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Renal function in chronic heart failure: a cohort study

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Acknowledgement

"…You ought to know how to discern among incoherent and varying ideas and systems that which is true or fruitful in each. …In this patient search for truth and a habit of fairness that we ought to have toward others and their ideas, we need integrity of mind, clear judgment, and solid learning. You will gradually acquire these things, and you will do so more easily when your convictions become more consciously developed…" (Elisabeth Leseur died 1914). These thoughts expressed by Elisabeth Leseur, a French married laywoman whose cause for canonisation is underway, not only reflect the spiritual life; life in general but are particularly pertinent to the PhD process. One realises it is only by God's grace, '*I can do all things in Him who strengthens me' (Phil 4:12-14)*.

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NON NOBIS DOMINE, SE NOMINI TUO DA GLORIAM

Psalm *115:1*

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Certificate of original authorship

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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Abstract

Renal dysfunction is strongly associated with adverse health outcomes in chronic heart failure. The term cardio-renal syndrome has been proposed to describe the theoretical models developed to explain the pathophysiological mechanisms underpinning the condition and many observational studies undertaken to characterise and identify risk factors and morbidity and mortality outcomes. There is evidence baseline glomerular filtration rate is a stronger predictor of mortality in patients with Heart Failure than left ventricular ejection fraction or NYHA functional class. However, the ambiguity surrounding definitions and nomenclature for renal dysfunction in heart failure has impeded progress for a clearly defined risk profile and characterization for heart failure patients with renal impairment, chronic kidney disease, worsening renal function, or acute kidney injury. The focus of this study was to characterize an Australian cohort of hospitalised heart failure patient who developed acute kidney injury, and investigate this relationship in terms of morbidity and mortality at 12-months follow-up. A secondary purpose was to determine the prevalence of confirmed chronic kidney disease and renal impairment in the cohort and their outcomes. The results highlight the prevalence of Renal Insufficiency and Chronic Kidney Disease, 59% and 52% respectively. Acute kidney injury occurred in 1 in 4 patients when diagnosed using a modified AKIN definition. Characterization of HF patients with any type of renal abnormality revealed a history of multiple comorbidities where concurrent diabetes exposed hospitalised HF patients to an increased risk of AKI. From an original sample of 265 admissions, 166 had data available for the 12-month follow-up morbidity and survival analysis. The reduced sample size limited the study power, such that only renal impairment was trending towards significance. The Kaplan-Meier survival distributions for acute kidney injury and renal impairment at 12-months follow-up was not statistically significant, log-rank p=0.4714 and p=0.0579 respectively. The findings confirm the high incidence and prevalence of renal dysfunction in hospitalised heart failure patients and demonstrate the utility of the AKIN AKI definition. The study strengthens the call for

community monitoring of renal function and the need for definitional and nomenclature consensus. A move towards improved monitoring and a standardised taxonomy would assist with differentiating renal dysfunction types and may lead to better risk stratification of HF patients for adverse events.

Abbreviations

Abbreviation	Full term
ABS	Australian Bureau of Statistics
ACCF	American College of Cardiology Foundation
ACE	Angiotensin-converting enzyme
ACE -I	Angiotensin-converting enzyme - Inhibitor
ACR	Albumin Creatinine Ratio
ADHF	Acute Decompensated Heart Failure
AHA	American Heart Association
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ARB	Angiotensin II Receptor Blocker
BiPAP	Biphasic intermittent positive airway pressure
BMI	Body mass index
BSA	Body surface area
CAD	Coronary artery disease
CGE	Cockcroft-Gault Equation
CHF	Chronic Heart Failure or Congestive Heart Failure
CI	Confidence interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKMB	Creatine kinase myocardial band isoenzyme
COPD	Chronic obstructive pulmonary disease

Abbreviation	Full term
CPAP	Continuous positive airway pressure
CPGs	Clinical practice guidelines
CrCl	Creatinine clearance
CRF	Clinical or case report form
CRS	Cardiorenal syndrome
CVD	Cerebrovascular disease
DBP	Diastolic blood pressure
ECS	European Society of Cardiology
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EPR	Electronic patient record
GFR	Glomerular Filtration Rate
GTN	Glyceryl Trinitrate
HREC	Human Research Ethics Committee
HF	Heart Failure
HFpEF	Heart Failure preserved ejection fraction
HFrEF	Heart failure reduced ejection fraction
HHF	Hospitalised heart failure
HR	Hazard Ratio
hrs	Hours
ICD-10-AM Codes	International Classification of Diseases 10th revision Australian Modification based on the World Health Organization's internationally accepted classification of death and disease
ICU	Intensive Care Unit

Abbreviation	Full term
IQR	Inter quartile range
IV	Intravenous
IVI	Intravenous infusion
JVP	Jugular venous pressure
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KIM-1	Kidney injury molecule-1
LOS	Length of stay
LVF	Left ventricular function
MACE	Major acute cardiac event
MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
MRAs	Mineralocorticoid receptor antagonists
NGAL	neutrophil gelatinase-associated lipocalin
NKF	National Kidney Foundation
Non-STEMI	Non S-T Elevation Myocardial Infarct
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	Odds Ratio
RCT	Randomised Control Trials
RD	Renal dysfunction
RDW	Red cell distribution width
ReFinH	Renal function in heart failure study

Abbreviation	Full term
RI	Renal Impairment/ Insufficiency
RIFLE	Risk-Injury-Failure-Loss-Endstage renal disease
RR	Relative Risk
SaO2	Arterial oxygen saturation
SBP	Systolic blood pressure
SCr	Serum creatinine
SD	Standard deviation
SIEFA	Socio-economic Indexes for Areas
sMDRD	Simplified Modification of Diet in Renal Disease
SPSS	Statistical Package for Social Sciences
STEMI	S-T Elevation Myocardial Infarct
SWSLHN	South Western Sydney Local Health Network
UTS	University of Technology
VAD	Ventricle assist device
WRF	Worsening Renal Function

Glossary

Terms	Definition
Acute heart failure	De novo acute heart failure or decompensated chronic heart failure characterized by signs of pulmonary congestion, including pulmonary oedema
Acute kidney injury	AKI is a syndrome characterised by the *rapid* loss of the kidney's excretory function which is typically diagnosed by an significant increase in serum creatinine
Body mass index	A measure of an adult's weight (body mass) relative to height used to assess the extent of weight deficit or excess. BMI uses a simple calculation based on the ratio of someone's height and weight (BMI = kg/m^2).
Cardiovascular disease	A disease affecting the heart or blood vessels. Cardiovascular diseases include arteriosclerosis, coronary artery disease, heart valve disease, arrhythmia, heart failure, hypertension, orthostatic hypotension, shock, endocarditis, diseases of the aorta and its branches, disorders of the peripheral vascular system, and congenital heart disease
Chronic condition	A health condition that is long term; has a pattern of recurrence, or deterioration; has a poor prognosis and produces consequences, or sequelae that impact on the individual's quality of life
Chronic heart failure	A complex clinical syndrome with typical symptoms (e.g. shortness of breath, fatigue) that can occur at rest or on effort, and is characterised by objective evidence of an underlying structural abnormality of cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during physical activity).
Chronic kidney disease	Abnormalities of kidney structure or function, present for more than 3 months, with implications for health and classified based on cause, GFR category, and albuminuria category
Comorbidity	When a person has two or more health problems at the same

Terms	Definition
	time
Confidence interval (CI)	A statistical term describing a range (interval) of values within which we can be 'confident' that the true value lies, usually because it has a 95% or higher chance of doing so
Diabetes	A disease marked by high blood glucose levels resulting from defective insulin production, insulin action or both. The three main types of diabetes are type-1 diabetes, type-2 diabetes and gestational diabetes. Where a person has a history of diabetes; a diagnosis of diabetes.
Dyspnoea	Difficult or laboured breathing; shortness of breath
Ejection fraction	Refers to the amount, or percentage, of blood that is pumped out of the ventricles with each contraction; the left ventricle percentage is most frequently recorded
Health outcome	A change in the health of an individual, or a group of people or a population, which is wholly or partially attributable to an intervention or a series of interventions
Heart failure	Described in physiological terms HF is a syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction.
Incidence	Refers to the number of individuals who develop a specific disease or experience a specific health-related event during a particular time period (such as a month or year)
Length of stay	Duration of hospital stay, calculated by subtracting the date the patient is admitted from the day of separation. A same-day patient is allocated a length of stay of 1 day
Local hospital network	LHNs are small groups of local hospitals, or an individual hospital, linking services within a region or through specialist networks across a state or territory.
Morbidity	Refers to ill health in an individual and to levels of ill health in

Terms	Definition
	a population or group
New York Heart Association – functional class	Mainly describes the functional limitations of the patient such that Class I – ordinary physical activity does not cause undue fatigue, palpitations, dyspnoea and/or angina; Class II - ordinary physical activity does cause undue fatigue, palpitations, dyspnoea and/or angina; Class – III Less than ordinary physical activity cause undue fatigue, palpitations, dyspnoea and/or angina; and Class- IV fatigue, palpitations, dyspnoea and/or angina occur at rest.
Orthopnoea	Discomfort or difficulty breathing when lying flat
Prevalence	Refers to the total number of individuals in a population who have a disease or health condition at a specific period of time, usually expressed as a percentage of the population
Principal diagnosis	The diagnosis listed in hospital records to describe the problem that was chiefly responsible for the patient's episode of care in hospital
Quality of life	A generic term that measures the individual's perception of their life experience. It is a multidimensional concept measuring important aspects or domains of a person's life including physical functioning, psychological processes and social and economic concerns, as well as spiritual and existential aspects.
Renal impairment	Acute or chronic kidney failure also known as 'renal insufficiency' or 'renal dysfunction' It is a medical condition in which the kidneys fail to adequately filter waste products from the blood.
Risk Factors	A risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury
Stroke	Diagnosis for ischaemic: non-haemorrhagic cerebral infarction or haemorrhagic: intracerebral haemorrhage supported by

Terms	Definition
	cerebral imaging
Taxonomy	A classification containing domains and subcategories for the measurement properties and aspects of measurement properties which are the subcategories
Albuminuria	An abnormal excretion rate of albumin (protein) in the urine
Glomerular filtration rate	The amount of ultrafiltrate formed by plasma flowing through the glomeruli of the kidney.

Chapter 1 Introduction

1.1 Introduction

This chapter provides an introduction to the '*Renal function in chronic heart failure: a cohort study' (ReFinH Study)* reported in this thesis. The study investigated the cardio-renal relationship in patients admitted to tertiary level hospital with a principal discharge diagnosis of heart failure (HF). The composite endpoint of all-cause mortality, myocardial infarction, cardiac arrest and stroke against index admission worsening renal function (WRF) presenting as acute kidney injury (AKI), renal impairment (RI) or chronic kidney disease (CKD) were assessed. The predictors for acute kidney injury for the cohort were identified and recommendations for an international consensus definition for acute kidney injury made. Recommendations for the monitoring of renal function in community and hospitalised heart failure have been suggested.

The chapter opens with the background (section 1.2) and context (section 1.3) of the research, and its purpose (section 1.4). Section 1.4 explains the significance and scope of the ReFinH Study and provides a summary table of key terms with their definitions (Tables 1.5, 1.6 & 1.7). Finally, section 1.6 is an overview of the remaining chapters of the thesis.

1.2 Background

Chronic heart failure (CHF) and chronic kidney disease (CKD) are known to be substantial contributors to the worldwide chronic disease burden (Braunwald 2013; Eckardt et al. 2013). Where these conditions are concurrent some clinicians refer to this phenomenon as the cardio-renal syndrome (CRS) (Ronco & Ronco 2012). However the theoretical modelling for CRS has not yet been validated nor is it universally accepted (Damman, Tang, et al. 2014). Other terms such as renal dysfunction, renal impairment, worsening renal function or renal insufficiency are still commonly used terms to describe altered renal function in HF. Renal impairment (RI) and worsening renal function (WRF) are the terminologies most frequently used in cardiology. RI has two descriptors which have been defined in numerous ways. RI may refer to a baseline reduction in glomerular filtration rate, or worsening of renal function (WRF) over time (Damman, Valente, et al. 2014). The renal biomarker, timeframe for change and degree of change are discretionary, yet the most common thresholds are an estimated glomerular filtration rate (eGFR) of less than 60mls.min for RI or a serum creatinine increase of ≥26.5µmol/l for WRF (Damman, Valente, et al. 2014).

1.2.1 Cardiorenal syndrome

The most recently coined term to describe the cardio-renal relationship is cardiorenal syndrome which entered the medical lexicon only 10 years ago. In 2004 a working group

convened by the National Heart, Lung and Blood Institute (NHLBI) met to consider the relationship between abnormalities in cardiac function and renal function where there was no apparent underlying kidney pathology. They (NHLBI 2004) noted a number of issues specific to the understanding and management of this syndrome; such as the lack of cross-discipline collaboration needed to gain insight into the mechanisms responsible for the cardio-renal relationship; and the lack of clinical trial evidence for the management of these patients as they are usually excluded from the trials. They introduced the following working definition to help meet the challenge to improve the knowledgebase for the prevention and management of the CRS:

> *"In heart failure, it is the result of interactions between the kidneys and other circulatory compartments that increase circulatory volume and symptoms of heart failure and disease progression and exacerbation. At its extreme, cardio-renal dysregulation leads to what is termed "cardio-renal syndrome" in which therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function*"(NHLBI 2004).

In 2008 Ronco, House and Haapio (Ronco et al. 2008) refined the CRS definition noting the complexity and the bi-directional nature of the syndrome. They identified several sub-types which were further developed under the sponsorship of the Acute Dialysis Quality Initiative (ADQI) consensus conference (Ronco, McCullough, Anker, Anand, Aspromonte, Bagshaw, Bellomo, Berl, Bobek, Cruz, et al. 2010). At this conference a definition and classification system for CRS were proposed. The current definition (Table 1.1) identifies five syndrome sub-types and defines the broad concept 'cardio-renal syndromes' as:

> "...*disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other."* (Ronco, McCullough, Anker, Anand, Aspromonte, Bagshaw, Bellomo, Berl, Bobek, Cruz, et al. 2010).

Table 1.1 Cardio-renal syndrome subtypes

CRS Subtype	Primary organ	Criteria for event	Definition
	Heart		
Acute cardio-renal Type 1	Heart - ACS or ADHF	ESC, ACCF/AHA AKIN, RIFLE	Acute worsening of heart function leading to kidney dysfunction/ injury
Chronic cardio-renal Type 2	Heart - CHD or CHF	ESC, ACCF/AHA KDOQI	Chronic abnormalities in heart function leading to kidney dysfunction/ disease
	Kidney		
Acute reno-cardiac Type 3	Kidney - AKI	AKIN, RIFLE	Acute worsening of kidney function leading to heart dysfunction &/or injury
Chronic reno-cardiac Type 4	Kidney - CKD	KDOQI	Chronic kidney function leading to heart dysfunction, disease &/or injury
	Systemic		
Secondary CRS Type 5	Systemic Disease-Example: specific Sepsis criteria	Systemic conditions leading to simultaneous dysfunction &/or injury of heart & kidney	

(Adapted from (Ronco, McCullough, Anker, Anand, Aspromonte, Bagshaw, Bellomo, Berl, Bobek & Cruz 2010) *Source:* Adapted from (Ronco et al 2010) Abbreviations: CRS, Cardio-renal syndrome; ACS, Acute coronary syndrome; ADHF, Acute decompensated heart failure; ECS, European Society of Cardiology; ACCF/AHA, American College of Cardiology Foundation with the American Heart Association; RIFLE, Risk-Injury-Failure-Loss-End stage renal disease; AKIN, Acute Kidney Injury Network; KDOQI, Kidney Disease Outcomes Quality Initiative; AKI, Acute kidney injury; CKD, Chronic kidney disease.

1.2.2 Cardio-renal research challenges

Today the cardio-renal relationship challenge remains one of establishing:

- causation for renal dysfunction in heart failure which is complex, and far from clear (Damman, Tang, et al. 2014)
- complete characterisation of the predictor profile for AKI in heart failure
- consensus for an AKI definition in heart failure
- an evidence-base to inform the development of practice management guidelines for these patients
- the level and impact of current guideline implementation in HF patients with AKI, and
- for Australia, characterization of hospitalised HF patients who develop AKI, and
- the significance of renal dysfunction as AKI, RI or CKD in these Australian patients in terms of prevalence and outcomes.

While the intrigue of the cardio-renal relationship, lay in why the sequelae of acute and/or chronic renal dysfunction at any time in HF have such a synergetic, devastating impact on outcomes.

It is these challenges together with my professional background as a cardiovascular and renal nurse that has drawn me to this topic. Participation in evidence-based practice guideline development, and an interest and post-graduate qualifications in health informatics are additional aspects of my professional development relevant to this topic. The opportunity to combine these elements and potentially deliver new knowledge and resources that could help improve HF patients' outcomes is my inspiration.

1.3 Context

Heart failure (HF) as a global and personal burden is well documented (Braunwald 2013; Clark et al. 2004; Cowie et al. 2000; McMurray & Stewart 2000; Stewart et al. 2001). As is the burden of acute and chronic kidney disease and injury (Ftouh & Thomas 2013; Go et al. 2004; Levey et al. 2003). The contingent effect of these conditions has become an area of concern as the management challenges and the negative prognostic impact of renal impairment and acute worsening renal function in heart failure have emerged. These challenges have driven contemporary research to re-examine cardio-renal homeostasis and their deregulating co-dependency.

The prevalence, predictors and the relationship with morbidity and mortality outcomes for worsening renal function (WRF) presenting as acute kidney injury (AKI) in an Australian cohort of hospitalised heart failure (HHF) patients remains unknown. This is despite the prognostic importance of renal dysfunction (RD) in heart failure. Such a knowledge gap has implications for hospitalised HF patients with regards to their diagnosis, management and prognosis. To appreciate the significance of renal dysfunction in heart failure it is important to provide the context from which this syndrome emerges, this can be achieved through an understanding of the key features of heart failure and kidney disease epidemiology.

1.3.1 Chronic heart failure

One in ten Australians over the age of 65-years will develop heart failure (Krum et al. 2006). Within 5 years of the diagnosis fifty percent of these patients will have died (Braunwald 2013). Heart Failure (HF) can be described in physiological terms as a syndrome "*characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction*"(Heart Failure Society of America 2010) or simply as "*a condition where the heart is unable to maintain adequate*

circulation blood pressure to meet the body's needs" (Australian Institute of Health and Welfare 2011b). The terms 'congestive', 'chronic' or 'cardiac' failure are often used to describe this complex syndrome of HF which is frequently preceded by a history of myocardial infarction or long-standing hypertension (Schwinger 2010). Typically, first presentations or subsequent decompensated episodes of HF are characterised by varying degrees of dyspnoea at rest or on minimal exertion, fatigue and evidence of fluid retention (Faris et al. 2006). Chronic heart failure (CHF) is predominantly a condition affecting those aged over 65-years (Roger et al. 2012).

1.3.2 Acute decompensated heart failure

Acute decompensated heart failure (ADHF) is a common cause of hospital admission, particularly in the elderly, (Jugdutt 2012; Krumholz et al. 2000; Mosterd & Hoes 2007) accounting for up to 80% of HF hospitalisations (Dickstein et al. 2008). ADHF is often a rapid exacerbation of chronic heart failure signs and symptoms (McMurray et al. 2012) such as peripheral or pulmonary oedema, dyspnoea and fatigue. These episodes may be triggered by conditions such as arrhythmias, acute myocardial infarction, pneumonia or septicaemia (Blecker et al. 2013). This is a period of vulnerability both in altered pathophysiology and also the potential for iatrogenesis due to therapeutic interventions (Heywood et al. 2007). CHF and ADHF are common and inflict a burden on both the individual and the community.

1.3.3 Global heart failure burden

Globally it is difficult to determine how many people suffer HF (Cook et al. 2014). Most of the data come from industrialised countries where HF prevalence is estimated to be 2 to 3% (Chen et al. 2011; Clark et al. 2004; Dickstein et al. 2008; Krum et al. 2006) of the population where approximately 10% of men and 8% of women over the age of 60-years affected (Braunwald 2013). However, in Australia it is more prevalent in females than in males except for those aged less than 25 years (Australian Institute of Health and Welfare 2011a). A feature of HF prevalence is that it increases with age. In developed countries 20% of octogenarians are estimated to have the HF (Dickstein et al. 2008).

Recent Australian data (National Heart Foundation of Australia 2013) indicated annual HF costs to be an estimated 30,000 people diagnosed and more than $1 billion dollars spent. In the United States of America (USA) HF prevalence has been put at 5.8 million out of 300 million (Lloyd-Jones et al. 2010) while for countries comprising the European Society of Cardiology (ESC) at least 15 million suffer HF from a potential pool of 900 million (Dickstein et al. 2008). The prevalence of HF will continue to increase as the percent of a nation's population over the

age of 65 years increases. Evidence for this trend toward an aging population is seen in the Australian demographic data where the proportion of the national population over 65 years went from 8% 1970-71 to 13% in 2001-02 with projections indicating that this group will make up 25% of the population by 2040 (The Treasury Social Policy Division 2004). In addition, survival in the context of cardiovascular disease and other chronic comorbidities continues to improve (Braunschweig, Cowie & Auricchio 2011; Cook et al. 2014) resulting in greater complexity of patient management. The significance of the HF burden is realised when the economic and population data for a specific country or a region is examined.

The impact of HF is a function of the costs linked to its morbidity and mortality rates (Go et al. 2013). These costs can be referred to as direct or in-direct costs. Direct costs cover items such as payment of health clinicians, hospital services, prescribed medication while the indirect cost are those associated with lost productivity due to morbidity and premature HF mortality, and economically include the payment of welfare and sickness benefits (Braunschweig, Cowie & Auricchio 2011; Cook et al. 2014).

Cook and co-authors (Cook et al. 2014) recently published global data on the economic burden associated with HF. They observed that the percentage of gross domestic product (GDP) spent on health and HF is proportional to the country's level of economic development, the greater the development the greater the percentage of GDP spent. Their calculations for direct and indirect costs for HF for the USA in 2012 estimated that 17.9% of GDP was consumed by health expenditure of which HF accounted for 1.42% and 0.006% of GDP in direct and indirect cost respectively for a combined cost of 30.7 billion dollars (Cook et al. 2014).

The global economic burden linked to HF will continue to grow as prevalence increases. As noted above populations are aging and with a greater percentage of a population over 65-years, it is inevitable HF rates will surge. This prediction is supported by the projected HF prevalence figures for the USA where estimates suggest a 25% increase in HF over the next 15 years (Go et al. 2013). The magnitude of these increases will stress USA health systems where HF is already the most common cause of hospitalisations (Braunwald 2013; Dunlay et al. 2009). Other westernised countries are likely to follow this trend.

1.3.4 Individual heart failure burden

The individual burden of HF intensifies as the patient progresses along the illness trajectory (Dunlay et al. 2011; Goodlin 2009). Physical functioning (Masoudi et al. 2004), mental health (Dracup K et al. 1992; Juenger et al. 2002), social interaction (Juenger et al. 2002) and personal finances (Berry, Murdoch & McMurray 2001; Dunlay et al. 2011) come under pressure as HF progresses to its advanced stages. The monetary costs for an individual are mainly due to

medications and hospitalisation. For example in the American Olmsted County, Minnesota Study (Dunlay et al. 2011) the majority of lifetime personal HF costs were due to hospitalizations (77.0%), with an average lifetime cost calculated to be $73,762 per person.

HF sufferers not only face a financial burden there are also physical and psychosocial issues. Quality versus quantity of life may become the goal (Lewis et al. 2001; Stevenson et al. 2008) as symptoms increase and become more debilitating leading to episodes of HF exacerbation with more frequent hospitalisations (Krumholz et al. 1997)and a loss of autonomy(Dracup K et al. 1992; Heo et al. 2008). Physical functioning and psychosocial aspects of HF are especially important as the patient approaches end-stage HF and the need to consider palliative care management. Palliative care planning including advanced care directives are an important consideration as the in-hospital, 30-day and long-term mortality rates for HF remain poor. Once diagnosed 30-40% of patients will not survive 12-months (Cowie et al. 2000) while only about 50% live for 5 years (Go et al. 2013).

Mortality estimates however are somewhat dependent on population demographics (Norton et al. 2011). Factors such as age, severity of HF and the degree to which evidenced-based management is implemented can effect morbidity and mortality (National Institute for Cardiovascular Outcomes Research 2013). Data from the recent England and Wales annual heart failure audit demonstrated for the first time an annual improvement for in-hospital and follow-up survival rates improving from 11.1% to 9.4% and 26.2% to 24.6% respectively (National Institute for Cardiovascular Outcomes Research 2013). The 30-day post discharge mortality rate was 6.1%. The short-term combined 30-day and in-hospital mortality rates were equivalent to 1 in 7 HF patient deaths.

Never-the-less improvements in HF mortality rates have not seen the same progress as other cardiovascular conditions (Lloyd-Jones et al. 2010). Survival is further compromised if CKD or AKI is evident at any stage in HF as renal dysfunction adds another level of complexity to patient management and threatens adverse outcomes (Damman et al. 2012; Forman et al. 2004).

1.3.5 Kidney disease

The Kidney Disease Improving Global Outcomes group (KDIGO) have characterised kidney disease “as an abnormality of kidney structure or function with implications for the health of an individual, which can occur abruptly, and either resolve or become chronic”. The global pattern and management for both acute and chronic kidney disease differs based on a country’s economic classification. Such an approach allows the presentation of information to be stratified highlighting the dominate aetiology and management.

1.3.6 Chronic kidney disease

Chronic kidney disease (CKD) is a term use for a diverse range of disorders affecting kidney function and structure. CKD is defined as "abnormalities of kidney structure or function, present for more than three (3) months, with implications for health and … classified based on cause, GFR category, and albuminuria category"(Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013).The diagnostic threshold for CKD occurs once the estimated GFR (eGFR) falls below 60 ml/min/1.73m² body surface area (BSA) at which point more than 50% of kidney function has been lost. Alternatively an albumin creatinine ratio (ACR) greater the 3mg/g (≥3mg/mmol) can also be used as a threshold for CKD diagnosis (Couser et al. 2011; Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013) (Table 1.2). Relevant to HF sufferers is a history of CKD, acute kidney injury or a cardiovascular event is a risk factor for each of the other conditions (Eckardt et al. 2013; Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013).

Table 1.2 Chronic kidney disease definition and stages

Stage	**Description**	**CKD - GFR*** **mls.min.1.73m²**	**Albuminuria categories - ACR** **Description and range**		
1	Normal or high	>=90mls	**A3- CKD**	**A2**	**A1**
2	Mildly decreased	60-89 mls	**Severely increased**	Moderately increased	Normal to mildly increased
3a	Mildly-moderately decreased	**CKD** 45-59 mls	**Macro** **>30 mg/mmol** **>300 mg/g**	Micro 3-30 mg/mmol 30-300 mg/g	Micro <3 mg/mmol <30 mg/g
3b	Moderately-severely decreased	**CKD** 30-44 mls	**CKD is defined as eGFR < 60ml.min.1.73m² (3a -5) and/or Albuminuria > 30mg/g for >= 3 mouths irrespective of cause.**		
4	Severely decreased	**CKD** 15-29 mls	*** GFR = glomerular filtration rate**		
5	**Kidney failure**	**Endstage CKD** <15 mls			

With permission from (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013)

1.3.7 Acute kidney injury

Acute kidney injury (AKI) historically referred to as acute renal failure is a syndrome characterised by the rapid (≤48-hours) loss of the kidney's excretory function which is typically diagnosed by an increase in serum creatinine or decreased urine output, or both (Bellomo, Kellum & Ronco 2012). AKI diagnostic criteria are a relatively recent development with the RIFLE (Risk-Injury-Failure-Loss-Endstage) acute kidney injury criteria first published in 2004 (Bellomo et al. 2004). The RIFLE criterion uses eGFR, serum creatinine or urinary output as the metrics for diagnosis and for its severity scale. A modification of the RIFLE criteria was published by the Acute Kidney Injury Network (AKIN) in 2007 (Mehta et al. 2007). The AKIN definition removed eGFR and modified the temporal component and severity scale of the RIFLE diagnostic metric.

These criteria have now been combined in the 2012 KDIGO Clinical Practice Guidelines for Acute Kidney Injury (Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group 2012) and are presented in Table 1.3. Serum creatinine, eGFR and urinary output are the metrics most commonly used for the diagnosis and staging of AKI and CKD.

Table 1.3 Acute Kidney Injury definition and stages: KDIGO 2012

AKI is defined as any of the following (Not Graded): • Increase in SCr by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours; **or** • Increase in SCr to>1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; **or** • Urine volume <0.5 ml/kg/h for 6 hours.		
Severity Stage	**Serum creatinine**	**Urine output**
1	1.5–1.9 times baseline **OR** ≥0.3 mg/dl (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for X12 hours
3	3.0 times baseline **OR** Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) **OR** Initiation of renal replacement therapy **OR** In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for X24 hours **OR** Anuria for X12 hours

1.3.8 Chronic kidney disease burden

Worldwide kidney disease has been recognised as a major public health burden with CKD prevalence estimated to be 8 to 16%(Jha et al. 2013; Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013). The global burden for CKD over the last 20-years has significantly increased such that its mortality ranking has gone from 27th in 1990 to 18th in 2010 (Jha et al. 2013). Years-of-life lost for CKD is now third behind that of HIV-AIDS and Diabetes (Jha et al. 2013).

CKD prevalence increases with age albeit the demographic varies worldwide (Eckardt et al. 2013). For example, in the USA CKD prevalence for the age group 40 to 59 years was estimated at 9.1% while for those aged over 60-years it increases to 35.0% (Go et al. 2013). In sub-Saharan Africa it is a younger age demographic that presents with CKD, they are mainly age in the 20 to 50-years age group whereas studies from India and China reported the mean age at presentation to be 51.0 (SD 13·6) and 63·6 (14·7) years respectively (Jha et al. 2013). Australian data published for 2011-12 (Australian Bureau of Statistics 2013)reported the prevalence of CKD to be 10% of the adult population (>18yrs) or 1.7 million people. Australian CKD prevalence increases markedly with age from 5.5% for those aged less than 55-years to 42.2% in those aged 75-years and over.

Universally hypertension and diabetes are common precipitators for CKD. However in parts of Asia and Africa the cause of CKD is frequently unknown or attributed to glomerulonephritis (Jha et al. 2013). Finally, the financial burden reaches extreme levels when CKD is end-stage and renal replacement therapy is required (Jha et al. 2013).

1.3.9 Acute kidney injury burden

Patient settings and definitions influence AKI incidence and prevalence. In the setting of less economically developed countries it occurs in the context of one predisposing disease in the young or previously healthy individual (Lameire et al. 2013). In parts of Africa the incidences of AKI can be up to 60% in patients with heavy parasitaemia or HIV/AIDS (Lameire et al. 2013).Individuals at risk in developed (high-income) countries are more likely to be critically ill patients managed in intensive care units (ICU)(Kellum, Bellomo & Ronco 2008). High risk ICU patients have a recent history of significant blood or volume losses, major surgery or sepsis (Bellomo, Kellum & Ronco 2012). The prevalence of AKI in these patients can range from 1 to 25% leading to mortality rates of 15 to 60%(Kellum, Bellomo & Ronco 2008).

AKI may also be an iatrogenic complication due to the use of radiographic contrast medium resulting in contrast-induced nephropathy (CIN) (Deek et al. 2014). CIN accounts for approximately 10% of AKI (Benko et al. 2007) as some contrast medium can be nephrotoxic. Once diagnosed with AKI there is an increased risk of CKD, end-stage renal disease and death (Lameire et al. 2013; Singbartl & Kellum 2012). Even a transient increase in serum creatinine of greater than 26 µmol/l has been shown to increase the risk of death in hospitalised patients(Coca et al. 2007).

1.3.10 Renal impairment and worsening renal function in heart failure

In the last decade interest in the role of renal function in heart failure has experienced a renaissance as it has become evident that renal impairment or worsening renal function signals a poor prognosis (Heywood et al. 2007; Hillege et al. 2006). The significant prevalence of chronic kidney disease in heart failure has also attracted the attention of researchers and clinicians (Atherton et al. 2012; Campbell & Ahmed 2012). This renewed focus is underscored by the high comorbidity burden of heart failure and the influence of renal function on altering the illness trajectory and clinical outcomes.

In a recent meta-analysis by Damman and colleagues (Damman, Valente, et al. 2014), which examined the impact of renal impairment and worsening renal function on outcomes in HF, no standard definition for these conditions were noted. Twenty six definitions for renal impairment reported as chronic kidney disease were given; and nine for WRF (Damman, Valente, et al. 2014). In the scientific literature, the reporting authors' definitions inform the reader as to the nature of the renal dysfunction.

Although multiple metrics have been used in cardiology to define RI and WRF some are more common. For acute worsening of renal function, absolute or percentage change in the renal biomarker serum creatinine serum (Gottlieb et al. 2002; Krumholz et al. 2000), cystatin-C (Sarnak MJ 2005) or creatinine clearance as estimated from the Cockroft-Gault equation (eGFR) (Dries et al. 2000) are regularly used. The timeframe and the degree of change in the renal biomarker for defining WRF can vary from study to study making it difficult to determine what is meant by WRF regarding the acute or chronic nature of the condition. The usual practice has been to specify the magnitude of change for the biomarker and reference it against its baseline value usually taken as the admission value. However, the timeframe can be vague such as during admission(Forman et al. 2004; Krumholz et al. 2000) or during follow-up(de Silva et al. 2006).

Renal impairment is frequently reported using the baseline eGFR, where an eGFR of < 60.ml.min is a common threshold for the definition. However, the chronic nature of the renal dysfunction may not have been confirmed (Chew et al. 2006; Hillege et al. 2006). The eGFR value has been calculated using either the creatinine clearance estimation equation by Cockcroft, and Gault (Cockcroft & Gault 1976) or the eGFR equation Modification of Diet in Renal Disease (MDRD) (Levey et al. 1999) or the more recent the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al. 2009). Occasionally other renal biomarkers are used to define RI such as cystatin-C(Sarnak MJ 2005), blood urea nitrate (BUN)(Klein et al. 2008) or a specific serum creatinine value (Atherton et al. 2012). These biomarkers have also been used for defining WRF.

Irrespective of the acute WRF definition used it is important to note that the serum creatinine definitions, which are the most common are closely aligned to diagnostic thresholds used in RIFLE or AKIN criteria for acute kidney injury. This commonality opens the opportunity to review the AKI definitions and their utility for defining acute worsening of renal function in HF. HF studies reporting eGFR are more frequently referencing their findings against the KDIGO CKD guidelines staging classifications. The KDIGO guideline threshold for the diagnosis of CKD is <60mls/min/1.73m² (BSA) or an albumin-to-creatinine ratio (ACR) ≥30 mg/g (≥3 mg/mmol) (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013); an admission eGFR<60mls/min/1.73m² is also a common threshold for renal impairment (Bibbins-Domingo et al. 2004; Damman, Valente, et al. 2014).

1.3.11 Worsening renal function in heart failure burden

The prevalence of CKD and acute worsening renal function in HF have been variously estimated to be 33% to 65% (Heywood et al. 2007; Khan et al. 2006) and 11% to 45% (Damman et al. 2009; Smith et al. 2003; Verdiani, Lastrucci & Nozzoli 2010) respectively. These variations are attributed to the absence of a consensus definition and to the diversity in patient populations and settings (Atherton et al. 2012; Coca et al. 2007; Damman et al. 2009; Heywood et al. 2007; Smith et al. 2006). Irrespective of whether renal dysfunction is acute or chronic in HF mortality rates trend towards an inverse graded relationship (Damman et al. 2007; Smith et al. 2006). The greater the severity of RD the greater the mortality risk. The seminal paper by Smith and co-authors (Smith et al. 2006) highlight this association. They found “mortality worsened incrementally across the range of renal function, with 15% (95% CI 14% to 17%) increased risk for every 0.5 mg/dl (44.0 μmmol/l) increase in creatinine and 7% (95% CI 4% to 10%) increased risk for every 10 ml/min decrease in eGFR” (Smith et al. 2006).

Heart failure and kidney disease are not rare conditions. The presented epidemiology data highlight their prevalence and the significant impact these conditions have at the individual, national and global levels. Individually they are challenging but when combined as cardio-renal dysregulation they present new challenges to both clinicians and researchers. Among the most pressing AKI and CKD in HF research challenges are the need to establish cause, identify predictors and the development of management strategies that preserve renal function and improve patient outcomes. Part of this challenge is the need for standardisation of the nomenclature and agreed definitions.

1.4 Purpose

The ReFinH Study investigated the cardio-renal relationship in hospitalised HF patients (HHF) and its association to outcomes. Renal dysfunction has been described as the most important predictor for clinical outcomes in heart failure patients (Damman et al. 2012). For northern hemisphere studies, evidence is strong that WRF in heart failure delivers poor outcomes in terms of mortality, re-hospitalisations and costs (Butler et al. 2010; Coca et al. 2007; Damman et al. 2007; Krumholz et al. 2000; Smith et al. 2006). In the Australian context, there is a knowledge gap regarding the prevalence, morbidity and mortality associated with renal dysfunction presenting as renal impairment, CKD or AKI in hospitalised heart failure patients as it has not been adequately characterised.

1.4.1 Study aims

The primary aim of the present study was to investigate the cardio-renal relationship in patients admitted to an Australian tertiary level hospital with a principal discharge diagnosis of heart failure using a retrospective single-centre chart audit study design. Specific aims of the study were to:

i. Investigate the impact of in-hospital worsening renal function (WRF) present as acute kidney injury (AKI) defined using a modified AKIN definition of AKI (Sheerin et al. 2014) for the composite outcome all-cause mortality and major acute cardiovascular events (Non-STEMI; STEMI Cardiac arrest and Stroke) at 12-months follow-up

ii. Investigate the impact of in-hospital worsening renal function present as acute kidney injury (AKI) defined using a modified AKIN definition of AKI (Sheerin et al. 2014)for the secondary outcomes at 12-month follow-up for:
    - hospital re-admissions
    - emergency department presentations
    - total hospital bed days

1.4.2 Study objectives

To fulfil the study aims for the cohort the objectives were to:

i. Determine the incidence of AKI
ii. Determine the prevalence of Renal Impairment and CKD
iii. Characterise an Australian cohort of hospitalised HF patients who develop in-hospital AKI defined using a modified AKIN acute kidney injury definition
iv. Identify the risk factors (predictors) associated with the development of AKI in the study cohort
v. Determine event free survival for hospitalised patients with CHF discharged with an index admission history of AKI, or RI or CKD, and
vi. Identify the relationship between hospitalised HF patients discharged with an index admission of AKI, or history RI or CKD and secondary outcomes for the study.

An additional aim was to assess the utility of a modified AKIN acute kidney injury definition as an operational definition for acute kidney injury in HHF patients (Table 1.4). The promotion and adoption of standardised nomenclature, definitions and a risk algorithm have the potential to raise awareness of CKD and AKI (Lameire et al. 2013) in patients with CHF. Awareness of these potential scenarios may result in management strategies that protect renal function and improve HHF patient outcomes.

Table 1.4 ReFinH acute kidney injury definition

ReFinH Study AKI definition:
• **Increase in SCr by ≥26.5 µmol/l (≥0.3 mg/dl) within 72 hours of baseline value.**

1.5 Significance, Scope & Definitions

1.5.1 Significance

In Australia, there are clinical and epidemiological gaps in the knowledge base for renal dysfunction in hospitalised HF patients. The acute worsening renal function in heart failure is one area where there is a paucity of information. Northern hemisphere research has identified renal dysfunction as a predictor of rehospitalisation and adverse outcome in heart failure patients, while in Australia the impact of acute WRF or AKI is yet to be described. Furthermore, the processes of identification and management of risk in these patients are less well considered.

The present study is the first Australian study to describe the outcomes from a single centre cohort of HHF patients who develop in-hospital WRF. The information derived from the study has the potential to:

i. Contribute to the knowledgebase for the Australian characterisation of renal dysfunction in hospitalised patients with CHF
ii. Provide epidemiological data on the incidence of AKI and prevalence of RI and CKD for an Australian cohort of patients with CHF
iii. Assist with the development of a metric to categorize patients at high, moderate or low risk for AKI,
iv. Inform evidence-based management regarding AKI definition in patients with CHF, and
v. Inform the development of data elements that could be embedded in information systems to improve the preservation of renal function, inform current HF evidence-based practice and facilitate increased epidemiological and public health understanding of the syndrome.

Identifying heart failure patients at risk of acute kidney injury is important in preventing progression to chronic kidney disease or further worsening of renal function, informing adjustment to medication management and potentially preventing adverse events. AKI whether a new finding or superimposed on already diagnosed chronic kidney disease (CKD) requires definitive monitoring and treatment. Defining and identifying AKI or establishing CKD stage is important for effective treatment (Bellomo, Kellum & Ronco 2012; Eckardt et al. 2013). In addition, ensuring communication between health professionals requires consistency of the taxonomy. As a consequence, data elements for the definition and demonstration of utility in the clinical setting are critical.

The lack of an international consensus within cardiology for definitions for the various manifestations of renal dysfunction in heart failure has hindered the development for an evidence-based approach to its diagnosis, prevention and management. Germane to this issue has been the concern regarding the limitations of serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) the current standards for assessment of renal function. The result is these metrics are now being challenged by a new generation of renal biomarkers such as Interleukin-18, neutrophil gelatinase-associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1) and cystatin-C. However, these new renal biomarkers are yet to replace serum creatinine and eGFR in standard care.

Although there are clinical practice management guidelines for CHF (McMurray et al. 2012), chronic kidney disease (Levey et al. 2011) and acute kidney injury (Brochard et al. 2010) there

is a lack of continuity and concordance across these guidelines creating a certain ambiguity as to the diagnosis of AKI and the management of the stages of chronic kidney disease in heart failure. The introduction of the CRS sub-types and associated definitions has added another layer of detail and theory to this area of management and research. The CRS theoretical model attempts to identify the underlying pathophysiology mechanisms implicit in heart-kidney co-dependency.

Results from the present *ReFinH Study* will contribute towards an understanding of renal function in HHF patients in the Australian context; inform the development of a consensus definition for AKI in HHF and potentially encourage further Australian research into this area. ReFinH by exploring the possibility for standardised definition and taxonomy for an acute kidney injury in HHF has provided an entrée to further investigate the prevalence and impact of AKI and CKD in Australian HF cohorts. ReFinH in testing AKIN acute kidney injury definition and by identifying the predictors may also provide the basis for the development of data elements for improved monitoring. Such data elements should be suitable for inclusion in national metadata registries.

1.5.2 Scope

The study focus was the prevalence of RI and CKD on admission and the development of AKI in an Australian cohort of patients with CHF and the influence these conditions had on morbidity and mortality. The study population consisted of consecutive HF patients admitted between July 1st 2010 and December 31st 2010 at a single tertiary level facility and discharged with a principal diagnosis of HF as defined by the ICD-10AM-Codes (Table 3.1). The cohort was drawn from a culturally diverse catchment population of just under 1 million people. Data were collected for all eligible admitted patients, exclusion criteria were only applied after completion of the data collection for the entire cohort.

Taxonomy for describing acute worsening of renal function in HHF also fell within the scope of the ReFinH study. The study tested a modification of the AKIN acute kidney injury definition (Table 1.3) defined as a serum creatinine increase of ≥26.5µmol/l in ≤72hours from the admission first blood result (Table 1.4) for the diagnosis of AKI in HHF. The justification for increasing the timeframe for the diagnosis of AKI from ≤ 48 hours as specified in the AKIN definition to ≤ 72 hours was based on a review of the heart failure worsening renal function literature (Sheerin et al. 2014). Prevalence, predictors and outcomes were assessed against the modified definition. The prevalence of RI and CKD as comorbidities in the cohort were also determined and investigated for their impact on the study outcomes.

1.5.3 Definitions

For the ReFinH Study definitions are central to the investigation as a means to minimise any ambiguity for interpreting the results and for ensuring effective communication. Definitions pertinent to the study are presented in Table 1.5, Table 1.6 and Table 1.7. It is also noted that often in the literature the terms heart failure and chronic heart failure are used interchangeably.

Table 1.5 Key heart failure definitions

Term	Definition
Heart failure (HF)	Described in physiological terms HF is a syndrome "characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction" (Heart Failure Society of America 2010).
Chronic heart failure (CHF)	CHF is a complex syndrome where underlying structural abnormalities or cardiac dysfunction results in irregularities of contraction or relaxation which, have been present for a prolonged period (> 3-months) result in ventricular remodelling. Typical signs and symptoms include oedema, fatigue and breathlessness (National Heart Foundation of Australia 2013).
Acute decompensated heart failure (ADHF)	ADHF is a syndrome characterised by a rapid deterioration in heart function which frequently presenting as shortness of breath (SOB) at rest; either or both pulmonary and systemic venous congestion and severe limitation of physical activity due to HF signs and symptoms.

Table 1.6 Key cardio-renal definitions

Worsening renal function: heart failure (WRF)	There is no internationally agreed working or consensus definition for WRF; it is an over-arching term that encompasses CKD or acute reduction in renal function in HF. The reporting author's definition is usually based on changes to serum creatinine, eGFR or cystatin-C for absolute or percentage change where the timeframes for change can also vary. WRF in HF is often defined as an increase in serum creatinine of ≥26µmmol/l (≥0.3 mg/dL) from baseline (Forman et al. 2004; Krumholz et al. 2000).
Renal impairment (RI)	Defined as an admission or baseline eGFR<60ml.min.1.73m^2
Cardiorenal syndromes (CRS)	*"…disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other…" (Ronco, McCullough, Anker, Anand, Aspromonte, Bagshaw, Bellomo, Berl, Bobek, Cruz, et al. 2010)*
CRS Type 1 Acute cardio-renal	"Acute worsening of heart function leading to kidney injury and/or dysfunction"
CRS Type 2 Chronic cardio-renal	*"Chronic abnormalities in heart function leading to kidney disease or dysfunction"*
CRS Type 3 Acute reno-cardiac	"*Acute worsening of kidney function leading to heart injury and/or dysfunction"*
CRS Type 4 Chronic reno-cardiac	"*Chronic kidney disease leading to heart injury, disease and/or dysfunction"*
CRS Type 5 Secondary CRS	"*Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney*"

Table 1.7 Key renal definitions

	Renal
Kidney disease (KD)	*"as an abnormality of kidney structure or function with implications for the health of an individual, which can occur abruptly, and either resolve or become chronic"*
Chronic kidney disease (CKD)	The diagnosis of CKD is based on three factors: an estimate of glomerular filtration rate (eGFR) (<60ml.min.1.73m^2), the presence of renal damage (such as proteinuria or hematuria) ACR >3mg/g, and chronicity (≥3 months).

1.6 Thesis Outline

The thesis focused on the cardio-renal relationship in hospitalised HF patients. Chapter 1 has provided an introduction to the burden of CHF and renal dysfunction, framing the case for the study and its objectives. Chapter 2 is an integrative review of the contemporary cardio-renal literature. The literature review as an integrative method produced a diverse range of medical literature from which a number of themes emerged. The themes guidelines, demographics, definitions, eGFR formulae, biomarkers, prevalence, predictors, outcomes and nomenclature provided the framework to develop the review. These themes informed the study aims and the content of the case record form (CRF), gave the review both depth and focus, and demonstrated how knowledge in one area of medical science can inform gaps in another and influence the taxonomy across medical genres.

