68 NS

Note: ^ reported as median (IQR). # result was significant but favoured the control. * statistically significant.

Abbreviations: ACS = acute coronary syndrome, AF = atrial fibrillation, HF = heart failure, NS = not statistically significant (P>0.05).

Refer to Figure 2.1 for the PRISMA flow chart of article selection. As studies of interventions typically included highly selected populations, we report our findings for observational and those of interventions separately from herein.

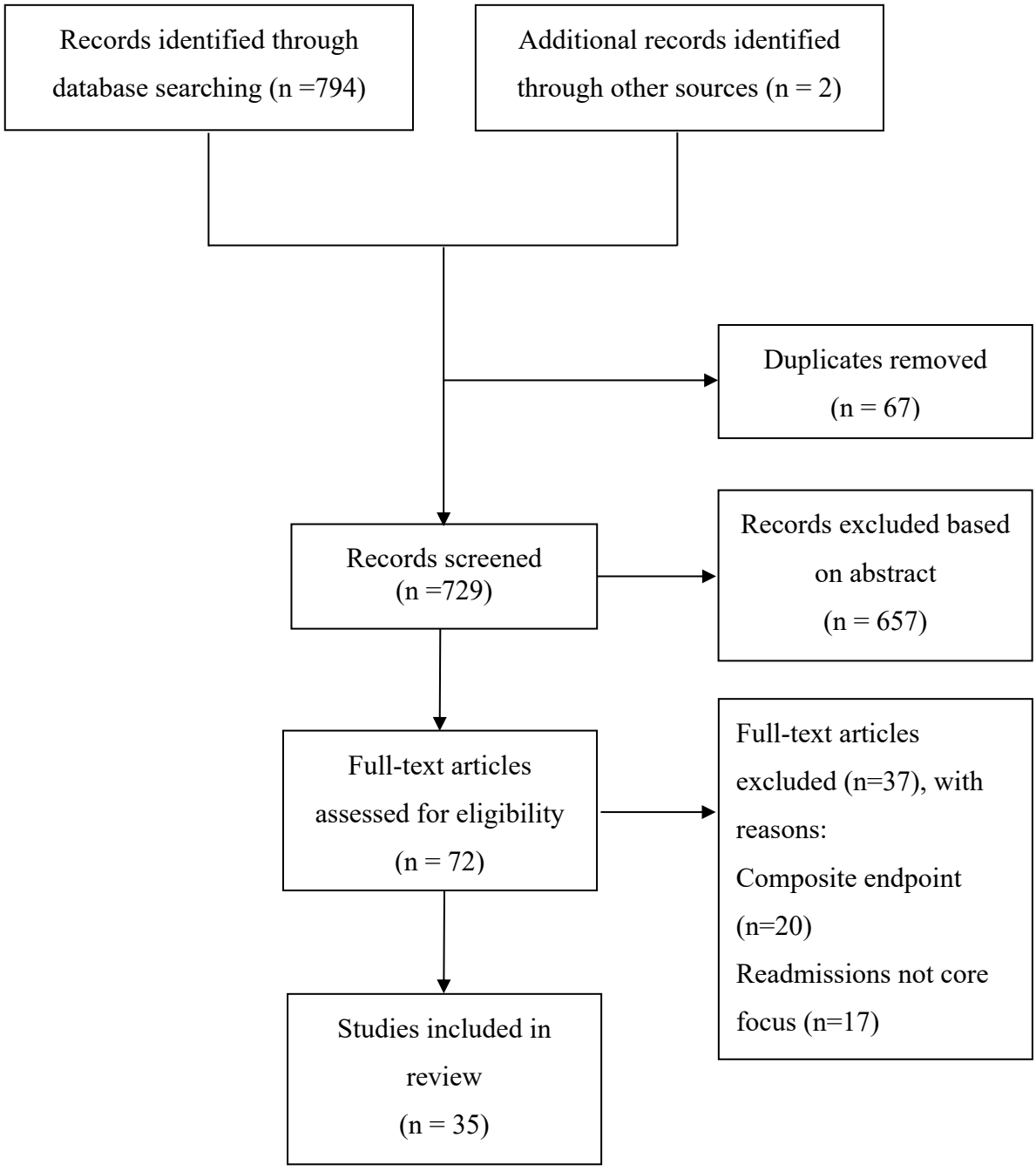

Figure 2.1: PRISMA flow chart of article search and selection for inclusion in the systematic review.

2.2.1 Characteristics of Observational Studies of Readmissions

Of the 25 included articles and reports, most (n=11) were single centre[333,336,340,344-346,348,350-352]. Less frequently, they were multicentre (n=7)[331,334,335,338,339,341,342] or state-wide (n=5) studies[208,332,343,349,353] with two[337,347] failing to report the number of centres. The sample sizes of these studies varied from 133 to 29,961 participants, with a median value of 1,660. Fourteen study designs involved retrospective cohorts[208,331,332,338-341,343,346,347,349,350,353,354] with the majority limited to Victoria (n=9)[334,337,338,340,342,346,349,351,353] and NSW (n=8)[208,335,339,341,344,345,348,350].

Most studies reported readmissions following a hospitalisation for HF (n=10), acute coronary syndrome (ACS) (n=7) and stroke (n=6) with some studies reporting readmission rates for more than one condition. In addition, four publications reported readmission rates following procedures: PCI (n=1) and coronary artery bypass graft (CABG) surgery (n=3). Readmission rates following hospitalisation for other cardiovascular conditions and procedures were infrequently reported.

When the primary objective of studies was considered, most (n=14) focused on determining the frequency of readmission[331,333,336-340,342,343,345,349,350,365], while several (n=8) studies evaluated one or more factors associated with readmissions including the development of a readmission risk model[332,335,344,346,348,351-353]. Two studies evaluated the burden (defined as bed days and costs) of readmissions on the health care system[208,354] and a single study compared Australian readmission rates to other nations[347].

2.2.2 Definition of Readmissions and Methods for Data Collection

The definition of readmission was highly variable between publications. All-cause readmission was reported in 16 studies[331-334,337-342,345,347,349,353], eight studies[334-336,343,344,348,352,354] chose to report only patients returning to hospital for the same cardiovascular diagnosis as their index hospitalisation and one study[351] did not report the type of readmission measured. About half of the studies (n=13) fully captured readmissions by counting readmissions to any hospital in the same state[208,325,331,332,334,338-340,342,349,351-354], while the remainder (n=12) only counted readmissions to the same hospital[333,335,337-339,341,343-347,350]. The time interval following discharge ranging from seven days to five years with most reporting readmission rates at 30 days post-discharge.

Methods used to collect readmission data varied greatly. Telephone follow-up (n=3) [333,342,351], hospital medical records (n=3) [341,343,346], linked hospital administrative data (n=10) [208,331,332,336,338-340,349,353,354], or a combination of more than one of these methods[344,345,348,350,352] were used to determine readmissions status of patients and four studies[334,335,337,347] did not report a method. The completeness of follow-up was not reported for most studies[208,332,334-336,340,341,343,345-347,349,350,352-354,366]. Among those that did report complete follow-up of all participants enrolled in the study, only three[331,333,337] reported complete follow-up, with the remaining reporting loss to follow-up rates ranging from 0.2% to 52% of the study population[338,339,342,344,348,351].

2.2.3 Frequency of Readmissions

All studies reported the frequency of readmissions at various time points (Table 2.1), with readmission rates generally (and expectedly) increasing with time. Eleven studies[331,333,337-342,345,349,350] reported all-cause readmissions and as expected, these studies reported higher rates of readmission compared to studies reporting readmissions for the same diagnosis as the index hospitalisation (Figures 2.2 and 2.3).

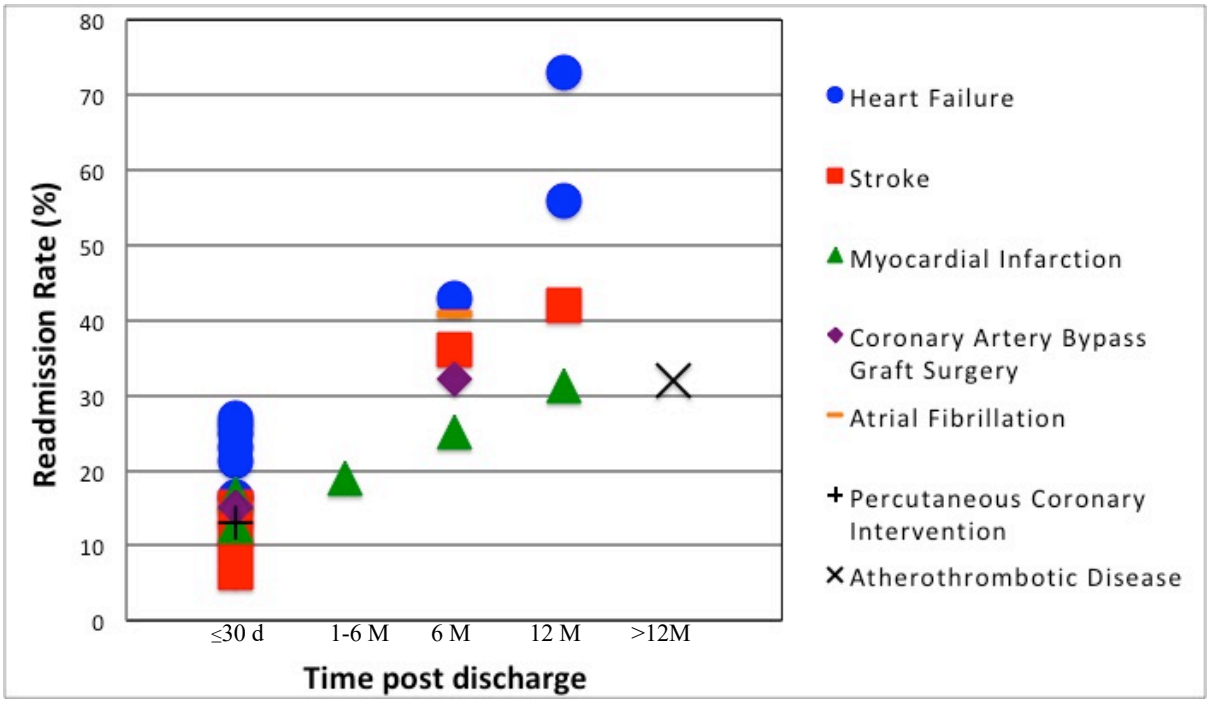

Figure 2.2: All-cause rates of readmissions by disease or procedure.

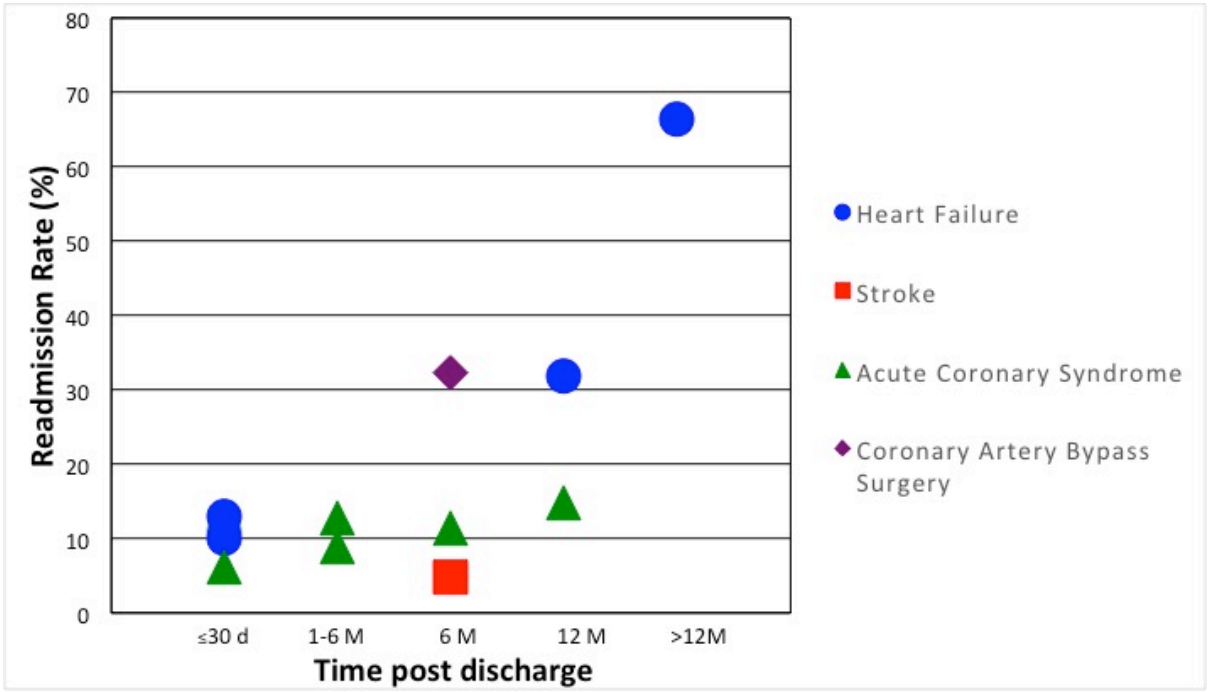

Figure 2.3: Same cause readmission studies by disease or procedure.

Of the studies that reported readmissions as a proportion of all patients discharged, readmissions were most commonly reported at, or within 30 days of the index hospitalisation (n=14) [208,331,332,334-336,338-341,346,347,351,353]. The all-cause readmission rate among these studies was highly variable, ranging from 6.3% to 27%, with a median value of 13%. When individual conditions for the initial hospitalisation were assessed, 30-day all-cause readmission following HF (n=8 studies) ranged from 10.1% to 27% (median 18.9%), stroke (n=3 studies) ranged from 6.5% to 11% (median 11%), AMI (n=3 studies) ranged from 12.7% to 17% (median 12.9%).

Extractable 30-day data were available in 11 studies (n= 123,874, Figure 2.3). However, we could not pool the results of the individual studies to provide a summary frequency of readmissions due to high heterogeneity among studies (Q-test: $\chi^2 = 2395.9$, $p<0.001$; $I^2 = 99.5$). Significant heterogeneity persisted when individual conditions were evaluated prohibiting pooling of results by condition: HF (n=6 studies)[208,331-333,338,339] $\chi^2 = 177.27$, $p<0.001$, $I^2 = 97.2\%$; AMI (n=3 studies)[339,346,347] $\chi^2 = 21.65$, $p<0.001$, $I^2 = 90.8\%$; stroke (n=3 studies)[339-341] $\chi^2 = 54.71$, $p<0.001$, $I^2 = 96.3\%$).

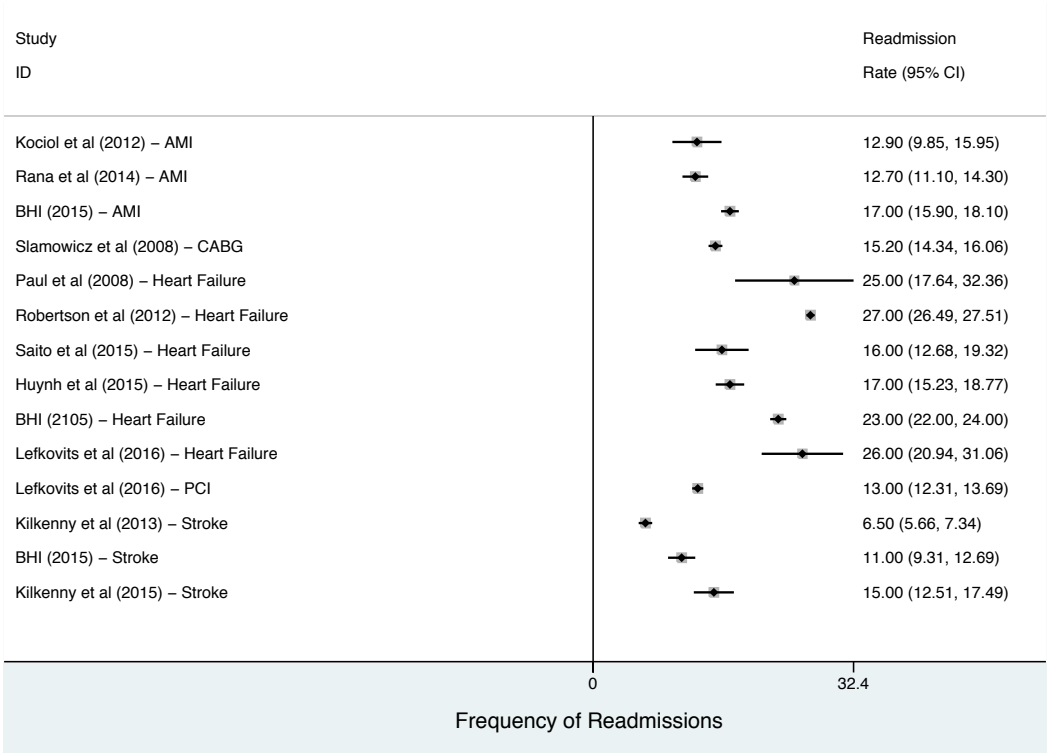

Figure 2.3: Forest plot of 30-day all-cause readmissions. Note that some studies reported data for more than one cohort. Abbreviations: AMI = acute myocardial infarction, CABG = coronary artery bypass graft surgery, PCI = percutaneous coronary intervention.

Of the studies that reported 30-day readmission rates, one study assessed variation in readmission rates among hospitals for AMI, HF and stroke with the results indicating marked institutional variation in the risk standardised readmission ratio at 30 days although the range among hospitals was not reported[339]. Of the studies that reported readmission rates beyond 30 days, the highest number of readmissions were reported among patients with HF (76.9% of patients were readmitted for a cardiovascular-related diagnosis, during a median follow-up time of 5.3 years)[336].

2.2.4 Risk Factors Associated with Readmissions

A risk model to predict readmission or evaluate specific patient factors associated with an increased risk of readmission was developed in eight studies[332,335,344,346,348,351-353]. These used data from single[332,344,346,348,351,352] and multiple[335,353] centres and evaluated readmissions following an index hospitalisation for HF[332,335], ACS[346,348], CABG surgery[351-353] and ischaemic stroke[344]. Appendix B (S6) provides a list of all patient factors tested in risk prediction models.

Patient factors that were significant in models were varied but included length of stay[332] and living alone[332,351], prior emergency department attendance[346,353], prior cardiac diagnosis and procedures[346], renal impairment[346], electrolyte disturbance[346], sedentary lifestyle[339], older age[339] and a higher score on the Charlson comorbidity index[335,353]. Two studies[348,352] evaluated whether psychiatric comorbidities increased the risk of readmission. A study of ACS patients found readmissions to be more prominent in patients with pre-existing depression or developed depression after their ACS, compared to patients without a history of depression (χ^2=8.84, df=2, p=0.01) [348]. Similarly, patients with increased stress, anxiety and

depression prior to CABG surgery had increased rates of six-month readmission[352]. Finally, only one study[343] from the Northern Territory evaluated whether Indigenous status increased the risk of readmissions following a stroke. The study concluded the risk of readmission for stroke was almost doubled in Indigenous patients compared to the Caucasian population (HR 1.82, 1.32-2.51).

2.2.5 Studies that Reported the Burden of Readmissions

The burden of readmissions can be measured in various ways including cost, bed days and from the perspective of the patient or health care system. Two studies estimated the burden of readmissions in Australia[208,354]. A single centre study from Western Australia found patients who were readmitted following an index hospitalisation for atherothrombotic disease cost the health care system $101 million over two years, representing approximately 42% of the total cost of care over this period[354]. A study of 29,161 HF patients followed for five years using linked data from NSW measured the burden placed on the health care system by counting the number of bed days[208] showing that there were 954,888 hospital bed-days utilised over the study period as a result of all-cause readmissions.

2.2.6 Studies of Interventions to Reduce Readmissions

Interventions testing the reduction of readmissions as a key outcome were reported in ten studies[355-364], including five randomised control trials[355,357,359,362,363] (Table 2.2). Almost all interventions (8/10) targeted HF[355-362] and consisted of a health professional conducting a structured intervention at either the patients' home (such as home visits by a nurse,

pharmacist or other health care professional) or at a medical facility usually within a few weeks after discharge (refer to Appendix B (S7) for a description of all interventions).

Similar to the observational studies, the definition of a readmission varied. Readmissions were measured at <30 days[360], 6 months[356,359], 12 months[355,358,364] and over 12 months[357,361-363]. Readmissions were counted using linked data by one study[358], another study used a phone call to the patient[362] and the remaining studies used hospital records.

A statistically significant decline in readmissions in favour of the intervention was observed in four studies, although only one was a randomised trial. Davidson et al[355] evaluated an individualised 12-week nurse-coordinated multidisciplinary rehabilitation program for patients with HF in a randomised trial. Patients in the intervention group had a lower 12-month all-cause readmission rate compared to the control group (44% vs 69%, p=0.01). Driscoll et al[356] examined the effect of chronic HF management programs across 27 centres (a mixture of hospital and home-based programs). This study did not evaluate the outcome of the HF management programs against a control group. Instead, each program was ranked using a quality improvement tool (intervention score) based on their level of evidence. Results indicated that those with a high intervention score had a lower readmission rate (14% vs 25%, p=0.005). Roughead et al[358] evaluated whether a home medication review by both a general practitioner and pharmacist among veterans diagnosed with HF reduced readmissions in an observational cohort. A 45% reduction in readmissions was observed for patients who received home medication review. Finally, Scott et al[360] tested hospital performance feedback and a multifaceted quality improvement intervention using a before and after study design. A significant reduction in same-cause readmission was observed with the intervention in patients with HF (7.2% vs. 2.4%, p=0.02) but not in patients with an ACS.

2.3 Discussion

We performed this scoping review to summarise the contemporary Australian literature on readmissions following hospitalisation for CVD. We found 25 studies evaluating hospital readmissions over the past 16 years. We observed a median 30-day readmission rate of 13% (range 6.3% to 27%) with reported readmission rates of 10.1%-27% for HF, 6.5% to 11% for stroke and 12.7% to 17% for AMI. These findings parallel the high readmission rates observed in the international literature. However, these figures should be interpreted with caution as we could not pool readmissions data due to the substantial heterogeneity among studies. Notably, the time point at which readmissions were measured, whether disease-specific or all-cause readmissions were counted, and the method and accuracy of ascertaining the readmissions status varied considerably. Furthermore, we found only few interventions that successfully reduced readmissions highlighting the need for clinical trials to find more effective strategies to reduce readmissions.

Our review also identified several knowledge gaps in the Australian literature. While readmission after HF, stroke and AMI were reported, other common and important conditions such as atrial fibrillation and peripheral arterial disease were rarely studied and readmission rates for these common conditions are unknown. Similarly, the risk of readmission among disadvantaged populations relevant to the Australian setting such as those in regional and remote areas and Indigenous populations are uncertain. Moreover, only one Australian study evaluated hospital variation in early readmission rates despite early readmissions being correlated with quality of hospital care[367]. The substantial variation in the readmission rates among hospitals reported in this study suggests concerning variation in care quality although

whether such variation extends to other Australian regions is uncertain. Finally, we found a paucity of studies assessing the impact of hospital readmissions on the health care system. This information is crucial for developing effective clinical and policy strategies to reduce readmissions because costs and resource considerations are a major driver of decision making for health. Taken as a whole, our research indicates the need for Australia-wide studies of readmissions for common cardiovascular conditions to determine the frequency, the extent of variation among Australian hospitals and regions.

Our review also highlights the need to develop and test clinical interventions to reduce readmissions. Interventions to reduce readmissions that have been trialled in Australia have focused almost exclusively on home or hospital-based management of HF. These long-term disease management programmes focus on reducing disease-specific (HF) readmissions, even though most readmitted patients return to hospital with diagnoses that differ from their index hospitalisation[368,369]. Thus, interventions that solely target the initial condition may be inadequate to reduce all-cause readmissions, which may partially explain the limited effectiveness of interventions observed in our review. While some readmissions inevitably occur due to disease progression the quality of care transition from hospital to community also contribute to early readmission[370,371]. While none of the existing interventions reviewed specifically targeted care transition practices, comprehensive care transition interventions have been shown to be effective in the international literature. For example, Re-Engineered Discharge consisting of seven strategies to improve the transition from hospital to the community, reported a 30% reduction in 30-day readmissions and lowered hospital costs by $416 per patient[372]. However, discharge and follow-up care processes are highly contextual and due to differences in health systems, interventions tested internationally may not be effective in the Australian setting. Thus, it is essential that such interventions are customised and tested in the local setting to determine their effectiveness in reducing readmissions.

Our review also highlights the need for standardised methods to measure and report readmissions in Australia. Standardised methods are necessary for sustained quality improvement efforts. For example, the United States Government's Centre for Medicare and Medicaid Services and the American College of Cardiology (ACC) publicly report readmission rates for AMI[14], stroke[373], HF[12] and PCI[374] among hospitals in the United States using nationally standardised methods. These efforts have stimulated clinical and policy interventions such as the American Heart Association's Target HF program and the ACC's Hospital to Home initiative as well as policy initiatives by the United States government such as the Hospital Readmission Reduction Program (HRRP)[375] and is thought to contribute to the declining readmission rates in the United States Medicare population[376]. Developing standardised methods to report and compare readmission rates in Australia may act as a catalyst for similar large-scale clinical and policy efforts to reduce readmissions.

Our review has important limitations. We chose to focus solely on readmissions following hospitalisation for CVD and our findings may not be generalisable to other conditions. We included grey literature, although they have not been academically peer-reviewed they are an important contribution to our study because we present a more in-depth evaluation of readmissions in the Australian setting.

2.4 Conclusions

Relatively high rates of readmissions are reported for cardiovascular conditions in Australia, paralleling the high rates of readmissions reported in the international literature although the Australian literature should be interpreted with caution due to the substantial methodological heterogeneity among studies. Furthermore, several knowledge gaps exist, most notably a paucity of studies assessing the impact of hospital readmissions on the health care system.

Moreover, only a few interventions have been shown to successfully reduce readmissions. Further research is required to fully determine the burden of readmissions, develop standardised measure to report readmissions, and to test interventions to reduce readmissions in the Australians setting.

Chapter III

Frequency, Trends and Institutional Variation in 30-day All-cause Mortality and Unplanned Readmissions Following Hospitalisation for Heart Failure in Australia and New Zealand

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This chapter is reproduced in the exact form as it appears in the manuscript, "**Frequency, Trends and Institutional Variation in 30-day All-cause Mortality and Unplanned Readmissions Following Hospitalisation for Heart Failure in Australia and New Zealand**" authored by **Clementine Labrosciano**, Dennis Horton, Tracy Air, Rosanna Tavella, John F. Beltrame, Christopher J. Zeitz, Harlan M. Krumholz, Robert J. T. Adams, Ian A. Scott, Martin Gallagher, Sadia Hossain, Saranya Hariharaputhiran and Isuru Ranasinghe and has been submitted to *Circulation*, August 2019.

In keeping with the style of this thesis, the abstract has been removed, the tables and figures re-numbered, the references incorporated into the thesis's master reference list and the manuscript repaginated.

Chapter III

Statement of Authorship

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Contribution to the paper	Acquisition of data, analysis and data interpretation, draft manuscript, critical revision and study conception and design.		
Overall Percentage (%)	80		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24/06/2019

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By signing the Statement of Authorship, each author certifies that:

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3.0 Introduction

Heart failure (HF) is a common and costly cause of hospitalisations. All-cause mortality and unplanned readmission within 30-days of a hospitalisation are widely accepted measures of HF care quality and outcomes. In the United States, where these outcomes are widely reported high rates of 30-day all-cause mortality and unplanned readmission following HF hospitalisations have been observed among hospitals, suggesting considerable variation in HF practice[12,377]. Moreover, improving these outcomes is the focus of policy innovation including public reporting of institutional rates and penalties for hospitals with high outcome rates. The Hospital Readmissions Reduction Program (HRRP)[378] introduced in 2012 has been credited with a rapid decline in risk standardised 30-day readmission rates from 21.5% to 17.8%[379]. Although considerable debate has centred on whether the HRRP has contributed to an increase in 30-day all-cause mortality[214] with previous studies showing conflicting results.

Health care systems are known to differ in patient characteristics and factors such as access to care and funding models, which may impact the observed frequency of HF outcomes and the extent of institutional variation[380]. However, national studies of outcomes following hospitalisations for HF outside of the United States are rare[381,382]. Moreover, no national study has systematically evaluated institutional variation in HF 30-day mortality or readmission rates beyond the United States Medicare population. Thus, whether the outcomes observed in the United States are generalisable to other health care systems is uncertain. This information is critical for health services and policymakers globally who are seeking to implement similar policy measures to improve HF outcomes. Examining the pattern of 30-day HF outcomes in different health care systems may also be useful to United States health services and policymakers who are seeking to understand the impact of current United States policies to improve HF outcomes.

This study assesses 30-day all-cause mortality and unplanned readmissions following a HF hospitalisation using national data from Australia and New Zealand, countries with advanced health care systems but without coordinated national policy framework to improve HF outcomes. This chapter specifically sought to determine the extent of institutional variation in these outcomes that may suggest variation in care quality among hospitals. This chapter also evaluated trends in these outcomes over a period that corresponded with the implementation of HRRP in the United States, to determine how HF outcomes have changed in the absence of policy intervention.

3.1 Methods

3.1.1 Data Source

Administrative hospitalisation data was collected from each Australian state and territory's Admitted Patient Data Collection and the equivalent New Zealand National Minimum Dataset (Hospital Events). This data included all inpatient and day-only admission records from all public hospitals and most (~80%) private hospitals irrespective of age and payer. Hospitals routinely collect standardised sets of variables for every encounter including patient demographic characteristics, primary and secondary diagnoses, procedures performed and patient status at discharge. Both Australia and New Zealand use the coding standards developed by the Australian National Centre for Classification in Health coded as per the International Classification of Diseases, tenth revision, Australian Modification (ICD-10-AM) and Australian Classification of Health Interventions (ACHI), for diagnoses and procedures respectively. Prior studies have shown cardiovascular diagnoses and procedures are well coded with >85% accuracy[144]. In this chapter, hospitalisation data were available from New Zealand (100% of the population) and seven of the eight Australian states and territories encompassing 99% of the population, as data were unavailable from the Northern Territory.

