The impact of a pharmacist involvement in a multidisciplinary team on the management of patients with heart failure

Daya Ram Parajuli

B. Pharm, M. Pharm

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Abstract

Heart Failure (HF) is a complex syndrome characterized by high rates of hospitalisations and mortality, poor medication adherence, and polypharmacy. Recent studies demonstrate that approximately 50% of hospitalised patients with HF are readmitted within 6 months and 50% of patients die within five years of diagnosis. The rate of medication non-adherence in HF patients is 40–60%. There is emerging evidence that HF patients who receive pharmacist-involved multidisciplinary care have better clinical outcomes than those who do not. The overall aim of this thesis was to investigate how advancements in the management of HF can be achieved through a pharmacist-involved multidisciplinary management model of care to improve patient outcomes. A systematic review and meta-analysis was utilised to review existing randomized controlled trials (RCTs) of pharmacist-involved multidisciplinary management of HF to determine the effectiveness on different clinical outcomes. Subsequently, a retrospective data analysis of chronic heart failure (CHF) patients was used to evaluate the comparability of two multidisciplinary clinics through describing differences in demographic and clinical characteristics, comorbidities utilisation of evidence-based practice and predictors of evidence-based therapy in outpatients from a tertiary referral hospital.

The retrospective analysis compares those attending a pharmacist involved Multidisciplinary Ambulatory Consulting Service (MACS) with the General Cardiology Heart Failure Services (GCHFS) without a pharmacist. 18 RCTs (n=4630) were included for the systematic review and 16 (n=4447) for the accompanying meta-analysis. The meta-analysis showed a significant reduction in

HF hospitalisations {odds ratio (OR) 0.72 [95% confidence interval (CI) 0.55-0.93], p=0.01 but no effect on HF mortality. Similarly, a significant reduction in all-cause hospitalisations [OR 0.76, 95% CI (0.60-0.96), p=0.02] was revealed but there was no effect on all-cause mortality. The overall trend was an improvement in medication adherence and significant improvements in HF knowledge ($p<0.05$).

The mean age of patients in this study was 79 ± 10 years for HF with preserved ejection fraction (HFpEF), 76.5 ± 11 years for HF with mid-range ejection fraction (HFmrEF) and 71 ± 13.4 years for HF with reduced ejection fraction (HFrEF) patients. The prevalence of HFpEF, HFmrEF and HFrEF was 31%, 13% and 56%, respectively. Compared with HFpEF patients, HFrEF patients were younger (71 years v. 78 years) and more likely to be male (64% v. 43%), more likely to have ischemic aetiology (57% v. 51%) but less likely to have hypertension (55.4% v. 82%) and AF (44% v. 53%). Comparing patients with reduced to mid-range and preserved ejection fraction, patients were at least 7 years older and much more likely to be female, had higher SBP, more polypharmacy, higher prevalence of diabetes, COPD, hyperlipidaemia, GORD, osteoarthritis, worse renal impairment and worse anaemia.

CHF patients in the pharmacist-involved multidisciplinary clinic (MACS) were significantly older, less likely to be female, had higher SBP and DBP, were under polypharmacy and had a high prevalence of multiple comorbidities; thus, they represented a complex group of individuals compared with the GCHFS clinic patients. Both the clinics in the cohort study had similar rates of guideline-based prescribing of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), and their maximum tolerated doses in HFrEF and

HFpEF patients. However, significantly lower ($p<0.001$) β-blockers and mineralocorticoid receptor antagonists (MRAs) prescribing rates were revealed in the MACS clinic in HFpEF and HFrEF patients.

The pharmacist-involved multidisciplinary team in HF management significantly reduced HF and all-cause hospitalisations and improved medication adherence as well as HF knowledge. Older age of patients, heart rate, blood pressures, contraindications, comorbidities and polypharmacy were the potential reasons for lower prescription of β-blockers and MRAs in MACS clinic in HFrEF and HFpEF patients.

Based on the findings presented in this thesis, the pharmacist is an essential member of the multidisciplinary team and should be included in HF management irrespective of setting.

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List of Abbreviations

ACCF	American College of Cardiology Foundation
ACEIs	Angiotensin converting enzyme inhibitors
AHA	American Heart Association
AT1	Angiotensin 1
AF	Atrial fibrillation
ARBs	Angiotensin receptor blockers
BNP	B-type natriuretic peptide
BP	Blood pressure
CAD	Coronary artery disease
CCM	Chronic care model
CHF	Chronic heart failure
CNS	Clinical nurse specialists
COPD	Chronic obstructive pulmonary disease
CR	Cardiac rehabilitation
CTP	Care transition pharmacist
cAMP	Cyclic adenosine monophosphate
CVA	Cardiovascular accident
DDIs	Drug–drug interactions
DBP	Diastolic blood pressure
DHF	Diastolic heart failure
EBT	Evidence-based therapy
ED	Emergency department
EDV	End diastolic volume

EF	Ejection fraction
GCHFS	General Cardiology Heart Failure Service
GORD	Gastroesophageal reflux disease
GPs	General practitioners
HBA1c	Glycated haemoglobin
HF	Heart failure
HF-MP	Heart failure management program
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
IHD	Ischemic heart disease
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MACS	Multidisciplianry Ambulatory Consulting Service
MTD	Maximum tolerated doses
MI	Myocardial infarction
MRAs	Mineralocorticoid receptor antagonists
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PET	Positron emission tomography
PICO	Population, interventions, comparison, and outcomes
QoL	Quality of life
RAAS	Renin-angiotensin-aldosterone system

RCT	Randomized controlled trial
RM	Remote monitoring
SBP	Systolic blood pressure
SHF	Systolic heart failure
SPECT	Single-photon emission computed tomography
STS	Structured telephone support
SV	Stroke volume
TM	Telemonitoring

Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed.....

Date.....25-01-2019.....

Chapter 1: Introduction

1.1 Introduction

The overall aim of this thesis is to investigate how advancements in the management of heart failure (HF) can be achieved through a pharmacist-involved multidisciplinary management model of care to improve patient outcomes. In this introductory chapter, the background information contextualises this aim and provides a rationale for this study. Definitions and classifications of HF, as well as the epidemiology and treatment of HF, are included. Further, the research aim, objectives and associated research questions are outlined. Finally, the overall thesis structure and chapter summary are provided.

1.1.1 Background and rationale

HF remains a major public health burden globally. It is a rapidly growing debilitating disease with an estimated 38 million people diagnosed worldwide (Ziaeian & Fonarow, 2016). It has poor prognosis (Page et al., 2014), high rates of mortality and morbidity (Al-Khazaali, Arora, & Helu, 2016; Jessup et al., 2016), increasing prevalence (Benjamin et al., 2018; Mozaffarian et al., 2015) and high readmission rates (Blecker et al., 2013; Inamdar & Inamdar, 2016). Additionally, HF is substantially more prevalent in elderly people (van Riet et al., 2016). It limits functional capacity, is associated with impaired quality of life (Fry et al., 2016; Hoekstra et al., 2011) and imposes a high economic burden on health care (Heidenreich et al., 2013; Rohde et al., 2013).

Despite encouraging improvements in outcomes with medical therapy (Loudon et al., 2016), recent studies demonstrate that approximately 25% of hospitalised patients with HF are readmitted within 30 days of discharge (Dharmarajan et al.,

2013) and 50% are readmitted within six months (O'Connor, 2017). Further, 50% of patients die within five years of diagnosis (Halushka, Mitchell, & Padera, 2016). While significant and convincing evidence has been available for heart failure management with reduced ejection fraction (HFrEF), little evidence exists regarding effective therapies for heart failure with preserved ejection fraction (HFpEF); the result is a cohort of patients with significant unmet clinical needs (Lekavich et al., 2015; Redfield et al., 2013). The prevalence of HFpEF is rapidly growing due to various risk factors; at present, the prevalence is at least 50% (Basaraba & Barry, 2015). Clinical characteristics and overall management of HFrEF and HFpEF are different (Abebe et al., 2016; Yancy et al., 2013). Therefore, an understanding of patient demographics, clinical characteristics and pharmacotherapy may help optimise HF management.

As reported by the Heart Failure Society of America and the American College of Clinical Pharmacy Cardiology Practice and Research Network, multiple benefits potentially exist for a pharmacist to be involved in clinical interventions for HF. These include an increase in evidence-based therapy (EBT), a decrease in HF hospitalisations and emergency department (ED) visits and a decrease in all-cause readmissions (Milfred-Laforest et al., 2013). Mortality in HF patients has lessened with the use of EBT (Burnett et al., 2017; Maggioni, Dahlstrom, et al., 2013). Underutilisation of EBT and poor adherence to recommended guidelines in HF management are common clinical problems (Deticek et al., 2016; Saito, Negishi, & Marwick, 2016). In an Australian-based study, the implementation of a care model that included pharmacist-involved multidisciplinary management used evidenced-

based guidelines in chronic HF patients, despite underlying multiple comorbidities and polypharmacy (Ho, Caughey, & Shakib, 2014).

A previous systematic review of randomised controlled trials (RCTs) reported that pharmacist involvement in HF management significantly reduced the risk of all-cause and HF hospitalisations and demonstrated a non-significant reduction in mortality, particularly if the pharmacist was a member of a multidisciplinary team (Koshman et al., 2008). The multidisciplinary approach for managing HF incorporates the implementation of evidence-based guidelines advocated by Australian (Atherton et al., 2018), American (Yancy et al., 2013) and European Ponikowski et al., 2016 professional society guidelines (Ponikowski et al., 2016). However, the role of a pharmacist within the multidisciplinary team, as well as the most effective interventions were not extensively described in these guidelines. Therefore, this present study explores evidence regarding the role of the pharmacist within the multidisciplinary team for HF management to improve clinical outcomes. This study is expected to broaden the current scientific evidence and, subsequently, the findings can be transferred into clinical practice.

1.1.2 Motivation for the research

The central motivation for my doctoral journey is the desire to be an independent researcher through gaining insights into transferable skills; including time management, project management, negotiation skills, communication and collaboration skills, creativity, and fundamental skills in clinical research. For some time, I have been curious and passionate about how the engagement of pharmacists, within the multidisciplinary team in HF management, overcomes the challenge of high hospitalisations, poor drug adherence and a lack of implementation of

evidence-based practice. Therefore, intensive research is required to investigate the role of the pharmacist-involved multidisciplinary management of HF.

1.2 Definitions

There exists some confusion in various communities, i.e. lay versus professional concerning the definition of HF. The definition provided is the most relevant and updated.

1.2.1 Heart failure

Multiple definitions of HF exist; some notable examples are from the HF societies across Australia (Krum et al., 2011), America (Yancy et al., 2013) and Europe (Ponikowski et al., 2016). According to the European Society of Cardiology (ESC) 2016 Guidelines that are used as the reference guidelines for this study (Ponikowski et al., 2016, p. 85):

> "HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intra-cardiac pressures at rest or during stress".

1.2.2 Ejection fraction

HF is classified based on ejection fraction (EF) (Mentz et al., 2014; Pandey et al., 2016). EF is the amount of blood pumped out of the left ventricle during each contraction (Iwano & Little, 2013). According to the American College of Cardiology Foundation and American Heart Association (AHA), EF is $\leq 40\%$ in HFrEF, while it is $\geq 50\%$ in HFpEF (Yancy et al., 2013). Despite the well-

established consensus for HFrEF having an EF value of ≤ 40%, the cut-off point for HFpEF varies (McMurray et al., 2012; Yancy et al., 2013). This variation includes > 40%, > 45%, > 50% and ≥ 50%.

Heart failure with mid-range ejection fraction (HFmrEF) was first introduced by AHA in 2013 but later in 2016 was further defined (Hsu, Ziaeian, & Fonarow, 2017). The first time that HF was classified into three categories, according to left ventricular ejection fraction (LVEF), was in 2016 by the ESC (Ponikowski et al., 2016). The LVEF value is < 40% for HFrEF, 40–49% for HFmrEF and ≥ 50% for HFpEF—which is also called HF in the presence of a normal LVEF (McMurray et al., 2012).

The prevalence of HFpEF is rapidly growing globally (Basaraba & Barry, 2015; Iwano & Little, 2013; Upadhya et al., 2015). HFpEF was initially referred to as diastolic HF and HFrEF as systolic HF (Katz & Rolett, 2016; Rogers et al., 2015). HFpEF is more prevalent among women, the elderly and patients with hypertension, diabetes, anaemia and atrial fibrillation (AF) compared to HFrEF (Brouwers et al., 2012; Guo et al., 2016; Zacharias et al., 2016). Table 1.1 illustrates the HF classification based on the EF cut-off point.

Table 1.1

Types of heart failure based on ejection fractions value.

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HFrEF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HFpEF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential non-cardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HFpEF, borderline	41 - 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.
b. HFpEF, improved	>40	It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

Adapted from 2013 ACCF/AHA Guideline for the Management of Heart Failure (Yancy et al., 2013)

EF: Ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ACCF: American College of Cardiology Foundation; AHF: American Heart Association.

1.3 Diagnosis of HF

The initial diagnosis of HF can be made based on signs and symptoms; however, these vary among individuals due to factors including including the age of the patient and existence of comorbidities (Ponikowski et al., 2016). The most common clinical symptoms of HF are dyspnoea, fatigue, exercise intolerance and fluid retention (Alpert et al., 2016; Kaminsky & Tuttle, 2015; Kupper et al., 2016). These symptoms are non-specific to HF; therefore, further diagnostic investigation is required for proper diagnosis - including using the New York Heart Association (NYHA) classification, chest X-ray, echocardiography, nuclear imaging and cardiac magnetic resonance imaging (MRI). HFpEF diagnosis is still controversial due to a lack of standardised guidelines, as well as a heterogeneous and inconsistently described population (Lekavich et al., 2015; Vaduganathan et al., 2016). If patients present with the signs and symptoms of HF for the first time, the initial recommendation is to perform an assessment of HF probability with the patient's clinical history of coronary artery disease, of arterial hypertension and of diuretic use.

The next step is a careful physical examination for the presence of bilateral oedema, increased jugular venous pressure and displaced apical beat, as well as measurement of their resting electrocardiogram. If any of the above are abnormal, it is highly recommended that plasma natriuretic peptides (NPs) are measured. If all the aforementioned examinations are normal, then the symptoms are due to a cause other than HF (Ponikowski et al., 2016). In certain situations, measurement of NPs in the blood and plasma electrolytes, as well as a full blood count, are also recommended (Krum et al., 2011).

1.4 Epidemiological diversity of HF in the global context

The prevalence of HF was estimated to be approximately 2% in the adult population, increasing to ≥10% in people >70 years of age in developed countries (Ponikowski et al., 2016). In the United States (US), an estimated 5.7 million people aged over 20 years have been diagnosed with HF, which is projected to increase to 46% between 2012 and 2030 (Mozaffarian et al., 2016). HF affects individuals in sub-Saharan Africa at a much younger age than those in the US and Europe (Damasceno et al., 2012). A recent international congestive HF study involving young African and Asian participants showed lower health literacy and insurance coverage, and poor EBT usage rates (Dokainish et al., 2016). HF patients in Middle Eastern countries are also younger and have different aetiology, ethnicity and risk factors compared to Western nations (AlHabib et al., 2014; Saheb Sharif-Askari et al., 2014).

1.4.1 Variation in HF aetiology

The aetiology of HF varies across the world. Ischemic heart disease is the most common cause of HF globally, except in Africa, where hypertension is the primary cause (Dokainish et al., 2016; Khatibzadeh et al., 2013). Similarly, hypertension is the primary cause of HF in Japan (Konishi et al., 2016; Nagai et al., 2018). Little is known about the underlying causes of HF in Nepal. However, existing literature (Shrestha UK, 2015) reported ischemic heart disease as the most prevalent condition, which is more in line with high-income Western countries. Consistent with global figures, ischemic heart disease, hypertension and cardiomyopathy are the leading causes of HF in Australia (Krum et al., 2011).

1.4.2 Risk factors and comorbidities in HF

The risk factors for HF depend on geographical location (Khatibzadeh et al., 2013). Many risk factors are common in HF patients, such as gender (particularly women), age, ischemic heart disease, hypertension, smoking rates and diabetes (Benjamin et al., 2018; Bui, Horwich, & Fonarow, 2011). These risk factors are significant drivers that worsen the symptoms of HF patients and interfere with effective management (Atherton et al., 2018). Hypertension is the most significant cause of HFpEF, with a prevalence ranging from 60% to 89% (Bhuiyan & Maurer, 2011). The lifetime risk of HF for people with higher blood pressure (BP) (>160/90 mm Hg) is double that of those with BP<140/90 mm Hg (Mozaffarian et al., 2016).

The burden of comorbidities is more prevalent in HFpEF patients than it is with HFrEF patients (Streng et al., 2018). Non-cardiovascular comorbidities include chronic obstructive pulmonary disorder, anaemia, diabetes, renal impairment, arthritis, cognitive dysfunction and depression (Lang & Mancini, 2007; Sharma et al., 2018). The prevalence of diabetes, anaemia and obesity is higher in HFpEF patients than in HFrEF patients (Mentz et al., 2014). The existence of comorbidities contribute to a substantial risk of morbidity and mortality in HF patients (Rushton et al., 2015). Generally, the presence of comorbidities has a similar effect on mortality, regardless of whether the patients have preserved and reduced EF (Ather et al., 2012). Polypharmacy associated with the presence of multiple comorbidities in HF patients reflects the complexity and accompanying challenge for effective management (Mastromarino et al., 2014). As experts in medicine, pharmacists can

educate patients and other health care professionals about the optimal use of prescribed medications.

1.4.3 Hospitalisation and readmission

Annually, more than one million people are hospitalised in the US and Europe (Ambrosy et al., 2014). Previous hospitalisation, non-cardiovascular comorbidities (chronic kidney disease, cerebrovascular disease and hyponatremia), poor physical condition and failure to use EBT are strong contributing factors for readmissions (Bello et al., 2014; Saito et al., 2016) Similarly, a growing elderly population, increased prevalence of HF and recurrent hospitalisations are the most significant predictors for increased health care costs in Asian countries (Kang & Cho, 2015).

The predictors of HF readmission differ between HFpEF and HFrEF patients (Setoguchi et al., 2015). According to Lekavich et al. (2015), patients with HFpEF represent at least 50% of all hospital admissions for HF. HFpEF patients predominantly have less social support, higher hospitalisation and readmission rates, and worse survival outcomes compared to HFrEF patients (Steinberg et al., 2012).Conversely, Loop et al. (2016) found similar readmission rates and lengths of stay between HFpEF and HFrEF patients. Effective treatment options may provide important insights into strategies for decreasing hospitalisation rates and patient suffering, as well as offer considerable financial savings (Corrao et al., 2014).

1.4.4 Mortality

The factors responsible for the high mortality in HF patients need to be identified to create tailored management strategies. High mortality and hospitalisation in CHF patients is predictable due to underlying comorbidities, such as diabetes, chronic

kidney disease and anaemia (van Deursen et al., 2014). A more recent study also found that inn addition to cardiovascular conditions, physical (arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, CKD and cancer) and mental health conditions (depression, dementia, schizophrenia and substance abuse) are also considerable causes of death and hospitalisations in HF patients (Manemann et al., 2016). Numerous factors, including previous hospitalisations (Bello et al., 2014), comorbidities (Ahluwalia et al., 2012), age (Butrous & Hummel, 2016), living alone and disease severity were closely associated with higher mortality in HF patients (Mard & Nielsen, 2016; Rahimi et al., 2014). Influenza virus infection for HF patients severely exacerbates the existing disease state. Patients who received an influenza vaccine during the influenza season showed less risk of death compared to those who did not (Blaya-Novakova, Prado-Galbarro, & Sarria-Santamera, 2016).

Mortality risk in ambulatory chronic HFrEF patients is reduced with improvements in guideline adherence that focus on dose optimisation, as highlighted in the Austrian Heart Failure Registry (Poelzl et al., 2014). A cardiovascular cause was dominant for the mortality of HFpEF patients, compared to non-cardiovascular causes (Zile et al., 2010). The European Society of Cardiology Heart Failure Long-Term Registry update (Crespo-Leiro et al., 2016) reported a lower one-year mortality rate in CHF patients compared to acute heart failure (AHF) patients. An increase in systolic blood pressure (SBP) is also a predictor of mortality (Segal et al., 2017). More recent evidence on improvement in medication adherence (Ruppar et al., 2016) and better utilisation of EBT (Burnett et al., 2017) resulted in a decreased mortality in HF patients.

1.4.5 Economic burden of HF

The patient's economic status is a crucial determinant of the health care service offered. Therefore, one of the goals of the pharmacist's involvement in HF management is to decrease the significant financial burden on health care systems (Hollingworth et al., 2016; Lim & Lam, 2016; Rohde et al., 2013). It is suggested that poor quality of life is a significant predictor of health care costs in HF patients ($p < 0.001$) (Mejhert et al., 2013). Patients with more severe symptoms and renal dysfunction impose a higher economic burden due to higher HF hospitalisations (Parissis et al., 2015).

Informal caregiving costs also need to be considered when estimating the total cost of HF management (Joo et al., 2015). The annual cost of the informal caregiving associated with HF was $3 billion in 2010 in the US (Joo et al., 2015). Projections show that, by 2030, the total cost of HF will increase by approximately 130% from $31 billion in 2012 (Heidenreich et al., 2013). Studies have shown that cardiovascular disease is the major non-communicable disease in Nepal (Bhandari et al., 2014; Vaidya, 2011). Although exact data on the effect of the health care burden by HF in Nepal is lacking, there is a notable burden of non-communicable diseases, rising from 51% in 2010 to 60% in 2014 (Aryal et al., 2015). In Australia, approximately $900 million is annually spent on HF management, based on the 2014 Australian Bureau of Statistics report regarding population data (Chan et al., 2016). Further, nearly $2.7 billion is estimated for the additional cost of inpatient care (including per diem hospital costs). This study also showed a concern that the cost of HF management would increase to $3.8 billion within the next 10–15 years.

1.5 Quality of life and functional status in HF patients

Quality of life and functional status remain at the forefront with respect to successful HF management programs. Impairment of functional capacity is associated with poor quality of life in HF patients (Jaarsma et al., 2010; Lesman-Leegte et al., 2009). Hospitalised elderly CHF patients in Serbia experienced poor health that was related to quality of life mediated by depressive symptoms, lower incomes, polypharmacy and longer disease duration (Erceg et al., 2013). Mental health and lifestyle modifications are important considerations for achieving improvements in HF patients' health-related quality of life (Heo et al., 2014). Poor knowledge of HF is also a major underlying factor contributing to impaired quality of life in rural HF patients in the US (Nesbitt et al., 2014).

In certain clinical situations, improvement of quality of life and functional status (e.g. depression, exercise capacity) becomes more important than the reduction in readmission and mortality rates (Hamo, Gheorghiade, & Butler, 2017). Interventions aimed at improving self-care maintenance may be key to better quality of life in HF patients (Buck et al., 2015). Evidence, in RCTs, of significant improvement in the health-related quality of life of HF patients has been reported from pharmacist-involved multidisciplinary interventions (Korajkic et al., 2011; Sadik, Yousif, & McElnay, 2005).

1.6 Drug adherence in HF

Adherence to drug therapy has been a primary concern in HF patients, as it adversely affects health outcomes. According to Wu et al. (2008), the rate of medication non-adherence in HF patients is 40–60%. New diagnosis, old age, comorbid conditions, polypharmacy and poor sleep have been identified as the key

factors responsible for poor medication adherence in HF (Knafl & Riegel, 2014; Reed, Rodgers, & Sueta, 2014). Approximately 50–60% of patients do not take their medications as prescribed in chronic diseases (Lavsa, Holzworth, & Ansani, 2011). Non-adherence to HF medication has also been associated with an increase in cardiac-related events, including ED visits and hospitalisations, an increase in health care costs and a reduction in quality of life (Lopert et al., 2012). A recent systematic review revealed that the significant reduction of readmissions and mortality rates was mediated by interventions to improve medication adherence among HF patients (Ruppar et al., 2016). Therefore, improvement of medication adherence through pharmacist involvement in HF management leads to better clinical outcomes.

1.7 Health literacy and HF knowledge

It is well accepted that good health literacy is a contributing factor to understanding medication therapy and lifestyle modifications. Unfortunately, even in developed countries (according to data from 25 countries), approximately 50% of the population exhibited low health literacy (Westlake, Sethares, & Davidson, 2013). Tung et al. (2014) reported that approximately 60% of patients with HF in Taiwan possess inadequate or low health literacy. A study by Lee et al. (2012) revealed that interventions to provide health education and counselling focusing on patient needs are the most effective ways to improve outcomes in patients with low literacy who are suffering from cardiovascular disease. Higher hospitalisation rates, all-cause mortality, increased medication errors and higher costs all accompany low health literacy in HF patients (Wu et al., 2013).

Health literacy in patients affects HF knowledge; it is a strong predictor of HF knowledge (Cajita, Cajita, & Han, 2016). A similar hypothesis of the proportional relationship between health literacy and HF knowledge among HF patients was reported by Macabasco-O'Connell et al. (2011). Our previous review found that improvement in HF knowledge is one of the benefits of a pharmacist being engaged in a HF management program (Parajuli et al., 2017). To help strengthen the available evidence, the major focus of the current study is the evaluation of the effect of pharmacist involvement on HF knowledge of patients.

1.8 Self-care in HF patients

Self-care is an essential domain for improving health outcomes in HF patients. The ability of self-care is poor among HF patients worldwide (Jaarsma et al., 2013) . Self-care knowledge is directly related to health-related quality of life in HF patients (Buck et al., 2015). Patients with multiple comorbidities have poor self-efficacy and self-care maintenance abilities (Buck et al., 2015; Dickson, Buck, & Riegel, 2013). HF is a disease that severely affects quality of life and coexists with multiple comorbidities. Therefore, it can be argued that improvement of self-care may be linked with favourable clinical outcomes in HF patients. A growing body of literature demonstrates that encouraging family to be involved in the care process and in managing HF symptoms positively affects clinical outcomes (Cameron et al., 2016; Cene et al., 2016; Lainscak et al., 2011; Spaling et al., 2015). Some strong benefits of good self-management in HF patients exist, including improved compliance, better quality of life, reduction in readmissions and, eventually, a reduction in hospitalisation costs (Toback & Clark, 2017). Therefore, a focus on on improving self-care in HF patients is needed.

1.9 HF management

According to the National Heart Foundation of Australia, management of CHF should involve evidence-based, multidisciplinary, patient-centred care, which leads to better health outcomes (Page et al., 2014). The growing complexity of elderly HF patients and patients having multiple comorbidities suggests the need for newer models of primary care to improve the management of HF patients (Mastromarino et al., 2014). Consideration of the emotional, social and spiritual aspects of HF patients is another aspect of a successful treatment strategy (Alpert et al., 2016). Treatment and management strategies in HF are described in Sections 1.9.1–1.9.4.

1.9.1 Pharmacological treatment of HF

Pharmacists are a critical source of information for ensuring that patients are receiving the best available medicines. The inclusion of a pharmacist within the multidisciplinary team is necessary due to the complex nature of HF characterised by polymorbidities (Murad et al., 2015) and polypharmacy (Mastromarino et al., 2014; von Lueder & Atar, 2014). The role of a clinical pharmacist is to ensure the best use of EBT in HF patients who are administrating multiple medications. ACEIs, ARBs and β-blockers are well-established EBTs in the treatment of HFrEF (Aronow, 2016; Atherton et al., 2018; Chatterjee et al., 2013; Howlett et al., 2016; Yamamoto, 2015).

In contrast, the pathological mechanisms underlying HFpEF and the efficacy of available drugs for the management of HFpEF are controversial and poorly understood (Borlaug & Paulus, 2011; Sharma & Kass, 2014). HFpEF treatment has focused mainly on the alleviation of symptoms, comorbidities and volume optimisation with diuretics, as RCTs of various therapeutic strategies have not

demonstrated consistent and widely accepted results (Asrar ul Haq et al., 2014; Dhingra et al., 2014; Edelmann et al., 2011). Despite several clinical trials, robust evidence-based effective therapies are still lacking for patients with HFpEF (Ferrari et al., 2015; Kao et al., 2015; Rogers et al., 2015; Senni et al., 2014). Today, an increasing body of research on novel clinical trials of new drugs for the management of CHF are also available (Berliner & Bauersachs, 2017; Greenberg, 2016; Hinder, Yi, & Langenickel, 2018; Lother & Hein, 2016; Nyolczas, 2016). Various grades of recommendations for the pharmacological treatment of HF are described based on Australian guidelines for the management of CHF (Krum et al., 2011) (see Tables 1.2–1.4).

Table 1.2

Grades of recommendation based on level of evidence.

Grade of recommendation	**Description**
A	Rich body of high-quality RCT data.
B	Limited body of RCT data or high-quality Non-RCT data.
C	Limited evidence.
D	No evidence available—panel consensus judgement.

RCT = randomized controlled trial; Non-RCT; refers to data from observational studies.

Adopted from 2011 Guidelines for the prevention, detection and management of chronic heart failure in Australia (Krum et al., 2011).

Table 1.3
Recommendations for preventing chronic hf and treating asymptomatic left ventricular dysfunction.

Condition of HF	Grade of Recommendation
All patients with asymptomatic systolic left ventricular dysfunction should be treated with an ACEI indefinitely, unless intolerant.	A
Anti-hypertensive therapy should be used to prevent subsequent CHF in patients with elevated blood pressure.	A
Preventive treatment with an ACEI may be considered in individual patients at high risk of ventricular dysfunction.	B
Beta-blockers should be commenced early after an MI, whether or not the patient has systolic ventricular dysfunction.	B
Statin therapy should be used as part of a risk management strategy to prevent ischemic events and subsequent CHF in patients who fulfil criteria for lipid-lowering.	B

* Refer to Table 1.2 for description of grades of recommendation

Adopted from Adopted from 2011 Guidelines for the prevention, detection and management of chronic heart failure in Australia (Krum et al., 2011).

ACEI: angiotensin converting enzyme inhibitor; CHF: chronic heart failure; MI: myocardial infarction

Table 1.4

Recommendations for pharmacological treatment of symptomatic CHF.