A highlight of the literature discussion was the appraisal of current AKI definitions used predominately in intensive care management against those used in cardiology. The barriers and enablers for the implementation of the AKI and CKD KDIGO definitions and stages in the context of HF were considered. In addition, the debate and status of the new renal biomarkers for kidney injury and cause were reviewed as well as issues associated with eGFR formulae and the need for cross referencing at the international guideline level.

In chapter 3 the methodology and analysis strategy are presented. The rationale for the study design as a retrospective single-centre chart audit cohort and the appropriateness of this method are featured as is the process to generate the cohort. Participant demographics are detailed and the data management and analysis plan outlined.

Chapter 4 reports the results from the study. Prevalence and characterisation data are presented followed by analysis results for predictors of AKI. Then the significance of the AKI definition for the study's primary and secondary outcomes is presented and the status of the study hypothesis. The bearing the comorbidity CKD and the condition RI had on both the development of WRF and the impact on outcomes are also reported.

Chapter 5 is a discussion which focuses on the key outcomes of the study within the context of international knowledge. The results are considered with respect to the contribution they play for informing future research into acute kidney injury in HF, and management of CKD in community-based CHF with specific reference to the Australia context.

The final chapter, chapter 6 details the conclusions that have been drawn from the study results and their interpretation in light of the international and local literature and the Australian context of the study. This information is presented within the context of policy, practice, education and research. Limitations of the study are also discussed. The chapter concludes with recommendations for multidiscipline clinical practice based on key findings from the study and opportunities for further research.

References are provided at the end of the chapters.

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Chapter 2 Literature Review

2.1 Introduction

Chapter 1 has provided an introduction to the burden of renal dysfunction and heart failure (HF). In this chapter, a review of the contemporary cardio-renal literature is developed using an integrative review method. A challenge for the review is worsening renal function (WFR) in cardiology is without an evidence-base to inform clinical practice guideline development, consensus definitions or standardised nomenclature. Moreover, the clinical management of HF is a delicate balance of optimising therapies which are known to have a potentially deleterious effect on renal function and preserving renal function.

The prognostic importance of WRF, its' nomenclature, characterisation, data sources and the degree of dissonance across medical genre guidelines are investigated. Against this background a thematic narrative is developed by exploring the guideline, definition, biomarker, eGFR equations, outcome, demographic, prevalence and predictor themes. These themes link to the study aims and informed the clinical research form (CRF) of the study described in Chapter 3, give the review both focus, depth, and demonstrated how knowledge from one area of medical science can inform another influencing the taxonomy across the medical disciplines.

A feature of the discussion is the appraisal and contrasting of current acute kidney injury (AKI) definitions predominately used in intensive care and nephrology management against those used in cardiology. The barriers and enablers for the implementation of the Acute Kidney Injury Network (AKIN) acute kidney injury definition (Mehta et al. 2007) and the chronic kidney disease (CKD) Kidney Disease Improving Global Outcomes (KDIGO) guideline definitions and stages (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013) in the context of HF are also considered. In addition, the current debate and status of the new renal biomarkers for kidney injury and cause are addressed as well as issues associated with eGFR formulae and the need for guideline concordance across medical fields. This literature review has been published in the International Journal of Cardiology (Appendix 1).

2.2 Literature review

The contemporary cardio-renal literature was sourced using an integrative review (Whittemore & Knafl 2005) search method (Table 2.2). This methodology ensures a comprehensive and diverse sampling of the literature pertinent to the medical fields responsible for the management of renal dysfunction in HF as either a comorbidity or independent entity. HF aetiology is heterogeneous and the concept of cardio-renal syndromes (CRS) is complex so it is important to consider the scientific literature form a broad array of

sources before focusing on the core issues. The integrative review enables such an assessment of the experimental and non-experimental research and provides a process to summarise the current state of the science including the knowledge gaps. This information can then inform theory development, clinical practice guidelines, policy and research.

Table 2.1 Integrative review process for renal dysfunction in heart failure

Stage of review	Illustration of decisions and issues
Problem identification	Worsening renal function (WRF) in heart failure has been the focus of renewed interest over the last 15 years as the prognostic impact of this development in HF has become apparent. Currently there are no evidence-based practice management guidelines to inform the diagnosis and management of these patients. It is also unclear as to the incidence, prevalence and characterization of renal dysfunction in Australian hospitalised heart failure (HHF) patients. Therefore the purpose of this integrative review was to analyze the concept of WRF in HF and its predictors and relationship to health outcomes across various settings; and to inform hypothesis development for a WRF in HHF study for the Australian context.
Literature search	The specific focus of worsening renal function in the context of heart failure as related to outcomes informed the literature search strategy. The concepts 'heart failure' and 'renal insufficiency' were initially searched using the databases Medline Ovid and PubMed. The key words 'cardio-renal or cardiorenal or cardio renal' were then searched. After removing duplicates and applying the search filters 104 publications remained of which 53 meet pre-defined inclusion criteria.
Data evaluation	The resulting sample included empirical and narrative reviews. Empirical articles were either retrospective analyses of randomised clinical trials, post hoc analysis, prospective observational studies or local, regional or international HF registries. There were 3 meta-analyses. Cardiorenal syndrome featured in a number of the narrative reviews.
Data analysis	Data were summarized for study design, WRF status, sample characteristics, and outcomes. Themes identified were: guidelines, definitions, biomarkers, eGFR formulae, demographics, predictors, and prevalence.
Presentation	A summary table (Table2.3) of the key data sources is presented to display the diversity of definitions used in describing the concept of WFR in HF and the impact definition variation has on prevalence and outcome measures.

2.2.1 Search strategy

MEDLINE (Ovid) and PubMed were searched using the concepts 'heart failure' and then 'renal insufficiency'. These terms were exploded to maximise the potential to include any more specific terms related to our subject headings. Search limiters were English language, human, all adults 19-years plus and the timeframe January 1985 to December 2013. These limiters were applied to the second concept search result. The next phase was to search and map the keywords 'cardiorenal or cardio-renal or cardio renal' and applied the same limiters. The Medline (Ovid) search strategy and results are displayed in the following table (Table 2.2).

Table 2.2 Medline (Ovid) search strategy and results

	Medline Ovid - Searches	Results	Search Type
7	4 and 6	74	Advanced
6	limit 5 to (English language and year="1995 -Current")	1130	Advanced
5	(Cardiorenal or cardio-renal or cardio renal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1388	Advanced
4	1 and 2	604	Advanced
3	limit 2 to (English language and year="1995 -Current")	8980	Advanced
2	Renal Insufficiency/	10896	Advanced
1	Heart Failure/	87852	Advanced

The final action was to combine the MEDLINE (Ovid) and PubMed search results and remove any duplication this provided 104 publications for greater scrutiny (Figure 2.1).

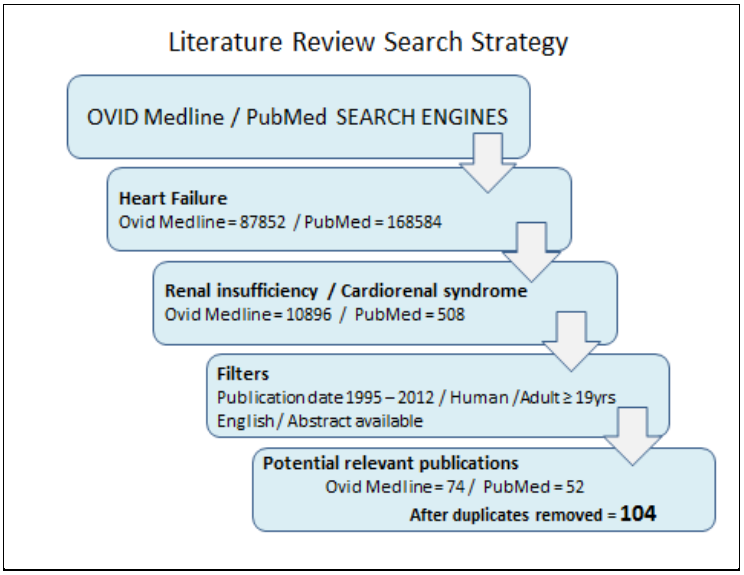

Figure 2.1 Literature review database search results

Identified articles were then culled against pre-defined criteria. Where references did not include HF patients or identify a definition for HF or renal impairment they were excluded as were articles which focused on cardiorenal anaemic syndrome. Case studies, editorials and letters were also removed. The reference lists from the 104 retrieved articles were search for any additional articles. This finalised the literature search process.

Fifty three publications were considered relevant to literature review. There were 3 meta-analyses, 11 retrospective secondary analyses of randomised control trials (RCTs), 4 post hoc analysis, 26 narrative reviews, 6 prospective observational cohort studies, and 3 heart failure registry reviews. International HF, chronic kidney disease and acute kidney injury guidelines were also obtained. Key references from the literature review are summaries in the following table (Table 2.3).

The thematic analysis of the literature begins with an examination of HF guidelines for information pertinent to issues of renal function. Definitions and their importance for patient care, research and improved communication are then considered. CKD and AKI definitions adopted by nephrology and critical care clinicians are highlighted and compared to commonly used cardiology HF worsening renal function definitions. The discussion around the definitions leads into the biomarkers theme and eGFR formulae and their significance in HF. The final phases of the review focus on outcomes, demographic, prevalence and predictor themes. The review concludes with a summary highlighting the key points which have informed the present study. The literature search was conducted under the supervision of a senior health librarian.

Table 2.3 Summary: key references for the literature review renal function in heart failure

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
Hillege et al. 2000 ***Circulation***	To determine if renal function is a **predictor for mortality** in advanced CHF;	Retrospective Observational* **PRIME-II**	1906	European Hospitalised	64.7 (±9.5)	80.4%	GFR was calculated using the Cockroft Gault equation (CrCl)	Mortality GFRc more powerful than NYHA class re mortality	**WRF Definition** GFRc <44 mL/min) mortality RR 2.85; *P*<0.001 almost 3 x the **risk of mortality** in the highest quartile GFRc >76 mL/min
Krumholz et al. 2000 ***Am J Cardiology***	To determine the: **Incidence**, **predictors for WRF** >65yr ADHF; and Impact for **clinical & economic outcomes**.	Retrospective Observational Multicentre Medical Audit Cohort 18 sites	1681	North America Connecticut Hospitalised	79.1 (±7.7)	42%	WRF as defined in the ELITE study as an ↑ in SCr>0.3mg/dl **during admission**	Mortality, 30-day, & 6-month Readmission	**Predictors WRF**: male / systemic hypertension/ rales >basilar / pulse >100 bpm SCr >1.5 mg/dl SBP >200 mm Hg
# Gottlieb et al. 2002 ***J Card Fail***	To determine the **prognostic importance** of various **definitions** of WRF & their frequency in HHF patients	Retrospective Observational Medical Audit Cohort	1002	North America Hospitalised	67.0 (±15) 18%>80yrs	51.0%	SCr ↑ by 0.1mg/dl (8.8µmol/L) increments - 0.5mg/dl(44.2µmol/L) or SCr ↑ by 10% increments 10% - 50% from admission	All-cause Mortality and LOS	**WRF Definition** ↑SCr>0.3mg/dl (26.5µmol/L) = 81% Sensitivity & 62% Specificity for **death**; 64% & 65% for **LOS** >10days
Smith et al. 2003 ***J Card Fail***	To determine how various **definitions** of WRF, defined as elevations in SCr impact **outcomes**: mortality, readmission, & functional decline in the 6 mths after DC	Prospective Observational single site cohort (Data:1996-98)	412	North America Hospitalised	72.0 (±11.0)	51%	**Absolute** SCr ↑≥0.1 to ≥0.5 mg/dl and 25% **Relative** elevation from baseline **during admission.**	All-cause mortality, Readmission, and Functional decline 6-months	**WRF Definition/ Outcomes.** The SCr threshold for WRF impacts **prevalence** & **mortality.** **WRF Prevalence 45%** when SCr≥0.3mg/dl, (HR 1.68, 95% CI 0.98-2.85)
Butler et al. 2004 ***American Heart Journal***	**Does acute treatment** for HHF patients **contribute to WRF** i.e.: medications, fluid	Nested case-control study (Data:1997-98)	382 cases 191 controls	North America Hospitalised	70.0	50%	WRF, defined as a rise in SCr level >26.5 µmol/L [0.3 mg/dl]	**WRF**	**Predictors of WRF**: ↑ SCr at admission, Uncontrolled HTN, and History: HF or DM **ACE** not associated

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
	intake/output, and weight								with WRF. High **haematocrit** associated ↓risk WRF
# Forman et al. 2004 ***JACC***	To determine the **prevalence** of WRF in HHF patients; **clinical predictors** of WRF; & **outcomes** associated with hospital WRF	Retrospective Observational Medical Audit Cohort (Data:1997-98)	1004	North America Hospitalised	67.0 (±15) 18%>80yrs	51%	Increase in SCr of >0.3mg/dl (>26.5µmol/L) from admission	**WRF**	WRF **prevalence** 27% **Predictors**: Hx of HF or DM, admission SCr ≥1.5 mg/dl (132.6 µmol/L), and SBP >160 mm Hg. **Question** from authors. Is WRF the cause of ↑ morbidity & mortality & therefore a target for intervention, or simply a marker of more severe pathophysiology derangement in HF?
Akhter et al. 2004 ***Am J Cardiology***	Investigated ↑SCr on admission; WRF during hospitalization, and the **outcomes** in ADHF	*Post hoc* analysis RCT **VMAC Trial** (2002)	480	North America Hospitalised 55 centres	62.0 (±14)	69%	**Renal insufficiency** (RI) was defined as a SCr level >1.5 mg/dl on admission **WRF** >0.5 mg/dl ↑of SCr from baseline at any time **during admission**.	**LOS** **Readmission rate** at 30 days **Mortality**: 30-day & 6-months	**Prevalence RI:** 44.7% **Prevalence of WRF**: 25% **Outcomes: Mortality 30-d** 5.3% (CI 3.0%–8.5%). **Mortality at 6-mo12**.3% (8.6%–16.7%) (95% CI) **LOS** (d) 8.2 ±7.1 (6) **Readmission within 30 d** of discharge: 17%
Bibbins-Domingo et al. 2004 ***JACC***	To explore the association **between RI & mortality in women with HF** and to evaluate this risk by the presence **HFpEF or HFrEF.**	Retrospective Cohort **HERS Study**	2763 702 HF	**Community**	69.0 Excluded >79yrs	0%	**CrCl** defined categories: >60 ml/min, 40 to 60 ml/min, & <40 ml/min	**RI & mortality &** **RI, mortality & clinical factors**	**RI is a common (57%) powerful predictor of mortality in women with HF.** Women Mortality RFs in order effect: **↓GFR<60ml.min DM/**

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
									Age>70/ Limited exercise/ Smoker /MI<1yr ago; NYHA III/IV & AF. HFpEF or HFrEF equally effected. ACE-I mortality protective.
Cowie et al. 2006 ***Heart***	To determine the **prevalence** & **risk factors** for WRF in ADHF (**EF≤40%**) & the association with subsequent re-hospitalization & mortality.	Prospective Observational multi-centre Cohort (17) **POSH Study**	299	European Hospitalised	68 (±12)	74%	SCr ↑>0.3mg/dl (>26µmol/L) during admission up to 15-days	**WRF** and: **Prevalence**, **Re-admissions**, **Mortality**. In-hospital, 1 & 6-months	**Prevalence:** 29% (95%CI 26–32%) WRF excluding HHF with major in-hospital complication likely to compromise RF. **Risk WRF** independently associated: Admission **SCr** OR: 3.02 (1.58–5.76), **PO**: OR 3.35 (1.79–6.27), and **Hx AF**: OR 0.35 (0.18–0.67). **Outcomes:** LOS ↑ in WRF, mortality, re-admissions similar.
Khan et al. 2006 ***J Am Soc Nephrol***	To determine the **value of KDOQI CKD stages for prevalence** & to **predict outcomes; and the effect of ACE-I on rate of RF decline**	*Post hoc* Analysis **SOLVD Trial** (1992)	6,640	North America & Belgium **Community**	60.0 (±10.0)	86%	**eGFR ml/min.1.73m²** ≥90 60 – 89 30 – 59 15 – 29 **Change over 1 year. Rapid decline RF from baseline:** >15ml/min/1.73m² /yr. (5ml.min increments)	All-cause mortality Follow-up to 34.2 (±14)months	**Prevalence CKD** 33% **Inverse relationship between** eGFR & Mortality when eGFR <90ml.min.1.73m². Rate of decline in RF is a **strong predictor** of ↑mortality in LVSD HF. Comorbidity prevalence ↑ by ↓ eGFR stage
de Silva et al. 2006 ***European Heart***	To determine the prevalence & incidence of renal dysfunction in CHF;	Prospective Observational	1,216	United Kingdom **Community**	71 (±10.1)	69%	**During 6-month**s: **From baseline WRF**=↑or ↓ SC r >0.3mg/dl	Mortality Follow-up At 3-months	**Prevalence CKD 57%.** During 6 months **the Prevalence WRF 13%** Baseline RD & WRF

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
Journal	to ID predictors of WRF, & the relationship between RD & mortality.						(>26.5µmol/L). **RD** defined as SCr >130µmol/L(1.5mg/dl) and a GFR<60mL/min	& 6-months	predicted ↑ mortality (P<0.001); Improvement RF in first 6 months predicted lower mortality (HR 0.8, 95% CI 0.6–1.0).
Owan et al. 2006 ***J Card Fail***	To determine if RD **severity**, **incidence** of WRF or **outcomes changed over time in HHF patients**	Retrospective Observational Chart audit single site	6,440	North America Hospitalised	73.0 (±13)	56%	WRF either SCr ↑≥25%, or Absolute ↑SCr >0.3mg/dl during admission	Mortality 3-months to 4.8 years	**Outcomes:** WRF predicts both short-term & long-term mortality.
Klein et al. 2008 ***Circ. Heart Failure***	To investigate the relation between admission values and changes in eGFR and BUN and rate of death by 60-days post discharge in hospitalization ADHF	*Post hoc* Analysis RCT **OPTIME-CHF**	936 of 949	North America Hospitalised	By BUN Quartiles 1 to 4 1. 59 yrs. 2. 66 yrs. 3. 70 yrs. 4. 72 yrs.	~66% 60% 66% 70% 68%	Using the MDRD formula ≥25% ↓in **eGFR** or a ≥25% ↑ in serum **BUN** from admission to discharge	Mortality Readmissions 6-months	**Outcomes:** lowest eGFR quartile had higher rates of **death** or **re-admission** at 60 days. Admission **serum BUN**, when modelled linearly, remained a significant predictor of ↑60-day **death rate** HR 1.11 per 5-mg/dl ↑(CI, 1.07 to 1.15; P<0.01). **Other predictors** (death) Age, SBP, NYHA, Hb & Na^{++}
Damman et al. 2009 ***European Journal of Heart Failure***	Investigate the effect of WRF post discharge in HF patients on standard care compared to intensive	RCT **COACH**	1023	European	71 (±11)	62%	sMDRD for eGFR WRF>26.5µmol/l during admission. Follow up assessment: discharge, 6, 12 & 18 months	Composite All-cause Mortality & HF admission	**In-hospital WRF 11% & RI = 59%.** Both in @ out of hospital WRF associated with poor outcomes.

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
Verdiani et al. 2010 ***International Journal of Nephrology***	To determine the **prevalence**, the clinical **predictors**, and the **prognostic** significances of WRF in hospitalized ADHF.	Prospective observational Single centre	394	European Hospitalised	77.9 (±10.1) 69.5%>75	67%	SCr ↑ of ≥0.3mg/dl (≥26.5µmol/L) **from baseline to discharge**. Plus:↓ eGFR ≥20% **from baseline to discharge.**	LOS, Death and Re-admission risks at 1 & 6 months, and 1 year.	**Transient increases in SCr or** ↓ eGFR **not classified as WRF = therefore prevalence** 10.9% & 11.6%. **No significant** differences re LOS, re-admissions or mortality at any time point in follow-up.
Breidthardt et al. 2011 ***Am J Cardiology***	Establish the **prevalence** and effect of WRF on **survival** among patients with ADHF.	Prospective Observational Single centre	657	European Hospitalised	79 (71 – 85)	55%	Admission **MDRD** into **3 Groups** eGFR <30 ml/min, 30 to 60 & >60 ml/min/1.73m² for >3-months. **WRF** ↑ SCr >0.3 mg/dl (>26. 5µmol/L) from admission	**Clinical parameters at admission to predict WRF** assessed. 2nd end point **all-cause mortality** at 360 days	**Prevalence** 21% WRF Multivariate regression analysis found WRF to independently predict **mortality** (HR 1.92, p <0.01). **Hx of CKD only independent predictor of WRF.**
Maeder et al. 2012 ***American Heart Journal***	To determine the **incidence** & **prognostic impact of WRF**; to assess clinical& treatment factors associated with a relevant degree of WRF in contemporary cohort of elderly CHF undergoing intensive medical treatment following prespecified sequential assessment of RF	*Post hoc* Analysis **TIME-CHF** RCT	566	**Community** Post index hospitalisation	76.7 (±7.7)	60%	↑SCr by WRFI 0.2 to 0.3 mg/dl, WRFII 0.3 to 0.5, or **WRFIII ≥0.5 mg/dl from baseline** value within the **first 6 months CKD by eGFR Stages 1-5**	**Incidence** WRF, **Predictors** WRF, **Impact WRF re mortality** **Assessed over** 18-months	**WRFIII analysis:** definition significance re predictors & mortality**. WRFIII in 20%** by 6-mths Strong independent **predictor of death HR 2.00** [1.24-3.23], patients on High doses **loop diuretics and/or Aldost. Antag** more likely to develop WRFIII**. ACE/ ARB & βBlocker** therapy not associated with WRFIII. **Characterises** WRF in community CHF.

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
Registries									
ADHERE **Heywood et al.** **2007** ***J Cardiac Fail***	To **characterise** ADHF patients according to CKD severity. To determine the **prevalence and severity of RD** on admission in ADHF, and to relate the degree of RD to treatments and **in-hospital outcomes**.	Retrospective Observational Cohort Audit	118,465 of 124,885	United States of America Hospitalised	Age by eGFR stage 1. 61.7 2. 70.1 3. 75.7 4. 76.3 5. 67.4	eGFR stage % Males 57% 53% 46% 42% 46%	**MRDR formulae** used to estimate GFR at the time of hospital admission. **Classified by eGFR** KDIGO stages.	**In-hospital clinical outcomes worsened with ↑severity of RD**. At admission, 9.0% = normal RF; 27.4% = mild RD; 43.5% = moderate RD; 13.1% = severe RD, 7.0% = kidney failure. Despite this, **only 33.4% of men and 27.3% of women were diagnosed with RIs**. **RI in 63.6% (inclusive mild to ESKF)** Diuretic dose, inotrope use, and nesiritide use↑, whereas ACE or ARB use↓, with ↑RD (all P<.0001 across eGFR stages). **In-hospital mortality** ↑ from 1.9% (normal RF) to 7.6%; and 6.5% for severe RD and kidney failure, respectively (P < .0001). The majority of patients admitted with ADHF had significant RI, which influences treatment and outcomes.	
IMPROVE-HF **Heywood et al.** **2010** ***Am J Cardiology***	To determine the rates & **severity of CKD** in a cohort of **HF patients** receiving **community-based** cardiology care and to assess the effect of CKD on **guideline recommended therapies adherence**.	Retrospective cohort analysis	13,164 1 =1,346 2 =4,941 3 =5,809 4 =1,068	United States America **Community** **HF with** **EF ≤35%**	**Median** 57 67 74 75	**Male** 74.6% 77.5% 67.4% 59.3%	**MDRD formula** and stages according eGFR **at baseline**: 1. >90ml.min.1.73m² 2. 60–89ml.min. 3. 30–59ml.min. 4. <29ml.min.	Effect of CKD on **adherence to guideline recommended therapies in HF**: ACE-I/ARB ß Blocker Aldost. Antag Anticoag for AF CRT ICD/CRT-D HF education	**Prevalence CKD**: **52.2%** of the patients had **≥ stage 3 CKD.** The rates of **comorbidities** were **significantly >** among patients **with more severe CKD.** ACE-I/ARB & ß blocker therapy significantly less likely to be administered to patients with more severe CKD.
ADHERE-AP **Atherton et al.** **2012**	**Characterisation** of HF Index hospitalisation	Retrospective Observational Cohort	10,171	**Asia-Pacific** Hospitalised	**Median** **67**	57%	**Baseline** RI: SCr >1.5mg/dl	LOS: 6 days In-hospitality mortality:	**ADHERE-AP Patient origin**: Singapore = 29%

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
J Cardiac Fail	for the Asia-Pacific region	Audit			**(53 to 77)**		(>133µmol/L)	4.8% **RI = 41%**	Thai20%, Indonesia: 17%; Aust 8.9%; Malaysia 8.9% Philippines 7.1%; Taiwan =5.3%; Hong Kong: 3.9%.
Meta-analyses									
Smith GL. et al. 2006 **JACC**	To estimate the **prevalence** of renal impairment in HF patients & the magnitude of associated **mortality risk**	Meta-analysis Observational studies (16 studies)	80,098	Nth. America, Europe Community & Hospitalised	52.0 (±4.0) to 78.0 (±11.0)	0% (1 Study) to 86%	Renal function categories: **Moderate/Severe RI**: SCr≥1.5mg/dl (>133µmol); eGFR <53ml.min; Cystatin-C≥1.5mg/dl. **Any RI:** sCr>1.0mg/dl; eGFR<90ml.min or Cystatin-C<1.03mg/dl. **WRF in Hospital** change SCr≥0.3mg/dl	All-cause Mortality; CVD Mortality, & Functional decline at 6-months up to 5yrs	**Prevalence** of RI: Any = 63%; Moderate/ severe 29% **Death at ≥1 yr. follow-up:** None = 24% Any = 38% Moderate/ severe 51% **Mortality** worsened incrementally across the range of renal function.
Damman et al. 2007 ***J Cardiac Fail***	Establish the **proportion** of patients with HF that exhibits WRF; and The **associated risk** for **mortality & hospitalization**	Meta-analysis (8 studies)	18,634	European & Nth. America Community & Hospitalised	Range 59 - 79	Range 42% to 86%	**WRF** ↑SCr ≥0.2 mg/dl (≥17.7 µmol/L) or corresponding ↓ eGRF of ≥5mL/min/1.73 m^2 **WRF I** SCr 0.2 - 0.3 mg/dl (17.7 - 26.5µmol/L) or eGFR↓ 5 - 10mL.min.1.73m^2 **WRF II** SCr↑> 0.3 - 0.5 mg/dl (>26.5 - 44.2 µmol/L) or eGFR↓ 11 - 15 mL/min. **WRF III** SCr↑ >0.5 mg/dl or eGFR↓ >15 mL.min.	WRF Re-admissions Mortality Minimum follow up ≥ 6 months median follow up of 4.8 Years.	**Prevalence WRF = 25%** WRF predicts substantially higher rates of mortality and hospitalization in HF patients. **RI at baseline ↑ risk for WRF. Mortality OR**: 1.62; (95% CI 1.45 -1.82, P<.001) ↑ Severity WRF → ↑mortality risk; and **Hospitalization OR**: 1.30, (95% CI 1.04 - 1.62, P= .022).
Coca SG. et al. 2007 ***Am J Kidney Dis***	Investigated the **prognostic** association with small	Meta-analysis (8 studies)	78,855	European N. America **Hospitalised**	**Range** 53-72	N/A	**Mild AKI**: SCr ↑ 10% to 24% or 0.3 to 0.4 mg/dl 26 - 35µmol/L).	**Unadjusted Short-term mortality**	Short-term mortality associated with SCr levels by absolute

Author Year Journal	Primary Study Aim	Study Type	Study Size	Patient Population	Age	Male (%)	WRF Definition	Primary Outcome/ Endpoint	Relevance to ReFinH Study
	acute decreases in kidney function. Determine if small changes in renal function and **mortality** transcend different patient 57 studies 1,076,104patients: CKD; 28 studies 49,890 patients: WRF types			**Studies**: 2 Cardiac Surgeries; ICU; ADHF. 1 Coronary Angiography. Broad range hospitalised			**Moderate AKI**: SCr ↑ 25% to 49% or 0.5 to 0.9 mg/dl (44 to 80µmol/L) **Severe AKI**: SCr↑≥ 50% or ≥1.0 mg/dl or (≥88µmol/L)	(≤30 days). **Secondary** Relative risk (RR) for short-term **mortality** adjusted for other **prognostic factors**	change. **Mild AKI**= RR 2.3 (1.8 -3.0) **Moderate AKI** = RR 6.2 (3.2 - 11.7) **Severe AKI** = RR 12.4 (4.0-38.5). **Small ↑s SCr associated with ↑ risk ≤30-d death**. The study authors raise several **questions**: 'should definition vary with clinical setting; is the duration of sCr increase important; are other biomarkers superior in terms of sensitivity?"
Damman K. et al. 2014 *European Heart Journal*	2007 up-dated meta-analysis of the relationship between baseline: **RI**, **WRF**, & outcomes, & clinical **predictors** of WRF in HF.	Meta-analysis 57 studies HF & RI/ CKD 28 Studies HF & WRF	1,076,104 49,890	European & Nth. America & Community & Hospitalised	69 (±7)	62%	**Defined according to the individual studies** Most commonly used: **RI** <60ml.min.1.73m² **WRF:** SCr ↑>26.5 mmol/L (0.3 mg/dL) from baseline	**All-cause mortality** **CKD:** mean follow-up of 681+704 days **WRF**: mean follow-up 0o 448+569 (range 10-2555) days	Across all subgroups of patients with HF, CKD, and WRF are prevalent and associated with a strongly ↑ed mortality risk, especially CKD. Specific conditions may predict the occurrence of WRF especially CKD → poor prognosis.

Note: **post hoc* analysis of randomised clinical trial (RCT); *LOS* length of stay; *WRF* worsening renal function; *HTN* hypertension; *HF* Heart failure; *DM* diabetes mellitus; ADHF acute decompensated heart failure; *ACE-I* Angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; *#* same data source; *VMAC* Vasodilation in the Management of Acute Congestive Heart Failure trial; HHF hospitalised heart failure; HR hazard ratio; RR relative risk; OR odds ratio; PO pulmonary oedema; Hx history; AF atrial fibrillation; SCr serum creatinine; DM diabetes; D/C discharge; CrCl creatinine clearance; MDRD Modification of Diet in Renal Disease; Hb haemoglobin; Na^{++} serum sodium; LVSD left ventricular systolic dysfunction; ADHERE Acute Decompensated HEart Failure National Registry; RD renal dysfunction;↑ increasing; ↓ decreasing; RF renal function; RI renal impairment; RIs renal insufficiency; IMPROVE-HF Evidence-Based Heart Failure Therapies in the Outpatient Setting; CRT cardiac resynchronization therapy; CRT-D cardiac resynchronization therapy with defibrillator; ICD implantable cardioverter-defibrillator; Aldost. Antag Aldosterone antagonist; Anticoag Anticoagulation; HERS Heart and Estrogen /progestin Replacement Study; HFpEF *heart failure preserved* left ventricular *ejection fraction*; HFrEF *heart failure reduced* left ventricular *ejection fraction; ADHERE-AP Acute Decompensated Heart Failure Registry Internationale Asia Pacific; N/A not available; Thai Thailand; Aust Australia.*

2.3 Clinical Practice Guidelines

2.3.1 Background

Clinical practice guidelines (CPGs) are intended to "*improve outcomes due to better deployment of evidence-based strategies" (Gibbons et al. 2013)*. The focus is on evidence-based recommendations, promoting the quality and standards of care, empowering consumers, informing primary and tertiary clinicians and public healthcare policy makers while for researchers they can help identify knowledge gaps (Gibbons et al. 2013). CPGs collate the latest evidence for the diagnosis, management and risk factor identification for the condition of interest. They set the standards for consistency in definitions and nomenclature to ensure effective, meaningful communication and understanding. Guidelines in characterising the condition may also describe the likely illness trajectory (National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel) 2011 October).

Heart failure guidelines recognise acute decompensated heart failure (ADHF) as a common cause of hospitalization particularly in the elderly (Yancy et al. 2013). They accept renal dysfunction as a powerful prognostic marker (McMurray et al. 2012a) and the increasing impact of cardio-renal syndromes (McKelvie et al. 2011). CRS identified as an area lacking an evidence-base to inform management (Yancy et al. 2013). The CRS recently defined as "*disorders of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other"* (Ronco, House & Haapio 2008). This flurry of interest in the cardio-renal HF relationship and sequelae has led to a research and publication renaissance for this area in heart failure. Interest generated by the need to establish the incidence, prevalence, impact, cause and management options for the syndrome for heterogeneous populations and settings. Clinical practice guidelines require such information.

2.3.2 Heart failure guidelines and renal function

The attention given to renal dysfunction in HF guidelines is variable. The Canadian Cardiovascular Society Heart Failure Management Guidelines published in 2011 (McKelvie et al. 2011) includes a section on cardio-renal syndrome in advanced HF. These guidelines make reference to management and deterioration of renal function noting the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2002 classification of CKD (Eknoyan & Levin 2002) and acute kidney injury RIFLE (Risk-Injury-Failure-Loss-Endstage renal disease) criteria (Bellomo et al. 2004). However, the Canadian guidelines do not specifically address these criteria for diagnosis or staging of CKD or acute kidney injury in HF. Management

options such as ultrafiltration, haemodialysis and transplantation are mentioned but not presented in a way to clearly differentiate primary HF from primary end-stage kidney disease patients. The lack of clarity makes it difficult to interpret their intent for informing management decisions.

The European Society of Cardiology (ESC) (McMurray et al. 2012a) and the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) (Yancy et al. 2013) have recently published updated guidelines for the management of HF. These eminent guideline development organisations follow internationally recognised criteria for grading the strength of the evidence and rating their recommendations. It is therefore surprising there is no discussion of several meta-analyses (Coca et al. 2007; Damman et al. 2007; Smith et al. 2006) that address outcomes for the cardio-renal relationship. There is also no examination of the barriers or enablers to implementing the KDIGO acute kidney injury and chronic kidney disease classifications and severity stages despite their relevance to HF.

2.3.3 European Society of Cardiology Heart Failure Guidelines

Much of the renal focus of ESC HF guidelines is directed towards monitoring in medication management. The use of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARBs) and to a lesser extent diuretics and mineralocorticoid receptor antagonists (MRAs) are the medications most commonly identified to impact renal function. The practical guidance and problem solving tables in the ESC guidelines addenda (McMurray et al. 2012b) for the introduction or up-titration of the above drugs gives inconsistent information regarding the threshold at which renal dysfunction is sufficient to require adjustment to medication therapy. For example, with the introduction of ACE-I an "*increase in creatinine of up to 50% above baseline, or 266 µmol/L (3 mg/dl)/ eGFR <25mL/min/1.73 m^2, whichever is the smaller, is acceptable*" while for MRA drugs the message is if "*creatinine rises to 221 µmol/L (2.5 mg/dl)/eGFR <30 mL/min/1.73 m^2, halve dose and monitor blood chemistry closely*" or if with MRA drug use there is a rise in "*creatinine to >310 µmol (3.5 mg/dl) eGFR <20 mL/min/1.73 m^2, stop MRA immediately and seek specialist advice*." There is no explanation as to why the thresholds should vary and no apparent evidence-base to support the identified cut-off points. Most alarming is the ACE-I and MRA renal function changes deemed acceptable in these drug regimens are changes which under RIFLE, Acute Kidney Injury Network (AKIN) or KDIGO criteria or the most commonly used WRF definitions in cardiology would equate to acute kidney injury or WRF respectively. The information concerning the use of diuretics is less clear. Here renal impairment is described as a rise in

serum creatinine or blood urea nitrogen (BUN) without the provision of a laboratory value or percentage change to identify unacceptable rise in these biomarkers.

The ESC guidelines note that the management of HF can be influenced by drug treatments associated with comorbidity management for certain chronic conditions. Here medications such as non-steroidal anti-inflammatory drugs (NSIADs) and ß-Blockers are flagged. The conditions anaemia and diabetes are noted for their potential to worsen HF clinical status (McMurray et al. 2012a). However, acute and/or chronic renal dysfunction is not dealt with in a similar manner.

2.3.4 American College of Cardiology Foundation & American Heart Association HF Guidelines

A feature of both the ACCF/AHA and ESC guidelines is the absence of empirical definitions and standardised nomenclature when addressing renal dysfunction. The documents use terms such as 'renal impairment', 'adequate' or 'marginal' renal function but there is no consistency in their definitions. Renal impairment or insufficiency (RI) is usually reported as a SCr > 1.5mg/dl (>133µmol/L) as this value represents the upper limit of the 95th percentile of normal established from the Framingham Study (Akhter et al. 2004; Culleton et al. 1999). However, the ACCF/AHA refer to 'adequate' renal function as a serum creatinine <2.0mg/dl (<177µmol/L) or 'marginal' with an eGFR 30-49mls.min.1.73m^2; whereas ESC describe adequate renal function as serum creatinine ≤2.5mg/dl (≤221µmol/L) or eGFR ≥30mls.min/1.73m^2. The use of the terms 'adequate' and 'marginal' could be considered misleading. Established, internationally recognised acute (Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group 2012) and chronic kidney disease (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013) guidelines would identify patients with such values as having AKI, or if the change endured for three or more months chronic CKD rated as moderate (CKD stage 3a/3b) to severe (CKD stage 3b/4); not adequate and not just marginal.

The ESC and the ACCF/AHA HF guidelines focus on the management of renal function as a drug management issue and do not focus on preserving renal function or about the holistic management of the individual. Given the prognostic significance of AKI and CKD in HF, the failure to cross reference the AKI or CKD nephrology clinical practice guidelines is disappointing. Acute kidney injury and chronic kidney disease are prevalent in hospitalised HF (Akhter et al. 2004; Cowie et al. 2006; Khan et al. 2006) and carry increased morbidity and mortality risk (Khan et al. 2006; Smith et al. 2003). The failure to discuss the renal definitions

and staging criteria could be predicated upon the view that a definition that only incorporates a measure of function without reference to cause lacks precision and as such is unacceptable. However, this approach falls short in acknowledging the substantial evidence that any reduction in renal function in HF at any time conveys an increased mortality risk (Smith et al. 2003).

Concordance across these HF guidelines does occur in regarding the need for serial monitoring of renal function and electrolytes in managing certain drug therapies and the potential role of ultrafiltration. As noted earlier the ESC guideline acknowledge acute and chronic renal dysfunction as an important prognostic issue in HF but neglect to offer any further guidance. The ACCF/AHA concede significant gaps in the knowledgebase for some fundamental aspects of HF care and acknowledge limitations of the available evidence conceding cardio-renal syndrome is such an area (Yancy et al. 2013). The importance of definitions for renal dysfunction in HF and the opportunity to differentiate de novo from chronic renal dysfunction in HF needs consideration. The following definitions theme takes up the discussion.

2.4 Definitions

Definitions support shared understanding and knowledge development. In the absence of definitions, ambiguity hinders our ability to collect data which when interpreted provides information to inform the knowledgebase. Without diverting into an epistemological debate regarding the notion of knowledge suffice to say here knowledge is what we know (Terra & Angeloni 2003). As such definitions can serve as the foundation for building a field of research (Tobe et al. 2011); enable comparisons across studies and encouraging further research to validate the definition for various settings and populations.

Without consensus definitions and standardised nomenclature for worsening renal function in HF, there has been a proliferation of definitions for the condition (Butler et al. 2010), making the reporting of WRF in heart failure research problematic (Anderson & Glynn 2011; Butler et al. 2010). A possible solution to the issue would be the endorsement and implementation by cardiology of the AKIN acute kidney injury and CKD Kidney Disease Improving Global Outcomes (KDIGO) guideline definitions and stages. Differences and similarities between the KDIGO definitions and those commonly used by cardiology for WRF in heart failure are discussed. Finally, the evidence to support cardiology adopting renal AKI definitions and classification criteria for hospitalised HF patients is presented. A summary of worsening renal function definitions in HF and international definition for AKI and CKD are provided (Table 2.4).

Table 2.4 Kidney function definitions

Authors	Year	Type	Population	Biomarker	Definition	Time	Staging / Severity	Key findings
Worsening Renal Function in HF								
Krumholz et al.	2000	Retrospective Cohort	Hospital	SCr	↑SCr >0.3mg/dl (>26.51µmol/L) from admission	LOS	Nil	28% developed WRF. WRF associated with ↑costs, LOS & mortality
Gottlieb et a.l	2002	Retrospective Cohort	Hospital	SCr	SCr ↑ by 0.1mg/dl (8.8µmol/L) increments to 0.5mg/dl(44.2µmol/L) or SCr ↑ by 10% increments 10% - 50% from admission	LOS	0.1mg/dl(8.8µmol/L) 0.2mg/dl(17.1µmol/L) 0.3mg/dl(26.5µmol/L) 0.4mg/dl(35.4µmol/L) 0.5mg/dl(44.2µmol/L) 10%;20%;30%;40%;50%	↑SCr>0.3mg/dl (>26.5µmol/L) = 81% Sensitivity & 62% Specificity for death; 64% & 65% for LOS >10days. Adding a requirement of final creatinine of ≥1.5 mg/dl (≥133µmol/L) improved specificity.
Forman et al.	2004	Retrospective Cohort	Hospital	SCr	↑SCr >0.3mg/dl (26.51µmol/L) from admission	LOS	Nil	27% developed WRF. Developed a risk score for WRF
Smith et al.	2006	Meta-analysis Cohort studies & secondary analysis of some RCTs	Hospital Community & Clinical trials HF	SCr CrCl eGFR cystatin-C	Defined based on categorizations in the published studies. Additionally authors defined WRF as ≥0.3mg/dl (26.51µmol/L) from admission	LOS & Follow-up period	**Any renal impairment** **SCr** >1.0mg/dl(88.4µmol/L), **CrCl** or eGFR <90 ml/min, or **cystatin-C** >1.03 mg/dl) **Moderate/severe** impairment SCr ≥1.5, CrCl or eGFR<53mls, or cystatin-C≥1.56 - Estimated using fixed-effects meta-analysis	All-cause mortality worsened incrementally against reducing renal function. 15% ↑ risk with every 0.5mg/dl ↑in SCr & 7% ↑risk for every 10ml.min ↓ in eGFR; & WRF HR=1.47, 95% CI 1.26 – 1. 72
Damman et al.	2007	Meta-analysis Cohort studies & secondary analysis of some RCTs	Hospital	SCr eGFR	↑ SCr ≥ 0.2mg/dl (≥17.7µmol/L) *or* ↓ eGFR: ≥ 5 mls.min.1.73m^2	LOS	**Class I**: ↑ SCr 0.2mg/dl to 0.3 mg/dl (17.7 - 26.5µmol/L)↓ eGFR: 5 - 10mls.min.1.73m^2 **Class II**: ↑ SCr >0.3mg/dl to 0.5mg/dl (>26.5 - 44.2µmol/L) ↓eGFR:11-15mls.min.1.73m^2 **Class III**: ↑ SCr > 0.5 mg/dl	Graded, inverse relationship between all-cause mortality; re-admission and degree of worsening renal function.

Authors	Year	Type	Population	Biomarker	Definition	Time	Staging / Severity	Key findings
							(44.2µmol/L) ↓ eGFR>15mls	
Coca et al.	2007	Meta-analysis Heterogeneous settings & populations. 2 HF	Hospital	SCr	2 methods percentage or absolute change in serum creatinine levels. SCr level of 10% to 24% or 0.3 to 0.4 mg/dl (26-35µmol/L).		**Mild AKI** SCr level of 10% to 24% *or* 0.3 to 0.4 mg/dl (26-35µmol/L). **Moderate AKI** SCr ↑25% to 49% *or* 0.5 to 0.9 mg/dl (44 to 80µmol/L). **Severe AKI** SCr ↑50% *or* ≥1.0 mg/dl (≥88µmol/L)	SCr by absolute change 30-day mortality unadjusted relative risk: RR Mild: 2.3(1.8-3.0) RR Mod: 6.2(3.2-11.7) RR Severe:12.4(4.0-38.5)
Atherton et al.	2012	ADHERE-Asia-Pacific Registry	Hospital	SCr	SCr>133 mmol/L or >1.5 mg/dl on admission	Baseline	.	41% CKD on admission.
Roy et al.	2013	Single centre Cohort	Hospital	SCr eGFR (Urine Output)	RIFLE, AKIN & KDIGO and often used HF-WRF = ↑SCr ≥0.3mg/dl	Various: Baseline 48hrs LOS	RIFLE - 5 stages; AKIN - 3 stages KDIGO - 3 stages WRF – no stages	Found predictive ability between definitions was only marginal. Advantage of AKIN, RIFLE and KDIGO definitions over HF-WRF is these definition criteria have a severity scale.
Acute Kidney Injury								
RIFLE Bellomo et al.	2004	.	Hospital	SCr eGFR (Urine output)	↑SCr≥1.5 times baseline or ↓eGFR ≥25%	Baseline	Risk ↑SCr x 1.5 or ↓eGFR >25% *or* UO <0.5ml.kg.hr x 6hrs Injury ↑SCr x 2 *or* ↓eGFR >50% *or* UO <0.5ml.kg.hr x 12hrs Failure ↑SCr x 3 *or* ↓eGFR >75% *or* Cr≥4mg/dl (354µmol/L) with an acute rise ≥0.5mg/dl (44 µmol/L) *or* UO <0.3ml.kg.hr x 24hrs *or* Anuria x 12hrs Loss Persistent AKI > 4 weeks Endstage RRT, ≥ 3-months	Change to be maintained for >24hrs and occur within a 7-day period. Most server classification used to describe severity of Acute renal failure (ARF) now known as AKI.
AKIN Mehta et al.	2007	.	Hospital	SCr (Urine	An abrupt (within 48-hrs) absolute ↑ SCr≥	Baseline	**Stage 1** ↑SCr x 1.5 or ≥0.3mg/dl (≥26.5 µmol/L) or	Occurring within 48- hour hospitalisation period. Staging

Authors	Year	Type	Population	Biomarker	Definition	Time	Staging / Severity	Key findings
				output)	0.3mg/dl (≥26.5 µmol/L) or a % increase in SCr≥50% (1.5-fold) from baseline or UO <0.5ml.kg.hr x 6hrs.		UO <0.5ml.kg.hr x 6hrs **Stage 2** ↑SCr x 2 UO <0.5ml.kg.hr x 12hrs **Stage 3** SCR ↑ x 3 or SCr ≥4mg/dl (354µmol/L) with an acute rise ≥0.5mg/dl (44 µmol/L) or UO <0.3ml.kg.hr x 24hrs or Anuria x 12hrs	occurs over 7-day period. Most server classification used to describe severity of AKI.
KDIGO	2012		Hospital	SCr UO	↑ SCr by ≥0.3 mg/dl (≥26.5 µmol/L) ≤ 48 hours; or ↑ SCr ≥ 1.5 x baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume <0.5 ml/kg/hr x 6 hrs.	Baseline	**Stage 1** SCr ↑1.5–1.9 x baseline *or* ≥0.3 mg/dl (≥26.5 mmol/l) *or* UO <0.5ml/kg/h for 6–12hrs **Stage 2** SCr x 2-2.9 baseline *or* UO <0.5 ml/kg/h for ≥ 12 hrs. **Stage 3** SCr x 3 *or* ↑ in SCr to ≥ 4.0mg/dl (≥ 354µmol/L) *or* Initiate RRT, or **UO** <0.3 ml/kg/h for ≥ 24 hrs. *or* Anuria for ≥12 hrs. **Patients <18 years**, ↓ in eGFR to <35 ml.min.1.73m²	
Chronic Kidney Disease								
KDIGO Levey et al.	2011		General	eGFR ACR (Spot urine)	eGFR<60ml.min.1.73m² and/or Albuminuria >3mg/g for ≥3-months irrespective of cause	For ≥3 months	**Stage 1** Normal or high ≥90mls **Stage 2** Mildly ↓ 60 – 89mls **Stage 3a** Mild-Moderately ↓ 45 -59mls **Stage 3b** Moderate/Severely ↓ 30-44mls **Stage 4** Severely ↓ 15 – 29mls **ESKF** <15mls	

Abbreviations: ACR, Albumin to creatinine ratio; AKI, acute kidney injury; CKD, chronic kidney disease; WRF, worsening renal function; eGFR estimated glomerular filtration rate; HF, Heart Failure; CrCl, calculated creatinine clearance; *SCr – Serum creatinine; UO, urinary output;* LOS, length of stay; ↑, increasing; ↓ decreasing; KDIGO, Kidney Disease: Improving Global Outcomes.