Within each Australian state and territory, each patient's hospitalisation encounter was linked to subsequent hospitalisation records to track all-cause readmissions to any hospital. To capture deaths occurring in the community, hospitalisation records were also linked to each state and territory's Registry of Deaths which records all deaths including out of hospital deaths. Health records were linked using probabilistic matching techniques based on multiple patient identifiers by designated data-linkage units within each region with linkage accuracy reported to be >99%[150]. In New Zealand hospital encounters are linked nationally using a unique patient identifier and all deaths are recorded in the National Minimum Dataset (Hospital Events).

3.1.2 Study Cohorts

Patients aged >18 years hospitalised between 2010 and 2015, who were a resident of Australia or New Zealand with a primary diagnosis of HF were included in the cohort. HF was defined as ICD-10-AM codes I11.0 (*hypertensive heart disease with congestive HF*), I13.0 (*hypertensive heart and kidney disease with congestive HF*), I13.2 (*hypertensive heart and kidney disease with both congestive HF and kidney failure*), and I50.0-9 (*HF*). Consistent with methods used to publicly report these outcomes in the United States[12,377], separate cohorts were created to assess mortality and readmission. The mortality cohort included all patients with a primary diagnosis of HF at the first admitting hospital. For hospitalisations involving subsequent transfers to another hospital, a primary HF diagnosis was required at every hospital for the patient to be retained in the cohort. Patients transferred in from another hospital were excluded. The cohort for evaluating 30-day readmissions included all patients discharged alive with a primary diagnosis of HF at the final discharging hospital. Patients transferred in from other hospitals were included while patients transferred out to another hospital were excluded.

Patients in both cohorts were required to have at least one year of prior data to assess comorbidities and at least 30 days of follow-up data available to assess 30-day outcomes. Both cohorts excluded patients that (1) had been admitted to hospital with a primary diagnosis of HF in the preceding 30 days as this is an outcome of the prior hospitalisation; (2) patients with a length of stay that was less than one day, unless death or a transfer to another hospital occurred, as this may not indicate a true episode of acute HF; and (3) patients who self-discharged against medical advice as their outcomes may not reflect quality of hospital care.

3.1.3 Study Outcomes

30-Day All-Cause Mortality

All-cause mortality within 30 days of the admission date, irrespective of whether the death occurred in hospital or in the community.

30-Day All-Cause Unplanned Readmissions

All-cause unplanned readmissions were measured within 30 days of the discharge date. Consistent with prior methods, we did not count planned readmissions in the outcome as these do not reflect differences in quality of care. Planned readmissions were removed using an algorithm as outlined in Figure 3.1. The 'Care Type' variable removed most scheduled hospital readmissions for rehabilitation, palliative care, maintenance care and other non-acute care types and day-only admissions for routinely scheduled treatments such as dialysis. The adapted Medicare Planned Readmission Algorithm[180] (Figure 3.1) removed admissions for diagnoses and procedures always considered as planned (such as maintenance chemotherapy and transplant surgery) and non-acute admissions for scheduled procedures (for example total hip replacement).

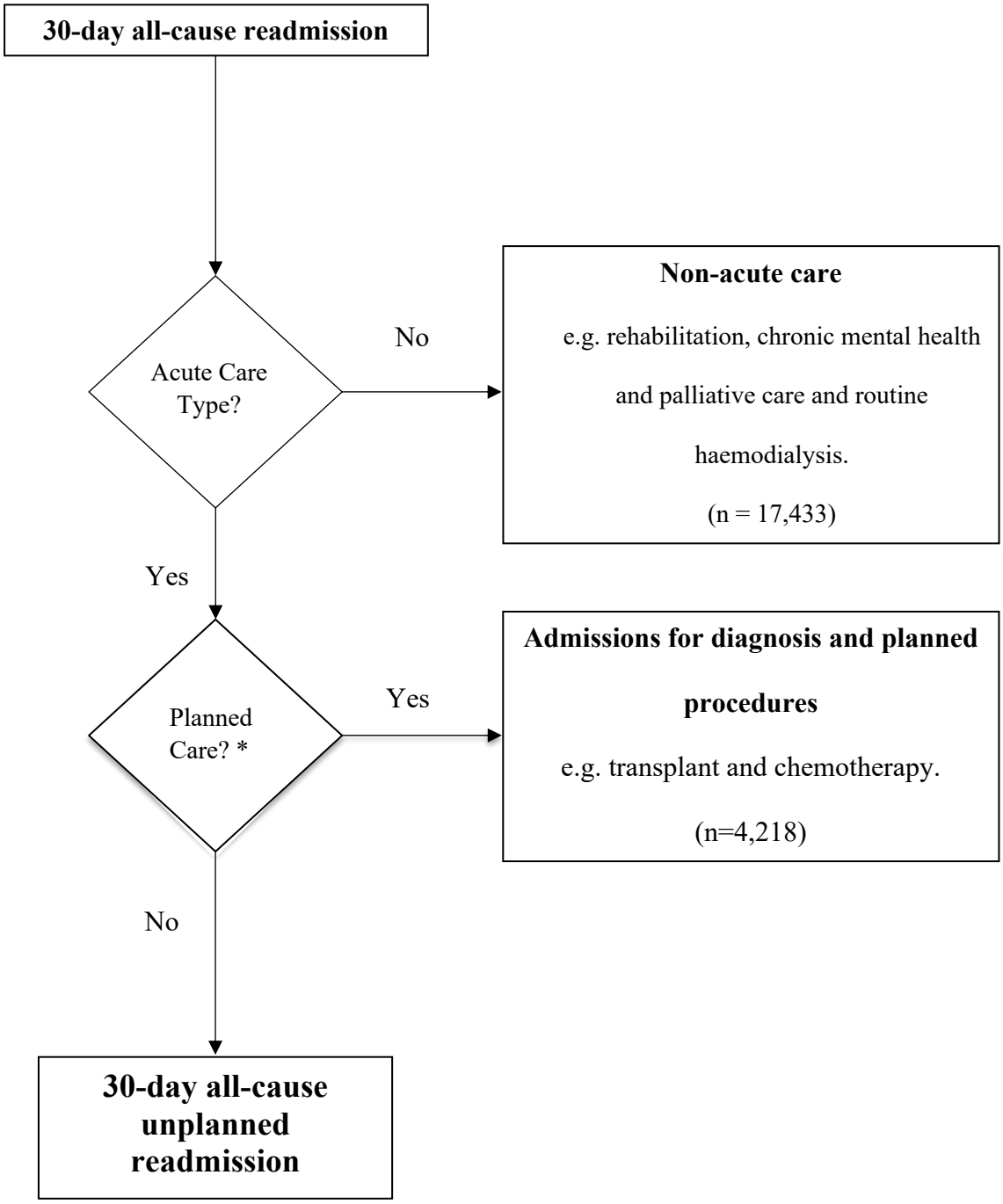

Figure 3.1: Algorithm for identifying Planned Readmissions. Note that this algorithm was only applied to the first readmission.

3.1.4 Hospital-Level Risk Standardised Mortality and Readmission Rates

Hospital-level outcomes rates were estimated by calculating each hospitals' risk standardised mortality and readmission rates using a hierarchical generalised linear model (HGLM) to account for differences in the hospital case-mix, sample-size, and clustering of patients within hospitals.

To develop the risk-adjustment models, patient factors were independently identified and associated with each outcome by fitting a logistic regression model using a randomly selected 50% sample of each cohort (derivation sample). Candidate variables included age, sex and patient comorbidities. Patient comorbidities were derived using the administrative data using the Condition Category (CC) classification[383] that grouped ICD codes into 180 clinically meaningful conditions using diagnosis codes from the index admission and hospitalisations in the preceding 12 months. Variables that may impact quality such as length of stay or race were purposely excluded from the model. All candidate variables were included in the model and non-significant variables were iteratively removed from the initial model using a stepwise purposeful selection approach[224] and evaluated for interaction terms. The final model contained all variables significant at $p<0.05$ and interactions at $p<0.01$. The model discrimination was assessed by calculating the area under the receiver operating characteristic curve as expressed by the C-statistic. The model calibration was assessed by comparing observed outcome rates with predicted outcome rates in deciles of patient risk. The model performance was then reassessed in the remaining 50% sample of each cohort (validation sample).

We then used the HGLM to estimate a random-intercept term that reflects each hospital's contribution to the risk of the outcome accounting for actual outcome rate, performance of

other hospitals with similar case-mix and sample size. The hospital specific risk standardised mortality rate (RSMR) was calculated as the ratio of predicted hospital deaths over expected hospital deaths, multiplied by the crude national average mortality rate. Likewise, the risk standardised readmission rate (RSRR) was calculated as the ratio of predicted hospital visits over the expected hospital visits, multiplied by the crude national average rate. The predicted number of outcomes was calculated based on the hospitals case-mix and the estimated hospital-specific intercept term. The expected number of outcomes was calculated based on the hospital's case-mix and national average intercept. The ratio was then multiplied for each hospital by the overall crude rate of mortality or unplanned readmissions, respectively for ease of interpretation. Bootstrapping with 1000 replications was used to empirically construct a 95% confidence interval estimate for each hospital's RSMR or RSRR using the percentile method. A hospital was deemed a statistical outlier if the hospital's entire 95% interval estimate was above or below the national average. This approach for estimation of the RSMR and RSRR ensured that the observed variation among hospitals was not due to underlying differences in case- or procedure-mix and is consistent with best-practice guidelines for profiling variation in outcomes among hospitals[384]. All hospital-level analyses were limited to unique hospitals with at least 25 HF hospitalisations during the study period to enable a robust estimate of the hospital rate.

3.1.5 Trend in Risk-Adjusted 30-day Mortality and Readmission Rates

Patient-level trends in outcomes from 2010 to 2015 were analysed by evaluating monthly change in risk-adjusted 30-day mortality and readmission rates using generalised linear models to adjust for differences in other patient characteristics and clustering of patients among hospitals.

3.1.6 Ethical Approval

Human Research Ethics Committees of the University of Adelaide and respective Australian States and Territories provided ethical approval with a waiver of informed consent to use de-identified patient data. De-identified data from New Zealand was obtained under a data user agreement with the New Zealand Ministry of Health. All ethical approvals with associated reference numbers are summarised in Table 3.2.

Table 3.2: State and territories Human Research Ethics Committee approvals.

Ethics Committee	**Reference Number**
New South Wales Population & Health Services Research Ethics Committee.	2015/06/591
Australian Capital Territory Health Department Human Research Ethics Committee.	ETH.7.15.143
Australian Capital Territory Calvary (Bruce) Hospital Human Research Ethics Committee.	Dated 07/10/2015
South Australian Depart of Health and Aging Human Research Ethics Committee.	HREC/15/SAH/102
West Australian Department of Health Human Research Ethics Committee.	2016/47
Tasmanian Department of Health Human Research Ethics Committee.	H0016011
Queensland Human Research Ethics Committee.	Public Health Act Approval
Victorian Human Research Ethics Committee.	Mutual Acceptance of NSW HREC approval
New Zealand Ministry of Health.	Data user agreement

3.1.7 Statistical Analysis

Data were summarised as frequencies and percentages for categorical variables. Continuous variables were presented as mean ± standard deviation or median and interquartile range. All significance levels were two-sided with a $p<0.05$. The Technical Appendix outlines the RSMR calculation. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). The hierarchical generalised linear model was estimated using the GLIMMIX procedure in SAS.

3.2 Results

3.2.1 Study Cohort Characteristics

Mortality Cohort

The mortality cohort comprised of 153,592 patients with a primary diagnosis of HF that met the selection criteria (Figure 3.3).

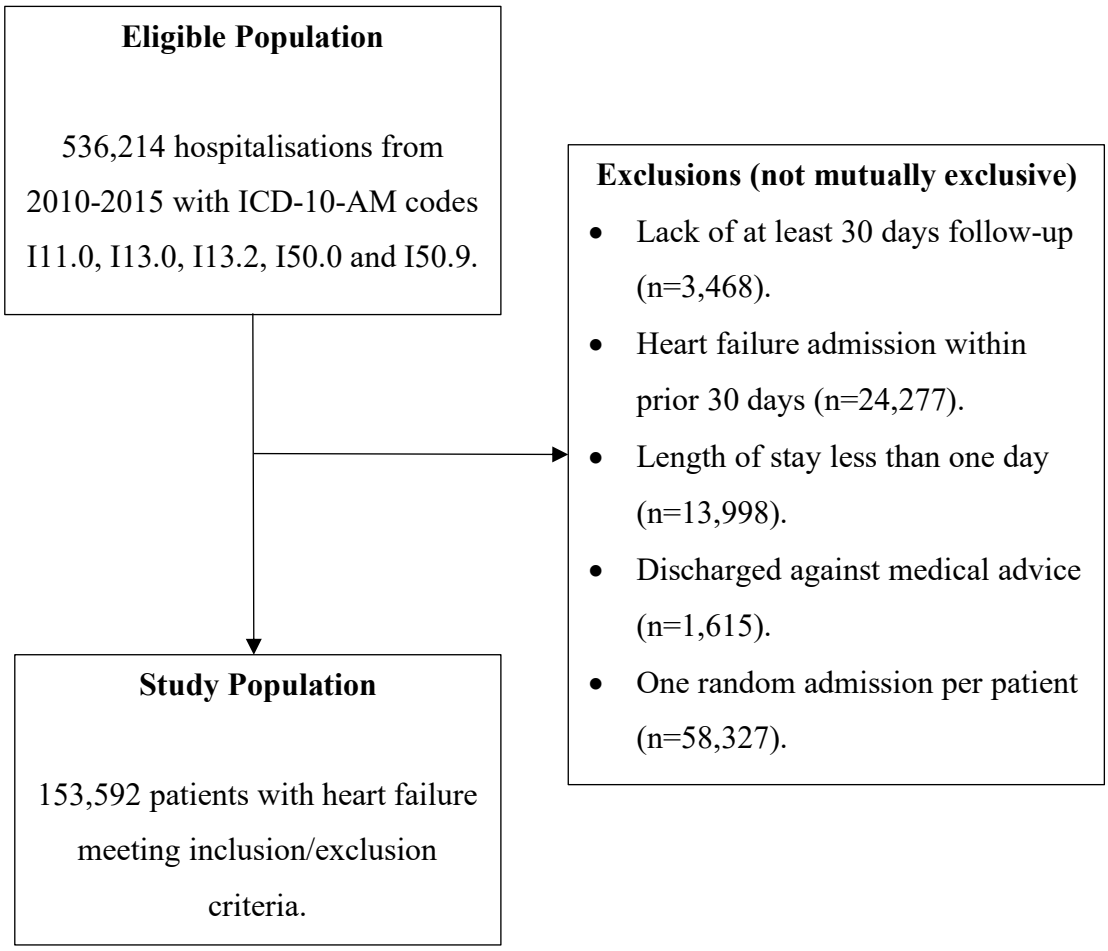

Figure 3.3: Patient Selection for the Heart Failure Mortality Cohort.

Patients had a mean age 78.9±11.8 years, 51.5% were male with hypertension (43.0%), prior history of HF (36.6%) and arrhythmias (20.1%) being the most common cardiovascular comorbidities, while chronic lung disease (20.4%), renal failure (21.6%), and protein-calorie malnutrition (9.1%) were common non-cardiac comorbidities (Table 3.2).

Table 3.2: Selected Baseline Patient Characteristics.

	Mortality Cohort				Readmission Cohort			
	Total (n=153,592)	**Dead (n=16,442)**	**Alive (n=137,150)**	**p**	**Total (n=148,704)**	**Readmitted (n=33,158)**	**Not Readmitted (n=115,546)**	**p**
Demographics								
Age (years)	78.9±11.8	83.0±10.02	78.4±12.0	<0.01	78.6±11.9	78.67±11.69	78.57±12.02	0.17
Male (n, %)	79,158 (51.5)	8,351 (50.8)	70,807 (51.6)	0.04	76,842 (51.7)	17,409 (53.0)	59,433 (51.3)	<0.01
Length of Stay (days)	5.0 (3.0-9.0)	5 (2-10)	5 (3-9)	0.86	5.0 (3.0-9.0)	6 (3-9)	5 (3-9)	<0.01
Cardiac Comorbidities (n, %)								
Congestive Heart Failure (CC 80)	56,163 (36.6)	7,330 (44.6)	48,833 (35.6)	<0.01	57,572 (38.7)	14,870 (44.8)	42,402 (36.7)	<0.01
AMI and Unstable Angina (CC 81-82)	16886 (11.0)	2142 (13.0)	14744 (10.8)	<0.01	17,026 (11.5)	4,827 (14.7)	12,199 (10.5)	<0.01
Chronic Atherosclerosis (CC 83-84)	30357 (19.8)	3464 (21.1)	26893 (19.6)	<0.01	29,756 (20.0)	7,321 (22.3)	22,435 (19.4)	<0.01
Valvular and Rheumatic Heart Disease (CC 86)	20,789 (13.5)	2,652(16.1)	18,137 (13.2)	<0.01	20,177 (13.6)	4,713 (14.4)	15,464 (13.4)	<0.01

Hypertension (CC 89-91)	66,043 (43.0)	7,106 (43.2)	58,937 (43.0)	<0.01	64,700 (43.5)	15,442 (47.0)	49,258 (42.5)	<0.01
Specified Heart Arrhythmias (CC 92)	30,866 (20.1)	3,515 (21.4)	27,351(19.9)	<0.01	33,259 (22.4)	8,677 (26.4)	24,582 (21.2)	<0.01
Percutaneous Coronary Intervention	3,448 (2.2)	230 (1.4)	3,218 (2.4)	<0.01	3,524 (2.4)	928 (2.8)	2,596 (2.2)	<0.01
Coronary Artery Bypass Graft	1,679 (1.1)	56 (0.3)	1,623 (1.2)	<0.01	1,729 (1.2)	377 (1.2)	1,352 (1.2)	0.78
Non-cardiovascular Comorbidities (n, %)								
Major and Metastatic Cancer (CC 7-9)	5,471 (3.6)	1,217 (7.4)	4,254 (3.1)	<0.01	5,015 (3.4)	1,489 (4.5)	3,526 (3.0)	<0.01
Diabetes with Renal or PAD Complications (CC 15)	26,516 (17.3)	3,173 (19.3)	23,343 (17.0)	<0.01	25,360 (17.1)	6,836 (20.8)	18,524 (16.0)	<0.01
Disorders of Fluid/Electrolyte/Acid-Base (CC 23)	31,114 (20.3)	4,390 (26.7)	26,724 (19.5)	<0.01	30,288 (20.4)	8,645 (26.3)	21,643 (18.7)	<0.01
Renal Failure (CC 130-131)	33,192 (21.6)	4,657 (28.3)	28,535 (20.8)	<0.01	32,364 (21.8)	9,461 (28.8)	22,903 (19.8)	<0.01
Cirrhosis and other Liver Disease (CC 25-29)	5,157 (3.4)	897 (5.5)	4,260 (3.1)	<0.01	4,782 (3.2)	1,383 (4.2)	3,399 (2.9)	<0.01
Pneumonia (CC 111-113)	27,468 (17.9)	4,623 (28.1)	22,845 (16.7)	<0.01	24,791 (16.7)	6,404 (19.5)	18,387 (15.9)	<0.01

Chronic Lung Disease (CC 108,109, 114)	31,284 (20.4)	4,274 (13.7)	27,010 (19.7)	<0.01	30,376 (20.4)	8,043 (24.5)	22,333 (19.3)	<0.01
Dementia (CC 49)	8,659 (5.6)	1,819(11.1)	6,840 (5.0)	<0.01	7,923 (5.3)	1,723 (5.2)	6,200 (5.4)	0.47
Protein-calorie malnutrition (CC 21)	13,977 (9.1)	2,477 (15.1)	11,500 (8.4)	<0.01	13,142 (8.8)	3,456 (10.5)	9,686 (8.4)	<0.01
Hemiplegia, Paraplegia, Paralysis, Functional Disability (CC 67-69, 100-102, 177-178)	8,114 (5.3)	1,226 (7.5)	6,888 (5.0)	<0.01	7,223 (4.9)	1,990 (6.1)	5,233 (4.5)	<0.01
Chronic Skin Ulcers (CC 148-149)	7,569 (4.9)	1,432 (8.7)	6,137 (4.5)	<0.01	7,117 (4.8)	1,962 (6.0)	5,155 (4.5)	<0.01
Cellulitis (CC 152)	8,949 (5.8)	1,334 (8.1)	7,615 (5.6)	<0.01	8,642 (5.8)	2,510 (7.7)	6,132 (5.3)	<0.01
Psychiatric Disorders (CC 54-60)	10,702 (7.0)	1,558 (9.5)	9,144 (6.7)	<0.01	8,816 (5.9)	2,468 (7.5)	6,348 (5.5)	<0.01

Refers to revascularisation in the preceding year

Abbreviations: AMI= Acute Myocardial Infarction; CC= condition Category; PAD= Peripheral Artery Disease

Readmission Cohort

The readmission cohort was comprised of 148,704 patients who met the selection criteria (Figure 3.4). Patients were of similar age (mean age 78.6±11.9 years) and sex (51.7% males) to the cohort evaluating mortality and had a similar distribution of cardiac and non-cardiac comorbidities (Table 3.2).

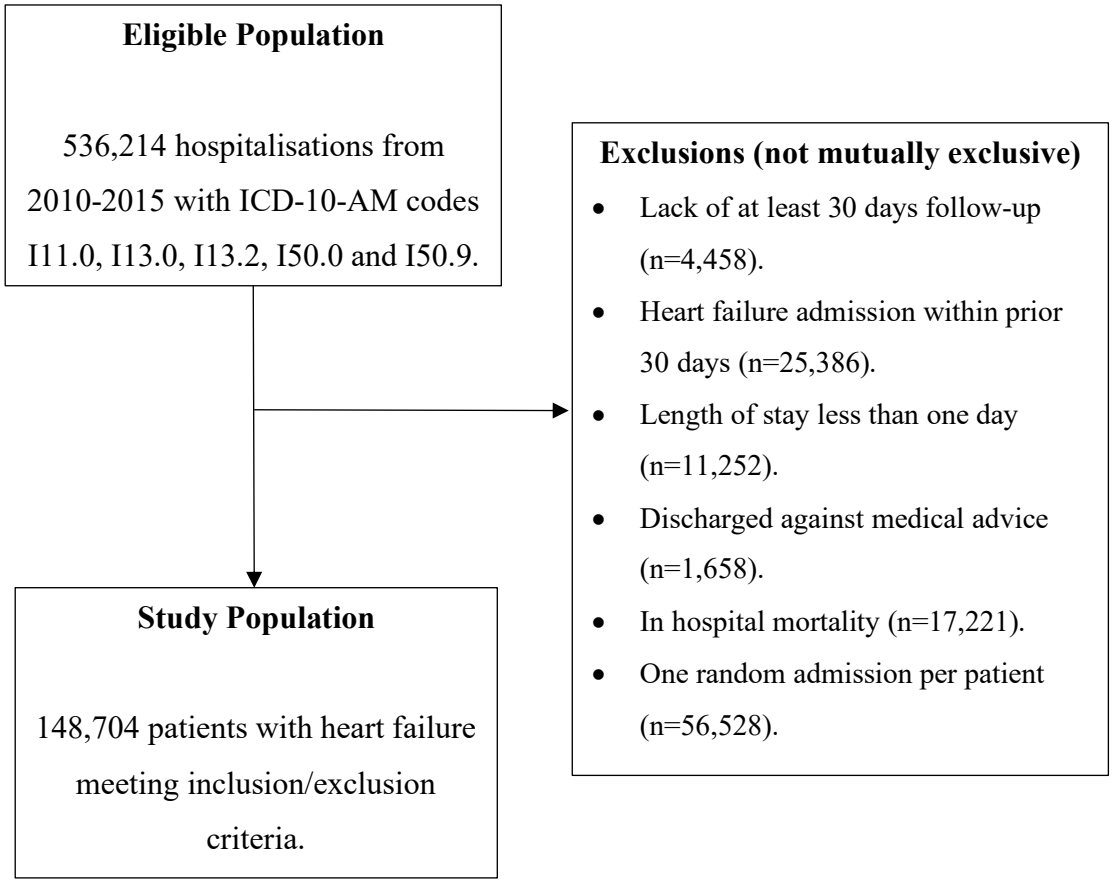

Figure 3.4: Patient Selection for the Heart Failure Readmission Cohort.

3.2.2 Study Outcomes

30-Day All-cause Mortality

Overall, 16,442 (10.7%) patients died within 30 days of admission with 10,086 (6.6% of the cohort, 61.0%) of all deaths occurring in hospital and 6,356 (4.1% of the cohort, 39.0%) of all deaths occurring post discharge.

30-day All-cause Unplanned Readmissions

Overall, 65,551 readmissions occurred within 30 days of hospital discharge, including multiple readmissions for the same patient. Of these, 17,433 readmissions occurred for planned non-acute care and were excluded from the outcome. A further 4,218 readmissions were identified as planned by the planned readmission algorithm (refer to Figure 3.1) and were excluded. Thus, 33,158 (22.3%) patients had at least one unplanned readmission within 30 days of discharge.

The most common primary diagnosis associated with unplanned readmission was HF (33.9%). The remaining 66.1% of patients were readmitted with an array of diagnoses including exacerbation of chronic obstructive pulmonary disease (4.1%), pneumonia (3.2%) and atrial fibrillation and flutter (2.9%).

3.2.3 Patient-level Risk-adjustment Model

Mortality

Age and 23 comorbidities were independently associated with the outcome of 30-day mortality (Table 3.3). The model performance showed good discrimination (C-statistic 0.70) and was well calibrated across deciles of patient risk, with predicted mortality of 2.5% in the lowest decile of risk and 23.4% in the highest decile of risk closely matching the observed

mortality (Figure 3.5). When re-tested in the validation sample, the model showed similar discrimination (C-statistic 0.70) and calibration.

Table 3.3: Mortality Risk Adjustment Model with Development and Validation Samples.