	Grade of Recommendation
First-line agents	
ACEIs, unless not tolerated or contraindicated, are recommended for all patients with systolic heart failure (LVEF < 40%), whether symptoms are mild, moderate or severe.	A
Every effort should be made to increase doses of ACEIs to those shown to be of benefit in major trials. If this is not possible, a lower dose of ACEI is preferable to none at all.	B
Diuretics should be used, if necessary, to achieve euvolaemia in fluid-overloaded patients. In patients with systolic LV dysfunction, diuretics should never be used as monotherapy, but should always be combined with an ACEI to maintain euvolaemia.	D
Beta-blockers are recommended, unless not tolerated or contraindicated, for all patients with systolic CHF who remain mildly to moderately symptomatic despite appropriate doses of an ACEI.	A
Beta-blockers are also indicated for patients with symptoms of advanced CHF.	B
Aldosterone receptor blockade with spironolactone is recommended for patients who remain severely symptomatic, despite appropriate doses of ACEIs and diuretics.	B
Aldosterone blockade with eplerenone should be considered in systolic heart failure patients who still have mild (NYHA Class II) symptoms despite receiving standard therapies (ACEI, beta blocker).	B
Angiotensin II receptor antagonists may be used as an alternative in patients who do not tolerate ACEIs due to kinin-mediated adverse effects (e.g. cough). They should also be considered for reducing morbidity and mortality in patients with systolic CHF who remain symptomatic despite- receiving ACEIs.	A
Direct sinus node inhibition with ivabradine should be considered for CHF patients with impaired systolic function and a recent heart failure hospitalization who are in sinus rhythm where their heart rate remains > 70 bpm despite efforts to maximize dosage of background beta blockade.	B

Second-line agents	
Digoxin may be considered for symptom relief and to reduce hospitalization in patients with advanced CHF. It remains a valuable therapy in CHF patients with AF.	B
Hydralazine-isosorbide dinitrate combination should be reserved for patients who are truly intolerant of ACEIs and angiotensin II receptor antagonists, or for whom these agents are contraindicated, and no other therapeutic option exists.	B
Fish oil (n-3 polyunsaturated fatty acids) should be considered as a second-line agent for patients with CHF who remain symptomatic despite standard therapy which should include ACEIs or ARBs and beta-blockers if tolerated.	B
Other agents	
Amlodipine and felodipine can be used to treat comorbidities such as hypertension and CHD in patients with systolic CHF. They have been shown to neither increase nor decrease Mortality.	B
Iron deficiency should be looked for and treated in CHF patients to improve symptoms, exercise tolerance and quality of life.	B

* Refer to Table 1.2 for description of grades of recommendation.

Adopted from Adopted from 2011 Guidelines for the prevention, detection and management of chronic heart failure in Australia (Krum et al., 2011).

ACEI: angiotensin converting enzyme inhibitor; LVEF: left ventricular ejection fraction; LV: left ventricular; CHF: chronic heart failure; NYHA: New York Heart Association; bpm: beats per minutes; AF: atrial fibrillation; ARBs: angiotensin receptor blockers.

a) Angiotensin-converting enzyme inhibitors (ACEIs)

Angiotensin-converting enzyme inhibitors remain ubiquitous in the treatment of HF. They inhibit the conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor that stimulates aldosterone secretion from the adrenal cortex (Weber, 2001) and reduces vasodilation mediated by the degradation of a vasodilator substance (bradykinin) (Aronow, 2016). Activation of angiotensin II increases sodium and water retention due to aldosterone release, eventually leading to a rise in BP (Bollag, 2014; Weber, 2001). Moreover, the stimulation of aldosterone destroys normal myocardial tissues by scarring and increases the risk of cardiovascular events (Struthers, 2004). Therefore, ACEIs may have several potential benefits by blocking the production of angiotensin II. They are recommended for all patients with EF ≤40% (Ponikowski et al., 2016).

Cardiac remodelling is a condition in which the size, shape and function of the heart is affected due to cellular and molecular changes. ACEIs have shown a beneficial role in cardiac remodelling (Cohn, Ferrari, & Sharpe, 2000). They should be up-titrated to the maximum tolerated dose (MTD), unless contraindicated or not tolerated in all symptomatic HF patients. ACEIs are also recommended in patients with asymptomatic left ventricular (LV) dysfunction to reduce the risk of HF development, hospitalisation and death. Contraindications to use ACEIs include bilateral renal artery stenosis, angioedema, pregnancy, intolerance or hypersensitivity, significant renal dysfunction—serum creatinine >221μ mol/L or 2.5 mg/dL or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and SBP on sitting or standing of <90 (whichever is less) (Ponikowski et al., 2016). If

recommended in appropriate doses, ACEIs can significantly reduce deaths in HF patients (Ouwerkerk et al., 2017; Tai et al., 2017).

b) Angiotensin receptor blockers (ARBs)

The ARBs act by selective binding to angiotensin II type 1 receptor (AT1) to inhibit their activation (Burnier & Brunner, 2000). The AT1 stimulate the contraction of the muscles surrounding blood vessels resulting in an increase in blood pressure (Singh & Karnik, 2016). ARBs block the renin-angiotensin-aldosterone system (RAAS), a critical system responsible for regulating fluid and blood pressure in human body (Burnier, 2001; Carey & Siragy, 2003). ARBs are recommended as alternative therapies for patients who are intolerant to ACEIs due to severe side effects (Willenheimer, 2000; Yancy et al., 2013). These drugs may also help to reduce mortality and morbidity if used appropriately (Yancy et al., 2016). Contraindications to ARBs include pregnancy, bilateral renal artery stenosis, previous intolerance or hypersensitivity to ARBs, significant renal dysfunction-serum creatinine >221μ mol/L, 2.5 mg/dL or eGFR <30 mL/min/1.73 m^2 and SBP on sitting or standing of <90 (whichever is less) (Ponikowski et al., 2016).

c) Beta-blockers (β-blockers)

The β-adrenergic G-protein-coupled β_1 receptors in the heart (Lopez-Sendon et al., 2004) are stimulated by activation of the sympathetic nervous system (SNS) leading to an increase in heart rate (HR) (Brodde et al., 1986; Madamanchi, 2007). The neurotransmitter-catecholamine's (epinephrine: adrenaline; norepinephrine: noradrenaline) produced from the adrenal medulla and the post-ganglionic fibres are the significant stimulants for the activation of the SNS (Eisenhofer, Kopin, & Goldstein, 2004). Cardioselective β-blockers (e.g. bisoprolol, carvedilol,

nebivolol) work by competitive inhibition of the positive chronotropic effects (increase in heart rate) of β_1-receptors located in heart (Guo & An, 2011). The β_1-receptors stimulate the activation of the second messenger, cyclic adenosine monophosphate (cAMP) by the adenylyl cyclase. The ultimate effect of activated cAMP increases the calcium entry into the cytosol thereby leading to a positive inotropic effect (Baker, Hall, & Hill, 2003; Lemoine, Schonell, & Kaumann, 1988). The magnitude of reduction of HR is associated with the reduction in mortality rates in HF patients (McAlister et al., 2009). The *β*-blockers help reduce mortality and morbidity in symptomatic patients with HFrEF, if used in sufficient doses as recommended by the guidelines (Bhatt et al., 2017; Corletto et al., 2018). They should be up-titrated to the MTD, unless contraindicated or not tolerated in all stable symptomatic HFrEF patients (Basile, 2003). Contraindications to *β*–blockers include a second or third-degree atrioventricular block (in the absence of a pacemaker), critical limb ischemia, severe or poorly controlled asthma, known allergic reactions or other adverse reactions that are drug specific, severe hypotension, systemic BP <90mm Hg (lower of sitting or standing) and HR <50 beats per minute (bpm; unless a pacemaker is present) (Ponikowski et al., 2016).

d) Mineralocorticoid/ receptor antagonists (MRAs)

The MRAs antagonise the physiological changes of aldosterone stimulation, particularly the remodelling of LV dysfunction (Vizzardi et al., 2014). Evidence from a meta-analysis of RCTs suggests a significant reduction in mortality and hospitalisation in HFrEF patients after the use of MRAs (Berbenetz & Mrkobrada, 2016). These medicines are prescribed in all symptomatic HFrEF patients with EF ≤40%, despite treatment with ACEIs and *β*-blockers. Contraindications to MRAs

include known allergic or other adverse reactions, including hyperkalemia (K^+ > 5 mmol/L) and significant renal dysfunction (serum creatinine >221μ mol/L, 2.5 mg/dL or eGFR <30 mL/min/1.73m^2) (Ponikowski et al., 2016).

e) Diuretics

Diuretics are the most commonly used medications in HF patients for controlling the accumulation of unwanted fluids (Ellison & Felker, 2017). Diuretics are recommended to achieve and maintain a euvolaemic state with the lowest possible dose. These medicines increase urine sodium excretion and decrease signs of fluid retention. Diuretics reduce the signs and symptoms of congestion in HF patients (Guglin, 2011; Volz & Felker, 2009). Loop diuretics produce a more intense and shorter diuresis compared to thiazides, although they act synergistically. A combination of the loop and thiazide diuretics are clinically useful for resistant oedema (Jentzer, DeWald, & Hernandez, 2010).

f) Drugs to avoid in chronic heart failure

The avoidance of a particular group of drugs depends heavily on the type of HF. The use and choice of a particular group of medicines should be based on an evidence-based approach. Generally, drugs should be avoided if they exacerbate a condition, by direct myocardial toxicity, by drug-drug interactions, or by both (Wettersten & Maisel, 2016). There are several orally administered drugs that are contraindicated in HF patients, as recommended by the scientific statements from the AHA 2016 (Page et al., 2016). These medications include certain traditional anti-inflammatory drugs, metformin, thiazolidinedione, class I and II antiarrhythmic, calcium channel blockers, centrally acting α-adrenergic medications, azole antifungal agents, certain anti-cancer medications, haematologic

medications, some neurological and psychiatric medications, salbutamol, hydroxychloroquine and urological alpha blockers. The benefit of having a pharmacist in the multidisciplinary team is that pharmacists can identify these contraindicated medications.

1.9.2 Non-pharmacological management of HF

Non-pharmacological management strategies and assessment of non-cardiovascular comorbidities in HF are recommended along with pharmacological treatment (Hummel & Kitzman, 2013; Scott & Jackson, 2013). Various non-pharmacological approaches for the management of CHF, as recommended by Australian guidelines, are outlined in Table 1.5 (Krum et al., 2011). The major non-pharmacological approaches include physical activity, restricting dietary sodium intake, montoring fluid intake, alcohol restriction, smoking cessation, weight reduction, vaccination against influenza and pneumococcal disease and dietary control. Pharmacists as important members of the multidisciplinary team can assist patients with the implementation of various non-pharmacological strategies for effective HF management (McNeely, 2017; Milfred-Laforest et al., 2013; Omboni & Caserini, 2018).

Table 1.5

Recommendations for non-pharmacological management of CHF.

Non-pharmacological approaches	Grade of Recommendation
Regular physical activity is recommended. All patients should be referred to a specially designed physical activity program, if available.	B
Patient support by a doctor and pre-discharge review and/or home visit by a nurse is recommended to prevent clinical deterioration.	A
Patients frequently have coexisting sleep apnoea and, if suspected, patients should be referred to a sleep clinician as they may benefit from nasal CPAP.	D
Patients who have an acute exacerbation, or are clinically unstable, should undergo a period of bed rest until their condition improves.	D
Dietary sodium should be limited to below 2 g/day.	C
Fluid intake should generally be limited to 1.5 L /day with mild to moderate symptoms, and 1 L /day in severe cases, especially if there is coexistent hyponatremia.	C
Alcohol intake should preferably be nil, but should not exceed 10–20 g a day (one to two standard drinks.	D
Smoking should be strongly discouraged.	D
Patients should be advised to weigh themselves daily and to consult their doctor if weight increases by more than 2 kg in a two-day period, or if they experience dyspnoea, oedema or abdominal bloating.	D
Patients should be vaccinated against influenza and pneumococcal disease.	B
High-altitude destinations should be avoided. Travel to very humid or hot climates should be undertaken with caution, and fluid status should be carefully monitored.	C
Sildenafil and other phosphodiesterase V inhibitors are generally safe in patients with heart failure. However, these medicines are contraindicated in patients receiving nitrate therapy, or those who have hypotension, arrhythmias or angina pectoris.	C
Obese patients should be advised to lose weight.	D
A diet with reduced saturated fat intake and a high fibre intake is encouraged in patients with CHF	D
No more than two cups of caffeinated beverages per day recommended.	D
Pregnancy should be avoided in patients with moderate to severe CHF. Pregnancy in patients with mild CHF is reasonable.	D

* These grades of recommendation apply only to patients with chronic heart failure. Refer to Table 1.2 for description of grades of recommendation. Adopted from 2011 Guidelines for the prevention, detection and management of chronic heart failure in Australia (Krum et al., 2011). CPAP: continuous positive airway pressure; CHF: chronic heart failure.

1.9.3 Multidisciplinary management of HF

There is an increasing focus on a care model involving general practitioners (GPs) and liaising with specialists co-located in multidisciplinary community-based general practices (Scott & Jackson, 2013). In multidisciplinary care, different health care professionals (including pharmacists) work and foster their diverse expertise for effective shared decision-making to deliver the best outcomes for HF patients; they do so by managing patient symptoms, improving clinical outcomes and, eventually, reducing health care costs (Cooper & Hernandez, 2015; Odum & Whaley-Connell, 2012). The role of the multidisciplinary team in HF management to improve outcomes has been described in multiple meta-analyses (Gwadry-Sridhar et al., 2004; Holland et al., 2005; McAlister et al., 2004).

1.9.4 Importance of a pharmacist-involved multidisciplinary team in the management of HF

Evidence exists that well-trained clinical pharmacists within the multidisciplinary team can recommend EBT, improve drug adherence, reduce readmission rates, prevent adverse drug reactions, reduce costs and educate patients and health care providers about medications (Milfred-Laforest et al., 2013). Increasingly, consistent evidence supports that pharmacists should be routinely involved in the multidisciplinary team for the management of HF patients, particularly in safely transitioning a patient between care settings (Chang & Rising, 2014), providing awareness to HF specialists about drug-related adverse outcomes (Gastelurrutia et al., 2011) and optimising care for elderly HF patients to prevent readmissions (Kitts, Reeve, & Tsu, 2014). Pharmacists also act as a patient advocates for medication-related issues within a community paramedical team (Crockett et al., 2016). There

are other clinical benefits to a pharmacist within the multidisciplinary team, including a significant reduction in 90-day HF readmissions in patients who have been recently discharged (Jackevicius et al., 2015) and increased cost-effectiveness, as reported by Bellam, Kelkar, and Whellan (2015).

An earlier meta-analysis found that the involvement of pharmacists in collaborative care led to more significant reductions in the rate of HF compared to pharmacist-directed care (Koshman et al., 2008). Several recent review papers have recommended a multidisciplinary approach for the pharmacist's involvement in HF management. The authors of these reviews have highlighted numerous benefits of the pharmacist-involved multidisciplinary approach in the improvement in hospital readmission and hospitalisations (Cheng & Cooke-Ariel, 2014), in promoting medication adherence and dose titration during safe transition of care (Anderson & Marrs, 2018) and in collaborative medication management (Cheng, 2017). Recent guidelines in the treatment and management of HF have strongly recommended the pharmacist as an essential member of a multidisciplinary team (Atherton et al., 2018; Ponikowski et al., 2016; Yancy et al., 2013).

The collaboration of health care professionals within a multidisciplinary team and the factors contributing to the effective multidisciplinary management of HF to improve clinical outcomes in patients are illustrated respectively in Figures 1.1 and 1.2 (Davidson et al., 2015).

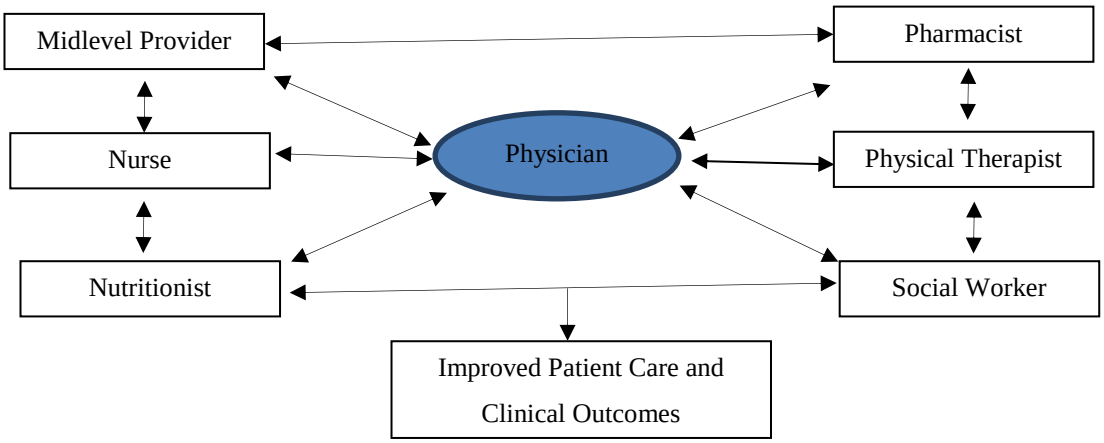


Figure 1.1. Schematic displaying the multidisciplinary heart failure team.

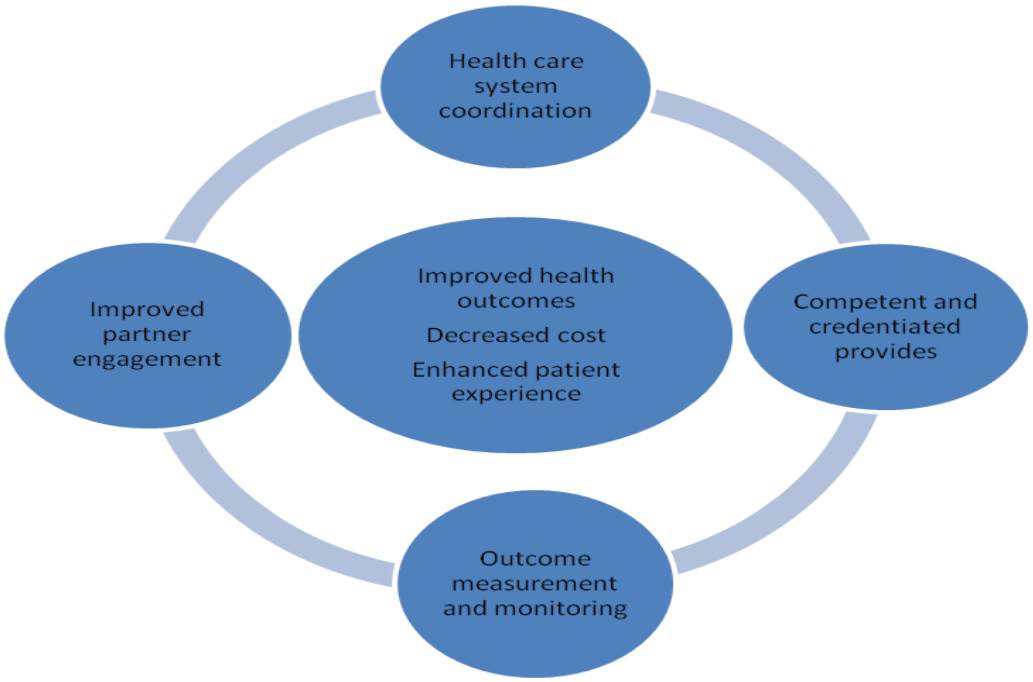


Figure 1.2. Factors contributing to the optimal multidisciplinary management of chronic heart failure.

Adopted from multidisciplinary management of chronic heart failure: principles and future trends

(Davidson et al., 2015).

1.10 Research Aim

This study aims to explore how a multidisciplinary management model including a pharmacist improves clinical outcomes in HF patients.

1.11 Objectives

The objectives of this study are:

a) To determine the effectiveness of pharmacist-involved multidisciplinary management of HF in relation to HF hospitalisations, HF mortality, all-cause hospitalisations, all-cause mortality, medication adherence (compliance), HF knowledge, health care costs, self-care and composite endpoint (all-cause hospitalisations and all-cause mortality)

b) To compare two multidisciplinary clinics, with and without pharmacist involvement, by evaluating the differences in demographic and clinical characteristics, comorbidities, use of EBT and the predictors of EBT in CHF outpatients within an Australian setting.

1.12 Research questions

The research questions are:

a) Is there evidence from a meta-analysis of RCTs for the efficacy of pharmacist-involved multidisciplinary management of HF patients to improve mortality and hospitalisations?

b) Can the pharmacist-involved multidisciplinary care model of HF management make better use of evidence-based therapy in an Australian setting?

1.13 Thesis structure

This thesis is divided into six chapters, with Figure 1.3 outlining each chapter.

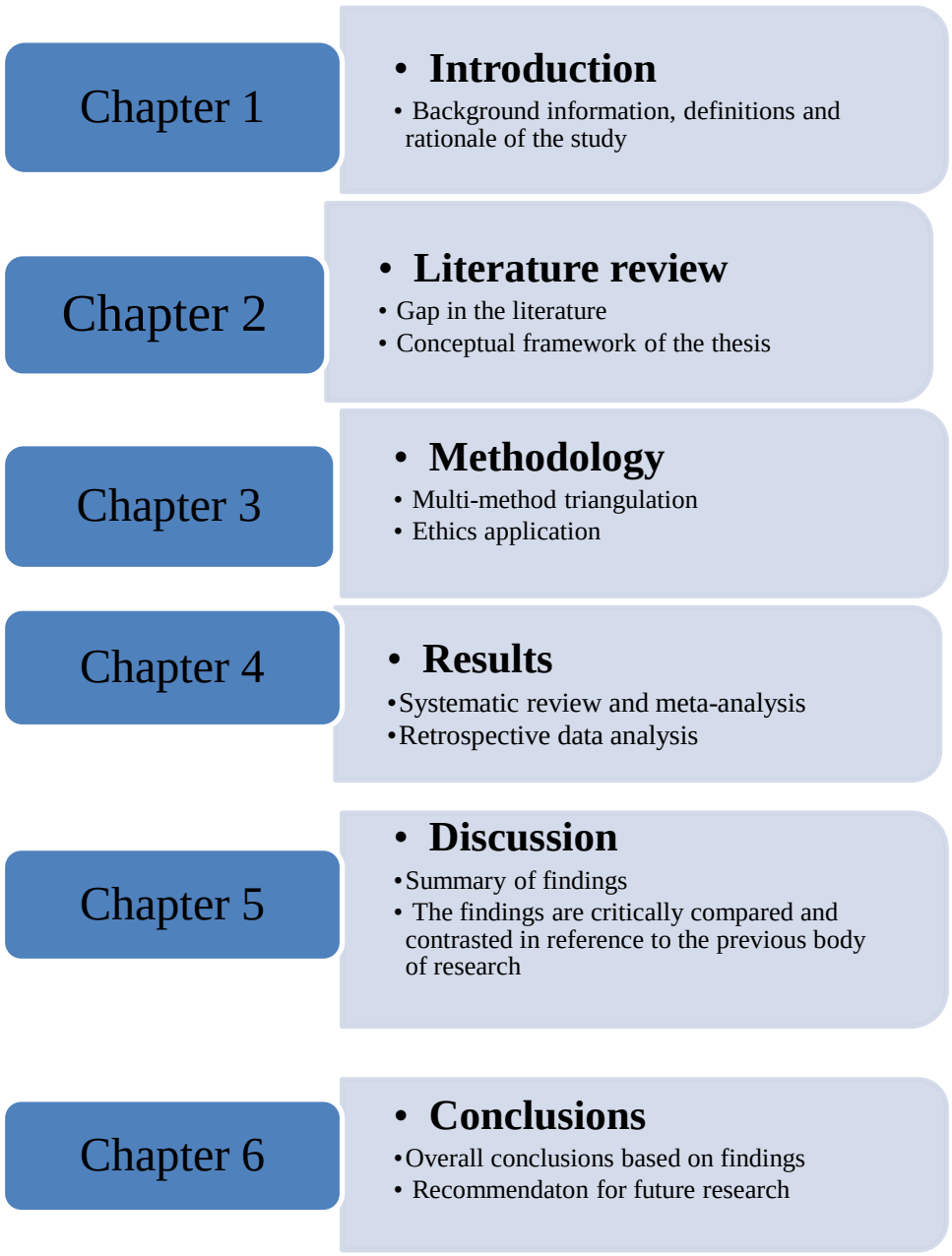


Figure 1.3. Structure of thesis.

1.13.1 Chapter 1: Introduction

This chapter outlines the background information and rationale for this study. It also contains definitions of HF and its epidemiology, diagnosis and treatment. The research aim, objectives and research questions are also included. Chapter 1 also outlines the thesis structure, provides a flowchart of the thesis, a brief overview of research methodology used and, finally, the chapter summary.

1.13.2 Chapter 2: Literature review

This chapter outlines the review of the available relevant literature on the role of a pharmacist within the multidisciplinary team in HF management. It identifies the gap in the existing knowledge, which provides the rationale for this research.

The content relevant to this section was published as a review paper in an international, peer-reviewed journal *Current Heart Failure Reports* (2017, pp. 78–86) (Parajuli et al., 2017).

Chapter 2 also includes the conceptual framework used in this study, which is the Expanded Chronic Care Model.

1.13.3 Chapter 3: Methods

This chapter includes the protocol for the systematic review and retrospective comparison of two cohorts of CHF patients in the Australian context. These two studies are triangulated for the central research question of determining the role of the pharmacist within the multidisciplinary management of HF. This chapter further describes the ethical approval process required for this study.

1.13.4 Chapter 4: Results

This chapter outlines the research findings, based on the applied methodology, to answer the research questions presented in Chapter 1. The results are presented in a logical sequence according to the specific objectives and outcomes to be measured.

1.13.5 Chapter 5: Discussion

This chapter summarises and interprets the findings, critically comparing and contrasting these in reference to the existing literature. This chapter highlights the potential justification for the results obtained. The research limitations are presented, which will establish the basis for future research.

1.13.6 Chapter 6: Conclusions

The conclusion consolidates the research findings to establish the importance to the role of the pharmacist within the multidisciplinary management of HF. The intention is to outline what has been discovered about the role of the pharmacist, how the gap in the literature has been addressed, and recommendations for clinical practice and opportunities for future research.

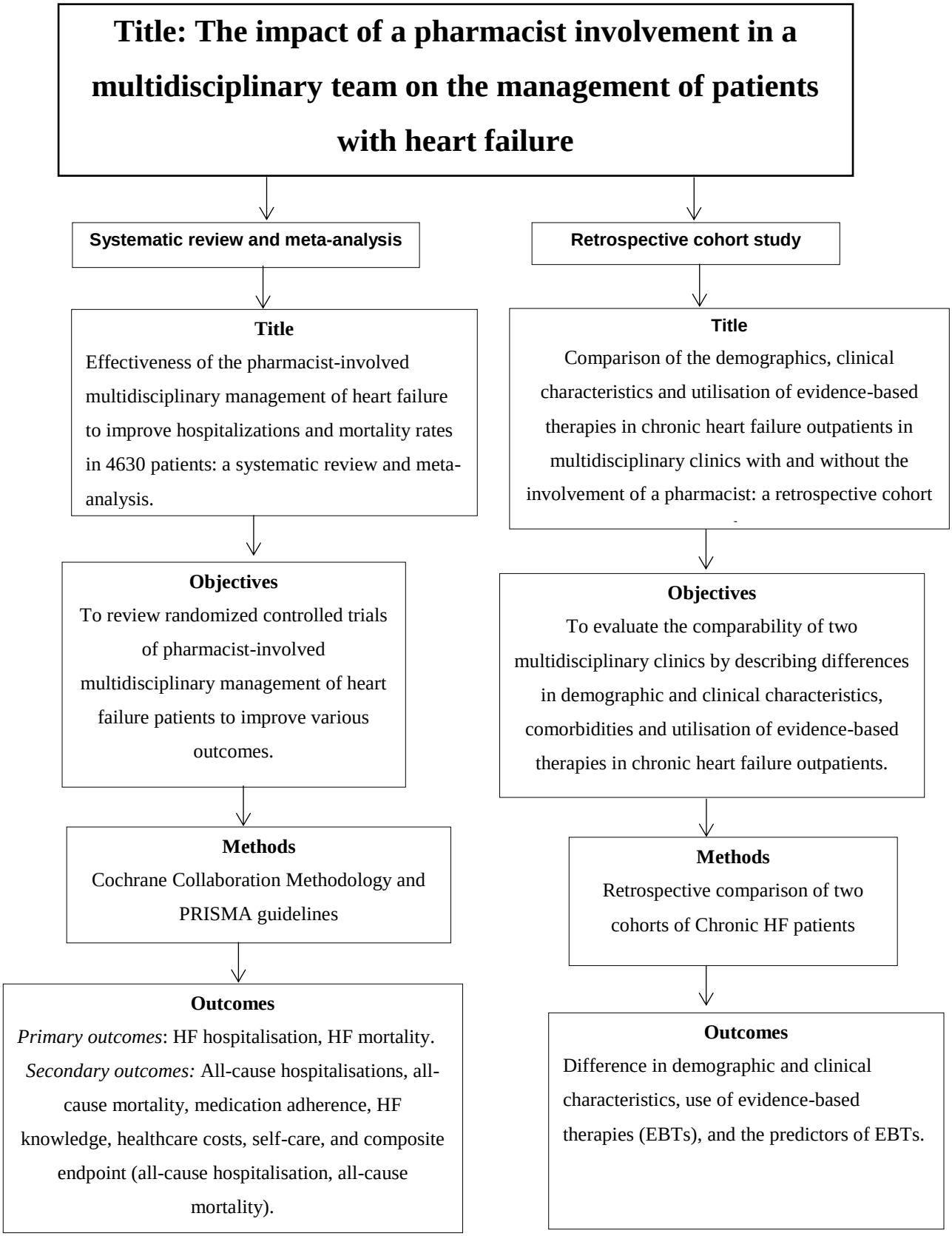


Figure 1.4. Summary of Thesis.