2.4.1 Chronic kidney disease

As acknowledged previously, there are internationally agreed consensus definitions and staging for chronic and acute kidney disease and injury respectively. These definitions continue to be refined. In 2002 the NKF-KDOQI (Eknoyan & Levin 2002) proposed a five stage model for defining and classifying CKD based on GFR and chronicity. This model, with minor changes, was later endorsed by Kidney Disease: Improving Global Outcomes (KDIGO) group in 2004. CKD was defined as a GFR <60ml.min.1.73m²[1] or evidence of kidney damage regardless of cause for a period of at least 3-months. This GFR threshold has been identified as representing half the normal GFR value for young adults. It is also the point at which there is increased prevalence and severity of several cardiovascular (CVD) risk factors and the onset of laboratory abnormalities characteristic of kidney failure (Sarnak et al. 2003).

The KDIGO categorisation of kidney function is based on GFR. Classification ranges from normal through to end-stage kidney failure (Introduction Chapter: Table 1.2). The most recent changes to the definition and staging criteria took place following the 2009 Kidney Disease Outcomes Quality Initiative Controversies Conference (Levey et al. 2011). An outcome from this conference saw stage III CKD (GFR <60ml.min.1.73m²) split into stage III a: GFR 45 – 59mls.min.1.73m² and stage III b: 30 – 44mls.min.1.73m² based on mortality relative risk point estimates from the meta-analyses. The meta-analysis also provided evidence to support the inclusion of Albuminuria (Albumin Creatinine Ratio (ACR) = albuminuria > 30mg/g) as a criteria for CKD (Levey et al. 2011). Traditionally, a serum creatinine (SCr) of greater than or equal to 1.5mg/dl (133µmol/L) can also be used to define renal impairment (RI) (Brandimarte et al. 2012; Culleton et al. 1999).

To highlight the cardio-renal relationship and the impact of deteriorating renal function on outcomes, Levey et al. (Levey et al. 2011) provides a number of matrix that summarize the pooled relative risks for various eGFR and ACR values, expressed as continuous or categorical variables, respectively. These matrixes are for all-cause and cardiovascular mortality, end-stage kidney failure, acute kidney injury and progression to CKD. This seminal publication draws data from 45 cohort studies involving over 1. 5 million participants from general, high-risk, and kidney disease populations, and provides crucial epidemiological evidence for the relationship of albuminuria and eGFR with a significant range of key clinical outcomes (Levey et al. 2011). The question of the prognostic significance of stage 3 CKD (eGFR<60ml/min/1.73m2) and the ACR >30mg/g in the elderly (>65years) and the potential for over diagnosis is considered. Their

[1] $1.73m^2$ is the population mean body surface area (BSA)

findings identify stage 3 and the ACR >30mg/g as important markers in the elderly who commonly have a reduction in GFR without elevated albuminuria, and incidence rates for mortality and kidney outcomes particularly acute kidney injury are high.

The appropriateness of the KDIGO chronic kidney disease definition criteria and classifications in HF has already been substantiated for the threshold eGFR <60ml.min.1.73m². This cut-point has been used in a number of HF studies (Chew et al. 2006; de Silva et al. 2006; Khan et al. 2006) and registries (Heywood et al. 2007; Heywood et al. 2010) to document renal impairment and its significant prognostic association with morbidity, mortality and cost outcomes. What remains from a HF perspective is whether the KDIGO chronic kidney disease criteria will be endorsed by cardiology's HF guidelines development groups and implemented as part of risk factor assessment in community managed HF.

2.4.2 Acute kidney injury

Acute kidney injury, formerly referred to as acute renal failure, has followed a similar pathway to CKD in developing definitions and staging criteria. The RIFLE kidney disease classification scheme for acute renal failure in the critically ill was first published in 2004 (Bellomo et al. 2004). The original RIFLE staging criteria were based on changes from baseline values for serum creatinine and/or percentage eGFR or urinary output where the criterion that resulted in the most severe classification was used. These criteria were developed to define and describe acute or abrupt deterioration of renal function resulting from a broad range of aetiologies in the critically ill (Bellomo et al. 2004). Since the introduction of the RIFLE criteria several revisions have occurred.

The convening of the Acute Kidney Injury Network (AKIN) was a strategy to enable international consensus and endorsement by scientific societies and healthcare organizations for an advanced acute kidney injury definition and criteria, and as a means to fostering a collaborative network (Mehta et al. 2007). AKIN published its definition and criteria for acute kidney injury in 2007 (Mehta et al. 2007). This evidence-based classification and staging definition maintained the components serum creatinine, urinary output and introduced chronicity reflecting aspects of the five stage RIFLE criteria while compressing it to three stages. Importantly the initiation of renal replacement therapy was now subsumed into stage III of the new definition. The use of the AKIN diagnostic system carries a number of caveats flagging the need to assess adequacy of hydration status and eliminate urinary tract obstruction while considering the impact of body mass index, sex and age for serum creatinine values resulting in the option for use of absolute or percentage change for creatinine. AKIN

define acute kidney injury as "*an abrupt (within 48 hours) reduction in kidney function expressed as an absolute increase in serum creatinine of ≥0.3mg/dl (≥ 26.4 µmol/L), a percentage increase in serum creatinine ≥50% (1.5 fold from baseline), or a reduction in urine output documented oliguria < 0.5 ml/kg per hour for more than six hours*" (Mehta et al. 2007)

The most recent revision of AKI definitions was managed under the auspices of the KDIGO and informed by a systematic review of relevant trials published prior to February 2011 (Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group 2012) (Table 2.5). Creatinine values for the diagnosis of AKI remain unchanged while the staging now occurs over 7-days. It is noteworthy that serum creatinine (SCr) and equations for estimating glomerular filtration rate (GFR) feature in the CKD and AKI definitions and their thresholds for diagnosis are the same or very similar to the criteria use in HF worsening renal function incidence, prevalence and outcome studies (Gottlieb et al. 2002; Krumholz et al. 2000). In the case of the AKI definition, urinary output is an additional metric. RIFLE and AKIN criteria have been validated as systems for the diagnosis and staging of AKI through a series of epidemiological studies including many multicentre approaches involving over half a million patients (Kidney Disease, Improving Global Outcomes & Acute Kidney Injury Work Group 2012).

A confounding factor regarding acute kidney injury criteria in hospitalised HF patients is whether the acute changes in serum creatinine and / or eGFR are valid indicators of renal injury and outcomes or a reflection of effective de-congestion therapy (Metra et al. 2011; Núñez et al. 2014). Metra et al. (2011) has reported when defining WRF based on serial serum creatinine measurements alone WRF is not an independent determinant of outcomes in patients with acute HF. They suggest it is an additive prognostic marker only in WRF with persistent congestion. This finding puts into doubt the results of Smith et al. (Smith et al. 2006; Smith et al. 2003) and later Damman et al. (Damman et al. 2009) for any reduction in renal function in HF at any time conveying an increased mortality risk (Damman et al. 2009; Damman & McMurray 2014; Smith et al. 2006; Smith et al. 2003). Conflicting findings highlight the need for further investigation and characterisation of hospitalised WRF.

The AKIN definition carries the caveats to assess adequacy of hydration and eliminate urinary tract obstruction (Mehta et al. 2007). These caveats could be broadened to include monitoring the status of HF congestive signs and symptoms (Gheorghiade et al. 2010) to inform the interpretation of acute serum creatinine changes regarding AKI diagnosis. AKI could still be provisionally diagnosed flagging the need for close renal monitoring during the hospitalised

episode and into the community. Never-the-less the variability in study outcomes may be contributing to the hesitancy by HF professional guideline groups to commit to a consensus definition for WRF. But it also highlights the need to validate definitions in diverse populations and settings and across specialties.

2.4.3 Defining renal dysfunction in heart failure – the evidence

The definition for worsening renal function in HF remains arbitrary (Butler et al. 2010). Given it is more than twelve years since Gottlieb et al. (Gottlieb et al. 2002) identified an in-hospital rise in serum creatinine of >0.3mg/dl (>26.5µmol/L) as having a "*sensitivity of 81% and specificity of 62% for death; 64% and 65% for length of stay greater than 10 days*" it is surprising this remains the case. Forman et al. (Forman et al. 2004) in 2004 confirmed increases in serum creatinine "*were clinically consequential in all subgroups of subjects regardless of baseline or peak serum creatinine level*". Currently the majority of evidence supports the notion that in hospitalised heart failure increments in serum creatinine of ≥0.3mg/dl (≥26.5µmol/L) have a significant impact on 30-day and long term mortality where the increasing severity of renal dysfunction conveys an increased all-cause mortality (Atherton et al. 2012; Brandimarte et al. 2012; Cleland et al. 2012). This threshold for WRF is consistent with the diagnostic threshold for acute kidney injury recommended by AKIN (Mehta et al. 2007).

Several meta-analyses have investigated the association of WRF in heart failure with prevalence and prognosis (Coca et al. 2007; Damman et al. 2007; Smith et al. 2006) (Table 2.3). Damman and colleagues (Damman et al. 2007) and Smith and colleagues(Smith et al. 2006) report prevalence and prognostic outcomes for a broad range of patients with respect to the severity of heart failure and settings including hospital, clinical trial or community-based. Coca's group (Coca et al. 2007) examined 30-day mortality impact of acute kidney injury characterised by small changes in serum creatinine (greater than 10% or greater than 0.3 mg/dl [>26µmol/L]) in hospitalised cardiac surgery or angiography patients, acute decompensated congestive heart failure patients, acutely ill intensive care patients and an a diverse group of hospitalised patients.

Smith's team (Smith et al. 2006) analysed 16 high-quality studies with over 80,000 patients with various degrees of HF severity and an average age of 74-years. The prevalence of renal impairment for all categories of patients at baseline was determined using serum creatinine, creatinine clearance or estimated glomerular filtration rate or cystatin-C. Renal impairment (RI) was most commonly defined as a glomerular filtration rate of < 60mL.min. Yet for the

analysis, RI was classified as 'any' (eGFR <90mL.min) or 'moderate to severe' (eGFR <53mL.min) and additionally as worsening renal function for hospitalised patients (Table 2.3). All-cause mortality findings suggested a linear relationship for renal function and mortality risk when renal impairment was expressed as a continuous variable for either serum creatinine or eGFR. Mortality risk increased either by '33% per 1mg/dl creatinine increase in three studies or by 7% per 10ml/min eGFR' decrease in two of the randomised control trials.

Damman et al. (Damman et al. 2007) sought to determine the proportion of HF patients with worsening renal function and the association with hospitalisations and mortality. They defined worsening renal function as a fall in eGFR of ≥5ml.min.1.73m² or increase in serum creatinine of ≥0.2mg/dl (≥17.7µmol/L) as these limits identify normal physiological variability. Severity of WRF was categorised as class I to III to enable assessment of outcome against commonly used thresholds for defining WRF (Table 2.3) and aligned with those used by Smith et al. (Smith et al. 2003) to define the sensitivity and specificity of various WRF definitions.

All-cause mortality and hospitalisation linked to WRF were calculated based on a minimum 6-month follow-up. The total all-cause combined mortality odds ratio was 1.62, 95% CI 1.45 – 1.82, $P < 0.001$ for patients with worsening renal function increasing with severity of WRF, and substantially increasing when eGFR fell by >9mls.min.1.73m² or serum creatinine increased by 0.5mg/dl (44µmol/L). All-cause hospitalisations OR 1.30, 95% CI 1.04 – 1.62, $P = 0.022$. A trend towards a linear relationship between baseline renal function and worsening of renal function was also observed supporting the findings of Smith et al. (2006). Of interest is the 6-month mortality odds ratio (OR) for hospitalised versus community HF patient showed no real difference; OR = 1.61, 95% CI 1.35 - 1.93, P < .001 compared to OR = 1.69, 95% CI1.45 - 1.94, P < .001 respectively. One concerning factor is the time variations within definitions for change in the biomarkers. This was a factor of length of hospital stay blurring the nature of what could be considered acute.

The meta-analysis of Coca and colleagues (Coca et al. 2007) described the importance of small acute reductions in kidney function and 30-day mortality in a variety of hospitalised patients. Their objective was to determine the nature of the relationship between WRF and short-term mortality in study populations and settings that were heterogeneous. Over 78,000 patients with an age range of 53 to 72 years were included in the analysis. A 'small' serum creatinine change during hospitalisation was defined as '*any change beyond that expected by normal variations in laboratory measurements'* which is similar to the approach of Damman. Coca's (Coca et al. 2007) results show an association between small increases in serum creatinine and

short-term mortality unadjusted RR 1.8, (95% CI 1.3 – 2.5) and 2.3 (95% CI 1.8 - 3.0) when these increases are in the order of 10-24% or 0.3 to 0.4mg/dl [26-35µmol/L] respectively.

Importantly, the similarity in the thresholds used to define WRF in these meta-analyses involving a diversity of heart failure presentations is closely aligned with the diagnostic criteria and staging for AKI presented in the RIFLE and AKIN definitions. This suggests the possibility for continuity for criteria for defining renal dysfunction of an acute nature in diverse populations. This proposition is supported by the investigation of Roy and associates (Roy et al. 2013) who compared the outcome predictive ability of the traditional definitions for acute kidney injury (RIFLE, AKIN & KDIGO) and the often used worsening renal function definition (serum creatinine rise of ≥0.3mg/dl) in a single centre cohort of hospitalised heart failure patients. They found predictive ability between definitions was only marginal but that AKIN, RIFLE and KDIGO acute kidney injury classification systems have the advantage over the commonly used worsening renal function in HF definition as they include in their definition criteria a severity scale. This additional feature enhanced the ability of the clinician to identify those patients at greatest risk of adverse events.

Analysis of the scientific literature addressing AKI and CKD definitions and nomenclature suggest there are more similarities than disparities across medical genre definitions. Renal impairment could be used to describe an admission or baseline renal function or to describe transient renal dysfunction where on-going patient monitoring failed to establish the diagnosis of CKD and its stage. The adoption of the KDIGO acute and chronic definitions and nomenclature or the adoption of AKIN definition for AKI in HF would offer a solution to the arbitrary nature of defining these conditions in HF and assist with improved communication and the knowledgebase through meta-analyses and validation of the definitions in HF populations and diverse settings.

2.5 Biomarkers

The role of a biomarker is to identify normal or pathogenic processes, or the response to a therapeutic intervention; but it does not need to be involved in the disease process (Tesch 2010). Both serum creatinine and eGFR are central to the diagnosis and staging of CKD, AKI and worsening renal function in spite of limitations and the arrival of several promising new renal biomarkers (Damman et al. 2012).

Serum creatinine has remained as the renal ‘gold standard’ biomarker contingent on the ease with which it can be obtained, its low cost, clinician familiarity with its interpretation and the evidence to support its use in the clinical setting. Studies investigating the impact of worsening

renal function in HF are not an exception to this approach. (Akhter et al. 2004; Cowie et al. 2006; Forman et al. 2004; Gottlieb et al. 2002; Krumholz et al. 2000). Other biomarkers such as blood urea nitrogen (BUN) (Heywood et al. 2007) and serum cystatin-C (Aronson, Mittleman & Burger 2004) have also been used to assess renal function in HF. They too were found to be strong prognostic markers.

BUN has been shown to correlate with HF outcomes (Aronson, Mittleman & Burger 2004). In post hoc analysis of OPTIME-HF registry a BUN increase over baseline hospitalisation value of 10mg/dl or more was an independent predictor of 60-day mortality (Klein et al. 2008). Cystatin-C has been assessed as a serum and urinary biomarker for differential diagnosis of AKI, early detection of AKI and prognosis (Coca et al. 2008). As a standard care renal biomarker cystatin-C is disadvantaged in comparison to serum creatinine by cost and paucity of physicians familiar with its normal values or use in eGFR formula (Damman et al. 2012).

Traditional renal biomarkers provide no information for site or cause of dysfunction. They may be influenced by nutrition, muscle mass, gender, medication and clinical issues. Blood urea nitrogen levels are subject to liver function, gastrointestinal bleeding, dehydration, steroid use and protein intake (Tesch 2010). Cystatin-C levels can be affected by thyroid dysfunction or steroid use and lack specificity in the circumstances of concurrent infection or inflammation (Damman et al. 2012) both of which may be antecedents to HF hospitalisation compromising the cystatin-C result.

Serum creatinine limitations include its slow response compared to the new, novel renal biomarkers. It is effected by age, gender, race, body mass, diet and the patient not being in a steady physiological state (Damman et al. 2012). These limitations have encouraged researchers to look for biomarkers that are more sensitive to renal damage, site of injury and can detect changes before the development of renal dysfunction (Carubelli et al. 2012).

2.5.1 Focus on diagnosis

Several novel renal biomarkers are showing promise for detecting WRF in HF. They include neutrophil gelatinase-associated lipocalin (NGAL), Interleukin-18, Kidney injury molecule-1 (KIM-1) and N-Acetyl-ß-D-glucosaminidase (NAG) (Cole et al. 2012). NGAL is the product of toxic or ischaemic injury to the kidney and can be measured in urine or plasma. In CHF it's urinary value has been shown to be associated with increased mortality risk(Metra et al. 2012). Both KIM-1 and NAG are urinary biomarkers for proximal tubular injury in AKI. These biomarkers have been studied in HHF and been associated with increased risk of

hospitalisation and death independent of eGFR (Damman et al. 2011). Interleukin-18 in the context of AKI will increase before that of serum creatinine but it has not been evaluated in HF; it also has the disadvantage of increasing with inflammatory conditions (Metra et al. 2012). Despite the promising results from these new biomarkers, they have not replaced serum creatinine in standard care. This is mainly due to their cost and availability.

2.6 Estimated glomerular filtration rate (eGFR) equations

Glomerular filtration rate (GFR) is recognised internationally as the best overall index of kidney function (Eknoyan & Levin 2002). It is the product of the filtration rate of the kidney's nephrons (Stevens & Levey 2005) usually reported in millilitres per minute (ml/min). GFR is not routinely measured in clinical practice due to time requirements, complexity and costs. Rather clinicians rely on equations to estimate glomerular filtration rate (eGFR). Creatinine-based prediction equations are the most common. Current clinical practice tends to favour the Cockcroft-Gault equation (Cockcroft & Gault 1976) for estimated creatinine clearance (CrCl) measured in millilitres per minute; the Modification of Diet in Renal Disease (MDRD) (Levey et al. 1999) equation and the most recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey et al. 2009) formula.

The MDRD and CKD-EPI formulae standardise to population mean body surface (BSA) of 1.73m². An important consideration when using the Cockcroft-Gault formula is it estimates creatinine clearance instead of GFR and it requires a 24-hour urine collection. Because creatinine is not only filtered by the glomeruli but also secreted by the tubules, creatinine clearance overestimates the GFR (Botev et al. 2009). The following table **(**Table 2.5**)** provides a timeline for the development of these equations and the variables they include.

Table 2.5 Creatinine-based eGFR prediction equations

Equation	Date	Biomarkers	Variable 1	Variable 2	Variable 3	Comments
Cockcroft-Gault (CGE) (CrCl): estimates creatinine clearance (GFR) Reported as: mL.min.	1976	SCr	age	24-hour urine collection required	gender lean body weight	- validated in HF - age bias - more precise in mild CKD
Modification of Diet in Renal Disease (MDRD) Reported as: mls.min.1.73m² (BSA)	1999	SCr SU SAlb	age	population mean BSA	gender race	- systematic underestimation of GFR when GFR >60ml.min.1.73m² (McAlister et al. 2012) - validated in HF - age bias
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Reported as: mls.min.1.73m² (BSA)	2009	SCr for min/max SCr value for gender	age	population mean BSA	gender race	- validated in HF - age bias

Abbreviations: SCr= Serum creatinine; SU: serum uric acid; SAlb: serum albumin BSA = body surface area; min: minimum; max: maximum.

Serum creatinine is a core element in eGFR equations and although equations adjust for some of the variables that impact creatinine such as age, gender and race, estimates of GFR should be interpreted with caution (Michels et al. 2010). An additional concern with eGFR is the under representation or non-representation in test populations of the elderly in the development of the CGE and MDRD equations and limited representation in the CKD-EPI. These issues should be considered when investigating WRF in HF as the vast majority of participants in these studies are aged over 65 years (Rich 2001) and eGFR usually declines with increasing age (Lindeman, Tobin & Shock 1985). Nevertheless, the MDRD formula up until recently had been the preferred eGFR equation in HF having been validated in this population (Smilde et al. 2006), however the CKD-EPI has now been validated for HF and is more accurate under some circumstances (McAlister et al. 2012). For all commonly used equations it should be kept in mind age remains a source of bias (Michels et al. 2010).

Finally, diminished renal reserve indicates a reduced capacity of the kidneys to adjust to an altered clinical state or change in medication regime. Negative changes observed in serum creatinine or eGFR even if not diagnostic can be indicative of a lack of renal reserve as it is known serum creatinine only increases in the advanced stages of renal dysfunction (Carubelli et al. 2012). The monitoring of renal biomarkers is an important management observation as it may help identify those at risk of progressing to AKI, CKD and adverse outcomes. Renal dysfunction also signals the need for caution regarding medication management. Such insights could be the rationale informing the approach taken by the cardiology international guideline groups with respect to drug therapy advice (McMurray et al. 2012b; Yancy et al. 2013).

2.7 Outcomes

No matter the outcome of interest, the literature demonstrates worsening renal function is associated with adverse outcomes in HF (Heywood et al. 2007; Hillege et al. 2000; Jose et al. 2006; Krumholz et al. 2000; Smith et al. 2003). All-cause mortality (Hillege et al. 2000; Krumholz et al. 2000), including cardiovascular death (Hillege et al. 2006; Jose et al. 2006; Smith et al. 2006), in-hospital mortality (Amsalem et al. 2008), 30-day mortality (Coca et al. 2007), community-based mortality (Bibbins-Domingo et al. 2004), hospitalisation rates (Damman et al. 2009) and hospital length of stay (Forman et al. 2004) are negatively impacted when renal dysfunction is present in HF. Even small acute increments in serum creatinine in the order of 10-24% or 0.3 to 0.4mg/dl [26 - 35µmol/L] in a diverse group of hospitalised cardiovascular and critically ill patients resulted in a 30-day mortality RR of 1.8 and 2.3 respectively (Coca et al. 2007). HF patients with CKD or acute kidney injury are also at risk of progression to end-stage renal failure (Levey et al. 2011; Singbartl & Kellum 2012).

The reported morbidity and mortality outcomes are influenced by the definition for renal dysfunction. Worsening renal function defined as a serum creatinine (sCr) increase of ≥26.5µmol/L (≥0.03mg/dl) as compared to ≥44.2µmol/L (≥0.05mg/dl) will result in different sensitivity and specificity for predicting mortality; a more restrictive definition (i.e. the higher serum creatinine cut-off) sees sensitivity decreased while specificity is increased (Butler et al. 2010; Smith et al. 2003). As shown in the summary table of key references for renal function in heart failure (Table 2.4) authors have used multiple definitions for WRF. Definitions have been based on serum creatinine, creatinine clearance, various eGFR grouping ranges and cystatin-C to quantify morbidity and mortality outcomes. Where authors have provided groups based on increments in the biomarker for the degree of severity it can be seen that the greater the

severity of renal dysfunction the greater the negative impact on the outcomes of interest (Bibbins-Domingo et al. 2004; Heywood et al. 2007; Klein et al. 2008; Maeder et al. 2012).

Hospital re-admissions and length of hospital stay are common morbidity outcomes for WRF in HF (Akhter et al. 2004; Cowie et al. 2006; Damman et al. 2009; Gottlieb et al. 2002; Smith et al. 2003; Verdiani, Lastrucci & Nozzoli 2010). Generally, such studies find a significant relationship between WRF in HF and the outcome of interest. However, several studies have questioned this relationship. Verdiani and colleagues (Verdiani, Lastrucci & Nozzoli 2010) found no difference for rehospitalisation, length of stay or mortality for WRF in HF. Cowie et al. (Cowie et al. 2006) studied the prevalence and outcomes associated with WRF in acute decompensated heart failure with reduced ejection fraction (HFrEF). They observed WRF was common in ADHF yet only those who experience major in-hospital complications (sepsis, acute coronary syndrome, cardiac arrest, hypotension or circulatory shock) and develop WRF experience significant increased length of stay, but similar mortality and re-hospitalisation rates compared to those without WRF.

A central linking factor for the Cowie and Verdiani studies is their WRF definitions. Both studies defined WRF as an increase in serum creatinine of more than 26µmol/L (>0.3mg/dl) from baseline during hospitalisation. This definition allowed for a variety of time intervals to determine WRF as it was dependent on the duration of hospitalisation for the increase in the biomarker. This raises the question of 'transient' renal dysfunction as Verdiani notes or the potential of acute on chronic renal decline and the importance of the WRF definition for interpreting the data. Metra and colleagues (Metra et al. 2011) question the role of congestion with the development of hospital stay WRF. They and others (Núñez et al. 2014) suggest worsening renal function in hospitalised HF only becomes significant for mortality outcomes when congestion persists or where renal impairment is present on admission.

The systematic review by Butler et al. (Butler et al. 2010) continues the theme for characterisation of WRF. They examined the effect of renal impairment (RI) and WRF in ADHF patients for a range of definitions and the association with short and long term health outcomes and resource expenditure. They grouped the studies by definition biomarker and by study design. Reporting renal insufficiency (chronic kidney dysfunction/ renal impairment), they found the majority of studies described increased readmissions, were as for WRF the finding was inconsistent. However, for both RI and WRF they found significant increases in length of stay. They note the need to establish consensus definitions for RI and WRF in heart

failure in order to strengthen the research into the cardio-renal relationship and its characterisation.

2.8 Demographics

Demographic information is frequently used to characterise the cohort under investigation contextualising the findings. Quantifying the extent of both acute WRF and CKD in HHF or community-based CHF patients is difficult when cardiology clinical practice guidelines have not recommended CKD and AKI classification and staging criteria. Multiple definitions for chronic or acute WRF results in significant variability for the outcomes as already noted in the preceding discussion. Accurate depiction for the WRF demographic is as a consequence limited. To address what is known of the demographic for worsening renal function in HF the discussion begins with the evidence for CKD in HF in the hospital and community settings. Acute WRF in hospitalised HF is then addressed. Where the information is available, reference is made to the type of HF as either HF with preserved ejection function (HFpEF) or with reduced ejection fraction (HFrEF). Other demographic variables are discussed under predictors due to their cardio-renal impact.

2.8.1 Chronic kidney disease/ renal impairment in hospitalised heart failure

Chronic kidney disease in hospitalised HF (HHF) is common (Blair et al. 2011; Damman et al. 2007; Heywood et al. 2007). Reports frequently suggest more than fifty percent of HHF patients will have a level of renal dysfunction (eGFR <60ml.min.1.73m^2) consistent with a diagnosis of CKD (Heywood et al. 2007; Khan et al. 2006). This statistic highlights CKD as comorbidity and prognostic indicator in chronic heart failure (CHF). However, some of the study data infer CKD; reporting a single eGFR admission or baseline value as renal impairment/ chronic renal insufficiency (Chew et al. 2006; Damman et al. 2009; Khan et al. 2006). This occurred most recently in and up-dated meta-analysis by Damman et al (Damman, Valente, et al. 2014) resulting in several definitions for baseline renal function tabulated in summaries labelled chronic kidney disease. The trend has seen these types of studies reporting eGFR against CKD criteria for CKD stage but there is no assurance the timeframe metric for chronicity has been met. Such reporting of renal dysfunction leaves the status as acute or chronic ambiguous making it difficult to correctly characterise the renal impairment and interpret the findings. Once again, attention is drawn to the need to standardise definitions and the nomenclature. Nevertheless, it has been demonstrated HHF patients with reduced

renal function on admission are at greater risk for in-hospital WRF and its associated outcomes (Chew et al. 2006; Damman, Tang, et al. 2014; Núñez et al. 2014).

2.8.2 Chronic kidney disease in heart failure: the community setting

The recognition of CKD in community managed HF patients is an important quality, safety and outcome issue. Renal function status can influence choice and dose of drug therapies and identify HF patients at increased risk of adverse outcomes, including in-hospital WRF. The prevalence, incidence and relationship of renal impairment (RI) or worsening renal function and outcomes from registries (Heywood et al. 2007; Heywood et al. 2010) and in community managed CHF have been reported (Bibbins-Domingo et al. 2004; Damman et al. 2009; de Silva et al. 2006; Khan et al. 2006; Maeder et al. 2012; McAlister et al. 2004). In all of these studies, there was a consistent finding of increased mortality risk with increasing severity of renal dysfunction. A baseline eGFR of <60mls.min by any eGFR equation signals an increased risk for in-hospital WRF (Damman et al. 2009). Authors (Butler et al. 2010; Chew et al. 2006; Dries et al. 2000; Hillege et al. 2000; Owan et al. 2006) who reported outcomes against the baseline eGFR metric consistently observe adverse outcomes and increased costs associated with hospitalisation.

Nevertheless, the extrapolation of clinical trial data to real world management is problematic. As a consequence, there is an increasing emphasis on registry studies and community managed CHF patients with renal impairment. Analysis of the Acute Decompensated Heart Failure National Registry (ADHERE) (Heywood et al. 2007) using the abbreviated Modification of Diet in Renal Disease eGFR formula found only 9.0 % of the 118,465 HHF patients had normal renal function (GFR ≥90 mL.min.1.73 m^2) at the time of admission. In this cohort, approximately 64% were recognized as having CKD when defined as a baseline eGFR of <60ml.min.1.73m^2. It is not unreasonable to credit the outcomes in these HHF patients to chronic renal dysfunction rather than to acute worsening of renal function during hospitalisation as RI is not an outcome of the admission. Such patients are known to be at greater risk of acute WRF (Akhter et al. 2004; Damman et al. 2007). The Achilles' heel of this statistic is the inability to confirm the chronic or acute nature of the renal dysfunction if determined solely on a baseline or admission eGFR value.

The *post hoc* analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trial by Khan and colleagues (Khan et al. 2006) is no exception to these findings even with its stringent exclusion criteria of SCr >2.5mg/dl (>177mmol/L). In this cohort, 33% of the participants had baseline RI when defined as an eGFR <60ml.min.1.73m^2; 86% were male and their mean age was 60 (±10)

years. A unique feature of this study was the use of the Kidney Disease Outcomes Quality Initiative (K/DOQI) (Eknoyan & Levin 2002) classification system for categorizing kidney impairment in HF. The study findings support the use of eGFR as a potent predictor of mortality in an independent, high-risk population. They found that approximately one third of their cohort experienced a significant decline in eGFR at 1-year follow-up where a rapid rate of decline of >15ml.min eGFR for the 12-month period was a strong prognostic marker for mortality risk resulting in an adjusted HR 5.63 (CI 4.90 – 5.46) *P*<0.0001.

In women with either HFrEF or HFpEF, there appears to be an equal likelihood for developing significant renal dysfunction (Bibbins-Domingo et al. 2004). Secondary analysis of a subset of women from the Heart and Estrogen/progestin Replacement Study (HERS)(Bibbins-Domingo et al. 2004) informs our understanding of the independent association of renal insufficiency and mortality risk in 702 women with HF in community settings. Bibbins-Domingo etal defined renal insufficiency (RI) using the Cockcroft-Gault equation to estimate creatinine clearance (CrCl) and calculated mortality in these women mean age 66.7 (±6.7) years stratified by preserved (HFpEF) or depressed (HFrEF) systolic function (EF≤50%). They found CKD was common in these women and the severity of CKD increased the mortality risk. HF with reduced or preserved ejection fraction was equally impacted; mortality risk independent of a history of diabetes or hypertension.

A prospective observational study by McAlister and colleagues (McAlister et al. 2004) investigated the prevalence, prognostic importance, and impact of renal insufficiency and the benefits of ACE inhibitors and ß-blockers in community-dwelling patients with HF. In this predominately male cohort of 754 CHF patients with a median age 69-years baseline CKD was determined using the Cockcroft-Gault equation (CrCl <60mL.min). They found CKD was common being present in more than half the cohort. This non-trial study which included patients with either systolic or diastolic dysfunction confirmed survival was significantly associated with creatinine clearance (log rank 27.98, *P*<0.0001), even after adjusting for other risk factors. They also confirmed in patients with and without mild to moderate renal insufficiency ACE inhibitors and ß-blockers are safe, and have a survival benefit.

In community-managed elderly CHF patients with advanced HF and a significant co-morbidity burden renal dysfunction is less well characterised (Maeder et al. 2012). Maeder et al. (Maeder et al. 2012) in a *post hoc* analysis of the Trial of Intensified Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) investigated such a cohort. A feature of this study was the average age of the participants 77 (±8) years. The primary outcome of interest was all-

cause mortality at 18-months follow-up. Baseline analysis identified 64% of the cohort to have at least stage 3 CKD. To define WRF they classified WRF by serum creatinine increases of >0.2mg/dl (WRFI), >0.3 mg/dl (WRFII), or >0.5 mg/dl (WRFIII) occurring within the first 6 months. This definition resulted in an incidence of 12%, 19%, and 22%, respectively for the 3 classifications. Outcome events assessed at 18-months found only HF patients with WRF III had a significant mortality risk, hazard ratio 1.98 [95% CI 1.27-3.07, P < .002] versus no WRF.

Conclusions drawn from the examination of the scientific literature addressing CKD in community-managed CHF are:

- it is common
- effects both men and women
- it is prevalent in both HFrEF or HFpEF, and
- it is a powerful prognostic indicator.

The utility of KDIGO criteria for defining and classifying CKD in this population is supported. The need for clinical practice guideline development groups to endorse and reference KDIGO chronic kidney disease definition and staging criteria is an important step for raising awareness of this significant condition in CHF.

2.8.3 Worsening renal function in hospitalised heart failure

A limitation in characterising renal dysfunction in hospitalised HF as with community patients is the investigator determined definitions and severity grading criteria. This situation may have come about as much of the published cardio-renal research is founded on the analysis of data collected for other purposes. Retrospective analysis of observational studies (Heywood et al. 2007; Krumholz et al. 2000; Owan et al. 2006), post hoc (Akhter et al. 2004; Klein et al. 2008) or secondary analysis of randomised control trials (RCTs) (Aronson, Mittleman & Burger 2004; Hillege et al. 2000) or data from HF registries (Atherton et al. 2012; Heywood et al. 2007; Heywood et al. 2010) have been the major sources for the cardio-renal research literature. A feature of many of these studies is that they are hospital based, focus of HF with reduced ejection fraction (HFrEF), set stringent inclusion and exclusion criterion eliminating many potential cardio-renal patients. Subsequently the data for acute WRF is limited by what information is available to the WRF definition. This has led to variation in biomarkers and duration for defining the condition compounding the difficulties when characterising acute kidney injury in hospitalised HF.

Variations in determining WRF have the potential to introduce bias and misclassification. To help identify appropriate definitional criteria several researchers have tested the comparative sensitivity and specificity of various definitions of WRF in heart failure (Gottlieb et al. 2002; Smith et al. 2003). These studies and the acute kidney injury definitions used by nephrologists and intensivists (Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group 2012) inform the following discussion and highlight the potential for AKI/ hospital WRF definitional synergy.

The most common duration metric for defining WRF has been any time within the hospital admission (Akhter et al. 2004; Gottlieb et al. 2002; Krumholz et al. 2000; Owan et al. 2006; Smith et al. 2003). Yet data have shown that the vast majority of WRF (increase in the renal biomarker) occurs early after hospital admission, within the first few days (Forman et al. 2004; Gottlieb et al. 2002; Smith et al. 2003). Gottlieb et al. (Gottlieb et al. 2002) studied the prognostic importance of various definitions of WRF in hospitalized congestive heart failure (CHF) patients. Fifty one percent of their cohort was male and the mean age was 67 (±15) years. Gottlieb's group evaluated definitions determined during hospitalisation by either absolute (0.1 to 0.5mg/dl) or percentage (10% to 50%) increments in serum creatinine alone or in combination with renal impairment which was identified as a baseline serum creatinine of 1.5mg/dl (>133μmol/L) or 2.0mg/dl (177μmol/L). Their research predicted both in-hospital mortality and length of stay > 10 days. The threshold of 0.3mg/dl (26.5μmol/L) SCr increase had a sensitivity of 81% and specificity of 62% for death and 64% and 65% for length of stay greater than 10 days. They also observed WRF frequently occurred by day 3 with very few patients subsequently developed renal decline.

The investigation by Smith and associates (Smith et al. 2003) was to determine the optimal definition of clinically significant WRF in hospitalised heart failure patients. Fifty one percent of their cohort was male and the mean age was 72 (±11) years. They studied various creatinine definitions for WRF and their association with mortality, re-admissions and functional decline at 6-months post discharge. Serum creatinine values at discharge, admission and peak value were considered against increases of ≥0.1, ≥0.2, ≥0.3, ≥0.4 and ≥0.5. A percentage increase in serum creatinine of 25% from admission value to a peak value of less than 2.0mg/dl (176.8μmol/L) was also used to define WRF. As expected the frequency of WRF varied by definition. When defined as a SCr increase of ≥0.5mg/dl (44.2μmol/L), the most restrictive definition, 24% developed WRF compared to 75% with the most inclusive definition ≥0.1mg/dl (8.8μmol/L). They found the more restrictive the WRF definition in terms of absolute increase

in serum creatinine the stronger the association with death. Irrespective of the SCr value used, admission, peak or discharge value independently predicted mortality in unadjusted analysis but disappeared when WRF was added. The threshold of ≥0.3mg/dl (≥26.5μmol/L) was supported as sufficiently inclusive to be of value in detecting adverse outcomes. They suggest WRF could be considered as a continuous variable with a continuous spectrum of risk.

The studies by Gottlieb et al. and Smith et al. investigated the optimal or clinically significant WRF definition using absolute and relative increments in serum creatinine for hospitalised HF against several outcomes including length of stay, in-hospital and 6-month mortality. Both studies reported the severity of the renal dysfunction effect outcomes. Yet without testing severity staging as such, their results demonstrated the significance for various stratification models for WRF definitions in predicting outcomes. These findings highlight the similarities with the KDIGO acute kidney injury definition and staging criteria.

The KDIGO have published acute kidney injury guidelines which provide definition and classification criteria for acute kidney injury (Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group 2012). Their definition for the diagnosis of AKI includes an increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/L) within 48 hours. In addition, there are staging criteria for AKI severity based on absolute or percentage increase in serum creatinine. All these criteria are very similar to those identified and discussed above regarding the comparative sensitivity and specificity of various definitions of WRF in heart failure and flag the potential for cardiology, specifically HF to adopt the HDIGO definition. AKI definition could be modified to allow a slightly longer timeframe of a 72 hour informed by the WRF heart failure literature (Gottlieb et al. 2002; Smith et al. 2003). Acute kidney injury would be diagnosed, graded by the SCr increment, and defined according to CKD criteria where it persisted for more than 3 months. These are relevant considerations as unrecognised renal impairment and its significance threatens HF patient outcomes.

Unidentified and unmonitored CKD in HF is prevalent. As significant as the ADHERE data for renal impairment are, Heywood (Heywood et al. 2007) reported RI went un-diagnosed in approximately 26% of men and 40% of women. This situation has been confirmed in a study by Amsalem and colleagues (Amsalem et al. 2008). Their analyses of a prospective survey engaging 25 public hospitals in Israel found RI was not diagnosed in 41% of the 57% of HF patients with criteria for CKD. Unrecognized RI was most common in women, the elderly, and those with better New York Heart Association (NYHA) functional class, compared with patients with recognized RI. The extent of undiagnosed renal dysfunction in either community or

hospitalised HF draws attention to the need to interpret prevalence and predictors data with caution.

2.9 Prevalence

The prevalence of WRF in heart failure is primarily dependent on the definition of worsening renal function. Where the definition has a low diagnostic threshold for acute WRF prevalence will be higher compared to those requiring a greater change in the renal biomarker (Gottlieb et al. 2002; Smith et al. 2003). Diversity in patient populations, settings and timeframes for the diagnosis will likewise contribute to variability in prevalence. Given these circumstances worsening renal function and chronic kidney disease prevalence are variously estimated to be 11% to 45% (Damman et al. 2009; Smith et al. 2003; Verdiani, Lastrucci & Nozzoli 2010) and 33% to 64% (Heywood et al. 2007; Khan et al. 2006) respectively.

2.9.1 Acute worsening renal function in hospitalised heart failure

Examining the studies for WRF in hospitalised HF patients at the prevalence continuum extremes reveals some interesting findings. Verdiani et al. (Verdiani, Lastrucci & Nozzoli 2010) using a serum creatinine increase of ≥0.03mg/dl (≥26.5µmol/L) reports a WRF prevalence of 11%, while Smith et al. (Smith et al. 2003) using the same serum creatinine increase reports prevalence of 45%. In terms of the WRF definition, the serum creatinine threshold is their only common metric. Variation occurs for the time-at-risk in which the biomarker change is used for determining WRF. Verdiani use the baseline (admission) and discharge serum creatinine values whereas Smith's team compare baseline, discharge and peak serum creatinine. Verdiani et al. (Verdiani, Lastrucci & Nozzoli 2010) suggest that "…*transitory increase in serum creatinine (or eGFR) which did not persist till the moment of discharge were not classified as WRF"* hence the relative low prevalence.

2.9.2 Chronic kidney disease in hospitalised heart failure

The prevalence of chronic kidney disease in HF varies from 33% (Khan et al. 2006) to 64% (Heywood et al. 2007). The Khan et al. study with a 33% prevalence of CKD was a *post* hoc analysis of the previously mentioned the SOLVD trial. This trial had stringent exclusion criteria for baseline 'SCr >2.5mg/dl (>177mmol/L)' which can explain the low CKD prevalence. The Australian study by Chew and colleagues (Chew et al. 2006) investigated the relationship between renal impairment defined as baseline eGFR <60ml.min.1.73m² and morbidity, mortality and economic outcomes in patients admitted to a cardiac intensive care. They also found a CKD prevalence of 33%, these patients notable in carrying the greater portion of the mortality and morbidity burden.

2.9.3 Chronic kidney disease in community-managed heart failure

Registry data has become an important source of data to inform our understanding of the prevalence of chronic kidney disease in community-managed HF. An outpatient HF registry study from Norway reported a CKD prevalence of 44.9% (Waldum et al. 2010). For this cohort there were 3,605 participants of which 70.1% were male with a median age 73-years. Other large CKD in HF prevalence studies have accessed data from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) (Heywood et al. 2010) and ADHERE HF (Heywood et al. 2007) registry. The IMPROVE HF (Heywood et al. 2010) registry is a United States based registry from which Heywood extracted data collected between 2005 and 2007 to quantify the degree of renal dysfunction in CHF. Of the 13,164 participants eligible from IMPROVE data 52.2% were classified as having at least CKD stage III (eGFR<60ml.min.1.73m^2). Finally, the ADHERE (Heywood et al. 2007) database with data for 118,465 HF participants revealed 64% of its registrants met criteria to classify them as having CKD. These are staggering statistics and underscore the importance of renal dysfunction in HF and the importance of identifying the predictors for this complication.

2.10 Predictors of worsening of renal function in hospitalised heart failure

Since the study of Hillege etal (Hillege et al. 2000) which established renal function as a predictor of mortality in HF there has been a resurgence of interest in the cardio-renal relationship. Krumholz and colleagues (Krumholz et al. 2000) were among the first to look for predictors for WRF in hospitalised HF patients. Their retrospective medical record audit identified women, systemic hypertension, admission rales >basilar, pulse rate >100bpm, systolic blood pressure (SBP)>200mmHg and admission serum creatinine >1.5mg/dl (>133µmol/L) as predictors for in-hospital WRF. Other investigators have identified additional WRF predictors or risk factors. Butler et al (Butler et al. 2004) found a history of diabetes and heart failure were predictors while Maeder et al (Maeder et al. 2012) observed patients on high dose loop diuretics and/ or aldosterone antagonists at the time of hospitalisation were more likely to develop WRF defined as a serum creatinine increase of ≥0.5mg/dl.

Hospital presentation examination findings can assist in identifying HF patients at increased risk of adverse outcomes including WRF. Among the most important are advanced age and renal function at the time of presentation. In females the retrospective analysis of the HERS (Bibbins-Domingo et al. 2004) data revealed women with more severe renal dysfunction were older, more likely to have elevated systolic blood pressure, a history of coronary artery bypass grafting, more likely to be taking digoxin and diuretics, and less likely to be taking beta-

blockers, and had a lower body mass index. Women with preserved or depressed ejection fraction were equally at risk. McAlister et al. (McAlister et al. 2004) in a mixed gender cohort has confirmed WRF is an independent prognostic factor in diastolic and systolic dysfunction and more recently using the CKD-EPI equation more accurately categorises mortality risk where renal function is more closely related to outcomes in HFrEF than in HFpEF (McAlister et al. 2012).

Studies where males dominated the cohort show similar predictor relationships to HERS findings. Breidthardt et al. (Breidthardt et al. 2011) reported CKD on admission to be the only independent predictor of WRF. Forman et al. (Forman et al. 2004) identified several factors strongly associated WRF including elevated serum creatinine (>1.5mg/dl [133µmol/L]) , SBP >160mmHg; and a history of HF and medication managed diabetes. Anaemia and serum sodium levels have also been implicated in the development of WRF (Klein et al. 2008).

When examining the characteristics for the Smith and Verdiani study cohorts it is difficult to identify why they should differ regarding mortality outcomes for WRF when they defined WRF as SCr≥0.3mg/dl (≥26.5µmol/L). For this threshold, Smith reported an adjusted HR of 1.67 at 6-months follow-up yet Verdiani found no significant difference for 1, 6 or 12 months of follow-up. In terms of comorbidity burden, the cohorts are similar. Smith and Verdiani report a history of HF and diabetes of 72% versus 62%, 47%, and 33% respectively; the mean ejection fraction (EF) 39% versus 39.6% and admission renal impairment in 25% and 28% respectively when defined as an admission serum creatinine of ≥2.0mg/dl (≥177µmol/L) and >1.5mg/dl (≥133µmol/L) in turn. Differences occur regarding when data was collected and the mean age for the cohorts. Smith's team initiated data collection in 1998, the cohort having an average age of 72 (±11) years. Verdiani et al began patient recruitment in 2002; the average age of their participants was 77.9 (±10.1) years. The supposition could be made that the more recent cohort may have benefited from improved comorbidity management or that those with more advanced HF had already died reducing the number susceptible to WRF.

Consistent findings from the individual studies (Breidthardt et al. 2011; Butler et al. 2004; Cowie et al. 2006; Hillege et al. 2000; Smith et al. 2003) and meta-analyses (Damman et al. 2007; Smith et al. 2006) is the robust relationship between baseline creatinine, in-hospital WRF and adverse outcomes. This observation highlights the importance of routine monitoring of serum creatinine and underscores the significance of recognising CKD in community-based CHF management.