	Development Split Sample (50%)					Validation Split Sample (50%)				
	Estimate	**SE**	**P Value**	**OR**	**95% CI**	**Estimate**	**SE**	**P Value**	**OR**	**95% CI**
Intercept	-5.96	0.12	<0.01			-5.81	0.11	<0.01		
Age (per year increase)	0.04	<0.01	<0.01	1.04	1.04 – 1.05	0.04	<0.01	<0.01	1.04	1.04 – 1.043
Metastatic Cancer (CC 7-9)	0.92	0.05	<0.01	2.51	2.27 – 2.77	0.95	0.05	<0.01	2.596	2.36 – 2.86
Diabetes with Renal or PVD Complications (CC 15)	0.30	0.04	<0.01	1.44	1.33 – 1.56	0.28	0.04	<0.01	1.33	1.23 – 1.44
Diabetes with Other Manifestations or No Complications (CC 16-20, 119-120)	-0.28	0.04	<0.01	0.76	0.71 – 0.81	-0.24	0.04	<0.01	0.79	0.73 – 0.84
Protein-Calorie Malnutrition (CC 21)	0.33	0.04	<0.01	1.39	1.30 – 1.49	0.27	0.04	<0.01	1.31	1.22 – 1.41
Cirrhosis and Other Liver Diseases (CC 25-29)	0.76	0.06	<0.01	2.15	1.92 – 2.40	0.71	0.06	<0.01	2.04	1.82 – 2.28
Infectious and Inflammatory Joint Disease (CC 37-38)	0.20	0.08	0.01	1.22	1.05 – 1.42	0.17	0.08	0.03	1.19	1.02 – 1.38
Osteoarthritis and Other Degenerative Joint Disease (CC 39-43)	-0.22	0.03	<0.01	0.81	0.75 – 0.86	-0.22	0.03	<0.01	0.80	0.75 – 0.86
Dementia (CC 49)	0.63	0.04	<0.01	1.87	1.72 – 2.03	0.47	0.04	<0.01	1.59	1.47 – 1.73
Seizure Disorders and Convulsions (CC 74)	0.27	0.13	0.03	1.32	1.03 – 1.68	0.59	0.11	<0.01	1.81	1.45 – 2.26
Congestive Heart Failure (CC 80)	0.20	0.03	<0.01	1.22	1.16 – 1.29	0.31	0.03	<0.01	1.36	1.29 – 1.43
Ischaemic Heart Disease (CC 81-84)	0.20	0.03	<0.01	1.22	1.15 – 1.29	0.21	0.03	<0.01	1.23	1.16 – 1.31

Valvular Heart Disease including Endocarditis (CC 86)	0.19	0.03	<0.01	1.20	1.13 – 1.29	0.17	0.03	<0.01	1.19	1.11 – 1.27
Hypertension (CC 89-91)	-0.13	0.03	<0.01	0.88	0.83 – 0.92	-0.10	0.03	<0.01	0.90	0.86 – 0.95
Atrial Fibrillation/Flutter and Supraventricular Tachycardia (CC 92)	-0.1983	0.0315	<0.01	0.82	0.77 – 0.87	-0.2145	0.03	<0.01	0.81	0.76 – 0.86
Chronic Lung Disease (CC 108-109, 114)	0.20	0.03	<0.01	1.22	1.16 – 1.29	0.2301	0.03	<0.01	1.26	1.19 - 1.33
Pneumonia (CC 111-113)	0.38	0.03	<0.01	1.46	1.38 – 1.55	0.43	0.03	<0.01	1.53	1.45 – 1.62
Renal Failure (CC 130 & 131)	0.13	0.03	<0.01	1.14	1.07 – 1.22	0.11	0.03	<0.01	1.11	1.05 – 1.19
Incontinence (CC 134)	0.30	0.04	<0.01	1.35	1.24 – 1.47	0.38	0.04	<0.01	1.47	1.35 – 1.59
Cellulitis and Chronic Skin Ulcer (CC 148-149, 152)	0.46	0.05	<0.01	1.58	1.44 – 1.73	0.30	0.05	<0.01	1.35	1.23 – 1.49
Significant Endocrine and Metabolic Disorders (CC 22)	0.12	0.05	0.02	1.13	1.02 – 1.25	0.32	0.05	<0.01	1.37	1.25 – 1.51
Revascularisation with PCI or CABG (CC 203-204)	-0.62	0.09	<0.01	0.54	0.45 – 0.65	-0.75	0.09	<0.01	0.47	0.39 – 0.56
Fracture or Dislocation of Hip (CC 158)	0.13	0.07	0.06	1.14	0.99 – 1.31	0.15	0.07	0.04	1.16	1.01 – 1.33
Psychiatric Disorders (CC 54-60)	0.19	0.05	<0.01	1.21	1.11 – 1.32	0.26	0.05	<0.01	1.3	1.19 – 1.42

Abbreviations: CABG = Coronary Artery Bypass Grafting, CC = Condition Category, PCI = Percutaneous Coronary Intervention, PVD = Peripheral Vascular Disease

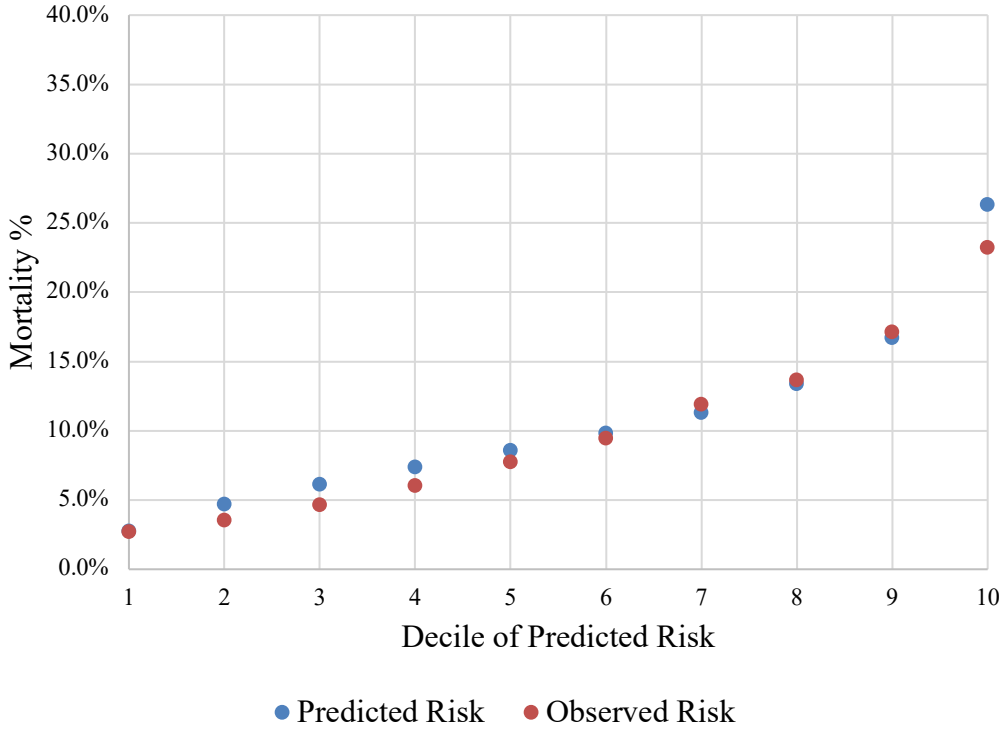

Figure 3.5: Calibration Plot of Predicted vs Observed of 30-day all-cause Mortality by Risk Decile**.**

Unplanned Readmission

Age, sex and 22 comorbidities were independently associated with the outcome of unplanned readmissions (Table 3.4). The model showed moderately good discrimination (C-statistic 0.60) and calibration, with predicted readmission rates of 15.8% in the lowest decile to 35.3% in the highest decile of risk closely matching the observed readmission risk (Figure 3.6). Model discrimination (C-statistic 0.60) and calibration were similar in the validation sample.

Table 3.4: Readmission Risk-Adjustment Model with Development and Validation Samples.

	Development Sample (50%)					Validation Sample (50%)				
	Estimate	**SE**	**P**	**OR**	**95% CI**	**Estimate**	**SE**	**P**	**OR**	**95% CI**
Intercept	-1.90	0.07	<0.01			-1.94	0.07	<0.01		
Age (per year increase)	<0.01	<0.01	<0.01	1.00	1.00 – 1.00	<0.01	<0.01	<0.01	1.00	1.00 – 1.01
Male Sex	0.07	0.02	<0.01	1.07	1.03 – 1.11	0.04	0.02	0.05	1.04	1.00 - 1.07
Infection (CC 1-6)	0.07	0.03	0.01	1.07	1.02 – 1.12	0.07	0.03	0.01	1.07	1.02 – 1.12
Major and Metastatic Cancer (CC 7-9)	0.36	0.05	<0.01	1.44	1.32 – 1.57	0.23	0.05	<0.01	1.26	1.15 – 1.38
Diabetes with Renal or PVD Complications (CC 15)	0.11	0.03	<0.01	1.12	1.06 – 1.17	0.15	0.03	<0.01	1.17	1.11 – 1.23
Disorders of Fluid/Electrolyte/Acid-Base (CC 23)	0.09	0.02	<0.01	1.09	1.04 – 1.15	0.10	0.02	<0.01	1.10	1.05 – 1.16
Cirrhosis and other liver Disease (CC 25-29)	0.16	0.05	<0.01	1.18	1.07 – 1.30	0.19	0.05	<0.01	1.20	1.10 – 1.32
Rheumatoid Arthritis and Other Musculoskeletal and Connective Tissue Disorders (CC 38, 43)	0.18	0.02	<0.01	1.20	1.14 – 1.26	0.10	0.02	<.0001	1.11	1.06 – 1.16
Psychiatric Disorders (CC 54-60)	0.10	0.04	<0.01	1.11	1.03 – 1.19	0.15	0.04	<0.01	1.16	1.09 – 1.25
Acute Myocardial Infarction and Unstable Angina (CC 81-82)	0.17	0.03	<0.01	1.18	1.12 – 1.25	0.17	0.03	<0.01	1.19	1.12 – 1.25
Vascular Disease (CC 104-106)	0.09	0.02	<0.01	1.09	1.04 – 1.15	0.07	0.02	<0.01	1.07	1.02 – 1.13
Chronic Lung Disease (CC 108, 109 & 114)	0.15	0.02	<0.01	1.17	1.12 – 1.22	0.18	0.02	<0.01	1.20	1.15 – 1.25
Renal Failure and Dialysis (CC 130-131)	0.18	0.03	<0.01	1.20	1.14 – 1.26	0.15	0.03	<0.01	1.16	1.10 – 1.22
Neuropathy and Other Neurological Disorders (CC 71, 76)	0.16	0.04	<0.01	1.18	1.08 – 1.28	0.09	0.04	0.04	1.09	1.00 – 1.19
Peptic Ulcer, Haemorrhage and Other Specified Gastrointestinal Disorders (CC 34)	0.08	0.04	0.04	1.08	1.00 – 1.16	0.08	0.04	0.03	1.09	1.01 – 1.17
Iron Deficiency and Other/Unspecified Anaemias and Blood Disease (CC 47)	0.02	0.02	0.40	1.02	0.97 -1.07	0.06	0.02	0.01	1.06	1.01 – 1.11

Heart Failure (CC 80)	0.13	0.02	<0.01	1.14	1.10 -1.18	0.15	0.02	<0.01	1.17	1.12 – 1.21
Cellulitis, Local Skin Infection (CC 152)	0.10	0.04	0.01	1.11	1.03 - 1.19	0.11	0.04	<0.01	1.12	1.04 – 1.20
Prior CABG (CC 204)	-0.39	0.09	<0.01	0.68	0.57 – 0.80	-0.29	0.08	<0.01	0.75	0.63 – 0.88
Other Gastrointestinal Disorders (CC 36)	0.11	0.02	<0.01	1.11	1.07 – 1.16	0.10	0.02	<0.01	1.10	1.06 – 1.15
Angina Pectoris/Old Myocardial Infarction (CC 83)	0.12	0.04	<0.01	1.13	1.06 – 1.21	0.12	0.03	<0.01	1.13	1.06 – 1.21
Major Symptoms, Abnormalities (CC 166)	0.14	0.02	<0.01	1.15	1.11 – 1.20	0.13	0.02	<0.01	1.13	1.09 – 1.18

Abbreviations: CABG = Coronary Artery Bypass Grafting, CC = Condition Category, PVD = Peripheral Vascular Disease.

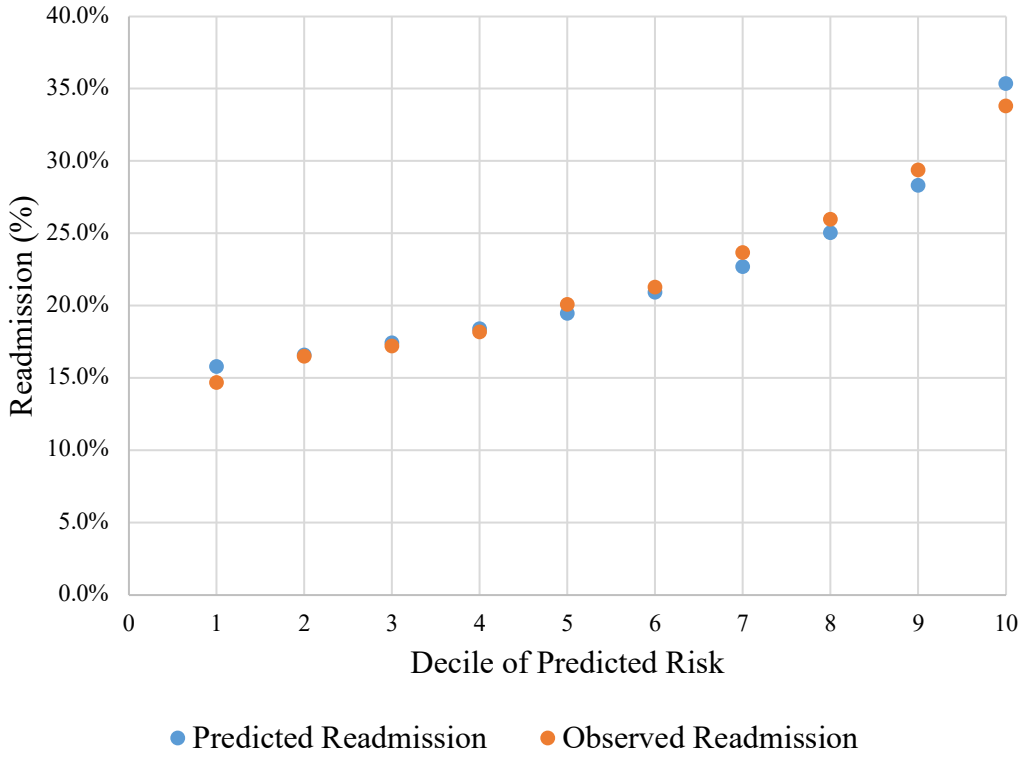

Figure 3.6: Calibration Plot of Predicted vs Observed of 30-day all-cause Readmission by Risk Decile.

3.2.4 Hospital Level Risk Standardised Outcome Rates

Risk standardised 30-day mortality rate (RSMR)

During the study period, 392 hospitals were identified as having at least 25 HF hospitalisations. Among these hospitals, the crude 30-day mortality rate ranged from 0 to 26.9%. Following risk standardisation, the median RSMR was 10.7% and ranged from 6.1% to 17.3% (IQR 9.5%-12.0%, Figure 3.7). Of these hospitals, 59 (15.1%) were statistical outliers with nine (4.8%) having an entire 95% confidence interval estimates below the national average mortality rate, while 40 (10.2%) had an interval estimate above the national average.

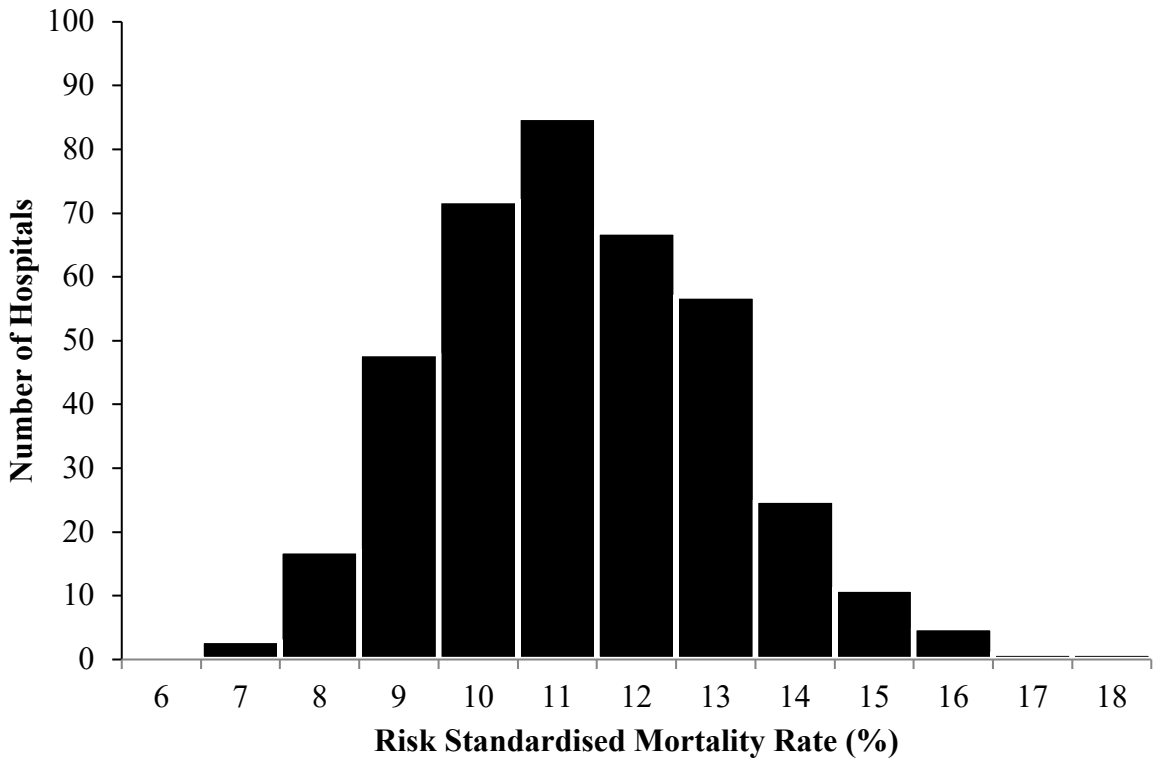

Figure 3.7: Variation of Hospital Level 30-day Risk Standardised Mortality Rates (RSMR).

Risk standardised 30-day readmission rate (RSRR)

There were 391 hospitals identified as having a minimum of 25 HF hospitalisations. Among these hospitals, the crude hospital 30-day readmission rate ranged from 4.9% to 45.6%. Following risk standardisation, the median RSRR was 22.3% and ranged from 17.7% to 27.1% (IQR 21.4% to 23.4%, Figure 3.8). Of the 391 hospitals, 24 (6.2%) were statistical outliers with 12 (3.1%) having an interval estimate below the national average readmission rate and 12 (3.1%) having an entire interval estimate above the national average.

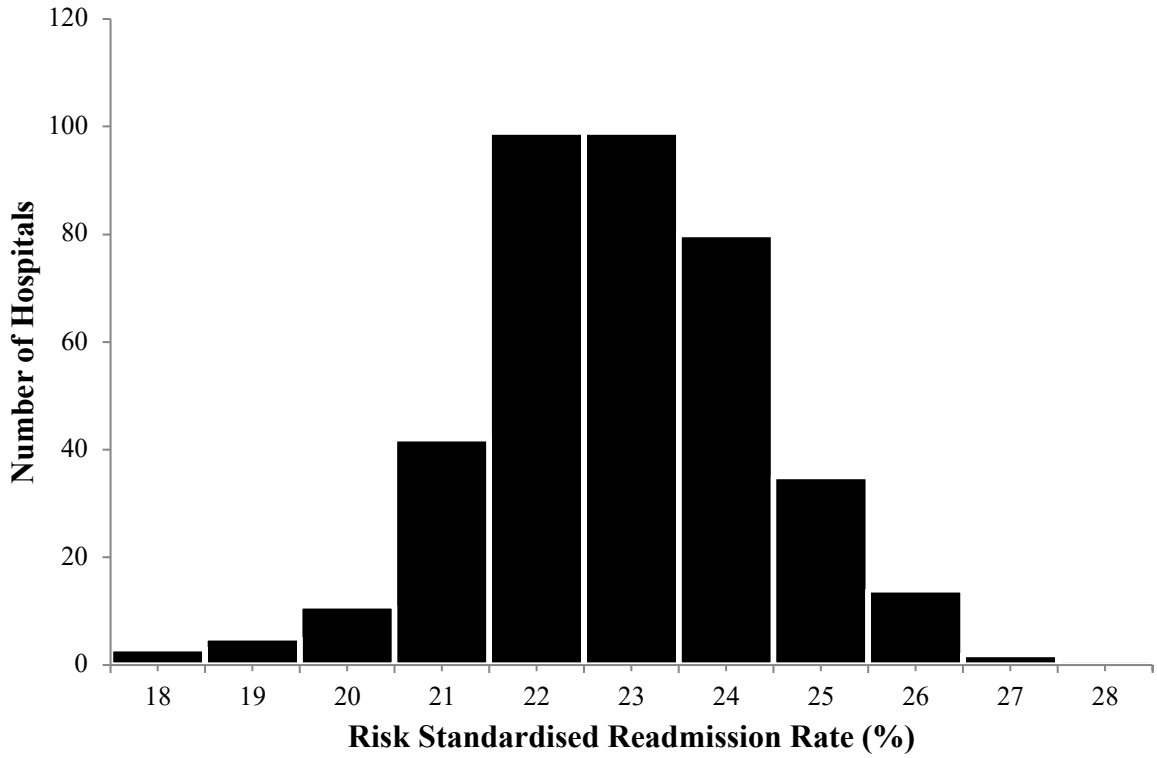

Figure 3.8: Variation of Hospital Level 30-day Risk Standardised Readmission Rates (RSRR).

3.2.5 Trend in Risk-Adjusted 30-Day Mortality and Readmission Rates

Thirty-day all-cause mortality declined by 4.4% from 12.5% in 2010 to 8.1% in 2015, an average decline of -0.88% per year (Table 3.5 and Figure 3.9). The decline was observed for both the in hospital (-3.2%) and post-discharge (-1.6%) components of 30-day mortality. The decline in 30-day mortality remained statistically significant following adjustment for differences in patient characteristics over the same period (adjusted OR 0.991 per month from January 2010, 95%CI 0.990-0.992, $p<0.01$). Over the same period, 30-day unplanned readmission rate declined by 1.3% from 23.2% to 21.9%, an average decline of 0.26% per year (Table 3.5 and Figure 3.10). The decline in 30-day readmission rate remained statistically significant after adjustment for covariates (adjusted OR 0.998 per month, 95% CI 0.998-0.999, $p<0.01$).

Table 3.5: Change in overall mortality and unplanned readmission rates over the study period.

Outcome (%)	2010	2011	2012	2013	2014	2015	Diff 2015-2010 (%)	Avg yearly Change (%) #	Adj OR‡	Lower 95% CI	Upper 95% CI	p Value for trend
30-Day Mortality	12.5	11.7	11.4	10.3	9.2	8.1	-4.4	-0.88	0.991	0.990	0.992	<0.01
- In-Hospital Component	7.9	7.4	6.8	5.9	5.6	5.1	-2.8	-0.56	0.991	0.990	0.992	<0.01
- Post-Discharge Component	4.6	4.3	4.6	4.3	3.6	3.0	-1.6	-0.32	0.993	0.991	0.994	<0.01
30-day Unplanned Readmission	23.2	21.7	21.8	22.0	21.9	21.9	-1.3	-0.26	0.998	0.998	0.999	<0.01

Refers to the average annual change in outcome (expressed as a percentage) from 2010 to 2015.

‡ Adjusted odds ratio (OR) refers to the odds of change in outcomes per month increase from January 2010 onwards, adjusting for other covariates significant in the patient-level risk model and clustering of patients among hospitals.

Abbreviations: Adj= Adjusted Avg=average; CI = Confidence Interval.

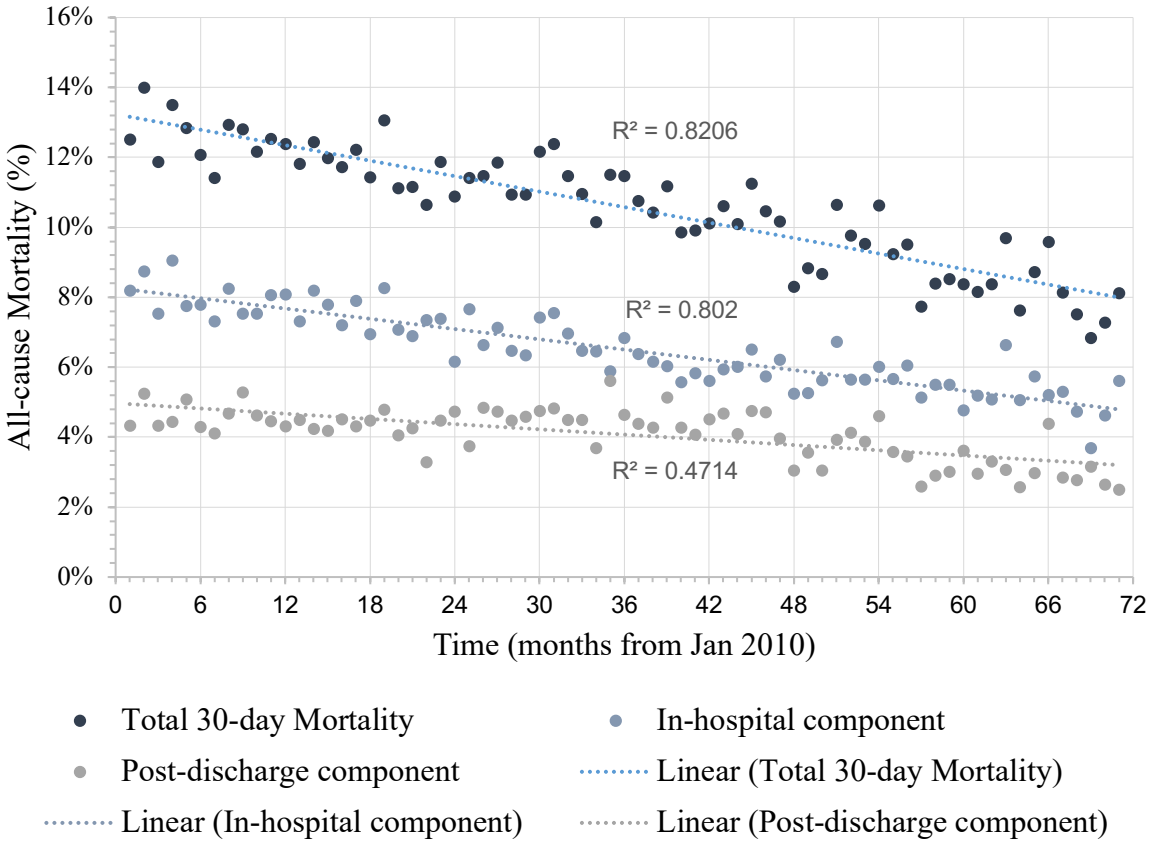

Figure 3.9: Overall Trend in 30-day Mortality Rates During the Study Period.

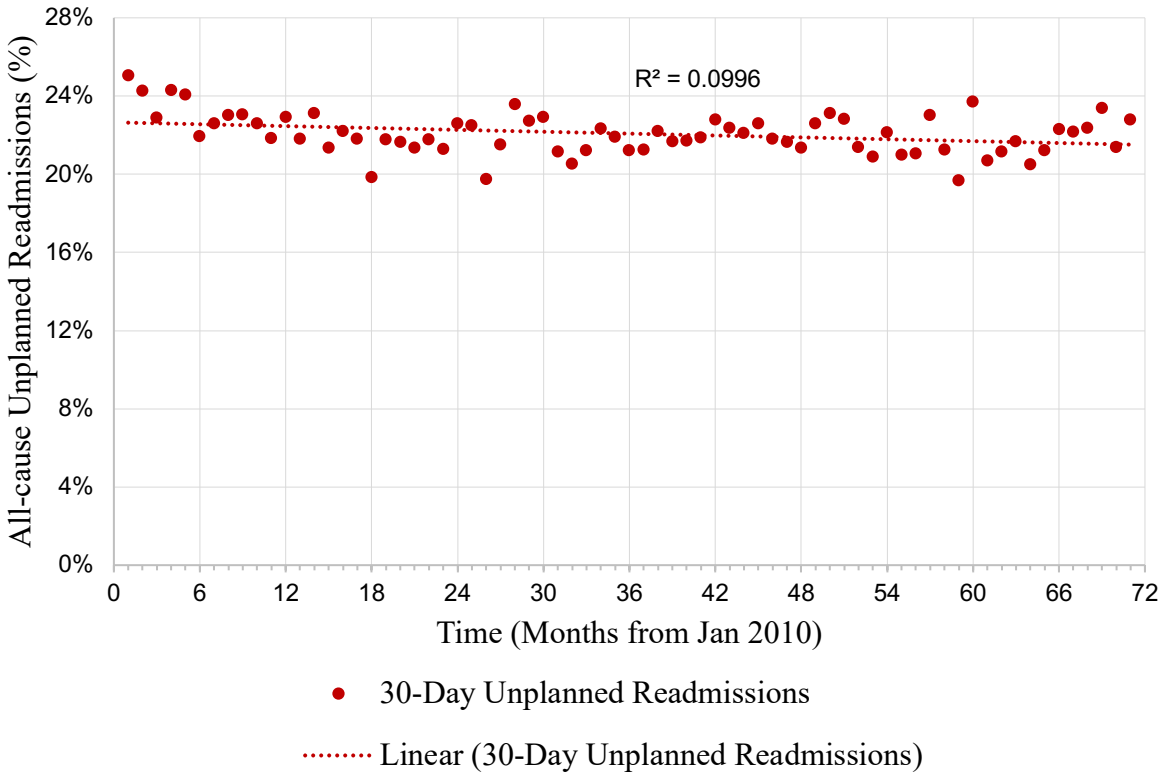

Figure 3.10: Overall Trend in 30-day Readmission Rates During the Study Period.

3.3 Discussion

This bi-national study of early outcomes following HF hospitalisations in Australia and New Zealand, found that one in ten patients died and almost a quarter experienced an unplanned readmission within 30 days of their hospital discharge. Additionally, a substantial decline in 30-day all-cause mortality over the study period accompanied by modest reductions in readmission rates – trends that contradict the trends in HF outcomes that have been observed in the United States following implementation of HRRP[214,379]. However, the risk adjusted 30-day mortality and readmission rates varied two to three-fold among hospitals with clear outlier facilities that had mortality and readmission rates statistically different from their peers. Such marked variation in HF outcomes implies variation in HF care practices and quality among hospitals and a need for coordinated clinical and policy interventions to standardise HF care across hospitals in Australia and New Zealand.

Prior studies in the United States have reported 30-day mortality rates of 10.7% to 12.8% and readmission rates of 17.2% to 24.8%[385-387] following HF hospitalisations although national studies of HF outcomes from other comparable countries are rare. The reported 30-day mortality (5.3% to 19.2%) and readmission (12.0%)[381,382,388] rates from these countries are also highly heterogenous and challenging to compare due to differences in methodology and outcome definitions. These findings extend the existing literature by reporting 30-day outcomes from two comparable Economic Co-operation and Development countries, using similar administrative data and analytical methods used for public reporting among Medicare patients. The overall 30-day mortality (10.7%) and readmission (22.3%) rates that we found are higher than currently reported in the United States[379,389] which may be a reflection of an older cohort (mean age ~79 years) and typically higher comorbidity burden among older patients. Indeed, only ~12% of patients in the study were <65 years of age, far less than reported in studies in the United States, of all-payer populations[390].

The comparatively high rates of 30-day mortality and readmission may also reflect the limited application of broad clinical and policy initiatives to improve these outcomes in Australia and New Zealand. In the United States hospital-specific 30-day mortality and readmissions rates after HF hospitalisations are publicly reported with feedback of individual patient data to hospitals to facilitate quality improvement activities. In Australia and New Zealand, hospital-specific HF outcomes are rarely reported either publicly or confidentially, except for the Australian state of New South Wales[163,391], creating a critical information and quality measurement gap. A recent systematic review found that public reporting on mortality for a variety of conditions was associated with a 15% reduction in mortality[392]. Moreover, public reporting stimulates hospitals to undertake quality improvement initiatives[29,393] and improve process of care indicators[394]. Our findings support public reporting of HF outcomes in Australia and New Zealand to inform patients and to stimulate clinicians and hospitals to invest in strategies to improve HF care. The methods used in this chapter are similar to that used in the United States[12,377], providing a feasible approach for national reporting.

While the overall outcome rates were elevated, a substantial temporal decline in 30-day mortality was observed. The decline in mortality parallels the decline in HF hospitalisations observed in Australia and New Zealand. The fact that in-hospital mortality declined more than post-discharge mortality may indicate the need for proportionately greater emphasis on optimising patient enrolment in post-discharge HF recovery and rehabilitation services that have been shown to be effective in reducing all-cause mortality and readmissions in HF patients.[395] For many Australian patients, there is still limited access to such programs with a recent study showing differences in early readmission rates after hospitalisation for HF being primarily explained by differences in post-discharge management[396]. In contrast, the fact that fewer patients are dying from HF, especially in hospital, may build a reservoir of patients who

are at higher risk of readmission[361] and may explain the limited reduction in readmission rates over the study period.