HF: heart failure; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

1.14 Summary of chapter 1-introduction

HF is a rapidly growing global health challenge with a significant number of people affected worldwide. It is a complex clinical syndrome with increasing prevalence in the elderly and has persistently high morbidity, mortality and hospital readmission rates. Polypharmacy, due to the existence of multiple comorbidities and poor adherence to prescribed medications, are common characteristics of HF patients. There is a dearth of evidence on the stringent diagnostic criteria and treatment for HF with preserved EF which consists of approximately 50% of HF cases. As a chronic condition, HF needs a unique approach for effective management, including pharmacological and non-pharmacological support. Although the effectiveness of a pharmacist's role within the multidisciplinary team in HF management has been demonstrated by published studies, further research is needed to confirm these findings.

The research literature strongly supports that it is a critical challenge to reduce high readmission and mortality rates, improve drug adherence and health-care costs as well as improve the self-care abilities of HF patients. The aim of this study is to explore the scientific evidence for the effective HF management by a pharmacist-involved multidisciplinary care model using a triangulated approach of a systematic review and meta-analysis of RCTs and a retrospective comparison of two cohorts of CHF patients in an Australian context.

Chapter 2 outlines the literature review and identifies the gap in the existing knowledge.

Chapter 2: Literature Review

The first purpose of this chapter is to identify, describe and synthesise the currently available literature that reports and reflects on the role of pharmacists in HF management. The second purpose is to identify gaps in the existing knowledge to establish a rationale for this research and how it can make a meaningful contribution to the field. This chapter focuses on the rationale for the literature review, search processes, criteria for the selection of publications relevant to the research topic, description of the evidence and the findings.

2.1 Aim of the literature review

The overall aim of this literature review is to identify the gap in knowledge from the currently available literature on the role of the pharmacist-involved multidisciplinary management of HF. This literature review is expected to contribute to the following: 1) the development of the systematic review methodology and meta-analysis of RCTs regarding the pharmacist-involved multidisciplinary management of HF patients and 2) the design of an Australian observational study that compares the pharmacist-involved multidisciplinary care model with a similar multidisciplinary HF team without a pharmacist.

2.2 Inclusion and exclusion criteria

Studies were eligible if they included adults (≥18 years) with a confirmed diagnosis of HF according to diagnostic methods, such as the NYHA classification, echocardiography, nuclear imaging and cardiac MRI. English-language peer-reviewed systematic review and meta-analysis, RCTs and any kind of observational studies available in full-text or peer-reviewed conference papers were included. Studies that were included were those conducted in primary or secondary care (any

setting) to evaluate the effect on any type of outcome including all-cause mortality, all-cause hospitalisation, HF hospitalisation, length of stay, emergency visits, drug adherence, HF knowledge, quality of life, self-care, health literacy, medication errors, drug–drug interactions and cost effectiveness. Further, some seminal papers published prior to 2011 were also considered to determine any potential gaps in the knowledge. Studies published before 2011, studies that were not published in English and studies in which the pharmacist was not included in the HF management were excluded. The inclusion and exclusion criteria implemented in this literature review are outlined in Table 2.1.

2.3 Information sources

Studies were identified through systematic searches of the different databases from 2011 through November 2016. These included PubMed (NLM), MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), Web of Science (Thomson Reuters), Scopus (Elsevier) and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. The bibliographies of relevant studies and systematic reviews were searched manually. The search strategies used are outlined below (see heading 2.4).

2.4 Keywords used for searching

The keywords used during the searching included; "heart failure" OR "left ventricular dysfunction" OR cardiomyopathy OR "left ventricular ejection fraction" OR "LV dysfunction" OR "systolic dysfunction" OR "diastolic dysfunction" OR "cardiac failure" OR "preserved ejection fraction" OR HFpEF OR "reduced ejection fraction" OR HFrEF) AND pharmacist* OR "pharmaceutical care" OR "pharmaceutical service*"

2.5 Critical appraisal of the included studies

The critical appraisal of the included studies is illustrated in Appendix II.

2.6 Results-screeing and seleciton of the articles

The initial search strategy identified 230 potentially eligible studies. After excluding duplicates, the remaining 192 studies were carefully screened by title and abstract. The full text of 62 publications was reviewed. Five RCTs, one systematic review and meta-analysis and 13 observational studies were found. The manual search of the references cited in each publication helped to identify one seminal systematic review and meta-analysis published prior to 2011 (Koshman et al., 2008). The resulting 22 articles were finally included as most relevant and key. The reasons for exclusion of studies is illustrated in Figure 2.1.

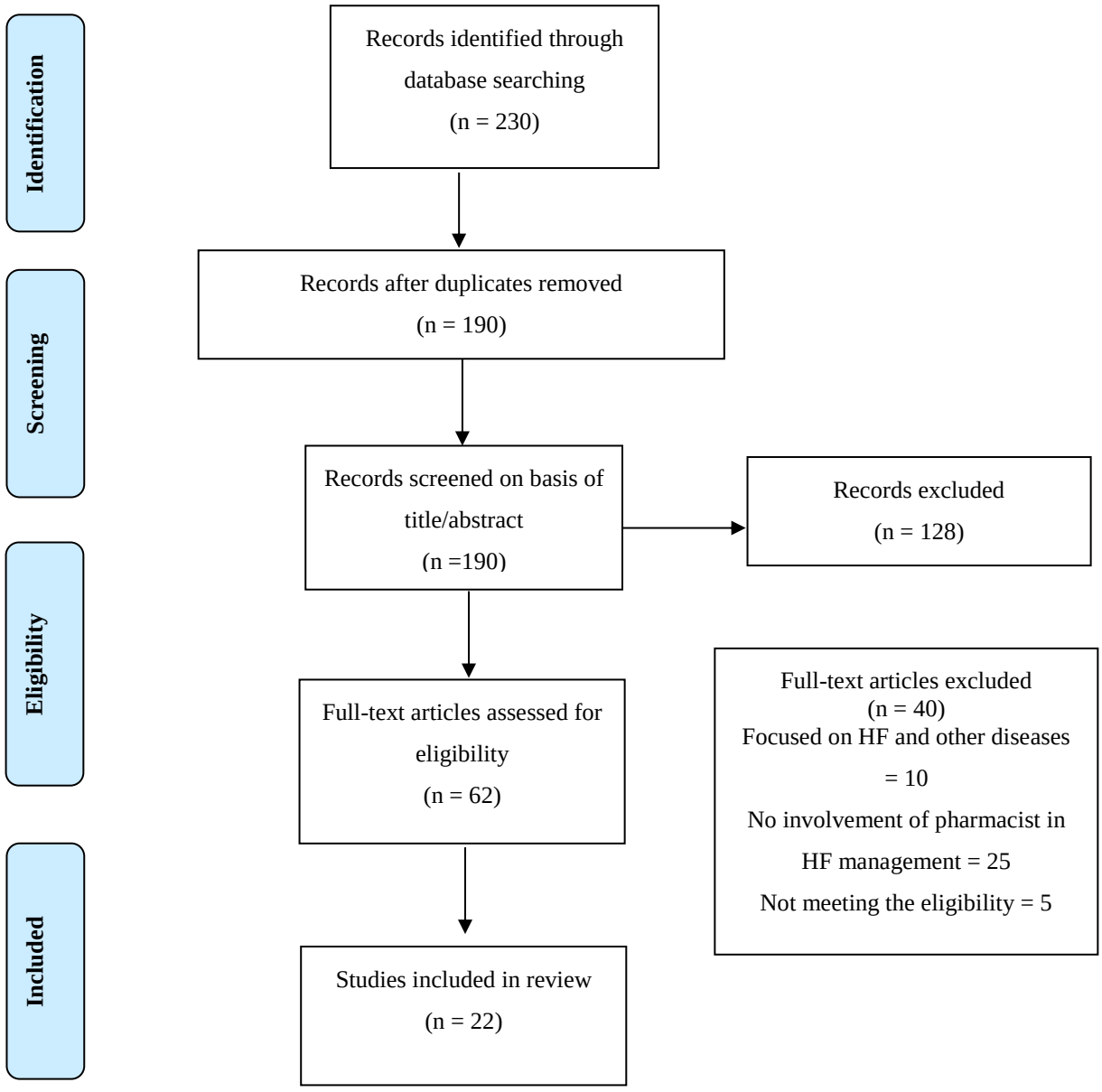
Table 2.1

Inclusion and exclusion criteria for included studies in literature review.

Categories	**Inclusion Criteria**	**Exclusion Criteria**
Type of participants	Patients diagnosed with HF	Studies that focused on other diseases than HF
Study setting	Any setting	NA
Primary study focus	Systematic review and meta-analysis, RCTs and any observational study	NA
Type of study paper	Primary and secondary research	Media releases, and discussion papers
Time framework	Peer reviewed journal articles published mostly after 2011 to 2016.	Publications prior to 2010
Language	English language	All other language

HF: heart failure; RCT: randomized controlled trials; NA: not applied.

Figure 2.1. Flow diagram for study screening and selection in literature review.



2.7 Results - evidence from systematic review and meta-analysis

A systematic review and a meta-analysis were selected to extract the evidence (Kang et al., 2016; Koshman et al., 2008). The study conducted by Koshman et al. (2008; 12 RCTs; 2060 patients) was clearly published before 2011; however, this study was included in this literature review as it was the first meta-analysis to evaluate the effect of pharmacist care on different clinical outcomes in HF patients. This study demonstrated a significant reduction in the rate of all-cause hospitalisations (OR = 0.71; 95% CI [0.54, 0.94]) and HF hospitalisations (OR = 0.69; 95% CI [0.51, 0.94]) and a non-significant reduction in mortality (12 studies; OR = 0.84; 95% CI [0.61, 1.15]). Further, pharmacist-involved collaborative care led to greater reductions in the rate of HF hospitalisations (OR = 0.42; 95% CI [0.24, 0.74]) compared to pharmacist-directed care (OR = 0.89; 95% CI [0.68, 1.17]). This study recommended that pharmacists must be involved in HF management as a member of a multidisciplinary team.

Folowing on from the Koshman et al. (2008) study, the meta-analysis conducted by Kang et al. (2016; 26 studies; 2060 patients) is a more recent study in this field and it included both RCTs and observational studies of pharmacist involvement in care for HF and acute coronary syndrome. The authors evaluated most of the studies qualitatively and 14 studies were also assessed using a meta-analysis to determine the pooled effect. A significant reduction in all-cause hospitalisation in HF patients (OR = 0.74; 95% CI [0.58, 0.94]) was found. The prescription rates for ACEI (OR = 1.43; 95% CI: [1.07, 1.91]) and β-blockers (OR = 1.92; 95% CI [1.24, 2.96]) were significantly higher in the intervention group compared to the control group.

The number of RCTs used to evaluate the pharmacist's role has significantly increased in recent years. Relying on old meta-analysis results, even after the publication of new studies, may lead to misleading decision-making and detrimental outcomes to patients (Garner et al., 2016; Simmonds et al., 2017). Therefore, a systematic review and meta-analysis was necessary given the knowledge gap and will provide current and rigorous evidence of pharmacist-involved multidisciplinary HF management.

2.8 Results-evidence from RCTs

Five RCTs evaluated the effect of pharmacist involvement in HF management. One study (N = 70 patients; intervention group = 35 patients and control group = 35 patients) measured the pharmacist's role in diuretic dose adjustment in ambulatory HF patients in Australia (Korajkic et al., 2011). The pharmacist's intervention (follow-up: 3 months) focused on improving self-care, daily weight measurement and self-adjustment of diuretic dose (furosemide). There was a significant improvement ($p = .006$) in the dose adjustment of furosemide and significant decrease in hospital readmission ($p = .04$) in the intervention group.

Another RCT was also conducted in Australia (N = 120; intervention group = 64 patients and control group = 56 patients) to determine the effect of a pharmacist-led home medication review on different clinical outcomes in CHF patients (Barker et al., 2012). The intervention was provided at each patient's home and comprised counselling regarding medications, checking expired medications and reminding patients about the follow-ups with doctors. The total follow-up time of this study was 6 months. Unfortunately, no significant difference in hospitalisations and mortality was observed between the intervention and control groups. The key lesson from this study regarding

home medication review was that pharmacists worked in isolation rather than in collaboration. The importance of pharmacist-involved multidisciplinary HF management was further highlighted by this RCT.

Another RCT was conducted in the UK and was the largest and longest study ever conducted in this field (N = 2160; intervention group = 1090 patients and control group = 1070 patients; duration = 4.7 years) (Lowrie et al., 2012). Pharmacists received basic training regarding HF management and EBTs to be recommended for the population. This was a collaborative approach with family doctors and nurses. Despite such a rigorous design, this study found no significant improvement in the primary outcomes regarding death and hospital admission. The authors concluded that the short course of training provided to pharmacists was insufficient for medication optimisation. A requirement of trained pharmacists for effective HF was a key theme generated by this study.

A small pilot RCT (N = 16; intervention group = 9 patients and control group = 7 patients) was conducted in the US to examine the effect of pharmacist involvement in discharge counselling on medication adherence and hospital readmission in elderly HF patients (≥65 years) (Vinluan, Wittman, & Morisky, 2015). Intervention comprised counselling (on Days 3, 30, 60 and 90) regarding disease, medications, and importance of medication adherence, medication side effects, lifestyle modifications and telephone follow-up. An improvement in medication adherence and decrease in readmission was observed in the first month; however, the beneficial effect was not maintained in the consecutive months. Rather than a monthly follow-up, the authors recommended a more frequent follow-up.

A more recent RCT was conducted in Slovenia (N = 51; intervention group = 25 patients and control group = 36 patients) to evaluate the effect of clinical pharmacist intervention

on the prevention of drug interractions and the ultimate effect on hospitalisations and readmission (Roblek et al., 2016). The intervention comprised providing lifestyle modifications and introductory drug–drug interaction information to patients. The clinically significant drug-drug interactions were evaluated by the pharmacist in consultation with an expert group of clinicians. The follow-up time for this study was 6 months. There was a significant reduction in the number of drug-drug interactions in the intervention group compared to the control group (8 v. 18; p = .003); however, no reduction in hospitalisations and mortality was observed.

Therefore, to summarise the evidence from the RCTs regarding pharmacist-involved HF management, there was a beneficial effect in HF management. In particular, there was a significant improvement in diuretic dose adjustment and medication adherence (at 1 month) and heterogeneous results on readmission; however, there was no effect on mortality. A recommendation for the pharmacist's role within a multidisciplinary team was suggested. All five RCTs were published after the previous meta-analysis conducted by Koshman et al. Therefore, an update on the pharmacist's role in multidisciplinary team HF management may provide current evidence into this field.

2.9 Results-theme extracted from observational studies

In the literature review, there were 15 observational studies included to summarise the theme. Of these, two studies (Herring et al., 2014; Lee et al., 2015) are described here and the remaining 13 were included in a review paper published as a part of a literative review for this study. Lee et al. (2015) assessed the effectiveness of pharmacist involvement on HF prevention in high-risk patients in elderly community centers in Hong Kong. A total of 103 patients (≥65 years) participated in this prospective uncontrolled study. The

invervention comprised a medication review; review of blood pressure, blood glucose, cholesterol levels and HF symptoms; and counselling regarding medication adherence. There was a significant reduction in several outcomes observed: HF symptoms ($p < .001$), low density cholesterol ($p = .038$), triglyceride ($p < .001$) and medication adherence score ($p = .005$); however, no effect on blood pressure and blood glucose was observed.

Another prospective study conducted in the US by Herring et al. (2014) evaluated wheather pharmacist involvement during discharge counselling may help increase compliance regarding HF management guidelines (follow-up time = 3 months). A total of 45 (49%) patients' profiles were reviewed (n = 92 patients). Pharmacists reviewed the patients' profiles before providing tailored counselling and medication review. There were several barriers to compliance including poor documentation, lack of collaborative management and a shortage of sufficient human resources. Overall, the pharmacist-initiated counselling did not significantly improve the compliance rate compared to situations without pharmacist involvement.

The remaining 13 observational studies are outlined extensively below in a literature review that was published as a review paper in the international peer-reviewed journal, Current Heart Failure Rep*orts* (Parajuli et al., 2017, pp. 78–86) (Parajuli et al., 2017). The final publication is available at Springer Nature via 10.1007/s11897-017-0323-2.

This review paper found that pharmacists are contributing to HF management in a variety of settings, including hospitals, clinics, and communities. Different interventions which may be mediated by the pharmacist include drug adherence, discharge counselling, medication reconciliation, telephone follow-up, and recommendation of EBT.

Manuscript title: Role of the pharmacist for improving self-care and outcomes in heart failure.

Adopted from Research Publication, Authorship and Peer Review Policy of the Flinders University;
https://www.flinders.edu.au/content/dam/documents/staff/policies/research/research-publication-authorship-and-peer-review.pdf

Name of the Author	Contribution
Daya Ram Parajuli 70%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Julie Franzon 6%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Ross McKinnon 6%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Sepehr Shakib 6%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Robyn Clark 12%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.

2.10 Defining HF

HF is a clinical syndrome "characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress"(Ponikowski et al., 2016). It is often complicated by multiple comorbidities and is characterized by poor prognosis (Page et al., 2014) and high rates of morbidity and mortality (Al-Khazaali et al., 2016; Jessup et al., 2016; McMurray et al., 2012), with hospital readmission rates unacceptably high (Blecker et al., 2013; Inamdar & Inamdar, 2016). Overall prevalence is high and increasing (Chong et al., 2015; Heidenreich et al., 2013; Mozaffarian et al., 2015), and there is a substantial burden of disease in the elderly (Chong et al., 2015; Loudon et al., 2016; Mazurek & Jessup, 2015; van Riet et al., 2016). As such, it represents a rapidly growing public health burden with an estimated 38 million people currently living with HF worldwide (Ziaeian & Fonarow, 2016).

2.11 Self-care/management in HF

As with any chronic condition, patient self-care is essential to minimize the impact and progression of the disease. HF self-care covers a wide range of behaviours including medication adherence and recognition of symptoms as well as management strategies such as daily weighing, exercise, cessation of smoking, healthy diet, and the ability to seek timely help (Jaarsma et al., 2009; Jaarsma et al., 2003; Lainscak et al., 2011; Lorig & Holman, 2003; Oosterom-Calo et al., 2012; Riegel et al., 2004; Riegel et al., 2009). Self-care is a process of learning over time from experience, and an individualized

management approach that emphasizes self-care behaviours that must be adopted for HF patients to develop the necessary skills required (Harkness et al., 2015; Jonkman et al., 2016; Spaling et al., 2015). The ability to implement effective self-care practices into daily life, including integrating family into the care process and responding to HF symptoms, are the cornerstones to optimize the outcomes of individual patients (Cameron et al., 2016; Clark et al., 2014; Spaling et al., 2015; Srisuk et al., 2017). Despite this knowledge, self-care in HF patients is poor worldwide (Jaarsma et al., 2013). However, a trend in improvement was revealed; a recent study has concluded that the level of self-care in HF patients is moderate (Bagheri –Saweh, Lotfi, & Salawati Ghasemi, 2018). The most effective component of self-care to improve clinical outcomes in HF is currently unknown. An ongoing meta-analysis may provide the most rigorous results thus far (Ruppar et al., 2018). The published literature review is a snaphot of the pharmacist's role in self-care as an intervention model to evaluate the overall effect on numerous clinical outcomes.

HF patients with multiple comorbidities have been shown to have poor self-efficacy, eventually contributing to low self-care maintenance (Buck et al., 2015; Dickson et al., 2013). Improving self-care management is one of the most promising strategies in HF management (Gandhi, McCue, & Cole, 2016; Lambrinou, Protopapas, & Kalogirou, 2014; Mastromarino et al., 2014). In addition, consensus guidelines from Australia (Krum et al., 2011), Europe (Ponikowski et al., 2016), and America (Yancy et al., 2013) have advocated self-care as a critical component of HF management. Incorporation of self-care strategies in the management of HF patients eventually leads to better clinical outcomes,

particularly reductions in all-cause and HF-related hospitalization (Jovicic, Holroyd-Leduc, & Straus, 2006; Linn, Azollin, & Souza, 2016; Riegel, Lee, & Dickson, 2011).

2.12 Pharmacist-involved multidisciplinary team in HF

HF patients are optimally supported by a multidisciplinary team, which may include any combination of clinicians appropriate to oversee the ongoing management of the condition. Counselling about self-care in HF has been recommended as a best practice guideline for the clinical pharmacist (Wiggins et al., 2013). When deliberately engaged with HF patients, pharmacists have been successful in the reduction of all-cause and HF related hospitalization (Koshman et al., 2008), appropriate medication prescribing (Lowrie et al., 2012), reduction of medication discrepancies and prescription errors (Eggink et al., 2010), appropriate use of EBT (Kang & Cho, 2015), and the reduction of clinically relevant drug-drug interactions (Roblek et al., 2016).

To date, the specific benefits of pharmacist involvement in HF management for improving self-care and clinical outcomes have not been thoroughly reported. Therefore, this review focuses on literature published within the past 4 years and examines the issue regarding the findings of previous studies, aiming to highlight the current and emerging approaches in the contemporary management of HF. A summary of the studies reviewed can be found in Table 2.2.

2.13 Methods

Different databases were searched; Medline (Ovid), PubMed (Ovid), Scopus (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO), Cochrane library, and Web of Science (Thomson Reuters) encompassing the period from

2013 through to October 2016 for all relevant articles published in English. The following keywords for all the databases mentioned above were applied: “heart failure” OR “left ventricular dysfunction” OR “cardiomyopathy” OR “left ventricular ejection fraction” OR “LV dysfunction” OR systolic dysfunction” OR “diastolic dysfunction” OR “cardiac failure” OR “preserved ejection fraction” OR “HFpEF” OR “reduced ejection fraction” OR “HFrEF” AND pharmacist* OR “pharmaceutical care” OR “pharmaceutical service*” AND “*self-care” OR “self-management” OR “self-monitoring” OR “self-efficacy*”.

2.14 Results

The preliminary search yielded 82 articles published between 2013 and 2016. After excluding duplicates, 49 articles remained. They were further reviewed by title and abstract as well as full text to remove irrelevant articles. A total of four articles were included. The manual search of the references cited in each publication identified helped us to identify an additional ten relevant articles. The resulting 14 articles were retained for review.

Table 2.2

Characteristics of included studies.

Source	Study Design	Sample size	Study Population (Country)	Mean age of patients (years)	Key components of pharmacist intervention (setting)	Usual Care (control group) description	Duration of follow-up (months)
Anderegg et al. 2014	Observational pre-post analysis	3,316	Hospital patients (USA)	54	Medication reconciliation on discharge for high risk patients (Hospital)	No/limited medication reconciliation	1
Andhuvan et al. 2014	Prospective interventional	83	HF patients (India)	-	Counselling for medication adherence (Hospital)	-	6
Donaho et al. 2015	Retrospective chart review	169	HF patients (USA)	59	Medication education and reconciliation, medication up-titration, discharge planning (Clinic)	-	1
Fera et al 2014	Retrospective observational	175	HF/COPD patients (USA)	175	Medication therapy review, patient education, telephone follow-up (Hospital/Clinic)	-	1
Kalista et.al 2015	Observational	10	Recently discharged HF patients (USA)	81	A community pharmacist–provided in-home medication reconciliation and teaching service for patients within 1 week of admission, 2 follow-up telephone calls 1 week and 4 weeks after the visit (Outpatients)	-	1
Kinugasa et al. 2014	Retrospective review	277	Hospitalized HF patients (Japan)	-	Intensive medication education and medication adherence review on admission and discharge	-	-

Lowrie et al. 2012	Focus groups and interviews	65	Chronic HF patients (Scotland)	67	Community pharmacy based cognitive services (Community)	-	-
Martinez et al. 2013	Retrospective chart review	28	HF patients (USA)	79	Prescribing privileges, adjust medication dosages under specific protocols jointly established by cardiology and pharmacy staff (Outpatient HF clinic)	Nurse or physician runs the titration clinic without pharmacist	6
Salas et al. 2015	Prospective pilot	30	HF Patients (USA)	57	Tailored medication and disease counselling, discharge medications, telephone follow-up (Hospital/Outpatients)		1
Shepherd et al. 2015	Prospective interventional	48	HF patients (USA)	69	Education on HF pathophysiology and its pharmacologic and non-pharmacologic treatment (Community hospital)	-	1
Szkiladz et al. 2013	Non-randomized intervention	180	HF patients (USA)	71	Discharge counselling (Hospital)	Standard discharge counselling by nurse	1
Truong et al. 2015	Retrospective review	632	HF patients (USA)	68	Medication reviews, daily monitoring, discharge counselling, post-discharge follow up (Hospital/Outpatients)	Usual inpatient and discharge care – usually written instructions or educational material	1
Vinluan et al. 2015	RCT - pilot	16	HF patients (USA)	-	Individualized inpatient counselling (disease, medications, self-care) and telephone call follow-up	Standard discharge counselling by nurse	3
Warden et al. 2014	Quasi-experimental pre-post analysis	115	HF patients (USA)	56	Data collection, admission monitoring, discharge medication reconciliation, recommendations, instructions and advice. Telephone follow-up	Admission medication reconciliation by physicians. Discharge counselling by nursing staff	1

HF: heart failure; USA: United States of America; COPD: chronic obstructive pulmonary diseases.

2.14.1 Description of extracted evidence

The included studies have been grouped into themes based on the nature of the intervention carried out by the pharmacist. These are as follows:

a) Discharge counselling, medication reconciliation, and educational intervention

These types of interventions are most often initiated at the time of discharge from hospital, and sometimes throughout the hospital stay. Pharmacists can be involved in general counselling about disease, medicines, and self-care behaviours as well as specific tasks such as medication reconciliation and patient education (Vinluan et al., 2015). The major objective of medication reconciliation is to check whether the patients are receiving the actual list of medicines as prescribed (Aronson, 2017), while educational interventions are targeted to provide information about HF, medications, and self-care management.

b) Pharmacist-managed heart failure medication titration clinic-based intervention

In pharmacist-managed HF clinics, pharmacists are engaged particularly in the optimization of the prescription of current medications (Martinez et al., 2013). This is generally an ongoing role.

c) Community pharmacist intervention

Community pharmacists provide services to HF patients about disease, medications, and self-care management either in a community pharmacy setting, or in their homes (Lowrie et al., 2014) .

d) Pharmacist role in transition of care intervention

Pharmacists may have a specific role during the transition of patients from hospital to home to provide optimal care (Anderson & Marrs, 2018). While this care may cover some of the same aspects as the in-hospital counselling, education, and medication reconciliation described in the first theme, care transition pharmacists are focused on the continuum of care from hospital to home and will usually provide follow up care for a period of time.

Discharge counselling, medication reconciliation, and educational intervention

A small RCT, which was the only RCT identified, conducted by Vinluan et al. (2015) assessed the impact of pharmacist vs nurse discharge counselling on medication adherence and hospital readmission rates in a very small sample of elderly HF patients (n = 16) in the USA. They found evidence to suggest that pharmacist intervention resulted in improved medication adherence within the first 2 months after discharge, but that effect disappeared after 3 months. Mortality was lower, but readmissions were higher in the pharmacist intervention group. This RCT was significantly limited by a high rate of attrition on an already small initial sample, and the authors do suggest that longer term and/ or more intense follow-up may be necessary to maintain the improvement in medication adherence.

While the RCT provides the highest level of evidence, other types of studies are also valuable to illustrate the types of interventions which are being adopted, and the results which are being obtained. A number of non-RCT studies have investigated the effects of pharmacist participation in education for HF patients

either during hospitalization or at discharge (Andhuvan, Venkatachalam, & Sankar, 2014; Shepherd et al., 2015; Szkiladz et al., 2013; Truong & Backes, 2015; Warden et al., 2014). Improvements in medication adherence and/or patient knowledge about their medications were reported in all cases, and this is likely to translate into improved self-care capability and more positive clinical outcomes.

Hospital readmission rates are the most frequently reported outcome of pharmacist involvement in HF patient management. Patient education by a pharmacist has been shown to reduce both all-cause (Anderegg et al., 2014; Fera et al., 2014; Kinugasa et al., 2014; Truong & Backes, 2015; Warden et al., 2014) and HF-specific (Kalista, Lemay, & Cohen, 2015) readmission rates in a number of studies. However, results are not entirely consistent, with several studies including the RCT discussed earlier finding either no difference or a higher rate of readmissions (Shepherd et al., 2015; Szkiladz et al., 2013; Vinluan et al., 2015). Mortality rates are also of particular interest as a clinical outcome of HF management strategies. While the duration of the majority of studies reviewed was limited to a 30-day follow-up, two studies did report all-cause mortality. Results were mixed, with one study reporting lower mortality (Vinluan et al., 2015) and one reporting no effect (Kinugasa et al., 2014). It is likely that a longer follow up time is needed to detect any significant mortality patterns.

Readmission and mortality rates are important statistics for demonstrating the efficacy of interventions; however, many studies report additional findings which both inform and support the importance of pharmacist involvement in the management of HF. A study conducted in India additionally identified some of the

main barriers to effective medication adherence in their study population, including forgetfulness (63.0%), being reliant on others to purchase medication (39.7%), and polypharmacy (27.7%) (Andhuvan et al., 2014). Based on these results, the authors concluded that continuous follow-up was an important factor in ongoing medication adherence. Further to this, a review of HF self-management interventions in general concluded that patient characteristics such as low income, poor literacy, and low education levels were more likely to be associated with poor self-management capacity than characteristics such as age, gender, and ethnicity (among others) (Kalista et al., 2015). While the barriers are likely to change in different settings, pharmacist awareness of these constraints is essential for them to effectively contribute to and monitor self-care behaviour. There can also be additional economic benefits beyond hospitalization costs. A study by Szkiladz et al. (2013) reported that, despite no significant difference in readmission rates being observed in the intervention group (n = 86), a total of 34 medication errors were documented and it was estimated that the detection of these resulted in a cost avoidance of over $4,000. Donaho et al. (2015) also reported a high rate of medication errors detected. The proportion of HF patients receiving optimal care—for example, all facets of discharge planning and instruction completed—has also been shown to improve with the inclusion of a pharmacist in the care team (Kinugasa et al., 2014; Martinez et al., 2013; Truong & Backes, 2015); while overall patient satisfaction with their care, and confidence in their level of knowledge, has also been an important outcome for some studies (Lowrie et al., 2014; Warden et al., 2014). The majority of clinical studies do not include a qualitative component, or even administrative assessments, but measures of adherence to best practice and the level of patient

satisfaction may reflect improved engagement with both professional and self-care HF management and may be an important component of improved clinical outcomes.