Many of the above predictors or risk factors for acute WRF are also known risk factors for cardiovascular disease and CKD. A history of hypertension, diabetes, dyslipidaemia and obesity increase the risk to develop either or both CKD and CVD. Albuminuria, ethnicity and exposure to nephrotoxic agents such as angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blocker (ARBs) and to a lesser extent diuretics and mineralocorticoid receptor antagonists (MRAs) have been associated with the progression of renal dysfunction (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013) and have been previously discussion.

2.11 Summary

The worsening of renal function, whether a new finding or superimposed on already diagnosed chronic kidney disease (CKD), requires definitive monitoring and treatment as it portends adverse outcomes. In this literature review under the outcome and preceptor themes confirmation of renal dysfunction as a prognostic indicator in HF has been established. The lack of a standardised definition for WRF and the degree of dissonance across medical specialty guidelines is problematic. Without international consensus for defining the various manifestations of WRF in HF, (chronic, acute and transient) interpreting data is challenging as it may lead to inappropriate management strategies and risk patient outcomes. The biomarker and eGFR equation to define WRF in HF is dependent on the preference of the investigator limiting comparison of data. This choice influences predictor and prevalence findings and our understanding of WRF.

Specialty based issues and the compartmentalisation of knowledge challenge comprehensive care, particularly in clinical conditions, such as HF where comorbidities are common. The review has enabled the analysis of the concept of WRF in HF and its predictors and relationship to health outcomes across various settings.

The findings from this review have informed the decision to consider adopting the AKIN definition for acute kidney injury, extending the 48-hour timeframe to 72-hours for HHF patients. Classification and staging criteria recommended by the KDIGOs will be referenced for CKD.

Importantly this review has identified numerous factors with the potential to influence cardio-renal relationships and outcomes.

The following chapter details the methodological approach taken for the '*Renal function in heart failure: a cohort study' (ReFinH Study)*.

2.12 References

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Chapter 3 Methodology

3.1 Introduction

This chapter presents an overview of the methodology for the 'Renal function in chronic heart failure: cohort (ReFinH)' study.

The chapter outlines the rationale for the study design, describes the piloting process for the study and puts forward the hypotheses. Detailed information describing participants, study setting, sample size, sampling process, exclusion criteria, definitions and data processes, including the structure of the case record form are presented. Study measurements for the research variables contained in the case record form (CRF) and study endpoints are then provided. Finally, analysis procedures including re-coding of select variables and ethical issues are presented.

3.2 Rationale for the study design

The literature review chapter (Table 2.3) has provided numerous examples for the efficacy of a retrospective observational medical record review or chart audit (Forman et al. 2004; Krumholz et al. 2000; Owan et al. 2006) as a sound method to investigate incidence, prevalence, predictors and outcomes for independent group analyses for HF and renal function study endpoints. Informed by this finding and given the intentions of the study to characterise and determine the cardio-renal relationships for hospitalised HF patients with renal dysfunction at a single site, retrospective chart audit was deemed to be the most appropriate design.

3.3 Chart audit as the research methodology

3.3.1 Introduction

A feature of the chart audit or medical record review is it reflects the 'real world' every day clinical practice of an inclusive cohort. In a chart audit the daily electronic or hard-copy medical, nursing, allied health professional notes and laboratory, procedural and investigative test results are used as the primary source for patient data to answer research questions (Worster & Haines 2004). Although the approach has several limitations including the potential for inter-observer inconsistency for identifying information correctly and the issue of validity of the data recorded in the medical record (Boyd et al. 1979), data collection processes can minimise these limitations.

The term "medical record review" and "chart audit' can be used interchangeably and are defined as any study that makes use of "pre-recorded, patient focused data as a primary

source of information to answer a research question" (Worster & Haines 2004). The use of the chart audit as a method of research has been in use for decades (Butler & Quinlan 1958) and continues to be frequently used in the clinical setting as part of reviewing processes and outcomes to improve safety, protocol adherence and patient care (Hajjar et al. 2005). In epidemiological investigations, the chart audit enables questions on prevalence, practice patterns and quality of care to be answered while informing prospective study design (Hess 2004; Worster & Haines 2004).

3.3.2 Limitations of the chart audit

Selection bias, variability in interpretation and handling of uncertain or missing data, errors in transcription and chart availability (Taylor & Bogdan 1984) are potential limitations for a chart audit investigative study. The quality of the individual medical record itself can be a limiting factor as errors, inconsistencies, and omissions are commonly identified in medical records during the data extraction process (Feinstein, Pritchett & Schimpff 1969; Gilbert et al. 1996; Johnson et al. 2009). Yet many of these limitations can be overcome with proper planning, organization and consistency (Jansen et al. 2005; White 2005) when implementing medical record review study.

3.3.3 Pilot study

Informed by the preceding discussion for the potential limitations of a chart audit study, a pilot study was planned and conducted to test both resources and process. A case record form (CRF) and data dictionary were developed to standardise data collection and address the situation where data variables are open to subjective interpretation and tested in the pilot study (Jansen et al. 2005). The first 25 cases generated in the sampling process constituted the sample for testing. Conducting the pilot study provided the opportunity to assess the effectiveness of the cohort generating process and all aspects of data extraction. Specifically, it tested data availability, appropriateness of the procedures for securing and accessing medical records and data collector performance.

Through performing a pilot study, ambiguities and inconsistencies in the case record form (CRF) layout and data items were identified. There was also the problem of unforeseen conflicts or ambiguities with respect to certain data items and helpful information on the time required to complete a specific number of case reports. An example of conflict was the situation were haematocrit had been identified in the literature review as a variable that could be used to help identify hospitalised heart failure patients at risk of acute WRF. The pilot process discovered haematocrit was not reported by the study site pathology services and

instead red cell distribution width (RDW) and mean cell volume (MCV) would need to replace haematocrit in the CRF.

Piloting also provided the opportunity to assess the set-up of the study database. The database format followed the CRF to aid the flow of data entry, minimise time requirements and the potential for data entry errors. This aspect of the pilot study facilitated testing of data entry, the practicality of the coding and analysis processes. Twenty five patients had their medical record accessed to complete the CRF. The information was entered into SPSS and basic descriptive analyses were run including frequencies to check for missing, inconsistent, or conflicting data. The CRF was then revised informed by the outcomes from the pilot study.

The problem of inter-observer error was avoided by having all the data collected by the same trained nurse researcher using a standardised protocol and definitions. Validity of the data recorded for the index admission, if inconsistent with other comments within the medical record for the admission, were crossed-checked against other summary data such as discharge summaries, specialist referral letters or the historic electronic medical record to maximise data validity. These strategies were actioned to address the potential limitations of the chart audit design. Following completion of the pilot study, the data from the 25 patients involved in the pilot was quarantined from the study cohort and was not included in the final analysis for the study outcomes.

3.4 Study hypotheses

The ReFinH Study examined the cardio-renal relationship in patients hospitalised with HF. Specifically the study investigated the prevalence and impact of worsening renal function present as acute kidney injury defined using a modified AKIN definition, in patients with a principal discharge diagnosis of heart failure as coded by using the International Classification of Diseases 10th revision Australian Modification (ICD-10-AM) codes.

The study null hypotheses were:

1. There is no difference in the composite outcome all-cause mortality and major acute cardiovascular events (non-ST elevation myocardial infarction; ST elevation myocardial infarction, cardiac arrest and stroke) at 12-months follow-up between participants who develop in-hospital worsening renal function within 72-hours of their index admission presenting as acute kidney injury and participants who did not.

2. There is no difference at 12-months follow-up in hospital re-admissions; emergency department presentations, or total hospital beds days between participants who develop in-hospital worsening renal function within 72-hours of their index admission presenting as acute kidney injury and participants who did not.

3.5 Participants

3.5.1 Setting

A New South Wales metropolitan, tertiary level hospital with a capacity in excess of 500 beds and servicing nearly a million people was the setting for the study. The South Western Sydney Local Health Network (SWSLHN) is one of fifteen local health districts or networks for the State of New South Wales, Australia.

SWSLHN is an area that is socially, economically, culturally and linguistically diverse. The local government areas that constitute this health network jurisdiction are characterised by a high proportion of citizens born overseas (52%); and where 72% of people in this area speak a language other than English at home (South Western Sydney Local Health Network 2012). Its diversity extends to the socio-economic and age-range demographic. Several suburbs within the SWSLHN experience high rates of un-employment and are among some of the poorest communities in NSW as measured by the Socio-Economic Indexes for Areas (SIEFA), data formulated and provided by the Australian Bureau of Statistics (ABS) (Australian Bureau of Statistics (ABS) 2006). Such a demographic profile is consistent with high rates of CVD so it is not surprising that cardiovascular diseases were the number one cause of death for the health network area in the period 2003 to 2007; CVD accounting for 35% of deaths (South Western Sydney Local Health Network 2012). Given the high mortality rate from CVD for the area and the evidence survivors of cardiovascular events are at increased risk of heart failure especially in those over 65-years (Krumholz et al. 2000), heart failure morbidity and mortality are important health issues for the health network and its communities.

Although the SWSLHN has a relative young demographic, population projections over the next decade suggest the most significant change will occur in the population aged 65 years and over. The growth estimate for this group is 48% which is an increase from “98,089 (2011) to 145,538 people (2021)” while there will be a 48% increase in those aged 85-years and over for the same period (South Western Sydney Local Health Network 2012). The following figure (Figure 3.1) highlights the age group projections for the SWSLHN.

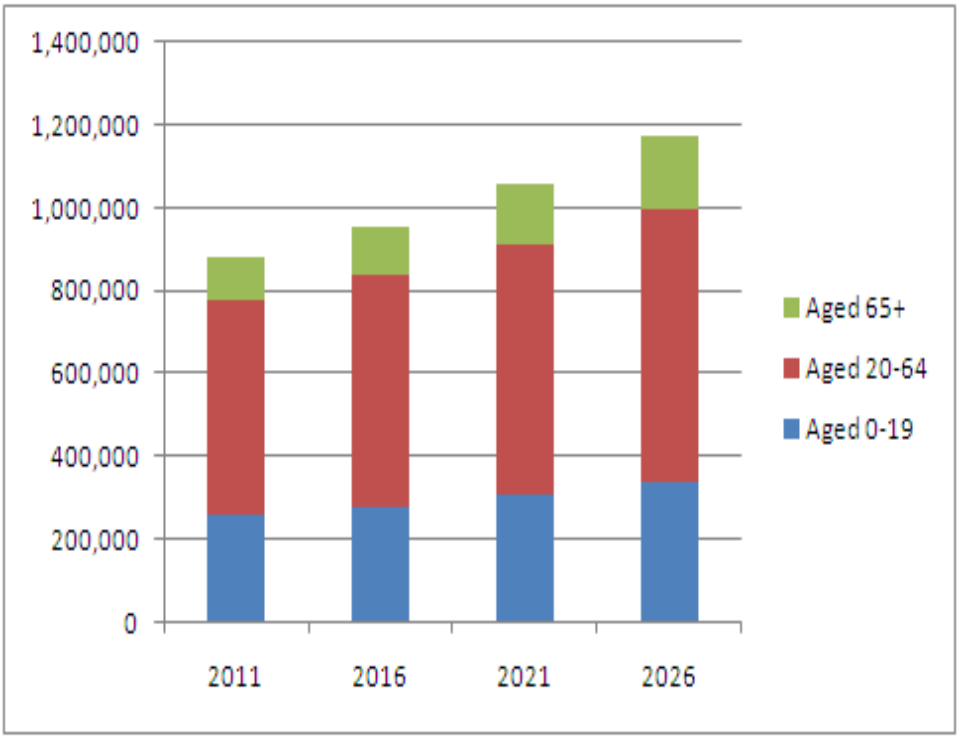

Figure 3.1 South Western Sydney Local Health Network Projected Population Growth 2011-2026

Source: Department of Planning and Statewide Services Branch NSW Health, March 2009 Accessed 30/01/2014 http://www.swslhd.nsw.gov.au/planning/content/pdf/CommunityProfileSummary.pdf

3.5.2 Sample size

We expected the frequency of worsening renal function during hospitalisation (i.e. AKI) in HF to be 25% (Breidthardt et al. 2011; Cowie et al. 2006; Damman et al. 2007; Krumholz et al. 2000) based on international studies which used a WRF definition of a serum creatinine increase of ≥26.5µmol/l (≥0.3mg/dl). 288 participants would be required to give a two-sided 95% confidence level for the frequency of WRF extending 5% from the observed proportion.

3.5.3 Cohort sampling

The study participants were identified by running a SWSLHN, Health Information Department, data query. Adults sequentially admitted to the study site for the six month period July 1st to 31st December 2010 and discharged with a primary discharge diagnosis of heart failure defined using the International Classification of Diseases 10th revision Australian Modification (ICD-10-AM) codes in Table 3.1. The rationale for selecting the participant recruitment timeframe July to December 2010 was to ensure participants' medical records would only be accessed on one occasion to collect all relevant data for the index admission and outcomes of interest for the 12-month follow-up period.

Table 3.1 Cohort - Heart Failure Principal Discharge Diagnosis ICD-10-AM Codes

ICD-10AM-Code	Condition
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
142.0	Dilated cardiomyopathy
142.6	Alcoholic cardiomyopathy
142.7	Cardiomyopathy due to drugs or other external agent
142.9	Cardiomyopathy, unspecified

Source: (National Centre for Classification in Health 2010)

The health data linkage query generated the cohort from a database which comprises administrative electronic patient records (EPRs). EPR databases focus on information gathered by a provider relevant only to services provided by the health network for patients attending its services. The EPR is an administrative health care database. It does not contain or access lifetime health records, nor include medication, dental, behavioural, or medical care information.

To maximise accuracy for the site of hospitalisation and patient identification the following search variables were included in generating the study cohort: facility identifier, stay number, episode sequence number; days sequence number, medical record number, surname, given names, birth date, patient suburb, patient postcode, episode start date, episode end date, diagnostic type, diagnostic code, description-3-digit and length of stay. The data query produced a chronologically sequenced list of adult admissions for the study site for the condition of interest, and minimised recruiter bias. For the six-month study period two-hundred and sixty-five admissions were retrieved representing two hundred and eighteen individual participants. Application of the exclusion criteria resulted in 176 cases for analysis.

3.5.4 Selection of the cohort

All patients aged 18-years and older discharged with principal discharge diagnoses of HF defined by the ICD-10AM-Codes I50.0, I50.1; I42.0; 142.6; 142.7 or 142.9 for the period 1st July to the 31st December 2010 inclusive were included (Table 3.1).

3.5.5 Exclusion criteria

Exclusion criteria were applied once the data collection process had been completed for the 218 cases. This approach ensured the ability to describe the clinical features of those excluded and kept the recruiting process transparent thereby avoiding bias in cohort selection and reporting. Cases identified as having a history of renal replacement therapy, chemotherapy, organ transplant, a ventricular assist device or if they were a hospital transfer or lacking at least two blood test results (i.e. short stay less than 2-days) for the index admission, younger than 18 years were excluded from the analyses (Gottlieb et al. 2002) (Table 3.2). These criteria were applied due to their potential to impact on renal function or the ability to assess renal function. Hospital transfers were excluded as initial patient baseline blood results and clinical assessment may not have been available.

Table 3.2 Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Adult ≥ 18years	**< 18-years** of age
Admitted to the study site between 1st July & 31st December 2010 inclusive	**Receiving** renal replacement therapy
HF ICD-10-AM Codes I50.0; I50.1; I50.9; 142.0; 142.6; 142.7 & 142.9	**History** of chemotherapy
Medical record available for audit including index discharge summary	**Organ** transplant recipient
At least 1 Heart Failure Sign (increased jugular venous pressure; S3 gallop; peripheral oedema; respiratory rate > 24 & bilateral pulmonary rales or crackles > basilar)	**Recipient** of a ventricular assist device
At least 1 Heart Failure Symptom (Dyspnoea at rest or with exertion; Orthopnoea or Fatigue)	**Hospital** transfer
	< **two blood test** results - index admission (i.e. short stay less than 2 days)

3.6 Definitions

A definition enables the clinician to determine the presence or absence of a disease or condition and the degree of severity thereby facilitating and ensuring a shared understanding (Cruz, Ricci & Ronco 2009) and effective communication. Key definitions for this study are

relevant to the primary and secondary endpoints of the study. Definitions for the conditions acute kidney injury (AKI) and chronic kidney disease (CKD) were referenced against the Acute Kidney Injury Network criteria (Mehta et al. 2007) and the appropriate international practice management guidelines (Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group 2012; Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013). The definition of heart failure was determined by ICD-10-AM coding classifications (National Centre for Classification in Health 2010) (Table 3.1). All independent variable definitions are documented in the following section or under the sub-headings 3.8 Study measurements or 3.10 Study outcomes.

3.6.1 Heart failure

The participants' hospital discharge summary with the principal diagnosis was the data source for defining heart failure. The study's sampling method used the HF ICD-10-AM Codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7 and I42.9 (Table 3.1) to define and identify these participants.

Recent European heart failure guidelines (McMurray et al. 2012) define heart failure as an abnormality of cardiac structure or function that results in inadequate oxygen delivery at a rate required for metabolizing tissues, and where the typical clinical syndrome presentation is one of patient symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) that result due to underlying cardiac structure or function abnormalities. These signs and symptoms were collected as dichotomous variables except for 'displaced apex beat' which was not collected as it is infrequently documented in the medical record. However, the signs and symptoms were not used to substantiate the diagnosis of heart failure, only to characterise the admission.

3.6.2 Chronic kidney disease and renal impairment

A confirmed eGFR of <60ml/min/1.73m^2 for at least 3-months was the definition adopted for chronic kidney disease (CKD) (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013). The diagnosis of CKD is made at stage 3a when eGFR has fallen to <60ml/min/1.73m^2. It is at this point there is a reduction in kidney function of up to 70%, and where relative risk for all-cause mortality and cardiovascular mortality steadily increase (van der Velde et al. 2011). Renal impairment is most commonly defined as an admission eGFR of less than 60mls.minute (Damman et al. 2014).

Chronic kidney disease (CKD) and its stages were classified using the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management

of Chronic Kidney Disease (CKD) (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013). In these guidelines CKD is defined as all kidney conditions where a person has evidence of kidney damage and/or reduced kidney function, lasting at least 3 months, regardless of the specific condition causing the disease (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013). CKD is composed of a heterogeneous group of disorders characterized by alterations in kidney structure and function, and is classified based on glomerular filtration rate (GFR) (Table 3.3) and albuminuria category, and cause. Glomerular filtration rate as the name implies is the amount of blood the kidneys clear of waste products in one minute. Standard practice is to estimate GFR (eGFR) using a validated formula such as the Modification Diet in Renal Disease (Levey et al. 1999) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey, Stevens & Coresh 2009) formula.

Table 3.3 Chronic kidney disease stages categorised by glomerular filtration rate

Stage	Glomerular filtration rate (GFR)	Description
	GFR mls.min.1.73m²	
1	GFR ≥ 90ml/min/1.73m^2	normal or high GFR
2	GFR 60 - 89ml/min/1.73m^2	kidney damage - mild decreased GFR
3a	***GFR 45 - 59ml/min/1.73m^2***	***kidney damage – mild-moderate decreased GFR***
3b	GFR 30 - 44ml/min/1.73m^2	kidney damage - moderately-severely decreased GFR
4	GFR 15 - 29ml/min/1.73m^2	kidney damage - severe decrease in eGFR
5	GFR <15ml/min/1.73m^2 or On dialysis	kidney failure end stage kidney disease

Source: Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD).

Verification of the CKD diagnosis was made by electronic medical record (EMR) review for the eGFR biochemistry results. CKD status was confirmed if the EMR showed a minimum of 3-months where the eGFR was <60ml.min.1.73 m² prior to the index admission. The Modification of Diet in Renal Disease (MDRD) formula was used to estimate the GFR as this formula was the method employed by the pathology services at the study site. The MDRD formula requires values for age, gender and serum creatinine with the eGFR value being

standardised to a population mean body surface area of 1.73m². The MDRD formula is appropriate as it has been validated in HF patients (Smilde et al. 2006). The limitations of the equation (Earley et al. 2012) and the data elements that it consists of have been presented in the literature review chapter.

3.6.3 Worsening renal function

As discussed in Chapters 1 and 2, there is no international consensus definition for worsening renal function in heart failure (Sheerin et al. 2014). This lack of consistency potentially challenges clinical management. Ronco and colleagues (Ronco & Ronco 2012) have described the cardio-renal interaction as a syndrome with five sub-types. Their diagnostic criteria for the cardio-renal syndrome (CRS) sub-type have been presented in the Introduction Chapter (Table 1.1) and are based on AKI and CKD guideline recommendations. However, within cardiology, international HF practice management guidelines are yet to recommend a WRF definition despite the substantial volume of literature published on the topic (Butler et al. 2010; Coca et al. 2007; Damman et al. 2007; Smith et al. 2006).

Due to the absence of a consensus definition for WRF in heart failure, and as WRF was a key dependent variable in the study, attention turned to other medical professional genre for a definition. The literature review chapter has noted criteria to defining acute kidney injury (AKI) evolved over the last decade in response to a need to define and describe acute or abrupt deterioration of renal function emanating from a broad range of aetiologies in the critically ill. Critical care specialists and nephrologists were leaders in recognising the need for and developing a definition.

The Acute Dialysis Quality Initiative (ADQI) group (Bellomo et al. 2004) was the first to produce a definition and staging criteria for worsening renal function in the critically ill. The ADQI group published the Risk-Injury-Failure-Loss-Endstage Kidney Disease (RIFLE) criteria in 2004 while the Acute Kidney Injury Network (AKIN) modification of this definition was published in 2007 (Mehta et al. 2007). The ADQI and AKIN held in common the renal biomarkers serum creatinine and urinary output with eGFR an option in the ADQI criteria. As mentioned elsewhere in this thesis, the advantage of the RIFLE and AKIN definitions over commonly use heart failure worsening renal function definitions is that they incorporate stages for the degree of severity. The nuances of the acute kidney injury definition discussion are covered extensively in the literature review chapter.

Worsening renal function for the study's cohort was defined as an increase in serum creatinine of >26.5µmol/l (>0.3mg/dl) occurring in ≤72hrs of the admission value. This modified AKIN acute kidney injury definition was based on the findings from the heart failure WRF literature. The serum creatinine cut-point of >26.5µmol/l (>0.3mg/dl) is commonly used in HF worsening renal function studies (Forman et al. 2004; Krumholz et al. 2000) and has been shown to be significant in terms of morbidity and mortality outcomes (Butler et al. 2010; Damman et al. 2007). This serum creatinine increase is also the threshold for AKI using the AKIN definition (Mehta et al. 2007) with the increase to occur within 48-hours. The evidence for extending the time-frame to 72-hours for the creatinine increase is also informed by HF the literature (Brandimarte et al. 2012; Forman et al. 2004; Gottlieb et al. 2002). Heart failure studies documenting the elapsed time for the diagnosis of WRF in hospitalised HF patients observed the majority of patients who develop WRF did so within 72hrs of admission (Brandimarte et al. 2012; Forman et al. 2004; Gottlieb et al. 2002).

1.1.1 Blood pressure

METeOR the Australian Institute of Health and Welfare (AIHW) metadata online registry2 describes systolic blood pressure (SBP) as reflecting the maximum pressure to which the arteries are exposed, while diastolic blood pressure (DBP) reflects the minimum pressure to which the arteries are exposed. Systolic and Diastolic BP are measured in millimetres of mercury (mmHg). Episodes of severe hypotension were defined as a mean arterial pressure (MAP) of <80mmHg.

3.7 Data collection

A broad range of cardio-renal data elements associated with hospitalised heart failure, worsening renal function and its outcomes were identified through the literature review as described in Chapter 2. Informed by the literature review, 553 variables were incorporated into the case record form (CRF). Many of the variables were repeat measures for haemodynamic items (n=38), blood pathology results (n=120) and medication management information (n=120). The data from the CRF enabled a comprehensive description of the patient's clinical and biological status during the course of the index admission, and provided the basis for relationship analyses.

[2] Australian Institute of Health and Welfare METeOR website METeOR http://meteor.aihw.gov.au/content/index.phtml/itemId/181162 last accessed 15/09/2014.

3.7.1 Case record form (CRF)

A design feature of the CRF (Appendix 2) was it mirrored the medical record structure as closely as possible in order to minimise data errors. The architecture of the medical record at the study site was a problem-orientated medical record which provided a systematic method for documentation by the admitting medical officer. It followed a process of defining the clinical problems and organising them in a way that priorities for solutions organised in chronological order. For example, the format of documentation was presenting complaint/illness including the nature duration and symptoms (CRF acute precipitating factors, admission examination); past medical history; family history and review of bodily systems. A provisional diagnosis completed the admission medical history and informed patient management. By ordering the CRF in this way, data collection efficiencies were maximised. The CRF was divided into 18 sections to follow the medical record format. The CRF sections are outlined below in Table 3.4. The study CRF document is available in the appendices (Appendix 2).

Table 3.4 Case record form (CRF) section headings

Sections	Sections	Sections	Sections
Participant details	Current medications	Complications	Medications
Acute precipitating factors	Cardiac imaging & catheter results	Procedures	Peak, nadir blood results
Admission examination	Charlson Index	Pre-discharge planning	Series results: Blood & haemodynamic measures
Admission Troponin & CKMB results	Medical history & Other comorbidities	On discharge fluid status	
HF Aetiology	Index admission management	Discharge status & destination	

Abbreviations: CKMB: Creatine kinase myocardial band isoenzyme; HF: heart failure

3.8 Study Measurements

3.8.1 Demographics – participant details

Section 1 of the CRF accounted for the participant's demographic information, medical administration details, exclusion criteria, and additional presentations data for the 12-month follow-up period as represented in table 3.5. Participant identifying information was not

included in the analysis database to ensure cases were de-identified to protect the privacy of participants. Additional hospital admissions or emergency department presentations for the 12-month follow-up period were also collected. These data covered the date of the episode, length of stay, precipitating factors and discharge destination. The participant's survival status at 12-month follow-up was also documented.

Table 3.5 Case report form: demographic & medical administration details

Demographics	Age, gender, primary health care doctor, ethnicity, need for interpreter and 12-month census date status: alive, dead or unknown**.**
Medical administrative detail	Admission & discharge date, length of stay, ICD-10-AM code principal and secondary diagnosis, and the availability of the discharge summary. Type of admission: elective, admitted, hospital transfer, residential care transfer or dead on arrival.
Exclusion criteria	History of: renal replacement therapy, chemotherapy, ventricular assist device, organ transplant or hospital transfer.
Prior HF and/ or CKD	Documented history for a prior HF admission and/or confirmed CKD
Index admission discharge destination	Home or relative; residential care; hospital transfer or died
Additional presentations for the 12-month study period	Documentation of subsequent hospital or emergency department presentations, precipitating cause and type of admission: elective, emergency department only, admitted, transferred hospital, transferred rehabilitation or dead on arrival.

3.8.2 Admission examination

Items for the patient's index admission examination focused on the signs and symptoms of HF and its management. Variables include the baseline haemodynamic measures, signs and symptoms of fluid overload (e.g. peripheral oedema, rales, raised jugular venous pressure, ascites) and the diagnosis and management of heart failure as listed in table 3.6. Admission heart rate, systolic and diastolic blood pressure, peak troponin or creatine kinase myocardial band isoenzyme (CKMB) value and arterial oxygen saturation (SaO2) percent were the physical examination continuous variables. The remaining categorical variables were the New York Heart Association (NYHA) functional class, heart rhythm, heart sounds, primary acute

precipitating factor, weight monitoring and tobacco use status, and the admission/ discharge ward. Index admission examination variables are listed in the following Table 3.6.

Table 3.6 Index admission clinical examination variables

Clinical status (ordinal or dichotomous variables: yes/no)	NYHA functional class; infection; pacemaker; implanted cardiac defibrillator; ascites; raised jugular venous pressure; lung crepitations; orthopnoea; peripheral oedema; heart sounds S1/S2 or S3 or S4; systolic or diastolic murmur; weight monitored daily; tobacco use category
Haemodynamic variables (scale variables)	First recorded: systolic & diastolic blood pressure; heart rate; percent oxygen saturation and respiratory rate
Ward: on admission/ at discharge (dichotomous variables: yes/no)	Cardiology; intensive care or high dependency unit; respiratory; aged care; other; no data
Cardiac enzyme results (scale variables)	Peak Troponin & CKMB (Creatine kinase myocardial band isoenzyme)
Acute precipitating factor (dichotomous variables: yes/no)	Dyspnoea; Angina (Canadian Cardiovascular Society functional class I, II,III or IV); Chest pain; Arrhythmia; Recent (<1-month) myocardial infract (MI); Acute MI; Respiratory infection; Fatigue; Iron infusion; Fever; Fall; Cough; Oedema; Confusion; Vomiting; Anaemia; Loss of consciousness; Elective admission; Thyroid disease; Change of cardiac drugs < 7-days; Non-compliance; NSAIDs induced; Acute renal failure; Bacterial endocarditis; Exacerbation or new on-set non-cardiac disease; Acute cardiac mechanical complication.

3.8.3 Aetiology of heart failure, management and co-morbidity burden

These CRF variables detailed the nature of the heart failure and if there was documentation to support the diagnosis. Echocardiography and cardiac catheter results were recorded when available; the Charlson Index results completing this component of the patient's profile. These variables are shown in table 3.7. These variables were either dichotomous (yes/ no) or ordinal.

Table 3.7 Heart failure aetiology

HF Aetiology (Dichotomous: yes/no)	Ischaemic; dilated; idiopathic; valvular; hypertension; familiar; congenital; endocarditis; pulmonary hypertension; sarcoidosis; viral; chemotherapy; alcoholic; amyloidosis.
Current medications - (Dichotomous: yes/no)	Angiotensin converting enzyme inhibitor; angiotensin receptor blocker; Beta blockers; diuretics; aldosterone antagonist; anticoagulant; antiplatelet; digitalis; lipid lowering agent; nitrate; anti-arrhythmic; calcium channel blocker, Non-Steroidal Anti-inflammatory Drugs (NSAIDs); other vasodilator
Cardiac imaging or catheter (mix of Dichotomous: yes/no and ordinal variables)	Test type – echocardiography, gated heart-pool scan, angiography; aortic stenosis; mitral stenosis; right atrial pressure; aortic regurgitation; mitral regurgitation; ejection fraction percent; fractional shortening; left ventricle function; right ventricle function; pulmonary hypertension; date of latest test
Charlson Index (mix of Dichotomous: yes/no and ordinal variables)	AIDS; cerebrovascular disease; chronic obstructive pulmonary disease; chronic heart failure; connective tissue disease; peripheral vascular disease; dementia; hemiplegia; leukaemia; malignant lymphoma; myocardial infarction; peptic ulcer disease; lymphoma; diabetes mellitus; liver disease; renal disease; malignant solid tumour.

3.8.4 Medical history

Not all co-morbidities were covered by the Charlson Index. Other health conditions such as depression and atrial fibrillation were documented for their potential relevance when investigating the cardio-renal relationship as depression and atrial fibrillation are known cardiovascular risk factors (Mendis, Puska & Norrving 2011). As such, other medical history events or conditions were recorded as dichotomous yes/no variables in table 3.8.

Table 3.8 Medical history: comorbidities

Cardiac arrest	Diabetes – insulin	Heart valve disease	Cancer treatment
Hypertension	Atrial fibrillation	Depression	Nursing home care
High cholesterol	Coronary artery disease	Thyroid disease	Other serious condition
Type 1 Diabetes	History arrhythmia	Sleep apnoea	Other chronic condition
Diabetes non-insulin	Aneurysm (abdominal)	Recent major bleed	

3.8.5 Index event management

Management variables address intermittent and / or continuous use of intravenous (IV) diuretics and the need for support therapies such as IV inotropes or Glyceryl Trinitrate (GTN); percutaneous cardiac interventions (PCI), pacing devices and the need for oxygen therapy or ventilation and intubation. These data items help describe the severity of the patient's

condition during the admission. The diuretics dose may be used to help interpret changes in renal function. Again, these items were in the main dichotomous, yes/no, except for diuretics days and dose variables in table 3.9.

Table 3.9 Index admission clinical management options

IV Diuretics >24-hours	Intra-aortic balloon pump
IV Diuretic infusion > 24-hours	Oxygen therapy
IV Glyceryl Trinitrate (GTN) infusion	Continuous or Biphasic positive airway pressure therapy (CPAP or BiPAP)
IV inotrope infusion	Mechanical ventilation
Referred for VAD/ Heart transplant	Intubation
Percutaneous coronary intervention (PCI)	IV diuretics total number of days
Insertion of pacemaker	IV diuretics infusion total number of days
Insertion internal cardiac defibrillator	Highest total daily IV and/or infusion diuretic dose

Abbreviations: IV: intravenous; BiPAP: Biphasic intermittent positive airway pressure; CPAP: Continuous positive airway pressure; VAD: ventricular assist device.

3.8.6 Complications

Complications during the course of an admission have been linked with worsening renal function in heart failure patients (Cowie et al. 2006). For this reason, it was considered important to include items on cardiac arrest, S-T elevation myocardial infarction (STEMI), Non-STEMI, stroke, pulmonary embolus, deep vein thrombosis, respiratory tract infection, urinary tract infection, cardiogenic or septic shock, the need for renal replacement therapy, un-planned admission to intensive care, coronary care or general operation theatres and death. These variables were recorded as dichotomous yes/ no variables. Table 3.10 lists these variables.

Table 3.10 Index admission complications variable list

Cardiac arrest	Trans ischaemic attack (TIA)	Unplanned admission Coronary Care Unit	Pulmonary embolus (PE)
STEMI	Deep vein thrombosis (DVT)	Unplanned admission Intensive Care Unit	Cardiogenic shock
Non-STEMI	Respiratory tract infection (RTI)	Unplanned visit to operating theatre	Septic shock
Stroke	Urinary tract infection (UTI)	Renal replacement therapy	Died

Abbreviations: STEMI, S-T elevation myocardial infarction

3.8.7 Procedures

Information on coronary angiography for the index admission or a history of this procedure and the result was also collected to help identify those cases with documented coronary artery disease and the use of contrast medium a potential cause of renal damage. The variables were either dichotomous or ordinal except for one date variable (Table 3.11). Information from these data items help informs the context for the study outcomes. Unfortunately, the information for these items was minimal with much of the potential data missing due to lack of documentation. For example, left ventricular ejection fraction percentage was often not recorded; instead, there was .a description of left ventricular function as normal or mildly, moderately or severely impaired.

Table 3.11 Coronary angiography status, management and result variables

Coronary angiography	Pre-hydration	Coronary angiography result
Date angiography	Ultra-filtration	Coronary disease extent
Contrast used	N-acetylcysteine used	

3.8.8 Discharge planning

Readmission and emergency department presentations are secondary study outcomes. It was therefore thought relevant for pre-discharge planning and post discharge management be documented (Table 3.12). This section of the CRF notes allied health assessments and interventions, access and appointments for outpatient services such as cardiac rehabilitation

and documentation of follow-up arrangements with the patient's general practitioner and/ or cardiologist. All variables were dichotomous yes/ no responses.

Table 3.12 Discharge planning variables

Discharge medication list	Dietician review	Aged care assessment team (ACAT) review	Outpatient HF clinic appointment noted
Physiotherapy assessment	Pharmacist review	General Practitioner (GP) appointment	Cardiologist follow-up documented
Occupation therapy assessment	Social worker consult	Discharge summary to GP	

3.8.9 Fluid status on discharge

There is some evidence in the scientific literature that only HF patients who have experienced WRF during the admission and continue to have signs of fluid overload on discharge have worse outcomes (Metra et al. 2011; Núñez et al. 2014). Hence, the ability to collect this information was included in the CRF (Table 3.13). These variables listed in the following table were dichotomous yes/ no (included not recorded). Unfortunately, these variables are again not frequently documented in the EMR.

Table 3.13 Discharge fluid overload status variables

Ascites	Raised JVP
Peripheral oedema	Lung Crepitations

3.8.10 Participant discharge destination status

The destination at discharge was recorded to identify carer support as living alone is a risk factor for further CVD events. These variables were dichotomous yes/ no response options (Table 3.14).

Table 3.14 Participant discharge destination variables

Discharge home or to relative	Transferred to rehabilitation facility
Discharged to residential care	Died during admission
Transferred to another hospital	

3.8.11 Medications

The patient's medication regime at the time of admission and discharge was recorded. For both time-points the name of the drug, the route of administration, the daily dose and international units were collected. In addition, it was noted at discharge whether the drug

remained unchanged, increased, decreased or was new. There was the capacity to record up to 20 medications per patient. If medications exceeded this capacity, medications not included in order were aperients, eye drops, topical creams, and analgesics. The generic name for each drug was a string variable, route of administration, international units name and drug statuses on discharge were categorical nominal variables. The dose was a scale variable.

3.8.12 Biochemistry and haematology results

Baseline, peak, nadir and final values for the variables serum sodium, urea, creatinine, albumin, haemoglobin, mean cell volume, red cell diameter width, C-reactive protein and calculated eGFR were recorded. These data were collected for the first five days of admission if available. Additional biochemistry and haematology values recorded for admission or first blood result and final blood result in addition to above values included serum potassium, corrected calcium, phosphate, parathyroid hormone, alkaline phosphate, iron, white cell count, platelets, thyroid stimulating hormone and total cholesterol. These values as continuous variables were measures classified as a scale in IBM's SPSS version 21 (IBM Corp, Armonk, NY).

3.8.13 Haemodynamic clinical series

Documentation was made for the highest and lowest daily values for systolic and diastolic blood pressure and heart rate. These haemodynamic variables were collected for the first 5-days of the index admission where available. Episodes of severe hypotension defined as a mean arterial pressure (MAP) of <80mmHg could be identified. As continuous variables, they were classified as a scale in SPSS.

3.9 Instruments and reliability

3.9.1 Modification of Diet in Renal Disease (MDRD) eGFR formula

Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) equation as this was the standard used by the pathology services at the study site. The MDRD equation has been validated in hospitalised HF patients and shown to be an appropriate method for the indirect assessment of renal function in these patients (O'Meara et al. 2006; Smilde et al. 2006). The limitations of the MDRD equation have been presented in the literature review where it was noted that the CKD-EPI equation is now the preferred formula for estimating GFR in HF.

3.9.2 Acute kidney injury network (modified) acute kidney injury metric

Worsening renal function was defined as an increase in serum creatinine of >26.5µmol/l (>0.3mg/dl) from baseline in the period of ≤ 72-hours from the admission value. This value and timeframe have been previously discussed in this chapter under the sub-heading of definitions and again extensively in the literature review chapter. Importantly the >26.5µmol/l (>0.3mg/dl) threshold in hospitalised HF patients has been demonstrated to have the maximum specificity and sensitivity for prognostic outcomes (Gottlieb et al. 2002) and is the AKIN acute kidney injury threshold. The extension of the timeframe for AKIN acute kidney injury diagnosis from ≤48-hours to ≤72-hours is based on the results from several HF studies which investigated the incidence and outcomes associated with its occurrence (Brandimarte et al. 2012; Forman et al. 2004; Gottlieb et al. 2002). These studies found that the majority of HF patients who developed acute WRF did so with the first 3-days (72-hours) of hospitalisation.

3.9.3 Haemodynamic measures

Systolic and diastolic blood pressure and heart rate are bed-side measures for which the electronic equipment calibration and technique used by the health professional to determine these metrics cannot be checked or verified respectively. The data for these variables were a direct transcription from the medical record to the CRF. METeOR the Australian Institute of Health and Welfare (AIHW) metadata online registry3 describes systolic blood pressure (SBP) as reflecting the maximum pressure to which the arteries are exposed, while diastolic blood pressure (DBP) reflects the minimum pressure to which the arteries are exposed. Systolic and Diastolic BP are measured in millimetres of mercury (mmHg). The measurement of heart rate is defined as the person's heart rate measured in beats per minute (bpm).

3.10 Study outcome measures

3.10.1 Primary endpoint

The primary endpoints for the study were the incidence of acute worsening of renal function present as acute kidney injury (AKI) during the index admission and the composite outcome of all-cause mortality or major acute cardiovascular or cerebrovascular (MACE) event at 12-months follow-up from the date of discharge for the index admission. Acute worsening renal function was defined using a modified AKIN acute kidney injury definition. This definition required a serum creatinine increase of >26.5µmom/l over the baseline value within 72-hours

[3] Australian Institute of Health and Welfare METeOR website METeOR http://meteor.aihw.gov.au/content/index.phtml/itemId/181162 last accessed 15/09/2014.

of admission. MACE was defined as ST elevation myocardial infarction (STEMI), non-STEMI, cardiac arrest or a stroke.

For worsening renal function, the scale of measure was serum creatinine which is a participant's serum creatinine (SCr) level measured in micromoles per litre (µmol/L). The point of comparison was between the admission baseline SCr value and the first value within the 72-hour time window that resulted in an increase of >26.5µmol/l (0.3mg/dl) in this renal biomarker (Forman et al. 2004; Gottlieb et al. 2002). All-cause mortality at 12-months follow-up was determined using both the electronic medical record and the hardcopy medical record of participants. If status as alive or dead could not be verified 'unknown' was recorded. For the outcome analyses participants with and 'unknown' census date status were included in the 'Alive' category.

3.10.2 Secondary endpoints

Secondary endpoints for the study were the number of hospital re-admissions, emergency department presentations, and total bed days at 12-month follow-up for group comparisons for those with AKI and no AKI. To complete the characterisation of renal dysfunction in hospitalised heart failure patients secondary study endpoints were also assessed: patients with renal impairment (RI) or confirmed chronic kidney disease (CKD) on admission compared to those without RI or CKD. Data for these analyses were collected by access to the electronic medical record for each participant. This process enabled documentation for a count of hospital or emergency department presentations, date of presentation, precipitating factors and discharge date for all hospitals within the area serviced by the SWSLHN. A limitation of this data is the inability to identify private hospital admissions and out-of-area admissions or emergency department (ED) presentations.

3.11 Data analysis

Data analyses were supervised by Professor David Sibbritt, University of Technology, Sydney and Dr Chakra Budhathoki, Johns Hopkins University, Baltimore. All statistical analyses were performed using IBM's SPSS for Windows, version 21.0 (IBM Corp, Armonk, NY). A significance level of .05 was set to indicate statistical significance. The literature review informed definition for AKI to describe in-hospital worsening renal function was as a serum creatinine increase of ≥26.5µmol/l above admission value within 72-hours of admission. This definition was used to categorise patients into no-AKI and AKI groups. To examine differences between AKI and non-AKI and clinical characteristic variables for AKI groups' the Pearson's chi-square test or Fisher's exact test for categorical variables and the independent-sample t-test for continuous variables

if normally distributed or the Mann-Whitney U (Dinneen & Blakesley 1973) test if not normally distributed were used. To provide additional detail for characterising renal dysfunction in hospitalised HF patients differences between patients with renal impairment and no-renal impairment at baseline; and confirmed chronic kidney disease and no chronic kidney disease and the cohort variables age, gender and development of AKI were also analysed. Again the between group associations and differences between groups were analysed using the Pearson's chi-square test or Fisher's exact test for categorical variables and the independent-sample t-test for continuous variables if normally distributed or the Mann-Whitney U test if not normally distributed.

Table 3.15 Key study variables: type

Dichotomous	Nominal	Ordinal	Continuous (interval/ ratio)
Worsening renal function in 72hrs	Gender	New York Heart Association functional class	Age calculated
Renal impairment status	ICD-10AM-Codes for heart failure	Chronic kidney disease stage	Index admission date
Confirmed chronic kidney disease status	Patient discharge status	Charlson Index renal function status	Index admission discharge date
Hospital transfer	Census date status	Charlson Index diabetes status	Length of stay
Chemotherapy history	Patient discharge destination	Charlson Index liver function status	First recorded systolic blood pressure
Ventricular assist device	ECG rhythm	Tobacco use	First recorded heart rate
Additional admissions	Admission type	Left ventricular function	First recorded respiratory rate
Emergency department presentations	Admission primary precipitating factor		First recorded oxygen saturation percent
ACE on admission	Admission type		Admission values for all biochemistry and haematology results
B.blockers on admission	Index death cause		Final values for all biochemistry and haematology results
Diuretics on admission			Left ventricular ejection fraction

The list of key study variables by type is provided in the above table 3.15. The majority of the variables were quantitative, and either nominal or dichotomous. For example, variables for the presence of co-morbidities, tests performed, complications or heart failure aetiology fell into the nominal, dichotomous category. Other categorical variables were ordinal. The NYHA functional class, tobacco use, left ventricular function and CKD stage are some of the ordinal variables in the dataset. Continuous, quantitative variables included all the blood result items

and SBP, DBP and heart rate. Each variable was explored using univariate analysis to determine its range and the measures of central tendency. For categorical variables frequency distributions were run, and median and interquartile range recorded, while for continuous variables histograms with normal distribution curves super-impose were generated to guide further analyses with mean and standard deviation noted if distribution was symmetric, otherwise median and interquartile range were reported.

3.11.1 Data checking

Prior to any analyses, the raw data for each case was checked for missing information and frequency analysis for outliers. On the few occasions missing or conflicting data were identified, the original CRF was referred to and if this did not resolve the issue the original medical record was consulted. Syntax was then written to remove from the analyses those cases who recorded one or more exclusion criteria. Excluded cases, their identification code and reason for exclusion were documented. This aspect of the analysis was completed under the leadership of a senior statistician. The next phase involved running frequency tables for all the variables to ensure data for included cases was consistent with the count, that is 176 cases and the case count correct once excluded cases were removed. When certainty for the raw data was established by the preceding processes descriptive, then inferential statistical tests were run to answer the study questions and test the study hypotheses.

3.11.2 Descriptive analyses

Descriptive analyses were applied to generate the baseline index admission characteristics for the cohort stratified by WRF status. Categorical data were presented as a count and percentage. Continuous data were summarised by mean and standard deviation or by median and inter-quartile range if skewed. To check variable data distribution, frequency distributions (histograms) for continuous variables were generated to help define the appropriate analysis procedure. As noted above, the independent-sample t-test or Mann-Whitney U test was used to compare the differences between the two groups (worsening renal failure status, yes/no) using the mean or median for outcomes of interest, while the Pearson's chi-squared test or Fisher's exact test was used to determine if there were significant differences between the two groups for a categorical variable. The study's independent variable was the participants' status for index admission worsening renal function (WRF_72) presenting as AKI.

3.11.3 Recoding and formulation of new variables

Several original variables were recoded for analysis purposes. One of the issues with medical record audit is that the detail available in the medical record can be dependent on the author,

the situation regarding the patient's admission as either a new heart failure presentation or as a chronic re-presenter or admission status as either acute or elective (Jamrozik K et al. 2001). In such situations, it is often prudent to recode data items to represent the patient status rather than detail its components. For example when 'Admission examination' items for signs and symptoms of fluid status ('raised jugular venous pressure', 'crepitations', orthopnoea, ascites and 'peripheral oedema') were analysed for frequencies variously data for one or other of the items was missing we therefore recoded these data elements into the variable 'Fluid status' for analyses. This approach was followed for electrocardiograph rhythm (sinus or other; atrial fibrillation or other); heart failure aetiology (ischaemic or other; Idiopathic or other; hypertension or other or Dilated or other); left ventricular function (normal/mild or moderate/ severe dysfunction); and New York Heart Association (NYHA) classification (NHYA I & II or NYHA III & IV) and CKD stage (No CKD = Stage I & II or CKD = Stage IIIa, IIIb, IV or V).