The relatively modest decline in the 30-day readmission rates observed is in contrast to the rapid decline in 30-day readmissions following HF hospitalisations observed in the United States following the introduction of HRRP[378]. The divergent trends in readmissions highlight the effectiveness of broad policy reforms such as HRRP in reducing readmissions. The Australian Government has proposed implementing similar financial penalties to reduce avoidable readmissions[397], and such policy reform may have a similar effect in reducing readmissions in Australia. Nevertheless, considerable debate has centred on whether such financial penalties may inadvertently contribute to an increase in HF mortality with some studies from the United States suggesting an increase in HF mortality, although others suggest a decline in risk-adjusted mortality. Despite these conflicting results, it is important to note that no study has shown a statistical association between HRRP implementation and excess mortality. The British National Heart Failure Audit has also reported largely unchanged in-hospital and 30-day mortality trend over the same period in the absence on policy intervention to reduce readmissions. Further studies are required to understand the divergent trends in mortality observed across these countries.

Several limitations need consideration when interpreting these results. The use of administrative data, while routinely collected and readily accessible, is less granular than data purposely collected for research. However, validation studies have shown relatively high accuracy of diagnoses and procedures coding within administrative data compared to medical records[144]. Although data from the Northern Territory of Australia was unavailable, this region represents less than 1% of the Australian population and does not affect the generalisability of our findings. Finally, this was an observational study and the possibility of

residual confounding due to unmeasured factors that influenced outcomes independent of hospital care quality cannot be excluded.

3.4 Conclusions

Among patients hospitalised for HF in Australia and New Zealand, more than one in ten died and almost a quarter experienced an unplanned readmission within 30 days. These outcomes varied widely among hospitals implying differences in patient outcomes due to variation in HF care quality. Thirty-day mortality, nevertheless, declined substantially during the study period with modest reductions in 30-day readmission rates over the same period. Concerted clinical and policy interventions including routine public reporting of these outcomes may improve patient care and minimise unwarranted variation of outcomes among hospitals.

Chapter IV

Is the LACE index a predictor of Mortality and Readmission in patients with Acute Myocardial Infarction? Insights from the CADOSA Registry

4.0 Introduction

An estimated 55,000 Australians suffer an acute myocardial infarction (AMI) every year[27] and reducing the number of adverse events following AMI is vital to improve patient outcomes. With advancement in therapies, in hospital survival following AMI has significantly improved, however AMI survivors discharged from hospital into the community are at risk for readmissions. International data demonstrates a significant problem with high readmission rates in the initial period following AMI[163,196-202]. Although national rates of AMI readmission are currently unknown, the New South Wales (NSW) Bureau of Health Information reports the 30-day all-cause risk standardised rate of readmission in NSW public hospitals is 17% following an index hospitalisation for AMI[163]. As such, 30-day readmission rates are attracting major attention in Australia[398,399] but little is known regarding the causes of readmission following an AMI.

The use of risk prediction models have been promoted as a valuable tool in determining the best treatment for Australian patients with cardiovascular disease (CVD) and thus the same logic is transferable in promoting optimal outcomes for these patients[400]. Risk prediction models hold a valuable place in clinical practice and research, however current risk prediction models have been shown to be quite poor at predicting readmission[401]. Notwithstanding, various models have been derived and validated for use in generic cohorts. One such model is the LACE index, developed in Canada to predict a patient's risk of 30-day all-cause unplanned readmission and mortality[222]. Initially validated in a cohort of general medical and surgical patients, the LACE index was found to have good accuracy (C-statistic of 0.68)[222]. Among cardiovascular cohorts, the LACE index has been most widely assessed in those with heart failure (HF) as an index diagnosis. Two separate models reported a C-statistic of 0.59 in cohorts of Canadian HF patients[235,236]. In contrast, a study from the United States of patients with HF found that the LACE index was not a reliable measure to predict readmission[237].

Although the LACE index has been well cited in the literature, it has never been assessed in an AMI cohort, and more specifically among patients with an AMI undergoing angiography. Thus, this study primarily aims to validate the LACE index score to predict (a) 30-day all-cause unplanned readmission and (b) the combined outcome of 30-day all-cause mortality and readmission in patients following an AMI undergoing angiography. The study also aims to determine which component(s) of the LACE index are the strongest predictors for both outcomes.

4.1 Methods

This retrospective observational cohort study evaluated the 30-day outcomes of patients following an AMI undergoing coronary angiography enrolled in the Coronary Angiogram Database of South Australia (CADOSA) Registry.

4.1.2 The CADOSA Registry

The CADOSA Registry is a prospective, state-based procedural clinical registry established in 2012 which evaluates the safety, quality and appropriateness of care received by South Australian patients undergoing angiography. The registry enrols consecutive patients undergoing coronary angiography and/or percutaneous coronary intervention (PCI) procedures performed in all South Australian public hospitals via opt-out consent. The CADOSA Registry collects baseline demographic, clinical and procedural information which includes all data elements corresponding to the American College of Cardiology National Cardiovascular Data Registry™ (ACC-NCDR™)[402] and Cath PCI Registry[403] Version 4.0. Registry data collection is undertaken by dedicated trained data abstractors in each participating facility using a standardised case report form. Regular data audits are undertaken by the registry management team which includes complete adjudication of all adverse events.

4.1.3 Patient selection criteria

Patients who had an AMI, aged ≥18 years, who were discharged alive between July 2016 and June 2017 from two teaching hospitals in the Central Adelaide Local Health Network were included in this study. Patients who were discharged to a nursing home, rehabilitation facility or palliative care were excluded from this study, as the process of care differs from patients in the community and is compliant with the exclusion criteria used in the original LACE study[222]. Non-South Australian residents were also excluded from this study, as follow-up for interstate and overseas patients could not be attained from South Australian administrative datasets.

4.1.4 Ethical Approval

The study cohort was derived from patients enrolled in the CADOSA Registry and the protocol for this study, which did not require informed consent, was approved by the Central Adelaide Local Health Network Human Ethics Committee (HREC reference number HREC/19/CALHN/17 and CALHN reference number: Q20190104).

4.1.5 Study Protocol

Clinical variables were extracted from the CADOSA Registry and additional variables that were not collected by the Registry (explicitly diabetes (with or without complications), liver or renal disease, tumours/cancers, dementia, connective tissue diseases AIDS and emergency department (ED) encounters in the past 12 months) were retrospectively obtained from electronic medical records. Similarly, the 30-day outcomes of patients were sourced via electronic medical record review.

4.1.6 The LACE index

The LACE index is comprised of four main questions that can be answered retrospectively from case notes[222]. The four component scores correspond to the index length of stay, whether or not the patient arrived via emergency, the comorbidities (defined using the Charlson comorbidity score[234]) and the number of emergency encounters suffered by the patients in the six months prior to the index admission (Table 4.1). Scoring of the LACE index was compliant with the original scoring system[222]. Lengths of stay which were between one and three days were scored accordingly, lengths of stay between four and six days were scored four points, lengths of stay between seven and 13 days were scored five points and lengths of stay of ≥14 days were scored seven points. If the index hospitalisation was an admission via ED this was scored as three, if the patient's hospitalisation did not begin via the ED the domain was scored as zero. Definitions of the Charlson comorbidities are summarised in Table 4.1.1. All encounters that occurred in the 12 months prior to the index hospitalisation were assessed for any of the Charlson comorbidities and scored as follows: prior myocardial infarction, cerebrovascular disease, peripheral artery disease and diabetes without complications were all scored one point. HF, diabetes with end organ damage, chronic pulmonary disease and mild liver or renal disease were all scored two points. Any tumour (including lymphoma or leukemia), dementia and connective tissue diseases were all scored three points. Patients with acquired immunodeficiency syndrome (AIDS) and moderate or severe liver or renal disease were scored four points. Patients who had a metastatic solid tumour within the past five years were scored six points. The comorbidities domain was calculated by the addition of comorbidities, if the score was four or greater it was entered as the maximum of five points. If the patient had between zero and three ED encounters in the six months prior to their enrolment in CADOSA, they were given zero to three points accordingly. If the patient had four or more ED encounters, they were scored a maximum of four points for this domain. The LACE index total score was individually calculated for each

patient by the summation of the four domains. The total scores ranged from one to 19, where higher scores indicated a higher risk of readmission.

Table 4.1: Scoring the LACE index.

LACE Attribute	Score/Points
Length of Stay (days)	
1	1
2	2
3	3
4 – 6	4
7 – 13	5
≧14	7
Admission type	
Not admitted via the Emergency Department	0
Admitted via the Emergency Department	3
Charlson comorbidity index score	
Previous myocardial infarction	1
Cerebrovascular disease	1
Peripheral artery disease	1
Diabetes without complications	1
Congestive heart failure	2
Diabetes with end organ damage	2
Chronic pulmonary disease	2
Mild liver or renal disease	2
Any tumour (including lymphoma or leukemia)	3
Dementia	3
Connective tissue disease	3
AIDS	4
Moderate or severe liver or renal disease	4
Metastatic solid tumour	6
Emergency department visits in the prior 6 months	
None	0
1	1
2	2
3	3
≧4	4

Table 4.1.1 The following table provides the definitions used to define the Charlson comorbidities.

Comorbidity	Definition
Previous myocardial infarction	Any previous definite or probable myocardial infarction.
Cerebrovascular disease	Any previous stroke or transient ischemic attack (TIA).
Peripheral artery disease	Intermittent claudication, previous surgery or stenting, gangrene or acute ischemia, untreated abdominal or thoracic aortic aneurysm.
Diabetes without complications	No retinopathy, nephropathy or neuropathy.
Congestive heart failure	Any patient with symptomatic congestive heart failure.
Diabetes with end organ damage	Diabetes with retinopathy, nephropathy or neuropathy.
Chronic pulmonary disease	Chronic lung conditions (i.e. chronic obstructive pulmonary disease).
Mild liver or renal disease	Cirrhosis but no portal hypertension (i.e., no varices, no ascites) OR chronic hepatitis Chronic Renal Disease.
Any tumour (including lymphoma or leukemia)	Solid tumours must have been treated within the last 5 years; includes chronic lymphocytic leukemia and polycythaemia vera.
Dementia	Any cognitive deficit.
Connective tissue disease	Systemic lupus erythematosus (SLE), polymyositis, mixed connective tissue disease, moderate to severe rheumatoid arthritis, and polymyalgia rheumatica.
AIDS	AIDS-defining opportunistic infection or CD4 < 200.
Moderate or severe liver or renal disease	Cirrhosis with portal hypertension (e.g., ascites or variceal bleeding), End stage Renal Disease, Haemodialysis or Peritoneal Dialysis.
Metastatic solid tumour	Any metastatic tumour.

4.1.7 Study Outcomes

The primary outcome of this study was all-cause unplanned readmission, defined as any unplanned inpatient admission to a public South Australian hospital within 30 days of discharge. The secondary outcome was a combined outcome of 30-day all-cause mortality and unplanned readmission. Additionally, a tertiary outcome reported in this study was the number of returns to the ED, defined as patients who were treated in the ED and discharged home without an inpatient admission.

4.1.8 Statistical Analyses

Descriptive statistics were used to summarise the baseline characteristics for readmitted and non-readmitted patients. Categorical variables were analysed using chi^2 tests and presented as frequencies and percentages. Continuous variables were analysed using Mann-Whitney U tests and presented as medians with interquartile ranges. The frequency of readmissions and mortality were calculated as the number of events divided by the number of patients and expressed as a percentage.

4.1.9 Goodness of Fit Metrics

Receiver Operating Characteristic (ROC) curves were used to determine the optimal cut-point for the desired endpoints. The performance of the LACE score as a predictor for readmission was evaluated according to its discriminatory power (area under the curve (AUC)), calibration (Hosmer-Lemeshow goodness-of-fit test[404]) and overall accuracy (Brier score[405]). As a secondary outcome, the same analyses were conducted to determine the ability of the LACE index to predict a combined outcome of 30-day all-cause unplanned readmission and mortality.

A logistic regression model was fitted with the four components of the LACE score to estimate the relative performance of the LACE index components in predicting 30-day all-cause unplanned readmission or the combined measure of 30-day unplanned readmission and mortality, as the outcome.

A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using STATA 14 (StataCorp., College Station, TX, USA).

4.2 Results

4.2.1 Patient Demographics

Amongst the 1051 patients who met the inclusion criteria for this study, 216 patients were excluded for the reasons listed in Figure 4.1. Explicitly, patients were excluded for the following reasons: 151 were non-South Australian residents, 54 were discharged to rehab, 14 were nursing home residents, two patients were discharged for palliative care and one patient was discharged for ongoing psychiatric care. Thus, the final cohort for this study consisted of 829 patients (30.6% female, median age 63 (54-74) years), of whom 306 (36.9%) were coded as ST-segment Elevated Myocardial Infarction (STEMI).

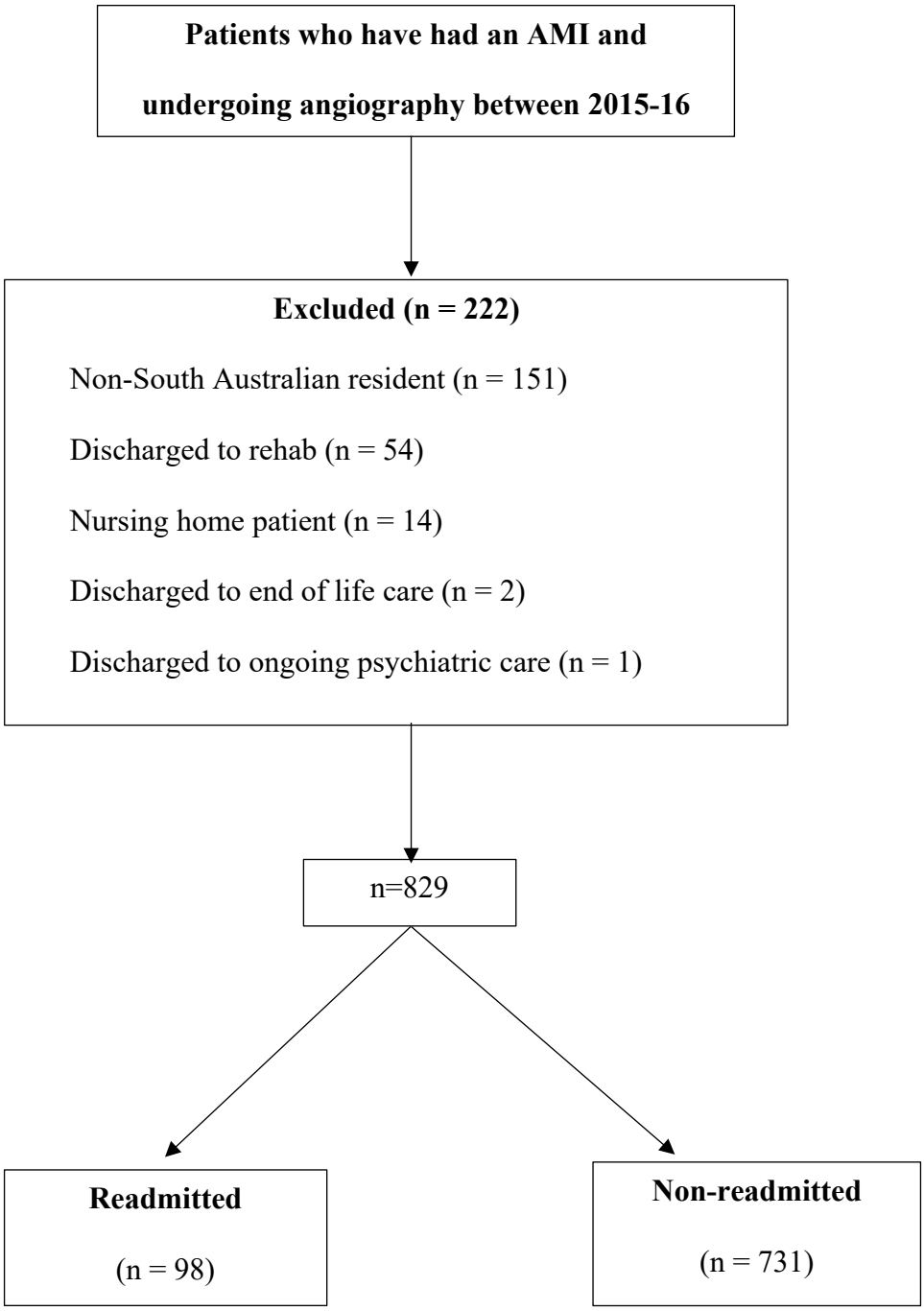

Figure 4.1: Patient selection consort diagram.

The baseline characteristics of readmitted and non-readmitted patients were similar (refer to Table 4.2). Relative to the non-readmitted patients, readmitted patients had a longer length of stay (5 (4-9) vs. 4 (3-6) days, p=0.0029) and a lower GRACE score (129 (109-155) vs. 137 (122-165), p=0.0171). Readmitted patients were less likely to be smokers (24.4% vs. 35.6%, p=0.04), but more likely to have peripheral artery disease (18.4% vs. 8.8%, p=0.003), diabetes with end organ damage (15.3% vs. 6.8%, p=0.003), connective tissue disease (8.2% vs. 3.6%, p=0.03) and moderate or severe liver or renal disease (8.2% vs. 4.0%, p=0.06). The distribution of total LACE scores among all patients was slightly negatively skewed (Figure 4.2) and readmitted patients had a significantly higher total LACE index score (9 (7-12) vs. 8 (7-10), p=0.0001).

Table 4.2: Baseline characteristics for readmitted vs. non-readmitted patients.

	Readmitted (n=98)		Not readmitted (n=731)		p-value	Total (n=829)	
	n	%	n	%		n	%
Demographics							
Age, years (median, IQR)	67.5	56-77	63	53-73	0.08	63	54-74
Females	39	39.8	215	29.4	0.04	254	30.6
Length of stay, days (median, IQR)	5	4-9	4	3-6	0.0029	4	3-6
Active smoker	21	24.4	239	35.6	0.04	260	34.3
Emergency department arrival^	96	98.0	699	95.6	0.42	795	95.9
Emergency department encounters in the past 6 months (median, IQR)	0	0-1	0	0-0	0.0000	0	0-0
Total LACE Score (median, IQR)	9	7-12	8	7-10	0.0001	8	7-11
Cardiovascular history based on hospitalisations in the preceding year (n, %)							
Cerebrovascular disease	7	7.1	52	7.1	0.99	59	7.1
Heart failure	6	6.1	52	7.1	0.72	58	7.0
Dyslipidaemia	62	63.9	411	60.1	0.47	473	60.6
Hypertension	68	71.6	457	65.6	0.25	525	66.3
Family history of coronary artery disease	18	29.0	204	39.3	0.12	222	38.2
Prior myocardial infarction	25	25.5	166	22.7	0.54	191	23.0
Atrial fibrillation	14	15.9	96	14.3	0.68	110	14.5
Prior percutaneous coronary intervention	11	12.9	133	19.7	0.13	144	19.0
Prior coronary artery bypass graft	11	11.8	65	9.3	0.44	76	9.6
Peripheral artery disease	18	18.4	64	8.8	0.003	82	9.9
Multivessel disease	56	69.1	395	65.8	0.56	451	66.2
STEMI	32	32.7	274	37.5	0.35	306	36.9
GRACE score (median, IQR)	129	109-155	137	122-165	0.0171	131	109-157
Comorbidities based on hospitalisations in the preceding year (n, %)							

Chronic lung disease	8	8.2	70	(9.6)	0.65	78	9.4
Diabetes without complications	32	32.7	187	25.6	0.14	219	26.4
Diabetes with end organ damage	15	15.3	50	6.8	0.003	65	7.8
Mild liver or renal disease	8	8.2	35	4.8	0.16	43	5.2
Any tumour	8	8.2	52	7.1	0.71	60	7.2
Dementia^	0	0	6	0.8	1.00	6	0.7
Connective tissue disease	8	8.2	26	3.6	0.03	34	4.1
AIDS	0	0	0	0	-	0	0
Moderate or severe liver or renal disease	8	8.2	29	4.0	0.06	37	4.5
Metastatic solid tumour^	2	2.0	13	1.8	0.695	15	1.8
Depression	24	28.2	147	22.8	0.27	171	23.4
Recommended therapy							
None	4	4.1	14	1.9	0.67	18	2.2
Medical therapy	25	25.5	201	27.5		226	27.3
PCI without CABG	53	54.1	391	53.5		444	53.6
CABG	9	9.2	80	10.9		89	10.7
Other cardiac therapy	7	7.1	45	6.2		52	6.3

^denotes a Fischer's exact test was performed.

p value corresponds to t-test or chi^2 test.

Multivessel disease is defined as: (1 MVD) vs. (2-VD + 3-VD). Abbreviations for the recommended therapies: Medical therapy (includes counselling). CABG (coronary artery bypass graft) includes planned hybrid CABG or PCI (percutaneous coronary intervention). Other cardiac therapy excludes CABG or PCI.

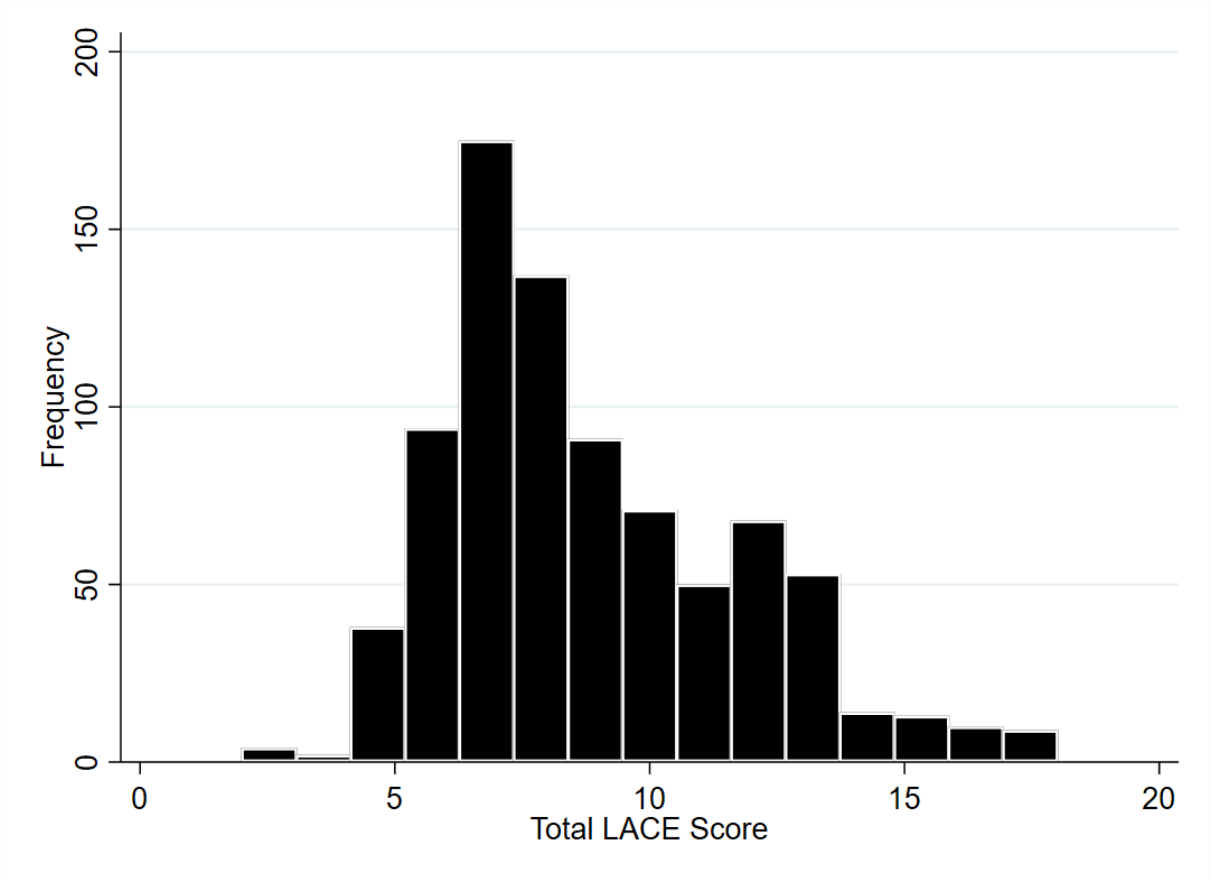

Figure 4.2: Distribution of total LACE scores among all patients.

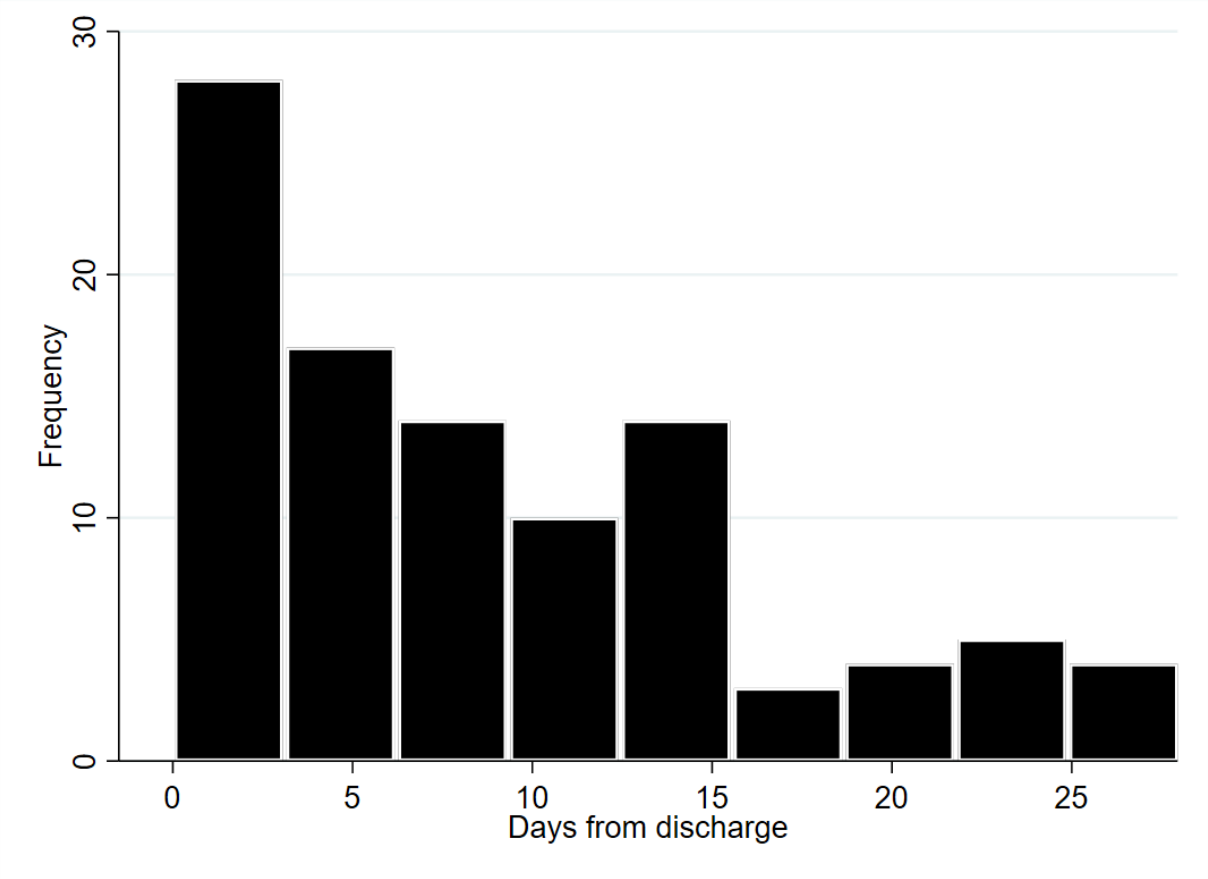

Figure 4.3: The frequency of patients who were readmitted to hospitals, measured as days post-discharge.

4.2.2 Study Outcomes

Of the 829 patients, 98 (11.8%) suffered a 30-day all-cause unplanned readmission. Of the 98 readmissions, the primary diagnosis of 55 (56%) patients was cardiovascular-related. The timing of these readmissions ranged from same day to 28 days post-discharge. These readmissions generally occurred within the first 15 days post-discharge (Figure 4.3). Nine patients (1.1%) were readmitted with HF and another nine patients (1.1%) were readmitted for reinfarction.

Six patients (0.72% of the total cohort) died within 30 days of discharge, three of these deaths occurred in hospital. Additionally, 99 (11.9%) patients reached the combined endpoint of unplanned readmission and or mortality.

It was noted that 32 (3.86%) patients presented to an ED within 30 days of discharge. These patients were treated and released back home without being admitted to hospital. Of these 32 ED presentations, nine (28%) had a cardiac related principal diagnosis.

4.2.3 Model Performance

The model had optimal balance between sensitivity and specificity for predicting 30-day all-cause unplanned readmission when the LACE score was ≥10. This threshold (cut-off point) yielded a sensitivity of 47.96% and specificity of 67.03%. It was preferable to compromise the sensitivity of the model over the specificity to allow for the inclusion of all potential unplanned readmissions. The model was satisfactory, with a Brier score of 0.1016, a non-significant Hosmer-Lemeshow test ($\chi 2=3.62$, $p=0.73$), and an AUC of 0.62 (95% CI 0.56-0.68) (refer to Table 4.3 and Figure 4.4).

Table 4.3: Validity of LACE index models for 30-day all-cause readmission. The ROC AUC (or C-statistic) was 0.6192 (95%CI 0.56-0.68).