The majority of the studies discussed above have reported on the role of the pharmacist in a hospital setting, particularly their involvement in discharge procedures and education. Some also report some level of post-discharge follow up-usually by telephone (Shepherd et al., 2015; Truong & Backes, 2015). However, pharmacists operate in many different settings, and can contribute to the management of HF through different models of care. The following sections discuss some specific examples where pharmacists operate in unique settings to deliver medication expertise and advice, either directly to HF patients or to support the wider clinical team.

Pharmacist-managed heart failure medication titration clinic-based intervention

Pharmacists are often involved in HF management in a clinic setting, usually as part of a multidisciplinary team. Martinez et al. (2013), described the impact of a pharmacist-managed medication titration clinic in the USA, operating as an adjunct to the regular care multidisciplinary clinic, on the percentage of HF patients (n = 28) achieving optimal dosages of critical medications. The pharmacists used patient telephone interviews and tele-monitoring technology to track patient's clinical measurements daily and were able to adjust medication dosages in line with specific protocols as well as offering education and advice during each telephone contact.

Outcomes for these patients were compared to those whose dosage titrations were carried out by other clinicians in a multidisciplinary clinic setting only. The results of this study found that target medication doses were achieved in a significantly higher percentage of pharmacist-managed titration clinic enrolees for the EBT prescribed. The outcomes of this study did not include mortality rates or HF-related hospital readmissions. The intervention used in that study was unique among those reviewed for the high intensity of engagement and the subsequent dosage control, as well as the innovative use of technology.

Community pharmacist intervention

Pharmacists can also contribute to HF management in a community setting, often as part of a community pharmacy practice. Lowrie et al. (2014) investigated the impact of a community pharmacist HF service in the UK on medication adherence and self-care management in chronic HF patients (n = 65), using a focus group with pharmacists and semi-structured interviews with individual patients. The results suggestthat the community pharmacists felt confident in providing adequate information to improve adherence and self-care in HF patients, and valued the opportunity to contribute to this program. In addition, patients welcomed the opportunity for discussion with the pharmacist to supplement the care and information they received from their general practitioner. Expressed views indicated that patients generally had an increased understanding of their condition and its treatment, and that participating in this service improved medication adherence for at least some patients.

In another UK-based study, in conjunction with the visiting nurse service, a community pharmacist-provided in-home medication teaching service was initiated and evaluated for medication adherence and hospital readmission rates for HF patients following recent hospital discharge (Kalista et al., 2015). Each patient received one in-home visit followed up by telephone calls at 1 and 4 weeks after the pharmacist's visit. Although only a small study (n = 10), the results showed that this type of support helped facilitate the successful transition of care from an inpatient to outpatient setting, improved medication adherence, and reduced hospital readmission rates. The expansion of this service to reach a wider range of patients would serve to augment these benefits.

Pharmacist-led transition of care intervention

The engagement of pharmacists to support the transition of patients from hospital to home is an emerging area of research in HF management. A recent systematic review (Albert, 2016) of transitional care strategies, while not specifically evaluating pharmacist contributions, stresses the importance of medication reconciliation and adherence and does recommend that pharmacists be involved in medication reconciliation as part of a transitional care team. Fera et al. (2014) described a USA-based case study about the contribution of the care transition pharmacist (CTP) in a primary care resource centre. The CTP reviewed medications and provided patient education and support during admission. The CTP then provided follow-up support via telephone within 3 days of discharge. The likelihood of 30-day hospital presentation was reduced among the patients receiving a follow-up telephone call from a CTP.

Similarly, a prospective, single-centre pilot study in the USA was conducted where a pharmacy resident ran a transition of care service to determine its impact on readmission rates in patients (n =30) with HF (Salas & Miyares, 2015). Pharmacists were engaged in counselling about medications and diseases, medication reconciliation, and follow up appointment reminder telephone calls. Overall, the 30-day HF readmission rate decreased from 28.1 to 16.6%, and the majority of patients (88%) attended their follow up appointments. In a third study from the USA, Donaho et al. (2015) performed a retrospective chart review to determine the effect of a pharmacist-involved multidisciplinary clinic on 30-day hospital readmissions in newly discharged congestive HF patients (n = 169). The team monitored physical and clinical signs and performed education, medication adjustment and titration, care coordination, and referral recommendations as warranted. This approach showed a 44.3% reduction compared to the hospital's average 30- day readmission rates.

2.15 Discussion

There has been a large range of interventions studied internationally addressing different potential contributions pharmacists can make in relation to the HF client 'journey'. However, it should be noted that the role of pharmacists in different countries and different healthcare settings is not standardized. That said, some overall trends are evident. This review suggests that pharmacist involvement in HF self-care generally leads to positive clinical outcomes, although there are some exceptions for mortality outcomes. Evidence for the current review has come from a number of settings and several countries over the past four years. To our knowledge, this study is the first to comprehensively summarize the specific role

of the pharmacist in improving self-care and outcomes in HF patients over this time period.

The pilot RCT by Vinluan et al. (2015) showed improved drug adherence as well as a decrease in readmission rates in the first month after discharge. However, the outcomes were not maintained in successive months. This result agrees with earlier findings that improved medication adherence in the pharmacist-involved management of HF were not sustained after the end of the intervention (Davis, Packard, & Jackevicius, 2014) and that only longer duration interventions in self-management can bring improvement in clinical outcomes related to HF (Jonkman et al., 2016). In this context, one could hypothesized that pharmacist-mediated drug intervention to improve long-term adherence must be ongoing to result in improved clinical outcomes. Although the RCT by Vinulan et al. used a very small sample size and a significant proportion of participants were lost to follow up, these results are important in demonstrating the potential of pharmacist contributions to improved drug adherence in HF management. This is supported by the results of the observational studies, which also found improvements in drug adherence (Andhuvan et al., 2014; Kalista et al., 2015; Lowrie et al., 2014; Warden et al., 2014), as well as reduction of 30- day readmission rates, and improved patient satisfaction with information provided by pharmacists regarding self-care (Anderegg et al., 2014; Kalista et al., 2015; Lowrie et al., 2014; Warden et al., 2014).

A recent systematic review identified a significant reduction of readmission and mortality rates associated with the implementation of interventions to improve

medication adherence among HF patients (Ruppar et al., 2016). The results of the studies reported here support these findings. Reduction of 30-day all-cause readmission rates has been found to be mediated by pharmacist-involved medication reconciliation, and discharge education (Anderegg et al., 2014) as well as pharmacist led-transition of care intervention (Donaho et al., 2015; Fera et al., 2014; Salas & Miyares, 2015). Similarly, improved 30-day HF-specific readmission rates have been found (Anderegg et al., 2014; Andhuvan et al., 2014; Eggink et al., 2010; Fera et al., 2014; Kang et al., 2016; Kinugasa et al., 2014; Roblek et al., 2016; Salas & Miyares, 2015; Shepherd et al., 2015; Szkiladz et al., 2013; Truong & Backes, 2015; Vinluan et al., 2015; Warden et al., 2014). However, some contrasting results on the impact of the pharmacist on readmission rates were noted. Despite other benefits (increased knowledge, detection of medication errors), no significant change in readmission rates was found in several studies (Shepherd et al., 2015; Szkiladz et al., 2013; Vinluan et al., 2015). Despite these anomalies, the trends reported here generally support the findings of the earlier meta-analysis (Koshman et al., 2008), including only RCTs, to assess the role of pharmacists in the care of patients with HF. In this review, pharmacist care was associated with significant reductions in the rate of all-cause hospitalizations (11 studies [2026 patients]; OR= 0.71; 95% CI =0.54–0.94) and HF hospitalizations (11 studies [1977 patients]; OR= 0.69; 95% CI =0.51–0.94) and a non-significant reduction in mortality (12 studies [2060 patients]; OR=0.84; 95% CI= 0.61– 1.15).

Pharmacist-collaborative care (pharmacist role is a component of a multidisciplinary intervention) led to greater reductions in the rate of HF hospitalizations (OR= 0.42; 95% CI= 0.24–0.74) than pharmacist-directed care

(pharmacist initiates and manages the intervention) (OR = 0.89; 95% CI= 0.68–1.17). The findings of the study by Koshman et al. indicate that pharmacist care in the management of patients with HF greatly reduces the risk of all-cause and HF-specific hospitalization, particularly if the pharmacist was a member of a multidisciplinary team, and this finding is supported by the more recent evidence gathered here.

A more recent systematic review performed by Kang et al., which included both RCTs and non-RCTS, of pharmacist involvement in care for HF and acute coronary syndrome (ACS) also reported beneficial outcomes (Kang et al., 2016). Reductions in all cause hospitalization and increased prescription rates of ACEIs and β-blockers were found in the pharmaceutical care group, but the authors concluded that the strength of evidence for other outcomes was insufficient or low. They suggested that then diversity of care and the heterogeneity of patient populations and clinical settings likely contributed to the inconclusive results, and these same effects could also explain the mixed findings in these areas in our review.

The strongest evidence of the benefits of pharmacist involvement in HF management and self-care from both the recent systematic review (Kang et al., 2016) and our current review is around medication management, including medication reconciliation, use of EBT, appropriate prescribing, dose-titration, and patient adherence. This finding is also in accordance with earlier studies, where pharmacist counselling in self-care in HF patients has been reported to support the appropriate adjustment of diuretic dose (Korajkic et al., 2011) and the use of EBT improved after the incorporation of a pharmacist-involved multidisciplinary team

despite a high number of comorbid conditions and the resulting complexity of management (Ho et al., 2014). The findings of this literature review are derived heavily from observational studies published between 2013 and 2016, and the RCTs and systematic review point to a gap in the knowledge regarding the role of the pharmacist in HF management. Therefore, further research in this field would broaden the current scientific evidence, which could then be translated into clinical practice.

2.16 Conclusion of review paper

Pharmacist involvement in HF self-care has demonstrated specific benefits, particularly around improvements in drug adherence, decreased 30-day readmission, HF-hospitalization, better utilization of EBT, increased self-care management ability, increased patient satisfaction, and increase in HF knowledge. However, the results are mixed especially for improvement in readmission rates, and this is probably driven by the heterogeneity of the studies reviewed and the relatively short length of follow up in most studies.

Despite these mixed results, some consistent evidence for the benefits of pharmacist involvement in HF management around medication management, and improving self-care behaviours, particularly drug adherence was observed. These benefits are likely to translate into improved clinical outcomes, but interventions may have to include extended patient contact and longer follow-up to observe related improvements in hospital admission and mortality rates. This review highlights the importance of large-scale randomized trials with extended follow-up time to

definitively measure the impact of the role of the pharmacist in HF self-care; particularly through multidisciplinary-based interventions.

2.17 Summary of chapter 2-literature review

A systematic review and meta-analysis were necessary given the knowledge gap after a previous meta-analysis (Koshman et al., 2008) to provide current and rigorous evidence of pharmacist-involved multidisciplinary HF management. The evidence from RCTs showed several clinical benefits of pharmacist involvement in HF management. In particular, there was a significant improvement in diuretic dose adjustment and medication adherence (at one month) and mixed results on readmission; however, there was no effect on mortality. A recommendation for the pharmacist's role within a multidisciplinary team was suggested. All five RCTs included in the literature review were published after the previous meta-analysis conducted by Koshman et al. Therefore, an update on the pharmacist's role in multidisciplinary team HF management will provide more current evidence into this field. There are some notable findings from the observational studies included in this literature review, for example a significant reduction in HF symptoms, improvement in drug adherence, readmission rates, medication management, self-care ability, and patient satisfaction and HF knowledge. More research in this field would broaden the current scientific evidence for the role of the pharmacist in HF management, which could then be translated into clinical practice.

Chapter 3: Methodology and Methods

This chapter outlines the methodologies used in this study, which include a multi-method triangulated analysis (see Figure 3.1) aligned to the central research question in order to achieve the aims and objectives presented in Chapter 1. The first section is a rationale for using a combination of methods within a framework of multi-method triangulation. The second section of this chapter culminates in a diagrammatic representation of the conceptual framework (see Figure 3.2) serving to outline the study's context and explain how it was conducted. The conceptual framework used in this study is based on the expanded *Chronic Care Model (*Expanded CCM).

The third section comprises the protocol for the systematic review and meta-analysis of the evidence of the pharmacist's role within the multidisciplinary team's management of HF. This review identifies emerging strategies to improve the range of clinical outcomes in HF management. The fourth section outlines the methodology for a retrospective comparison of two cohorts of CHF patients; to compare and contrast the similarities and differences in HF management. The last section discusses the ethical approval process associated with the research methods used in this study.

3.1 Rationale for methodology

To answer the research questions highlighted in Chapter 1, a combination of methods was implemented to gain extensive insights into the field of study. The use of more than one method in research to increase the robustness of the findings and provide alternate and complimentary outcomes relates to multi-method study design (Goertz, 2016; Stange, Crabtree, & Miller, 2006). It is also based on the

principles of methodological pluralism; this involves the investigation of a particular research question using pluralistic approaches (Barker & Pistrang, 2005). The fundamental basis for methodological pluralism is theoretical pluralism (Midgley, 2000, pp. 171-216). From a philosophical perspective, the term pluralism is fundamentally derived from ontology (Dow, 2012, pp. 129-139). The rationale of combining methods in research is guided by the principle of strengthening the level of evidence to be extracted to generate a reliable and valid answer (Borkan, 2004). A triangulated design of two quantitative methods was used in this current study to add rigour to the overall findings. A systematic review/ meta-analysis and a retrospective comparison of two cohorts of CHF patients are the two complementary quantitative methods used in this study.

Quantitative studies generally use a deductive approach to test a known hypothesis. A deductive method is also called a top-down approach that examines an already-known theory based on causality (Cummings, 2013; Kyriacou, 2004). The concept of a theory- or hypothesis-based investigation to describe cause and effect quantitatively to elucidate the prediction or pattern of relationship relates to positivism (Alderson, 1998). Triangulation potentially refers to four different approaches in research: data triangulation, investigator triangulation, theory triangulation and methodological triangulation (Carter et al., 2014). Methodological triangulation is defined as the process of using two or more methods to understand a single research question through cross verification (Duffy, 1987; Laws et al., 2013; Risjord, Moloney, & Dunbar, 2001). It aims to combine findings from different methods in order to achieve a more rigorous understanding and provide further insights (Howe, 2012).

Methodological triangulation, in research, offers a wider approach of different perspectives to answer the same research question, or related questions, to develop consistency of the findings (Whitehead & Schneider, 2013, pp. 264-266). It has numerous advantages such as enhancing the quality of the research and consistency of the findings, providing an in-depth understanding of the problem and improving the validity of the research outcomes (Bekhet & Zauszniewski, 2012; Jones & Bugge, 2006; Risjord, Dunbar, & Moloney, 2002).

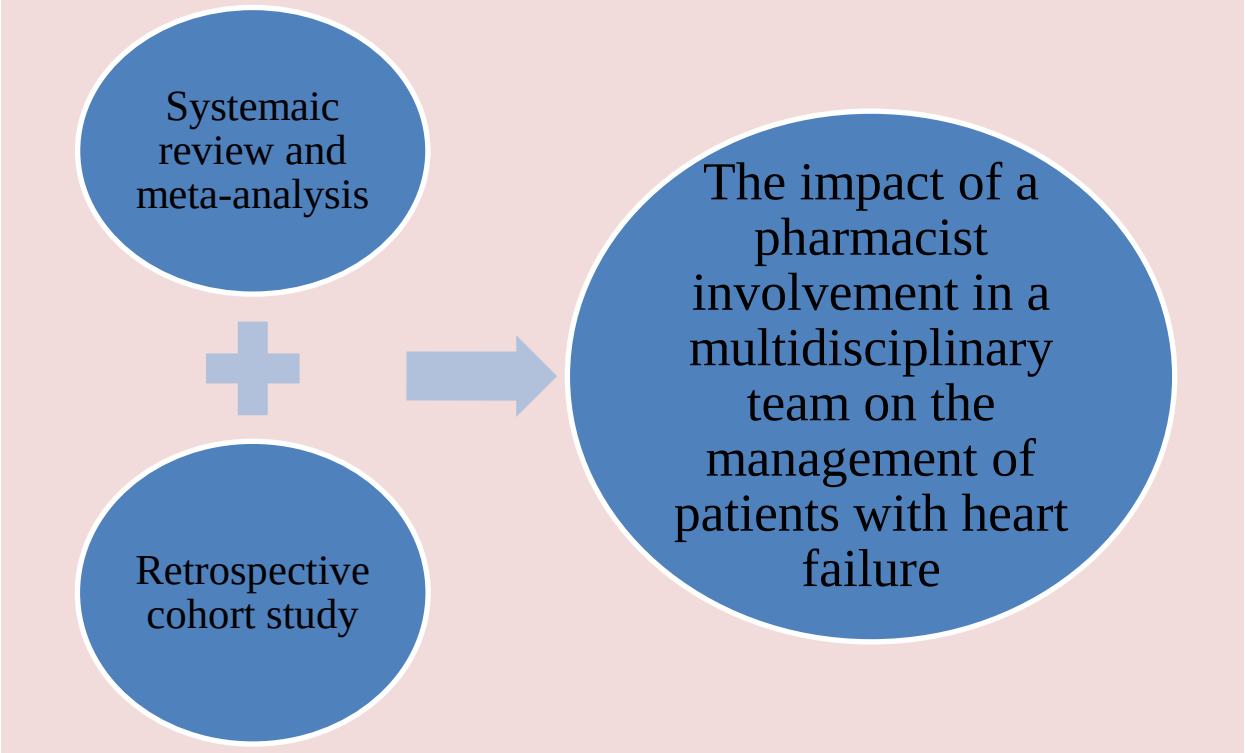


Figure 3.1. Triangulation of methods.

A systematic review involves reviewing the evidence for a clearly formulated research question. It incorporates explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the included studies in the review (Clarke, 2007; Gopalakrishnan & Ganeshkumar, 2013; Pollock & Berge, 2018). The hallmark of a systematic review is that it generates a robust and sensible answer to a focused research question (Malletta et al., 2012). On the other hand, narrative reviews possess a significant limitation of subjective bias while collecting and interpreting data to support theories or ideas by primary authors without a comprehensive search of all the relevant available databases (Pae, 2015). It is very challenging for clinicians in everyday practice to trust entirely on one particular study due to the existence of heterogeneous and conflicting results from multiple studies (Uman, 2011).

The validity of a systematic review particularly depends on whether it was conducted following a recommended guidelines such as PRISMA as well as the methodological heterogeneity of included RCTs such as bias and sample size (Murad et al., 2014). If conducted explicitly, the systematic review is considered as a reliable source of high-level evidence due to its robustness (Charrois, 2015; Møller & Myles, 2016). A meta-analysis is quantitative study which utilises a statistical technique to combine results from several studies included in a systematic review given the fact that enough data are available (Gurevitch et al., 2018; Haidich, 2010). Systematic review and meta-analysis rank the highest level in evidence pyramid in clinical research (Murad et al., 2016; Paul & Leibovici, 2014; Wright et al., 2007). Therefore, a systematic review and meta-analysis was considered as a method for this study.

A retrospective study focuses on relevant previous outcomes that occurred at the time of the study (Snyder et al., 2016). A cohort is a group of people with similar characteristics. In a retrospective cohort study, the relevant outcomes are compared with an equivalent cohort not exposed to the factor under investigation (Setia, 2016; Song & Chung, 2010). The importance of the pharmacist-involved multidisciplinary model has only been studied in a limited way within an Australian setting. Thus, a retrospective analysis of two cohorts of CHF patients from a tertiary referral hospital comparing those attending a pharmacist-involved Multidisciplinary Ambulatory Consulting Service (MACS) with the General Cardiology Heart Failure Service (GCHFS) without the pharmacist is another potential study. This study is expected to provide new insights for the emerging role of the pharmacist-involved multidisciplinary management model as an alternative approach in contemporary HF management.

The in-depth MACS clinic model of care is in accordance with previous publications (Ho et al., 2014; Shakib et al., 2016). The MACS model was delivered for patients with multiple chronic conditions and who were recently discharged from a metropolitan tertiary health-care service. It is a holistic management model for patients with multiple comorbidities and incorporates multidisciplinary assessments and the determination of individualised and reconciled evidence-based recommendations. The holistic assessment in the MACS clinic comprised a self-administered questionnaire, which covered living circumstances, activities of daily living, fall histories and vaccination status (influenza or pneumococcal); appetite and depression questionnaires may have also been included.

On a clinic visit, patients first had a nursing assessment comprising an averaged sitting BP, standing BP and a social assessment. They then underwent a medical review by a pharmacist before seeing a physician. This model of care also included follow-ups, outpatient HF nurse home visits, dial-in services for advice or facilitated access to tertiary care and access to allied health services, such as an exercise physiologist and clinical psychologist, as needed. This was underpinned by a regular GP being included in communication and feedback being provided regarding the patient's management. The pharmacists in the MACS clinic took medication histories, monitored adverse drug responses, assessed medication compliance, counselled patients regarding disease and medications, communicated with community pharmacies (particularly regarding any change in drug regimens) and participated in regular meetings with other team members.

Patients managed through the GCHFS clinic were seen by a specialist HF nurse and received a holistic assessment that included a review of their risk factors, medications, geriatric depression scale questionnaire results, vaccination history and smoking status, which is similar to the MACS service. These patients commonly had home visits through HF specialist nurses and, similar to MACS patients, had access to a clinical psychologist and exercise physiologist.

3.2 Conceptual framework based on the expanded chronic care model

In considering a conceptual framework for this study, several possible models were reviewed. One model deemed appropriate was the CCM, which highlighted the importance of a combination of multi-pronged strategies to improve outcomes in chronic diseases (Wagner et al., 1999). This model has been widely used as a foundation for chronic disease management. However, according to Barr et al.

(2003), the Wagner et al. (1999) CCM has some limitations; for example, it is restricted to a clinically oriented system and, while it is suitable for providers and health care organisations, it is not suitable for patients because it lacks the patient's perspective in self-management. Therefore, Barr et al. (2003) described an expanded CCM that integrates health promotion in the prevention and management of chronic diseases. The Expanded CCM focuses on reducing the burden of chronic disease. This not only motivates practitioners to concentrate on the improvement of functional and clinical outcomes for patients, but also supports the health of people and communities. The benefits of the CCM model in promoting the health of people and communities in the context of this thesis is described below (see section 3.2.1 to 3.2.7).

Therefore, the most suitable conceptual framework for this study is the Expanded CCM (see Figure 3.2). According to this model, improved population health outcomes in disease management, as well as functional and clinical outcomes, result from productive interactions and relationships between informed activated HF patients and a prepared and proactive practice team. An active community combined with prepared and proactive community partners is also crucial. It is important to describe each component of the Expanded CCM based on the model outlined by Barr et al. (2003). The four internal blocks—self-management support, decision support, delivery system design and information systems—function across both the health system and the wider community. Improvement in clinical outcomes for HF patients - such as increased HF knowledge and self-care, and reduced hospitalisations and mortality- needs collaboration between informed activated HF patients, prepared and proactive practice teams and proactive community partners.

Therefore, when determining this study's primary and secondary outcomes, the theme of the collaborative approach in the Expanded CCM was used.

3.2.1 Self-management/development of personal skills

This refers to an individual's ability to guard against disease by enhancing the skills needed to maintain health and wellness (Barr et al., 2003). More specifically, self-management of HF includes restricting sodium, reducing fluid retention, limiting alcohol intake,undertaking physical activity, ceasing smoking, self-monitoring signs and symptoms and retaining follow-up appointments (Oosterom-Calo et al., 2012). Self-care skill development is a phenomenon of learning that is dependent on personal experience. One of the best approaches in self-care is an individual model-based care that assists patients in acquiring the necessary HF self-care skills (Jonkman et al., 2016; Spaling et al., 2015). Further, an important navigator for effective self-care is the incorporation of family members into the care process (Clark et al., 2014; Spaling et al., 2015). Studies from numerous countries have reported that the level of self-care skills in HF patients is poor (Jaarsma et al., 2013). Therefore, to increase the efficiency of self-care, patients in the pharmacist-involved multidisciplinary care group in our retrospective cohort study received counselling regarding the basic concept of self-management and its implications. The individualised self-care management approach was one of the key strategies in HF management. As family support and education are key to this strategy, the concept of self-care was also explained to the patients' family members or carers. Evaluation of self-care was one of the secondary outcomes in the systematic review and meta-analysis study.

3.2.2 Delivery system design/reorientation of health services

This encourages health care professionals to support individuals and communities by using a more holistic approach, rather than by limiting care to clinical and curative services. It focuses on improving the patients' quality of life via an emphasis on design, implementation and practice of healthy public policies. This may be achieved by working within a team that incorporates members from different health care professions who can contribute their diverse expertise (Cooper & Hernandez, 2015; Khalil et al., 2015).

In a pharmacist-involved multidisciplinary cohort, a holistic approach to patient care was incorporated. This approach involves collecting patient information, particularly regarding living circumstances, fall history and vaccination status. Patients may have home nursing visits through the hospital's HF service, as well as access to clinical psychology and exercise physiology services.

3.2.3 Decision support

This is an important data collection domain for disease management and the development of strategies to promote and sustain healthy living. Patients in the pharmacist-involved multidisciplinary care group in the retrospective cohort received information regarding disease, medicines and self-management skills from the multidisciplinary team in collaboration with GPs and community pharmacies. Decision support emphasises the implementation of evidenced-based guidelines (Khalil et al., 2015). Therefore, the goal was to apply both pharmacological and non-pharmacological methods in the management of HF, as supported by different HF guidelines (Krum et al., 2011; Ponikowski et al., 2016; Yancy et al., 2013).

3.2.4 Information systems

Information systems refers to how comprehensive information beyond the health care system can be obtained such as a patient's poverty status, information regarding public transportation facilities and crime rates. Here, demographic information and overall health status of the population, as well as the cultural background and economic status of HF patients, are considered during the implementation of strategies to achieve improved outcomes in these patients. The unique and individual needs of each community can be identified if access to comprehensive information regarding HF patients is broadened to municipalities, local advocacy groups, recreation centres and service clubs. The holistic management of the MACS cohort involved capturing those factors along with the disease condition in HF patients. Taking all these factors into consideration, the MACS model of care was expected to improve HF patient outcomes.

3.2.5 Building health public policy

The development and implementation of health policies to promote health equity in society can help create a healthy environment. The current study's purpose was to test whether the pharmacist-involved multidisciplinary model of care could improve HF patient outcomes through a holistic disease management approach. The ultimate goal of this project was to encourage patients, clinicians and community partners to practice and work towards collaboration to create a healthy environment.

3.2.6 Creating supportive environments

Creating supportive enviroments primarily focuses on prioritising the development of optimum living and employment conditions that have a direct relationship with an individual's overall health status. The model of care proposed in this study of

HF management involves not only treating the disease condition, but holistically providing individualised care. Triggering factors that may have relationships with the health status of the individual were addressed while making a care plan. Family members were encouraged to closely monitor these factors. Some patients in the pharmacist-involved multidisciplinary cohort received home nursing visits through the hospital's HF service and had access to clinical psychology and exercise physiology services, so that the best care could be provided on an individual basis.

3.2.7 Strengthening community action

Strengthening of the community action involves working in partnership with the community to promote and maintain the health status of the individual within a community. Collaboration with GPs and community pharmacies were two major approaches in this study.

Based on the above description, it can be concluded that this thesis's study design fits well into the Expanded CCM for HF management. Pharmacist-involved multidisciplinary intervention offers an integrated approach to encourage patients, clinicians and community partners to work collaboratively to create a healthy environment. As highlighted, to best achieve these outcomes, it is recommended that pharmacists work as an important member of a multidisciplinary team in HF management.

To address the knowledge gap highlighted in the literature review and reinforce the currently available evidence, it is recommended that a systematic review and meta-analysis of RCTs in the pharmacist-involved multidisciplinary management of HF to determine the effect on different clinical outcomes is required. Further, pharmacists have been involved in the recommendation and practice of EBT in HF

management. Therefore, another potential study could be an investigation into the use of EBT with HF patients within a pharmacist-involved multidisciplinary care model in an Australian setting.