3.11.4 Survival analysis

The time-to-composite endpoint was compared between in-hospital worsening renal function status (yes/no) presenting as acute kidney injury (AKI) using a log-rank test. Survival curves were estimated using Kaplan-Meier method (Collett 2002). As an additional analysis, a Chi-square test was used to investigate associate between number of composite endpoints and WRF status.

The Kaplan-Meier (Collett 2002) and log-rank tests were used to compare the time to composite endpoint all-cause mortality and major cardiovascular event (ST elevation myocardial infarction [STEMI], non-STEMI, Cardiac arrest or Stroke) survival: 1) between patients who developed in-hospital worsening of renal function presenting as AKI and non-AKI patient groups a and represented in the SPSS database as WRF_72 a dichotomous variable.

To understand the relationship between renal dysfunction in hospitalised HF patients Kaplan-Meier log-rank tests were also used to compare the time to composite endpoint all-cause mortality and major cardiovascular event (ST elevation myocardial infarction [STEMI], non-STEMI, Cardiac arrest or Stroke) survival: 1) between patients with renal impairment (RI) and no-RI groups and 2) in the presence or absence chronic kidney disease (CKD).

In addition to primary outcome (time to composite endpoint and number of composite endpoints), three secondary outcomes (hospital readmissions, emergency department presentations and total hospital bed days) were compared between WRF status presenting as AKI using a Mann-Whitney U test.

3.11.5 Regression modelling

Binary logistic regression modelling (Hosmer, Lemeshow & Sturdivant 2000) was used to find a set of explanatory variables to predict an outcome of acute kidney injury (AKI) for the cohort. AKI represented by the variable worsening renal function in 72-hours (WRF 72). The method used was backward stepwise logistic regression a sequential method. Variables included in the first modelling step had a *p*-value ≤0.1 in the baseline cohort characteristics table stratified by AKI; or had previously been identified as AKI predictors in the scientific literature. The eight variables eligible for step 1 of the analysis were: age, confirmed chronic kidney disease (stage 3a to 5 end-stage), first recorded systolic blood pressure, beta blocker use at the time of admission, admission values for serum creatinine, eGFR, haemoglobin and a history of diabetes. The number of variables in the initial equation was reduced to 6 to ensure a minimum of ten participants per variable (Hayat 2013; Vittinghoff & McCulloch 2007). A confirmed history of chronic kidney disease ≥Stage 3a at the time of admission was used as the renal variable to reduce the potential for multicollinearity. Four steps were required to complete the regression analysis.

3.12 Ethics procedures

Ethics approval for the study was granted in November 2011 by the Human Research Ethics Committees for the South Western Sydney Local Health District (SWSLHD) and by University of Technology Sydney in late December 2011 prior to cohort generation and data collection. The HRECs agreed that patient consent was not required as the study investigated relationships and patterns arising from the patients' clinical profile, care, test results and subsequent health outcomes of interest. The analysis could therefore be derived from the documentation evident in the patient's medical record and no intervention took place. Key ethical issues in this research were maintaining patient confidentiality. This was achieved by data management strategies described below.

The rationale for starting case recruitment and data collection from 1st July 2010 was to ensure outcomes data would be available for the 12-month follow-up period from the date of the index hospital admission. Data sources were both electronic and paper-based medical records. Both medical record systems permitted pre index event confirmation for the diagnosis of heart failure and the case status regarding chronic kidney disease.

3.12.1 Informed consent

Informed consent requirements were waivered by the Ethic Committees. The wavier was given as the study was low-risk as it did not interventional and patient privacy and identity would be

safeguarded. All data would be coded to de-identify cases and results would be published as group data.

3.12.2 Data management

Patient confidentiality and privacy was maintained by de-identifying the data and grouping for analysis and publication. Participant data collection forms and electronic data records were numerically coded. For data linkage purposes, a data linkage document was kept that detailed participants' personal identification information with their study numeric code; this document has been kept separate from the data collection and has been only accessible to authorized study staff. All computer based data storage was and remains password protected and accessed only by the chief investigator and authorized study personnel. Paper-based clinical research forms have and continue to be secured in a locked filing cabinet within a locked restricted access research studies storage area at the study site and will be kept at least for 5-years.

3.12.3 Governance

Co-investigators for this study included the supervisory team and a senior cardiologist and nephrologist at the study site. To ensure the ethics study requirements were met and the study remained on schedule, regular meetings were held with the supervisory team. These meetings would also address data collection issues or data definition queries. Annual HREC progress reports were forwarded to the SWSLHN and the UTS committees. Confirmation of continuing ethics approval was an outcome form the provision of these reports.

3.13 Conclusions

This chapter has provided a discussion of the methodological issues and considerations of the ReFinH: cohort study. Baseline biochemistry and haematology results, specifically creatinine, estimated glomerular filtration rate, urea and haemoglobin levels were assessed in all patients. Data for the index admission initial medical assessment, precipitating symptoms and signs, heart failure aetiology, medications, complications during the index admission, discharge planning and haemodynamic and blood results for a maximum of 5-days if available were collected. Emergency department presentations, hospital re-admissions, length of stay for the index admission, total number of bed days and mortality status for the 12-month follow-up period after discharge were also documented. Data were extracted for 265 events representing 218 individuals generating a baseline cohort of 176 and a follow-up cohort of 166 for analysis. The following chapter will present the results of the study using these data.

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Chapter 4 Results

4.1 Introduction

In the setting of patients hospitalised with heart failure, renal function status has been established as a strong prognostic marker. Acute worsening of renal function during hospitalisation is associated with adverse outcomes. The 'Renal function in chronic heart failure cohort study' sought to investigate relationships regarding the prevalence, predictors and prognostic importance of acute and chronic renal dysfunction in an Australian cohort of hospitalised heart failure patients. The chapter presents the study results.

In this single centre, retrospective chart audit, study participants were identified for inclusion in the cohort *a priori*. Data were collected for the index admission and the follow-up period for the outcomes of interest. The medical record audit enabled the identification of individuals who developed in-hospital worsening renal function (WRF) described in this thesis as acute kidney injury (AKI) during the index admission. These data facilitated the analyses to characterise HF patients with renal dysfunction, detect the risk factors associated with acute kidney injury and the relationship it had with the study primary and secondary outcomes. The prevalence of renal dysfunction as renal impairment (RI) and chronic kidney disease (CKD) are also reported.

The study null hypotheses were:

1. There is no difference in the composite outcome all-cause mortality and major acute cardiovascular events (ST elevation myocardial infarction (STEMI), non-STEMI; cardiac arrest and stroke) at 12-months follow-up between participants who develop in-hospital worsening renal function within 72-hours of their index admission presenting as acute kidney injury and participants who did not.

2. There is no difference at 12-months follow-up in hospital re-admissions; emergency department presentations, or total hospital beds days between participants who develop in-hospital worsening renal function within 72-hours of their index admission presenting as acute kidney injury and participants who did not.

To address the study hypotheses and to characterise the HF cohort the following objectives were addressed:

i. Determine the incidence of AKI
ii. Determine the survival for hospitalised HF patients discharged with an index admission episode of AKI

iii. Determine the relationship between hospitalised HF patients discharged with an episode of AKI and secondary outcomes for the study
iv. Identify the risk factors (predictors) associated with the development of AKI in the study cohort
v. Determine the prevalence of renal impairment and confirmed chronic kidney disease
vi. Describe the survival for hospitalised HF patients discharged with an index admission history of renal impairment and confirmed chronic kidney disease, and
vii. Describe the relationship between hospitalised HF patients discharged with an index admission history of renal impairment and confirmed chronic kidney disease and secondary outcomes for the study.

Participant recruitment results are presented first followed by baseline demographic and characteristics for the participants stratified by the main outcome of interest in-hospital worsening renal function categorised using a modified AKIN acute kidney injury (AKI) definition (Sheerin et al. 2014). AKI incidence is presented and defined as an increase in serum creatinine of greater than 26μmol/l over the admission value within the first 72-hours of admission. This definition has been informed by the literature review reported in chapter 2. This baseline characteristics table 4.1 highlights statistically significant differences for each variable for the WRF group.

The primary outcome, the impact AKI for the composite endpoint all-cause mortality and major acute cardiovascular event (ST elevation myocardial infarction (STEMI), non-STEMI; cardiac arrest and stroke) at 12-months follow-up post index hospitalisation is then presented. The 12-months follow-up outcomes for AKI and the secondary endpoints, number of hospital re-admissions; emergency department presentations and total hospital bed days follows. The Binary logistic regression modelling results for predictors or risk factors for acute kidney injury in the study cohort are then presented. The remainder of the chapter addresses characterisation of the cohort.

Characterisation of renal function in HF continues with data for the prevalence of renal impairment, determined by admission eGFR and the severity of RI at the time of index hospitalisation. Confirmed chronic kidney disease prevalence established at the time of admission by historic review of the electronic medical record is documented for the cohort. To complete the illustration of renal function in hospitalised HF patients, a brief report of RI and confirmed CKD on survival and their relationship to the secondary outcomes is given. Finally, attention other variables that enhances the characterisation of renal dysfunction in

hospitalised HF is presenting in data for gender, age groups, medication and comorbidities against the principal outcome of interest AKI.

4.2 Participant recruitment

For the 6 months of the clinical audit period (July 1st – December 31st 2010), there were 265 heart failure admissions representing 218 patients. All 218 patients were identified as potentially eligible for the study and had data extracted from their medical record. Exclusion criteria, conditions or situations which could potentially influence renal function or prevent baseline assessment of renal function were applied (Figure 4.1) resulting in a cohort for investigation of 176 patients. There were 10 deaths during the index admission reducing the cohort to 166 patients for the 12-month follow-up analysis. The patient recruitment results are presented in the following figure 4.1.

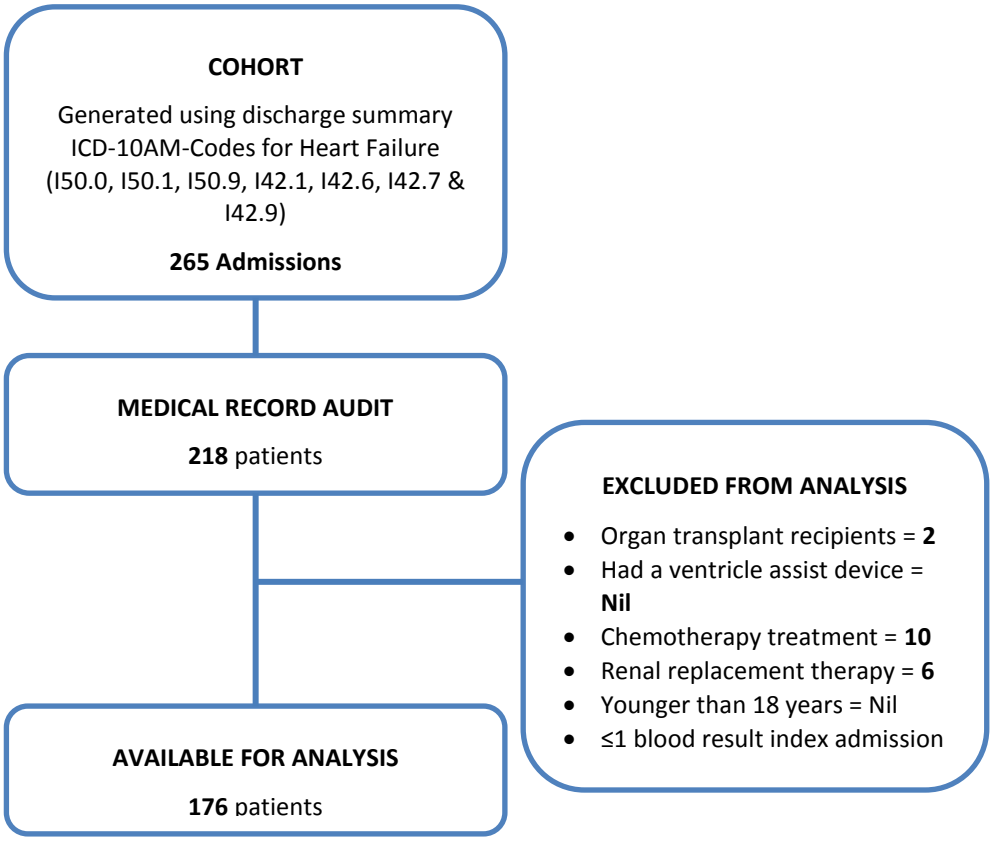

Figure 4.1 Cohort recruitment process

4.3 Baseline cohort characteristics stratified by in-hospital worsening renal function defined as acute kidney injury

Baseline characteristics for the cohort are presented stratified by patients' in-hospital worsening renal function (WRF) presenting as acute kidney injury (AKI). As discussed above, the AKI definition is a modification of the Acute Kidney Injury Network (AKIN) definition for AKI (Mehta et al. 2007). Categorical variables were summarized as frequency and percentage; and continuous variables were described using median and interquartile range (25^{th} and 75^{th}) or mean with standard deviation depending on distribution. Group comparisons were run using either χ^2 test or Fisher's exact test for categorical variables and a *t* test or Mann-Whitney U test for continuous variables depending on distribution. For a few variables, the cohort number was reduced owing to missing documentation in the medical record. This was the case for variables linked to the electrocardiogram (n=153) and echocardiogram (n=148). The lack of data in the medical record for these variables prevented the reporting for the cohort of left ventricular ejection fraction (EF %).

Renal impairment was specified as an admission eGFR of <60ml.min.1.73m^2. The baseline characteristics for the 176 participants eligible for inclusion in the analysis are summarised by in-hospital worsening renal function (acute kidney injury) group in the following Table 4.1.

Table 4.1 Baseline characteristics for cohort stratified by worsening renal function

Admission Characteristics	Cohort	WRF◈ ↑SCr>26µmol/l	No WRF	P value
Cohort	n = 176	42 (24%)	134 (76%)	<0.001
Age, years (Median, IQR)	76 (68, 83)	78(69, 83)	76 (68, 83)	0.505
Female (n, %)	79 (45)	19 (45)	60 (45)	0.958
HF Aetiology	n= 176			
Ischaemic (n, %)	66 (38)	13 (31)	53 (40)	0.315
Hypertensive (n, %)	19 (11)	5 (12)	14 (10)	0.791
Primary precipitating factor	n=174			
Dyspnoea (n, %)	79 (45)	19 (46)	60 (45)	0.890
Oedema (n, %)	17 (10)	5 (12)	12 (9)	0.550
Chest pain (n, %)	21 (12)	2 (5)	19 (14)	0.168
Heart rate (b.p.m.) Median (IQR)	88 (72, 106)	91 (79, 104)	85 (70, 106)	0.368
Systolic BP (mmHg) Mean (±SD)	141±30	148±35	139±28	0.103
Diastolic BP (mmHg) Mean (±SD)	78±20	79±24	78±18	0.754
Evidence of fluid overload◆◆ (n, %)	170 (97)	41 (98)	129 (96)	0.674
NYHA Class III, IV (n, %) (n=166)	100 (60)	25 (66)	75 (59)	0.426
Rhythm	n=153			
Sinus (n, %)	85 (56)	20 (56)	60 (56)	>0.99
Atrial fibrillation (n, %)	41 (27)	9 (25)	32 (27)	0.781
History Acute MI (n, %)	101 (57)	24 (57)	77 (58)	0.971
Left ventricular function	n=148			
Moderate/ severe (n, %)	90 (61)	23 (61)	67 (61)	0.967
Co-morbidities	n=176			
CHF (n, %)	167 (95)	41(98)	126 (94)	0.688
CKD ≥ Stage 3a (n, %)	91 (52)	29 (69)	62 (46)	0.010
CVD (n, %)	43 (24)	10 (24)	33 (25)	0.914
Hypertension (n, %)	152 (86)	38 (91)	114 (85)	0.373
Diabetes (n, %)	89 (51)	30 (71)	59 (44)	0.002
COPD (n, %)	80 (46)	21 (50)	59 (44)	0.498
IV Diuretics Max daily (Median, IQR)	80 (0, 80)	80 (0, 102)	80 (0, 80)	0.353
Charlson Index score Mean (±SD)	4.0±1.7	4.5±1.9	3.9±1.6	0.025
Index admission LOS (Median, IQR)	6 (3,11)	6 (3,12)	5 (3,10)	0.319
History smoking◊ (n, %)	103 (59)	25 (60)	78 (58)	0.880
Medications on admission	n= 176	n = 42	n = 134	
ACE inhibitor (n, %)	89 (51)	25 (60)	64 (48)	0.183
ARB (n, %)	45 (26)	11 (26)	34 (25)	0.916
Diuretics (n, %)	136 (77)	31 (74)	105 (78)	0.539
Aldosterone antagonist (n, %)	32 (18)	9 (21)	23 (17)	0.532
Beta blocker (n, %)	103 (59)	19 (45)	84 (63)	0.045
Digoxin (n, %)	6 (3)	0 (0)	6 (4)	0.338*
Blood tests	n=176	n = 42	= 134	
Sodium (mmol/L) Median (IQR)	140 (137, 142)	140(137, 142)	140 (137, 143)	0.841
SCr (µmol/L) ** **Median (IQR)**	110 (86, 153)	135 (91, 200)	108 (85, 148)	0.036
eGFR⊙ (mls.min.1.73m²) Median (IQR)	52 (35, 71)	39 (26, 69)	55 (39, 71)	0.052
Urea (mmol/L) Median (IQR)	10.0 (7.6,15.9)	10.1 (7.7, 17.0)	9.9 (7.5, 15.4)	0.515
Haemoglobin (g/dL) Mean (±SD)	124±18	118±18	126±18	0.023
MCV (fl) Mean (±SD)	89.5±7.5	88.7± 8.3	89.7±7.3	0.471
RDW Median (IQR)	13.8 (12.9, 15.6)	14.4 (12.9, 15.6)	13.7 (13.0, 15.6)	0.262

eGFR◈ estimated glomerular filtration rate admission value. HF, heart failure; CKD, chronic kidney disease; Left ventricular dysfunction moderate or severe dysfunction on Echocardiography or cardiac angiography; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association. Evidence of fluid overload◆◆ includes raised JVP, Crepitations, Orthopnoea or ascites; Smoker◊ includes current and former. ** In the cohort, there were 12 cases with significant renal dysfunction on admission serum creatinine range 260 - 370mmol/L and not on renal replacement therapy; eGFR⊙ **e**stimated using the Modification Diet in Renal Disease simplified (MDRDs) formula.

4.4 Incidence of acute kidney injury

In the 176 patients eligible for the cohort baseline analyses, 42 (24%) developed acute kidney injury during the index admission. AKI was more likely to develop in patients with a history of diabetes (P=.002), confirmed chronic kidney disease (P=.010), or on admission with an elevated serum creatinine (P=.036), reduced eGFR (P=.052) or anaemia (P=.023) or not on ß-blocker medication (P=.045). These findings are highlighted in the above Table 4.1.

4.5 Primary outcome for AKI by the composite endpoint all-cause mortality or major acute cardiovascular event (MACE)

The primary outcome for the study was the composite endpoint time to all-cause mortality or major cardiovascular event (MACE) at 12 months follow-up from the time of discharge. MACE was defined as a ST elevation myocardial infarction (STEMI) or Non-STEMI, cardiac arrest or stroke. The condition in-hospital acute kidney injury, for patients surviving the index admission was analysed for its relationship to the study primary and secondary endpoints.

A total of 166 patients were available for survival analysis, ten patients having died during the index admission. There were 93 (56%) males and 73 (44%) females in the remaining cohort. Kaplan-Meier survival analysis illustrates the group survival curves for patients who did or did not develop AKI during the index admission for the 12-months follow-up period post index hospitalisation (Figure 4.2).

4.5.1 Kaplan-Meier survival analysis for AKI (WRF_72) status and the composite outcome all-cause mortality and MACE

During the 12-month post index admission follow-up period, 43 patients (25%) experienced an event; of these 8 (21%) had developed AKI during the index hospitalisation and 35 (27%) did not develop AKI. For the log-rank test for AKI groups for time to the composite endpoint there was no statistically significant difference between the survival functions (p=0.471). The Kaplan-Meier survival curve for the comparison is presented in the following figure (Figure 4.2).

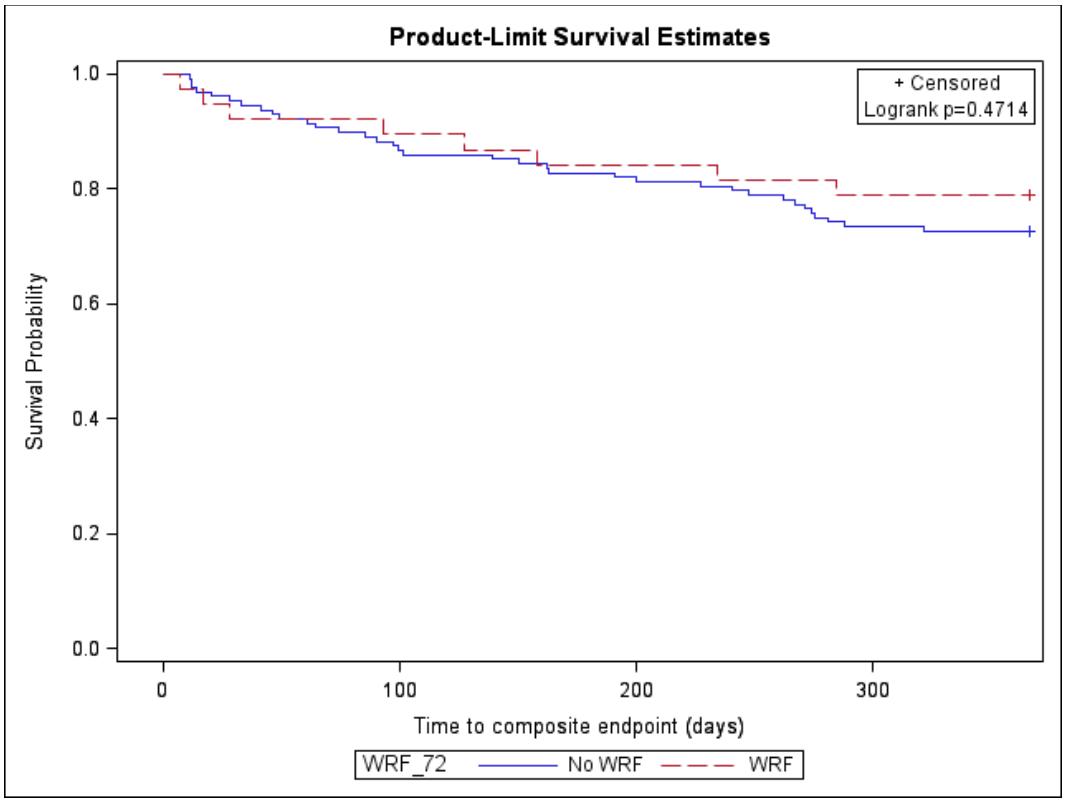

Figure 4.2 Kaplan-Meier survival curve acute kidney injury group status

The null hypothesis was retained, there being no statistically significant difference between AKI groups for the composite endpoint all-cause mortality and MACE. This result is examined in the discussion.

To determine if there was a statistically significant difference between groups for the number of events during the 12-month follow-up period a Chi Square analyse was performed. Again the Chi Square result showed no statistically significant difference between AKI groups, χ^2 (1) = 0.6042, *p*=0.437 (Table 4.2).

When comparing those without AKI to those with AKI the risk was 27% vs 21% (Table 4.3), for the composite event respectively, the difference is statistically non-significant (p=0.437) (Table 4.2).

Table 4.2 Statistic for composite outcome by AKI (WRF_72)

Statistic	**DF**	**Value**	**Probability**
Chi-Square	1	0.6042	0.4370

Table 4.3 Composite events by AKI (WRF_72)

Composite (Composite events)	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	35 (27%)	8 (21%)	43
No	93 (73%)	30 (79%)	123
Total	128	38	166

4.6 Secondary outcomes for acute kidney injury

The secondary outcomes of interest for the study cohort were again stratified by index admission AKI status. The intension was to determine if there was a significant difference between AKI groups for the total number of hospital re-admissions, emergency department presentations or total hospital bed days for the 12-month follow-up period from the time of index hospitalisation discharge. The index admission surviving cohort numbered 166 patients of which 38 (23%) had had an episode of AKI during the index admission leaving the remaining 128 (77%) patients AKI event free.

Table 4.4 summarises the test results for the Mann-Whitney U test for the independent variable acute kidney injury (AKI) defined in the database as WRF_72 for each of the dependent variables total re-admissions (Total_Hosp), total hospital bed days (TotalLOS) and emergency department presentations (TotalED_Presents). The statistical significance level was set at 0.05. Distributions of the dependent variables for AKI and no AKI were similar, as assessed by visual inspection. The following table (table 4.4) summary provides the medians and interquartile range (25^{th} and 75^{th}) for each outcome as well as the Mann-Whitney U value and p-value.

Table 4.4 Summary secondary endpoints for AKI group at 12-month follow-up

Outcome variable	AKI (WRF), Yes n= 38 (Median, IQR)	AKI (WRF), No n=128 (Median, IQR)	Mann-Whitney U (z-score)	P-value
Number of hospital readmissions	0 0 (0, 1)	0 (0, 1)	2596.5 (z=.654)	.513
Number of emergency department presentations	1 (0.75, 2.0),	1 (0.0, 2.0)	2677 (z=1.219)	.223
Total hospital bed days	13.5 (1, 26)	5.5 (0.0, 21.0)	2813 (z=1.480)	.139

For secondary endpoint 'Total re-admissions' there was no statistically significantly different between AKI status groups. Those with AKI median 0(0, 1), and those without AKI median 0(0, 1), U=2596.5, z=.654, p=.513. The mean ranks were AKI 87.83, no AKI 82.21. Again, for the endpoint 'Total emergency department presentations' AKI groups were not statistically significantly different: with AKI median 0 1(.75, 2.0), and those without AKI median 0 1(0.0, 2.0) U=2677, z=1.219, p=.223. The mean ranks were AKI 89.95, no AKI 81.59. Total hospital bed days were not statistically significantly different between those with AKI median 13.5(1, 26), and those without AKI median 5.5(0.0, 21.0) U=2813, z=1.480, p=.139. The mean ranks were AKI 93.53, no AKI 80.52. For each of the secondary outcomes measures at 12-months follow-up for an index admission of AKI the null hypothesis was retained.

4.7 Predictors for acute kidney injury

4.7.1 Introduction binary logistic regression modelling for predictors of AKI

Binary backward-step logistic regression was conducted to determine which variables were predictors for the development of worsening renal function (WRF) present as acute kidney injury. From the cohort characteristics Table 4.1, variables with a *p* value ≤0.1 were selected for inclusion in the modelling. Eight variables met this criteria, they were admission first systolic blood pressure (p=0.1), diabetes mellitus (p=0.002), Charlson Index (p=0.025), confirmed chronic kidney disease ≥Stage 3a (p=0.01), admission medication ß-blockers

(p=0.05), admission serum creatinine (p=0.04), estimated glomerular filtration rate (p=0.05), and haemoglobin (p=0.02). To address the possibility of multicollinearity and the impact this could have on the analysis and implications of the findings the renal function variables and the Charlson Index which includes renal and diabetes components were reviewed. The renal function variable 'confirmed chronic kidney disease ≥Stage 3a on admission' (*p*=0.01) was selected to represent renal function. Diabetes mellitus was included. The Charlson Index (CI) was not included in the regression analysis as renal disease and diabetes are components of the Index. Age was added giving a total of 6 independent variables for the regression analysis (admission first systolic blood pressure, diabetes mellitus, and confirmed chronic kidney disease ≥Stage 3a on admission, admission medication ß-blockers, haemoglobin and age calculated). With only six variables included in the regression analysis the rule of at least 10 participants per variable (Hayat 2013; Vittinghoff & McCulloch 2007) was satisfied.

One hundred and seventy five cases were included in the analysis, one case was missing due to the lack of haematology result and there were no unselected cases. The dependent variable worsening renal function was coded 0=no WRF, 1=WRF. All categorical variables were dichotomous (0=No; 1=Yes).

4.7.2 Regression modelling results for predictors of AKI

The overall model was statistically reliable in distinguishing between WRF status (i.e. acute kidney injury), χ^2 (3) = 18.691, p<.0001. In Table 4.5, the results for Cox & Snell R square and Nagelkerke R square which are considered pseudo-R^2 as this analysis was not a multiple regression explained 10.1% to 15.3% of the variance respectively. These values are relative low.

Table 4.5 Model summary

-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
171.850	.101	.153

The final model correctly classified 77.7% of cases. The specificity was 91.8%, the sensitivity 31.7% (Table 4.6), positive predictive value was 54.2%, and the negative predictive value was 81.5%.

Table 4.6 Model specificity and sensitivity

	PREDICTED WRF_72 (AKI)		
WRF_72 (AKI)	**NO AKI**	**AKI**	**PERCENTAGE CORRECT**
NO AKI	123	11	91.8%
AKI	28	13	31.7%
OVERALL PERCENTAGE			**77.7%**

For the final step, step 4, three variables remained; two were statistically significant. Regression coefficients are presented in Table 4.7 together with odds ratios and their 95% confidence intervals.

Table 4.7 Regression analysis results for predictors of AKI

Variable	df	Odds Ratio	95% CI	P-value
Diabetes (Composite Charlson Index – without & with end organ damage)	1	2.63	1.21, 5.71	**0.02**
Beta Blocker medication on admission	1	0.49	0.23, 1.03	0.06
CKD_Hx_Stage_III	1	2.63	1.21, 5.73	0.02

4.7.3 Summary: Predictors for AKI

The backward-step binary logistic regression was performed to determine the effect of diabetes mellitus (Type I & II), an admission history of chronic kidney disease, admission systolic blood pressure, age calculated, admission medication ß-blockers and admission haemoglobin on the likelihood of participants developing worsening renal function present as acute kidney injury. The logistic regression model was statistically significant, χ^2 (3) = 18.691, p< .0001.

Of the variables included, only two were statistically significant. Heart failure patients with the comorbidity diabetes at the time of admission were 2.63 (95% CI: 1.21, 5.71) times more likely to develop in-hospital worsening renal function present as AKI than patients without diabetes. Confirmed CKD at the time of admission was also identified as a predictor of AKI, Odds Ratio

2.63 (95%CI: 1.20, 5.73). Heart failure patients on ß-blockers at the time of admission were less likely to develop AKI (OR=0.48; 95%CI: 0.23, 1.03).

4.8 Characterisation of renal dysfunction in hospitalised heart failure patients

4.8.1 Prevalence of renal impairment, chronic kidney disease and severity by gender

From a total of 176 patients 104 (59%) were identified as having renal impairment (RI) at the time of the index hospital admission. RI determined by an admission estimated glomerular filtration rate (eGFR) of <60ml.min.1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation (O'Meara et al. 2006). Renal impairment (RI) is often reported as chronic kidney disease (CKD) (Damman et al. 2014) without necessarily confirming chronicity for the diagnosis. In the ReFinH Study, CKD was verified by historic review of the electronic medical record identifying 91 (52%) patients with confirmed chronic kidney disease. Figure 4.3 presents a breakdown of the cohort by gender and severity of renal dysfunction (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group 2013) based on the admission eGFR.

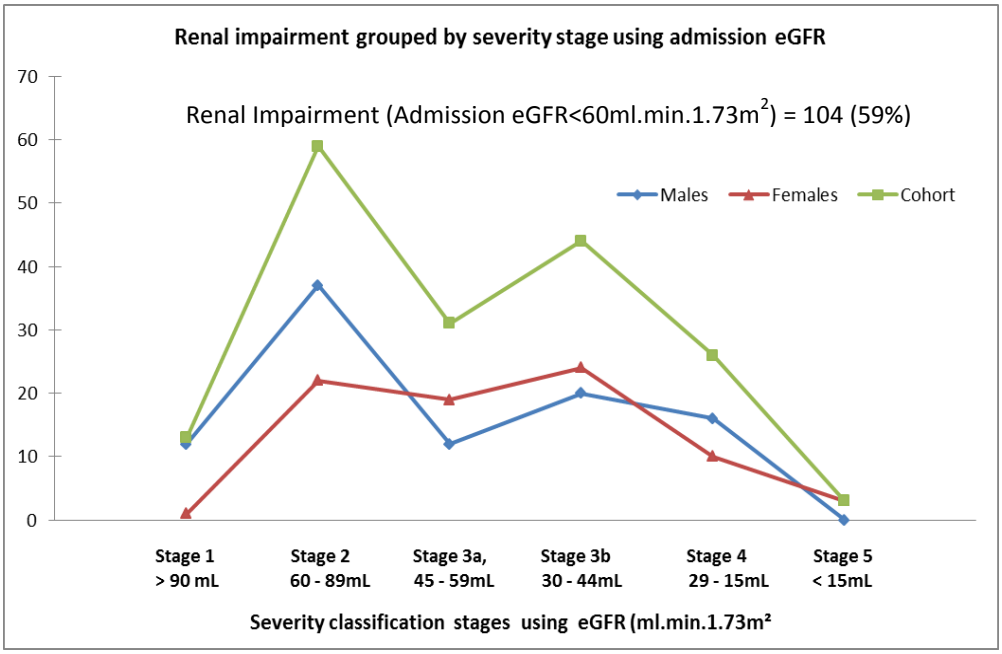

Figure 4.3 Renal impairment count for the cohort by gender and severity

A Chi-square test was run to test for an association between gender and chronic kidney disease. As women are considered to be more vulnerable to renal dysfunction table 4.8 shows the admission CKD stage, gender Chi-square crosstabulation.

Table 4.8 Admission chronic kidney disease stage by gender

Chronic Kidney Disease - Stage	Male (n=97)	Female (n=79)	Total (n=176)
Stage 1: >90 mL	12 (12.4%)	1 (1.3%)	13 (7.4%)
Stage 2: 60 to 89 mL	37 (38.1%)	22 (27.8%)	59 (33.5%)
Stage 3a: 45 to 59 mL	12 (12.4%)	19 (24.1%)	31 (17.6%)
Stage 3b: 30 to 44 mL	20 (20.6%)	24 (30.4%)	44 (25.0%)
Stage 4: 15 to 29 mL	16 (16.5%)	10 (12.7%)	26 (14.8%)
Stage 5: <15mL or RRT	0 (0%)	3 (3.8%)	3 (1.7%)
Total	97 (100%)	79 (100%)	176 (100%)
Association between gender and admission CKD stage χ^2 (5) = 17.759, p <0.003			

In the cohort, just over half (55%) of all patients were male (Table 4.1). However, for stages representing chronic kidney disease that is stages where the estimated glomerular filtration rate (eGFR) was <60mL, 71% of female and 51% of males can be classified as having CKD. Males (49%) were more likely to have normal or a mild decrease in renal function while in females this was only 29% (Table 4.8). A chi-square test for association was conducted between gender and confirmed chronic kidney disease (CKD). There was a statistically significant association between gender and CKD stage determined using admission eGFR, χ^2 (5) = 17.759, p <0.003.

4.8.2 Percent acute kidney injury (AKI) for confirmed CKD group and cohort

Figure 4.4 shows the association between chronic kidney disease and acute kidney injury.

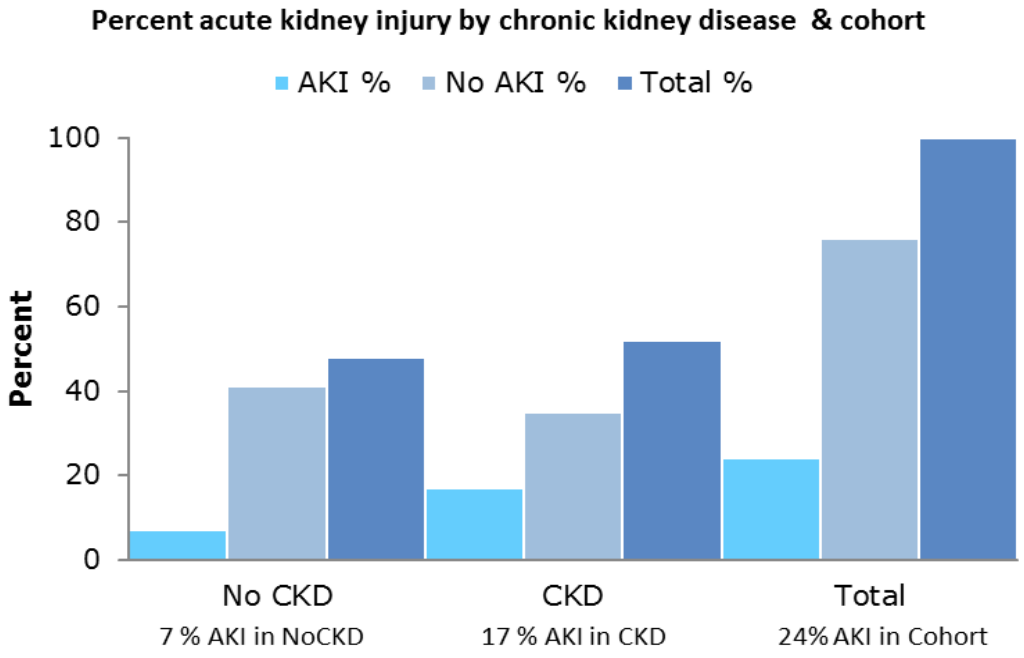

Figure 4.4 Percent acute kidney injury by chronic kidney disease and cohort

Patients with HF and CKD (eGFR<60ml.min.1.73m^2) are at greater risk for in-hospital worsening renal function (Cleland et al. 2012). For the cohort of 176 HF patients, 42 (24%) developed acute kidney injury (AKI) of which 91 (52%) had verified CKD. For those with CKD 17% developed AKI compared to only 7% in those without CKD.

A Chi-square test for association was run between confirmed chronic kidney disease (CKD) and development of acute kidney injury (AKI) represented by the variable WRF_72. There was a statistically significant association between confirmed CKD on admission and acute kidney injury χ^2 (1), 6.645, $p<0.01$. Of the 42 patients who developed AKI, 69% had confirmed CKD at the time of admission compared to 31% of AKI patients who did not have confirmed CKD (Table 4.9).

Table 4.9 Chronic kidney disease by AKI (WRF_72)

CKD (confirmed)	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	62	29	91
	46.3%	69.0%	51.7%
No	72	13	85
	53.7%	31.0%	48.3%
Total	134 (100%)	42 (100%)	176 (100%)
Association between CKD on admission and AKI: χ^2 (1), 6.645, p<0.01			

4.8.3 Age, gender and acute kidney injury

To explore the relationship between age group and acute kidney injury the file was split for gender (Table 4.10).

Table 4.10 Age group and acute kidney injury split for gender

Gender	Age groups (years)	AKI (WRF_72)		Total
		No-AKI	AKI	
Male	≤ 39	4 (5.4%)	1 (4.3%)	5 (5.2%)
	40 – 64	14 (18.9%)	6 (26.1%)	20 (20.6%)
	65 – 80	44 (59.5%)	13 (56.6%)	57 (58.8%)
	> 80	12 (16.2%)	3 (13.0%)	15 (15.5%)
	Total	**74** (100%)	**23** (100%)	**97** (100%)
Female	≤ 39	0 (0.0%)	1 (5.3%)	1 (1.3%)
	40 – 64	9 (15.0%)	0 (0.0%)	9 (11.4%)
	65 – 80	25 (41.7%)	6 (31.6%)	31 (39.2%)
	> 80	26 (43.3%)	12 (63.2%)	38 (48.1%)
	Total	**60** (100%)	**19** (100%)	**79** (100%)

Several cells for males and females had cell counts less than five. The less than 5 value for some cells violates one of the assumptions for running Chi-square test and the results are not reliable. However, it can be seen from the age group percentages by gender for AKI, there is a trend in females for acute kidney injury to occur in the older age groups with approximately two-thirds (63%) of those aged over 80-years experiencing AKI compared to only 13% for males. This observation is represented in the following figure 4.5.

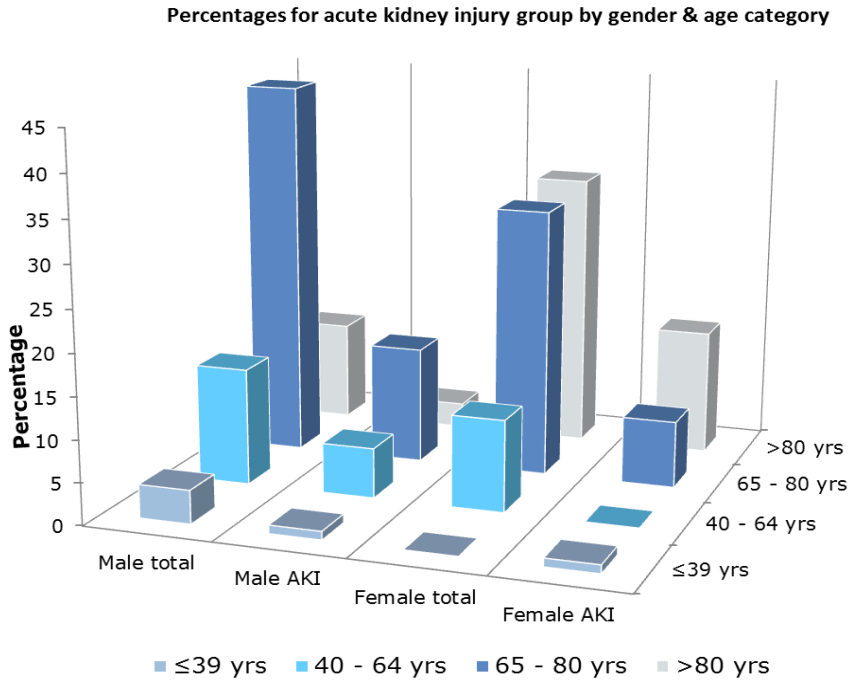

Figure 4.5 Cohort by age group, gender and acute kidney injury

A chi-square test for association was conducted between gender and age group. All expected cell frequencies were greater than five. There was a statistically significant association between gender and age group, χ^2 (3), 22.901, p<0.001. 87% of females were 65-years or over; while for men the percentage for over 65-years was 74%. For the entire cohort 50% were in the age category 65 to 80 years (Table 4.11).

Table 4.11 Age groups by gender

Age groups	In years	Gender		Total
		Male	Female	
	≤ 39	5 (5.2%)	1 (3.1%)	6 (3.4%)
	40 – 64	20 (20.6%)	9 (11.4%)	29 (16.5%)
	65 – 80	57 (58.8%)	31 (39.2%)	88 (50.0%)
	> 80	15 (15.5%)	38 (48.1%)	53 (30.1%)
	Total	**97** (100%)	**79** (100%)	**176** (100%)

4.8.4 Cohort comorbidities and acute kidney injury (AKI) group

Multiple comorbidities have become a clinical feature in chronic heart failure patients. They are an important aspect for characterising these patients as multiple comorbidities can complicate management and may influence renal function (Damman et al. 2014). Figure 4.6 highlights patient comorbidities and association with the incidence of AKI.

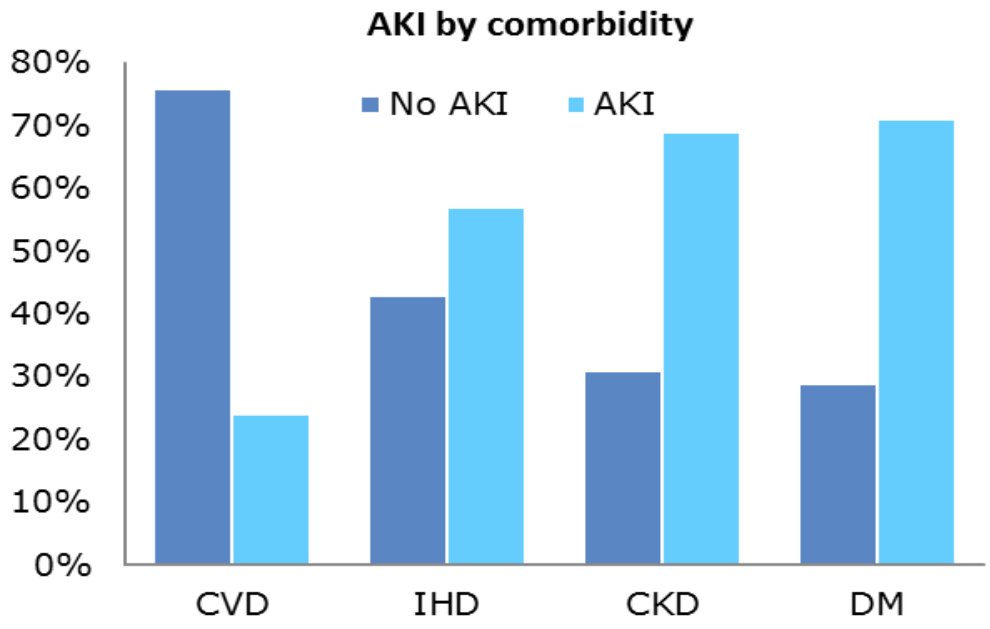

Figure 4.6 Prevalence of comorbidities by AKI status

Abbreviations: CVD: cerebrovascular disease; IHD: Ischaemic heart disease; CKD: Chronic kidney disease & DM: Diabetes mellitus. Percentages for comorbidities are based on Charlson Index results.

To determine if there was an association between the development of AKI and the most prevalent comorbidities (Figure 4.6) for the cohort Chi-square tests were used. Tables 4.12 to 4.16 summarise the results.

For cerebrovascular disease (CVD), the assumptions for Chi-square test were met. For the cohort 24% had a history of CVD and of those patients a quarter developed AKI (Table 4.12).

Table 4.12 AKI by Cerebrovascular disease (CVD)

CVD	**AKI (WRF_72)**		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	33 (24.6%)	10 (23.8%)	43 (24.4%)
No	101 (75.4%)	32 (76.2%)	133 (75.6%)
Total	134 (100%)	42 (100%)	176 (100%)
Association between CVD and the development of AKI: χ^2 (1), 0.012, p=.914			

A chi-square test for association was conducted between worsening renal function present as AKI and the presence of cerebrovascular disease (CVD). There was no statistically significant association between CVD and the development of AKI χ^2 (1), 0.012, p=.914.

For ischaemic heart disease (IHD), 101 patients (57%) in the cohort had a confirmed history of IHD. In patients with ischaemic heart disease, approximately 50% developed AKI compared to 43% of those without IHD (Table 4.13). A chi-square test for association was conducted between worsening renal function present as AKI and the presence of ischaemic heart disease (IHD). All expected cell frequencies were greater than five.

Table 4.13 AKI by Ischaemic heart disease (IHD)

IHD	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	77 (57.5%)	24 (57.1%)	101 (57.4%)
No	57 (42.5%)	18 (42.9%)	75 (42.6%)
Total	134 (100%)	42 (100%)	176 (100%)
Association between AKI and IHD: χ^2 (1), 0.001, p=0.971			

There was no statistically significant association between AKI and IHD χ^2 (1), 0.001, p=0.971.

Patients with CKD were more likely to developed AKI compared to those without CKD (Table 4.14).

Table 4.14 AKI by chronic kidney disease (CKD)

CKD (confirmed)	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	62 (46.3%)	29 (69.0%)	91 (51.7%)
No	72 (53.7%)	13 (31.0%)	85 (48.3%)
Total	134 (100%)	42 (100%)	176 (100%)
Association between AKI and confirmed CKD: χ^2 (1) 6.645, p< 0.01			

For patients with HF and confirmed CKD it has already been reported the prevalence was 52%. A chi-square test for association was conducted between worsening renal function present as AKI and the presence of confirmed chronic kidney disease (CKD). All expected cell frequencies were greater than five. There was a statistically significant association between AKI and confirmed CKD, χ^2 (1) 6.645, p< 0.01.