LACE Cut-point	Sensitivity (%)	Specificity (%)	Correctly classified (%)
≥2	100.00	0.00	11.82
≥3	100.00	0.27	12.06
≥4	100.00	0.55	12.30
≥5	100.00	0.82	12.55
≥6	96.94	5.61	16.41
≥7	92.86	17.92	26.78
≥8	73.47	39.26	43.31
≥9	58.16	55.95	56.21
≥10	47.96	67.03	64.78
≥11	40.82	75.79	71.65
≥12	36.73	82.08	76.72
≥13	24.49	89.74	82.03
≥14	13.27	95.49	85.77
≥15	10.20	96.99	86.73
≥16	7.14	98.36	87.58
≥17	2.04	99.04	87.58
≥18	0.00	99.86	88.06
>18	0.00	100.00	88.18

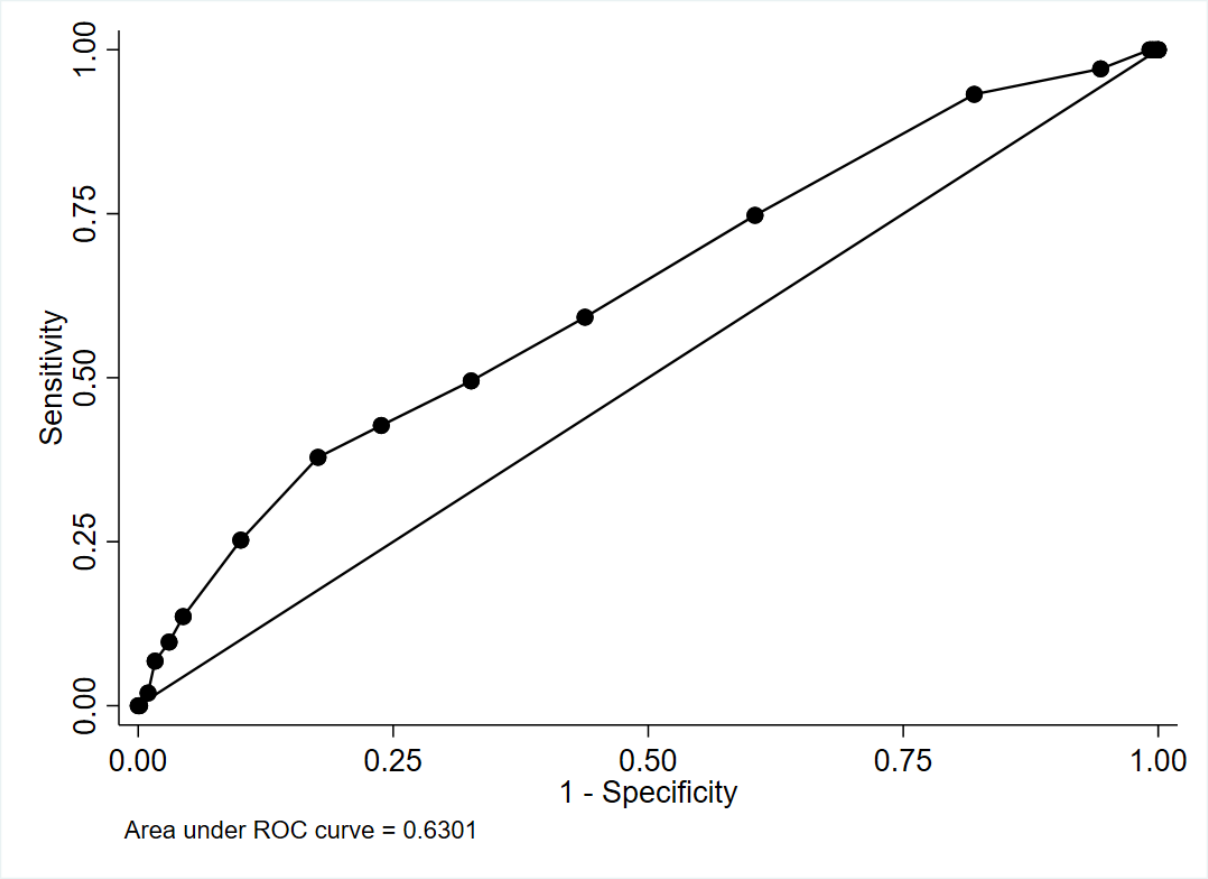

Figure 4.4: ROC curves for the LACE index models predicting 30-day all-cause unplanned readmission.

Similarly, there was optimal balance between sensitivity and specificity of the model for predicting a combined outcome of mortality and/or readmission at 30 days, when the LACE score was ≥10. This threshold had a sensitivity of 49.51% and specificity of 67.36%. It was preferable to compromise the sensitivity of the model over the specificity to allow for the inclusion of all potentially unplanned readmissions. The model for the composite outcome was also satisfactory, with a Brier score of 0.1017, a non-significant Hosmer-Lemeshow test ($\chi 2$=3.65, p=0.72), and an AUC of 0.63 (95%CI 0.57-0.69) (refer to Table 4.4 and Figure 4.5).

Table 4.4 Combined 30-day all-cause mortality and readmission. The ROC AUC (or C-statistic) was 0.6301 (95%CI 0.57-0.69).

LACE Cut-point	Sensitivity (%)	Specificity (%)	Correctly classified (%)
≥2	100.00	0.00	12.42
≥3	100.00	0.28	12.67
≥4	100.00	0.55	12.91
≥5	100.00	0.83	13.15
≥6	97.09	5.65	17.01
≥7	93.20	18.04	27.38
≥8	74.76	39.53	43.91
≥9	59.22	56.20	56.57
≥10	49.51	67.36	65.14
≥11	42.72	76.17	72.01
≥12	37.86	82.37	76.84
≥13	25.24	89.94	81.91
≥14	13.59	95.59	85.40
≥15	9.71	96.97	86.13
≥16	6.80	98.35	86.97
≥17	1.94	99.04	86.97
≥18	0.00	99.86	87.45
>18	0.00	100.00	87.58

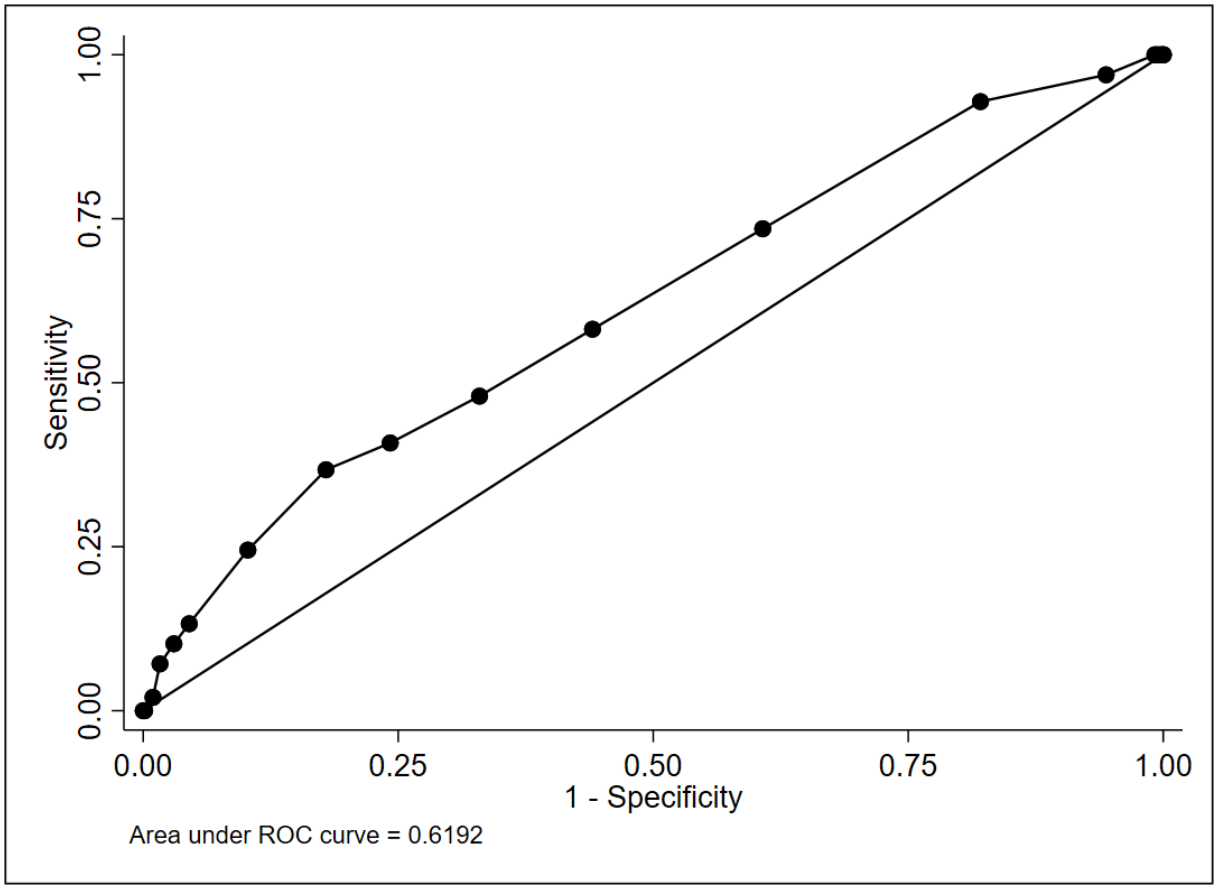

Figure 4.5: ROC curves for the LACE index models for the combined outcome of 30-day all-cause unplanned readmission and mortality.

The logistic regression identified that the two LACE index variables with the highest statistical significance were length of stay and the number of ED encounters in the prior six months (refer to Table 4.5).

Table 4.5: Performance assessment of the logistic regression model for 30-day all-cause unplanned readmission and the composite outcome of 30-day all-cause unplanned readmission and mortality.

Variable	p value	Odds Ratio (95%CI)
30-day all-cause unplanned readmission		
Length of stay	0.002	1.05 (1.01-1.08)
Admitted via the emergency department	0.251	1.33 (0.82-2.18)
Charlson comorbidity score	0.656	1.03 (0.91-1.16)
ED visits in the prior 6 months	0.000	1.51 (1.21-1.88)
Composite outcome of 30-day all-cause unplanned readmission and mortality		
Length of stay	0.002	1.05 (1.02-1.08)
Admitted via the emergency department	0.432	1.18 (0.78-1.78)
Charlson comorbidity score	0.419	1.05 (0.93-1.18)
ED visits in the prior 6 months	0.000	1.51 (1.22-1.88)

4.3 Discussion

This is the first study to explore the predictive power of the LACE index in a cohort of patients with AMI undergoing angiography in Australia. In this study cohort, a LACE score of ≥10 showed moderate discriminatory capacity to predict 30-day all-cause unplanned readmissions and the combined outcome of 30-day all-cause unplanned readmission and mortality. Akin to the findings of the LACE index study[222], this study found that the optimal score at which readmission was predicted was a score of ≥10, despite having a more refined cohort. When predicting readmission, the model yielded a sensitivity (true positives) of 47.96% and specificity (true negatives) of 67.03%. A higher cut-off score compromised the sensitivity of the model by substantially increasing the number of patients classified as high risk. For example, if the cut-off score was lowered to ≥9, the high risk group would have increased from 26% to 37%. If the cut-off was further lowered to ≥8, 53% of the group would have been considered at high risk. This study found a slightly improved fit of the model compared to a single centre study of general medical patients (n=432) found that the LACE index was a poor discriminator of hospital readmission (C-statistic = 0.58 (95%CI 0.48-0.68), but had good overall performance (Brier score = 0.082, Hosmer–Lemeshow χ^2=4.97, p=0.66)[406].

The inclusion and exclusion criteria used for this study were consistent with those used in the original LACE study[222] which derived and validated the model in a cohort of general medical and surgical patients. Despite the differences in cohort, the baseline characteristics of the original cohort were similar to the characteristics observed in this AMI population (52.6% female, mean age 61.3±17.0 years). The original LACE study[222] reported the most common index diagnosis was acute coronary syndrome (ACS) (6.4%), and the combined 30-day all-cause unplanned readmission and mortality rate was 6.0%. Similarly, the most common index procedure was angioplasty or coronary artery bypass graft (CABG) surgery (4.6% prevalence) and these patients had a combined 30-day all-cause unplanned readmission and mortality rate

of 4.6%. Despite the similarity in the baseline characteristics of these patient cohorts, the original rates are much lower to the 12.5% observed in this study. The observed difference in rates may be attributed to the inclusion of patients who were stable enough to undergo angiography. Thus, this potentially healthier cohort may explain why the observed readmission rate is lower than those previously published in AMI cohorts[163,196-202].

The logistic regression analysis of the LACE index variables identified length of stay and the number of ED encounters in the prior six months as the key drivers of the model. These findings corroborate with previous literature[407] that indicated that few simple factors were able to predict complex outcomes such as readmission among patients undergoing non-emergent non-cardiac procedures. Moreover, this study has shown that the incorporation of comorbidities, in this case the Charlson Index, into predictive models may not be of significant value in homogenous populations. Furthermore, the Charlson comorbidity index score may have proven more advantageous in the original paper (more heterogenous cohort) where patients may have been more likely to have comorbidities such as dementia and AIDS, which were negligible in this study.

The LACE+ index[229], is an updated version of the original LACE index was not examined this study due to the impracticality of variables required. Similarly, the HOSPITAL score[223] is a more complex model that incorporates laboratory test results. This model is again impractical for clinical use, as the required laboratory tests required to calculate the score may not be performed in all patients.

4.3.1 Future Directions and Implications

Currently, the are a limited number of risk prediction models in cardiac populations for readmission. Moreover, the clinical implementation of such models in Australia is an area

which requires further action. For models to be successfully implemented they need to be actionable. The design of a predictive model needs to be dynamic, simple and quick enough to be used by clinicians in a hospital setting whilst balancing and incorporating factors which are unique to the individual patient. Moreover, an optimal tool must be derived by using contextual factors that are personalised to the individual patient and take into consideration sociodemographic factors. In practice, a combined approach which incorporates both clinical judgment and insights from predictive models should aid determining which patients are at higher risk of readmission[408]. Additionally, derivation and validation of these models in disease specific cohorts may prove more accurate and may explain why generic tools such as LACE, LACE+ and HOSPITAL have had little success in large scale implementation.

Whilst the LACE index is a simple scoring tool, it is limited by the inclusion of length of stay as a predictive variable, thus it is difficult to implement this tool in practice. For a model implementation to be successful, it needs to be actionable and thus high risk patients must be quickly identified so that care pathways can be implemented to streamline individualised care needs. Although it would be ideal to provide all patients with optimal treatments to reduce readmissions, it is not practically or financially feasible. Hence, it is important to identify those at higher risk and to target those patients with additional support during their hospitalisation and post-discharge.

Developing risk-based protocols, implementing the tools and evaluating their impact on care, outcomes and costs are an important direction for future research to drive improvements in health care. In addition to producing better risk prediction models for readmission, future studies are required to implement interventions to reduce readmissions that are appropriately targeted to the needs of the individual patient. These interventions may focus on improving the transition period from hospital discharge to home in high risk patients. This has been exemplified in the United States through the implementation of the Re-Engineered

Discharged (RED) toolkit developed by the Agency for Health care Research and Quality, which lowered readmission rates by 30%[372]. These findings reiterate the importance of discharge planning for the patient throughout the patient's hospitalisation[409].

4.3.2 Study Limitations

The use of Registry data enabled the analysis of consecutive 'real world' AMI patients, however the analysis was limited to two registry centres due to accessibility of records to obtain the LACE index. Additionally, hospitalisation outcomes were restricted to public hospitals only. Similarly, the assessment of time and especially the cause of mortality was difficult to ascertain. This limitation could be improved in future by probabilistic linkage of the CADOSA Registry data to the National Death Index Registry data.

4.4 Conclusions

This study found that the LACE index was a satisfactory predictor of readmission in this South Australian cohort of patients who underwent angiography. Moreover, the two variables that predicted 30-day all-cause unplanned readmission (and combined readmission and mortality) were the length of stay and the number of ED encounters in the prior 12 months. Further investigations are required in larger samples to determine whether these two variables consistently predict readmission as they are easy to determine and would allow clinicians to determine which patients are at higher risk of readmission and provide additional support, therapies and treatment to prevent readmissions and mortality.

Chapter V

The Association between Sleep Quality and Quantity with Readmissions: An Exploratory Study among Cardiology Inpatients

This chapter is reproduced in the exact form as it appears in the manuscript, "**The Association between Sleep Quality and Quantity with Readmissions: An Exploratory Study among Cardiology Inpatients**" authored by **Clementine Labrosciano**, Rosanna Tavella, Amy Reynolds, Tracy Air, John F. Beltrame, Isuru Ranasinghe and Robert J. T. Adam, and submitted to the *Journal of Clinical Sleep Medicine*, July 2019.

In keeping with the style of this thesis, the abstract has been removed, the tables and figures re-numbered, the references incorporated into the thesis's master reference list and the manuscript repaginated.

Statement of Authorship

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Contribution to the paper	Acquisition of data, analysis and data interpretation, draft manuscript, critical revision and study conception and design.		
Overall Percentage (%)	80		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

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5.0 Introduction

Hospital readmissions are an important indicator of health care safety and quality. Readmission within 30 days of discharge is a key quality metric reported to government organisations[116,168,171]. Up to 30% of readmissions occur within 30 days of discharge from a cardiovascular condition, predominantly among patients with heart failure (HF)[12] and acute myocardial infarction (AMI)[410]. Defining the risk factors of readmissions is important in determining optimal interventions to reduce readmissions[411-413] and improving patient outcomes.

Readmission risk prediction remains a complex and poorly understood endeavour currently dominated by patient-level models. These models include factors such as comorbidities, basic demographic data and clinical variables[401]. Broader social, environmental, medical and functional factors are likely to contribute to readmission risk but have not been widely studied. Sleep disturbance is known to have negative physiological and psychological effects including altered emotions, poor memory, impaired cognitive function and reduced immunity[282]. The hospital environment is notorious for disrupting sleep[312], and sleep disturbance has been shown to interfere with healing[414]. A U-shaped relationship has been established indicating that both short and long periods of sleep result in adverse cardiovascular outcomes[309,277]. Thus, poor quality and quantity of sleep in the hospital environment may be a factor contributing to readmissions.

The association between sleep characteristics and readmission in cardiovascular inpatients has not been previously assessed. This study aims to determine if an association exists between sleep quantity and sleep quality with 30-day all-cause unplanned readmission among cardiology inpatients, using both objective and subjective measures of sleep.

5.1 Methods

This prospective observational cohort pilot study recruited patients spending a minimum of one night in the coronary care unit of The Queen Elizabeth Hospital, South Australia between June 2016 and March 2018. This study was approved by Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee.

5.1.1 Study Patients

The inclusion criteria for this study were (i) hospital admission with a cardiovascular diagnosis or procedure and (ii) ability to wear an ActiGraph device on the wrist. Patients were excluded based on discussion with nursing staff if they were (i) not residing permanently within South Australia, (ii) highly dependent on medical care, (iii) had a movement disorder, (iv) had a cognitive impairment or intellectual disability reported by a health practitioner or (v) were unable to provide informed consent or communicate sufficiently in English.

5.1.2 Study Protocol

Following informed consent obtained prior to the patient's first night in hospital and the administration of questionnaires assessing sleep and health status. These questionnaires included the Pittsburgh Sleep Quality Index (PSQI)[310], Euro Quality of life questionnaire – 5 Dimensions – 3 Levels (EQ-5D-3L)[415], Epworth Sleepiness Scale (ESS)[314] and the STOP BANG[416] questionnaire (a score based on patient snoring, daytime tiredness, observed apnea's, high blood pressure (BP), body mass index, age, neck circumference and gender). Medical history was attained via patient interview and medical record review. The ActiGraph GT3X+ (ActiGraph, LLC, Pensacola, FL) was placed on the patient's preferred wrist, taking into consideration placement of any medical devices (such as cannulas and tubing) and they were instructed to wear it continuously. Patients were invited to continue wearing the ActiGraph for two weeks following discharge and provided with a post-paid reply envelope to

return the device. If the patient preferred to return the ActiGraph at discharge, the ActiGraph was collected by the researcher following discharge.

30-Day All-cause Unplanned Readmission

A readmission was defined as a return to the emergency department or an unplanned admission to hospital for any reason within 30 days of discharge. Readmissions were determined via hospital administrative databases and medical records, or via from patient self-report at the 30-day follow-up point.

Follow-up

At 30 days post-discharge, patients were contacted via telephone, and by mail if there were two failed telephone attempts. Patients were asked whether they had returned to hospital since discharge, and both the PSQI[310] and EQ-5D-3L[415] questionnaires were reassessed verbally.

5.1.3 Sleep Parameters Assessment

Actigraphy

Polysomnography (PSG) is the gold standard measure of sleep quantity, however due to the intrusive nature of the device[304] it was not feasible for use in this cohort of patients. Actigraphy uses a piezoelectric transducer to measure wake and sleep states based on movement[300]. The ActiGraph GT3X+ has been validated in various cohorts against laboratory based PSG[417-420] with 90% sensitivity, 46% specificity and 84% accuracy[306]. All ActiGraph data was extrapolated using ActiLife v6.0 software (ActiGraph LLC).

The Troiano algorithm[421] was used to interpret sleep measures. A wear time threshold has not been previously defined in the literature, hence we assessed various thresholds for the total

sleep time (TST) of all patients who wore an ActiGraph. A 70% threshold was determined sufficient for data analysis of our cohort, refer to Appendix C for a full description.

The used the Cole-Kripe Sleep algorithm[422] was used to interpret the ActiGraph data into the endpoints defined below:

Total sleep time (TST): The average time (minutes) a patient was asleep during a 24-hour period.

Number of awakenings: The average number of times the patient awoke during a period characterised as sleep.

Wake After Sleep Onset (WASO): The average time (minutes) between sleep and wake. In healthy sleep, WASO should be <5% of TST[247].

Average time awake: The average amount of time (minutes) the patient was awake during a period of sleep.

Pittsburgh Sleep Quality Index (PSQI)[310]

The PSQI is a validated measure of a patient's perception of their sleep and is comprised of 19 questions and seven domains[310,311]. The global score is ranked from 0 to 21, where scores ≥5 are defined as poor sleep with 90% sensitivity and 87% specificity compared to PSG[310].

Epworth Sleepiness Scale (ESS)[314]

The ESS assesses the respondent's propensity to fall asleep during the day across a range of daytime activities and scenarios[314]. The ESS is comprised of eight questions with higher scores indicating increased daytime sleepiness[311,314,315]. The ESS has shown to have high internal consistency (Cronbach alpha = 0.88) in healthy medical students[315].

STOP BANG[416]

The STOP BANG questionnaire[416] is comprised of eight items and has been validated against PSG. It detects obstructive sleep apnea (OSA) for scores ≥5 with 72% (CI 54.4 – 89.6) sensitivity and 33.3% (CI 2.5 – 64.1) specificity[316].

Euro Quality of life questionnaire – 5 Dimensions – 3 Levels (EQ-5D-3L)[415]

The EQ-5D-3L is a well-established quality of life questionnaire[415] with acceptable construct validity[423] and excellent reproducibility[424].

5.1.4 Statistical Analyses

Descriptive data for the readmitted and non-readmitted patients were analysed using t-tests (for continuous variables) and chi^2 tests (for categorical variables). Mean TST was displayed as both a continuous and categorised variable into <6 hours[283,425-427], 6 to 9 hours and >9 hours as has been reported previously[426-434]. Effect size was measured using *Cohen's d* test to determine whether clinically significant difference exists between the mean values. All statistical analyses were performed using STATA 14 (StataCorp., College Station, TX, USA).

5.2 Results

5.2.1 Patient Demographics

Of the 222 patients screened, 112 patients consented to participate, 38 patients withdrew prior to completion. The remaining 75 patients formed the study cohort (Figure 5.1).

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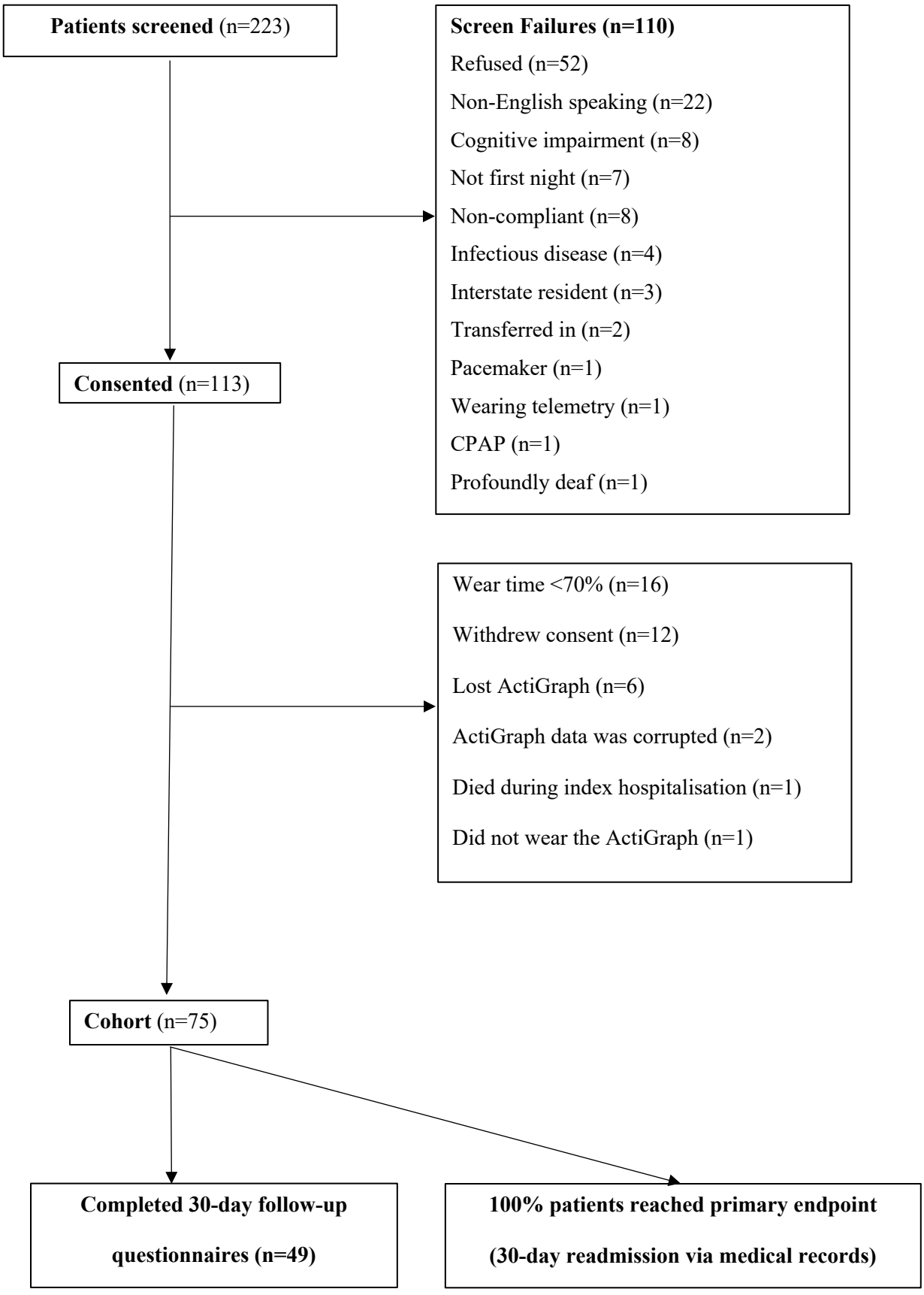

Figure 5.1: Consort diagram of study cohort.

The overall cohort was elderly (mean age of 66.9±13.1years) and male dominated (72%), with an average length of stay of 3.0±1.5 days. Baseline characteristics of readmitted and non-readmitted patients were similar (Table 5.1).

Table 5.1: Baseline characteristics for unplanned readmitted vs. non-readmitted patients.

	Readmitted		Not readmitted		P value
	Mean	**SD**	**Mean**	**SD**	
Demographics and Comorbidities					
n	15	-	60	-	-
Age (years)	64.5	18.7	67.5	11.5	0.43
Female (%)	40	-	25	-	0.25
Length of stay (days)	3.5	1.5	2.8	1.5	0.14
Private insurance (%)	47	-	38	-	0.57
Single room (%)	33	-	30	-	0.80
Live alone (%)	47	-	28	-	0.17
Cardiovascular risk factors and comorbidities					
AF (%)	33	-	32	-	0.90
HF (%)	33	-	15	-	0.10
Dyslipidaemia (%)	67	-	68	-	0.90
Hypertension (%)	60	-	75	-	0.25
Prior Stroke (%)	20	-	12	-	0.40
Prior Diabetes (%)	20	-	32	-	0.38
Prior Angina(%)	73	-	25	-	0.03
Prior MI (%)	33	-	18	-	0.21
Prior PCI (%)	13	-	22	-	0.47
Prior CABG (%)	20	-	8	-	0.19
PAD (%)	13	-	3	-	0.13
Current smoker (%)	20	-	23	-	0.95
Non-Cardiovascular risk factors or comorbidities					

COPD (%)	20	-	13	-	0.51
Arthritis (%)	13	-	22	-	0.47
Depression (%)	20	-	10	-	0.29
Anxiety (%)	7	-	5	-	0.81
No OSA (%)	87	-	90	-	0.84
OSA with CPAP (%)	7	-	7	-	
OSA w/o CPAP (%)	7	-	3	-	
Asthma (%)	20	-	12	-	0.40
GORD (%)	13	-	30	-	0.19
Procedures and medications					
Angiography (%)	27	-	47	-	0.15
Aspirin (%)	33	-	48	-	0.30
Statin (%)	40	-	50	-	0.49
ARB / ACE inhibitor (%)	40	-	42	-	0.91
GTN (%)	33	-	13	-	0.07

Abbreviations: AF = atrial fibrillation; HF = heart failure; PCI= Percutaneous Coronary Intervention; CABG = coronary artery bypass graft; AAA = Abdominal aortic aneurysm; MI = Myocardial infarction; OSA = obstructive sleep apnea; CPAP = continuous positive air pressure; GORD = gastro-oesophageal reflux disease; PAD = peripheral artery disease; COPD = chronic obstructive pulmonary disease; ARB = angiotensin II receptor blocker; ACE = angiotensin converting enzyme; GTN = glyceryl trinitrate.