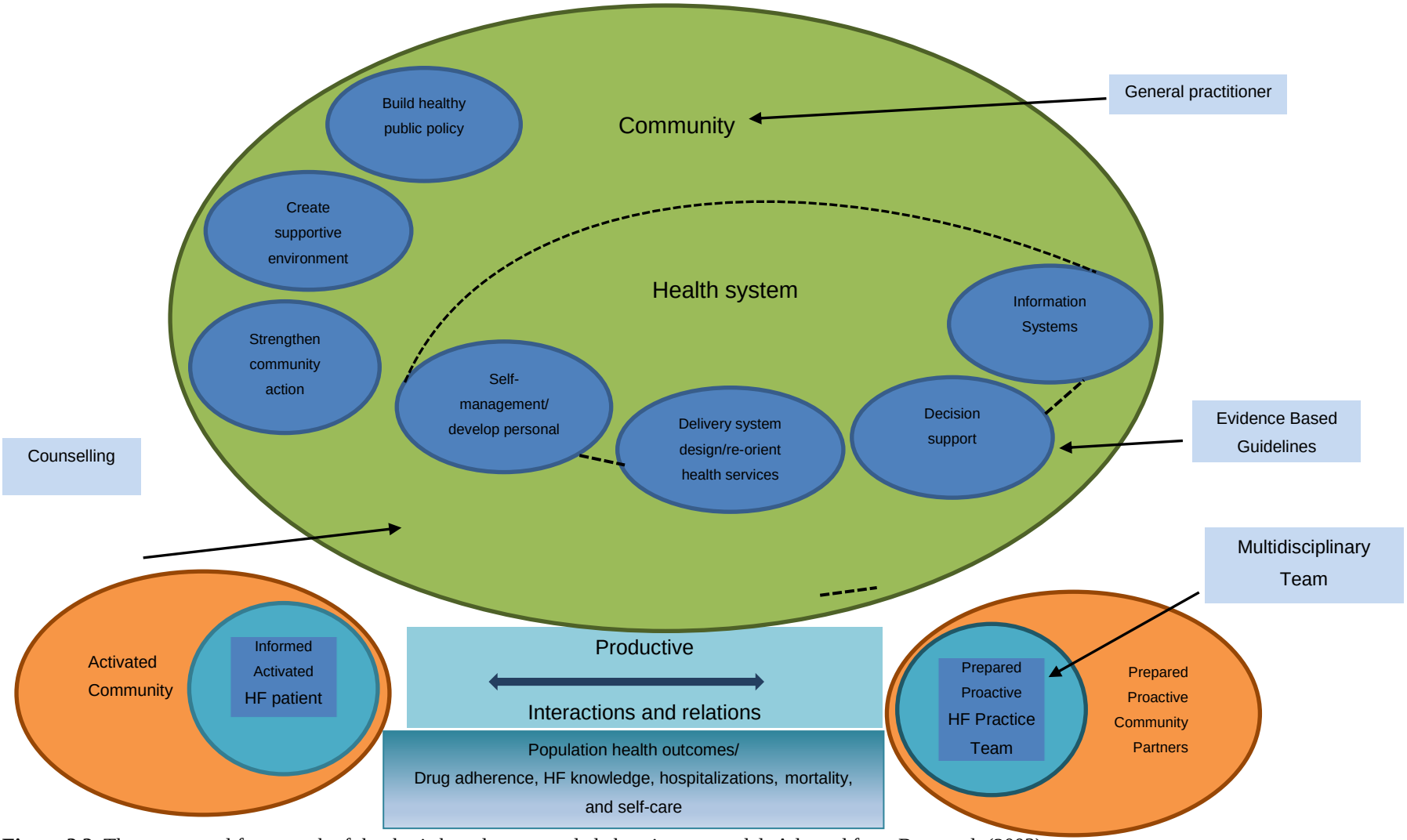


Figure 3.2. The conceptual framework of the thesis based on expanded chronic care model, Adopted from Barr et al. (2003).

3.3 Phase I: Effectiveness of the pharmacist-involved multidisciplinary management of heart failure to improve hospitalisations and mortality rates in 4630 patients: a systematic review and meta-analysis

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Name of the Author	Contribution
Daya Ram Parajuli 60%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Constance Kourbelis 28%	• Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Julie Franzon 2%	• Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Peter Newman 2%	• Conception and design of the research • Analysis and interpretation of research data
Ross McKinnon 2%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.

Sepehr Shakib 2%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Dean Whitehead 2%	• Drafting or revision of significant parts of the work so as to contribute to the interpretation.
Robyn Clark 2%	• Conception and design of the research • Analysis and interpretation of research data; and • Drafting or revision of significant parts of the work so as to contribute to the interpretation.

3.3.1 Description of the condition

The further relevant HF-related background information is outlined in Chapter 1. This systematic review and meta-analysis provides a more current and rigorous evidence-base related to pharmacist-involved multidisciplinary management of HF.

3.3.2 Description of the intervention

To date, there are different interventions mediated by pharmacists, including discharge counselling (Vinluan et al., 2015), pharmaceutical care (McCarren et al., 2013), telephone follow-up care by a transition pharmacist (Fera et al., 2014), pharmacist-initiated education to increase HF knowledge (Shepherd et al., 2015), in-home teaching about HF medications by a community pharmacist (Kalista et al., 2015) and pharmacist-managed HF clinics (Martinez et al., 2013). This systematic review is designed to establish evidence regarding the types of pharmacist-involved multidisciplinary interventions that are crucial to help improve HF patient outcomes.

3.3.3 How the intervention will work

Pharmacist involvement within a multidisciplinary team has a number of clinical benefits, including: recommending appropriate medication prescriptions (Lowrie et al., 2012); reducing medication errors and adverse drug reactions (Kripalani et al., 2012; Roblek et al., 2016); allowing for appropriate self-adjustment of diuretic doses, leading to an improvement in the quality of life of patients and decreasing hospital readmissions (Korajkic et al., 2011). The multidisciplinary efforts by the health care team are more likely to enhance the synergistic effects of interventions to improve HF patient outcomes when caring by conventional means is deficient.

3.3.4 The significance of this review

The area of pharmacist contributions in HF management gradually gained momentum after an earlier meta-analysis (Koshman et al., 2008). This study found that the risk of all-cause and HF hospitalisations was significantly reduced when the pharmacist was involved in HF management, particularly if the pharmacist was a member of a multidisciplinary team.

3.3.5 Objectives

The objective of this systematic review and meta-analysis was to comprehensively evaluate the role of pharmacist-involved multidisciplinary management of HF to determine its effect in relation to HF hospitalisations, HF mortality, all-cause hospitalisations, all-cause mortality, medication adherence (compliance), HF knowledge, health care costs, self-care and composite endpoint.

3.3.6 Methods

This study was conducted in accordance with the Cochrane Collaboration methodology (Higgins & Green, 2011), and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2010). An explicit method of quality measurement - Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach- -was incorporated to draw a summary for each outcome (Guyatt et al., 2011).

a) Protocol and registration

Our protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42016052195) (Parajuli et al., 2016).

b) Eligibility criteria

Studies were eligible if they included adults (≥18 years) with a confirmed diagnosis of HF according to diagnostic methods, such as the NYHA classification, echocardiography, nuclear imaging and cardiac MRI. RCTs which have enrolled patients with mid-range (EF, 41-49) (Ponikowski et al., 2016) or recovered EF (EF>40) (Yancy et al., 2013) were not excluded in our review. We included English-language peer-reviewed RCTs (pharmacist-involved multidisciplinary interventions), full-text articles and conference papers.

In the context of this review, a pharmacist-involved multidisciplinary intervention was defined as the condition of pharmacist (s) working in collaboration, at a minimum, with a physician within the intervention model. The intervention model may include interaction with other health care professionals as needed. Eligible pharmacist interventions include medication reconciliation, discharge counselling, patient education, collaborative medication management, telephone follow-up, home medication review, self-adjustment of diuretic dose, prevention of medication errors, adverse drug reactions and drug–drug interactions. Some of the duties could be offered to patients by physicians and nurse practitioners in different health care settings without involving the typical work profile of a pharmacist. These include patient education, telephone follow-ups, home medication review and assessment of drug–drug interactions. However, to be eligible for this meta-analysis, these interventions in RCTs must have been conducted within a multidisciplinary approach that did not exclude the pharmacist.

The intervention was compared with usual care, which involves either a follow-up by a cardiologist or GP in a hospital, outpatient clinic or family medical practice,

or under multidisciplinary HF-specialist care, and care that did not include the pharmacist undertaking an active role.

c) Information sources

Trials were identified through systematic searches of the databases recommended by the Cochrane Heart Group and other relevant databases from inception through March 2017. These included PubMed (NLM), MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), Web of Science (Thomson Reuters), Scopus (Elsevier) and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. The bibliographies of relevant studies and systematic reviews were searched manually. Corresponding authors were approached for further information regarding any missing, unreported or ongoing trial data whenever relevant. Additionally, ongoing clinical trials and unpublished studies on the following clinical trial registers were searched:

i. ClinicalTrials.gov (www.ClinicalTrials.gov)
ii. WHO International Clinical Trial Registry Platform (ICTRP) (http://apps.who.int/trialsearch/).

d) Search

The search strategies used in our review are outlined in Appendix IV.

e) Study selection

Two independent reviewers identified studies based on inclusion and exclusion criteria. Reasons for the exclusion of the ineligible studies were identified and recorded. Disagreements regarding the study selection process were resolved by consensus with a third reviewer.

f) Data collection process

Data were extracted from included studies and checked for accuracy and completeness. When sufficient data for meta-analysis was unavailable in the original RCTs, the corresponding authors were contacted (Bouvy et al., 2003; Lopez Cabezas et al., 2006; Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005). Data were not available for this meta-analysis from three RCTs (Azad, Molnar, & Byszewski, 2008; Gwadry-Sridhar et al., 2005; Holland et al., 2007). In these instances, data provided by the primary authors in previous meta-analyses were used (Koshman et al., 2008).

g) Data items

The data from the eligible RCTs were extracted, including author, date of publication, setting and country, sample size, study populations, mean age of the patients, intervention groups, major outcome descriptions, endpoint measurements and duration of follow-ups.

The following outcomes were considered:

i. Primary outcomes, which included HF hospitalisations and HF mortality.

ii. Secondary outcomes such as all-cause hospitalisations, all-cause mortality, medication adherence, HF knowledge, health care costs, self-care and composite endpoint. The composite endpoint is the combination of all-cause hospitalisations and all-cause mortality (Packer, 2016). Mortality as a sole endpoint to determine the clinical benefit of the intervention requires larger and longer trials. Therefore, composite endpoints of death and hospitalisations are combined to amalgamate the overall efficacy by increasing statistical power (Anker et al., 2016).

h) Risk of bias for an individual study

The risk of bias assessment was performed using the Cochrane Risk of Bias Tool (Higgins et al., 2011). Two reviewers independently assessed the methodological quality and a consensus was achieved through discussion or referral to the third reviewer. The risk of bias assessment was performed at the study level (Liberati et al., 2009). RCTs were included in the meta-analysis, irrespective of the risk of bias results; however, the GRADE approach was used to generate a summary of each outcome.

i) Summary measures

Forest plots were generated to estimate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the rates of HF hospitalisations, HF mortality, all-cause hospitalisations, all-cause mortality and composite endpoint. Meta-analysis was performed using RevMan 5.3 software (Collaboration, 2014). To measure the outcomes, the random-effects model was selected if there were more than five studies and a fixed-effects model was used if there were fewer than five studies (Tufanaru et al., 2015). The weight of a single study in a forest plot indicates the impact of that particular study on an overall pooled estimate in a meta-analysis as calculated by the inverse of the variance (Ried, 2006). The percentage value of the weight depends on the sample size and CI. A larger sample size and narrower CI means a higher weighting for a particular study (Perera & Heneghan, 2008). Overall effects in the forest plots were considered significant at $P \leq .05$.

j) Synthesis of results

Statistical heterogeneity indicates the presence of a true effect among studies rather than the variation by chance. It was measured using the standard chi-squared test

(χ^2) (Higgins et al., 2003) ($P<0.05$ is considered significant) and Higgins I^2 test. The I^2 values of 25%, 50%, and 75% were considered low, moderate and high variability respectively (Higgins et al., 2003). The calculation of I^2 depict the variation among studies as well as helps to decide whether the multiple studies can be pooled together (Fletcher, 2007). When meta-analysis was not possible, a descriptive synthesis was undertaken to extract the evidence for the four secondary outcomes.

k) Risk of bias across studies

The low publication bias is demonstrated by the symmetry of the funnel plot, the distribution of points (individual studies) scattered on both sides of the true effect in the shape of an inverted funnel (Sedgwick & Marston, 2015). Publication bias and selective reporting across studies may affect the cumulative evidence (Liberati et al., 2009). Publication bias to assess potential small study effects was measured by the generation of funnel plots (Sedgwick & Marston, 2015). Selective reporting (reporting bias) and poor reporting of certain outcomes due to negative results were also reported (Saini et al., 2014).

l) Additional analyses

Sensitivity analysis was performed to determine the pooled estimate of HF hospitalisations, all-cause hospitalisations and all-cause mortality by including four RCTs with sufficient statistical power (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005; Tsuyuki et al., 2004). Meta-analysis was further undertaken by polling only RCTs with statistical power and 12 months of follow-ups (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005) to determine the effect on HF-related hospitalisations, all-cause hospitalisations and all-cause mortality.

3.4 Phase II: Comparison of the demographics, clinical characteristics and utilisation of evidence-based therapies in chronic heart failure outpatients in multidisciplinary clinics with and without the involvement of a pharmacist: a retrospective cohort study

3.4.1 Background

A recent study reported that pharmacist involvement in HF management had significantly increased ($p < .05$) prescriptions and the MTD and target doses in HFrEF patients (Bhat et al., 2018). However, the importance of the pharmacist-inovlved multidisciplanry model has only been studied in a limited way in an Australian setting. This study provides a unique opportunity to both validate and build on the existing international research within an Australian context. The further relevant background is outlined in Chapter 1.

3.4.2 Objectives

General objective

The general objective was to evaluate the comparability of two multidisciplinary clinics with and without a pharmacist's involvement by describing the differences in demographic and clinical characteristics, comorbidities and use of EBTs in CHF outpatients.

Specific objectives

a) to determine the comparability of the two groups by describing the differences in demographics, clinical characteristics and comorbidities

b) to determine differences in the prescription and practice of EBTs between two clinics

3.4.3 Methods

This study followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007). Our study conformed to the principles outlined in the Declaration of Helsinki for conducting clinical research (Wilson, 2013). For the evaluation of EBTs, the individual data of 728 patients were reviewed for the type of medications prescribed, doses used and contraindications due to patient characterstics. To conduct the data analysis for HF management and treatment, a guideline was developed (see Appendix V) based on Australian and European guidelines (Krum et al., 2011; Ponikowski et al., 2016). Coding for each group of medications was performed by two independent researchers and checked for discrepancies. Any disagreements were resolved by consensus with a third researcher to increase the robustness of the research.

a. Study design

This was a retrospective comparison of two cohorts of CHF patients. We analysed the data of HF patients who attended either the MACS clinic or the General Cardiology Heart Failure Services (GCHFS) clinic at a tertiary hospital. The MACS clinic uses a pharmacist-involved model of multidisciplinary care, while the GCHFS uses a similar model, but without the active involvement of the pharmacist. The main difference between the two services was that the physicians in the MACS service are not only cardiologists, but may be clinical pharmacologists, general physicians or geriatricians. The other difference is the presence of a pharmacist in the MACS service. Both services used the same web-based clinical information system (Matrix) for patient management. It is predicted that it will be difficult to determine the use of EBT in HF patients if they do not visit the MACS clinics at

least twice. Therefore, for the comparison of the use of EBT, only the patients who had ≥2 visit in MACS clinics were included (n=359).

b. Setting

Setting, location and relevant dates

This study was conducted at a large metropolitan tertiary public teaching hospital with 680 beds. The study duration was from March 2005 to January 2017 for the MACS patients and from March 2006 to January 2017 for the GCHFS patients. There were two systems for the collection and storage of patient data within the hospital: Matrix and OACIS. Matrix is a tailored bespoke SQL-based database developed for the hospital that allows for the documentation of comorbidities, medications, patient assessments and summaries of important diagnostic results. Clinicians can use the system to document important information, generate evidence-based goals and create GP letters. OACIS (Telus Health, Montreal, Canada) was used as the patient administration system to record inpatient and outpatient visits and to view radiology and pathology results. The hospital's clinical pharmacology department oversees the running of the MACS service. The general cardiology department is separate, although they do use the Matrix database for their HF patients.

Period of recruitment

Recruitment of patients was not applicable because data were collected as part of routine clinical practice.

Exposure

This section includes the practice and clinical characteristics of the patients in the MACS or GCHFS groups.

Follow-up and data collection

The follow-up varied for all patients, depending on the date of first presentation in either clinic. We used the de-identified secondary data that was routinely collected in the hospital's Matrix and OACIS databases.

c. Participants

Inclusion criteria

We included all patients primarily diagnosed with HF and those who attended either the MACS or the GCHFS clinic. The method of diagnosis is explained below on subsequent section as a separate heading.

Exclusion criteria

Patients who were referred to, but did not attend, the clinics, those without echocardiography reports or those with insufficient information (e.g., cardiac function or prescribed medications) were excluded.

Sources and methods of selection of participants

Data were obtained using Matrix and OACIS; participants were selected based on the aforementioned inclusion and exclusion criteria.

Methods of follow-up

This was not applicable in this study.

d. Variables

Outcomes

These include demographic and clinical characteristics, comorbidities and use of EBT in the two clinics.

Exposures

Patients were exposed to either the MACS or GCHFS clinic.

Predictors

The main predictor in this study was the presence of a clinical pharmacist in the MACS clinic and no involvement of a pharmacist in the GCHFS clinic.

Potential confounders

The characteristics of the patients in the MACS and GCHFS clinics were the most important confounders. The series of guidelines created during our study period were also confounders.

Effect modifiers

These were the qualifications, experiences and expertise of the pharmacists in the MACS group and of nurses and clinicians in both groups.

Diagnostic criteria for HF

Patients were primarily assessed for signs and symptoms that included elevated jugular venous pressure, pulmonary crackles, peripheral oedema, breathlessness, ankle swelling and fatigue. The other confirmatory diagnosis procedures were performance-based, predominantly regarding echocardiography, nuclear imaging and cardiac MRI. The information available in the case notes from the external investigations was also taken into consideration. If the left ventricular function was defined as mildly or more impaired at any time, then patients were diagnosed as having reduced systolic function. If patients had multiple echocardiography or other forms of imaging, the worst value was considered.

e. Data sources/measurements

Data sources were the Matrix and OACIS databases, as outlined in the previous section. The variables of interest and methods of measurement are described in the quantitative variables and statistical analysis sections respectively.

f. Bias

Referral bias, in which different types of patients may be referred to the two different clinics, was the main potential bias. However, this was not relevant as the inclusion/exclusion criteria helped outline all data, and routine data collection regarding the left ventricular status of the patients was performed independently.

g. Study size

During the study period, the total number of HF patients who attended the MACS and GCHFS clinics, and who met our eligibility criteria, determined our sample size. The total sample size, which incorporated demographic and clinical characteristics, was 1,058 patients; for EBT use in HFrEF patients, there were 492 patients and, for EBT in HFpEF patients, there were 239 patients.

h. Quantitative variables

Patient age, weight, SBP, diastolic blood pressure (DBP), HR, EF and number of medications used were recorded. How these quantitative variables were measured is explained in the statistical analysis section.

i. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 25.0.0.1; Armonk, NY: IBM Corp). Continuous/discrete data were expressed as mean ± standard deviation) and categorical data as a number (percentages) to determine the demographic and clinical characteristics for each group. Group differences were evaluated using independent Student's *t*-tests for continuous variables and chi-squared statistics for categorical variables (McHugh, 2013). The two-way analysis of variance was used to compare the mean differences where there were more than two groups during the analysis. The proportion

comparison was performed using a *Z*-test in EpiTools. Statistical significance was set at $p < .05$. The value of Cramer's V (effect size) was 0.10 (small), 0.30 (medium) and 0.50 (large) for one degree of freedom, and 0.07 (small), 0.21 (medium) and 0.35 (large) for two degrees of freedom (Kim, 2017). The aim of the statistical data analysis is to identify the significant predictors of the use of ACIE's.

A binary logistic regression model was fitted to ascertain the effects of Age, Gender (male), Last Clinic SBP, Last Clinic DBP, Last Clinic HR, AF, any anaemia, IHD, diabetes, anxiety, CRF, hypertension, asthma, COPD, any cognitive impairment, any solid Cancer, hyperlipidaemia, any CVA, falls, depression/anxiety, and contraindications to ACEIs/ARBs, β-blockers and MRAs. The Hosmer and Lemeshow test was used to test the model for significance. Nagelkerke R^2 has been used to establish the amount of variance explained by the model. The dependent variable in the model is ACEIS/ARBs used (1-used; 0-not used). Any independent variable which showed a -value < 0.25 in univariate analysis was included in the multivariate analysis (Bendel & Afifi, 1977; Stoltzfus, 2011).

j. Ethical approval

Ethical approval was obtained from the Royal Adelaide Hospital Human Ethics Research Committee; the approval letter is provided in Appendix VI.

k. Study benefits

Participants received no direct benefit. However, the outcomes can be translated into clinical practice for improved patient-oriented care in the future. This study may provide a basis for the development of a future RCT to determine the role of pharmacist-involved multidisciplinary teams in the management of HF. This project could establish a collaborative relationship between Flinders University and

the Royal Adelaide Hospital, and has the potential to establish Flinders University as a Centre of Excellence in patient-oriented care and EBT use in HF. The findings may ultimately lead to a wider use of this model of care, and subsequently improve clinical outcomes for people living with HF.

l. Risks

Participants did not experience physical and emotional risks from this research. The main possible risks were a loss of privacy and breach of confidentiality; however, the strategies to reduce these risks can be found in the risk mitigation section. There were no risks to the researchers or local community.

Risk mitigation

This was a low/negligible risk research project. We were diligent in adhering to the confidentially and data storage regulations and requirements both during the analysis and after the completion of the project. No conflicts of interest exist.

m. Confidentiality, data storage and security

Data were stored in password-protected SA Health servers until de-identified. The de-identified data are stored in a password-protected secure server at the Flinders University School of Nursing and Health Sciences. Data will remain in the password-protected server at the Flinders University School of Nursing and Health Sciences for five years after the date of publication or five years after the conclusion or abandonment of the project, in accordance with Flinders University's regulations regarding general research data and results. After this time, paper-based data will be destroyed by shredding and electronic data will be permanently deleted.

3.5 Summary of chapter three - methodology

A multi-method triangulation approach was used for the methodology of this study. This included a systematic review and retrospective comparison of the two cohorts of CHF patients. The systematic review and meta-analysis were conducted using the Cochrane Collaboration methodology and the PRISMA Statement. The retrospective comparison of the two cohorts of CHF patients followed the STROBE guidelines. This chapter also explained the ethical approval process associated with the research methodology

Chapter 4 outlines the results from the systematic review and retrospective comparison of the two cohorts of CHF patients.

Chapter 4: Results

4.1 Results of systematic review and meta-analysis

4.1.1 Study selection

The initial search strategy identified 1294 potentially eligible studies, and another 72 were found from other sources, clinical trial registers. After excluding duplicates, the remaining 786 studies were carefully screened by title and abstract. The full text of 55 publications was reviewed. Eighteen RCTs (n=4630) were included for systematic review, and 16 (n=4447) for meta-analysis. The PRISMA flow chart (see Figure 4.1) demonstrates the screening process for the eligible studies and the reasons for exclusion (see Table 4.1). The major reasons for exclusion of studies were interventions not meeting our eligibility criteria, non-RCT and outcomes not included in our primary or secondary outcome list.

Figure 4.1. PRISMA flow diagram: study screening and selection.

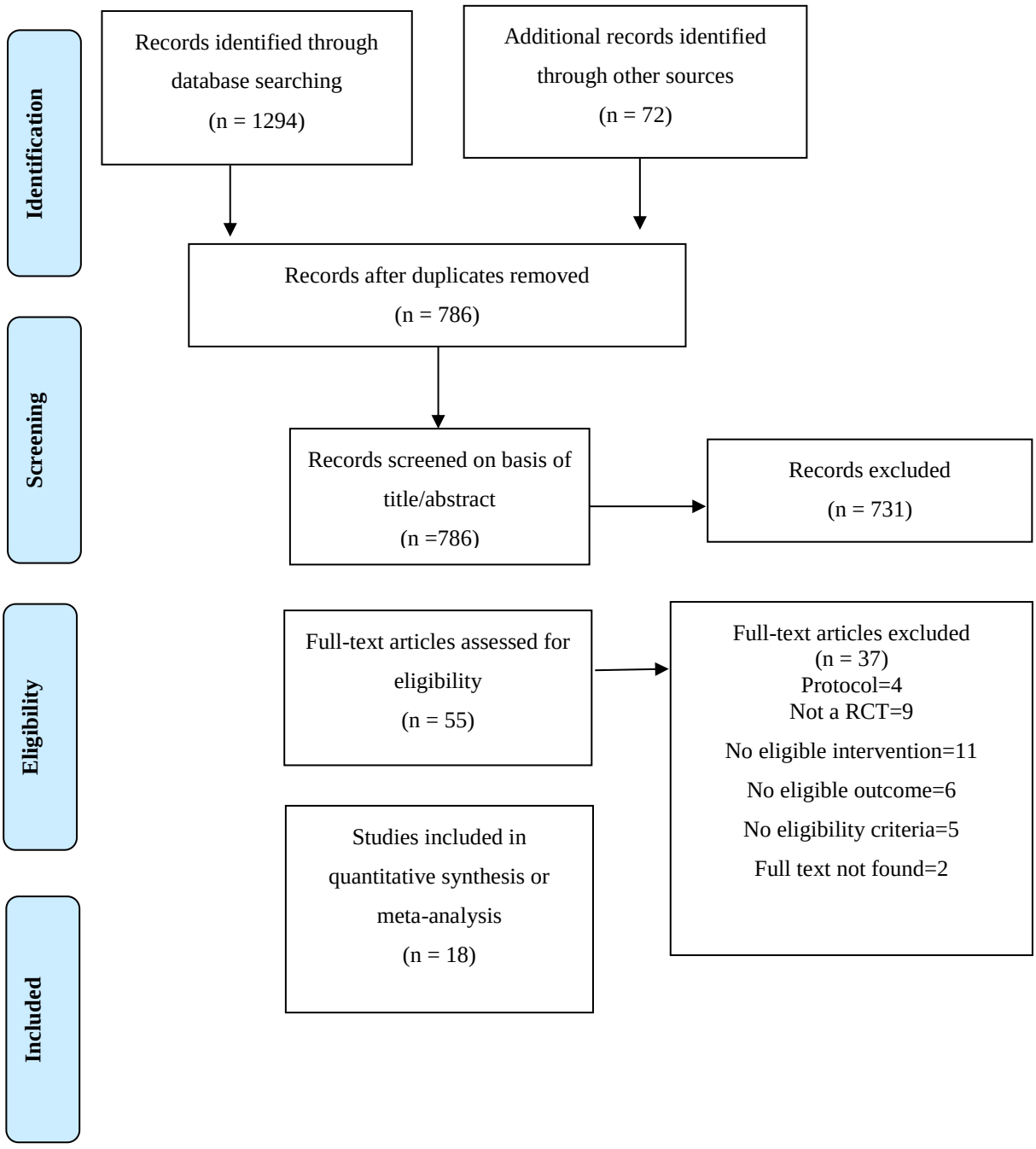

Table 4.1

Characteristics of excluded studies.

Study	**Reason for exclusion**
(Backes, Rizos, & Pricor, 2012)	It is a trial protocol (conference abstract). Full report not identified.
(Barker et al., 2012)	Not a pharmacist involved multidisciplinary intervention.
(Bell et al., 2016)	This study included acute coronary syndrome patients as well as heart failure patients.
(Bucci et al., 2003)	No measured outcome of interest.
(Forsyth et al., 2015)	Not an RCT (conference abstract).
(Gastelurrutia et al., 2011)	No measured outcome of interest: Not an RCT.
(Gupta et al., 2016)	Not an RCT.
(Gwadry-Sridhar et al., 2008)	It is a protocol paper. Full review not found.
(Hansen et al., 2009)	No measured outcome of interest.
(Koshman et al., 2007)	It is a protocol paper. Full review not found.
(Kripalani et al., 2012)	This study included acute coronary syndrome patients as well as heart failure patients.
Lim 2005 (Lim et al., 2005)	Full text not found
(Linné, Liedholm, & Israelsson, 1999)	Usual care is very different than what is done in most of the RCTs. The objective was to measure the impact of systematic education rather than pharmacist involved multidisciplinary intervention.
(Masterson Creber et al., 2015)	Not a pharmacist involved multidisciplinary intervention.
(Luzier et al., 2000)	Not an RCT.
(McAnaw et al., 1999)	Not an RCT.
(McCarren et al., 2013)	Not an RCT.
(Mineh et al., 2015)	It is a trial protocol (conference abstract). Full report not identified.
(Morrow et al., 2007)	No measured outcome of our interest.
(Moye et al., 2012)	Not a pharmacist involved multidisciplinary intervention.
(Nct, 2012)	Couldn't find abstract, and full text paper. This study has not recruited patients yet.
(Nimpitakpong, 2003)	Not an RCT.

(Noureldin et al., 2012)	It is a post hoc analysis of Murray 2007 RCT. No measured outcome of interest.
(Schou et al., 2013)	Not a pharmacist involved multidisciplinary intervention.
(Schou et al., 2014)	Not a pharmacist involved multidisciplinary intervention.
(Shaughnessy, 1998)	Not a pharmacist involved multidisciplinary intervention.
(Soflin, Young, & Clayton, 1977)	No measured outcome of interest.
(Swieczkowski et al., 2016)	Not an RCT.
(Trinkley et al., 2016)	Not a pharmacist involved multidisciplinary intervention.
(Tsang et al., 2013)	No measured outcome of interest.
(Tsuyuki & Arnold, 2006)	It is a commentary paper.
(Tsuyuki et al., 2012)	Not a pharmacist involved multidisciplinary intervention.
(Williams, Hauser, & De Luca, 2012)	This study included multiple diseases as well as heart failure patients.
(Wingen et al., 2014)	Not an RCT.
(Wu et al., 2012)	Not a pharmacist involved multidisciplinary intervention.
(Vinluan et al., 2015)	Not a pharmacist involved multidisciplinary intervention.
(Vorilhon et al., 2016)	Not a pharmacist involved multidisciplinary intervention.

RCT: randomized controlled trial

4.1.2 Study characteristics

The baseline characteristics in the included RCTs were not significant between intervention and usual care group. Eligible patients were those diagnosed with HF (≥ 18 years and NYHA class I-IV). Only 3 trials reported the value of EFs as their eligibility criteria; and EF ≤ 55 in one trial (Stewart, Pearson, & Horowitz, 1998), EF < 45 in one trial (Gattis et al., 1999), EF ≤ 40 in one trial (Gwadry-Sridhar et al., 2005). One RCT has excluded patients who have preserved EF from recruitment (Tsuyuki et al., 2004). One RCT only included patients suffering from left ventricular systolic dysfunction (Lowrie et al., 2012). The mean age of the participants in the RCTs ranged from 58 to 84 years. The follow-up time ranged from 6 weeks to 12 months. The sample size for the RCTs ranged from a minimum of 34 to a maximum of 2169. While most of the included studies (n=11) had a sample size of ≥100 participants, only 5 studies have more than 200 participants. Of the total participants (n=4630), 61% were male and 39% were female. One study was conducted only in female participants (Azad et al., 2008).