Table 4.15 AKI by diabetes mellitus

Diabetes	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	59 (44.0%)	30 (71.4%)	89 (50.6%)
No	75 (56.0%)	12 (28.6%)	87 (49.4%)
Total	134 (100%)	42 (100%)	176 (100%)
Association between AKI and diabetes: χ^2 (1), 9.603, p<0.002			

Diabetes mellitus (DM) is a composite for Type I and Type II, with a prevalence of 51% for the cohort. Of the HF patients with diabetes, 71% developed AKI compared to 29% (Table 4.15) without the condition. A chi-square test for association was conducted between worsening renal function present as AKI and the presence of diabetes. All expected cell frequencies were greater than five. There was a statistically significant association between AKI and diabetes, χ^2 (1), 9.603, p<0.002.

4.8.5 Admission haemoglobin by gender and AKI

The minimal normal haemoglobin (Hb) value for males is <130g/L and for females <120g/L (World Health Organization (WHO) 2011). For the cohort the mean Hb was 124g/L; Hb for those with AKI 118g/L (±18) compared to those without AKI 126g/L (±18) p=0.023. When Hb results were split by gender, the data no longer were normally distributed as a consequence a Mann-Whitney U Test was used to assess the Hb distribution for gender and AKI. The distribution for haemoglobin (Hb) for AKI and no AKI were similar for females but not for males, as assessed by visual inspection. Hence, for males the mean ranks are provided. The results are summarised in the following Table 4.16 which include the medians and interquartile range (25^{th} and 75^{th}) for each outcome as well as the mean ranks for the results.

Table 4.16 AKI by haemoglobin (Hb) and gender

Outcome variable	AKI (WRF), Yes n= 42 (Median, IQR)	AKI (WRF), No n= 134 (Median, IQR)	Mann-Whitney U (z-score)	P-value
Male haemoglobin (Hb)	**Mean rank 44.98** 124g/L (105,140)	**Mean rank 50.20** 126g/L (114,145)	758.5	0.433
Female haemoglobin (Hb)	112g/L (97,129)	122g/L (111,137)	350.5 (z=2.248)	0.025

Table 4.16 summarises the test results for the Mann-Whitney U test for acute kidney injury (AKI) defined in the database as WRF_72 admission haemoglobin by gender. The statistical significance level was set at 0.05. The table 4.16 summary provides the medians and interquartile range (25^{th} and 75^{th}) for each outcome as well as the Mann-Whitney U value and p-value. Haemoglobin was statistically significantly different in females between those with AKI median 112(97,129), and those without AKI median 122(111,137) U=350.5, z=-2.248, p=0.025. The mean ranks were lower for AKI 28.97 compared to no AKI 42.66. Haemoglobin was not statistically significantly different in males between those with AKI median 124(105,140), and those without AKI median 126(114,145) U=758.5, z=-0.785, p=.433 (Table 4.16) but as the distributions were no similar for males the presented; mean rank was lower in AKI 44.98 than for no AKI 50.25.

4.8.6 Admission medication management by AKI group

Characterisation of the cohort also involves a review of medications on admission. Figure 4.7 summarises baseline medication categories in the case report for acute kidney injury group.

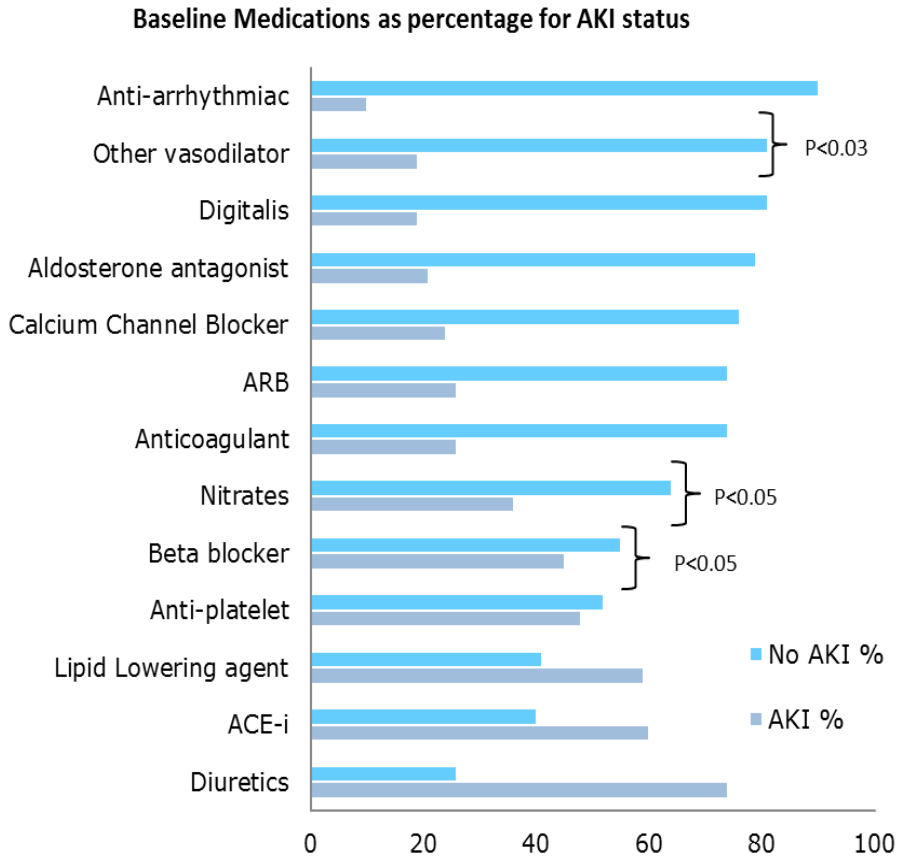

Figure 4.7 Admission medications by percent for AKI group

Chi-square tests were run to test for an association for each medication group with acute kidney injury. Test results showed only the drug categories ß-blockers (Table 4.17), Nitrates (Table 4.18) and 'Other vasodilators' (Table 4.19) had a statistically significant association with AKI.

4.8.7 Beta Blocker medication by AKI (WRF_72)

Table 4.17 depicts the chi-square output for acute kidney injury and ß-blocker medication on admission. For HF patients not taking ß-blocker 55% develop AKI compared to 45% taking the medication.

Table 4.17 AKI by ß-blockers medication on admission

Beta Blocker	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	84 (62.7%)	19 (45.2%)	103 (58.5%)
No	50 (37.3%)	23 (54.8%)	73 (41.5%)
Total	134 (100%)	42 (100%)	176 (100%)
Association between AKI and ß-blocker medication on admission: χ^2 (1), 4.011, p<0.05			

A chi-square test for association was conducted between worsening renal function present as AKI and the ß-blockers medication on admission. There was a statistically significant association between AKI and ß-blockers medication on admission, χ^2 (1), 4.011, p<0.05.

4.8.8 Nitrate medications and acute kidney injury

Chi-square test was run to determine if there was an association between nitrate medication use on admission and acute kidney injury (Table 4.18).

Table 4.18 AKI by Nitrate medication on admission

Nitrates	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	28 (20.9%)	15 (35.7%)	43 (24.4%)
No	106 (79.1%)	27 (64.3%)	133 (75.6%)
Total	134 (100%)	42 (100%)	176 (100%)
Association between AKI and nitrates on admission: χ^2 (1) 3.803, p = 0.05			

An association between nitrate medication use and acute kidney injury was evident. The percentage for those not taking nitrates and developing AKI was 64% compared to 36% in those on nitrates at the time of admission. There was a statistically significant association between AKI and nitrates on admission, χ^2 (1) 3.803, p = 0.05.

4.8.9 Other vasodilator medication on admission and acute kidney injury

A chi-square test for association was conducted between worsening renal function present as AKI and other vasodilator medication on admission (Table 4.19).

Table 4.19 AKI by Other vasodilator medications

Other Vasodilator	AKI (WRF_72)		
Frequency	**No AKI (WRF)**	**AKI (WRF)**	**Total**
Yes	10 (7.5%)	8 (19.0%)	18 (10.2%)
No	124 (92.5%)	34 (81.0%)	158 (89.8%)
Total	134 (100%)	42 (100%)	176 (100%)
Association: AKI and other vasodilator medication on admission: χ^2 (1), 4.674, p<0.03			

The variable 'Other vasodilator' was a composite variable consisting of medications that were not already covered by the medication categories identified in Figure 4.7. An example of the medications fall into the category 'Other vasodilator' are combination drugs such as Karvezide which is a combination of s diuretic and an angiotensin II receptor antagonist. There was a statistically significant association between AKI and other vasodilator medication on admission, χ^2 (1), 4.674, p<0.03.

4.8.10 Maximum intravenous diuretics daily dose and AKI status

Large doses of diuretics during HF hospitalisation have been identified as a potential predictor for worsening renal function (Butler et al. 2004). The variable Intravenous diuretics maximum daily dose (IV Diuretic MaxDD) failed the critical assumption of normality needed for a t-test. As a consequence, the Mann-Whitney U test was used to determine if there was a statistically significant difference in maximum intravenous (IV) diuretics daily dose for acute kidney injury groups (Figure 4.7). Distributions of the maximum IV diuretics daily dose for AKI groups were not similar as assessed by visual inspection. Maximum IV daily dose was not statistically

significantly different between the two AKI groups for the mean ranks. There was no statistical significant difference in the maximum daily dose of intravenous diuretics for the AKI group (mean rank 94.89) and for the group without AKI (mean rank 85.82), U= 2503.5, Z = -1.067, P =.286. The null hypothesis was retained. For this reason, the maximum IV diuretics daily dose variable was not included in binary logistic regression modelling.

4.8.11 Renal impairment status and the composite outcome all-cause mortality and MACE

The Kaplan-Meier survival curve for the composite outcome all-cause mortality and major acute cardiovascular event comparison for those with renal impairment is shown in Figure 4.8. This analysis enhances the characterisation of the cohort.

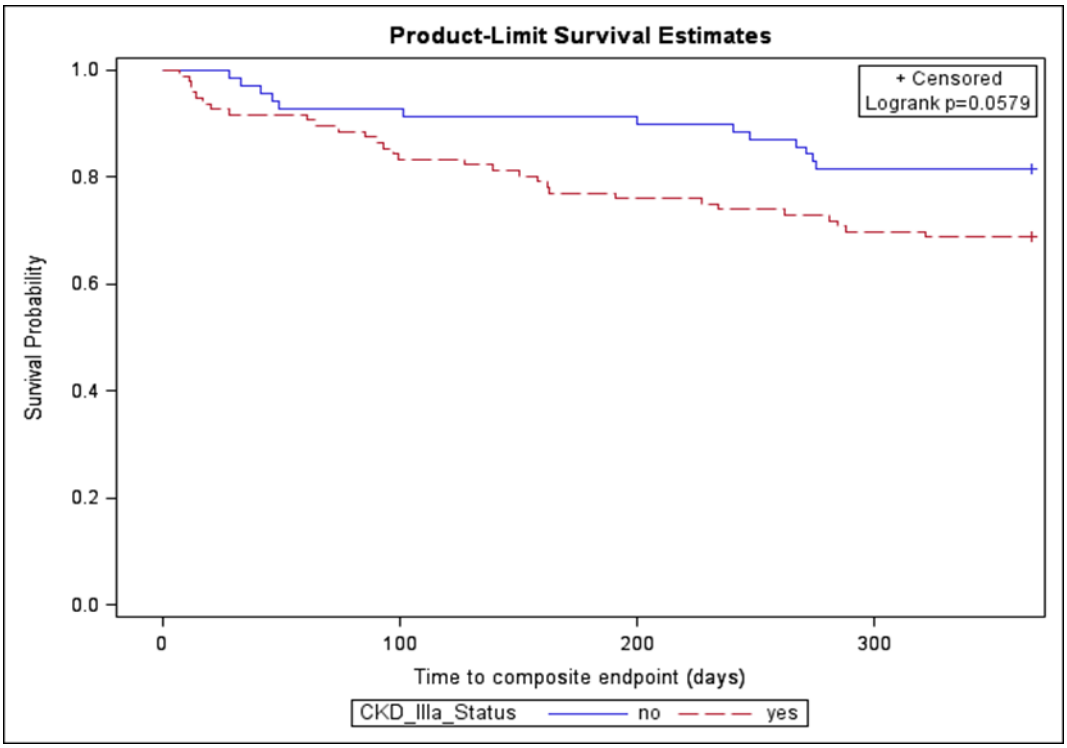

Figure 4.8 Kaplan-Meier survival analysis for renal impairment

A total of 166 patients survived the index hospitalisation; 96 (58%) patients were classified as having renal dysfunction. During the 12-month post index admission follow-up period of the 43 events, 30 (31%) had renal impairment while 13 (19%) did not. .The log-rank test for RI groups for time to the composite endpoint, there was no statistically significant difference between the survival functions (p=0.0579). However, it was trending towards significance, with RI patients at increasing risk. The null hypothesis was retained, there being no statistically significant difference between RI groups for the composite endpoint all-cause mortality and MACE.

To determine if there was a statistically significant difference between RI groups for the number of events during the 12-month follow-up period a Chi Square analyse was performed. When comparing those without RI to those with RI the risk was 15.6% vs 31.2% for the composite event respectively, there was no statistical significant difference, χ^2 (1) = 3.39, *p*=0.066.

4.8.12 Chronic kidney disease (CKD) status and the composite outcome all-cause mortality and MACE

Chronic kidney disease has been identified as a significant comorbidity in heart failure patients. Figure 4.9 represents the Kaplan-Meier survival curve for the two cohort groups defined as those with confirmed CKD on index hospitalisation and those free of CKD.

The Figure 4.9 highlights the finding of no statistically significant difference between groups for survival at 12-months follow-up from index discharged. For patients who were discharged from the index admission alive, 51% had CKD.

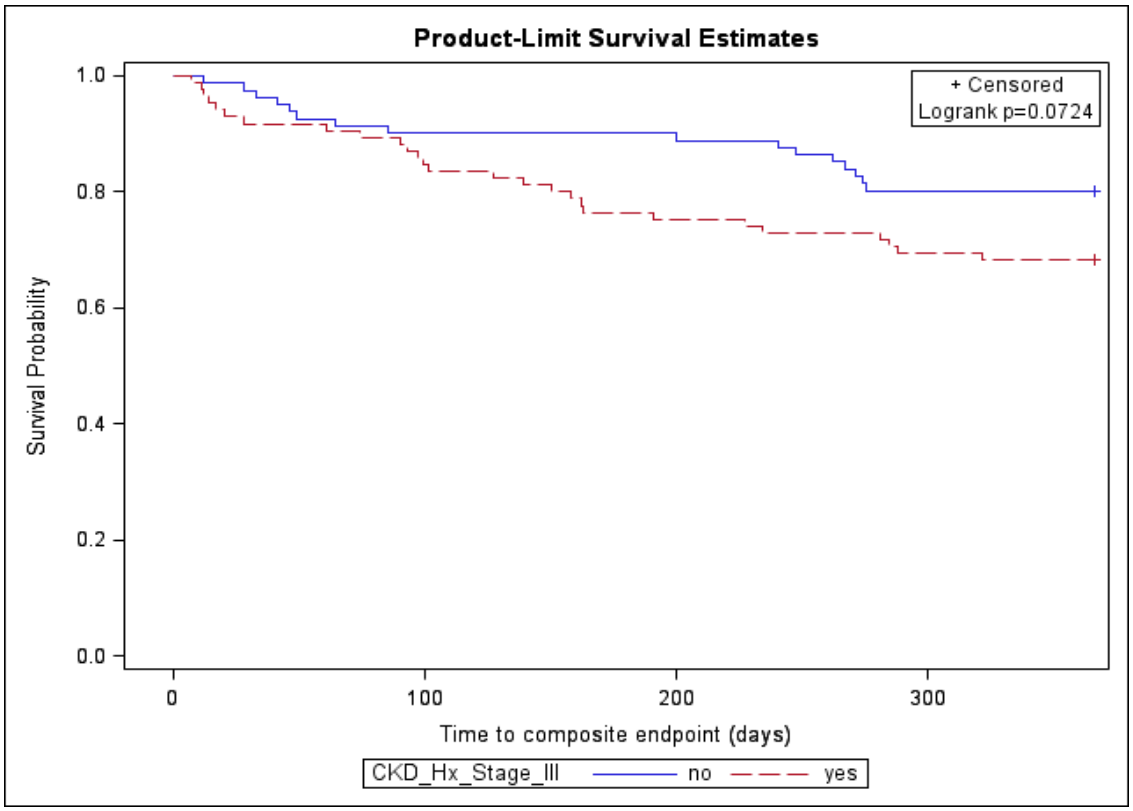

Figure 4.9 Kaplan-Meier survival analysis for confirmed chronic kidney disease

To determine if there was a statistically significant difference between CKD groups for the number of events during the 12-month follow-up period a Chi Square analysis was performed. When comparing those without CKD to those with CKD the risk was 19.8% vs 31.8% for the composite event respectively, there was no statistical difference, χ^2 (1) = 3.12, *p*=0.077

4.8.13 Renal impairment and chronic kidney disease secondary outcomes at 12-months follow-up

To complete the characterisation of renal dysfunction in hospitalised HF patients, features of the cohort by the presence of RI or CKD are described for the secondary outcomes of interest. Secondary outcomes for the cohort were the total number of hospital re-admissions, emergency department presentations and total hospital bed days for the 12-month follow-up period from the time of discharge from the index hospitalisation. The index admission surviving cohort numbered 166 patients, of which 96 (58%) had an RI while the remaining 70 (42%) were RI free on index admission.

Table 4.20 Secondary outcomes – renal impairment

Outcome variable	RI, Yes n= 96 (Median, IQR)	RI, No n=70 (Median, IQR)	Mann-Whitney U (z)	P-value
Number of hospital readmissions	1 (0,2)	1 (0,1)	3774.5 (1.402)	0.161
Number of emergency department presentations	0 (.00, 1.0)	0 (.00, 1.0)	3370 (0.42)	0.966
Total hospital bed days	9 (1.0, 27.5)	4 (0.0, 20.3)	3925 (1.867)	0.062

To test if there was a statistically significant difference in distribution for the dependent variables total readmissions, emergency department presentations and hospital bed days at 12-month follow-up between independent group variables RI and CKD the Mann-Whitney U test was run. The non-parametric test was used as all the dependent variables failed the critical assumption for normality for a t-test. All dependent variables met the assumption of a similar shape distribution for each independent variable (RI and CKD). Table 4.20 is the RI summary for the medians and interquartile range (25^{th} and 75^{th}) and Mann-Whitney U and z-score for each outcome.

4.8.14 Chronic kidney disease and secondary outcomes

The non-parametric Mann-Whitney U test was used to determine the impact of confirmed chronic kidney disease (CKD) on the secondary endpoints for the study; total hospital bed-days, emergency department presentations and hospital readmissions for the 12-month follow-up period. The results are summarised in the following table 4.21.

Table 4.21 Secondary outcomes – chronic kidney disease

Outcome variable	CKD, Yes n= 85 (Median, IQR)	CKD, No n=81 (Median, IQR)	Mann-Whitney U (z)	P-value
Number of hospital readmissions	1 (0.0, 2.0)	1 (0.0, 2.0)	4020.5 (1.931)	.053
Number of emergency department presentations	0 (0.0, 1.0)	0 (0.0, 1.0)	3445 (.010)	.992
Total hospital bed days	14 (1, 30)	3 (0.0, 17.0)	4372.5 (3.036)	.002

Table 4.21 summarises the hypothesis test results for the Mann-Whitney U test for the independent variable confirmed chronic kidney disease (CKD) for the database variable labelled CKD_III_ADM_Status for each of the dependent variables total re-admissions (Total_Hosp), total hospital bed days (TotalLOS) and emergency department presentations (TotalED_Presents). Distributions of the dependent variables for CKD and no CKD were similar, as assessed by visual inspection. Table 4.21 is a summary for the medians and interquartile range (25^{th} and 75^{th}) and Mann-Whitney U and z-score for each outcome.

4.9 Conclusions

The ReFinH study has shown every second patient had CKD, one in four developed acute kidney injury and this was associated with a history of CKD, diabetes, abnormal admission serum creatinine and eGFR, anaemia and the taking of ß-blocker medications. For the combined endpoint all-cause mortality and MACE for patients with and without WRF (i.e. AKI) the Kaplan-Meier survival analysis was not statistically different for WRF (AKI) groups (log-rank test: P=.471). There were no statistically significant differences between the AKI groups for the

secondary outcomes for the 12-month follow-up period for total hospital bed days, emergency department presentations or hospital readmissions. Potential predictors for in-hospital worsening of renal function present as acute kidney injury were a history of CKD, diabetes mellitus (Type I & II), admission systolic blood pressure, an elevated serum creatinine on admission and renal impairment defined as an eGFR<60ml.min.1.73m², ß-blockers medication and haemoglobin. The only statistically significant variables in the regression modelling were diabetes mellitus (Type I & II) and a confirmed history of CKD.

Investigation of characteristics associated with renal dysfunction in this cohort of hospitalised HF patients identified age, gender, and the association of incidence of AKI which was 24% and the prevalence of RI (59%) and confirmed CKD (52%). The only statistically significant difference for either the primary or secondary outcomes was for total hospital bed days for the 12-month follow-up period for HF patients identified with CKD.

In the following chapter, these results are discussed and the implications of the findings considered.

4.10 References

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Chapter 5 Discussion

5.1 Introduction

The main findings for this Australian 'Renal function in chronic heart failure cohort study' (ReFinH) were as follows. First, the composite outcome all-cause mortality and major acute cardiovascular event (MACE) for hospitalised heart failure patients who developed worsening renal function (WRF) present as acute kidney injury (AKI) compared to those who did not was not statistically significantly different. Second, there was no statistically significant difference between HF patients with AKI compared to no AKI for the secondary endpoints total re-admissions, emergency department presentations and total hospital bed days for the 12-month follow-up period. Third, several predictors for acute kidney injury in hospitalised heart failure were identified.

The study added support for the utility of a modified Acute Kidney Injury Network AKI definition for use in hospitalised heart failure patients by its incidence result and highlighted the need to differentiate renal impairment (RI) from confirmed chronic kidney disease (CKD). The analysis has provided insights into renal dysfunction in HF, an increasingly important clinical aspect of HF management and prognosis from an Australian perspective for which there has been a paucity of data. The ReFinH study has extended the characterisation of Australian hospitalised HF patients with renal dysfunction and exposed the importance of definitions and nomenclature for this clinical entity in HF.

The characterisation of the ReFinH cohort was facilitated by Kaplan-Meier survival analysis (Collett 2002) for the study's composite outcome all-cause mortality and MACE for HF patients with renal impairment (RI) versus those with normal renal function on admission and for HF patients with confirmed chronic kidney disease (CKD) against those patients without this condition. These analyses demonstrated no statistically significant difference between groups for RI/ no RI; or CKD/ no CKD respectively by demonstration of separation of the curves. HF patients who presented with an estimated glomerular filtration rate (eGFR) of ≤60ml.min.1.73m² defining renal impairment (RI) compared to HF patients with normal renal function also showed no statistically significant difference for the secondary outcomes for the 12-month follow-up period. The secondary outcomes for HF patients with a confirmed history of chronic kidney disease (CKD) compared to HF patients without CKD were similar except for total hospital bed days. In patients with CKD, 'total hospital bed days' were statistically significant, greater than for HF patients free of CKD. An important caveat when interpreting the above results is the limitation of the study in not achieving the required sample size of 288 participants.

Yet paradoxically a number of baseline characteristics were statistically significantly different for the cohort when stratified by the presences of acute kidney injury (AKI). The clinical variables of a history of diabetes or chronic kidney disease or anaemia on admission, or the use of ß-blocker medication at the time of admission were among these variables. This trend was continued for AKI versus no AKI for admission serum creatinine and estimated glomerular filtration rate (eGFR). Potentially the most interesting clinical variable with a statistical significant difference for AKI versus no AKI was the weighted Charlson Index which highlighted the increased comorbidity burden in patients who developed AKI.

Incidence and prevalence rates for AKI, and RI and CKD respectively were at the upper margins found in the published literature (Akhter et al. 2004; Breidthardt et al. 2011; Damman, Valente, Voors, O'Connor, et al. 2014; Forman et al. 2004). In ReFinH the incidence of acute kidney injury was 24% while the prevalence of renal impairment was 59%, and for confirmed chronic kidney disease 52%. In such a setting of high incidence and prevalence rates for the various manifestations of renal dysfunction in this HF cohort the non-significant mortality and morbidity findings are not what may have been expected, especially given the weight of the contemporary cardio-renal literature for the prognostic importance of renal dysfunction in hospitalised HF patients (Coca et al. 2007; Damman, Valente, Voors, O'Connor, et al. 2014). The findings may be the result of the study not achieving the projected sample size of 288 participants required for endpoint analyses.

In previous chapters, the importance of renal dysfunction as a prognostic marker in heart failure (HF) for adverse events has been established. The literature review which presented numerous studies and several meta-analyses (Coca et al. 2007; Damman, Valente, Voors, O'Connor, et al. 2014; Smith et al. 2006) were unequivocal in their finding that renal dysfunction described as renal impairment or in-hospital worsening renal function carried a substantial prognostic influence.

This chapter considers the findings from the ReFinH Study in the context of the published studies and meta-analyses. The implications of the findings are then presented.

The structure of the chapter begins with an examination of the incidence of AKI (section 5.2), and the prevalence findings for RI (5.3)) and CKD (5.4) against the international literature, and the influence definitions can have for these findings. Characterisation of the ReFinH cohort continues in sections 5.5 where age, gender, comorbidity burden and pre-existing renal disease for the cohort are discussed. In 5.6, the predictors of AKI for the ReFinH cohort are reviewed for their consistency with the published literature. Here again definitions for WRF are

woven into the discussion as they influence outcomes and hence the defining features for those who develop AKI. With the portrait of the cohort completed and the context established, section 5.7 examines the ReFinH survival analysis for the primary composite endpoint specifically for AKI status while in 5.8 the secondary outcomes with a morbidity focus are considered. In 5.9, the implications of the study findings are examined with an emphasis on the key contribution these results have for Australian clinical practice and more generally. Finally, in 5.10, the summary completes the chapter with closing remarks.

5.2 Incidence of acute kidney injury

Approximately one in four ReFinH patients developed acute kidney injury. This incidence rate of 24% AKI is comparable with previous published studies where the prevalence of worsening renal function in HF has been variously estimated to be 11% to 45% (Damman et al. 2009; Smith et al. 2003; Verdiani, Lastrucci & Nozzoli 2010). These variations have been attributed to the absence of a consensus definition and to the diversity in patient populations and settings (Atherton et al. 2012; Coca et al. 2007; Damman et al. 2009; Heywood et al. 2007; Smith et al. 2006). Informed by this caveat attention is given to the definitions, populations and settings.

5.2.1 Definitions and acute kidney injury in heart failure

In the literature review, it was noted definitions support shared understanding and knowledge development. In the absence of definitions, ambiguity hinders our ability to interpret the data. Mindful of the need for clarity the WRF criteria for the ReFinH Study necessitated consistency with the HF cardio-renal literature as well as ensuring definitive criteria that maintained continuity with established nephrology AKI metrics. Taking this position placed the concept of acute kidney injury alongside that or WRF and enabled the testing of the definition and its utility in a generalised population of hospitalised HF patients. For this reason, the ReFinH Study definition for worsening renal function incorporated the most commonly used cardiology increment in serum creatinine, an increase of ≥26.5µmol/l (≥0.3mg/dl) (Damman et al. 2007; Damman, Valente, Voors, O'Connor, et al. 2014; Gottlieb et al. 2002; Krumholz et al. 2000), which is also the diagnostic level for the Acute Kidney Injury Network (AKIN) definition (Mehta et al. 2007) which ReFinH modified by extending the timeframe for renal biomarker change to 72-hrs. The time modification having been informed by the studies of Gottlieb et al (Gottlieb et al. 2002) and Forman et al (Forman et al. 2004) who had observed the vast majority of hospitalised HF patients who developed in-hospital WRF did so within the first 3-days of admission.

The ReFinH cohort was a generalised population in a hospitalised setting. No distinction was made with regards to heart failure with preserved ejection fraction (HFpEF) versus HF with reduced ejection fraction (HFrEF). The available clinical data for the ReFinH cohort restricted the ability to make this differentiation as reference to the type of HF was rarely documented in the clinical notes nor were left ventricle ejection fraction or fractional shorting values consistently recorded. With these conventions in place, it facilitates meaningful comparisons of the ReFinH data against existing studies. Studies with similar definitions, populations and settings include those of Gottlieb et al (Gottlieb et al. 2002), Forman et al (Forman et al. 2004) Verdiani et al (Verdiani, Lastrucci & Nozzoli 2010), Breidthardt et al (Breidthardt et al. 2011), and the heart failure registry study, by Heywood et al (Heywood et al. 2007). It is these studies against which much of the discussion has been referenced. However, where relevant a broader approach has been adopted to reflect the scope of the cardio-renal published literature.

5.2.2 ReFinH with the context of published literature

Contemporary HF studies investigating the influence of renal function have focused on incidence, predictors and the relationship of worsening renal function with mortality. Hillege et al (Hillege et al. 2000) Krumholz et al (Krumholz et al. 2000) and Gottlieb et al (Gottlieb et al. 2002) were among the first investigators to establish the prognostic importance of in-hospital WRF.

Krumholz et al (Krumholz et al. 2000) defined WRF as an increase in serum creatinine of >0.3mg/dl (>26.5µmol/l) over the admission value which occurred during hospitalisation. They found 28% incidence of WRF for their cohort which after adjusting for confounders was associated with statistically significant hospital length of stay (2.3 days), higher admission costs, and an increased risk of in-hospital mortality with the odds ratio 2.72; (95% CI 1.62, 4.58).

In 2002 the prognostic importance of different definitions of WRF in hospitalised CHF patients were investigated by Gottlieb and colleagues (Gottlieb et al. 2002). Their method was a chart audit of patients who had a principle discharge diagnosis of HF using ICD-9-Codes, and confirmed by the documentation of at least one HF sign and symptom. The study criteria enabled the evaluation of the importance of various WRF definitions in a typical adult HF patient population for incidence, length of hospital stay and in-hospital mortality. ReFinH followed this methodology of patient identification and HF confirmation.

In the study by Gottlieb et al (Gottlieb et al. 2002) the incidence of WRF was depended on the definitional threshold and the timeframe. As the serum creatinine required for the definition

of WRF increased from 0.1mg/dl by 0.1mg/dl increments to 0.5mg/dl over a timeframe of up to 15 days, the incidence of WRF decreased from 72% to 20% respectively where the majority of patients developing WRF within 3-days. Although an increase, of ≥0.3mg/dl (≥26.5µmol/l) demonstrated the best overall specificity (62%) and sensitivity (81%) for mortality; as the threshold for WRF increased, the mortality specificity also increased. In Gottlieb's study, the incidence of WRF reflected the definitional threshold. Smith et al (Smith et al. 2003) conducted a very similar study confirming the findings by Gottlieb (Gottlieb et al. 2002) and noted a linear trend as the severity of WRF increased so also the mortality rate. Other investigators have also used the in-hospital WRF definition threshold of an increase in serum creatinine of >3mg/dl (26.5µmom/l) has been found to be relevant in terms of incidence and outcomes. Forman etal (Forman et al. 2004) and Belziti et al (Belziti et al. 2010) in their hospitalised HF cohorts also reported WRF prevalence as 27% and 23% respectively. The ReFinH Study in terms of the incidence of AKI (WRF) is consistent with these findings but did not support the increased mortality findings.

However, not all cardio-renal HF studies have found 20% plus incident rates for HF in-hospital WRF. A study by Verdiani, Lastrucci and Nozzoli (Verdiani, Lastrucci & Nozzoli 2010) used the common WRF criteria of an increase in serum creatinine of ≥0.3mg/dl (26.6µmom/l) from over admission value which need to be maintained until discharge. To account for the lower prevalence of WRF they suggested the biomarker was only transitorily affected hence the 11% prevalence.

5.3 Prevalence of renal impairment

Renal impairment is generally defined as a baseline (admission) estimated glomerular filtration rate (eGFR) of <60ml.min.1.73m² (Brandimarte et al. 2012; Damman, Valente, Voors, O'Connor, et al. 2014). The term renal impairment is sometimes incorrectly used to refer to chronic kidney disease as RI does not take into account the 3-month duration criteria required for a CKD diagnosis. This may help explain why the prevalence of renal impairment, or as it is sometime referenced, chronic kidney disease in HF varies from 33% (Khan et al. 2006) to 64% (Heywood et al. 2007). Here again settings and populations may affect these results. In the ReFinH Study RI prevalence was 59% which is towards the upper margins for RI in HF (de Silva et al. 2006; Heywood et al. 2007).

Numerous studies had investigated the relationship between hospitalised HF and renal impairment (Damman et al. 2009; Heywood et al. 2007; Hillege et al. 2000; Khan et al. 2006). A retrospective analysis of the randomised control trials (RCT) *Second Prospective Randomized*

study of Ibopamine on Mortality and Efficacy (PRIME-II) by Hillege et al. (Hillege et al. 2000) investigated the frequency and impact of RI in HF. Hillege calculated GFR using the Cockcroft-Gault (GFRc) equation (Cockcroft & Gault 1976) to determine study outcomes. They assessed GFRc at baseline and at various intervals over 1091-days of follow-up. Baseline GFRc of <59mL.min was present in approximately 50% of patients. The study reported a stepwise increase in mortality risk with decreasing GFRc quartiles.

In ReFinH, the GFRc equation was not used. Instead, the Modification of Diet in Renal Disease (MDRD) formula was used to determine the estimated GFR as this was the equation routinely used by the study site pathology laboratory. Other formulae can also be used to determine the estimates for GFR. The Cockcroft-Gault equation (Cockcroft & Gault 1976), or the MDRD (O'Meara et al. 2006) or the simplified MDRD equation have been validated in HF populations and shown to produce very similar values for eGFR (Smilde et al. 2006). The similarity in prevalence with the Hillege et al. (Hillege et al. 2000) study of at least 1 in 2 patients with RI confirms the ReFinH Study RI prevalence of 59% as a realistic finding.

Damman and colleagues (Damman et al. 2009), used the COACH Study (Jaarsma et al. 2004) data in a retrospective analysis to determine the effects of renal impairment and WRF by WRF post discharge care as either intensive or standard. COACH which was a multicentre RCT defined in-hospital WRF as a serum creatinine increase of >26.5µmom/l (>0.3mg/dl) or a >25% increase between two time points and renal impairment described as CKD as an eGFR<60ml.min.1.73m² has several relevant findings. The salient features to take from the COACH study results for ReFinH is the average eGFR and prevalence of RI. For COACH the mean eGFR was 55±21ml.min.1.73m² and renal impairment prevalence 59%, while for ReFinH the cohort had mean eGFR 54±24ml.min.1.73m² and RI of 59%. The results of the two studies were similar.

Another important source of data for studying the prevalence and impact of renal dysfunction in HF has been HF registries. Heywood and colleagues (Heywood et al. 2007) accessed data for the time period October 2001 to July 2004 from the multicentre database known as the 'Acute Decompensated Heart Failure National Registry (ADHERE) to investigate the prevalence of renal dysfunction and its impact on outcomes in 118, 465 patients who had data available for the analysis. The sMDRD formula was used to calculate eGFR. The ADHERE based study detected in-hospital clinical outcomes worsened with increasing severity of renal dysfunction. At admission, eGFR was normal in only 9.0% (eGFR ≥90ml.min.1.73m²) of the patients, the remaining 91% had varying degrees of renal dysfunction. In the ADHERE study when renal

dysfunction was defined as an eGFR of < 60ml.min.1.73m² 63.6% of the cohort had renal impairment. Yet only 33.4% of men and 27.3% of women were diagnosed with RI. Once more, these results highlight the significance of renal dysfunction in HF, confirming high prevalence which is compatible with the ReFinH result.

The inference from the studies presented on renal impairment and HF irrespective of setting is renal impairment at the time of admission in HF patients is exceedingly common and usually associated with increased mortality. The ReFinH Study found a high prevalence for RI but did not confirm the mortality relationship.

5.4 Chronic kidney disease prevalence

One of the confounding issues in the HF renal dysfunction literature involves the lack of reporting regarding the chronicity of renal impairment. This lack of confirmation makes it difficult to clearly determine prevalence of CKD in HF. In much of the literature an abnormal admission serum creatinine >1.5mg/dl (133µmol/l) or eGFR < 60 mL.min carries the implicit assumption that this single result can determine chronic kidney disease (Damman et al. 2009). As the ReFinH Study results show, renal impairment prevalence of 59% does not necessarily translate to CKD prevalence which for ReFinH was 52%. The CKD diagnosis for the ReFinH cohort was verified by historic review of the electronic medical record for an estimated glomerular filtration rate (eGFR) <60ml.min.1.73m² for at least 3-months prior to the index admission. If this information was not available the patient was not attributed the comorbidity CKD. Notwithstanding these limitations, there are a number of community-based cardio-renal studies (de Silva et al. 2006; Khan et al. 2006; Maeder et al. 2012) that have investigated the link between HF and renal dysfunction as CKD establishing its prevalence and effect on outcomes.

The Khan group (Khan et al. 2006) in a *post* hoc analysis of the Studies of Left Ventricular Dysfunction trial (SOLVD) investigated the rate of decline in kidney function and its consequences for HF patients. They referenced renal decline against the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI) (Levey et al. 2003) classification and staging system for CKD which has as its metric eGFR defined categories. The SOLVD trial had stringent renal criteria where a baseline serum creatinine >2.5mg/dl (>177mmol/L) meant exclusion. However when the K/DOQI stages were applied 33% of the cohort had an eGFR <60ml.min.1.73m² enabling the classification of CKD. Serial eGFR measurements were collected for up to 34.2 (±14) months to monitor eGFR rate of decline. Relevant outcomes from this study for ReFinH are that the K/DOQI CKD classifications were

shown to be associated with mortality in a well-characterised HF population, and that the rate of decline was a strong mortality predictor irrespective of baseline renal function, heart failure type or change in HF. These findings suggest the approach taken by ReFinH to differentiate RI from CKD is justified, and confirms the utility of the K/DOQI CKD metric in HF.

The most recently published meta-analysis by Damman and colleagues (Damman, Valente, Voors, O'Connor, et al. 2014) reported an overall CKD prevalence 32% of CKD as defined in the individual studies. In further selective analysis which excluded a study with an unusually lower CKD prevalence, they reported an overall CKD prevalence of 49%, which translated into 53% in acute HF and 42% in chronic HF. There is no doubt the various manifestations of renal dysfunction are prevalent in HF. Given the prognostic significance or acute and chronic renal dysfunction in HF, the ReFinH Study has attempted to differentiate and establish for the cohort the true incidence of AKI, and prevalence of CKD and renal impairment. These are important considerations as the ability to correctly identify which patients are at risk of acute deterioration in renal function may hold benefits for improving patients' outcomes and better inform future research.

5.5 Characterisation of renal dysfunction in heart failure

Heterogeneity is a feature of HF renal dysfunction cohort studies (Damman, Valente, Voors, O'Connor, et al. 2014). This limits comparisons and the conclusions that can be drawn from individual studies and meta-analyses. Nevertheless, the baseline characteristics table for the cohort is often useful to contextualise results. These tables usually include demographics, cardiovascular and medical history, admission signs, symptoms, haemodynamic, and blood chemistry variables, and medications at the time of admission. It is also common practice to give the setting, hospitalised or community; and where possible details of the type of HF population being investigated. It is from this suite of variables investigators characterise their study cohort. The presentation of the data typically follows the convention of stratifying by the outcome of interest such as WRF / no-WRF and includes the result of the univariate and bivariate analysis for the cohort and by group outcome respectively. The detailing data can be useful when collated in meta-analyses summary tables which make possible general comparisons across studies and help reference a study's results for similarities and disparities, characterisation of prevalence and severity for variables and their relationship to outcomes.

In the ReFinH study participants were a generalised population of hospitalised HF patients, the majority were male (55%) and cohort median age was 76-years (IQR 68, 83). Approximately

two-thirds (62%) of the cohort had had a previous documented HF admission. When the ReFinH cohort was stratified by the presence of AKI, there was neither a statistically significant dominant gender nor age difference; the median age for those with AKI was 78-years (IQR 69, 83) and without AKI 76-years (68, 83). Only eight (8) variables demonstrate a statistically significant difference by AKI group for the cohort of 176 patients in which 42 developed AKI. AKI was characterised by admission haemoglobin (Hb) 118g/dl (p=0.02), serum creatinine 135µmol/l (p=0.04), and ß-blocker medication being taken at the time of admission (p=0.05); Charlson Index weighted score (p=0.03), idiopathic aetiology for HF (p=0.03), RI that is and admission eGFR ≤60ml.min.1.73m² (p=0.05), confirmed CKD (p=0.01) and diabetes (p=0.002). The remaining 41 descriptive clinical variables were not significantly different for AKI groups.

The median age of 76-years (IQR 68, 83) places the ReFinH cohort in an age demographic for developed countries experiencing significant growth in terms of the proportion of the general population and prevalence of HF (Jugdutt 2012). In fact, HF patients over 75 years have been classified as the old elderly and those over 85-years as very old elderly (Jugdutt 2012). Studies investigating renal dysfunction and outcomes which are not retrospective analysis of RCTs tend to have older cohorts. For example the Krumholz and colleague's (Krumholz et al. 2000) retrospective chart audit inclusion criteria was ≥65years with a mean age of 79.1 (±7.7). The studies by Verdiani et al. (Verdiani, Lastrucci & Nozzoli 2010) and Breidthardt et al. (Breidthardt et al. 2011) were prospective observational studies, where participants' mean and median age were 77.9 (±10.1), and 79.0 (71, 85) respectively. These studies shared the WRF definition serum creatinine threshold of ≥26.5µmol/l used in ReFinH. Other characteristics these study cohorts share with ReFinH are similarities in terms of the incidence of in-hospital WRF, the presents of comorbidities and for the Breidthardt et al. study (Breidthardt et al. 2011) the definition for CKD.

WRF incidence for ReFinH, the Krumholz et al. (Krumholz et al. 2000) and Breidthardt et al. (Breidthardt et al. 2011) studies were 24%, 28% and 21% respectively. The 11% WRF incidence reported by Verdiani et al (Verdiani, Lastrucci & Nozzoli 2010) as noted earlier was attributed to their definition requiring the serum creatinine increase of ≥26.5µmol/l to persist till discharge, suggesting a transitory biomarker change. The similarity in comorbidity burden in the preceding studies is a characteristic of HF that is becoming more common, the presence of multiplemorbidity posing management challenges and impacting outcomes (Damman, Valente, Voors, O'Connor, et al. 2014; Owan et al. 2006).

Table 5.1 highlights the comorbidity prevalence for diabetes, ischaemic heart disease (IHD), chronic kidney disease (CKD) and renal impairment (RI) at admission for the ReFinH, Krumholz et al (Krumholz et al. 2000), Verdiani et al (Verdiani, Lastrucci & Nozzoli 2010) and Breidthardt et al (Breidthardt et al. 2011) studies.

Table 5.1 Study Cohort and WRF comorbidity percentages

Study	Diabetes		IHD		CKD		RI	
	Cohort	WRF	Cohort	WRF	Cohort	WRF	Cohort	WRF
ReFinH (2012)	51%	71%	57%	57%	52%	69%	59%	25%
Krumholz (2000)	38%	44%	37%	34%	21%	34%	41%	49%
Verdiani (2010)	33%	28%	57%	44%	24%	44%	28%	44%
Breidthardt (2011)	31%	36%	54%	58%	42%	58%	N/A	N/A

An additional chronic condition with significance in HF is anaemia frequently referred to as cardio-renal-anaemic syndrome or CRA. CRA has a reported prevalence range of 9% to 79% in HF (Go et al. 2006). Yet the most significant chronic condition in HF is CKD due to its pathophysiology role in HF and influence on prognosis (Breidthardt et al. 2011; Damman, Valente, Voors, O'Connor, et al. 2014; Forman et al. 2004; Khan et al. 2006; Krumholz et al. 2000). As a final point reinforcing the importance of the comorbidity burden in HF, especially where there is renal dysfunction the ReFinH result is the statistically significance difference for the Charlson Index (CI) weighted means for AKI group status: AKI 4.5 (SD±1.9), No-AKI 3.9 (SD±1.6), p=0.025 are indicative of the comorbidity problem associated with AKI incidence. Once certain cohort characteristics are deemed to have an association with the development of AKI the next phase is to assess if they are significance predictors for a study's primary outcome.

5.6 Predictors for the development of AKI in the study cohort

Although pathophysiological mechanisms responsible for in-hospital WRF are yet to be fully explained, a number of predictors of worsening renal function have been reported (Cowie et

al. 2006; Forman et al. 2004; Krumholz et al. 2000; Verdiani, Lastrucci & Nozzoli 2010). Part of the rationale behind attempts to document the predictors of WRF in HF is to help identify HF patients at high risk for WRF and to enable the early implementation of strategies with the potential to protect renal function or minimise renal deterioration and improve HF patients' outcomes.

Backward stepwise binary logistic regression was used to identify variables predictive of acute kidney injury presenting as in-hospital worsening renal function. Statistically significant continuous and categorical variables in the characteristics table (table 4.1) and variables with a p-value of ≤0.1 were considered for inclusion in the predictive modelling. The following variables were used in the regression analysis: age, admission systolic blood pressure, diabetes mellitus (combined Type I & II), a history of chronic kidney disease≥ Stage 3a, ß-Blocker medication on admission and admission haemoglobin. Other baseline variables that met the p-value of ≤0.1 criteria were the Charlson Index (CI) weighted score, the admission serum creatinine and admission eGFR. These last three variables were left out of the regression analysis due to the potential for multicollinearity. In the case of the CI weighted score, the component variables diabetes and renal disease were already included as independent variables. For all variables included in the analysis, the basic rule of 10 participants per variable was satisfied (Hayat 2013; Vittinghoff & McCulloch 2007).

In the final model reached in the 4th step 3 variables remained a history of CKD, diabetes, and ß-Blocker medication at the time of admission.

5.6.1 Chronic kidney disease history as a predictor of AKI

HF patients with a confirmed history of at least stage 3a (eGFR<60mls.min.1.73m²) chronic kidney disease on admission were 2.63 (95%CI: 1.21, 5.73; p<0.02) times more likely to develop AKI than patients with normal renal function. The robust nature of the evidence for CKD as a predictor of WRF is supported by Damman et al (Damman, Valente, Voors, O'Connor, et al. 2014) who recently published an updated meta-analysis in which 30 studies had identified baseline eGFR as either RI or CKD as a risk factor for worsening renal function. In this meta-analysis (Damman, Valente, Voors, O'Connor, et al. 2014) baseline CKD in HF patients was reported as a predictor for WRF with a HR 2.17 (95%CI: 1.79, 2.63; p<0.001). Further, they suggest renal impairment to be the most important comorbidity in HF due to its associated mortality risk. These authors tabled all RI and CKD results together as CKD.

A prospective observational cohort study by Breidthardt et al. (Breidthardt et al. 2011) using similar definitions for CKD and in-hospital WRF as the ReFinH Study reported hazard ratios for CKD history and incidence of WRF that were similar to the ReFinH results and the Damman and colleague meta-analysis. Breidthardt's team identified a hazard ratio (HR) of 2.31 (95%CI: 1.57, 3.40; p<0.01) for CKD history. Again, CKD was found to be a statistically significant predictor for in-hospital WRF. The hazard ratios for CKD as a predictor of in-hospital WRF for the Damman et al. meta-analysis (2014) and Breidthardt et al. (2011) study support the ReFinH results for CKD history as a significant risk factor for AKI.