**p values were taken from t-test or chi^2 test, as appropriate.

Comorbidities were similar, although a significantly greater number of readmitted patients presented with a history of prior angina (73% vs. 25%, p=0.03). Patient medications on admission were similar among all patients, although readmitted patients were more likely to be prescribed glyceryl trinitrate (GTN), consistent with their significant history of angina (33% vs. 13%, p=0.07).-The most common reason for the index admission was an elective procedure (33%) followed by ACS (27%) (Table 5.2).

Table 5.2: Primary Diagnoses of the Cohort

Diagnosis Category	n	%
Elective procedures	22	33
Acute coronary syndromes	18	27
Arrhythmias	8	12
Heart failure	7	11
Other	11	17

Note: All patients who came in with chest pain were listed under 'other'.

5.2.2 Readmission Timing and Causes

The 30-day follow-up rate for telephone calls was 65% (49 patients), however readmission status was available via medical records for all 75 patients. The 30-day all-cause unplanned readmission rate was 20%. Time to readmission varied from one to 27 days post-discharge, with an average time of 11.9±7.6 days. Patients wore an ActiGraph for an average of 2.8±1.8 (range: 0 to 8) nights in hospital. Of the 37 patients who continued to wear the ActiGraph post-discharge, the average wear time was 10.0±5.1 (range: 1 to 20) days. The most common cause of 30-day readmission were cardiac-related (nine of the 15 patients). A complete list of readmission diagnoses is available in Table 5.3.

Table 5.3: The causes of readmission of the 15 patients who returned to hospital. Nine of the 15 were readmissions for something cardiovascular-related.

Cardiovascular-related readmission	**Non-cardiovascular-related readmission**
ST-elevated myocardial infarction.	Return to Emergency Department for unknown reason (x2).
Exacerbation of heart failure.	Gynaecological pain.
Coronary spasm.	Haematoma on the arm.
Chest pain (x3).	Itchy skin rash.
Atrial fibrillation.	Accidental overdose.
Atypical angina.	
Unstable angina.	

5.2.3 Objective sleep measures

In-hospital TST recordings showed no difference between readmitted and non-readmitted patients (6.9±1.3 hours vs. 6.8±2.9 hours, p=0.96). A higher proportion of readmitted patients had a longer TST (6-9 hours vs. <6 hours, p=0.07) (Table 5.4). The post-discharge TST of non-readmitted patients was longer on average than readmitted patients however not statistically significant (7.4±1.3 hours vs. 8.9±12.6 hours, p=0.76) (Table 5.4).

Table 5.4: In-hospital and post-discharge ActiGraph data.

	Readmitted		Not Readmitted		p	Cohen's d (95%CI)
	Mean	**SD**	**Mean**	**SD**		
In hospital						
Total sleep time **(n)**	14	-	59	-	-	-
In hours	6.9	1.3	6.8	2.9	0.96	0.02 (-0.57-0.59)
0 to 6 hours (%)	21	-	44	-	0.07	-
6 to <9 hours (%)	71	-	37	-	-	-
≥ 9 hours (%)	7	-	19	-	-	-
Wake After Sleep Onset **(n)**	15	-	59	-	-	-
In minutes	84.5	85.3	61.9	51.3	0.14	0.43 (-0.14-1.00)
<30 mins (%)	0	-	12	-	0.16	-
30 to 60 mins (%)	33	-	46	-	-	-
≥ 60 mins (%)	67	-	42	-	-	-
Number of awakenings **(n)**	15	-	59	-	-	-
	13.6	4.2	11.9	5.2	0.25	0.33 (-0.23-0.91)
Average time awake **(n)**	15	-	59	-	-	-
In minutes	4.7	1.6	5.4	2.4	0.29	0.30 (-0.26-0.87)
Post-discharge						
Total sleep time **(n)**	7	-	30	-	-	-
Hours	7.4	1.3	8.9	12.6	0.76	0.13 (-0.69-0.94)
0 to 6 hours (%)	14.3	-	33	-	0.54	-
6 to <9 hours(%)	71.4	-	60	-	-	-
≥ 9 hours (%)	14.3	-	7	-	-	-
Wake After Sleep Onset **(n)**	7	-	31	-	-	-
In minutes	43.4	15.6	46.2	14.6	0.65	0.19 (-0.63-1.01)
<30 mins (%)	14	-	16	-	0.78	-
30 to 60 mins (%)	72	-	58	-	-	-
≥ 60 mins(%)	14	-	26	-	-	-
Number of awakenings **(n)**	7	-	31	-	-	-
	11.1	5.5	11.2	4.3	0.80	0.10 (-0.71-0.92)
Average time awake **(n)**	7	-	31	-	-	-
In minutes	5.6	2.8	4.9	1.7	0.47	0.31 (-0.51-1.13)

**p values were taken from t-test or chi^2 test, as appropriate.

WASO from actigraphy did not differ significantly between readmitted and non-readmitted patients, both in-hospital and post-discharge. However, in-hospital WASO recordings indicated that readmitted patients had longer WASOs compared to non-readmitted patients (84.5±85.3 minutes vs. 61.9±51.3 minutes, p=0.14) with a medium effect size (*Cohen's d*=0.43). Further, when categorised, 67% of readmitted patients had a mean WASO of ≥60 minutes compared to 42% of non-readmitted patients (p=0.16, Table 5.4). Although not statistically significant, in-hospital awakenings were increased in readmitted patients (13.6±4.2 vs.11.9±5.2, p=0.25), with a small to medium effect size (*Cohen's d*=0.33) for the number of awakenings in hospital. There were no differences in the awake times between readmitted and non-readmitted patients for both the in-hospital and post-discharge data (Table 5.4).

5.2.4 Subjective Measures

No differences between the readmitted and non-readmitted patients were observed in relation to daytime sleepiness as measured by the ESS. The STOP BANG questionnaire scores were also similar between groups. However, 40% of readmitted patients (compared to 13% of non-readmitted patients, p=0.02) reported that someone had observed them stop breathing while sleeping.

The EQ-5D-3L was answered by all 75 patients at baseline, with readmitted patients reporting a lower VAS (Visual Analogue Scale) score (48.7±21.9 vs. 63.3±28.7, p=0.07) indicative of poorer self-rated health, with small effect size (*Cohen's d*=0.10). At 30 days, the mean VAS scores were similar between readmitted and non-readmitted patients (74.3±15.1 vs. 76.5±22.3, p=0.80, respectively). The mobility domain of the EQ-5D-3L was significantly lower in readmitted patients at both baseline (p=0.003) and 30 days (p=0.004).

At baseline, readmitted patients had a lower PSQI global score, indicating worse sleep perception (9.13±3.6 vs. 6.4±4.1, p=0.02). The average 30-day PSQI global score were similar between readmitted and non-readmitted patients (6.3±4.2 vs. 6.0±3.9, p=0.84). All subjective sleep measures, both in hospital and post-discharge are summarised in Table 5.5.

Table 5.5: Sleep and quality of life questionnaires data (in-hospital and post-discharge).

	Readmitted		**Not readmitted**			**Cohen's d**
	Mean	**SD**	**Mean**	**SD**	**p**	**(95%CI)**
In-hospital						
n	15	-	60	-	-	-
ESS Mean Score	5.9	5.3	6.3	4.6	0.73	0.09 (-0.47-0.66)
STOP BANG	4.3	1.5	4.1	1.5	0.70	0.11 (-0.45-0.67)
PSQI	9.13	3.6	6.4	4.1	0.02	0.70 (0.12-1.27)
n	15	-	58	-	-	-
EQ-5D VAS	48.7	21.9	63.3	28.7	0.07	0.53 (-0.04-1.11)
Post-discharge						
n	7	-	40	-	-	-
EQ-5D VAS	74.3	15.1	76.5	22.3	0.80	0.10 (-0.70-0.91)
n	8	-	41	-	-	-
PSQI	6.3	4.2	6.0	3.9	0.84	0.08 (-0.68-0.83)

**p values were taken from t-test or chi^2 test, as appropriate.

5.3 Discussion

This is the first study to report sleep quality and quantity of cardiovascular inpatients, in relation to readmission. In line with previously published data[410], this study supports a significant rate of readmission in the first 30-days with one in five patients returning to hospital. In relation to sleep, all patients slept for almost seven hours on average in hospital, with a trend indicating that the majority of readmitted patients slept within the healthy range

(6 to <9 hours). On average, readmitted patients had a 20 minute longer WASO in hospital, implying greater disruption during sleep. While a moderate effect size was observed, statistical significance was not reached, suggesting a need to further examine periods of wakefulness during hospital stays in a larger sample size. Similarly, readmitted patients had two more awakenings on average, but spent less time awake during those awakenings. Evaluation of the ESS found higher than normal daytime sleepiness among all patients. The total scores for the STOP BANG questionnaire found that all patients had an intermediate to high risk of OSA. PSQI scores in all patients were greater than five at baseline and 30 days, thus patients' perceptions of their sleep quality was poor regardless of whether they were in or out of hospital. Importantly, the readmitted patients had a higher PSQI score at baseline indicating that their recent sleep quality was noticeably poorer prior to their index hospitalisation, compared to non-readmitted patients. Furthermore, readmitted patients had significantly more issues with mobility at baseline and at 30 days. This suggests that routinely unhealthy sleep may be associated with poorer quality of life and may be a contributor to higher risk of readmission in patients with cardiac-related conditions or diseases.

5.3.1 Sleep in the Inpatient Environment

Sleep disruption during hospitalisation is a significant concern for inpatients. The negative consequences on patient health have been well described as resulting from a number of factors intrinsic to the patient, the external environment and the care process[435]. A systematic review of multiple interventions to limit the impact of sleep disturbance in hospitalised patients identified the potential to make improvements in the quality of patient sleep[436]. An example of a modifiable factor is noise levels in hospital, which can be improved through the provision of earplugs and eye masks. Changing the sound and light and even aroma in the environment has been shown to positively improve sleep in hospital[437]. Nursing care activities have also been implicated as the cause of sleep disruption, but interventions have not been

demonstrated to improve sleep conditions[438].

5.3.2 Sleep and Readmissions

Management of hospitalised patients is focused on the acute illness that led to the admission and there is often little focus on managing stressors during hospitalisation that may contribute to the vulnerabilities and possible triggers that may lead to readmission. Changes to sleep, physical inactivity, social isolation, dietary changes, modifications in ambient brightness and temperature during hospitalisation produce observed responses such as delirium, immunosuppression and depression.

The consequence of the myriad of potential contributors have been expressed in the literature as '*post hospital syndrome*'[239]. Post hospital syndrome hypothesises that the index hospitalisation increases a patient's generalised risk and vulnerability for readmission[239]. As the index illness begins to heal and the patient is discharged, post hospital syndrome manifests and leads to readmission. The exact aetiology of post hospital syndrome is not well understood however allostasis overload during the index hospitalisation has been postulated[439], whereby the increased level of chronic stress can lead to cognitive, cardiovascular, immune and functional deterioration. These mechanisms are depicted in Figure 5.2[440]. Sleep disturbance during the index admission may be one of several factors contributing to a patient's vulnerability to readmission[239] and it is well established that acute sleep deprivation in particular causes disruptions to the circadian rhythm[441]. The long term impacts of disturbed sleep during hospitalisation include lower physical functioning, increased mortality and delirium[436], however there is little to no data specifically assessing sleep in cardiovascular inpatients and the impact on readmissions.

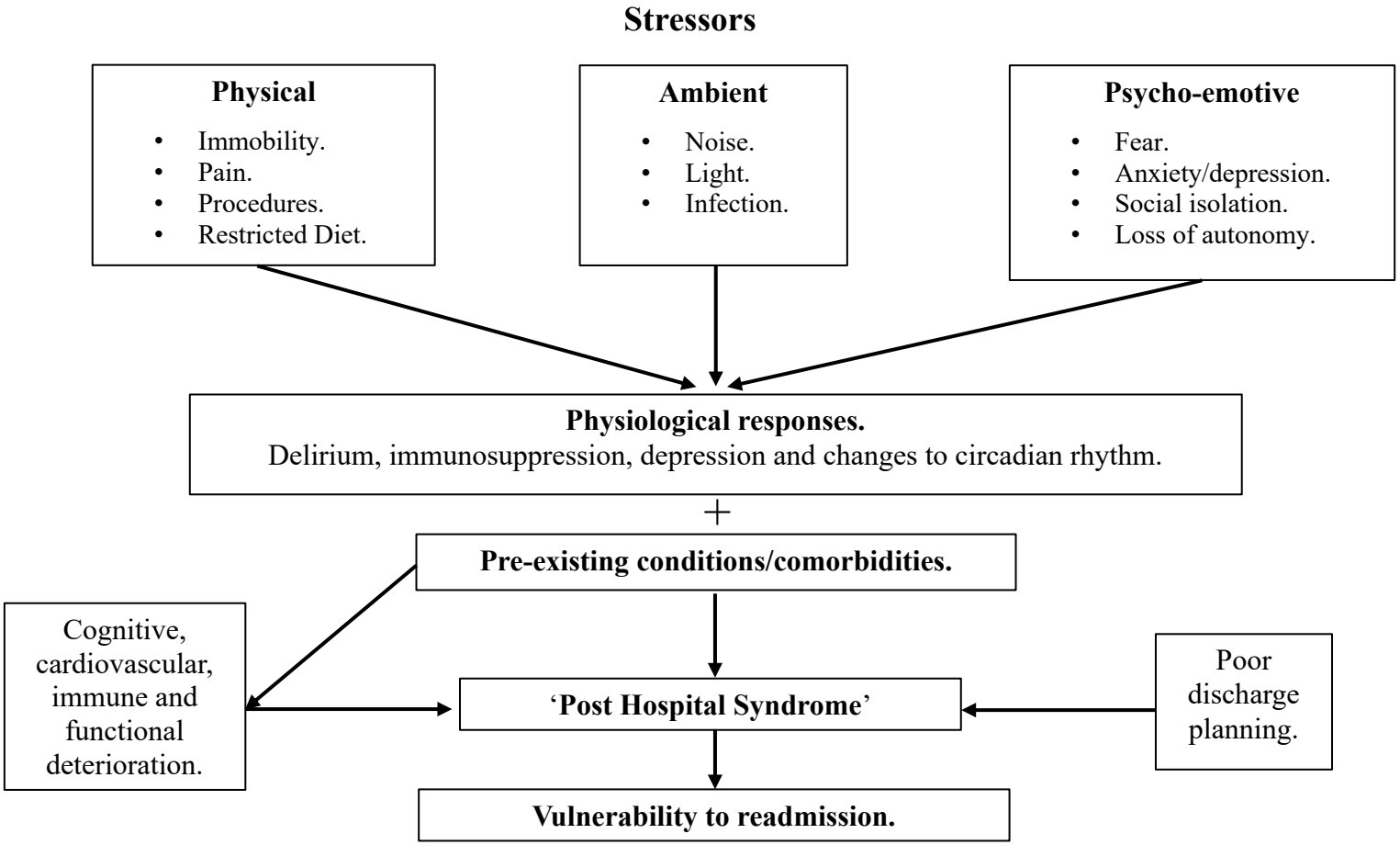

Figure 5.2: Possible mechanisms behind post hospital syndrome that result in patient readmission, adapted from Mesquita et al. 2015[440]. Sleep is a stressor that is partly physical, partly ambient and partly psycho-emotive. These in-hospital stressors result in physiological responses. In addition to pre-existing comorbidities, the cognitive, cardiovascular, immune and functional deterioration and poor discharge planning lead to increased risk of *Post Hospital Syndrome.* This then leads to patients increased vulnerability to readmission.

Our current understanding of sleep in patients with cardiovascular disease is focused on OSA with observational evidence showing that OSA is associated with both coronary and cerebrovascular morbidity and mortality[442,443]. Our study showed eight (11%) patients from the overall cohort had been previously diagnosed with OSA (Table 5.1). However, 14 patients (19%) of the overall cohort indicated that someone had observed them stop breathing while sleeping, suggesting a potential under diagnosis of OSA among patients with cardiovascular disease. A study in the United States, of general medicine patients reported OSA as a risk factor for readmission (11.4% vs. 7.6%, $p<0.01$)[444]. Thus, OSA may be important novel modifiable risk factor for cardiovascular readmissions.

A meta-analysis of sleep duration (assessed by various methods) in cardiovascular cohorts demonstrated that less than five hours and over nine hours of sleep was associated with poorer outcomes, specifically mortality and morbidity. However, none of the studies in the meta-analysis assessed readmission[275]. Few studies have compared sleep in-hospital to at home, moreover no data has been reported in a cardiovascular cohort. A large Dutch cross-sectional observational study[445] of 2000 general medicine and surgical inpatients, assessed quantity and quality of sleep and found that patients slept for 83 minutes less in hospital, on average. This study also found more nocturnal awakenings in hospital than at home, similar to the current study. An Australian study assessing the perceived duration of sleep in generally hospitalised patients also found that patients slept less in hospital than at home[446]. Both studies assessed sleep using subjective measures and thus we present the first objective measurement of sleep using actigraphy for hospitalised patients.

5.3.3 Limitations

The major limitation of this study was the small sample size, illustrated well by reasonable effect sizes between readmitted and non-readmitted patients but results which did not achieve statistical significance. Importantly, we have demonstrated the feasibility of using wearable devices for hospitalised patients although post-discharge use may require more monitoring for compliance. The small sample size also limited our ability to adjust for potential confounders related to readmissions. This study was limited due to the lack of a sleep diary, which has been previously shown to corroborate the findings of actigraphy particularly for non-compliant wear and when a patient is motionless but still awake[447]. The pilot study enrolled patients with any cardiovascular diagnosis, and to improve generalisability, future studies may be limited to patients with a specific cardiovascular condition such as AMI or HF.

5.4 Conclusions

This study did not find a statistically significant relationship between sleep quantity (as measured by actigraphy) and 30-day all-cause unplanned readmissions of cardiology inpatients. However poor perceived sleep quality (measured by the PSQI[310]) was associated with increased 30-day all-cause unplanned readmissions. Whilst the actigraphy data was not associated with readmissions, some aspects of sleep in the readmitted patients including the WASO and in-hospital awakenings suggest further exploration is warranted in larger studies. This may have implications for inpatient management if disturbance of sleep is linked to readmissions. If so, future research involving risk prediction models for hospital readmissions may be improved by wearable device technology to monitor and collect sleep data. Finally, it is important to characterise how changes in sleep pattern during hospitalisation correlate with physiological abnormalities that may increase the risk of adverse outcomes after hospitalisation.

Chapter VI

Conclusions

Chapter VI

Improving the health outcomes of patients with cardiovascular disease (CVD) via the reduction of readmissions has evolved in recent years. The improvement of health outcomes via a holistic and compassionate approach is not a novel concept. From the 5th Century Before the Common Era Hippocrates, Greek physician and father of modern medicine wrote the original Hippocratic Oath to emphasise the holistic and compassionate approach to medicine[448]. The bioethical principles in medicine still uphold the underlying principle from Hippocrates's Oath – *"do no harm".* Consistent with this principle, this thesis addresses the concept of reducing readmissions and improving the patient's health outcomes. It further emphasises the value of measuring, reporting and reducing readmissions in an Australian context. Additionally, this thesis has explored various methods to better understand which study designs could best enable researchers to answer specific questions. The major findings of the thesis are summarised below.

Chapter II employed a scoping review approach to explore the knowledge gap surrounding the prevalence and causes of readmission in Australian patients with CVD. This chapter concluded that readmission rates in the Australian context (1) were comparable to those observed overseas, (2) showed heterogeneity in the design, definition and measurement and (3) the need for future studies to test and implement interventions to reduce these rates and thus improve the health outcomes of patients with CVD.

The scope of this thesis then focused from the broader CVDs into heart failure (HF) and acute myocardial infarction (AMI) specifically, as these two conditions have been shown internationally to have the highest rates of readmission. **Chapter III** utilised linked administrative data from Australian and New Zealand patients with a primary discharge diagnosis of HF. This chapter concluded that (1) the 30-day all-cause mortality rate was 10.7% and (2) the 30-day all-cause unplanned readmission was 22.3%, which are comparable to previously reported rates. Moreover, this chapter found variability in the readmission rates

and a decline in both mortality and readmission rates between 2010 and 2015. Once again, Chapter III emphasised the need to standardise care provided to HF patients in Australia to reduce readmission and thus improve patient outcomes.

Chapter IV of this thesis assessed a risk prediction model (the LACE index) in a local cohort of patients with AMI undergoing angiography who were derived from registry data between 2016 and 2017, to determine which patients were most vulnerable for 30-day all-cause unplanned readmission and mortality. Chapter IV concluded that the LACE index (1) had moderate discriminatory capacity to predict readmission and mortality and (2) highlighted the need for more robust models to facilitate clinicians in determining which patients are at higher risk of readmission, allowing clinicians to adapt care to best suit the individual patient.

From the findings in previous chapters it was apparent that the notion of *post hospital syndrome* may be contributing to the observed rates of readmission in patients with CVD. **Chapter V** utilised a clinical pilot study to analyse, at the patient level, whether the quality and quantity of sleep in hospital could be a contributing factor to the observed readmission rates. Chapter V (1) did not conclusively find an association between sleep *quantity* and readmission, (2) found that patients who perceived their sleep *quality* as being poorer were more likely to be readmitted within 30 days and (3) highlighted the importance of improving sleep both in and out of hospital, to improve patient outcomes such as reducing readmissions in cardiology inpatients.

In summary, the data from this thesis advances the knowledge-based concerning readmissions in Australian patients with CVD demonstrating (1) the lack of contemporary resources available in Australia (2) readmissions following index admissions for HF and AMI are similar to international counterparts, (3) variation of readmission and mortality rates exist within Australia, (4) acknowledging the importance of risk prediction models in helping to

identify patients at higher risk and (5) the exploration of poor sleep both in (and potentially out of hospital) as a possible contributor to the readmissions.

Thus, readmission following an index hospitalisation for a CVD is a global problem, with the exact underlying mechanisms remaining unclear and a limited impact of current approaches. These include targeting, accommodating and personalising therapy or treatment for the individual patient, as opposed to a hospital-level solution. By grasping the concerns and needs of the individual patient and tailoring therapy to accommodate the individuals needs and unique situation, the clinician can improve the outcomes of that patient. Furthermore, despite best efforts to make changes to policy, such as the Hospital Readmission Reduction Program (HRRP) in the United States, the rates of readmission and mortality do not appear to be drastically reducing. This further emphasises the need for the clinician to work together **with** the patient to determine what is best for them and not the health care system. Only when we change the fundamental practice of clinicians will we reap the rewards of improving patient centred care and optimising the outcomes, such as reducing readmission, for all patients.

Future approaches to improve our understanding of the underlying causes of these readmissions include big data, personalised medicine and shared decision making. Big data analysis and the use of electronic health records have made positive change to the role of patients, in allowing them to work *with* their physician to make shared decisions. There has also been much controversy concerning the ethical considerations which must be maintained to uphold the confidentiality and autonomy of patients. Although it is beyond the scope of this thesis, health applications are now becoming a popular way to encourage patients to improve their own health. In such large datasets, the p-values <0.05 becomes irrelevant and there has been debate on this and the proposal to lower the threshold for significance to <0.005[449].

In addition to highlighting these findings regarding readmissions, this thesis has also explored the capability of using different sources of data to best utilise this data to improve patient outcomes. With such large datasets, the capability for such amounts of information to be produced and analysed in rapid succession, compromises the autonomy of medicine. The use of patient level data analysis and observational cohort study designs are still vital in medicine (and cardiology) today. The critical thinking and decision making are unique human capabilities and although artificial intelligence and big data techniques may improve current practice, some skills are best left to trained clinicians who have the ability to determine when exceptions to the "algorithm" are necessary. There is no "typical patient", each patient is unique, and this is why the guidelines may lack value in medicine today. A clinician has the expertise to weigh the risks and benefits and the capability to work with the patient to determine the optimal treatment for him or her.

In such a fast-paced evolving world, the use of machine learning and artificial intelligence are currently a hot topic in the literature in all aspects of medicine[450]. However, through the exploration of big data techniques in Chapter III of this thesis, it is noted that the technology has limitations. Therefore, although this technology is important and in the future may be beneficial in clinical practice, at present it needs to be refined and may in fact be detrimental to practice at present. The use of administrative data is continuing to prove useful for appraisal and improvement of health care policies[125,151].

Such large datasets are useful to grasp the generalised overview of what is happening in a population. Through infrastructure such as linkage between data sets, the sharing of administrative data for the purpose of research has facilitated the evolution of health care outcomes research[148].

However, what is most important (and what clinicians strive to achieve everyday) is to improve the quality of life of individual patients. Thus, the use of "big data", "machine learning" and automatic techniques will never replace the decision-making that a human is capable of formulating. Although, the use of such personalised medicine and advances in technology have allowed for the creation of applications or tools such as ePRISM, that provide the clinician with a real time, personalised tools to provide patients with the best possible therapy.

Future interventions that may reduce hospital readmissions in Australia may involve (a) health system policy changes – financial penalties for readmissions and (b) further exploring the concept of post hospital syndrome, and intervening in this pathological process, (c) continuing patient education to allow for patient self-help and (d) home-based intiatives as have been described earlier in chapter II of this thesis, in reference to the work by Stewart et al[362,451] in cohorts of patients with HF. It is anticipated that data linkage and personalised treatment for patients will provide optimal outcomes for patients. As was depicted in a recent study by Hammill and colleagues[134].This study of patients with HF, found that by using both administrative and registry data, compared to using administrative data alone, resulted in improved accuracy of a model to predict 30-day outcomes. This emphasises the importance of linking both sources of data, with an emphasis on outcomes data, and personalising and delivering the information to the patients in real-time. Additionally, the models used in this study had better accuracy for predicting 30-day readmission as opposed to 30-day mortality. This speaks to the enigma surrounding readmissions that thesis has begun to explore in an Australian context. Finally, this thesis has highlighted the importance and supports the need for future research to be conducted in order to improve the outcomes of patients hospitalised with CVD.

Appendices

Appendix A

Published Manuscript Chapter II

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Readmissions following hospitalisations for cardiovascular disease: a scoping review of the Australian literature

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Abstract

Objective. International studies suggest high rates of readmissions after cardiovascular hospitalisations, but the burden in Australia is uncertain. We summarised the characteristics, frequency, risk factors of readmissions and interventions to reduce readmissions following cardiovascular hospitalisation in Australia.

Methods. A scoping review of the published literature from 2000–2016 was performed using Medline, EMBASE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases and relevant grey literature.

Results. We identified 35 studies (25 observational, 10 reporting outcomes of interventions). Observational studies were typically single-centre (11/25) and reported readmissions following hospitalisations for heart failure (HF; 10/25), acute coronary syndrome (7/25) and stroke (6/25), with other conditions infrequently reported. The definition of a readmission was heterogeneous and was assessed using diverse methods. Readmission rate, most commonly reported at 1 month (14/25), varied from 6.3% to 27%, with readmission rates of 10.1–27% for HF, 6.5–11% for stroke and 12.7–17% for acute myocardial infarction, with a high degree of heterogeneity among studies. Of the 10 studies of interventions to reduce readmissions, most ($n = 8$) evaluated HF management programs and three reported a significant reduction in readmissions. We identified a lack of national studies of readmissions and those assessing the cost and resource impact of readmissions on the healthcare system as well as a paucity of successful interventions to lower readmissions.

Conclusions. High rates of readmissions are reported for cardiovascular conditions, although substantial methodological heterogeneity exists among studies. Nationally standardised definitions are required to accurately measure readmissions and further studies are needed to address knowledge gaps and test interventions to lower readmissions in Australia.

What is known about the topic? International studies suggest readmissions are common following cardiovascular hospitalisations and are costly to the health system, yet little is known about the burden of readmission in the Australian setting or the effectiveness of intervention to reduce readmissions.

What does this paper add? We found relatively high rates of readmissions following common cardiovascular conditions although studies differed in their methodology making it difficult to accurately gauge the readmission rate. We also found several knowledge gaps including lack of national studies, studies assessing the impact on the health system and few interventions proven to reduce readmissions in the Australian setting.

What are the implications for practitioners? Practitioners should be cautious when interpreting studies of readmissions due the heterogeneity in definitions and methods used in Australian literature. Further studies are needed to test interventions to reduce readmissions in the Australians setting.

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Introduction

Cardiovascular disorders are among the most common cause of hospitalisation in the Australian health system, with more than 500 000 hospitalisations occurring annually.[1] This care is expensive, consuming 40% of the total national healthcare expenditure on cardiovascular disease.[2] International studies have suggested that many of these hospitalisations are due to readmissions. Selected US populations have found that one in four patients with heart failure (HF) are readmitted within 30 days,[3] increasing to one in two at 6 months.[4] Similarly, 15% of stroke patients are readmitted by 30 days,[5] increasing to 20–40% by 1 year.[6] High rates of readmission are also reported in selected US populations for common conditions and procedures, such as acute myocardial infarction (AMI; 19% by 30 days), percutaneous coronary intervention (PCI; 15% by 30 days)[7] and peripheral artery revascularisation (17.6% by 30 days).[8] A proportion of these readmissions is inevitably due to the underlying condition. Nevertheless, a large proportion may be avoidable. Readmissions occurring due to preventable reasons, such as hospital acquired infection, thromboembolism and medication errors, are frequent, with a systematic review suggesting that at least one-quarter of all readmissions are preventable.[9] Thus, reducing hospital readmissions is highly desirable to improve patient care and minimise avoidable healthcare expenditure.

Driven by the international findings, clinicians and policy makers in Australia are also increasingly focusing on reducing readmissions, with cardiovascular conditions frequently touted as a priority condition. For example, the New South Wales (NSW) government plans to reduce the rates of unplanned readmissions by 2021.[10] However, readmissions may be driven by contextual factors and international data may have limited relevance to the Australian setting. For example, Australia's universal healthcare system allows equal access to healthcare services, compared with the fee-for-service model implemented in countries such as the US. More affordable and accessible health care in Australia may result in lower rates of readmission. Thus, efforts to reduce readmissions through clinical or policy intervention requires an understanding of readmissions in the Australian setting, including the frequency of readmissions, potential contributing factors and the effects of readmissions on the health system.