The included 18 RCTs were published from 1995 to 2016. These studies were conducted 4 in the United States, 3 in the United Kingdom, 2 in Australia, 3 in Canada, 1 in Ireland, 2 in Netherland, 1 in Spain, 1 in Slovenia and 1 in the United Arab Emirates. Half of the RCTs (n=9) were conducted in outpatient clinics, 1 in primary care centres, 5 in hospitals, 4 in patients' home and 1 in community pharmacy. There exists a wide variation on the type of intervention process incorporated in included RCTs. Pharmacist-involved multidisciplinary intervention offered an integrated approach to educational counselling focusing on HF knowledge and medications, improving lifestyle modifications, and self-care

behaviours, medication optimization, medication reconciliation, medication errors, collaborating with local GPs and community pharmacies, home visit, and telephone follow-ups. We found a high level of variation for the definition of usual care across included RCTs. The characteristics of the 18 included studies are shown in Table 4.2. Data for HF hospitalization (13 RCTs), HF mortality (2 RCTs), all-cause hospitalization (13 RCTs), all-cause mortality (15 RCTs) and composite endpoint (3 RCTs) were available to include in the meta-analysis. Additionally, data for medication adherence (10 RCTs), HF knowledge (2 RCTs), health care costs (4 RCTs), self-care (1 RCT) and health-related quality of life (8 RCTs) were available for narrative synthesis to extract the overall effect on these outcomes.

Table 4.2

Characteristics of included studies.

Source	**Setting (Country)**	**Sample size (n)**	**Study population**	**Mean age (years)**	**Intervention group and major outcome description**	**Follow-up (intervention frequency)**
Goodyear 1995	Outpatient clinics (United Kingdom)	100	Chronic stable HF patients (>70 years) who required no alteration of medications.	84	Patient counselling about the use of medications. Significant improvement in medication compliance in intervention group.	3 months (2, 4 weeks)
Stewart 1998	Home visits (Australia)	97	HF patients (NYHA II, III or IV) discharged from hospital, high risk for unplanned readmission, LVEF≤ 55.	75	Discharge counselling, home visit, recommendation to visit community pharmacist and liaison with GPs. Reduced unplanned readmissions and death rates in intervention group.	6 months (1 week)
Gattis 1999	Outpatients clinics (United States)	181	HF patients undergoing evaluation in general cardiology clinics, and LVEF <45.	68	Therapeutic recommendations, counselling about medications and potential drug effects, and telephone follow-up. Significant reduction in all-cause mortality and HF clinical events in intervention group.	6 months (2, 12, and 24 weeks)
Rainville 1999	Hospital (United States)	34	Patients >50 years, diagnosed with HF, and with medical history of the disease.	70	Education about HF and self-care, medication review, and telephone follow-up. Lower readmissions rates in intervention group.	12 months (1, 4, 12, 48 weeks)
Varma 1999	Outpatients clinics (Northern Ireland)	83	Patients >65 years, diagnosed with HF (NYHA I-IV) and cognitive status score of >6. Recruited from hospital or those attending outpatient clinics.	76	Education on HF, medications and self-care, medication optimization, written information provided to GP or community pharmacist. Improved knowledge about drug therapy and lower hospital admissions in intervention group.	12 months (3 monthly)

Bouvy 2003	Community Pharmacy (Netherlands)	152	HF patients being treated with loop diuretics (NYHA class II/III), admitted to hospital or attended specialist HF clinic.	70	Structure interview, medication review, compliance measurement, and monthly follow-up. Improved medication compliance intervention group. No significant differences in re-hospitalization and mortality between groups.	6 months (1 monthly)
Tsuyuki 2004	Outpatient clinics (Canada)	276	Patients (>18 years) admitted to hospital due to HF (reduced systolic dysfunction).	74	Patient support program, medication optimization, education about HF, medication, and self-care behaviours. No difference in medication adherence between groups. Reduction in cost of care in intervention group.	6 months (2 and 4 weeks and monthly thereafter)
Sadik 2005	Outpatient clinics (United Arab Emirates)	208	Patients with diagnosed HF (NYHA class I - IV) and cognitive status score >6.	58	Education on HF, medication, self-care, and lifestyle modification. Pharmacist discussion with physician to optimize therapy. Improved compliance, and lower hospitalizations in the intervention group.	12 months (3, 6, 9, 12 months)
Gwardy-Sridhar 2005	Hospital (Canada)	134	Patients with HF (≥18 years), low left ventricular ejection fraction (LVEF ≤ 40%), under long term treatment for HF or low LVEF.	67	Received 2 HF booklets, viewed video on congestive HF and multidisciplinary education medication compliance, diet and lifestyle modifications. Improved knowledge scores in intervention group.	12 months (2 to 4 days and every 3 months thereafter)
Lopez Cabezas 2006	Hospital (Spain)	134	Hospitalized patients for HF. Diagnosed using the Framingham criteria for HF (majority in NYHA I and II).	76	Education on HF, diet, and medications. Telephone follow-up and clinical assessment. Reduced readmissions rates and improvement of medication compliance in intervention group.	12 months (1, 2, 3, 4, 5, 6, 8, 10, 12 months)

Holland 2007	Home visits (United Kingdom)	293	Patients (>18 years) admitted to ED due to HF as an ongoing condition, and (majority in NYHA class III), prescribed two or more drugs on discharge.	77	Home visit (within 2 weeks of discharge) and education on medications, life style modifications and self-care. Feedback was provided to GPs and the local pharmacist. One follow-up visit between 6-8 weeks. No reduction on hospital admissions in intervention group.	6 months (2 weeks, 6-8 weeks)
Murray 2007	Outpatient clinics (United States)	314	Patients (>50 years) diagnosed with HF (majority in NYHA II) and using at least one cardiovascular medication.	62	Medication reconciliation, education on medication adherence, and HF. Communicating with clinic nurses, and primary physicians. Improved adherence during intervention and decreased health care cost in intervention group.	12 months (during , 3, 6, 9, 12 months)
Triller 2007	Home visits (United States)	154	Patients with primary or secondary diagnosis of HF (≥21 years) who were discharged and under home care.	80	Medication reconciliation, counselling on medication compliance and lifestyle modifications. Communication with nurses, and GPs. No significant difference in the composite endpoint.	6 months (7 to 10 and 18 to 21 days)
Azad 2008	Outpatient clinics (Canada)	91	Patients diagnosed with chronic HF (older women, ≥63 years).	77	The interdisciplinary intervention pathway including 12 visits over a 6-week period. Exercise program, educational counselling and dietary management. No significant difference in mortality in intervention group.	6 months (bi-weekly visits)
Eggink 2010	Hospitals (Netherlands)	85	Adults (≥18 years) diagnosed with HF, and prescribed five or more medications.	73	Medication review, discussion with cardiologists about prescribing errors, providing information to patients, providing written overview of the discharge medications, liaising with community pharmacy as well as with GPs. No difference in medication adherence between two groups.	6 weeks

Source	Setting (Country)	Sample size (n)	Study population	Mean age (years)	Intervention group and major outcome description	Follow-up (intervention frequency)
Korajkic 2011	Outpatient clinics (Australia)	70	Patient's (≥18 years) diagnosed with HF with NYHA class II, III, and IV and were on a daily dose of furosemide (other medications allowed).	57	Education on self-care, dose adjustment of furosemide, HF and medications. Lower readmissions rates in the intervention group. Significant improvements in HF related knowledge and medications in intervention group.	3 months (4, 8, and 12 weeks)
Lowrie 2012	Primary care center (United Kingdom)	2169	Patients (≥18 years) with left ventricular systolic dysfunction.	71	Training to pharmacist about HF and medications. Pharmacist collaborated with family doctors and patients for the optimization of treatment. No significant difference in death from any cause of hospital admissions for HF/cardiovascular cause/non-cardiovascular cause.	55 months (3-4 subsequent weekly or fortnightly).
Roblek 2016	Hospitals (Slovenia)	51	Patients diagnosed with HF, prescribed at least two medications during admission, and presence of at least one drug-drug interaction.	79	Evaluation of clinically relevant drug-drug interaction by the pharmacist. The relevance of the drug-drug interactions was checked by a panel of three clinicians with help of electronic database. Lifestyle modifications information provided. No reduction of composite endpoint (death and hospitalization), re-hospitalization, or death.	6 months (during hospitalization, and at patient discharge.

HF, heart failure; NYHA, New York Heart Association; ED, emergency department; LVEF, left ventricular ejection fraction; GPs, General practitioner

4.1.3 Risk of bias within studies

There are seven types of risk of bias defined by Cochrane risk of bias assessment tool (Higgins et al., 2011). These biases are random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting and other bias. The overall risk of bias was judged as low in the included studies, as demonstrated by Figure 4.2: summary of risk of bias. Selection bias in seven RCTs (39%), and detection bias in three RCTs (17%) were unclear (see Figure 4.3). Random sequence generation and reporting bias were low in all included RCTs. But the allocation concealment was high in only one RCT (Bouvy et al., 2003). Although the performance bias was found to be 100% given the open nature of interventions in the included studies, it is not valid for this review. The open nature of the interventions prohibited true blinding in the trials. The detection bias in seven RCTs (39%) and attrition bias in six RCTs (33.3%) was high.

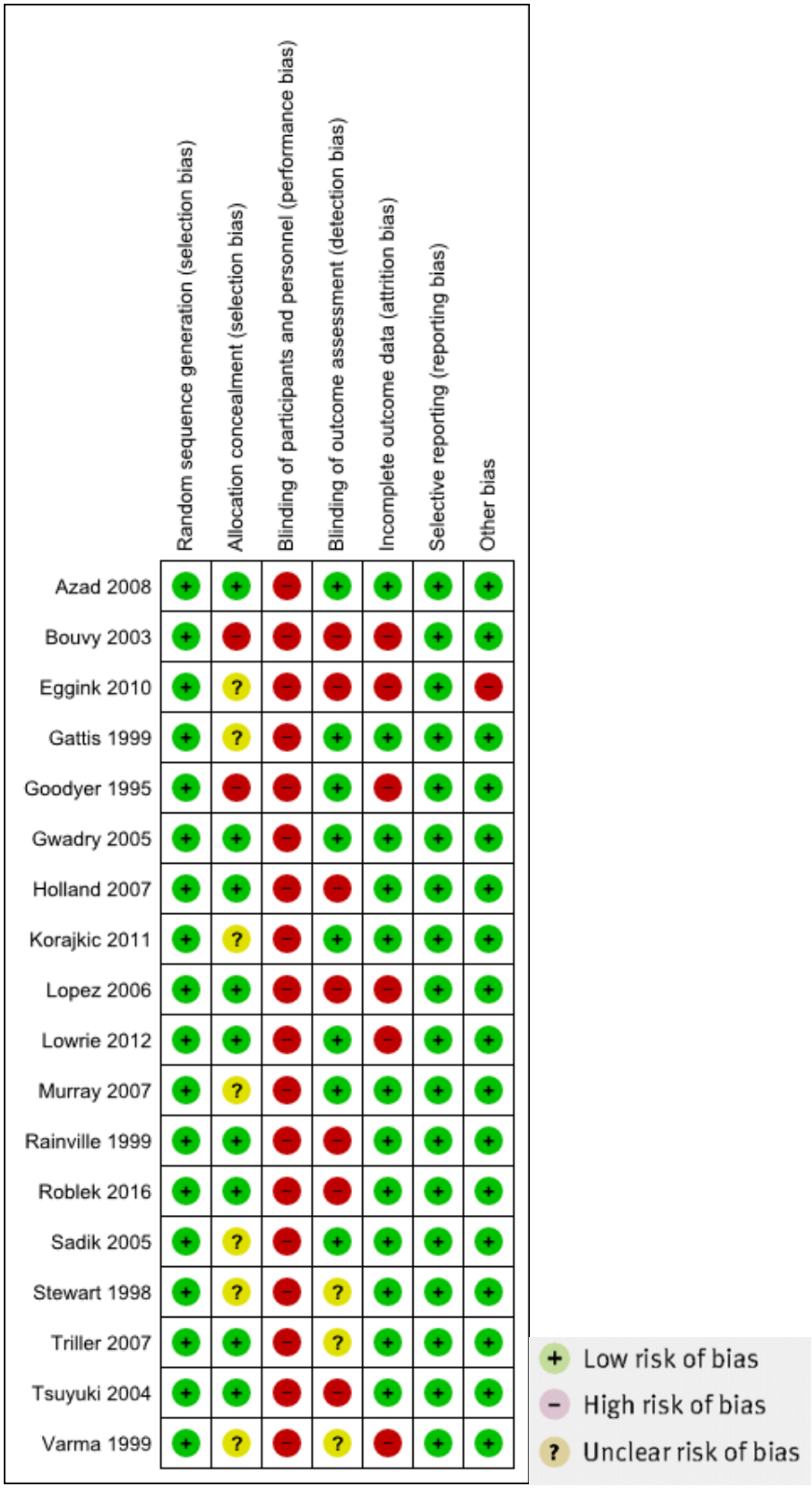

Figure 4.2. Risk of bias summary: review author's judgement about each risk of bias item for each included study.

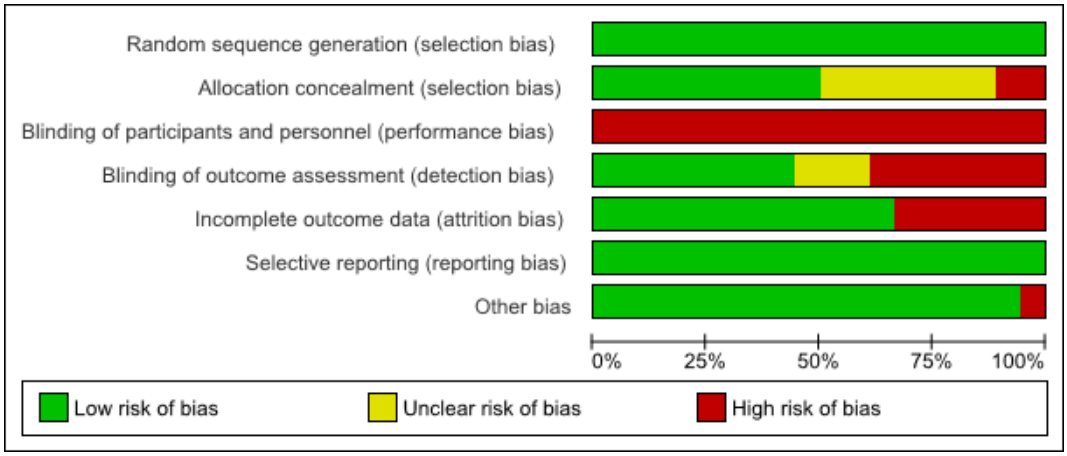

Figure 4.3. Risk of bias graph: review author's judgements about the each risk of bias item presented as percentages across all included studies.

4.1.4 Synthesis of results

a) Effect on heart failure hospitalisations

Thirteen RCTs (4211 patients) reported HF hospitalisations (patients hospitalised at least once) (Bouvy et al., 2003; Gattis et al., 1999; Gwadry-Sridhar et al., 2005; Holland et al., 2007; Korajkic et al., 2011; Lopez Cabezas et al., 2006; Lowrie et al., 2012; Murray et al., 2007; Rainville, 1999; Sadik et al., 2005; Stewart et al., 1998; Triller & Hamilton, 2007; Tsuyuki et al., 2004). Of these, eight RCTs showed a reduction in HF hospitalisation, but five had no effect. Only four had sufficient statistical power (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005; Tsuyuki et al., 2004). A pooled estimate of the thirteen RCTs showed a significant reduction in HF hospitalisations [OR 0.72, 95% CI (0.55- 0.93), p=0.01, I^2=39%] in a random-effects model (see Figure 4.4). The χ^2 test showed that the p value is not significant (p=0.07) for heterogeneity. The heterogeneity for the pooled effect on HF hospitalisations was medium (I^2=39%). In the meta-analysis of four RCTs with sufficient statistical power, there was no significant reduction in HF hospitalizations [OR 0.87, 95% CI (0.69–1.08), p = 0.20, I^2=0%] (see Figure 4.5). In addition, there was no statistically significant difference in the net effect on HF hospitalisations when the meta-analysis was restricted to three RCTs with statistical power and 12 months of follow-up (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005) (Figure not included).

b) Effect on heart failure mortality

Only two RCTs (2345 patients) reported HF mortality (Gattis et al., 1999; Lowrie et al., 2012). Only one included RCT had statistical power to detect effect on HF mortality (Lowrie et al., 2012). A pooled estimate of the two RCTs showed no reduction in HF

mortality [OR, 1.56, 95% CI (0.60- 4.03), p=0.36, I^2= 0%] (see Figure 4.6). There was no heterogeneity for net effect on HF mortality (I^2=0%).

c) Effect on all-cause hospitalisations

Thirteen RCTs (4241 patients) reported all-cause hospitalisations (Bouvy et al., 2003; Gattis et al., 1999; Goodyer, Miskelly, & Milligan, 1995; Holland et al., 2007; Lopez Cabezas et al., 2006; Lowrie et al., 2012; Murray et al., 2007; Roblek et al., 2016; Sadik et al., 2005; Stewart et al., 1998; Triller & Hamilton, 2007; Tsuyuki et al., 2004; Varma et al., 1999). Of these RCTs, only four had sufficient statistical power. Nine RCTs reported reduced all-cause hospitalisations, with four showing no effect. A pooled estimate of the thirteen RCTs showed a significant reduction in all-cause hospitalisations [OR 0.76, 95% CI (0.60 - 0.96), p=0.02, I^2= 52%] (see Figure 4.7). The χ^2 test showed that the p value was significant (p=0.01) for heterogeneity. The heterogeneity for the pooled effect on all-cause hospitalisations was slightly higher than medium (I^2=52%). In the meta-analysis of four RCTs with sufficient statistical power (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005; Tsuyuki et al., 2004), there was no significant reduction in all-cause hospitalisations [OR 0.97, 95% CI (0.84–1.13), p = 0.73, I^2 = 35%] (see Figure 4.8). In addition, there was no statistically significant difference in the net effect on all-cause hospitalisations when the meta-analysis was restricted to three RCTs with statistical power and 12 months of follow-up power (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005) (Figure not included).

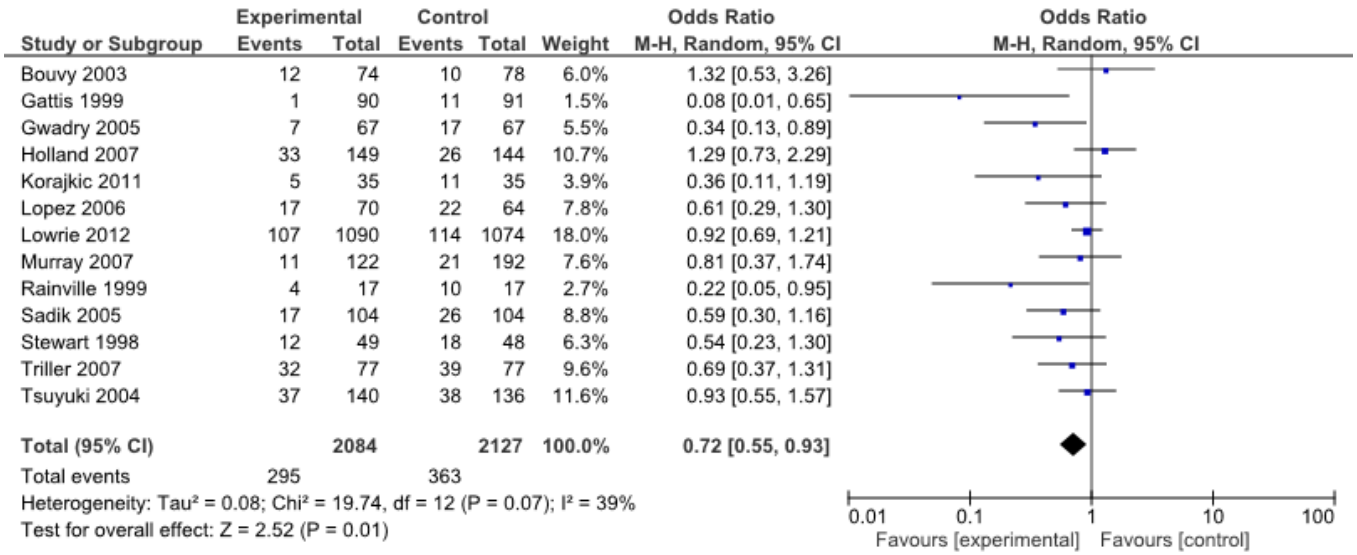

Figure 4.4. Forest plot of heart failure hospitalisations (random-effects model).

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

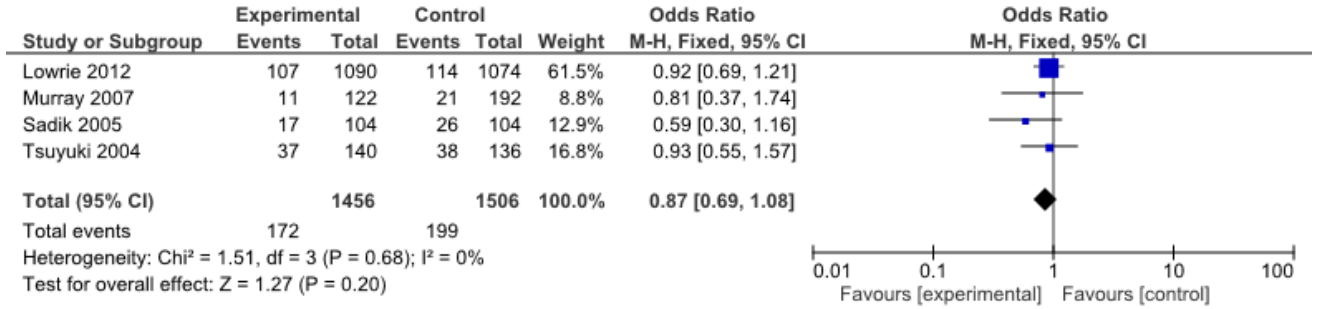

Figure 4.5. Forest plot of heart failure hospitalisations (fixed-effects model) with studies having sufficient (≥ 80%) statistical power.

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

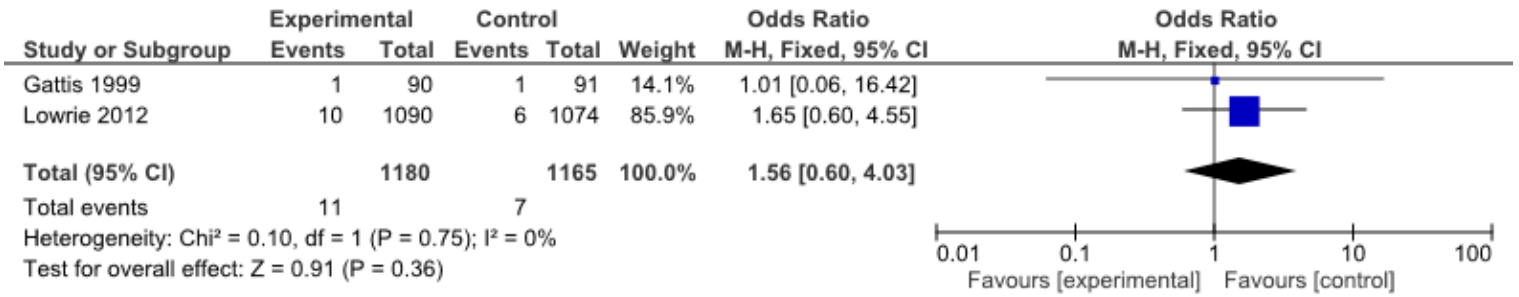

Figure 4.6. Forest plot of heart failure mortality (fixed-effects model).

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

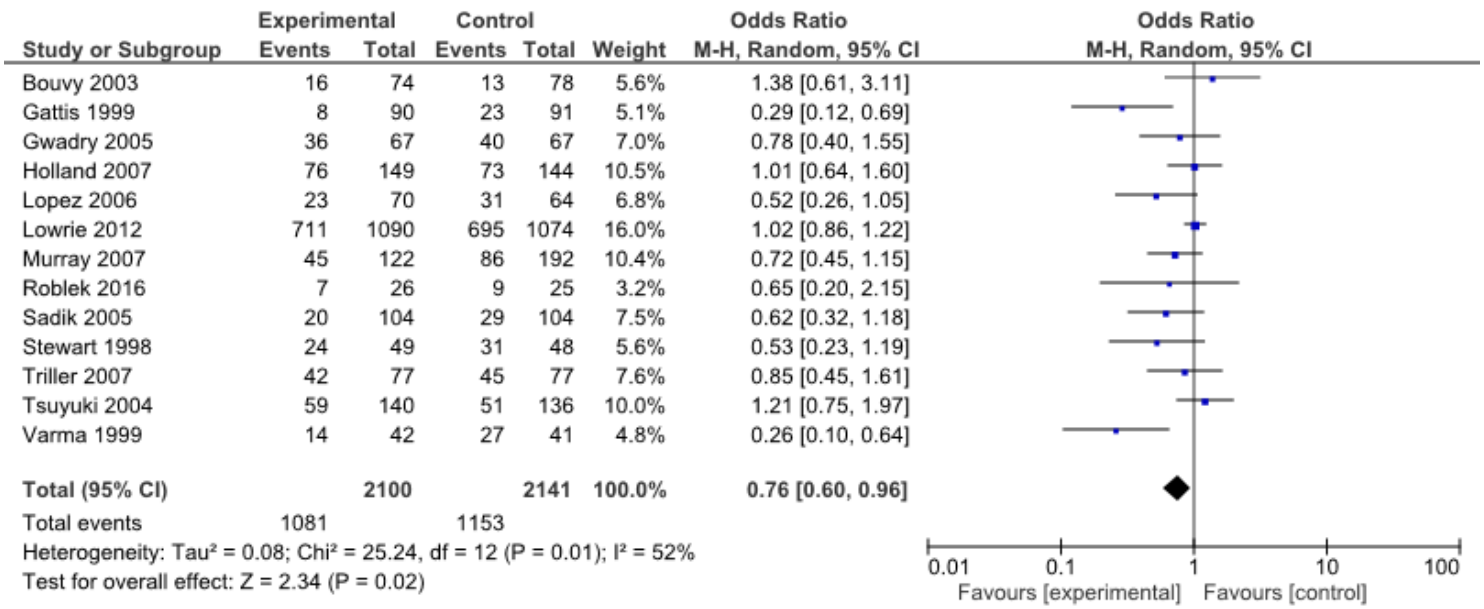

Figure 4.7. Forest plot of all-cause hospitalisations (random-effects model).

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

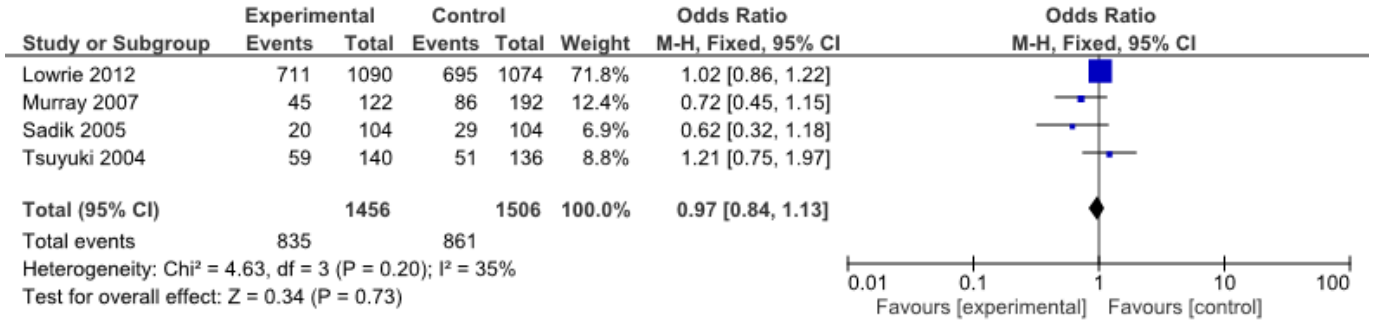

Figure 4.8. Forest plot of all-cause hospitalisations (fixed-effects model) with studies having sufficient (≥ 80%) statistical power.