Noteworthy is the finding CKD in HF is an strong, negative prognosticator for short and long-term mortality and morbidity outcomes (Breidthardt et al. 2011; Butler et al. 2010; Damman, Valente, Voors, O'Connor, et al. 2014; de Silva et al. 2006; Forman et al. 2004; Hillege et al. 2000; Verdiani, Lastrucci & Nozzoli 2010). The sine qua non for AKI is the cause precedes the event; a history of CKD having been identified as the most important prognostic indicator in HF (Damman et al. 2009; Damman et al. 2007) provides this temporal sequence and confirms the need for routine monitoring of renal function in CHF (Remuzzi et al. 2013). Adequate monitoring of renal function in HF patients may be the opportunity to preserve renal function and improve outcomes in HF patients.

5.6.2 Diabetes mellitus as a predictor of AKI

In the ReFinH study hospital HF (HHF) patients with diabetes were 2.63 (95%CI: 1.21, 5.71; p<0.02) times more likely to develop in-hospital AKI than HHF patients without the comorbidity diabetes. This finding is consistent with many heart failure studies investigating WRF predictors such as Breidthardt et al. (Breidthardt et al. 2011), Butler et al. (Butler et al. 2004), Forman et al. (Forman et al. 2004), and others (Cowie et al. 2006; Owan et al. 2006).

One of the most pertinent studies against which to position the ReFinH findings re a history diabetes is that of Forman et al. (Forman et al. 2004) as both studies share population, setting, methodology and definitional similarities. Forman et al. (Forman et al. 2004) investigated the prevalence of WRF in hospitalized heart failure (HF) patients, clinical predictors and hospital outcomes associated with WRF. The presence of diabetes was confirmed as a factor 'strongly and independently' associated with WRF such that diabetes was one of four parameters forming a risk prediction score for WRF. The other prediction score variables were renal dysfunction defined as an admission serum creatinine of >132.6µmol/l (≥1.5mg/dl); admission systolic blood pressure >160mmHg and a pre-existing history of HF (Forman et al. 2004).

Additional evidence to support diabetes as a predictor of WRF comes from a literature review by Dobre et al. (Dobre et al. 2012). Their intension was to summarise the predictors of renal dysfunction in CHF and present strategies to prevent or treat RD in chronic heart failure. Dobre and colleagues confirmed patients with diabetes were at risk of renal complications. They noted good control of glycaemic levels and treatment with renin-angiotensin aldosterone system (RAAS) inhibitors was essential to prevent RI in diabetic HF patients. They stressed the importance of monitoring urinary albumin concentrations in these patients. The observations of Dobre et al. (2012) strengthen the importance of the ReFinH study finding of diabetes as a predictor of WRF and the need for renal function monitoring.

5.7 Survival analysis acute kidney injury

Kaplan-Meier survival curves for the composite endpoint all-cause mortality and major cardiovascular event (MACE) defined as ST elevation myocardial infarction (STEMI), non-STEMI, cardiac arrest and stroke) were created for AKI groups. During the 12-month post index admission follow-up period, 43 patients (25%) experienced an event; of these 8 (21%) had developed AKI during the index hospitalisation and 35 (27%) did not develop AKI. The log-rank test was used to assess the significance for AKI groups for time to the composite endpoint. No statistically significant difference between the survival functions was observed (p=0.471). This finding is rare but not unique.

In the study by Verdiani et al (Verdiani, Lastrucci & Nozzoli 2010), in which 11% of patients developed WRF. These authors constructed survival probability curves according to the Kaplan-Meier method. Their mortality results were not statistically significantly difference for WRF status (P=947). This study is referenced as its methodology, patient population; setting and definition for WRF are very similar to the ReFinH study. As with ReFinH it is an appraisal of a general HF, population admitted to hospital and followed up for 1 year. Where it diverges from the ReFinH study is its WRF definition timeframe which is extended up to 15-days.

A second study with a primary outcome of all-cause mortality that found no significant difference for mortality at 18-months follow-up for HF patients developing WRF was that of Maeder et al. (Maeder et al. 2012). They investigated the incidence, predictors, and prognostic impact of WRF in elderly community-based heart failure patients. For this investigation, Maeder's team carried out a retrospective analysis of data from the trial of Intensified Medical therapy in the Elderly patients with Congestive Heart Failure (TIME-CHF) which was community-based. Their defined three levels of WRF to reflect increasing severity using the serum creatinine increases over baseline value of 0.2mg/dl to 0.3mg/dl (17.7µmol/l – 26.5

µmol/l) for WRF-I; >0.3mg/dl to 0.5mg/dl (>26.5 µmol/l - 44.2 µmol/l) for WRF-II and >0.5mg/dl (>44.2 µmol/l) for WRF-III during a 6-month period. Only WRF-III was associated with increased mortality hazard ratio 1.98 (95%CI: 1.27, 3.07, P=.002). Points of difference for ReFinH were that TIME-CHF was community-based and an extended timeframe for biomarker increase. Studies by Aronson et al (Aronson & Burger 2010) and Cowie et al (Cowie et al. 2006) reported increased mortality in WRF when Worsening renal function persisted or when major complications were associated with the admission respectively.

Even though the ReFinH study had a high prevalence of CKD at 52% and RI 59% it did not translate into significance in terms of mortality outcomes as seen in the studies by Breidthardt etal CKD prevalence of 42% CKD, and the meta-analyses of Damman et al (Damman, Valente, Voors, O'Connor, et al. 2014), CKD prevalence of 53% in hospitalised HF. For the Breidthardt's group (Breidthardt et al. 2011) the only independent predictor of WRF was CKD with a hazard ratio of 2.07 while for Damman the overall CKD prevalence of 32% was associated with an all-cause mortality odds ratio of 2.34 (95% CI2.20 – 2.50, p<0.001).

In general in-hospital WRF is associated with increased mortality risk (Damman, Valente, Voors, O'Connor, et al. 2014), in ReFinH this was not the case. Definitions, HF populations and settings will impact these findings as is evident from the data already presented. The ReFinH definition for WRF with its origin in a nephrology/ intensive care medicine; requires a very specific increase in serum creatinine over a timeframe which can be considered short in comparison to much of the cardiology literature. The implications are what some may call WRF may be CKD and hence the impact on mortality (Butler et al. 2010).

Finally, Kaplan-Meier (KM) survival analyses was also assessed for the cohort by renal impairment and chronic kidney disease status. When stratified by these criteria yet again no statistical differences between survival distributions for the groups were observed. This is contrary to results present in the majority of HF renal impairment studies as evident in Damman and colleagues (Damman, Valente, Voors, O'Connor, et al. 2014) 2014 revised meta-analysis.

5.8 Secondary endpoints and acute kidney injury

Secondary endpoints for the ReFinH Study were total hospital re-admissions, emergency department presentation or total hospital bed days for the 12-month follow-up by acute kidney injury status. Analysis was by way the Mann-Whitney U test. No statistically significant

differences for any of these secondary outcomes were detected. As with the survival analysis results these results are contrary to the majority of the literature (Butler et al. 2010).

When comparisons of the ReFinH secondary results are made against the studies mentioned previously for their similarity to ReFinH secondary outcomes are also analogous. For Verdiani et al (Verdiani, Lastrucci & Nozzoli 2010) there were no significant differences for re-hospitalisation over 1, 6 or 12-months for HF patients with WRF compared to those without WRF. Maeder et al (Maeder et al. 2012) reported only HF patients with WRF defined as a serum creatinine increase of ≥0.5mg/dl experienced increased re-admission rates over the 18-month follow-up period. Butler et al (Butler et al. 2010) in their systematic review of the literature also reported studies assessing WRF, defined as a ≥0.3 mg/dL increase in serum creatinine after admission appeared to be strongly associated with increased length of stay but not readmission. For the ReFinH study RI was not associated with any of the secondary outcomes and only a confirm history of CKD saw a statistically significant result, HF patients with CKD experiencing a greater number of total hospital bed days compared to HF patients without this comorbidity.

5.9 Implications

The 'Renal function in chronic heart failure cohort study' has provided insights into renal dysfunction in HF, from an Australian perspective for which there are limited data. The ReFinH study has extended the characterisation of Australian hospitalised HF patients with renal dysfunction and exposed the importance of definitions and nomenclature for this clinical entity in HF. The findings of Chew et al (Chew et al. 2006) with regards to the prevalence of renal impairment in hospitalised cardiac patients is confirmed by this cohort analysis. Analysis of ReFinH data justifies increased surveillance and regular reporting of renal function in HF. Monitoring and reporting renal function due to its prognostic importance should become a standard for inclusion in hospital discharge summaries and for on-going outpatient and community management.

To enable these clinical management changes the definition for in-hospital worsening renal function needs to be standardised. The ReFinH literature review made this point and the analysis of the results in the discussion has drawn attention to issues associated with ambiguous definitions and nomenclature. Definition consensus for in-hospital WRF and the endorsement of the KDIGOs chronic kidney disease classification and stages would assist with applications in health information technologies to enable better monitoring and

communication between health professionals. It would also support improved research and education.

Future research could test the utility of the modified AKIN, acute kidney injury definition used in the ReFinH study. Data definitions could be developed to standardise the nomenclature and informing health informatics applications.

5.10 Summary

Irrespective of whether renal dysfunction is acute or chronic in HF mortality rates trend towards an inverse relationship (Damman et al. 2007; Smith et al. 2006). The greater the severity of RD the higher the mortality risk. The seminal paper by Smith and co-authors (Smith et al. 2006) highlight this association. They found "*mortality worsened incrementally across the range of renal function, with 15% (95% CI 14% to 17%) increased risk for every 0.5 mg/dl (44.0 µmmol/l) increase in creatinine and 7% (95% CI 4% to 10%) increased risk for every 10 ml/min decrease in eGFR*" (Smith et al. 2006).

Subtle difference in the nomenclature can cause confusion when interpreting study outcomes and potentially have a negative influence patient management decisions. Professional communities and bodies (cardiology, nephrology, intensive care, etc.) develop their own renal impairment, worsening renal function notions. In the practice of empirical WRF definitions, we see comparisons of apples with oranges. WRF has been used as an umbrella term with many meanings due to its many definitions giving the impression of inclusiveness which is a barrier for measuring, analysis and decision making based on results. . Of concern is the continued selective use of the KDIGO CKD metric for a cut-point for renal dysfunction in the heart failure cardio-renal literature without the adoption of the nomenclature.

Heart failure and kidney disease are not rare conditions, the presented epidemiological data highlight their prevalence and the significant impact these conditions have at the individual, national and global level. Individually they are challenging but when combined as cardio-renal dysregulation they present new challenges to both clinicians and researchers.

5.10.1 Strengths and weakness of the study design

This study has several limitations. Firstly, as an observational study it is impossible to attribute causation; secondly, the limitations of administrative data need to be recognised in terms of coding of the discharge International Classification of Diseases (ICD) HF codes. However a study by Teng et al (Teng et al. 2008) in Western Australia established the high accuracy for HF coding using the HF ICD codes. Secondly, the data represent the findings from a single centre

cohort in an Australian tertiary level hospital and as such may not be representative of the broader Australian HF population. Thirdly, the study did not achieve its required sample size of 288 participants to adequately power the primary study endpoint of AKI and 12-month follow up all-cause mortality and MACE. The resulting small sample size has resulted in primary and secondary endpoints that were not statistically significant and broad confidence intervals for the AKI predictors. Post-hoc analyses were considered but in practice, it is usually concerned with finding patterns and/or relationships between variables where relationships are not previously understood so it was not performed. In contrast, the ReFinH study has increased the spotlight on renal impairment (acute and chronic) as a well recognised predictor of adverse outcomes, rather than discovery of a new relationship.

Yet in spite of these limitations, the study has several strengths. The prospective consecutive recruitment of patients minimised patient selection bias and provided a general hospitalised HF population. There were no exclusions based on language or nationality as all patients were included in the data collection, exclusion criteria only applied following completion of the chart audit. For biomarker results all analysis was conducted at a single facility, the case report form standardised data collection.

5.11 Conclusion

This chapter has provided a discussion of the ReFinH cohort study within the context of the existing literature. In addition, it has addressed the strengths and limitations of the study design. The following chapter will provide the implications of this study for policy, practice, education and research.

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Chapter 6 Conclusion

6.1 Introduction

This thesis has systematically identified factors influencing renal function in HF, including the assessment of these factors in a cohort study. Baseline glomerular filtration rate (GFR) is a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class (Bock & Gottlieb 2010). Identifying patients at risk of worsening of renal function and more importantly preserving renal function is an important consideration.

The results of the ReFinH study highlight the complexity of hospitalised HF patient management. These patients were typical of developed country's HF population (Jugdutt 2012). They were elderly with an average age of 74-years; had several comorbidities which due to the instability of their HF were at risk of exacerbation. Over 60% of the patients had 3 or more comorbidities when defined using the Charlson Index (Sundararajan et al. 2004), chronic kidney disease and diabetes the most common followed by chronic obstructive airway disease. The prevalence of confirmed CKD at admission was high at 51%; the incidence of acute worsening of renal function was also significant with approximately 1 in 4 patients developing AKI.

The ReFinH study is testament to HF patients requiring more than cardiac care. They need patient-centred, multi-system care which frequently involves renal, endocrine, respiratory, and connective tissue management. The challenge of multimorbidity, that is when no reference condition is considered (van den Akker et al. 2001) is a management concern for clinicians and health systems which have traditionally been single disease focused. Clinicians, researchers, health policy developers and health educators are increasingly acknowledging the need to move away from the single disease paradigm to a more holistic approach to care (Fortin et al. 2012). Comorbidity status has become an important issue in contemporary HF management (Damman, Valente, et al. 2014). In HF patients, the cardio-renal relationship is at the forefront of holistic care. This is due to the renal system having a strong prognostic position and association to medication management. Diuretics target the kidneys to relieve excess venous congestion in volume-overloaded HF patients. Drugs that focus on the renin-angiotensin-aldosterone system (RAAS) are also intrinsically involved in HF management as the RAAS is the endocrine system principally responsible for regulating blood volume and systemic vascular resistance (Krum, Iyngkaran & Lekawanvijit 2009). These drug classes are frequently involved in managing HF, renal and diabetic patients.

The primary aim of the study was to investigate the cardio-renal relationship in patients admitted to an Australian tertiary level hospital with a primary discharge diagnosis of heart

failure. The study design for the investigation was a retrospective single-centre chart audit. Specific aims of the study were to:

i. Investigate the impact of in-hospital worsening renal function (WRF) present as acute kidney injury (AKI)defined using a modified AKIN definition of AKI (Sheerin et al. 2014) in hospitalised HF patients for the composite outcome all-cause mortality and major acute cardiovascular events (Non-STEMI; STEMI Cardiac arrest and Stroke) at 12-months follow-up
ii. Investigate the impact of in-hospital worsening renal function present as acute kidney injury (AKI) defined using a modified AKIN definition of AKI (Sheerin et al. 2014) in hospitalised HF patients for the secondary outcomes at 12-month follow-up for:
    - hospital re-admissions
    - emergency department presentations
    - total hospital bed days

Briefly, the ReFinH study has shown every second patient had CKD, and one in four developed acute kidney injury. The composite outcome all-cause mortality and major acute cardiovascular event (MACE) for hospitalised heart failure patients who developed worsening renal function (WRF) present as acute kidney injury (AKI) compared to those who did not was not statistically significantly different. Second, there was no statistically significant difference between HF patients with AKI compared to no AKI for the secondary endpoints total re-admissions, emergency department presentations and total hospital bed days for the 12-month follow-up period. Several predictors for acute kidney injury in hospitalised heart failure were identified. A history of at least stage 3 chronic kidney, diabetes, anaemia, elevated serum creatinine or reduced eGFR were predictors for AKI. CKD and diabetes had a statistical significant impact as predictors of AKI with OR 2.63 (95% CI 1.21, 5.73; $p<0.02$) and 2.63 (95% CI 1.21, 5.71; $p<0.02$) respectively. The taking of a B-blocker at the time of admission protected against AKI but was not statistically significant OR 0.49 (95% CI 0.23, 1.03; $p=0.59$).

The acute worsening of renal function, whether a new finding or superimposed on already diagnosed chronic kidney disease (CKD), requires definitive monitoring and treatment as it portends adverse outcomes. The implications of these finding and the obligation to move form a single disease paradigm to holistic care will be discussed within the context of policy, practice, education and research.

6.2 Policy

6.2.1 The Australian context

Healthcare in Australia is a multi-faceted web of public and private providers, settings, participants and supporting mechanisms. Health policy development and implementation is also a complex process as the primary jurisdictions delivering health services, public and private hospitals and primary care providers have different funding sources (Australian Institute of Health and Welfare 2014). The public hospital system is funded by all levels of government while primary care receives federal and private support. In addition, there are currently no Australian national criteria for identifying and prioritising clinical practice guideline development (personal communication[4]); documents substantively relied upon to inform health policy. No national body co-ordinates and prioritises the identification, development and publication of evidenced-based clinical practice guidelines (CPGs).

The Australian Commission on Safety and Quality in Health Care (ACSQHC) a federal government agency, by establishing several safety and quality goals in 2012, has become a proxy organisation for health policy development. One of the ACSQHC goals is '*people receive appropriate, evidence-based care'(Australian Commission on Safety and Quality in Healthcare 2012)*. To fulfil this brief they develop national clinical care standards for specific conditions or practices, and provide frameworks to develop high quality, safe patient care. The current ACSQHC focus is acute coronary syndromes and acute stroke. In such a structured goal and time-frame, driven environment the initial challenge is to have cardio-renal policy on the agenda and then have the ReFinH Study results and international evidence inform the development of a clinical standard in a very competitive milieu is monumental but not impossible.

Linking the results of health research to the economic benefits associated with improved patient outcomes and cost efficiencies is the key (Fisk et al. 2011) for inclusion in health policy. ReFinH revealed a CKD prevalence of 59% based on admission eGFR and an AKI incidence of 24% in an Australian cohort of hospitalised HF patients. These results are not inconsistent with those reported in the international literature (Damman, Valente, et al. 2014) where the morbidity and mortality consequences associated with this degree of renal dysfunction have been described. This study is consistent with the international literature in identifying increased length of hospital stay in HF patients with renal dysfunction as an important cost

[4] Guideline International Network (G-I-N) Australia New Zealand Regional Group Inaugural Meeting 22 August 2014 Minutes

concern (Butler et al. 2010; Chew et al. 2006). Individually, chronic HF and renal disease are conditions already responsible for a substantial portion of the health budget and personal burden. The opportunity to identify HF patients at risk for renal deterioration and improve their management through better monitoring may result in these patients reducing their need for re-admission and increasing survival or the opportunity for advanced care planning.

Contemporary hospital and primary care, electronic medical records (EMRs) have the capacity to generate temporal serum creatinine, eGFR and urea graphs. The addition of this type of graph into the on-going clinical notes and as part of the discharge summary would be a simple policy step to facilitate greater awareness of renal function in these patients and possibly avert rapid functional decline. Heart failure guidelines already provide guidance for medication management while nephrology guidelines highlight CKD and AKI staging, classification and other management issues. However, the process of guideline and policy development is often protracted as the quality of evidence needs to be assessed, validated and compared to information gathered from other data sources. The knowledge gathering process is cyclical revolving around the research-policy-practice-education model where health consumers and carers, allied health professionals, clinicians, health bureaucrats and researchers identify and contribute to, and lobby for evidence-based care. The following figure (Figure 6.1) adapted from Elliott describes this iterative process.

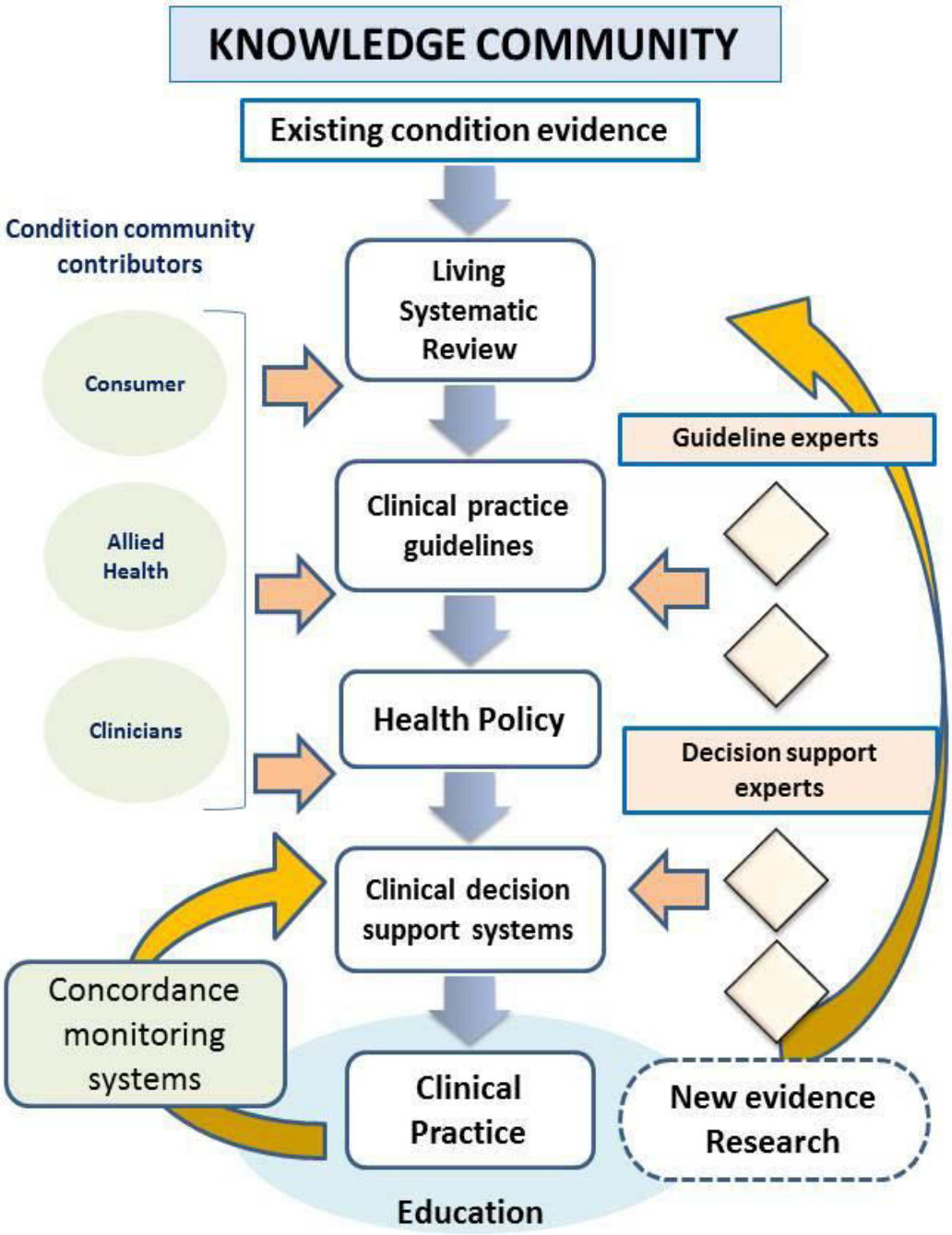

Figure 6.1 Knowledge into policy, practice, education and research

Adapted from Dr Julian Elliott's presentation "Living evidence" at the Guidelines International Network Conference, Melbourne 2014

6.2.2 Development processes

National health policy relies on national and international incidence, prevalence and outcome data for conditions of significance to inform public health policy priorities (Australian

Commission on Safety and Quality in Healthcare 2012). Policy developers also want information on the availability of effective treatments, their safety, and options for health care system efficiencies as well as how to engage consumers in policy development and implementation (Australian Commission on Safety and Quality in Healthcare 2010). Informing policy development are data from national health surveys, hospitals separation data for characterising the conditions, admission history (including adverse events) costings, primary care audits (Britt et al. 2008), death and disease registries and systematic reviews of the clinical research. Where there are common conditions with life-threating prognoses and the evidence-base is strong for a specific intervention and/ or management strategy for improve patient outcomes, safe with potential cost saving benefits then health policy is likely to embrace it. This approach is seen in policy programs such as screening initiatives for breast cancer, childhood immunisation programs and management policies for acute coronary syndromes.

6.2.3 Cardio-renal heart failure policy options

Heart failure and kidney disease are acknowledged as conditions that carry a substantial personal and health system burden (Braunschweig, Cowie & Auricchio 2011; Eckardt et al. 2013) as previously discussed in the literature review. Both conditions experience increasing prevalence in an aging population (Bleumink et al. 2004; Eckardt et al. 2013). For westernised countries this is specifically significant as their population are seeing increases in the over 65-years (Eckardt et al. 2013; Go et al. 2013; Roger 2008) and 80-year plus age (Dickstein et al. 2008) groups.

In older patients the issue has been raised as to whether they are managed to protect them from renal dysfunction particularly with regards to community AKI (Hsu et al. 2007). This is an important matter as HF patients with either acute or chronic kidney dysfunction experience significantly increased mortality (Shlipak & Massie 2004; Smith et al. 2006). Additional justification for protecting and persevering renal function in CHF patients is that they are already known to have a poorer quality of life and be frequent users of health services (Butler et al. 2010). The opportunity to improve the quality of life, safety and outcomes for these patients may rest with clinicians and health systems moving from a single disease focus to a holistic patient management model. A change in management strategy would require policy changes to drive practice, education and research. A multimorbidity model begins by having a common language, definitions and nomenclature.

6.3 Practice

6.3.1 Why we do what we do

Within the cyclic paradigm of research-policy-practice-education, the practice component is what we do in patient management. The patient management decisions clinicians make is often informed and directed by national health and institute policy, clinical practice guidelines (CPGs), CPG implementation strategies and by their graduate medical education (Grimshaw et al. 2005; Sackett et al. 1996). More recently, the implementation of CPGs is being facilitated by innovation in health informatics at both the primary and territory level. Health information technologies (IT) with built-in EMR decision support tools with concordance monitoring systems are being rolled out to support health professionals in their clinical practice. These IT applications are often designed for point-of-care use to encourage the health team to engage with the patient in management planning and decisions. In addition, the IT systems enhance our ability to review practice concordance with CPGs at the national, local and clinician level to help determine the impact evidence-based practice has for patients in terms of morbidity and mortality (National Institute for Cardiovascular Outcomes Research 2012). The National Institute of Cardiovascular Outcomes Research, National Heart Failure Audit published in the United Kingdom (UK) in 2012 highlighted areas for improved outcomes such as appropriate specialist follow-up care, and optimising medical therapy. These were key indicators of improved mortality, while noting the importance of integrated care beyond hospital admission (National Institute for Cardiovascular Outcomes Research 2012).

6.3.2 ReFinH results and practice implications

The ReFinH Study draws attention to the prevalence and consequence of renal dysfunction in patients with HF. Every second patient had CKD, one in four developed acute kidney injury. The prognostic impact of renal dysfunction in HF (Damman, Tang, et al. 2014) underlines the need for clinicians to monitor renal function in HF patients just as closely as they monitor medication management. The literature review described in Chapter 2 also emphasises the well described ‘silo’ approach to knowledge development and clinical management. Specifically there were specific bodies of literature in nephrology, cardiology and critical care.

International HF guidelines recommend the monitoring of electrolytes in HF when initiating or up-titrating medications such as angiotensin-converting enzyme (ACE) or diuretics (McMurray et al. 2012; Yancy et al. 2013). They also flag caution with the use of other potential nephrotoxic medications such as non-steroidal anti-inflammatory drugs (NSAIDs). These recommendations should be extended to include the monitoring of renal function in its own

right due to its prognostic significance. Irrespective of the effect renal dysfunction has in HF, the condition CKD is a potent risk factor for cardiovascular events and further deterioration in kidney function (Levey et al. 2011). The opportunity to protect, and or preserve renal function in CHF and acute episodes of exacerbated HF would be dependent on introducing clinical care practice standards addressing renal function monitoring using standard care renal biomarkers. Informed by the ReFinH Study results and the evidence from the scientific literature the following recommendations are proposed:

Heart failure renal function practice recommendations are to:

- In all community managed HF patients document baseline renal function status using the KDIGO chronic kidney disease staging classification system
- Monitor serum creatinine, eGFR and urea and urinary albumin in community HF patients. Monitoring frequency in accordance with current KDIGOs recommendations commensurate with CKD stage.
- Increase frequency of renal biomarker monitoring dependent on need; such as in the immediate post-hospital discharge period, or during introducing or re-titrating of potentially nephrotoxic drugs, and hydration status,
- In hospitalised HF patients use the modified AKIN acute kidney injury (AKI) definition for the **diagnosis** of AKI, (modified by increased timeframe for diagnosis to 72-hours), within the context of hydration status and urinary tract patency assessment,
- In hospitalised HF patients KDIGO acute kidney injury criteria can be applied to determine **severity** of AKI
- HF patients with transient changes in renal function for any reason monitored frequently until renal function stable and KDIGO classification documented, and
- Include in the patient EMR a chronological graphic produced using the renal biomarkers serum creatinine, eGFR and urea to monitor trends in renal function.

6.4 Education

Education on renal function in HF should be included in basic and on-going professional development. The connectivity outlined in Figure 6.1 recognises that clinical practice, research, concordance monitoring and decision support systems all require an educational component. The first step in the education process is to gather the evidence associated with the diagnosis, prevalence, outcomes, and management of the condition. The clinical and health system significance and characterisation of the condition once established, then lends itself to the development of education programs to raise awareness of the condition, who is at risk,

diagnosis, management options and knowledge gaps. Unfortunately, the pathogenesis of renal dysfunction in HF is yet to be fully explained and this had led to apparent hesitancy by HF guideline development groups to propose a consensus definition and nomenclature for the condition. This is in spite of the vast amount of evidence identifying renal dysfunction defined by delta change in either by eGFR, serum creatinine, urea or other renal biomarkers as a strong prognostic marker in HF (Damman et al. 2007; Gottlieb et al. 2002; Smith et al. 2003). Definitional ambiguity in my opinion has stymied education and the development of strategies to protect and or preserve renal function in HF patients. The educational process will remain checked until the international HF guideline development groups endorse consensus definitions and nomenclature for AKI and CKD. This action would remove the ambiguity in the taxonomy for cardio-renal dysfunction in HF and sets-up the opportunity to test their utility.

Awareness raising of the incidence, prevalence and cost germane to renal dysfunction in heart failure for the individual and the health system is the next phase of the education process. The public health threat associated with acute and chronic kidney dysfunction has been promoted in a recent series of article in the Lancet (Eckardt et al. 2013; Jha et al. 2013; Lameire et al. 2013). In Chapter 1 of this Thesis, the epidemiology data for acute kidney injury, chronic kidney disease and renal disease as a public health problem has been presented. Damman and colleagues (Damman, Valente, et al. 2014) have up-dated their renal dysfunction in HF meta-analysis of 2007 (Damman et al. 2007) regarding the epidemiology and impact of all forms of renal dysfunction in chronic and acute decompensated HF. Their results reinforce the very strong role renal dysfunction has for outcomes in HF. They confirm by their multivariate analysis, moderate renal impairment defined as an admission eGFR of <60mL/min had a hazard ratio (HR) 1.59, (95% CI 1.49–1.69), P<0.001, severe renal impairment (dependant on the published subgroup data, lowest estimated GFR, or highest creatinine/cystatin C group/quartiles), HR 2.17, (95% CI1.95–2.40), P<0.001, and WRF (defined most commonly as a serum creatinine increase of ≥26.5µmol/L), HR 1.95, (95% CI 1.45–2.62), P<0.001 were independent predictors of mortality (Damman, Valente, et al. 2014). These data leave no doubt as to the significance of renal dysfunction in HF and the publication of this highest form of evidence hopefully will raise the profile of this subject sufficiently to ensure its inclusion in CPGs, health policy and education.

In CHF and in ADHF education addressing renal function is frequently referenced against issue focused on medication management and the kidneys response to congestion relieving diuretic therapy. The idea of protecting and preserving renal function requires clinicians to make a

change in their thinking towards a holistic approach to management. Again, for change to occur it needs to be preceded by international HF guideline groups producing CPGs with consensus definitions and nomenclature for CKD and AKI in heart failure.

The education recommendations are:

- Raise awareness of the prevalence and incidence of CKD and AKI in HF respectively by ensuring this topic is included in professional development activities,
- Endorsement and promotion of the KDIGO CKD and AKIN definitions and staging criteria,
- Tertiary and primary health services as part of local health policy institute an electronic medical record (EMR) application to generate temporal renal biomarker graphs as part of hospital discharge summaries and as part of clinical notes.
- Tertiary and primary health services to deliver education on defining renal dysfunction in HF and its relevance to HF patients' outcomes.

6.5 Research

As shown in Figure 6.2 postulated relationships between HF and renal dysfunction are complex. These relationships are not *one-dimensional* but rather intricate bio-feedback mechanisms frequently operating simultaneously and not necessarily in a cause and effect scenario. Medication used in the management of HF signs and symptoms often modifies these relationships. As the population ages and the numbers of individuals with comorbidities increases, the need to understand complex pathophysiological, compensatory issues and medication interactions used in the treatment of comorbidities in HF patients becomes increasingly important.

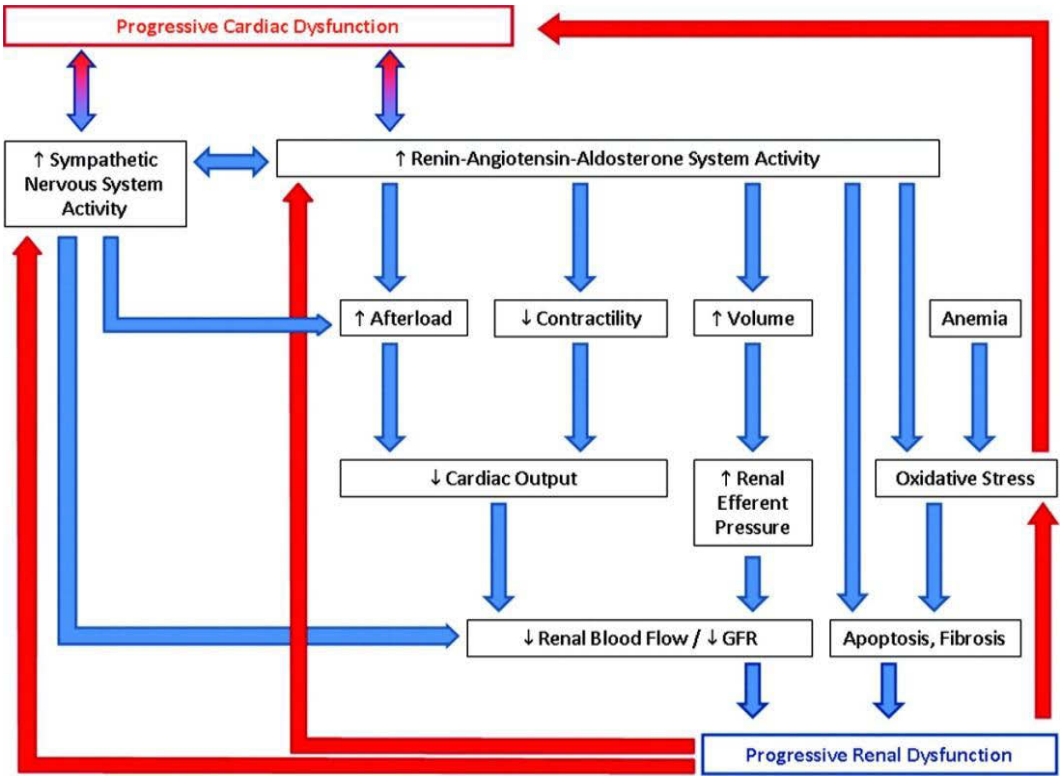

Figure 6.2 Cardio-renal interaction

Reference: Bock JS, and Gottlieb SS. Circulation. 2010; 121:2592-2600

Consequently, cardio-renal research has many areas requiring investigation. At this time, the pathogenesis of the syndrome is only partially understood; renal biomarkers for site of injury with enhanced specificity and sensitivity are needed; the development of an evidence-base for management and management strategies are just a few of the areas needing investigation. A timeframe for answering these research questions is difficult to forecast, however, there are other research opportunities currently available which could be pursued.

The new knowledge acquired from the ReFinH Study results provides the rationale for a randomised trial to test the utility of the ReFinH AKI definition and recommendations for renal function surveillance against standard practice. ReFinH has been the first Australian cohort study to characterised renal dysfunction in hospitalised HF patients', identify the predictors for AKI, and test a modified AKIN acute kidney injury definition. This information is foundational material for future research and offers the opportunity to further raise the profile of the importance of renal dysfunction in HF and the chance to test policy and practice for improved HF patient outcomes.

6.6 Conclusion

Renal dysfunction is one of the most important independent risk factors for adverse outcomes and all-cause mortality in patients with HF; it is also an area where the cardio-renal pathogenesis is poorly understood. Many research challenges into the cardio-renal relationship are yet to be addressed and these challenges will be difficult as this syndrome often occurs within the context of multimorbidity where diabetes is a significant and prevalent comorbidity. ReFinH highlighted the complexity of HF patient management, reporting HF patients frequently present with three or more comorbidities. Diabetes, vascular disease and connective tissue conditions were among the most common, all of which can be linked to CKD. Germane to the research challenges will be moving from a single disease paradigm to holistic care and finding opportunities for synergies across conditions for diagnosis and management.

Better health starts through the creation of new knowledge through our research activities (National Health and Medical Research Council 2012). Translating the lessons from research to clinical practice through education strategies, and knowledge translation into practice and policy is critical to improve the health care of the growing numbers of individuals living with CHF and renal dysfunction. ReFinH as a well characterized Australian cohort is a valuable resource for developing clinical practice guideline recommendations and powering clinical trials.

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Review

Worsening renal function in heart failure: The need for a consensus definition ☆

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ABSTRACT

Acute decompensated heart failure is a common cause of hospitalisation. This is a period of vulnerability both in altered pathophysiology and also the potential for iatrogenesis due to therapeutic interventions. Renal dysfunction is often associated with heart failure and portends adverse outcomes. Identifying heart failure patients at risk of renal dysfunction is important in preventing progression to chronic kidney disease or worsening renal function, informing adjustment to medication management and potentially preventing adverse events. However, there is no working or consensus definition in international heart failure management guidelines for worsening renal function. In addition, there appears to be no concordance or adaptation of chronic kidney disease guidelines by heart failure guideline development groups for the monitoring of chronic kidney disease in heart failure. Our aim is to encourage the debate for an agreed definition given the prognostic impact of worsening renal function in heart failure.

We present the case for the uptake of the Acute Kidney Injury Network criteria for acute kidney injury with some minor alterations. This has the potential to inform study design and meta-analysis thereby building the knowledgebase for guideline development. Definition consensus supports data element, clinical registry and electronic algorithm innovation as instruments for quality improvement and clinical research for better patient outcomes. In addition, we recommend all community managed heart failure patients have their baseline renal function classified and routinely monitored in accordance with established renal guidelines to help identify those at increased risk for worsening renal function or progression to chronic kidney disease.

1. Introduction

Acute decompensated heart failure (ADHF) is a common cause of hospitalisation, particularly in the elderly. This clinical presentation represents a period of vulnerability both in altered pathophysiology and the potential for iatrogenesis due to therapeutic interventions [1].

Renal dysfunction in heart failure (HF) is a strong marker of adverse outcomes [2]. Reduced kidney function in HF at any time in the illness trajectory carries an increased risk of death [3] and hospitalisation [4]. A theoretical model for the cardio-renal relationship has been proposed by Ronco and colleagues [5]. They describe cardiorenal syndrome (CRS) as disorders of the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. Acute kidney injury (AKI) formerly known as acute renal failure is also a syndrome which is characterised by the rapid loss (≤48 h) of the excretory function in the kidney. Loss of kidney function is typically diagnosed by an increase in creatinine and urea, or decreased urinary output, or a combination of these metrics [6,7].

The acute worsening of renal function, whether a new finding or superimposed on already established chronic kidney disease (CKD), requires definitive monitoring and treatment. Defining worsening renal

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function in HF is important in effective treatment. Ensuring communication between health professionals requires consistency of nomenclature. As a consequence, data elements for the definition and demonstration of utility in the clinical setting are critical.

HF is a heterogeneous, complex and progressive syndrome [8], with a poor prognosis and is most common in those over 65-years [9]. The prevalence of chronic kidney disease (CKD) and worsening renal function in HF is variously estimated to be 33% to 65% [10,1] and 11% to 45% [11–13] respectively. Variations in the estimate of prevalence can be attributed to the absence of a consensus definition and diversity in patient populations and settings. The increasing burden of CKD in heart failure and recent modification to the criteria for classifying and staging CKD have increased the focus on the bi-directional relationship between renal dysfunction and heart disease [14]. A recent review of cardio-renal syndromes by Ronco and Ronco [15] has reaffirmed the model for five CRS subtypes reflecting the time-frame and the primacy of organ dysfunction of the syndrome (Table 1).

Research over the last decade has advanced the understanding of the incidence, prevalence, complex pathophysiology and therapeutic implications of renal dysfunction in heart failure. Incidence and prevalence estimates for worsening renal function and chronic kidney disease and outcomes in HF in a variety of settings and populations have been described [1,4,16,17] and a theoretical model for the pathophysiological mechanisms underpinning the relationship has been proposed [18]. Yet an international consensus definition for worsening renal function in heart failure has remained elusive. Agreed definitions inform study design and comparison between studies [19] and raise clinical awareness and diagnosis for the defined condition. Numerically defined laboratory test thresholds for definitional elements facilitate the formulation of electronic evidence-based algorithms for point of care management [20] and data elements for clinical registries which can support quality improvement and future research [21]. The clinical utility of such definitions can be tested as treatment modes for HF evolve.

This discussion paper argues the need for a consensus definition for worsening renal function in HF to encourage the definition debate. We conclude by making some recommendations for defining and diagnosing worsening renal function in HF and the monitoring for CKD in community-based HF patients.

2. Current heart failure guidelines and kidney function

Although numerous HF guidelines exist, the focus on renal dysfunction is variable. The Canadian Cardiovascular Society Heart Failure Management Guidelines update published in 2011 [22] specifically addresses cardio-renal syndrome in advanced HF. Their recommendations make reference to management and deterioration of renal function noting the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2002 classification of CKD [23] and acute kidney injury Risk-Injury-Failure-Loss-Endstage renal disease (RIFLE) criteria [24]. However, they do not specifically address these criteria for diagnosis or staging of CKD or acute kidney injury in HF.

The European Society of Cardiology (ESC) [25] and the American College of Cardiology Foundation with the American Heart Association (ACCF/AHA) [26] have recently published updated guidelines for the management of HF. These eminent guideline development organisations follow internationally recognised criteria for grading the strength of evidence and rating their recommendations. Unfortunately, both sets of guidelines do not discuss the barriers or enablers to operationalising the Kidney Disease Improving Global Outcomes (KDIGO) acute kidney injury definition or chronic kidney disease stage classifications [27] despite their relevance to HF (Table 2). The lack of discussion could be predicated upon the view that a definition that only incorporates a measure of function without reference to cause lacks precision and as such is unacceptable. However this approach falls short in acknowledging the clear evidence that any reduction in renal function in HF at any time conveys an increased mortality risk [3,28]. Concordance across these HF guidelines does occur in reference to the need for serial monitoring of renal function and electrolytes in managing certain drug therapies and the potential role of ultrafiltration.

In both the ACCF/AHA and ESC guidelines addressing renal dysfunction there is an absence of empirical definitions and differing use of terminology. The documents use terms such as 'adequate' renal function, or 'marginal' renal function but there is no consistency in their definitions. For example the ACCF/AHA refer to adequate renal function as a serum creatinine < 2.0 mg/dl (< 177 μmol/l) or 'marginal' with an eGFR 30–49 ml·min·1.73 m^2; whereas ESC describes adequate renal function as serum creatinine ≤ 2.5 mg/dl (≤221 μmol/l) or eGFR ≥ 30 ml·min·1.73 m^2. The ESC guidelines acknowledge that acute and or chronic renal dysfunction is an important prognostic issue in HF but do not offer further guidance. The ACCF/AHA [26] do concede significant gaps in the knowledgebase for some fundamental aspects of HF care and acknowledges limitations of the available evidence. They note the recognition and treatment of cardio-renal syndrome is such an area.

3. Defining & classifying chronic kidney disease and acute kidney injury

As discussed above, there are internationally agreed consensus definitions and staging for CKD and acute kidney injury and that these definitions continue to be refined. In 2002 the NKF-KDOQI [23] proposed a five stage model for defining and classifying CKD based on GFR and chronicity. This model, with minor changes, was later endorsed by the Kidney Disease: Improving Global Outcomes (KDIGO) group in 2004. CKD was defined as a GFR < 60 ml·min·1.73 m^2 or evidence of kidney damage regardless of cause for a period of at least 3-months. The KDIGOD categorised kidney function by reducing GFR ranges, classification extending from normal through to end-stage kidney failure. Recently the definition and staging were revised following the 2009

Table 1
Cardio-renal syndrome subtypes.
Source: Ronco et al. For the acute dialysis quality initiative (ADQI) consensus group (2009). *Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative.* Eur Heart J 2010;31:703–711 by permission of Oxford University Press.

CRS Subtype	Primary organ	Criteria for event	Definition
Heart			
Acute cardio-renal Type 1	Heart — ACS or ADHF	ESC, ACCF/AHA, AKIN, RIFLE	Acute worsening of heart function leading to kidney dysfunction/injury
Chronic cardio-renal Type 2	Heart — CHD or CHF	ESC, ACCF/AHA, KDOQI	Chronic abnormalities in heart function leading to kidney dysfunction/disease
Kidney			
Acute reno-cardiac Type 3	Kidney — AKI	AKIN, RIFLE	Acute worsening of kidney function leading to heart dysfunction &/or injury
Chronic reno-cardiac Type 4	Kidney — CKD	KDOQI	Chronic kidney function leading to heart dysfunction, disease &/or injury
Systemic			
Secondary CRS Type 5	Systemic example: Sepsis	Disease-specific criteria	Systemic conditions leading to simultaneous dysfunction &/or injury of heart & kidney

Abbreviations: CRS, Cardio-renal syndrome; ACS, Acute coronary syndrome; ADHF, Acute decompensated heart failure; ESC, European Society of Cardiology; ACCF/AHA, American College of Cardiology Foundation with the American Heart Association; RIFLE, Risk-Injury-Failure-Loss-Endstage renal disease; AKIN, Acute Kidney Injury Network; KDOQI, Kidney Disease Outcomes Quality Initiative; AKI, Acute kidney injury; CKD, Chronic kidney disease.

Kidney Disease Outcomes Quality Initiative Controversies Conference. Results from the conference lead to stage III CKD (GFR < 60 ml·min·1.73 m^2) being split into stage III a: GFR 45–59 ml·min·1.73 m^2 and stage III b: 30–44 ml·min·1.73 m^2 and the inclusion of Albuminuria (Albumin Creatinine ratio (ACR) = albuminuria > 3.0 mg/g) as a criteria for CKD (Table 3). To highlight the cardio-renal relationship and the impact of deteriorating renal function on outcomes Levey et al. [14] provide a number of matrix that summarize the pooled relative risks of varying levels of eGFR and albuminuria, expressed as continuous or categorical variables, respectively, for all-cause and cardiovascular mortality, and for end-stage kidney failure, acute kidney injury and progression to CKD.