Accordingly, we conducted a scoping review of the Australian literature to identify and synthesise available evidence regarding readmissions following a hospitalisation for cardiovascular conditions. The primary objective of the study was to systematically evaluate the Australian literature with the intention of determining the frequency of readmission. Secondary objectives included: (1) identifying patient, hospital and social factors that contribute to the risk of readmissions; (2) detailing the potential effects of readmissions on the health system; and (3) describing interventions that have been assessed in the Australian setting to reduce readmissions.

Methods

Search strategy

We searched the Medline, EMBASE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) bibliographic databases, restricting the search to English language human clinical research articles published between 1 January 2000 and 11 March 2016 to review contemporary cardiovascular practice. The search was conducted using Medical Subject Heading (MeSH) terms including patient readmission, cardiovascular disease, coronary disease, cardiac surgical procedures and Australia. The full search strategy is provided in Appendices S1–S3, available as Supplementary Material to this paper.

We also searched the grey (not academically peer reviewed) literature by examining the reference lists of retrieved papers and conducting a Google search to identify any additional articles and other policy documents. This included an exhaustive search of Australian government and non-government stakeholder websites for publications on the topic of readmission following cardiovascular hospitalisations. A complete list of the grey literature identified is available in Appendix S4.

Study selection

Observational studies of cardiovascular readmissions were included, as were studies reporting outcomes of interventions to reduce cardiovascular readmissions. Articles relating to cardiovascular readmissions were defined as articles in which: (1) the primary or secondary objective related to readmissions; or (2) hospital readmission was the primary outcome or a substantive secondary outcome. Included studies were required to recruit at least 100 adult (age $\geq$18 years) cardiovascular patients from Australia and measure readmissions following an in-patient admission for a cardiovascular condition. The following types of publications were excluded: (1) review articles without original data; (2) studies that included readmissions as a composite end-point but failed to report readmission data separately; (3) multinational studies that included data from Australia without reporting Australian data separately; and (4) studies that reported more than 50% of the data collected before 2000.

Assessment of methodological quality

Abstracts were independently screened by two investigators (CL, IR). All potentially relevant articles were extracted and reviewed in full by the same two researchers for methodological validity before inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument

(JBI-MAStARI; Appendix S5). Disagreement on article selection was resolved by discussion between reviewers.

Data extraction and synthesis

Relevant data were extracted from each article and entered into a standardised database. Data extracted from all articles included sample size, study design, study period (years), number of centres, state(s), study aim, study hypothesis, primary outcome, time of readmission measurement, type of rehospitalisation (inpatient readmissions, emergency or both), factors affecting readmission, findings, strengths and weakness. Data heterogeneity was investigated by evaluating study design, methodology and reporting. A statistical test of heterogeneity was performed, where appropriate, using the I^2 test.[11] Findings are reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[12]

Results

The search yielded 794 articles and two government reports, of which 729 remained following exclusion of duplicates. Based on abstracts, 657 articles were removed, with 72 full-texts articles remaining. Twenty-five observational studies were identified that reported readmissions as an outcome (Table 1). Furthermore, 10 studies were identified that described the outcomes of interventions to reduce readmissions (Table 2). The PRISMA flow chart of article selection is given in Fig. 1. Because studies of interventions typically included highly selected populations, we report our findings for observational studies and studies of interventions separately.

Characteristics of observational studies of readmissions

Of the 25 included articles and reports, most ($n = 11$) were single-centre studies.[13–22] Less frequently, they were multicentre ($n = 7$)[23–29] or state-wide ($n = 5$)[30–34] studies, with two studies[35,36] failing to report the number of centres. The sample sizes of these studies varied from 133 to 29 961 participants, with a median value of 1660. Fourteen study designs involved retrospective cohorts,[15,18,20,23,26–28,30–35,37] with the majority limited to Victoria ($n = 9$)[15,18,21,24,26,29,33,34,36] and NSW ($n = 8$).[16,17,19,20,25,27,28,31]

Most studies reported readmissions following a hospitalisation for HF ($n = 10$),[13,14,23–26,28,30,31,36] acute coronary syndrome (ACS; $n = 7$)[14,18–20,28,33,35] and stroke ($n = 6$),[15,16,27,29,32] with three studies[14,26,28] reporting readmission rates for more than one condition. In addition, four publications reported readmission rates following procedures: PCI ($n = 1$)[26] and coronary artery bypass surgery ($n = 3$).[21,22,34] Readmission rates following hospitalisation for other cardiovascular conditions and procedures were infrequently reported.

When the primary objective of studies was considered, most ($n = 14$) focused on determining the frequency of readmission,[13–15,17,20,23,26,28,29,32,33,36,38] whereas several ($n = 8$) evaluated one or more factors associated with readmissions, including the development of a readmission risk model.[16,18,19,21,22,25,30,34] Two studies evaluated the burden (defined as bed days and costs) of readmissions on the healthcare system,[31,37] and a single study compared Australian readmission rates to other nations.[35]

Definition of readmissions and methods for data collection

The definition of readmission was highly variable between publications. All-cause readmission was reported in 16 studies,[13,15,17,23,24,26–30,33–36] eight studies[14,16,19,22,24,25,32,37] chose to report only patients returning to hospital for the same cardiovascular diagnosis as their index hospitalisation and one study[21] did not report the type of readmission measured. Approximately half the studies ($n = 13$) fully captured readmissions by counting readmissions to any hospital in the same state,[6,15,21–24,26,28–31,33,34,37] whereas the remainder ($n = 12$) only counted readmissions to the same hospital.[13,16–18,20,25–28,32,35,36] The time interval following discharge ranged from 7 days to 5 years, with most studies reporting readmission rates at 30 days after discharge.

Methods used to collect readmission data varied greatly. Telephone follow-up ($n = 3$),[13,21,29] hospital medical records ($n = 3$),[18,27,32] linked hospital administrative data ($n = 10$)[14,15,23,26,28,30,31,33,34,37] or a combination of more than one of these methods[16,17,19,20,22] was used to determine the readmission status of patients, and four studies[24,25,35,36] did not report a method. The completeness of follow-up was not reported for most studies.[14,15,17,18,20,22,24,25,27,30–35,37,39] Among those that did report complete follow-up of all participants enrolled in the study, only three[13,23,36] reported complete follow-up, with the remaining reporting loss to follow-up rates ranging from 0.2% to 52% of the study population.[16,19,21,26,28,29]

Frequency of readmissions

All studies reported the frequency of readmissions at various time points (Table 1), with readmission rates generally (and expectedly) increasing with time. Eleven studies[13,15,17,20,23,26–29,33,36] reported all-cause readmissions and as expected, these studies reported higher rates of readmission compared with studies reporting readmissions for the same diagnosis as the index hospitalisation (Fig. 2).

Of the studies that reported readmissions as a proportion of all patients discharged, readmissions were most commonly reported at or within 30 days of the index hospitalisation ($n = 14$).[14,15,18,21,23–28,30,31,34,35] The all-cause readmission rate among these studies was highly variable, ranging from 6.3% to 27%, with a median value of 13%. When individual conditions for initial hospitalisation were assessed, 30-day all-cause readmission following HF ($n = 8$ studies) ranged from 10.1% to 27% (median 18.9%), that following stroke ($n = 3$ studies) ranged from 6.5% to 11% (median 11%) and that following AMI ($n = 3$ studies) ranged from 12.7% to 17% (median 12.9%).

Extractable 30-day data were available in 11 studies ($n = 123\,874$, Fig. 3). However, we could not pool the results of the individual studies to provide a summary frequency of readmissions due to high heterogeneity among studies (Q-test, $\chi^2 = 2395.9$, $P < 0.001$; $I^2 = 99.5$). Significant heterogeneity persisted when individual conditions were evaluated, prohibiting pooling of results by condition (HF ($n = 6$ studies),[13,23,26,28,30,31] $\chi^2 = 177.27$, $P < 0.001$, $I^2 = 97.2\%$; AMI ($n = 3$ studies),[18,28,35] $\chi^2 = 21.65$, $P < 0.001$, $I^2 = 90.8\%$; stroke ($n = 3$ studies),[15,27,28] $\chi^2 = 54.71$, $P < 0.001$, $I^2 = 96.3\%$).

Table 1. Characteristics of observational studies

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ATD, atherothrombotic disease; CABG, coronary artery bypass surgery; CAD, coronary artery disease; HF, heart failure; IHD, ischaemic heart disease; Linked, linked data to other hospitals within the same state; NOCAD, non-obstructive coronary artery disease; NR, not reported; NSW, New South Wales; NT, Northern Territory; Qld, Queensland; PCI, percutaneous coronary intervention; SA, South Australia; Tas., Tasmania; Vic., Victoria; WA, Western Australia

Study	Condition(s)	No. hospitals	No. patients	Setting	All-cause vs disease-specific readmissions counted	Readmitted to same *v.* any hospital	Method to measure readmission	Rate (%, unless indicated otherwise) ≤30 days	1–6 months	6 months	12 months	≥12 months
Saito *et al.*[23]	HF	2	468	Tas.	All	Any	Linked	17				
Huynh *et al.*[30]	HF	State wide	1537	Tas.	All	Any	Linked	21				
Robertson *et al.*[31]	HF	State wide	29 161	NSW	All	Any	Linked	27				
					HF			11				
					All						73	
					HF						32	
Paul *et al.*[13]	HF	1	133	SA	All	Same	Telephone call	25		43		
Islam *et al.*[24]	HF	Multicentre	6252	Vic.	HF	Any	NR	10				
Betihavas *et al.*[25]	HF	3	280	NSW, Qld, SA	Cardiac condition	Same	NR	13				66
Pathik *et al.*[14]	HF	1	1704	SA	Cardiovascular	Same	Linked					74 treated by general cardiologist vs 77 subspecialists
	ACS		7763									57 treated by general cardiologist vs 50 subspecialists
	Arrhythmia		4398									61 treated by general cardiologist vs 50 subspecialists
Oldland *et al.*[36]	HF	NR	135	Vic.	All	Same	NR				56	
Lefkovits *et al.*[26]	HF	13	289	Vic.	All	Any	Linked	26				
	PCI	23	9166					13				
Bureau of Health Information[28]	AMI	53	27 325	NSW	All	Any	Linked	17				
	Stroke	47	12 776					11				
	HF	72	29 961					23				
Kilkenny *et al.*[15]	Stroke	1	788	Vic.	All	Any	Linked	15		36	42	
Kilkenny *et al.*[27]	Stroke	35	3328	NSW	All	Same	Hospital records	7				
Cadilhac *et al.*[29]	Stroke	40	3007	Vic.	All	Any	Telephone call		22 treated in stroke unit, 24 in other unit (P = NS)			
He *et al.*[32]	Stroke	5 (statewide)	2105	NT	Stroke	Same	Hospital records				8 Indigenous, 6 non-Indigenous	13 Indigenous, 10 non-Indigenous
Yu *et al.*[16]	Stroke	1	182	NSW	Stroke	Same	Hospital records and phone call			5		
Nguyen *et al.*[17]	AF	1	302	NSW	All	Same	Hospital records and telephone call			41		
Rana *et al.*[18]	AMI	1	1660	Vic.	IHD	Same	Hospital records	6	9	12	15	
					All			13	19	25	31	

Kociol *et al.*[35]	AMI	296 (no. from Australia NR)	Total = 5571, Australian = 465	NR	All	Same	NR	13 (Australia), 11 (overall)					
Parker *et al.*[19]	ACS	1	489	NSW	Cardiac related	Same	Hospital records and telephone call		13 (2–12 months)				
Worrall-Carter *et al.*[33]	ACS	Statewide	28 985	Vic.	All	Any	Linked						10 female, 11 male
Dwyer *et al.*[20]	ACS patients with and without significant CAD	1	180	NSW	All	Same	Hospital record and face-to-face assessment				7 NOCAD, 39 CAD		
					Cardiovascular							14 NOCAD, 11 CAD	
Murphy *et al.*[21]	CABG	1	181	Vic.	NR	Any	Telephone call	14					
Tully *et al.*[22]	CABG	1	222	SA	Related to the surgical procedure, cardiovascular or vascular disease	Any	Hospital record and telephone call			32			
Slamowicz *et al.*[34]	CABG	Statewide	6627	Vic.	All	Any	Linked	7 = 7 days; 15 = 30 days			32		
Atkins *et al.*[37]	ATD	1	6172	WA	ATD	Any	Linked						32

Of the studies that reported 30-day readmission rates, one study assessed variation in readmission rates among hospitals for AMI, HF and stroke, with the results indicating marked institutional variation in the risk-standardised readmission ratio at 30 days, although the range among hospitals was not reported.[28] Of the studies that reported readmission rates beyond 30 days, the highest number of readmissions was reported among patients with HF (76.9% of patients were readmitted for a cardiovascular-related diagnosis during a median follow-up of 5.3 years).[14]

Risk factors associated with readmissions

A risk model to predict readmission or evaluate specific patient factors associated with an increased risk of readmission was developed in eight studies.[16,18,19,21,22,25,30,34] These studies used data from single[16,18,19,21,22,30] and multiple[25,34] centres, and evaluated readmissions following initial hospitalisation for HF,[25,30] ACS,[18,19] coronary artery bypass graft surgery[21,22,34] and ischaemic stroke.[16] Appendix S6 provides a list of all patient factors tested in risk prediction models.

Patient factors that were significant in models were varied but included length of stay[30] and living alone,[21,30] prior emergency department attendance,[18,34] prior cardiac diagnosis and procedures,[18] renal impairment,[18] electrolyte disturbance,[18] sedentary lifestyle,[28] older age[28] and a higher score on the Charlson comorbidity index.[25,34] Two studies[19,22] evaluated whether psychiatric comorbidities increased the risk of readmission. A study of ACS patients found readmissions to be more prominent in patients who had pre-existing depression or developed depression after their ACS, compared with patients without a history of depression ($\chi^2 = 8.84$, d.f. = 2, $P = 0.01$).[19] Similarly, patients with increased stress, anxiety and depression before coronary artery bypass surgery had increased rates of 6-month readmission.[22] Finally, only one study[32] from the Northern Territory evaluated whether Indigenous status increased the risk of readmissions following a stroke. That study concluded that the risk of readmission for stroke was almost doubled in Indigenous patients compared with the Caucasian population (hazard ratio 1.82; 95% confidence interval 1.32–2.51).[32]

Studies that reported the burden of readmissions

The burden of readmissions can be measured in various ways, including cost, bed days and from the perspective of the patient or healthcare system. Two studies estimated the burden of readmissions in Australia.[31,37] A single-centre study from Western Australia found patients who were readmitted following an index hospitalisation for atherothrombotic disease cost the healthcare system A$101 million over 2 years, representing approximately 42% of the total cost of care over this period.[37] A study of 29 161 HF patients followed for 5 years using linked data from NSW measured the burden placed on the healthcare system by counting the number of bed days[31] and showed that there were 954 888 hospital bed-days used over the study period as a result of all-cause readmissions.

Studies of interventions to reduce readmissions

Interventions testing the reduction of readmissions as a key outcome were reported in 10 studies,[40–49] including five randomised control trials[40,41,43,45,49] (Table 2). Almost all

Table 2. Characteristics of studies reporting interventions to reduce readmissions

ACS, acute coronary syndrome; AF, atrial fibrillation; CHF, chronic heart failure; CI, confidence interval; GP, general practitioner; HF, heart failure; HR, hazard ratio; HMR, home medicines review; MI, myocardial infarction; NR, not reported; NSW, New South Wales; NT, Northern Territory; Qld, Queensland; RCT, randomised control trial; SA, South Australia; Tas., Tasmania; Vic., Victoria; WA, Western Australia

Study	Condition	Sample size	Design	Setting	No. centres	All-cause or disease-specific mortality	Same vs any hospital	Method to assess readmission	Intervention	Control group rate of readmission (%[C])				Intervention group rate of readmission (%[C])				*P*-value
										≤30 days	6 months	12 months	>12 months	≤30 days	6 months	12 months	>12 months	
Davidson *et al.*[41]	HF	105	RCT	NSW	1	All	Same	Not specified	Individualised multidisciplinary 12-week cardiac rehabilitation program			69				44		0.01
Driscoll *et al.*[42]	HF	573	Cross-sectional	NR	48	All	Same	Hospital records	CHF management program		25				14			0.005
Stewart *et al.*[49]	HF	280	RCT	Qld, SA, NSW	3	All	Same	Hospital records and telephone call	Home- vs clinic-based management program				69.3				67.1	0.887
Roughead *et al.*[44]	HF	5717	Retrospective cohort	NR	NR	All	Any	Linked	GP–pharmacist collaborative HMR			12				5.5		HR 0.55 (95% CI 0.39–0.77)
Barker *et al.*[45]	HF	120	RCT	Vic.	1	All	Same	Hospital records	Pharmacist-directed HMRs		39				53			0.417
Scott *et al.*[46]	HF ACS	1524	Before–after	Qld	9	Same	Same	Hospital records	Policy	7.2 5.2				2.4 4.2				0.02 0.02[B]
Mudge *et al.*[47]	HF	416	Prospective cohort	Qld	3	All	Same	Hospital records	Quality improvement program				36			49		0.009
Stewart *et al.*[43]	HF	280	RCT	NR	3	All	NR	NR	Home- vs clinic-based management plan				*n* = 547				*n* = 592	NS
Stewart *et al.*[40]	AF	335	RCT	SA, Vic., ACT	3	All	Same	Hospital records	AF-specific management strategy				502 (3254)[A] days in hospital				485 (2276)[A] days in hospital	NS
Martin *et al.*[48]	MI	470	Before–after	Vic.	1	Cardiac	Same	Hospital records	Strategy to reduce door to balloon time			12.8			11.1			0.68

[A]Median (interquartile range).
[B]Result significant, but favoured control.
[C]Unless specified otherwise.

interventions ($n = 8$ studies) targeted HF[41–47,49] and consisted of a health professional conducting a structured intervention at either the patient's home (e.g. home visits by a nurse, pharmacist or other healthcare professional) or at a medical facility, usually within a few weeks after discharge (for a description of all interventions, see Appendix S7).

Similar to the observational studies, the definition of a readmission varied. Readmissions were measured at <30 days,[46] 6 months,[42,45] 12 months[41,44,48] and >12 months.[40,43,47,49] Readmissions were counted using linked data by one study,[44] whereas another study used a telephone call to the patient;[43] the remaining studies used hospital records.

A statistically significant decline in readmissions in favour of the intervention was observed in four studies, although only one was a randomised trial. Davidson *et al.*[41] evaluated an individualised 12-week nurse-coordinated multidisciplinary rehabilitation program for HF patients in a randomised trial. Patients in the intervention group had a lower 12-month all-cause readmission rate than the control group (44% vs 69%; $P = 0.01$). Driscoll *et al.*[42] examined the effect of chronic HF management programs across 27 centres (a mixture of hospital and home-based programs). However, that study did not evaluate the outcome of the HF management programs against a control group. Instead, each program was ranked using a quality improvement tool (intervention score) based on their level of evidence, and the results indicated that those with a high intervention score had a lower readmission rate (14% vs 25%; $P = 0.005$).[42] Roughead *et al.*[44] evaluated whether a home medication review by both a general practitioner and a pharmacist among veterans diagnosed with HF reduced readmissions in an observational cohort. observing a 45% reduction in readmissions for patients who received the home medication review. Finally, Scott *et al.*[46] tested hospital performance feedback and a multifaceted quality improvement intervention using a before–after study design. A significant reduction in same-cause readmission was observed with the intervention in patients with HF (7.2% vs 2.4%; $P = 0.02$) but not in patients with an ACS.[46]

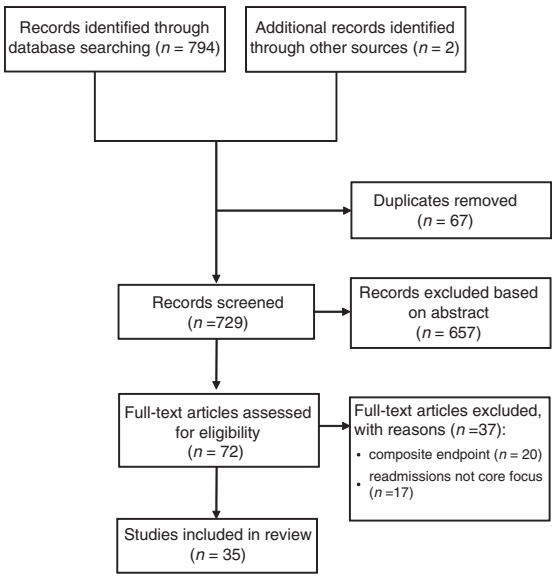

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of article search and selection for inclusion in the systematic review.

Discussion

This scoping review was performed to summarise the contemporary Australian literature on readmissions following hospitalisation for cardiovascular disease. We found 25 studies evaluating hospital readmissions over the past 16 years. We

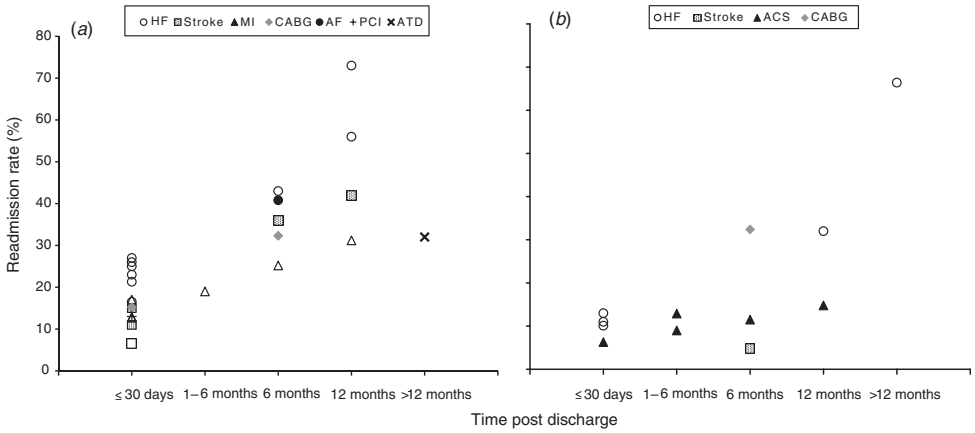

Fig. 2. (*a*) All-cause readmission rates reported from all observational studies classified by type of disease or procedure and (*b*) readmission rates of all observational studies that reported readmissions for the same cause as the initial hospitalisation. Studies have been classified into the disease or procedure reported at the patient's initial hospitalisation. ACS, acute coronary syndrome; AF, atrial fibrillation; ATD, atherothrombotic disease; CABG, coronary artery bypass graft surgery; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

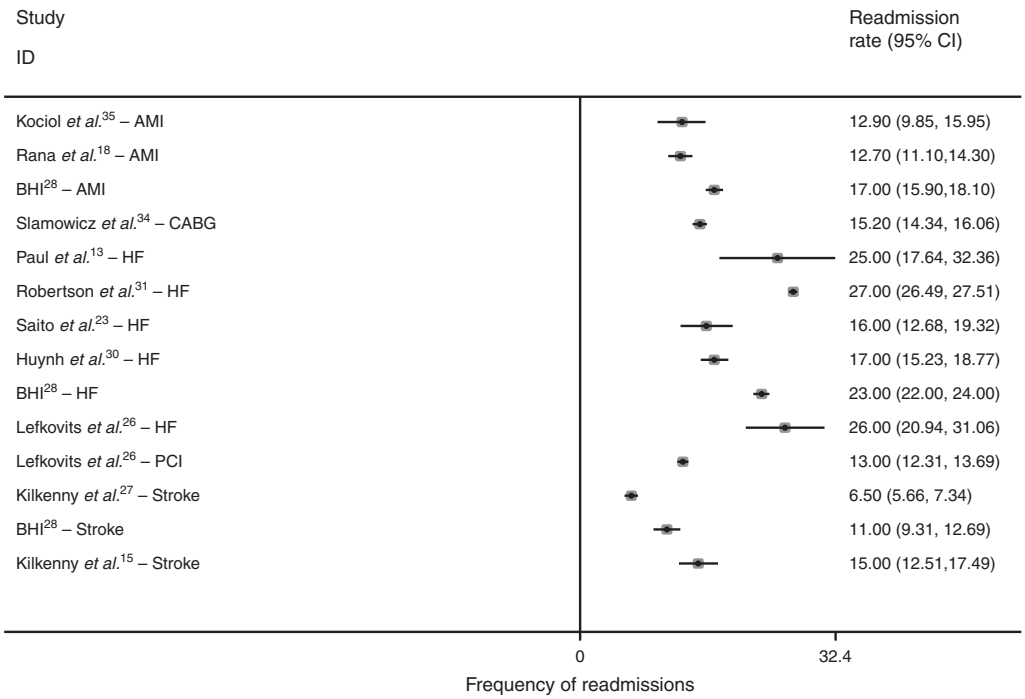

Fig. 3. Forest plot of 30-day all-cause readmissions. Note, some studies reported data for more than one cohort. AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; CI, confidence interval; HF, heart failure; PCI, percutaneous coronary intervention.

observed a median 30-day readmission rate of 13% (range 6.3–27%), with reported readmission rates of 10.1–27% for HF, 6.5–11% for stroke and 12.7–17% for AMI. These findings parallel the high readmission rates observed in the international literature. However, these figures should be interpreted with caution because we could not pool readmissions data due to the substantial heterogeneity among studies. Notably, there were considerable variations in time point at which readmissions were measured, whether disease-specific or all-cause readmissions were counted and the method and accuracy of ascertaining the readmissions status. Furthermore, we found only a few interventions that successfully reduced readmissions, highlighting the need for clinical trials to find more effective strategies to reduce readmissions.

This review also identified several knowledge gaps in the Australian literature. Although readmission after HF, stroke and AMI was reported, other common and important conditions, such as atrial fibrillation and peripheral arterial disease, were rarely studied and readmission rates for these common conditions are unknown. Similarly, the risk of readmission among disadvantaged populations relevant to the Australian setting, such as those in regional and remote areas and Indigenous populations, is uncertain. Moreover, only one Australian study evaluated hospital variation in early readmission rates despite early readmissions being correlated with quality of hospital care.[50] The substantial variation in the readmission rates among hospitals reported in this study suggests concerning variation in care quality, although whether such variation extends to other Australian regions is uncertain. Finally, we found a paucity of studies assessing the effects of hospital readmissions on the healthcare system. This information is crucial for developing effective clinical and policy strategies to reduce readmissions because costs and resource considerations are a major driver of decision making for health. Taken as a whole, this research indicates the need for Australia-wide studies of readmissions for common cardiovascular conditions to determine the frequency, as well as the extent of variation among Australian hospitals and regions.

This review also highlights the need to develop and test clinical interventions to reduce readmissions. Interventions to reduce readmissions that have been trialled in Australia have focused almost exclusively on home- or hospital-based management of HF. These long-term disease management programs focus on reducing disease-specific (HF) readmissions, even though most readmitted patients return to hospital with diagnoses that differ from their index hospitalisation.[51,52] Thus, interventions that solely target the initial condition may be inadequate to reduce all-cause readmissions, which may explain, in part, the limited effectiveness of interventions observed in this review. Although some readmissions inevitably occur due to disease progression, the quality of care transition from hospital to community also contributes to early readmission.[53,54] Although none of the existing interventions reviewed specifically targeted care transition practices, comprehensive care transition interventions have been shown to be effective in the international literature. For example, the Re-Engineered Discharge project in

the US, consisting of seven strategies to improve the transition from hospital to community, reported a 30% reduction in 30-day readmissions and lowered hospital costs by US$416 per patient.[55] However, discharge and follow-up care processes are highly contextual and, due to differences in health systems, interventions tested internationally may not be effective in the Australian setting. Thus, it is essential that such interventions are customised and tested in the local setting to determine their effectiveness in reducing readmissions.

This review also highlights the need for standardised methods to measure and report readmissions in Australia. Standardised methods are necessary for sustained quality improvement efforts. For example, the US Government's Centre for Medicare and Medicaid Services and the American College of Cardiology publicly report readmission rates for AMI,[56] stroke[57] HF[3] and PCI[58] among US hospitals using nationally standardised methods. These efforts have stimulated clinical and policy interventions, such as the American Heart Association's Target HF program (http://www.heart.org/en/professional/quality-improvement/target-heart-failure, accessed 20 January 2018) and the American College of Cardiology's Hospital to Home initiative (https://cvquality.acc.org/initiatives/hospital-to-home/about-h2h, accessed 20 January 2018), as well as policy initiatives by the US Government, such as the Hospital Readmission Reduction Program,[59] and is thought to contribute to the declining readmission rates in the US Medicare population.[60] Developing standardised methods to report and compare readmission rates in Australia may act as a catalyst for similar large-scale clinical and policy efforts to reduce readmissions.

This review has important limitations. We chose to focus solely on readmissions following hospitalisation for cardiovascular disease and the findings may not be generalisable to other conditions. In addition, grey literature was included; even though grey literature has not been academically peer reviewed, it makes an important contribution to this study because we can present a more in-depth evaluation of readmissions in the Australian setting.

Conclusions

Relatively high rates of readmissions are reported for cardiovascular conditions in Australia, paralleling the high rates of readmissions reported in the international literature, although the Australian literature should be interpreted with caution due to the substantial methodological heterogeneity among studies. Furthermore, several knowledge gaps exist, most notably a paucity of studies assessing the effects of hospital readmissions on the healthcare system. Moreover, only a few interventions have been shown to successfully reduce readmissions. Further research is required to fully determine the burden of readmissions, develop standardised measures to report readmissions and to test interventions to reduce readmissions in the Australians setting.

Competing interests

The authors declare that they have no competing interests.