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

d) Effect on all-cause mortality

Fifteen RCTs (4366 patients) reported all-cause mortality. Among them, only four had sufficient statistical power (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005; Tsuyuki et al., 2004). Six RCTs showed a significant reduction in all-cause mortality. A pooled estimate of the fifteen RCTs showed no significant reduction in all-cause mortality [OR 0.92, 95% CI (0.74-1.13), p=0.41, I^2= 9%] (see Figure 4.9). The heterogeneity for net effect was low (I^2=9%). In the meta-analysis of the four RCTs with sufficient statistical power, there was no significant reduction in all-cause hospitalizations [OR 1.03, 95% CI (0.87–1.23), p = 0.73, I^2 = 0%] (see Figure 4.10). In addition, there was no statistically significant difference in the net effect on all-cause mortality when the meta-analysis was restricted to three RCTs with statistical power and 12 months of follow-up (Lowrie et al., 2012; Murray et al., 2007; Sadik et al., 2005; Tsuyuki et al., 2004) (see Figure 4.11).

e) Effect on medication adherence (compliance)

Medication adherence was reported in 10 RCTs (see Table 4.3) with only fourhaving adequate statistical power. The interventions in these RCTs focused on HF education, medications, self-care, medication review, medication optimization, adverse drug reactions, providing written information, exposure to a video about HF, collaboration with GPs, and telephone follow-up. Among the 10 RCTs, only three had sufficient statistical power to detect effect on medication adherence (Murray et al., 2007; Sadik et al., 2005; Tsuyuki et al., 2004). Three RCTs showed significant improvement (p<.05), six found non-significant improvement and one found no difference in medication adherence.

f) Effect on heart failure knowledge

HF knowledge was reported in two studies (Gwadry-Sridhar et al., 2005; Korajkic et al., 2011) (see Table 4.3). These interventions mainly focused on educational sessions to improve knowledge of HF and self-care behaviours, provide booklets and show a video on congestive HF. Both RCTs found a significant improvement ($P<0.05$) in knowledge of HF, however, both studies were limited by alack of statistical power.

g) Effect on health care costs

The effect on health care costs was measured in four RCTs (see Table 4.3). Only two of the studies had sufficient statistical power to detect effect on health care costs (Murray et al., 2007; Tsuyuki et al., 2004). Cost-effectiveness was measured in different ways: mean cost of hospital-based care, health care cost, total health care cost, and composite cost (total health system cost, hospital cost, home care agency cost). All four RCTs reported a non-significant reduction in health care costs. The reduction in cost per patient in intervention group was not mentioned in two RCTs (Stewart et al., 1998; Varma et al., 1999). One study conducted in the USA reduced the cost in the intervention group by $2960 (CI, $-7603 to $1338) per patient (Murray et al., 2007). Another study from Canada reduced the cost by $1902 (current estimate of $CDN) per patient (Tsuyuki et al., 2004).

h) Effect on self-care

The impact on self-care was reported in one RCT (Gwadry-Sridhar et al., 2005) (see Table 4.3), which found a non-significant improvement. This RCT did not have statistical power to detect the effect on self-care. The intervention consisted of a home visit by a pharmacist within two weeks of discharge, focused on patient/career education regarding medications, exercise, diet, smoking cessation and self-care. After the home visit,

feedback recommendations were also provided to GPs and the local pharmacist. Self-care was measured using the European HF self-care behaviour scale (Jaarsma et al., 2009).

i) Effect on composite endpoint of all-cause hospitalisations and all-cause mortality

Three RCTs (2369 patients) reported a composite endpoint. Of the three RCTs, only one had adequate statistical power (Lowrie et al., 2012). A pooled estimate of the three RCTs showed no significant reduction in composite endpoint [OR 0.97, 95% CI (0.82-1.16), p=0.74, I^2= 0%] (see Figure 4.12).

j) Effect on health-related quality of life

Health-related quality of life was measured in eight RCTs (Bouvy et al., 2003; Gwadry-Sridhar et al., 2005; Holland et al., 2007; Korajkic et al., 2011; Lopez Cabezas et al., 2006; Murray et al., 2007; Sadik et al., 2005; Varma et al., 1999) (see Table 4.3). Of them, two had sufficient statistical power to detect the effect on health-reality quality of life (Murray et al., 2007; Sadik et al., 2005). Among the nine RCTs, only three studies reported a significant improvement and difference in health-related quality of life in HF patients (Gwadry-Sridhar et al., 2005; Korajkic et al., 2011; Sadik et al., 2005). The quality of life was measured by different instruments: the Chronic Heart Failure Questionnaire (Murray et al., 2007), EuroQol- 5 Dimension (Holland et al., 2007; Lopez Cabezas et al., 2006), the Minnesota Living With Heart Failure (MLHF) (Azad et al., 2008; Bouvy et al., 2003; Gwadry-Sridhar et al., 2005; Korajkic et al., 2011; Sadik et al., 2005; Varma et al., 1999), the 36-Item Short Form Health Survey (Gwadry-Sridhar et al., 2005; Sadik et al., 2005; Varma et al., 1999), the Dartmouth Primary Care Cooperative Information Project/World Organizations of National Colleges, Academics, Academic

Associations of General Practice/Family Physicians and the 15-item Geriatric Depression Scale (Varma et al., 1999).

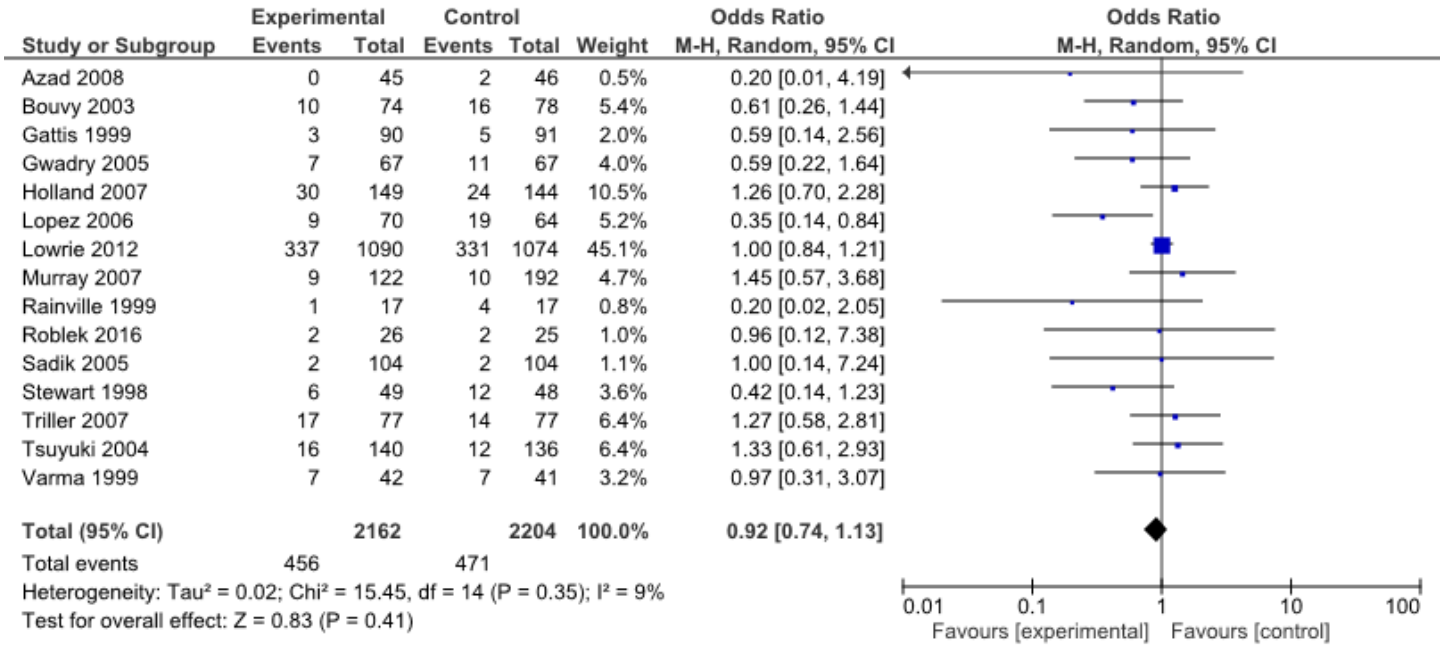

Figure 4.9. Forest plot of all-cause mortality (random-effects model).

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

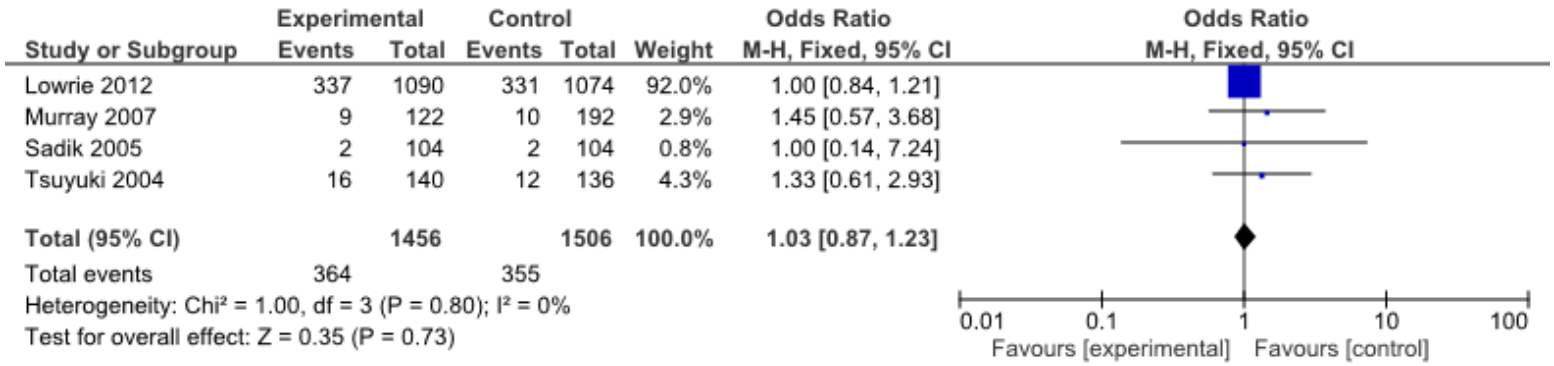

Figure 4.10. Forest plot of all-cause mortality (fixed-effects model) with studies having sufficient (≥ 80%) statistical power.

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

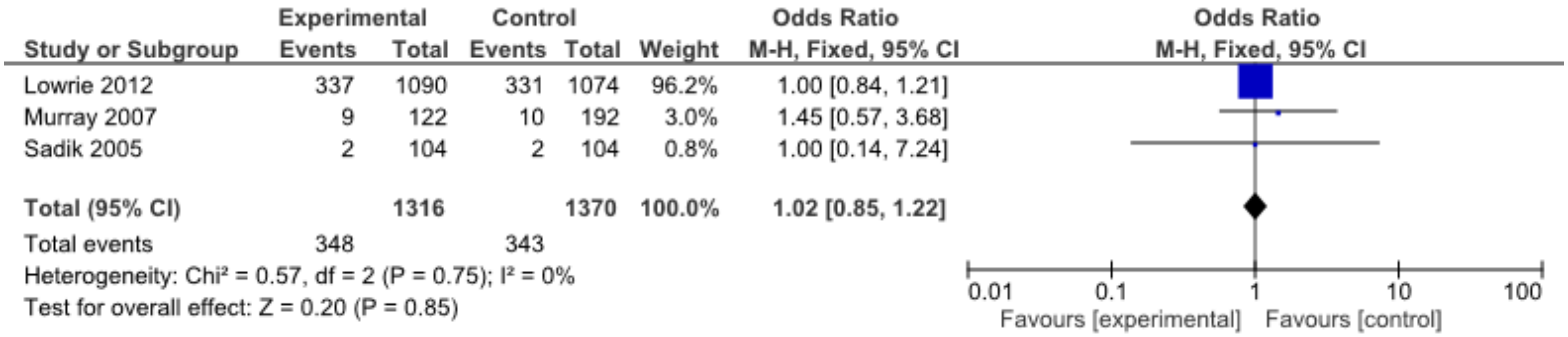

Figure 4.11. Forest plot of all-cause mortality (fixed-effects model) with studies having sufficient (≥ 80%) statistical power and 12 months of follow-up.

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

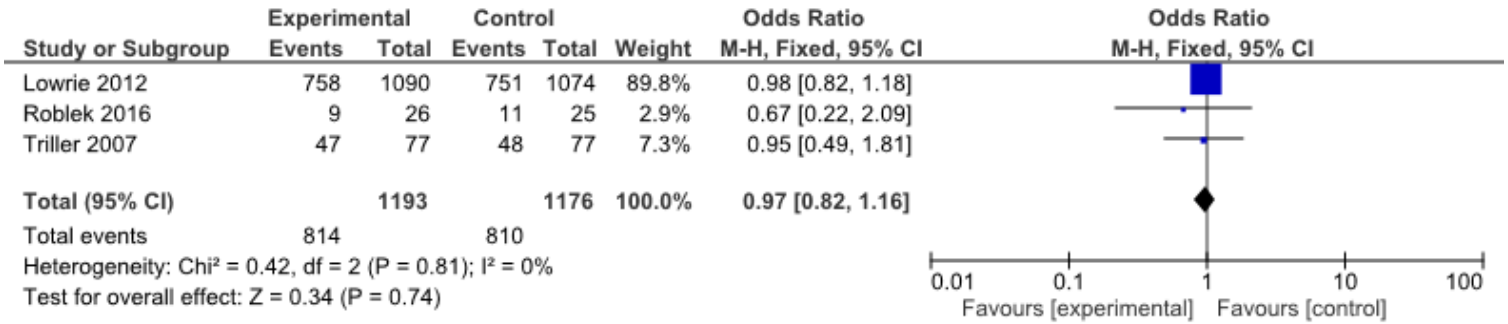

Figure 4.12. Forest plot of composite endpoint (fixed-effects model).

CI, confidence interval; OR: odds ratio. Test of overall effect (p) <.05 is considered significant. I^2 indicates heterogeneity in included studies. The diamond represents the overall effect estimate. The overall effect will be significant if the diamond is not touching the vertical line of no effect.

Table 4.3

Summary of secondary outcomes.

Study	Medication adherence (compliance)	P value
Goodyer (1995)	Mean compliance score after the intervention was 93% (SD, 11.7) for the intervention group, and 51% (SD 31.5) for usual care.	<.001
Varma (1999)	A total of 10 patients were compliant and 3 were noncompliant in the intervention whereas 3 were compliant and 7 noncompliant in the usual care group.	<.05
Sadik (2005)	The number of patients having self -reported compliance for prescribed medication was 85 for treatment and 35 for usual care group. Similarly, the compliance for lifestyle adjustment was 75 for treatment group and 29 for usual care group at 12 months.	<.05
Gwadry 2005	Noncompliance for intervention and usual care group for different medications class; Angiotensin converting enzyme inhibitors (ACEIs): 13% (4.1-22.5), 17% (7.2-26.8); β-blockers: 13% (1.8-24.5), 15% (2.7-26.7); digoxin: 15% (2.9-25.7), 19% (3.5-27.8); and diuretics 23% (11.1-35.8), 23% (10.7-35.1).	NS
Lopez 2006	The degree of compliance was 85% vs. 73.9% in the intervention and usual care group respectively at 12 months.	NS
Bouvy 2003	The intervention group had 140/7656 days without diuretics vs. 337/6196 for usual care, relative risk (0.33, 0.24-0.38, CI 95%).	-
Tsuyuki (2004)	Non-significant improvement of ACE inhibitor adherence over the 6 months; 83.5 ±29% in the intervention group vs 86.2 ±29% in the usual care group.	NS
Holland (2007)	Non-significant improvement of drug adherence in the intervention group (adjusted mean difference=0.12 units, −0.48 to 0.73 units).	.68
Murray (2007)	Non-significant improvement on drug adherence during the 9-month intervention period; 67.9% and 78.8% in the usual care and intervention groups, respectively (difference, 10.9 percentage points [95% CI, 5.0 to 16.7 percentage points]). However, this effect disappeared in the 3-month post intervention follow-up period; adherence was 66.7% and 70.6% for usual care and intervention group respectively (difference, 3.9 percentage points [CI, 5.9 to 6.5 percentage points]).	NS
Eggink (2010)	No difference on drug adherence; 79.5% in the usual care group vs 78.0% in the intervention group (RR: 1.07 (95% CI 0.47–2.44)).	NS

Study	Heart failure knowledge	P value
Gwardy-Sridhar (2005)	The change in knowledge score was 2.24 ± 2.46 (95% CI 1.63-2.85) in the intervention and 1.38 ± 2.16 (95% CI 0.85-1.91) in the usual care group, respectively.	<.02 (immediate), and 0.05 (over 1 year)
Korajkic 2011	Significant improvement in HF knowledge; 94% intervention vs 71% usual care.	.01
Health care costs		
Stewart 1998	The mean cost of hospital-based care was ($3200 [95 % CI, $ 1800–$4600]) for intervention group and ($5400 [95 % CI, $3200–$6800]) for usual care group The cost for community-based health care was $620 per patient to intervention group and $680 per patient for control group. The costs were estimated in Australian dollars.	NS
Tsuyuki et al 2004	Reduction in cost of care for intervention group (2,531 Canadian dollar less per patient). This amount is equivalent to current estimate of $1902.	NS
Murray et al 2007	The annual direct health care costs for intervention group was lower by $2960 (CI, $-7603 to $1338) per patient.	NS
Triller et al 2007	Non-significant reduction in cost (total health system cost, hospital costs, and home care agency cost)	NS
Self-care		
Holland et al 2007	Non-significant improvements of self-care score in the intervention group 26.58 vs 28.27 (low scores imply better self-care behaviour).	NS

CI, confidence interval; NS, Non-significant level of significant.

4.1.5 Risk of bias across studies

There are no small studies on the bottom right of the funnel plot of HF hospitalizations so that the typical inverted funnel-like shape was not observed indicating the presence of publication bias (see Figure 4.13). The studies in the funnel plot for all-cause hospitalizations are more closely clustered and equally distributed (see Figure 4.14). A degree of asymmetry and absence of small studies on the bottom right side of the plot was also observed in funnel plot of all-cause mortality (see Figure 4.15).

4.1.6 GRADE assessment of quality of evidence

The GRADE summary table (see Table 4.4) illustrates the summary of each outcome along with a description of the quality of the evidence. The grading of each outcome is based on potential risk of bias, impression, confidence interval, and number of studies measuring that particular outcome. We found moderate-quality evidence for significant reduction of HF hospitalizations, all-cause hospitalizations and overall improvement in medication adherence. Significant improvement in HF knowledge and non-significant reduction in health care costs were also of medium quality. Non-significant reduction in HF mortality, all-cause mortality and composite endpoint were of low quality. The evidence for non-significant improvement in self-care was found to be of very low quality.

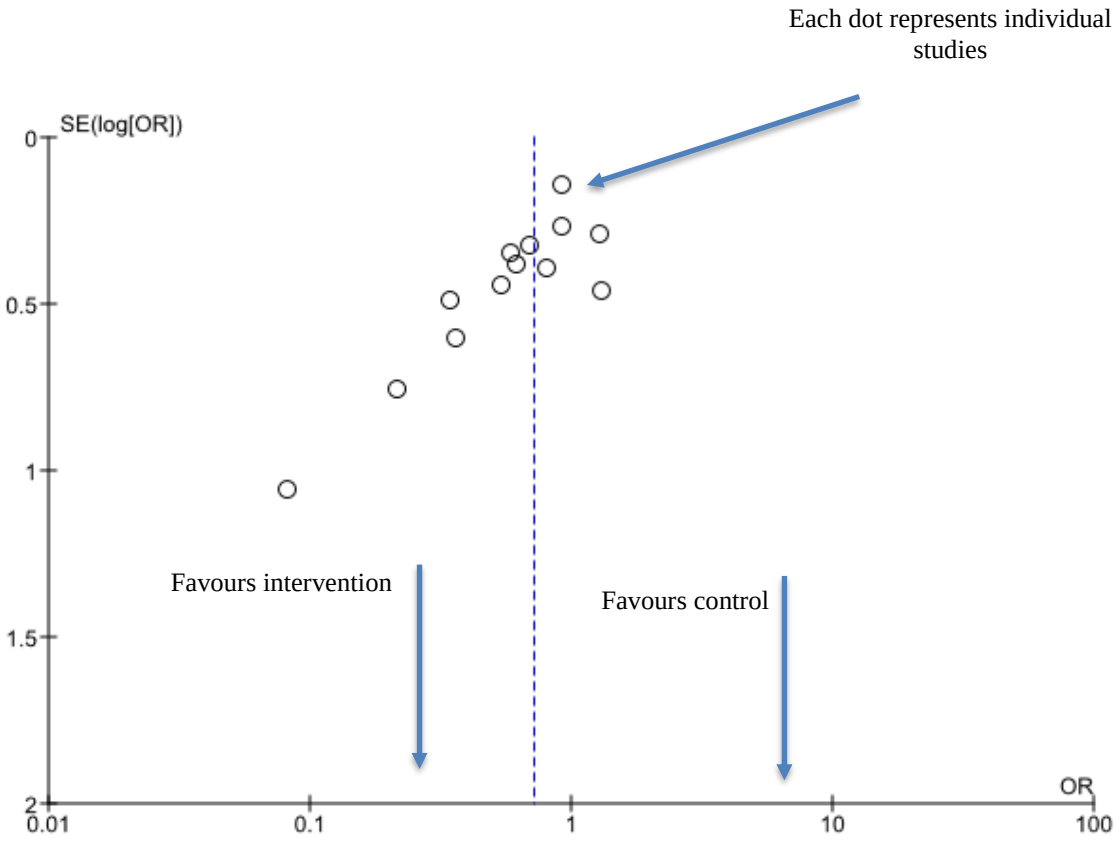

Figure 4.13. Funnel plot of heart failure hospitalisations.

The log value of effect size is in X-axis (odds ratio, OR) and log value of the standard error of the effect size (OR) is in Y-axis. An asymmetrical inverted funnel plot is a visual indication of the absence of publication bias. The effect from small studies is scattered around the bottom. The scattering dots are skewed in presence of publication bias.

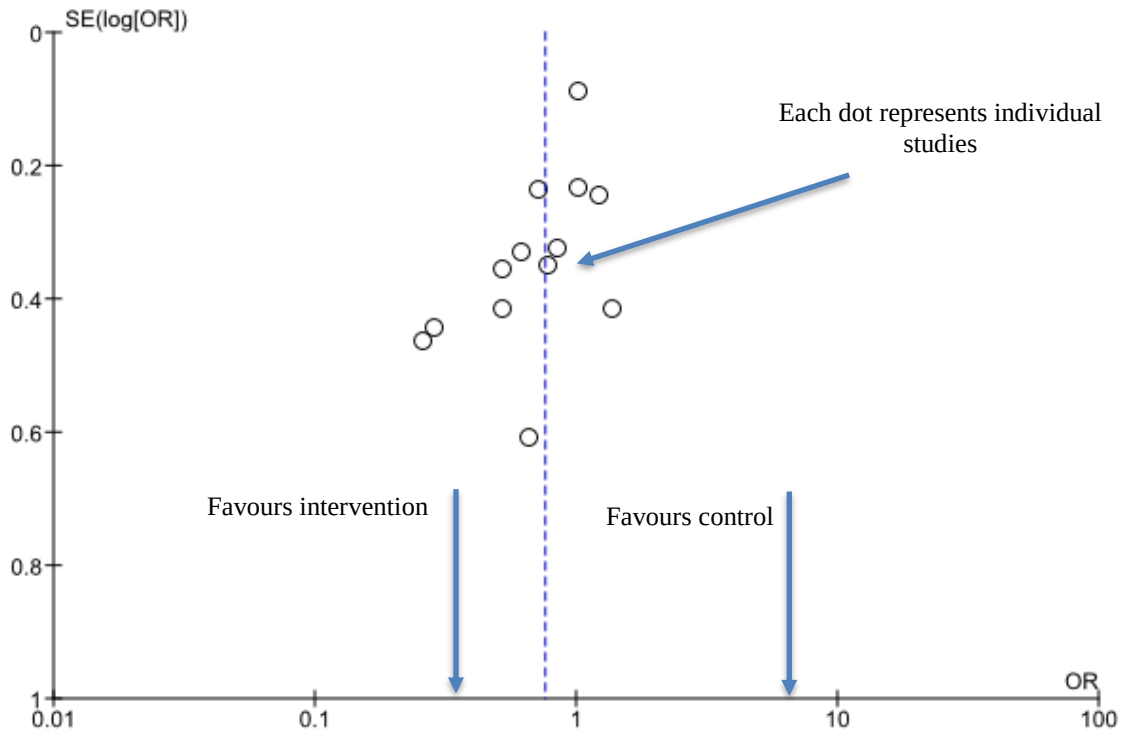

Figure 4.14. Funnel plot of all-cause hospitalisations.

The log value of effect size is in X-axis (odds ratio, OR) and log value of the standard error of the effect size (OR) is in Y-axis. An asymmetrical inverted funnel plot is a visual indication of the absence of publication bias. The effect from small studies is scattered around the bottom. The scattering dots are skewed in presence of publication bias.

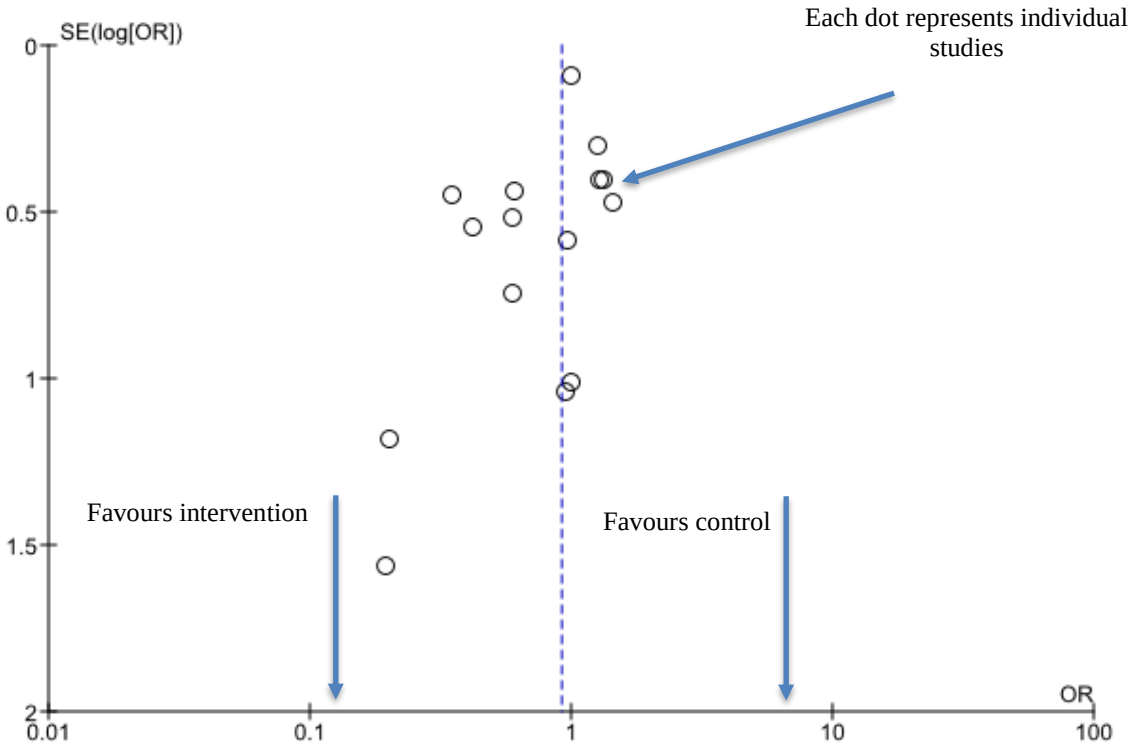

Figure 4.15. Funnel plot of all-cause mortality.

The log value of effect size is in X-axis (odds ratio, OR) and log value of the standard error of the effect size (OR) is in Y-axis. An asymmetrical inverted funnel plot is a visual indication of the absence of publication bias. The effect from small studies is scattered around the bottom. The scattering dots are skewed in presence of publication bias.

Table 4.4

GRADE summary table.

Impact of pharmacist-involved multidisciplinary management of heart failure on different clinical outcomes			
Patient or population: People with heart failure **Setting:** Outpatient clinics, primary care centres, hospitals, home visits and community pharmacies **Intervention:** Pharmacist-involved multidisciplinary team **Comparison:** Usual care			
Outcomes	**Observed effect**	**Number of participants (studies)**	**Quality of evidence (GRADE)**
HF hospitalisations	OR, 0.72 (0.55–0.93)	4211 (13)	Moderate [1,]
HF mortality	OR, 1.56 (0.60–4.03)	2345 (2)	Low [2]
All-cause hospitalisations	OR, 0.76 (O.60–0.96)	4241 (13)	Low [1, 3]
All-cause mortality	OR, 0.92 (0.74–1.13)	4366 (15)	Low [1, 3]
Medication adherence (compliance)	Overall trend was an improvement	1779 10)	Moderate [1, 4]
HF knowledge	Significant improvement. (P<0.05)	204 (2)	Moderate [5]
Health care costs	Non-significant reduction	841 (4)	Moderate [1]
Self-care	Non-significant improvement	293 (1)	Very Low [6,7]
Composite endpoint	OR, 0.97 (0.82–1.16)	2369 (3)	Low [1, 8]

GRADE: Grading of Recommendations Assessment, Development and Evaluation**; OR:** Odds ratio; **HF**, Heart failure; Composite endpoint (all-cause hospitalizations, all-cause mortality)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by two levels due to unclear and high risk of selection and detection bias in included RCTs, and high number of unpowered studies.

[2] Downgraded by 2 levels due to high imprecision attributed to confidence interval, and only two studies have measured the outcome.

3 Downgraded by 2 levels due to high imprecision attributed to confidence interval, and high number of unpowered studies.

[4] Downgraded by 1 level due to high impression. Out of ten included trials to measure the outcome, only three were sufficiently powered. Although three trials improved the outcome significantly, only one of them was sufficiently powered.

[5] Downgraded by 1 level due to high impression. Only two studies have measured this outcome, and both included studies were not sufficiently powered.

[6] Downgraded by 1 level due to high risk of detection bias in the included RCT.

[7] Downgraded by 2 levels due to high impression. Only one study has measured the outcome. The study is not sufficiently powered.

[8] Downgraded by 2 levels due to high imprecision attributed to confidence interval, and only two studies have measured the outcome.

4.2 Results of Retrospective Cohort Study-Phase II

4.2.1 Participants

A total of 1184 patients were eligible to participate; 723 patients were in the MACS clinic and 461 patients were in the GCHFS clinic (see Figure 4.16). After excluding 74 patients in the MACS clinic and 54 from the GCHFS clinic who did not have echocardiography, the remaining 651 patients in the MACS clinic and 407 patients in the GCHFS clinic were included to compare their demographics and clinical characteristics. To compare their demographics and clinical characteristics, patients were stratified into three groups: HFrEF (EF < 40%), HFmrEF (EF = 40–49) and HFpEF (EF > 50); however, EF < 50% for HFrEF and EF ≥ 50 for HFpEF were used for the evaluation of EBT use.