Acute kidney injury, formerly referred to as acute renal failure, has followed a similar path to CKD in developing definitions and staging criteria. The RIFLE kidney disease classification scheme for acute renal failure in the critically ill was first published in 2004 [24]. The original RIFLE staging criteria were based on changes from baseline values for serum creatinine and/or percentage eGFR or urinary output where the criterion that resulted in the most severe classification was used. These criteria were developed to define and describe acute or abrupt deterioration of renal function resulting from a broad range of aetiologies in the critically ill. Since the introduction of the RIFLE criteria several revisions have occurred.

The convening of the Acute Kidney Injury Network (AKIN) was a strategy to enable international consensus and endorsement by scientific societies and healthcare organisations for an advanced acute kidney injury definition and criteria, and as a means to foster a collaborative network [29]. AKIN published its revised definition and criteria for acute kidney injury in 2007 [29]. This evidence-based classification and staging definition maintained the components serum creatinine, and urinary output and introduced chronicity reflecting the aspects of the five stage RIFLE criteria while compressing it to three stages. Importantly the initiation of renal replacement therapy was now subsumed into stage III of the new definition. The use of the AKI diagnostic system carries a number of caveats flagging the need to assess adequacy of hydration status and eliminate urinary tract obstruction while considering the impact of body mass index, sex and age for serum creatinine values resulting in the option for use of absolute or percentage change for creatinine. Acute kidney injury is defined [29] as "an abrupt (within 48 h) reduction in kidney function expressed as an absolute increase in serum creatinine of ≥0.3 mg/dl (≥26.4 μmol/l), a percentage increase in serum creatinine of ≥ 50% (1.5 fold from baseline), or a reduction in urine output documented oliguria < 0.5 ml/kg per hour for more than six hours." AKI is staged for severity by either absolute or percentage increments in creatinine over baseline value or by diminishing urinary output criteria [7].

The most recent revision of the definition is informed by a systematic review of relevant trials published prior to February 2011 [7]. Creatinine values for the diagnosis of AKI remain unchanged, and the staging for AKI now occurs over 7-days. It is noteworthy that serum creatinine (SCr) and equations for estimating glomerular filtration rate (GFR) feature in the CKD & AKI definitions and that the values identified for these renal biomarkers are the same or very similar to the criteria use in HF worsening renal function incidence, prevalence and outcome studies [30,31]. In the case of the AKI definition, urinary output is an additional metric. RIFLE and AKIN criteria have been validated as systems for the diagnosis and staging of acute kidney injury through a series of epidemiological studies including many multicentre approaches with over half a million patients involved [32].

4. Defining renal dysfunction in heart failure — the evidence

The definition for worsening renal function in HF remains arbitrary [33]. Gottlieb et al. [31] identified an in-hospital rise in serum creatinine of > 0.3 mg/dl (>26.5 μmol/l) as having a "sensitivity of 81% and specificity of 62% for death; 64% and 65% for length of stay greater than 10 days." Forman et al. [34] confirmed that these increases in serum creatinine "were clinically consequential in all subgroups of subjects regardless of baseline or peak serum creatinine level". Increments in serum creatinine of ≥ 0.3 mg/dl (≥26.5 μmol/l) have a significant impact on 30-day and long term mortality where increasing severity of the renal dysfunction conveys increased all-cause mortality [35–37].

Several meta-analyses have investigated the association of worsening renal function in HF with prevalence and prognosis [3,4,38] (Table 2). Damman and colleagues [4] and Smith and colleagues [3] have reported prevalence and prognostic outcomes for a broad range of patients with respect to the severity of heart failure and settings including hospital, clinical trial or community-based. Coca et al. [38] examined the 30-day mortality impact of acute kidney injury characterised by small changes in serum creatinine (>10% or >0.3 mg/dl [>26 μmol/l]) in cardiac surgery or angiography patients, acute decompensated congestive heart failure patients, acutely ill intensive care patients and a broad range of hospitalised patients.

Smith et al. [3] analysed 16 high-quality studies with over 80,000 patients with various degrees of HF severity and an average age of 74-years. The prevalence of renal impairment for all categories of patients at baseline was determined using serum creatinine, creatinine clearance or estimated glomerular filtration rate or cystatin-C. Renal impairment was classified as 'any' or 'moderate to severe' and additionally as worsening renal function for hospitalised patients (Table 2). All-cause mortality findings suggested a linear relationship for renal function and mortality risk when renal impairment was expressed as a continuous variable for either serum creatinine or eGFR. Mortality risk increased either by 33% per 1 mg/dl creatinine increase in three studies or by 7% per 10 ml/min eGFR' decrease in two of the randomised control trials. The prevalence for 'any' or 'moderate to severe' renal impairment was 63% and 29%, respectively.

Damman et al. [4] sought to determine the proportion of HF patients with worsening renal function and the association with hospitalisations and mortality. They defined worsening renal function as a fall in eGFR of ≥5 ml·min·1.73 m^2 or increase in serum creatinine of ≥0.2 mg/dl (≥17.7 μmol/l) as these limits identify normal physiological variability. Severity of WRF was categorised as classes I to III to enable the assessment of outcome against commonly used thresholds for defining WRF (Table 2). All-cause mortality and hospitalisation linked to WRF were calculated based on a minimum 6-month follow-up. The total all-cause combined mortality odds ratio was 1.62, 95% CI 1.45–1.82, $P < 0.001$ for patients with worsening renal function increasing with severity of WRF, and substantially increasing when eGFR fell by >9 ml·min·1.73 m^2 or serum creatinine increased by 0.5 mg/dl (44 μmol/l). All-cause hospitalisation OR was 1.30, 95% CI 1.04–1.62, $P = 0.022$. A trend towards a linear relationship between baseline renal function and worsening of renal function was also observed supporting the findings of Smith et al. [3].

The meta-analysis of Coca and colleagues [38] described the importance of small acute reductions in kidney function and 30-day mortality in a variety of hospitalised patients. Their objective was to determine the relationship between WRF and short-term mortality in study populations and settings that were heterogeneous. Over 78,000 patients with an age range of 53 to 72 years were included in the analysis. A 'small' serum creatinine change was defined as "any change beyond that expected by normal variations in laboratory measurements" which is consistent with the approach of Damman. Coca's [38] results show an association between small increases in serum creatinine and short-term mortality (unadjusted RR 1.8, 95% CI 1.3–2.5) and 2.3 (95% CI 1.8–3.0) when these increases are in the order of 10–24% or 0.3 to 0.4 mg/dl [26–35 μmol/l] respectively.

Importantly, the similarity in the thresholds used to define worsening renal function in these meta-analyses is closely aligned with the diagnostic criteria and staging for AKI presented in the RIFLE and AKIN criteria. Further these studies confirm that baseline renal function and the degree of dysfunction experienced during an acute episode are

Table 2
Definition examples variously defined worsening renal function, acute kidney injury and chronic kidney disease.

Author	Year	Type	Population	Biomarker	General definition	Time	Staging/ Severity	Key findings
Worsening renal function in HF								
Krumholz et al.	2000	Retrospective cohort	Hospital	SCr	↑SCr > 0.3 mg/dl (26.51 μmol/l) from admission	LOS	Nil	28% developed WRF. WRF associated with room, LOS & mortality
Gottlieb et al.	2002	Retrospective cohort	Hospital	SCr	SCr ↑ by 0.1 mg/dl (8.8 μmol/l) increments to 0.5 mg/dl (44.2 μmol/l) or SCr ↑ by 10% increments 10%–50% from admission	LOS	0.1 mg/dl (8.8 μmol/l) 0.2 mg/dl (17.1 μmol/l) 0.3 mg/dl (26.5 μmol/l) 0.4 mg/dl (35.4 μmol/l) 0.5 mg/dl (44.2 μmol/l) 10%20%30%40%50%	↑SCr > 0.3 mg/dl (26.5 μmol/l) = 81% Sensitivity & 62% Specificity for death; 68% & 45% for LOS > 10 days.
Forman et al.	2004	Retrospective cohort	Hospital	SCr	↑SCr > 0.3 mg/dl (26.51 μmol/l) from admission	LOS	Nil	27% developed WRF. Developed a risk score for WRF
Smith et al.	2006	Meta-analysis Cohort studies & secondary analysis of some RCTs	Hospital Community & Clinical trials of HF	SCr CrCl eGFR cystatin-C	Defined based on categorizations in the published studies. Additionally authors defined WRF as ≥ 0.3 mg/dl (26.51 μmol/l) from admission	LOSIa Follow-up period	Any renal impairment SCr > 1.0 mg/dl (88.4 μmol/l), CrCl or eGFR <90 ml/min, or cystatin-C > 1.01 mg/dl. Moderate/severe impairment SCr ≥ 1.5, CrCl or eGFR < 53 ml, or cystatin-C ≥ 1.56 — Estimated using fixed-effects meta-analysis	All-cause mortality worsened incrementally against reducing renal function. 1% ↑ risk with every 10 ml·min ↓ in eGFR; & WRF HR = 1.47, 95% CI 1.26–1.72
Damman et al.	2007	Meta-analysis Cohort studies & secondary analysis of some RCTs	Hospital	SCr eGFR	↑ SCr ≥ 0.2 mg/dl to 0.3 mg/dl (17.7–26.5 μmol/l) or ↓ eGFR: ≥ 5 ml·min·1.73 m²	LOS	Class I: ↑ SCr 0.2 mg/dl to 0.3 mg/dl (17.7–26.5 μmol/l) ↓ eGFR: 5–10 ml·min·1.73 m² Class II: ↑ SCr > 0.3 mg/dl to 0.5 mg/dl (>26.5–44.2 μmol/l) eGFR: 11–15 ml·min·1.73 m² Class III: ↑ SCr > 0.5 mg/dl (44.2 μmol/l) or ↓ eGFR: >15 ml·min·1.73 m²	Graded, inverse relationship between all-cause mortality, re-admission and degree of worsening renal function.
Qazi et al.	2007	Meta-analysis Heterogeneous setting & populations. 2 HF	Hospital	SCr	2 methods' percentage or absolute change in serum creatinine levels. SCr level of 10% to 24% or 0.3 to 0.4 mg/dl (26–35 μmol/l).		Mild AKI: SCr level of 10% to 24% or 0.3 to 0.4 mg/dl (26–35 μmol/l). Moderate AKI: SCr change of 25% to 49% or 0.5 to 0.9 mg/dl (44 to 80 μmol/l). Severe AKI: SCr change of 50% or ≥ 1.0 mg/dl (≥88 μmol/l)	SCr by absolute change 30-day mortality unadjusted relative risk: RR Mild: 2.3 (1.8–3.0) RR Mod: 6.2 (3.2–11.7) RR Severe: 12.4 (4.0–38.5)
Atherton et al.	2012	ADHERE-Asia-Pacific Registry	Hospital	SCr	SCr > 132 mmol/l or >1.5 mg/dl on admission	Baseline	-	41% CKD on admission.
Roy et al.	2013	Single-centre cohort	Hospital	SCr eGFR (urine output)	RIFLE, AKIN & KDIGO and often used HF-WRF = ↑SCr ≥ 0.3 mg/dl	Variant: Baseline 48 h LOS	RIFLE – 5 stages; AKIN – 3 stages; KDIGO – 3 stages; WRF – no stage	Found predictive ability between definitions were only marginal. Advantage of AKIN, RIFLE and KDIGO definitions over HF-WRF is these definition criteria have a severity scale.

(continued on next page)

Table 2 (continued)

Author	Year	Type	Population	Biomarker	General definition	Time	Staging/ Severity	Key findings
Acute kidney injury								
RIFLE Bellomo et al.	2004	.	Hospital	SCr eGFR (urine output)	↑SCr ≥ 1.5 times baseline or ↓eGFR ≥ 25%	Baseline	Risk ↑SCr × 1.5 or ↓eGFR > 25% or UO < 0.5 ml·kg·h × 6 h Injury ↑SCr × 2 or ↓eGFR > 50% or UO < 0.5 ml·kg·h × 12 h Failure ↑ SCr × 3 or ↓eGFR > 75% or ↑ SCr ≥ 4 mg/dl (354 μmol/l) with an acute rise ≥0.5 mg/dl (44 μmol/l) or UO < 0.3 ml·kg·h × 24 h or Anuria × 12 h Loss Persistent ARF > 4 weeks Endstage RRT, ≥3 months	Change to be maintained for >24 h and occur within a 7-day period. Most severe classification used to describe severity of Acute renal failure (ARF) now known as AKI.
AKIN Mehta et al.	2007	.	Hospital	SCr (urine output)	An abrupt (within 48–h) absolute ↑ SCr ≥ 0.3 mg/dl (26.5 μmol/l) or a % increase in SCr ≥ 50% (1.5-fold) from baseline or UO < 0.5 ml·kg·h ×6 h.	Baseline	Stage 1 ↑SCr × 1.5 or ≥ 0.3 mg/dl (26.5 μmol/l) or UO < 0.5 ml·kg·h × 6 h Stage 2 ↑SCr × 2 UO< 0.5 ml·kg·h × 12 h Stage 3 SCR ↑ × 3 or SCr ≥ 4 mg/dl (354 μmol/l) with an acute rise ≥ 0.5 mg/dl (44 μmol/l) or UO < 0.3 ml·kg·h × 24 h or Anuria × 12 h	Occurring within 48-hour hospitalisation period. Staging occurs over 7-day period. Most severe classification used to describe severity of AKI.
KDIGO	2012	.	Hospital	SCr UO	↑ SCr by ≥0.3 mg/dl (≥ 26.5 μmol/l) ≤ 48 h; or ↑ SCr ≥ 1.5 × baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml·kg·h × 6 h.	Baseline	Stage 1 SCr ↑1.5–1.9 × baseline or ≥0.3 mg/dl (≥26.5 mmol/l) or UO < 0.5 ml·kg·h for 6–12 h Stage 2 SCr × 2–2.9 baseline or UO < 0.5 ml·kg·h for ≥ 12 h. Stage 3 SCr × 3 or ↑ in SCr no ≥ 4.0 mg/dl (≥ 354 μmol/l) or Initiate RRT, or UO < 0.3 ml·kg·h for ≥ 24 h or Anuria for ≥ 12 h. Patients < 18 years, ↓ in eGFR to <35 ml·min·1.73 m²	
Chronic kidney disease								
KDIGO	2012		General	eGFR ACR (spot urine)	eGFR < 60 ml·min·1.73 m⁻² and/or Albuminuria ACR> 3 mg/g for ≥3-months irrespective of cause	For ≥ 3 months	Stage 1 Normal or high ≥90 ml Stage 2 Mildly ↓ 60–89 ml Stage 3a Mild-Moderately ↓ 45–59 ml Stage 3b Moderate/Severely ↓ 30–44 ml Stage 4 Severely ↓ 15–29 ml Kidney failure Endstage <15 ml	

Abbreviations: ACR, albumin to creatinine ratio; AKI, acute kidney injury; CKD, chronic kidney disease; WRF, worsening renal function; eGFR, estimated glomerular filtration rate; HF, heart failure; CrCl, calculated creatinine clearance; SCr — serum creatinine; UO, urinary output; LOS, length of stay; ↑, increasing; ↓ decreasing; KDIGO, Kidney Disease Improving Global Outcomes.

Table 3
Stages of chronic kidney disease by GFR and albuminuria categories.
Adapted from [27]

Stage	Description	CKD — GFR* ml·min·1.73 m²	Albuminuria categories — ACR description and range		
1	Normal or high	≥90 ml	A3-CKD	A2	A1
2	Mildly decreased	60–89 ml	Severely increased	Moderately increased	Normal to mildly increased
3a	Mildly–moderately decreased	CKD 45–59 ml	Macro >30 mg/mmol >300 mg/g	Micro 3–30 mg/mmol 30–300 mg/g	Micro <3 mg/mmol <30 mg/g
3b	Moderately–severely decreased	CKD 30–44 ml	CKD is defined as eGFR < 60 ml·min·1.73 m² and/or Albuminuria ACR > 30 mg/g for ≥3 months irrespective of cause.		
4	Severely decreased	CKD 15–29 ml			
5	Kidney failure	Endstage CKD < 15 ml	*GFR — glomerular filtration rate		

aligned with outcomes. This suggests the possibility for continuity for criteria for defining renal dysfunction of an acute nature in diverse populations with multiple aetiologies. This premise is confirmed by the investigation of Roy and associates [39] who compared the outcome predictive ability of the traditional definitions for acute kidney injury (RIFLE, AKIN & KDIGO) and the often used worsening renal function definition (serum creatinine rise of ≥0.3 mg/dl) in a single centre cohort of hospitalised heart failure patients. They found that the predictive ability between definitions was only marginal but that the AKIN, RIFLE and KDIGO acute kidney injury classification systems have the advantage over the commonly used worsening renal function in HF definition as they include in their definition criteria a severity scale. This additional feature enhances the ability of the clinician to identify those patients at the greatest risk of adverse events and outcomes with the caveat that HF patients with CKD at baseline are already at increased risk.

5. Biomarkers & eGFR formulae

The role of the biomarker is to identify normal or pathogenic processes, or the response to a therapeutic intervention; but it does not need to be involved in the disease process [40]. Both serum creatinine and eGFR are markers of kidney function and remain central to the diagnosis and staging of CKD, AKI and worsening renal function in spite of limitations and the arrival of several promising new renal biomarkers [2].

The importance of serum creatinine in defining renal function has been contingent on the ease with which it can be obtained, the low cost, clinician familiarity with its interpretation and the evidence to support its use as a renal biomarker. The limitations of this approach are that it is an indicator of renal function not site of injury or disease; that it is slow to respond compared to the new, novel renal biomarkers and that it can be effected by age, gender, race, body mass, diet and the patient not being in a steady physiological state [2]. Never-the-less the novel renal biomarkers such as Interleukin-18 and neutrophil gelatinase-associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1) and cystatin-C have typically not replaced the use of serum creatinine mainly due to cost and lack of availability and also a lack of specificity under some circumstances such as concurrent infection or inflammation processes [2].

Glomerular filtration rate is not usually measured in clinical practice due to time requirements, complexity and costs, but instead glomerular filtration rate formulas are applied to estimate kidney function. The most commonly used formulas are the Cockcroft–Gault equation [41] for estimated creatinine clearance; the simplified Modification of Diet in Renal Disease (sMDRD) [42] equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [43] formula for estimated GFR. The sMDRD and CKD-EPI formulae standardise to population mean body surface area (BSA) of 1.73 m². Serum creatinine is a core element in the eGFR formulae and although formulae adjust for some of the variables that impact creatinine, estimates of GFR should be interpreted with caution as well as for the fact that older age groups have not been represented in the development of the eGFR formulae. Till recently the sMDRD equation had been the preferred eGFR equation in HF as it has been validated in this population [44], however the CKD-EPI formula has now been validated for HF and is more accurate under some circumstances [45].

Blood urea nitrogen (BUN) has been shown to correlate with HF outcomes [46]. A blood urea nitrogen increase over the baseline hospitalisation value of 10 mg/dl or more in a post hoc analysis of OPTIME-HF registry was an independent predictor of 60-day mortality [47]. BUN is also subject to certain limitations and can be affected by dietary protein intake, steroid use and catabolism [48].

6. Patient outcomes and settings

All-cause mortality [30,49], including cardiovascular death [3,50,51], in-hospital mortality [52], 30-day mortality [38], community-based mortality [53], hospitalisation rates [12] and hospital length of stay [34] are negatively impacted when renal dysfunction is present in HF. Even small acute increments in serum creatinine in the order of 10–24% or 0.3 to 0.4 mg/dl [26–35 μmol/l] in a diverse group of cardiovascular and critically ill patients resulted in a 30-day mortality RR of 1.8 and 2.3 respectively [38]. AKI is a syndrome with multiple aetiologies and is often the result of multiple insults [7]. HF patients with CKD or acute kidney injury are at risk of progression to end-stage renal failure [14,54]. Depending on the definition chosen for worsening renal function different cut-points for serum creatinine (SCr) such as increases of ≥26.5 μmmol/l (≥0.03 mg/dl) as compared to ≥44.2 μmmol/l (≥0.05 mg/dl) will result in different sensitivity and specificity for predicting mortality; a more restrictive definition (i.e. the higher serum creatinine cut-off) sees sensitivity decreased while specificity is increased [13,33]. Renal dysfunction in HF does not discriminate based on HF aetiology. Both sexes can be effected as can patients with heart failure with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF) [53,55]. To date, the ESC and the ACCF/AHA have not yet endorsed a preferred working definition for worsening renal function in HF or discussed the barriers or enablers to adopting the KDIGO definition and staging criteria for AKI. This is an important debate in view of mounting evidence for a definition in HF since 2002/2003 [13,31] and the similarity of the creatinine and eGFR thresholds for acute kidney injury RIFLE/AKI Network criteria which have been validated in studies involving more than 500,000 patients [54].

7. Discussion

The vast majority of published research addressing prevalence or the prognostic impact of worsening renal function in HF is based on serum

creatinine and/or eGFR. Yet there is no international consensus for a working definition of worsening renal function in HF. In addition, there appears to be no concordance or adaptation of CKD guidelines for the management of chronic kidney disease stages in HF. Eckardt and co-authors [56] have recently called upon generalist and specialist health-care professionals to collaborate in recognising the challenges present to fully address the problem to prevent acute and chronic kidney disease which have become major public health burdens. HF patients could benefit from such collaboration.

HF is and will continue to be a chronic condition primarily of the elderly (65–70 years), and very elderly (75–85 years) [57]. In an ageing population, multiple comorbidities such as diabetes and connective tissue diseases will be a common feature of HF presentation. In HF, CKD is already established as a co-morbidity [1]. Lack of diagnosis and staging system for worsening renal function in HF has limited the utility of cardio-renal research results [33]. Internationally agreed definitions allow clinicians, scientists and others to have a shared understanding of a condition or concept. A definition enables the clinician to determine the presence or absence of a disease or condition and the degree of severity thereby facilitating and ensuring a shared understanding [58]. In research agreed definitions and uniform nomenclature can support meta-analysis potentially increasing the strength of the evidence for or against an intervention.

Clinical definitions cannot remain static. For example, the definition for myocardial infarction has evolved as our understanding of the condition and its biomarkers has advanced. RIFLE and AKIN criteria have been refined and validated. Englberger et al. [59] report that "the calculated predictive ability RIFLE class as well as AKIN stage were found to be significant predictors of increased mortality, prolonged intubation, prolonged ICU and hospital stay using multivariate analysis".

These definitions and severity classifications have benefits for patients, clinicians and researchers. A uniform nomenclature better aids patient education and assessment, and the tailoring of therapy, and allows an objective diagnosis to be made regardless of the cause which is helpful for both clinical and public health research. Serum creatinine (SCr) and glomerular filtration rate (GFR) have long been the standard for assessing renal function notwithstanding their limitations. Novel renal biomarkers have, and are being identified to address these limitations, but are yet to replace them in standard care. Until there is a similar level of research evidence to support the use of the new generation renal biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) for ischemic renal injury, and the Kidney injury molecule-1 (KIM-1) [60] we recommend the AKIN acute kidney injury definition be adopted with the caveats that patients are volume assessed and that serum creatinine, eGFR and BUN are monitored for trends. The AKIN definition is recommended based on the ease with which it can be applied and interpreted; its sensitivity and similarity with commonly used serum creatinine threshold for defining worsening renal function in HF. Community managed HF patients should also be classified against the CKD stage criteria and routinely assessed for urinary albumin creatinine ratio (ACR). If this approach was adopted internationally, particularly the monitoring in community and during hospital episodes, there is the potential to identify HF patients with unrecognised progressive renal dysfunction and the potential to prevent adverse outcomes [61].

8. Conclusion

Renal dysfunction is common in HF and associated with adverse outcomes. Identifying individuals at risk of renal dysfunction is important in preventing acute kidney injury, and chronic kidney disease, evaluating therapy monitoring renal function, and potentially preventing adverse outcomes [62]. As such, we argue that there is a clear need for debate and discussion on defining worsening renal function. These definitional issues are not insignificant as they allow comparison across studies, inform clinical practice guidelines and assist in prognostic models.

9. Recommendations

1. The diagnosis and staging of worsening renal function for hospitalised heart failure presentations are defined based on the Acute Kidney Injury Network (AKIN) [29] definition for acute kidney injury and the following minor amendments.
   a) That the timeframe for diagnosis be amended from a 48 hour to a 72 hour period during hospitalisation [31,34] and that staging then continues to be 7 days or until discharge whichever occurs first.
   b) The urinary output criterion is used judiciously with the caveats that patients are volume assessed using both clinical assessment and biochemical and haematological markers for volume status and urinary tract obstruction is eliminated.
   c) Serum creatinine, blood urea nitrogen (BUN) and eGFR are monitored for trends while hospitalised and as a minimum monthly on discharge until stable or chronic kidney disease is diagnosed.
2. Transient worsening renal function is defined as worsening renal function that resolves by discharge or in less than 3 months to baseline level.
3. Community-based HF patients to be classified according to the CKD stage criteria and monitored in accordance with the KDIGO recommendations, or as indicated with change to medication regime or following hospitalisation and include assessment of the albumin creatinine ratio (ACR).

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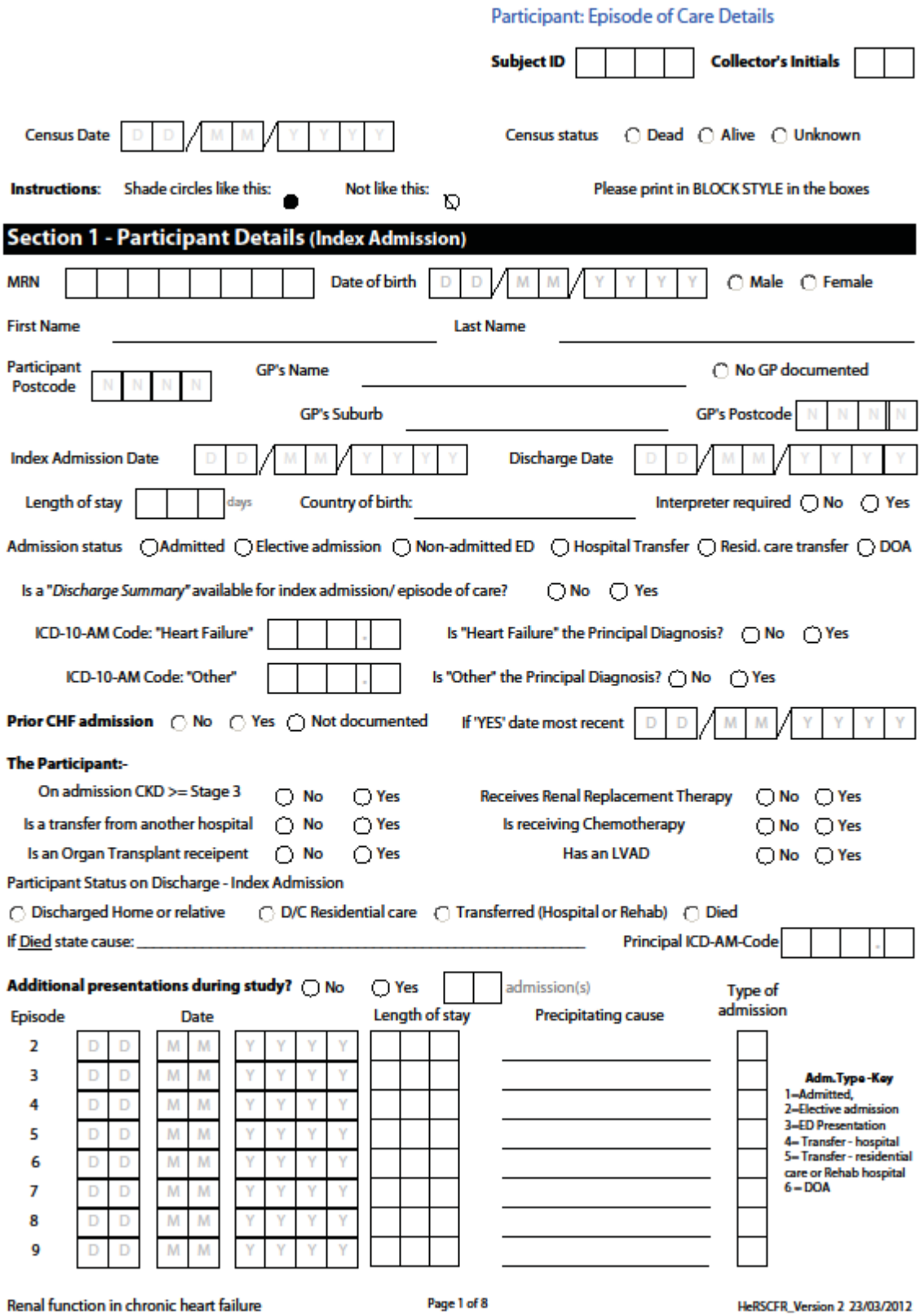
Appendix 2 Case record form



Participant: Episode of Care Details

Subject ID ☐☐☐☐ **Collector's Initials** ☐☐

Census Date D D / M M / Y Y Y Y Census status ◯ Dead ◯ Alive ◯ Unknown

Instructions: Shade circles like this: ● Not like this: ⊘ Please print in BLOCK STYLE in the boxes

Section 1 - Participant Details (Index Admission)

MRN ☐☐☐☐☐☐☐☐ Date of birth D D / M M / Y Y Y Y ◯ Male ◯ Female

First Name _____ Last Name _____

Participant Postcode N N N N GP's Name _____ ◯ No GP documented

GP's Suburb _____ GP's Postcode N N N N

Index Admission Date D D / M M / Y Y Y Y Discharge Date D D / M M / Y Y Y Y

Length of stay ☐☐☐ days Country of birth: _____ Interpreter required ◯ No ◯ Yes

Admission status ◯ Admitted ◯ Elective admission ◯ Non-admitted ED ◯ Hospital Transfer ◯ Resid. care transfer ◯ DOA

Is a "*Discharge Summary*" available for index admission/ episode of care? ◯ No ◯ Yes

ICD-10-AM Code: "Heart Failure" ☐☐☐.☐ Is "Heart Failure" the Principal Diagnosis? ◯ No ◯ Yes

ICD-10-AM Code: "Other" ☐☐☐.☐ Is "Other" the Principal Diagnosis? ◯ No ◯ Yes

Prior CHF admission ◯ No ◯ Yes ◯ Not documented If 'YES' date most recent D D / M M / Y Y Y Y

The Participant:-

On admission CKD >= Stage 3	◯ No	◯ Yes	Receives Renal Replacement Therapy	◯ No	◯ Yes
Is a transfer from another hospital	◯ No	◯ Yes	Is receiving Chemotherapy	◯ No	◯ Yes
Is an Organ Transplant receipent	◯ No	◯ Yes	Has an LVAD	◯ No	◯ Yes

Participant Status on Discharge - Index Admission

◯ Discharged Home or relative ◯ D/C Residential care ◯ Transferred (Hospital or Rehab) ◯ Died

If Died state cause: _____ Principal ICD-AM-Code ☐☐☐.☐

Additional presentations during study? ◯ No ◯ Yes ☐☐ admission(s)

Episode	Date	Length of stay	Precipitating cause	Type of admission
2	D D M M Y Y Y Y			
3	D D M M Y Y Y Y			
4	D D M M Y Y Y Y			
5	D D M M Y Y Y Y			
6	D D M M Y Y Y Y			
7	D D M M Y Y Y Y			
8	D D M M Y Y Y Y			
9	D D M M Y Y Y Y			

Adm.Type -Key
1=Admitted,
2=Elective admission
3=ED Presentation
4= Transfer - hospital
5= Transfer - residential care or Rehab hospital
6 = DOA

Renal function in chronic heart failure Page 1 of 8 HeRSCFR_Version 2 23/03/2012

Participant: Episode of Care Details

Subject ID ☐☐☐☐ **Collector's Initials** ☐☐

Census Date D D / M M / Y Y Y Y Census status ◯ Dead ◯ Alive ◯ Unknown

Section 2 - Admission examination

NYHA Class ◯ No data ◯ I ◯ II ◯ III ◯ IV

Infection ◯ No ◯ Yes ◯ No data

Pacemaker ◯ No ◯ Yes ◯ No data

ICD ◯ No ◯ Yes ◯ No data

Ascites ◯ No ◯ Yes ◯ No data

JVP ◯ No ◯ Raised ◯ No data

Crepitations ◯ No ◯ Basal ◯ Widespread ◯ No data

Orthopnoea ◯ No ◯ Yes ◯ No data

Oedema ◯ No ◯ Ankle ◯ Calf ◯ Knee ◯ Higher than knee ◯ No data

Respiratory rate ☐☐☐ breaths/min

SaO2 (Room air) ☐☐☐ % ◯ No Data

Weight monitored ◯ No ◯ Yes ◯ No data

ECG ◯ Sinus Rhythm ◯ Atrial Fibrillation ◯ Paced Rhythm ◯ Atrial Flutter ◯ 1st, 2nd or 3rd Degree Heart Block

Heart sounds

S1/S2	◯ No	◯ Yes	◯ No data
S3	◯ No	◯ Yes	◯ No data
S4	◯ No	◯ Yes	◯ No data
Systolic murmur	◯ No	◯ Yes	◯ No data
Diastolic murmur	◯ No	◯ Yes	◯ No data

Blood pressure: 1st ☐☐☐ / ☐☐☐ mm/Hg Heart rate b p m

◯ Tobacco use ◯ Never ◯ Current ◯ Ex-smoker ◯ No data

Admitted to:
- ◯ No data
- ◯ Cardiology
- ◯ Intensive Care/ HDU
- ◯ Respiratory
- ◯ Aged Care
- ◯ Other ward

Discharged from:
- ◯ No data
- ◯ Cardiology
- ◯ Intensive Care/ HDU
- ◯ Respiratory
- ◯ Aged Care
- ◯ Other ward

Section 3 - Admission Lab Results (Date)

D D M M Y Y Y Y Troponin ☐☐.☐☐ µg/L ◯ No data

D D M M Y Y Y Y CK-MB ☐☐☐☐ U/L ◯ No data

D D M M Y Y Y Y Albuminuria ◯ No ◯ Yes ◯ No data

D D M M Y Y Y Y Haematuria ◯ No ◯ Yes ◯ No data

D D M M Y Y Y Y Proteinuria ◯ No ◯ Yes ◯ No data

Section 4 - Acute precipitating factors

Dyspnoea/ SOB	◯ No	◯ Yes	Anaemia	◯ No	◯ Yes	AMI	◯ No ◯ Yes
Angina	◯ No	◯ Yes	Change in cardiac drugs <7 days	◯ No	◯ Yes	Fever	◯ No ◯ Yes
Chest pain	◯ No	◯ Yes	Non-compliance	◯ No	◯ Yes	Fall	◯ No ◯ Yes
Arrhythmia	◯ No	◯ Yes	Drug induced (NSAIDs)	◯ No	◯ Yes	Cough	◯ No ◯ Yes
Recent Infarct<1mth	◯ No	◯ Yes	Acute renal failure	◯ No	◯ Yes	Oedema	◯ No ◯ Yes
Respiratory Infection	◯ No	◯ Yes	Bacterial endocarditis	◯ No	◯ Yes	Confusion	◯ No ◯ Yes
Thyroid disease	◯ No	◯ Yes	Exacerbation *or* new on-set of non-cardiac disease	◯ No	◯ Yes	Vomiting	◯ No ◯ Yes
Acute mechanical complication (eg valve)	◯ No	◯ Yes				Other	◯ No ◯ Yes

Subject ID ☐☐☐☐ **Collector's Initials** ☐☐

Census Date D D / M M / Y Y Y Y Census status ◯ Dead ◯ Alive ◯ Unknown

Section 5 - Aetiology of heart failure

◯ Ischaemic ◯ Valvular ◯ Congenital ◯ Sarcoidosis ◯ Alcoholic
◯ Dilated ◯ Hypertension ◯ Endocarditis ◯ Viral ◯ Amyloidosis
◯ Idiopathic ◯ Familial ◯ Pulmonary hypertension ◯ Chemotherapy

Section 6 - Current medications

◯ ACE inhibitor ◯ Anticoagulant ◯ Antiarrhythmic
◯ Angiotensin Receptor Blocker ◯ Antiplatelet ◯ Cacium channel blockers
◯ Beta blocker ◯ Digitalis ◯ NSAIDs
◯ Diuretic ◯ Lipid lowering agent (Statins etc) ◯ Other vasodilator
◯ Aldosterone antagonist ◯ Nitrate

Section 7 - Echocardiography or GHPS

Date most recent D D M M Y Y Y Y ◯ No data Echo ◯ No ◯ Yes Scan ◯ No ◯ Yes

EF% ☐☐ % **Fractional shortening** ☐☐ % **Rt. Atrial pressure** ◯ Normal ◯ Increased

LV Function ◯ Normal ◯ Mild Dysfuntion ◯ Moderate Dysfunction ◯ Severe Dysfunction ◯ No data

RV Function ◯ Normal ◯ Mild Dysfuntion ◯ Moderate Dysfunction ◯ Severe Dysfunction ◯ No data

Pulmonary HPT ◯ Normal ◯ Mild Dysfuntion ◯ Moderate Dysfunction ◯ Severe Dysfunction ◯ No data

Section 8 - Charlson Index (Complete the appropriate response for each condition (give only 1 answer per item)

Does the participant have:

AIDS	◯ No ◯ Yes	Dementia	◯ No ◯ Yes
Cerebrovascular disease	◯ No ◯ Yes	Hemiplegia	◯ No ◯ Yes
COAD	◯ No ◯ Yes	Leukaemia	◯ No ◯ Yes
Chronic heart failure	◯ No ◯ Yes	Mailgnant lymphoma	◯ No ◯ Yes
Connective tissue disease	◯ No ◯ Yes	Myocardial infarction	◯ No ◯ Yes
Peripheral vascular disease	◯ No ◯ Yes	Peptic ulcer disease	◯ No ◯ Yes
		Lymphoma	◯ No ◯ Yes

Diabetes mellitus ◯ None ◯ Without end organ damage ◯ With end organ damage
Liver disease ◯ None ◯ Mild ◯ Moderate ◯ Severe
Renal disease ◯ None ◯ Mild ◯ Moderate ◯ Severe

Malignant solid tumor ◯ None ◯ Non-metastatic ◯ Metastatic

Subject ID ☐☐☐☐ **Collector's Initials** ☐☐

Census Date D D / M M / Y Y Y Y Census status ○ Dead ○ Alive ○ Unknown

Section 9 - Medical History

		Does the patient have a history of the condition? No	Yes	No Data
Cardiac arrest		○	○	○
Myocardial Infarction		○	○	○
Hypertension		○	○	○
High blood cholesterol		○	○	○
Type I Diabetes		○	○	○
Type II Diabetes	○ Non Insulin requiring	○	○	○
	○ Insulin requiring	○	○	○
Heart Failure		○	○	○
Stroke/Mini Stroke		○	○	○
Mental Illness	○ Depression	○	○	○
	○ Anxiety	○	○	○
Irregular Heart Beat / Atrial Fibrillation / Palpitations		○	○	○
Severe aortic stenosis		○	○	○
Coronary Artery Disease		○	○	○
Vascular disease	○ Peripheral arterial disease (PAD)	○	○	○
	○ Other - *Please specify* _____	○	○	○
Aneurysm *(Abdominal, thoracic)*		○	○	○
Heart Valve Condition		○	○	○
Thyroid disease		○	○	○
Liver disease		○	○	○
Renal Disease		○	○	○
Sleep Apnoea		○	○	○
Asthma / Lung Disease *(eg. Emphysema, COPD) (FEV1<50%)*		○	○	○
Substance dependence	○ Alcohol/drugs	○	○	○
	○ Tabacco	○	○	○
Active stomach ulcer		○	○	○
Recent major bleeding		○	○	○
Cancer treatment		○	○	○
Hostel/ Nursing Home or Residential care resident		○	○	○
Other serious condition		○	○	○

Please specify _____

Participant: Episode of Care Details

Subject ID ☐☐☐☐ **Collector's Initials** ☐☐

Census Date ☐☐/☐☐/☐☐☐☐ Census status ◯ Dead ◯ Alive ◯ Unknown

Section 10- Management

IV Diuretics >24hrs ◯ No ◯ Yes *If 'Yes' number of* ☐☐ days *Highest total IV daily dose* ☐☐☐ mgs

IV Diuretics Infusion >24hrs ◯ No ◯ Yes *If 'Yes' number of* ☐☐ days *Highest total IV daily dose* ☐☐☐ mgs

IV GTN Infusion ◯ No ◯ Yes	P P'maker inserted ◯ No ◯ Yes	O2 Therapy ◯ No ◯ Yes
IV Inotrope Infusion ◯ No ◯ Yes	ICD inserted ◯ No ◯ Yes	CPAP/ BiPAP ◯ No ◯ Yes
Referred - Heart Tx / LVAD ◯ No ◯ Yes	IAPB ◯ No ◯ Yes	Ventilated ◯ No ◯ Yes
		Intubated ◯ No ◯ Yes

Section 11 - Complications

Cardiac arrest ◯ No ◯ Yes	DVT ◯ No ◯ Yes	Unplanned CCU ◯ No ◯ Yes	Death ◯ No ◯ Yes
STEMI ◯ No ◯ Yes	PE ◯ No ◯ Yes	Unplanned ICU ◯ No ◯ Yes	
NSTEMI ◯ No ◯ Yes	URTI ◯ No ◯ Yes	Unplanned GOR ◯ No ◯ Yes	
CVA / TIA ◯ No ◯ Yes	UTI ◯ No ◯ Yes	Renal R Therapy ◯ No ◯ Yes	

Section 12 - Procedures

Coronary Angiography ◯ No ◯ Yes C.Angio result ◯ NAD ◯ Single ◯ Double ◯ Triple ◯ LAD ◯ Diffuse

Contrast used ◯ No ◯ Yes Contrast Hydration ◯ No ◯ Yes ◯ No data

N-acetylcysteine ◯ No ◯ Yes Ultra-filtration ◯ No ◯ Yes

Section 13 - Pre Discharge Planning

Social Worker consult	◯ No ◯ Yes	Dietician review	◯ No ◯ Yes	HF OP Clinic (Public) date documented	◯ No ◯ Yes
Physio assessment	◯ No ◯ Yes	Written list medications	◯ No ◯ Yes		
ACAT review	◯ No ◯ Yes	Clinical pharmacist review	◯ No ◯ Yes	Cardiologist appt. date documented	◯ No ◯ Yes
OT consult	◯ No ◯ Yes	GP follow-up appt. noted	◯ No ◯ Yes		
Cardiac Rehab referral	◯ No ◯ Yes	D/C Summary to GP	◯ No ◯ Yes		

Section 14 - On discharge

Ascites ◯ No ◯ Yes ◯ No data **JVP** ◯ No ◯ Raised ◯ No data

Crepitations ◯ No ◯ Basal ◯ Widespread ◯ No data

Oedema ◯ No ◯ Ankle ◯ Calf ◯ Knee ◯ Higher than knee ◯ No data

Section 15 - Discharge status

◯ Discharged home ◯ Discharged residential care ◯ Transfer to another hospital/ rehabilitation facility

◯ Died - Date: _____/_____/_____ Cause: _____

Participant: Episode of Care Details

Subject ID | | | | | **Collector's Initials** | | |

Census Date D D / M M / Y Y Y Y Census status ○ Dead ○ Alive ○ Unknown

Section 16 - Medications -		On Admission		On Discharge	
	Generic name	Route	Daily Dose /Units	Route	Daily Dose /Units
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					
16.					
17.					
18.					
19.					
20.					

Participant: Episode of Care Details

Subject ID | | | | | **Collector's Initials** | |

Census Date D D / M M / Y Y Y Y Census status ○ Dead ○ Alive ○ Unknown

Section 17 - Test results

Admission Date/ Day 1: D D / M M / Y Y Final Results Date: D D / M M / Y Y

Bloods		ND = No data	
Sodium		mmol/L	
Potassium	.	mmol/L	.
C. Calcium	.	mmol/L	.
Urea	.	mmol/L	.
Creatinine		umol/L	
eGFR		mL/min/1.73m^	
Phosphate	.	mmol/L	.
PTH	.	pmol/L	.
Albumin		g/L	
Alk Phos		mmol/L	
Fe		ug/L	
CRP	.	mg/L	.
Hb		g/L	
MCV	.	fL	.
RDW	.	%	.
WCC	.	x 10^9/L	.
Platelets		x 10^9/L	
TSH	.	mIU/L	.
Total chol	.	mmol/L	.

Peak / Nadir Values

Na - Peak		D D / M M / Y Y
Na - Nadir		D D / M M / Y Y
Urea - Peak	.	D D / M M / Y Y
Urea - Nadir	.	D D / M M / Y Y
Scr - Peak		D D / M M / Y Y
Scr - Nadir		D D / M M / Y Y
eGFR - Peak		D D / M M / Y Y
eGFR - Nadir		D D / M M / Y Y
Alb - Peak		D D / M M / Y Y
Alb - Nadir		D D / M M / Y Y
CRP - Peak	.	D D / M M / Y Y
CRP - Nadir	.	D D / M M / Y Y
Hb - Peak		D D / M M / Y Y
Hb - Nadir		D D / M M / Y Y
MCV- Peak	.	D D / M M / Y Y
MCV - Nadir	.	D D / M M / Y Y
RDW - Peak	.	D D / M M / Y Y
RDW - Nadir	.	D D / M M / Y Y

Subject ID ☐☐☐☐ **Collector's Initials** ☐☐

Census Date D D / M M / Y Y Y Y Census status ○ Dead ○ Alive ○ Unknown

Section 18 - Clinical & Lab Series

Blood results - take first result for the day Admission

	Day - 2	Day - 3	Day - 4	Day - 5
D D / M M / Y Y	○ No data	○ No data	○ No data	○ No data
Sodium	☐☐☐ mmol/L	☐☐☐	☐☐☐	☐☐☐
Potassium	☐.☐ mmol/L	☐.☐	☐.☐	☐.☐
C. Calcium	☐.☐☐ mmol/L	☐.☐☐	☐.☐☐	☐.☐☐
Urea	☐☐.☐ mmol/L	☐☐.☐	☐☐.☐	☐☐.☐
Creatinine	☐☐☐ umol/L	☐☐☐	☐☐☐	☐☐☐
eGFR	☐☐☐ mL/min/1.73m^	☐☐☐	☐☐☐	☐☐☐
Hb	☐☐☐ g/L	☐☐☐	☐☐☐	☐☐☐
RDW	☐☐.☐ %	☐☐.☐	☐☐.☐	☐☐.☐
MCV	☐☐.☐ fL	☐☐.☐	☐☐.☐	☐☐.☐
CRP	☐☐.☐ mg/L	☐☐.☐	☐☐.☐	☐☐.☐

Haemodynamic & Clinical Series

Blood pressure ☐☐☐ / ☐☐☐ mm/Hg **Heart rate** ☐☐☐ b p m

Daily	Admission/Day - 1	Day - 2	Day - 3	Day - 4	Day - 5
Highest	○ No data	○ No data	○ No data	○ No data	○ No data
	h h m m	h h m m	h h m m	h h m m	h h m m
BP	S S S / D D D	S S S / D D D	S S S / D D D	S S S / D D D	S S S / D D D
HR	b p m	b p m	b p m	b p m	b p m
Lowest	○ No data	○ No data	○ No data	○ No data	○ No data
	h h m m	h h m m	h h m m	h h m m	h h m m
BP	S S S / D D D	S S S / D D D	S S S / D D D	S S S / D D D	S S S / D D D
HR	b p m	b p m	b p m	b p m	b p m