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Australian Health Review

Supplementary Material for

Readmissions following hospitalisations for cardiovascular disease: a scoping review of the Australian literature

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Appendix S1 – Search terms for OVID Medline

Appendix S2 – Search terms for EMBASE

Appendix S3 – Search terms for CINHAL

Appendix S4 – Search term for grey literature

Appendix S5 – Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI)

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Appendix S1: Search terms for OVID Medline

Date searched – 11 March 2016

Patient Readmission OR re-presentation.mp. OR Patient Admission OR representation.mp. OR hospitalisation.mp. OR Hospitalization OR Treatment Outcome OR revisit$.tw. OR readmission$.tw. OR rehospitali$.tw. OR rehospitaliz$.tw. OR represent$.tw. OR rehospitali$.tw. OR unplanned.tw. OR return.tw. AND exp Australia OR western australia.tw. OR new south wales.tw. OR south australia.tw. OR victoria.tw. OR queensland.tw. OR northern territory.tw. OR australian capital territory.tw. OR tasmania.tw. OR australia.tw. OR perth.tw. OR sydney.tw. OR adelaide.tw. OR melbourne.tw. OR brisbane.tw. OR darwin.tw. OR canberra.tw. OR hobart.tw. AND *Cardiovascular Diseases OR Adult OR *Heart Failure OR *Stroke OR *Peripheral Arterial Disease OR *Peripheral Vascular Diseases OR *Atrial Fibrillation OR *Heart Valves OR *Aortic Valve OR *Heart Valve Diseases OR *Atherosclerosis OR *Myocardial Infarction *Coronary Disease/ or *Acute Coronary Syndrome or *Angina, Unstable or *Myocardial Ischemia or *Coronary Artery Disease OR *Cardiovascular Diseases OR *Cardiac Surgical Procedures OR *Angiography/ or *Coronary Angiography/ OR *Chest Pain OR *Coronary Artery Bypass OR *Cardiopulmonary Bypass/ OR *Cardiac Catheterization/

Limited to English language and humans and yr="2000 -Current" and "all adult (19 plus years)" and English and humans.

Appendix S2: Search Terms for EMBASE

Date searched – 28 July 2016

're presentation' OR hospitalisation OR revisit OR revisit* OR readmi* OR rehospitali* OR unplanned AND ('australia'/exp OR australia OR 'western australia' OR 'new south wales' OR 'south australia' OR 'victoria' OR 'queensland' OR 'northern territory' OR 'australian capital territory' OR tasmania OR perth OR sydney OR adelaide OR melbourne OR brisbane OR darwin OR canberra OR hobart) AND ('cardiovascular disease*' OR 'heart failure' OR stroke OR 'peripheral artery disease' OR 'peripheral vascular disease' OR 'atrial fibrillation' OR 'heart valves' OR atherosclerosis OR 'myocardial infarction' OR 'coronary disease' OR 'chest pain' OR 'coronary artery bypass' OR 'cardiopulmonary bypass' OR 'cardiac catheteri*ation') AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND [2000-2016]/py

Appendix S3: Search terms for CINHAL

Date searched - 21 September 2016

coronary disease OR acute coronary syndrome OR angina OR myocardial ischemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization) AND (australia OR western australia OR new south wales OR south australia OR victoria OR queensland OR northern territory OR australian capital territory OR tasmania OR perth OR sydney OR adelaide OR melbourne OR brisbane OR darwin OR canberra OR hobart)) AND (cardiovascular disease OR adult OR heart failure OR stroke OR peripheral artery disease OR peripheral vascular disease OR atrial fibrillation OR heart valve* OR aortic valve* OR heart valve disease OR atherosclerosis OR myocardial infarction OR coronary disease OR acute coronary syndrome OR angina OR myocardial ischemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization)) AND (Patient Readmission OR re-present* OR Patient Admission OR represent* OR hospitalisation OR hospitalization OR treatment outcomes OR revisit* OR readmission* OR rehospitali* OR unplanned AND coronary disease OR acute coronary syndrome OR angina OR myocardial ischemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization AND coronary disease OR acute coronary syndrome OR angina OR myocardial ischemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization

Limiters - Published Date: 200000101-20160831; English Language; Research Article; Human; Journal Subset: Australia & New Zealand; Publication Type: Journal Article; Language: English

Appendix S4: Search terms for grey literature

A Google search was conducted on Sunday 11 Sep 2016 using the terms 'Australia hospital readmissions cardiovascular'. The first 20 pages of about 149,000 results were analysed. There were 10 links per page so first 200 websites were searched.

The Australian and New Zealand clinical trial registry was searched on 1 October 2016 with search terms cardiovascular readmission and gave 14 results.

Moreover, the Australian clinical trials website was also searched on 1 October 2016 with the search parameters readmission cardiovascular and gave 16 results.

All federal and state government health websites, the Australian Institute of Health and Welfare, the Australian Bureau of Statistics, the Australian Heart Foundation, the Australian Commission on Safety and Quality in Health Care and the Bureau of Health Information were all searched for cardiovascular readmission data.

Appendix S5: Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix S6: Predictors of readmissions

Paper	Time	Condition	Significant Variables	Insignificant Variables	C-Stat
Murphy et al (2008)[1]	30 days	CABG surgery	Older age Being unmarried Living alone History of hypertension Higher HADS (anxiety) on admission	Sex Country of birth School leaving age Manual occupation High cholesterol Smoking status BMI Family history of CVD Diabetes Previous MI Length of time on waiting list Length of hospital stay NHYA class HADS (depression) on admission	Not given
Rana et al (2014)[2]	30-day IHD readmissio n	MI	Total time in emergency Number of emergencies Number of emergency-to-ward transfers Unstable angina Chest pain Sepsis Hyperkalaemia Hypokalemia Fluid overload Acute kidney failure	Nil given	AUC for 3 models HOSPITAL score = 0.60 Comorbiditi es =0.53 EMR model = 0.78

			Urinary tract infection Long-term use of anticoagulants Disorders of magnesium metabolism Left ventricular failure Presence of cardiac device Invasive coronary investigation undertaken in past year Debridement of skin and subcutaneous tissue		
Yu et al (2016)[3]	6 months cerebrovascular events	Ischemic stroke	Depression (but not after adjustment)	Anxiety	Not in the paper
Huynh et al (2015)[4]	30-day all cause	HF **death or readmission** with *nonclinical data*	Length of stay Living alone Age Discharge during winter Remoteness index categories Number of coded diagnoses at discharge Male	Not given	Can't find in paper
		death or readmission with *clinical data*	HF NYHA classification Blood urea nitrogen Serum albumin Heart rate Respiratory rate	Not given	0.72

			Diuretic use ACEI/ARB use Presence of life-threatening arrhythmia Presence of abnormal troponin		
		Death or readmission with *clinical and nonclinical*	HF NYHA classification Blood urea nitrogen Serum albumin Heart rate Respiratory rate Living alone Diuretic use ACEI/ARB use Presence of abnormal troponin Remoteness index Discharge during winter Presence of life threatening arrhythmia	Not given	0.76 for death or readmission 0.82 for death 0.69 for readmission
Parker et al (2008)[5]	1-year depression and CV outcome	ACS	Age CABG on admission Diabetes history LVEF <35% Past history of CVA/TIA New depression onset post baseline	Female sex Past admission for heart condition Current smo0ker Taking SSRI, TCA or MAOI Depressed pre-baseline Incident depression	Not reported
Betihavas et al (2015)[6]	28-day CV event	HF	Age	Female sex	0.8

			Living alone Sedentary lifestyle Multiple comorbidities	Years since HF diagnosis	
Tully et al (2008)[7]	6 month	CABG surgery	Peripheral vascular disease	Depression Aged ≥ 71 CCS class III/IV hypertension	Not in the paper
Slamowicz et al (2008)[8]	30 day*	CABG surgery (multivariate model)	Charlson comorbidity Multiple ED visits Female sex Index LOS	Waiting time Age	Not in the paper

*Models for 7 days and 6-month models not present.

HADS = hospital anxiety and depression scale

CABG = coronary artery bypass graft

CVD = cardiovascular disease

ACS = acute coronary syndrome

IHD = ischemic heart disease

MI = myocardial infarction

NYHA = New York Heart Association classification

LOS = length of stay

CCS = Canadian Cardiovascular Society (CSS) Functional Classification of Angina

Appendix S7: Description of the interventions

Study	Intervention Description
Davidson et al (2010) [9]	12-week multidisciplinary weekly cardiac rehab program. Patients were counselled to undertake home-based exercise program tailored to their needs, promote self-management and treatment. Nursing, pharmacy, physiotherapy occupational therapy and dieticians involved. Compared to usual care.
Driscoll et al (2013)[10]	A survey was mailed to 48 program coordinators asking them to identify specific interventions implemented in their program. Examined the effect of chronic heart failure management programs from 27 centres (mixture of hospital and home-based programs). Each program was given an intervention score
Stewart et al (2012)[11]	The nurse led clinic-based intervention group received ongoing management via specialist, multidisciplinary clinic without home visits. Home intervention was predominantly managed via out-reach program of home visits by a specialist heart failure nurse with close liaison with the patient's family physician and referral to other health care services as required.
Roughead et al (2009)[12]	The exposed group were veterans who had received Home Medicine Review (HMR) and had all health services fully subsidised by the Department of Veteran Affairs (DVA), were dispensed beta blocker subsidised for heart failure in the 6 months before the HMR and aged 65 years and older at time of review. The unexposed group were veterans who had all health services fully subsidised by the DVA and aged 65 years and older who had been dispensed a beta blocker but had NOT had an HMR.
Barker et al (2012)[13]	A pharmacist visited patients within 96 hours of discharge and a 6-month follow-up. Usual care discussion was generic about how they were feeling, no pharmacy advice was given unless patient asked. The intervention group had a discussion about medication regime to ensure medication use was as prescribed and followed evidence based guidelines, follow-up appointment and expired medications and disposed of them.
Scott et al (2004)[14]	Provision of comparative baseline feedback at a facilitative workshop combined with hospital-specific quality-improvement interventions supported by onsite quality officers and a central program management group.
Mudge et al (2010)[15]	Education and performance feedback for hospital and primary care practitioners, clinical decision support tools, individualised guideline-based treatment plans, patient education and self-management support and improved hospital community integration.
Stewart et al (1999)[16]	Both arms of the study were essentially nurse-led (two teams at each site) with tertiary qualified nurses with post-graduate qualifications in cardiac care and experience in heart failure management. The key point of differentiation was the mode of delivery, the clinic-based intervention group received ongoing management via a specialist, multi-

	disciplinary clinic and no home visits were applied. Alternatively, the home intervention group was predominantly managed via an out-reach program of home visits by a specialist heart failure nurse with close liaison with the patient's family physician and referral to other health care services as required. This approach did not preclude home-based intervention patients attending a cardiology outpatient clinic.
Stewart et al (2015)[17]	Face-to-face home visits with additional telephone support Communications with other health professionals delivered via automated reporting systems based on standardised and structured assessments
Martin et al (2016)[18]	A single and simultaneous page to the cardiology team to facilitate rapid access to the cardiac catheterisation laboratory, this was called the 'Cath Lab Code'. In addition, the Cath Lab Code with a pre-hospital notification system activated by paramedics in the field.

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Appendix B

Supplemental Material from Chapter II

Appendix S1: Search terms for OVID Medline

Date searched – 11 March 2016

Patient Readmission OR re-presentation.mp. OR Patient Admission OR representation.mp. OR hospitalisation.mp. OR Hospitalization OR Treatment Outcome OR revisit$.tw. OR readmission$.tw. OR rehospitali$.tw. OR rehospitaliz$.tw. OR represent$.tw. OR rehospitali$.tw. OR unplanned.tw. OR return.tw. AND exp Australia OR western australia.tw. OR new south wales.tw. OR south australia.tw. OR victoria.tw. OR queensland.tw. OR northern territory.tw. OR australian capital territory.tw. OR tasmania.tw. OR australia.tw. OR perth.tw. OR sydney.tw. OR adelaide.tw. OR melbourne.tw. OR brisbane.tw. OR darwin.tw. OR canberra.tw. OR hobart.tw. AND *Cardiovascular Diseases OR Adult OR *Heart Failure OR *Stroke OR *Peripheral Arterial Disease OR *Peripheral Vascular Diseases OR *Atrial Fibrillation OR *Heart Valves OR *Aortic Valve OR *Heart Valve Diseases OR *Atherosclerosis OR *Myocardial Infarction *Coronary Disease/ or *Acute Coronary Syndrome or *Angina, Unstable or *Myocardial Ischaemia or *Coronary Artery Disease OR *Cardiovascular Diseases OR *Cardiac Surgical Procedures OR *Angiography/ or *Coronary Angiography/ OR *Chest Pain OR *Coronary Artery Bypass OR *Cardiopulmonary Bypass/ OR *Cardiac Catheterization/

Limited to English language and humans and yr="2000 -Current" and "all adult (19 plus years)" and English and humans.

Appendix S2: Search Terms for EMBASE

Date searched – 28 July 2016

're presentation' OR hospitalisation OR revisit OR revisit* OR readmi* OR rehospitali* OR unplanned AND ('australia'/exp OR australia OR 'western australia' OR 'new south wales' OR 'south australia' OR 'victoria' OR 'queensland' OR 'northern territory' OR 'australian capital territory' OR tasmania OR perth OR sydney OR adelaide OR melbourne OR brisbane OR darwin OR canberra OR hobart) AND ('cardiovascular disease*' OR 'heart failure' OR stroke OR 'peripheral artery disease' OR 'peripheral vascular disease' OR 'atrial fibrillation' OR 'heart valves' OR atherosclerosis OR 'myocardial infarction' OR 'coronary disease' OR 'chest pain' OR 'coronary artery bypass' OR 'cardiopulmonary bypass' OR 'cardiac catheteri*ation') AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND [2000-2016]/py

Appendix S3: Search terms for CINHAL

Date searched - 21 September 2016

coronary disease OR acute coronary syndrome OR angina OR myocardial ischaemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization) AND (australia OR western australia OR new south wales OR south australia OR victoria OR queensland OR northern territory OR australian capital territory OR tasmania OR perth OR sydney OR adelaide OR melbourne OR brisbane OR darwin OR canberra OR hobart)) AND (cardiovascular disease OR adult OR heart failure OR stroke OR peripheral artery disease OR peripheral vascular disease OR atrial fibrillation OR heart valve* OR aortic valve* OR heart valve disease OR atherosclerosis OR myocardial infarction OR coronary disease OR acute coronary syndrome OR angina OR myocardial ischaemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization)) AND (Patient Readmission OR re-present* OR Patient Admission OR represent* OR hospitalisation OR hospitalization OR treatment outcomes OR revisit* OR readmission* OR rehospitali* OR unplanned AND coronary disease OR acute coronary syndrome OR angina OR myocardial ischaemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization AND coronary disease OR acute coronary syndrome OR angina OR myocardial ischaemia OR coronary artery disease OR Cardiac Surgical Procedures OR angiography OR Chest Pain OR coronary artery bypass* OR Cardiopulmonary Bypass OR cardiac catheterization

Limiters - Published Date: 200000101-20160831; English Language; Research Article; Human; Journal Subset: Australia & New Zealand; Publication Type: Journal Article; Language: English

Appendix S4: Search terms for grey literature

A Google search was conducted on Sunday 11 Sep 2016 using the terms 'Australia hospital readmissions cardiovascular'. The first 20 pages of about 149,000 results were analysed. There were 10 links per page so first 200 websites were searched.

The Australian and New Zealand clinical trial registry was searched on 1 October 2016 with search terms cardiovascular readmission and gave 14 results.

Moreover, the Australian clinical trials website was also searched on 1 October 2016 with the search parameters readmission cardiovascular and gave 16 results.

All federal and state government health websites, the Australian Institute of Health and Welfare (AIHW), the Australian Bureau of Statistics (ABS), the Australian Heart Foundation, the Australian Commission on Safety and Quality in Health Care and the Bureau of Health Information were all searched for cardiovascular readmission data.

Appendix S5: Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix S6: Predictors of readmissions

Paper	Time	Condition	Significant Variables	Insignificant Variables	C-Stat
Murphy et al (2008)[351]	30 days	CABG surgery	Older age Being unmarried Living alone History of hypertension Higher HADS (anxiety) on admission	Sex Country of birth School leaving age Manual occupation High cholesterol Smoking status BMI Family history of CVD Diabetes Previous MI Length of time on waiting list Length of hospital stay NHYA class HADS (depression) on admission	Not given
Rana et al (2014)[346]	30-day IHD readmission	MI	Total time in emergency Number of emergencies Number of emergency-to-ward transfers	Nil given	AUC for 3 models HOSPITAL score = 0.60 Comorbidities =0.53 EMR model = 0.78

			Unstable angina Chest pain Sepsis Hyperkalaemia Hypokalemia Fluid overload Acute kidney failure Urinary tract infection Long-term use of anticoagulants Disorders of magnesium metabolism Left ventricular failure Presence of cardiac device Invasive coronary investigation undertaken in past year Debridement of skin and subcutaneous tissue		
Yu et al (2016)[344]	6 months cerebrovascular events	Ischaemic stroke	Depression (but not after adjustment)	Anxiety	Not in the paper

Huynh et al (2015)[332]	30-day all cause	HF	Length of stay	Not given	Can't find in paper
		death or readmission with *nonclinical data*	Living alone Age Discharge during winter Remoteness index categories Number of coded diagnoses at discharge Male		
		death or readmission with *clinical data*	HF NYHA classification Blood urea nitrogen Serum albumin Heart rate Respiratory rate Diuretic use ACEI/ARB use Presence of life-threatening arrhythmia Presence of abnormal troponin	Not given	0.72
		Death or readmission with *clinical*	HF NYHA classification	Not given	0.76 for death or readmission

		and nonclinical	Blood urea nitrogen		
			Serum albumin		0.82 for death
			Heart rate		
			Respiratory rate		0.69 for readmission
			Living alone		
			Diuretic use		
			ACEI/ARB use		
			Presence of abnormal troponin		
			Remoteness index		
			Discharge during winter		
			Presence of life threatening arrhythmia		
Parker et al (2008)[348]	1-year depression and CV outcome	ACS	Age	Female sex	Not reported
			CABG on admission	Past admission for heart condition	
			Diabetes history	Current smo0ker	
			LVEF <35%	Taking SSRI, TCA or MAOI	
			Past history of CVA/TIA	Depressed pre-baseline	
			New depression onset post baseline	Incident depression	

Betihavas et al (2015)[335]	28-day CV event	HF	Age Living alone Sedentary lifestyle Multiple comorbidities	Female sex Years since HF diagnosis	0.8
Tully et al (2008)[352]	6 month	CABG surgery	Peripheral vascular disease	Depression Aged ≥ 71 CCS class III/IV hypertension	Not in the paper
Slamowicz et al (2008)[353]	30 day*	CABG surgery (multivariate model)	Charlson comorbidity Multiple ED visits Female sex Index LOS	Waiting time Age	Not in the paper

*Models for 7 days and 6 month models not present.

HADS = hospital anxiety and depression scale, CABG = coronary artery bypass graft, CVD = cardiovascular disease, ACS = acute coronary syndrome, IHD = ischaemic heart disease , MI = myocardial infarction, NYHA = New York Heart Association classification, LOS = length of stay, CCS = Canadian Cardiovascular Society (CSS) Functional Classification of Angina

Appendix S7: Description of the interventions

Study	Intervention Description
Davidson et al (2010)[355]	12-week multidisciplinary weekly cardiac rehab program. Patients were counselled to undertake home-based exercise program tailored to their needs, promote self-management and treatment. Nursing, pharmacy, physiotherapy occupational therapy and dieticians involved. Compared to usual care.
Driscoll et al (2013)[356]	A survey was mailed to 48 program coordinators asking them to identify specific interventions implemented in their program. Examined the effect of chronic heart failure management programs from 27 centres (mixture of hospital and home-based programs). Each program was given an intervention score
Stewart et al (2012)[362]	The nurse led clinic-based intervention group received ongoing management via specialist, multidisciplinary clinic without home visits. Home intervention was predominantly managed via out-reach program of home visits by a specialist heart failure nurse with close liaison with the patient's family physician and referral to other health care services as required.
Roughead et al (2009)[358]	The exposed group were veterans who had received Home Medicine Review (HMR) and had all health services fully subsidised by the Department of Veteran Affairs (DVA), were dispensed beta blocker subsidised for heart failure in the 6 months before the HMR and aged 65 years and older at time of review. The unexposed group were veterans who had all health services fully subsidised by the DVA and aged 65 years and older who had been dispensed a beta blocker but had NOT had an HMR.

Barker et al (2012)[359]	A pharmacist visited patients within 96 hours of discharge and a 6-month follow-up. Usual care discussion was generic about how they were feeling, no pharmacy advice was given unless patient asked. The intervention group had a discussion about medication regime to ensure medication use was as prescribed and followed evidence based guidelines, follow-up appointment and expired medications and disposed of them.
Scott et al (2004)[360]	Provision of comparative baseline feedback at a facilitative workshop combined with hospital-specific quality-improvement interventions supported by onsite quality officers and a central program management group.
Mudge et al (2010)[361]	Education and performance feedback for hospital and primary care practitioners, clinical decision support tools, individualised guideline-based treatment plans, patient education and self-management support and improved hospital community integration.
Stewart et al (1999)[451]	Both arms of the study were essentially nurse-led (two teams at each site) with tertiary qualified nurses with post-graduate qualifications in cardiac care and experience in heart failure management. The key point of differentiation was the mode of delivery, the clinic-based intervention group received ongoing management via a specialist, multi-disciplinary clinic and no home visits were applied. Alternatively, the home intervention group was predominantly managed via an out-reach program of home visits by a specialist heart failure nurse with close liaison with the patient's family physician and referral to other health care services as required. This approach did not preclude home-based intervention patients attending a cardiology outpatient clinic.

Stewart et al (2015)[363]	Face-to-face home visits with additional telephone support Communications with other health professionals delivered via automated reporting systems based on standardised and structured assessments.
Martin et al (2016)[364]	A single and simultaneous page to the cardiology team to facilitate rapid access to the cardiac catheterisation laboratory, this was called the 'Cath Lab Code'. In addition, the Cath Lab Code with a pre-hospital notification system activated by paramedics in the field.

Appendix C

Supplementary Material for Chapter V

The tables in this Appendix C depict the validity of ActiGraph wear time.

Table 1: For all patients who wore an ActiGraph (n=92), regardless of the wear time.

Average time worn (%)	Number of patients	% of patients
0	1	1.09
4.4	1	1.09
41.1	1	1.09
42.8	1	1.09
44	1	1.09
44.7	1	1.09
44.9	1	1.09
46.3	1	1.09
51.8	1	1.09
59.5	1	1.09
67	3	3.26
67.8	1	1.09
70.3	1	1.09
74	2	2.17
74.3	1	1.09
74.4	1	1.09
75	1	1.09
75.5	1	1.09
77	1	1.09
77.4	1	1.09
78.4	1	1.09
78.8	1	1.09
79.3	1	1.09
80	2	2.17
80.4	1	1.09
81.6	1	1.09
82	2	2.17
83.5	1	1.09
84.3	1	1.09
84.3	1	1.09
84.5	1	1.09

84.7	1	1.09
85.4	1	1.09
85.5	1	1.09
86	1	1.09
86.5	1	1.09
86.6	1	1.09
87	1	1.09
87.4	1	1.09
88.3	1	1.09
88.7	1	1.09
88.8	1	1.09
89	1	1.09
89.5	1	1.09
90	1	1.09
91.3	1	1.09
91.4	1	1.09
91.6	1	1.09
91.9	1	1.09
92	4	4.35
93.2	1	1.09
94.6	1	1.09
94.8	1	1.09
96.3	1	1.09
96.5	1	1.09
96.8	1	1.09
97.4	1	1.09
97.7	1	1.09
97.9	1	1.09
98	1	1.09
98.6	1	1.09
98.8	1	1.09
98.95	1	1.09
NA	3	3.26
100	18	19.6
Total	**92**	

Three patients who had NA as a wear time, this was because the data did not have useable or interpretable data.

So, there were 89 patients with ActiGraph data that were recorded with wear times wearing from 0 to 100% wear time.

From this data we lowered the average wear time being >= to 80% (there were 63 patients), shown in Table 2a and 2b.

Table 2a: Patients who had a wear time ≥ 80% (n=63).

Average time worn (%)	Number of patients	% of patients
80	2	2.2
80.4	1	1.1
81.6	1	1.1
82	2	2.2
83.5	1	1.1
84.3	1	1.1
84.3	1	1.1
84.5	1	1.1
84.7	1	1.1
85.4	1	1.1
85.5	1	1.1
86	1	1.1
86.5	1	1.1
86.6	1	1.1
87	1	1.1
87.4	1	1.1
88.3	1	1.1
88.7	1	1.1
88.8	1	1.1
89	1	1.1
89.5	1	1.1

90	1	1.1
91.3	1	1.1
91.4	1	1.1
91.6	1	1.1
91.9	1	1.1
92	4	4.4
93.2	1	1.1
94.6	1	1.09
94.8	1	1.09
96.3	1	1.09
96.5	1	1.09
96.8	1	1.09
97.4	1	1.09
97.7	1	1.09
97.9	1	1.09
98	1	1.09
98.6	1	1.09
98.8	1	1.09
98.95	1	1.09
100	18	19.6
Total	63	

Table 2b: Differences between patients with ≥80% wear time and <80% wear time. Simple t-test and chi^2 tests were performed to determine a P value.

	Weartime (%)		
	<80% (n=29)	**≥80% (n=63)**	**P value**
Age	71±12.1	66.5±13.3	0.1246
Female	11/29 =	15/63 =	0.162
ESS baseline	6.7±4.2	6.1±4.7	0.5964
EQ5D baseline	58.8±26.5	58.9±28.4	0.9789
PSQI baseline	5.2±3.1	7.1±4.2	0.0371
STOP BANG baseline	4.1±1.4	4.1±1.5	0.9415
Body Mass Index	28.1±5.6	30.1±5.4	0.1138
Neck circumference	39.4±2.5	39.2±4.1	0.8496
Length of stay	3.2±2.7	3.0±1.5	0.6345

Table 3a: Patients who had a wear time ≥ 75% (n=70).

Average time worn (%)	Number of patients	% of patients
75	1	1.09
75.5	1	1.09
77	1	1.09
77.4	1	1.09
78.4	1	1.09
78.8	1	1.09
79.3	1	1.09
80	2	2.17
80.4	1	1.09
81.6	1	1.09
82	2	2.17
83.5	1	1.09
84.3	1	1.09
84.3	1	1.09
84.5	1	1.09
84.7	1	1.09
85.4	1	1.09
85.5	1	1.09
86	1	1.09
86.5	1	1.09
86.6	1	1.09
87	1	1.09
87.4	1	1.09
88.3	1	1.09
88.7	1	1.09
88.8	1	1.09
89	1	1.09
89.5	1	1.09
90	1	1.09
91.3	1	1.09
91.4	1	1.09
91.6	1	1.09
91.9	1	1.09

92	4	4.35
93.2	1	1.09
94.6	1	1.09
94.8	1	1.09
96.3	1	1.09
96.5	1	1.09
96.8	1	1.09
97.4	1	1.09
97.7	1	1.09
97.9	1	1.09
98	1	1.09
98.6	1	1.09
98.8	1	1.09
98.95	1	1.09
100	18	19.6
Total	70	

Table 3b: Differences between patients with ≥75% wear time and <75% wear time. Simple t-test and chi^2 tests were performed to determine a p value.

	Wear time (%)		
	<75% (n=22)	**≥75% (n=70)**	**P value**
Age	71.3±13.3	66.8±12.9	0.1620
Female	10	16	0.0400
ESS baseline	6.5±4.2	6.2±4.7	0.8401
EQ-5D-3L baseline	55.2±29.1	60.0±27.3	0.4955
PSQI baseline	4.6±2.7	7.1±4.2	0.0101
STOP BANG baseline	3.9±1.4	4.1±1.5	0.5125
Body Mass Index	28.8±6.1	29.7±5.3	0.4895
Neck circumference	39.5±2.8	39.2±3.9	0.7898
Length of stay	3.5±3.1	3.0±1.4	0.3281

Table 4a: Patients who had a wear time ≥ 70% (n=75).

Average time worn (%)	Number of patients	% of patients
70.3	1	1.09
74	2	2.17
74.3	1	1.09
74.4	1	1.09
75	1	1.09
75.5	1	1.09
77	1	1.09
77.4	1	1.09
78.4	1	1.09
78.8	1	1.09
79.3	1	1.09
80	2	2.17
80.4	1	1.09
81.6	1	1.09
82	2	2.17
83.5	1	1.09
84.3	1	1.09
84.3	1	1.09
84.5	1	1.09
84.7	1	1.09
85.4	1	1.09
85.5	1	1.09
86	1	1.09
86.5	1	1.09
86.6	1	1.09
87	1	1.09
87.4	1	1.09
88.3	1	1.09
88.7	1	1.09
88.8	1	1.09
89	1	1.09
89.5	1	1.09
90	1	1.09

91.3	1	1.09
91.4	1	1.09
91.6	1	1.09
91.9	1	1.09
92	4	4.35
93.2	1	1.09
94.6	1	1.09
94.8	1	1.09
96.3	1	1.09
96.5	1	1.09
96.8	1	1.09
97.4	1	1.09
97.7	1	1.09
97.9	1	1.09
98	1	1.09
98.6	1	1.09
98.8	1	1.09
98.95	1	1.09
100	18	19.6
Total	**75**	

Table 4b: Differences between patients with ≥70% wear time and <70% wear time. Simple t-test and chi^2 tests were performed to determine a p value.

	Wear time (%)		
	<70% (n=17)	**≥70% (n=75)**	**p value**
Age	71.8±13.5	67.0±12.9	0.1727
Female	8	18	0.057
ESS baseline	6.1±4.2	6.3±4.7	0.8694
EQ-5D-3L baseline	49.1±28.6	61.1±27.1	0.1069
PSQI baseline	3.9±2.0	7.1±4.0	0.0031
STOP BANG baseline	3.7±1.4	4.2±1.5	0.2321
Body Mass Index	28.3±6.7	29.8±5.2	0.3420
Neck circumference	38.9±2.8	39.3±3.8	0.6807
Length of stay	3.8±3.5	2.9±1.4	0.0894

Appendix D

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