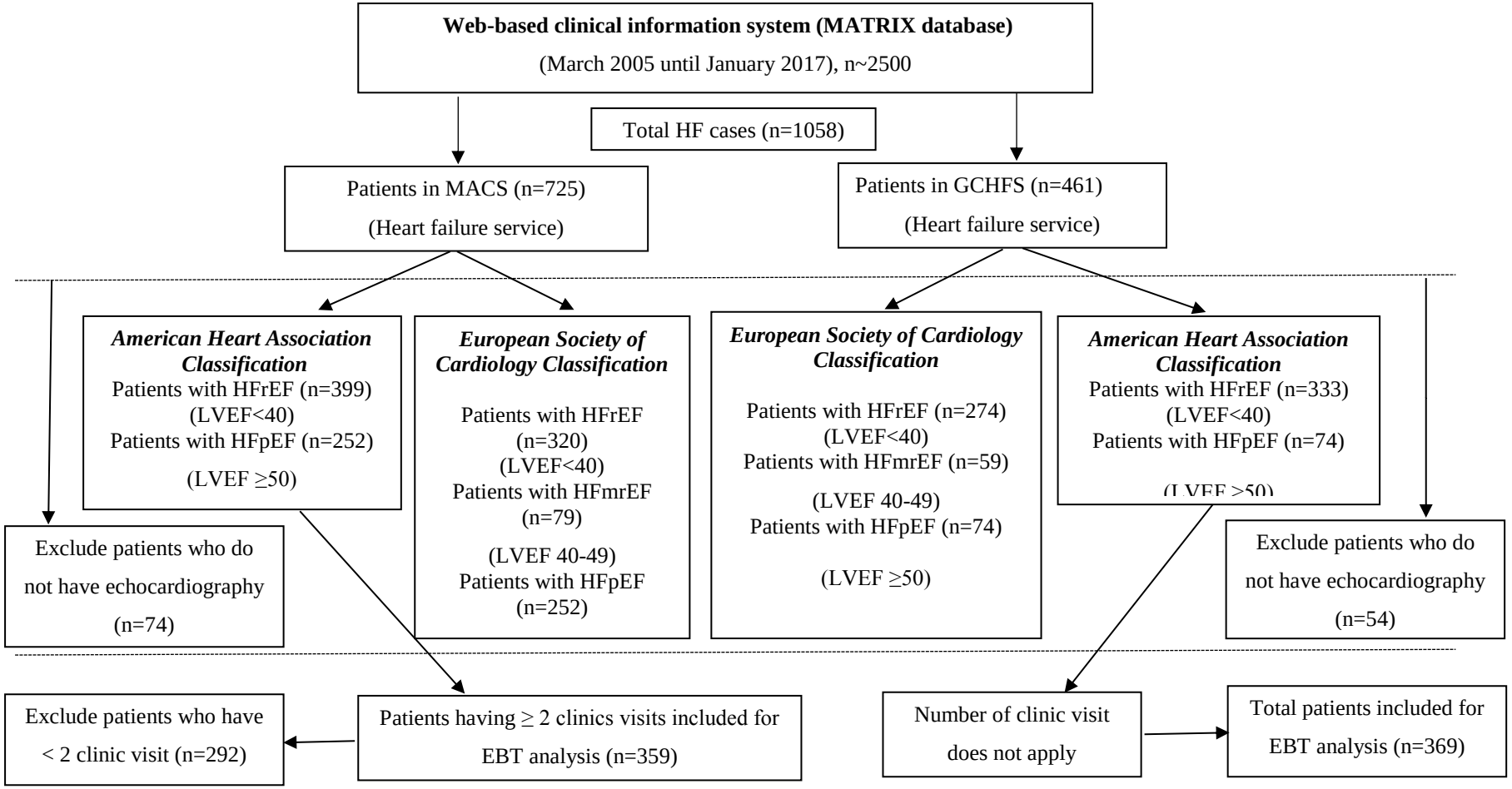

Figure 4.16. STROBE flow chart of the study.

MATRIX: hospital database; HF: Heart Failure; MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; LVEF: left ventricular ejection fraction; EBT: evidence-based therapies; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction.

4.2.2 Descriptive data

a) Comparison of the differences in demographics, clinical characteristics and comorbidities by clinics

Demographic and clinical characteristics of HF patients are illustrated in Table 4.5. MACS clinic patients were older (M = 77 ± 11.5 years; $p < .001$), less likely to be male (50.3 v. 66.6; $p < .001$), had similar mean weights and had a significantly high SBP (M = 125 ± 23 mm Hg) ($p < .001$) and DBP (M = 68.1 ± 12.6 mm Hg; $p < .05$) compared to GCHFS clinic patients. There was also a significant difference ($p < .001$) in the age group sizes between the two clinics, particularly for those aged >80 years, with the MACS clinic having a higher prevalence of older patients (45% v. 27.3%). However, heart rates were similar between the two clinics (71.2 ± 16 mm Hg v. 72.2 ± 14 mm Hg; MACS clinic v. GCHFS clinic). The number of medications used was significantly higher in MACS patients (M = 11.25 ± 4 v. 9.5 ± 3.5) ($p < .001$) compared to GCHFS patients. There also exist significance differences ($p < .001$) in polypharmacy (5–9 drugs) and hyperpolypharmacy (≥10 drugs). The incidence of polypharmacy and hyperpolypharmacy was 32% v. 48.3% and 64.4% v. 47% for the MACS and GCHFS clinics, respectively.

Among the risk factors, the prevalence for history of falls (8% v. 0.4%) and Vitamin D deficiency (4.1% v. 0.4%) were significantly higher ($p < .001$) for MACS clinic patients compared to GCHFS clinic patients, respectively. There was a non-significant difference between serum creatinine, haemoglobin and mean cell volume between the two clinics. The prevalence of major comorbidities, including hypertension (71% v. 55.5%), diabetes (45.4% v. 35%), osteoarthritis (24.2% v. 12.1%), chronic obstructive pulmonary disease

(27.5% v. 15.4%), anaemia (22.5% v. 14%), osteoporosis (16.2% v. 5.4%), cognitive impairment (11% v. 2%) and depression/anxiety (19.2% v. 13%) was significantly more common in MACS patients compared to GCHFS patients, respectively (see Table 4.6). However, there was no difference in prevalence of ischemic heart disease (56.2% v. 55.1%), AF (47.3% v. 45%), hyperlipidaemia (48.4% v. 50%), chronic renal failure (31% v. 29.5%), solid cancer (15.1% v. 14.1%) and gout (17.3% v. 14%) between the two clinics. The proportion of patients with comorbidities (≥3 = 92% v. 82% and ≥4 = 82% v. 65.5%) was statistically significant ($p < .001$) and the prevalence was much higher in the MACS patients compared to the GCHFS patients.

Table 4.5

Comparison of demographics and clinical characteristics between two clinics.

Demographics and clinical characteristics	**Total (n=1184)**	**MACS (n=723)**	**GCHFS (n=461)**	**P-value**
Age (years, mean ±SD)	73.7±12.9	77.1±11.5	70.3±14.2	<.001
Age group (years)				
(<40)	26 (2.2)	10 (1.4)	16 (3.5)	
(40-50)	49 (4.1)	13 (1.8)	36 (7.8)	
(50-60)	98 (8.3)	41 (5.7)	57 (12.4)	
(60-70)	180 (15.2)	92 (12.7)	88 (19.1)	<.001
(70-80)	380 (32.1)	242 (33.5)	138 (29.9)	
(>80)	451 (38.1)	325 (45)	126 (27.3)	
Gender, n (%)				
Male	671 (56.7)	364 (50.3)	307 (66.6)	<.001
Weight (Kg, mean ±SD) (n=934)	79.9±20.25	78.6±20.2	81.2±20.3	.064
Systolic blood pressure (mmHg, mean ±SD) (n=983)	120±22.5	125±23	115.4±20.1	<.001
Diastolic blood pressure (mmHg, mean ±SD) (n=982)	67±12.5	68.1±12.6	66±12	.011
Heart rate (beats/min, mean ±SD) (n=949)	71.5±15	71.2±16	72.2±14	.342
Number of medications used, mean ±SD (n=1036)	10.4±3.7	11.25±4	9.5±3.5	<.001
Non-polypharmacy (0–4 drugs)	44 (4.2)	21 (3.6)	23 (5)	
Polypharmacy (5–9 drugs)	406 (39.2)	184 (31.9)	222 (48.3)	<.001
Hyper polypharmacy (≥10 drugs)	586 (56.6)	371 (64.4)	215 (46.7)	
Risk factors n (%)				
Alcohol abuse	49 (4.1)	31 (4.3)	18 (3.9)	.881
History of falls	59 (5)	57 (7.9)	2 (0.4)	<.001
Vitamin D deficiency	32 (2.7)	30 (4.1)	2 (0.4)	<.001
Biochemical parameters				
Serum creatinine (mg/dL, mean ±SD) (n=704)	133±72	126±66.4	141.4±77	.234
Haemoglobin (g/L mean ±SD) (n=660)	122±21	122.1±19	121.6±23	.9
MCV (fL/red cells, mean ±SD) (n=659)	88±8	89.4±9	87±7.4	.233

The mean was compared using an independent sample t test. Chi square statistics for categorical variables; age group, gender, polypharmacy and risk factors. $p<.05$ was considered significant.

MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; SD: standard deviation; MCV: mean cell volume.

Table 4.6

Comparison of comorbidities between two clinics.

Comorbidities	**Total (n=1056)**	**MACS (n=723)**	**GCHFS (n=461)**	**P-value**
Hypertension	769 (64.9)	513 (71)	256 (55.5)	<.001
Ischemic heart disease	660 (55.7)	406 (56.2)	254 (55.1)	.764
Atrial fibrillation	549 (46.4)	342 (47.3)	207 (44.9)	.437
Hyperlipidaemia	578 (48.8)	350 (48.4)	228 (49.5)	.766
Diabetes	489 (41.3)	328 (45.4)	161 (34.9)	<.001
Gastroesophageal reflux disease	270 (22.8)	187 (25.9)	83 (18)	.002
Osteoarthritis	231 (19.5)	175 (24.2)	56 (12.1)	<.001
Chronic Renal failure	359 (30.3)	223 (30.8)	136 (29.5)	.650
Chronic obstructive pulmonary disease	270 (22.8)	199 (27.5)	71 (15.4)	<.001
Anaemia	226 (19.1)	163 (22.5)	63 (13.7)	<.001
Depression/Anxiety	198 (16.7)	139 (19.2)	59 (12.8)	.004
Osteoporosis	142 (12)	117 (16.2)	25 (5.4)	<.001
Any cardiovascular accident	197 (16.6)	140 (19.4)	57 (12.4)	.002
All ophthalmological conditions	124 (10.5)	87 (12)	37 (8)	.032
Peripheral vascular disease	160 (13.5)	114 (15.8)	46 (10)	.005
Any solid cancer	176 (14.9)	109 (15.1)	67 (14.5)	.867
Gout	188 (15.9)	125 (17.3)	63 (13.7)	.103
Asthma	108 (9.1)	80 (11.1)	28 (6.1)	.004
Hypo/Hyperthyroidism	144 (12.2)	102 (14.1)	42 (9.1)	.011
Thromboembolism	87 (8.2)	65 (9)	22 (4.8)	.006
Cognitive impairment	87 (7.3)	78 (10.8)	9 (2)	<.001
Obstructive sleep apnoea	126 (10.6)	71 (9.8)	55 (11.9)	.288
Benign prostatic hyperplasia	75 (6.3)	49 (6.8)	26 (5.6)	.46
Peptic ulcer disease	72 (6.1)	48 (6.6)	24 (5.2)	.383
Chronic liver disease	30 (2.5)	25 (3.5)	5 (1.1)	.013
Proportion of patients with				
≥3 comorbidities	1035 (87.4)	665 (92)	370 (80.3)	<.001
≥4 comorbidities	895 (75.6)	593 (82)	302 (65.5)	<.001

The mean was compared using independent sample t test. Chi square statistics was used for categorical variables; comorbidities. P<.05 was considered significant. MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; SD: standard deviation.

b) Comparison of the differences in demographics, clinical characteristics and comorbidities by ejection fractions.

The EF value is <40% for HFrEF, 40–49% for HFmrEF and ≥50% for HFpEF. A comparison of the same demographics and clinical characteristics among the patients in the two clinics (MACS and GCHFS) stratified by EF was also performed (see Table 4.7). For the MACS and GCHFS clinics, respectively, 77.3% v. 23% patients had HFpEF, 57.2% v. 43% had HFmrEF and 54% v. 46% had HFrEF. The prevalence of HFpEF, HFmrEF and HFrEF was 31%, 13% and 56%, respectively. A significant difference was observed in SBP (132.3 ± 22.2 mm Hg v. 124.4 ± 20.2 mm Hg) ($p < .05$) and DBP (69.3 ± 13 mm Hg v. 64 ± 11.6 mm Hg) ($p < .01$) among HFpEF patients between the MACS and GCHFS clinics, respectively. Similarly, in the MACS clinic compared to the GCHFS clinic, a significantly higher number of patients had a history of falls (9.15% v. 1.4%; $p < .05$) and a higher prevalence of hypertension (84.5% v. 73%; $p < .05$), COPD (29.4% v. 11%; $p < .05$) and osteoporosis (21% v. 9.5%; $p < .05$). Other demographic characteristics and comorbidities were similar for HFpEF patients in both clinics.

Interestingly, a statistically significant difference ($p < .05$) was observed in the number of medications used for HFmrEF patients (M = 12 ± 5 v. 10 ± 3.6) in the MACS and GCHFS clinic patients. All other demographic and clinical characteristics were similar for HFmrEF patients between the two clinics. Further, a significantly lower number of patients had ischemic heart diseases (56% v. 75%) in the MACS clinic compared to in the GCHFS clinic. A significantly higher prevalence of comorbidities, including GORD (27.3% v. 10.2%), COPD (31.2% v.

15.3%), osteoporosis (18.2% v. 5.1%) and gout (22.1% v. 8.5%) were present in the MACS clinic compared to in the GCHFS clinic.

Of note, significant differences in demographics and clinical characteristics between the two cohorts were found among HFrEF patients. In the MACS clinic compared to the GCHFS clinic, patients were older (74.39 ± 12.5 years v. 67.1 ± 14.4 years) ($p < .001$) and less likely to be male (57.5% v. 72%) ($p < .001$); they also had high SBP (M = 119.5 ± 22.4 mm Hg v. 112.3 ± 18.7 mm Hg) ($p < .001$) and were under polypharmacy (mean number of medications used: 11 ± 4 v. 9.1 ± 3.3) ($p < .001$). A significantly higher number ($p < .01$) of patients in the MACS clinic had low HR (<60) compared to in the GCHFS clinic (28.3% v. 8.2%). Similarly, more patients in the MACS clinic had low SBP (<115) compared to in the GCHFS clinic, although this did not reach the significance level. Further, 6.6% patients in the MACS clinic had low postural BP (≥20), but no patient in the GCHFS clinic had this.

For HFrEF patients, there was a significantly higher prevalence of comorbidities in the MACS clinic compared to in the GCHFS clinic: hypertension (61% v. 49%; $p < .01$), atrial fibrillation (48% v. 39.4%; $p < .05$, diabetes (45.3% v. 34.3%; $p < .01$), osteoarthritis (19.4% v. 9.5%; $p < .01$), CRF (35% v. 27%; $p<.05$), COPD (26.3% v. 16%; $p < .01$), anaemia (28.4% v. 9.1%; $p < .01$), depression anxiety (20% v. 11.3%;$p < .01$), any kind of cardiovascular accident (19.1% v. 13%; $p < .05$) and osteoporosis (12% v. 4%; $p < .001$). The proportion of patients with ≥3 (90% v. 74%; $p < .001$) and ≥4 (79.1% v. 58.4%) comorbidities was statistically significant ($p < .001$) and much higher in MACS patients compared to those in the HFrEF category (see Table 4.8).

A significantly higher percentage of patients had low HR (<60) in the MACS clinic compared to those in the GCHFS clinic (28.3% v. 8.2%; $p < .01$). Similarly, more patients in the MACS clinic had low SBP (<115) (33.2% v. 14%) with no significant group difference. Low postural BP was observed in 6.6% (11) patients in the MACS clinic; however, this was not observed in the GCHFS clinic patients (see Table 4.9).

Table 4.7

Comparison of demographics and clinical characteristics by ejection fraction in two clinics.

Demographics and clinical characteristics	**Preserved (n=326)**			**Mid-range (n=138)**			**Reduced (n=594)**		
	Total (n=326)	MACS (n=252)	GCHFS (n=74)	Total (n=138)	MACS (n=79)	GCHFS (n=59)	Total (n=594)	MACS (n=320)	GCHFS (n=274)
Age (years), mean ±SD	79±10	79.4±9.3	78.5±10	76.5±11.25	78±11	75±11.5	71±13.4	74.4±12.5	67.1±14.4 ***
Age group (years)									
(<40)	2 (0.6)	2 (0.8)	-	1 (0.7)	-	1 (1.7)	18 (3)	7 (2.2)	11 (4)
(40-50)	3 (0.9)	2 (0.8)	1 (1.4)	5 (3.7)	3 (3.9)	2 (3.4)	35 (6)	6 (1.9)	29 (11)
(50-60)	9 (2.8)	5 (2)	4 (5.4)	6 (4.4)	3 (3.9)	3 (5.1)	76 (13)	29 (9.1)	47 (17.2)
(60-70)	36 (11)	27 (10.7)	9 (12.2)	23 (17)	11 (14.3)	12 (20.3)	109 (18.4)	50 (16)	59 (21.5)
(70-80)	108 (33.1)	85 (33.7)	23 (31.1)	45 (33.1)	26 (33.8)	19 (32.2)	186 (31.3)	110 (34.4)	76 (28) ***
(>80)	168 (51.5)	131 (52)	37 (50)	56 (41.2)	34 (44.2)	22 (37.3)	170 (29)	118 (37)	52 (19)
Gender									
Male, n (%)	140 (43)	103 (41)	37 (50)	80 (59)	43 (56)	37 (63)	381 (64.1)	184 (57.5)	197 (72) ***
Weight (Kg, mean ±SD) (n=274)	81±18.6	80.4±20	81±17.3	80.2±23.4	78.4±22.4	82±24.4	80±20.25	78.5±20.3	81.2±20.2
Systolic blood pressure (mmHg, mean ±SD)	128.3±21.2	132.3±22.2	124.4±20.2 *	122.2±19.75	125±20	119.4±19.5	116±20.5	119.5±22.4	112.3±18.7 ***
Diastolic blood pressure (mmHg, mean ±SD)	66.6±12.3	69.3±13	64±11.6 **	67.5±12	69±12	66±12	67.1±12.35	67.5±12.4	66.7±12.3
Heart rate (beats/min, mean ±SD)	70.7±16	70.6±15.6	70.8±16.2	70.1±13.6	70±14.3	70.2±13	73±15.25	71.7±16.7	73.5±13.8
Number of medications used (mean ±SD)	11.35±4	11.4±4	11.3±4	11±4.3	12±5	10±3.6 *	10±3.65	11±4	9.1±3.3 ***
Non-polypharmacy (0–4 drugs),	6 (2.1)	5 (2.4)	1 (1.4)	6 (4.7)	4 (5.8)	2 (3.4)	25 (4.7)	10 (3.9)	15 (5.5)
Polypharmacy (5–9 drugs)	85 (30)	61 (29.2)	24 (32.4)	49 (38.3)	20 (29)	29 (49.2)	229 (43)	91 (35)	138 (50.5) ***
Hyper polypharmacy (≥10 drugs)	192 (68)	143 (68.4)	49 (66.2)	73 (57)	45 (65.2)	28 (47.5)	281 (52.5)	161 (61.5)	120 (44)
Risk factors									
Alcohol abuse history	14 (4.3)	11 (4.4)	3 (4.1)	7 (5.1)	5 (6.5)	2 (3.4)	25 (4.2)	14 (4.4)	11 (4)
History of falls	24 (7.4)	23 (9.1)	1 (1.4)*	5 (3.7)	5 (6.5)	-	23 (4)	22 (7)	1 (0.4)***
Vitamin D deficiency	13 (4)	12 (4.8)	1 (1.4)	6 (4.4)	6 (7.8)	-	11 (2)	10 (3.1)	1 (0.4)*
Biochemical parameters									
Serum creatinine (mg/dL, mean ±SD)	141±73.5	120.2±64	161.2±83	128.2±54	128.2±54	-	135.5±68	126±59	145.4±77
Haemoglobin (g/L mean ±SD)	119±24	119.3±18.7	118.4±28.7	120.5±18	120.5±18	-	125±21	125.5±19	124±23.1
MCV (fL/red cells, mean ±SD)	88±9.5	89±11.5	86.3±7.5	89±8	89±8	-	89±8	89.5±7.4	88±8.1

MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service. The proportion was comparred by Z test in EpiTools, and mean comparison using independent sample t test were performed for MACS and GCHFS clinics. P<.05 is considered significant. * p<.05, **p <.01, *** p<.001.

Table 4.8

Comparison of comorbidities between clinics stratified by ejection fractions.

Comorbidities (%)	**Preserved (n=326)**			**Mid-range (n=138)**			**Reduced (n=594)**		
	Total (n=326)	MACS (n=252)	GCHFS (n=74)	Total (n=138)	MACS (n=79)	GCHFS (n=59)	Total (n=594)	MACS (n=320)	GCHFS (n=274)
Hypertension	267 (82)	213 (84.5)	54 (73) *	94 (69.1)	56 (73)	38 (64.4)	329 (55.4)	195 (61)	134 (49) **
Ischemic heart disease	167 (51.2)	128 (51)	39 (53)	87 (64)	43 (56)	44 (75) *	338 (57)	192 (60)	146 (53.3)
Atrial fibrillation	172 (53)	127 (50.4)	45 (61)	64 (47.1)	37 (48.1)	27 (46)	261 (44)	153 (48)	108 (39.4) *
Hyperlipidaemia	165 (51)	124 (49.2)	41 (55.4)	79 (58.1)	41 (53.2)	38 (64.4)	285 (48)	157 (49.1)	128 (47)
Diabetes	153 (47)	121 (48)	32 (43.2)	58 (43)	37 (48.1)	21 (36)	239 (40.2)	145 (45.3)	94 (34.3) **
Gastroesophageal reflux disease	105 (32.2)	82 (32.5)	23 (31.1)	27 (20)	21 (27.3)	6 (10.2) *	116 (19.5)	71 (22.2)	45 (16.4)
Osteoarthritis	94 (29)	79 (31.3)	15 (20.3)	29 (21.3)	17 (22.1)	12 (20.3)	88 (15)	62 (19.4)	26 (9.5) **
Chronic Renal failure	101 (31)	74 (29.4)	27 (36.5)	42 (31)	21 (27.3)	21 (36)	185 (31.1)	111 (35)	74 (27)*
Chronic obstructive pulmonary disease	82 (25.1)	74 (29.4)	8 (11) **	33 (24.3)	24 (31.2)	9 (15.3) *	127 (21.4)	84 (26.3)	43 (16) **
Anaemia	91 (28)	70 (28)	21 (28.4)	29 (21.3)	19 (25)	10 (17)	84 (14)	59 (18.4)	25 (9.1) **
Depression/Anxiety	62 (19)	53 (21)	9 (12.2)	19 (14)	10 (13)	9 (15.3)	95 (16)	64 (20)	31 (11.3) **
Osteoporosis	59 (18.1)	52 (21)	7 (9.5) *	17 (12.5)	14 (18.2)	3 (5.1) *	47 (8)	37 (12)	10 (4) ***
Any cardiovascular accident	59 (18.1)	50 (20)	9 (12.2)	25 (18.4)	18 (23.4)	7 (12)	96 (16)	61 (19.1)	35 (13) *
All ophthalmological conditions	51 (16)	44 (17.5)	7 (9.5)	16 (12)	10 (13)	6 (10.2)	40 (7)	21 (7)	19 (7)
Peripheral vascular disease	53 (16.3)	43 (17.1)	10 (13.5)	19 (14)	14 (18.2)	5 (8.5)	72 (12.1)	45 (14.1)	27 (10)
Any solid cancer	50 (15.3)	40 (16)	10 (13.5)	22 (16.2)	12 (16)	10 (17)	83 (14)	41 (13)	42 (15.3)
Gout	48 (15)	36 (14.3)	12 (16.2)	22 (16.2)	17 (22.1)	5 (8.5) *	104 (17.5)	64 (20)	40 (15)
Asthma	40 (12.3)	33 (13.1)	7 (9.5)	13 (10)	10 (13)	3 (5.1)	41 (7)	25 (8)	16 (6)
Hypo/Hyperthyroidism	40 (12.3)	32 (13)	8 (11)	14 (10.3)	11 (14.3)	3 (5.1)	75 (13)	48 (15)	27 (10)
Thromboembolism	32 (10)	26 (10.3)	6 (8.1)	7 (5.1)	5 (6.5)	2 (3.4)	40 (7)	27 (8.4)	13 (5)
Cognitive impairment	25 (8)	22 (8.7)	3 (4.1)	10 (7.4)	10 (13)	-	41 (7)	37 (12)	4 (1.5) ***

The proportion comparison by Z test in EpiTools, and mean comparison using independent sample t test were performed for MACS and GCHFS clinics. P<.05 is considered significant. * p<.05, **p <.01, *** p<.001. MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service.

Comorbidities (%)	**Preserved (n=326)**			**Mid-range (n=138)**			**Reduced (n=594)**		
	Total (n=326)	MACS (n=252)	GCHFS (n=74)	Total (n=138)	MACS (n=79)	GCHFS (n=59)	Total (n=594)	MACS (n=320)	GCHFS (n=274)
Obstructive sleep apnoea	36 (11)	20 (8)	16 (22) ****	17 (12.5)	10 (13)	7 (12)	68 (11.4)	38 (12)	30 (11)
Benign prostatic hyperplasia	19 (6)	17 (7)	2 (3)	8 (6)	3 (4)	5 (8.5)	41 (7)	25 (8)	16 (6)
Peptic ulcer disease	24 (7.4)	17 (7)	7 (9.5)	9 (7)	7 (9.1)	2 (3.4)	34 (6)	22 (7)	12 (4.4)
Chronic liver disease	12 (4)	12 (4.8)	-	4 (3)	4 (5.2)	-	13 (2.2)	9 (3)	4 (1.5)
Proportion of patients with									
≥3 comorbidities	310 (95.1)	239 (95)	71 (96)	126 (93)	73 (95)	53 (90)	488 (82.1)	286 (90)	202 (74) ***
≥4 comorbidities	288 (88.3)	222 (88.1)	66 (89.2)	105 (77.2)	63 (82)	42 (71.2)	413 (69.5)	253 (79.1)	160 (58.4) ***

The proportion comparison by Z test in EpiTools, and mean comparison using independent sample t test were performed for MACS and GCHFS clinics. p<.05 is considered significant. * p<.05, **P <.01, *** p<.001.

MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service.

Table 4.9

Comparison of low HR, standing SBP, and postural BP between two clinics in HFpEF.

	Total (n=239)	**MACS (n=166)**	**GCHFS (n=73)**	**P-value**
Low heart rate (HR<60)	53 (22.2)	47 (28.3)	6 (8.2)	.001
Low standing SBP (BP<115)	47 (20)	37 (22.3)	10 (14)	.124
Low postural BP (postural drop≥20)	11 (4.6)	11 (6.6)	-	-

HR: heart rate; SBP: systolic blood pressure; BP: blood pressure; HFpEF: heart failure with preserved ejection fraction; MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service. Chi square statistics was used to compare group difference. P<0.05 is considered significant.

c) Comparison of the use of medications between clinics with heart failure with reduced ejection fraction patients (EF<50)

A total of 50.3% and 62% of patients in the MACS and GCHFS clinics received ACEIs without any contraindications. However, 27% of patients in the MACS and 30% in the GCHFS clinics did not receive ACEIs without any contraindications. The rate of appropriate use of ACEIs was similar in the MACS clinic compared to in the GCHFS clinic (65.1% v. 67.5%) (see Table 4.10). The rate of appropriate use of ACEIs was calculated as a percentage as follows: as the number of patients who received the ACEIs without any contraindications, divided by the denominator, which is the number of patients who should have actually received the ACEIs. There was a significant difference in contraindications for ACEI use in the MACS clinic patients ($p < .001$) compared with the GCHFS clinic patients (22.8% v. 8.4%).

The maximum tolerated dose was calculated as the dose given as a percentage of the target dose. A total of 33.2% and 44% of patients in the MACS and GCHFS clinics, respectively, received an MTD of ACEIs without any contraindications. However, 44% of patients in the MACS and 48% in the GCHFS clinics did not receive ACEIs without any contraindications. Likewise, regarding ACEIs, a similar pattern of a non-significant difference in the rate of appropriate use of the MTD of ACEIs was observed in the MACS clinic patients compared to in the GCHFS clinic patients (43% v. 48%). The rate of appropriate MTD use of ACEIs was calculated as the number of patients who received the MTD of ACEIs without any contraindications, divided by the denominator, which is the number of patients who should have actually received the MTD of ACEIs. There was a significant difference in contraindications ($p < .001$) for the use of the MTD of ACEIs in the MACS clinic patients compared with the GCHFS clinic patients (23% v. 8.4%). In

total, 36% of patients received a target dose of ACEIs (31.1% in the MACS clinic and 39% in the GCHFS clinic) as recommended by the guidelines. Likewise, in the ACEIs, the rate of appropriate use of ARBs was 42% v. 72% and the rate of the MTD of ARBs was 25% v. 21% for the MACS and GCHFS clinics, respectively. The MACS clinic had similar rates for the guideline-based prescriptions regarding appropriate use of ACEIs/ARBs (68.4% v. 72%) as well as the rate of appropriate use of the MTD of ACEIs/ARBs (46.3% v. 52%) compared with the GCHFS clinic patients. In total, 6.1% of patients received the target dose of ACEIs (6% in the MACS clinic and 6.4% in the GCHFS clinic) as recommended by the guidelines.

A significantly lower ($p < .001$) number of patients received β-blockers in the MACS clinic compared to those in the GCHFS clinic (79.3% v. 90.5%). Further, a significantly lower ($p < .01$) number of patients did not receive β-blockers without contraindications in the MACS clinic compared to those in the GCHFS clinic (16.1% v. 8.8%). Similarly, a significantly lower ($p < .01$) rate of appropriate use of β-blockers (83.1% v. 91.1%) and the MTDs of β-blockers (31.5% v. 47.3 %) was observed in the MACS clinic patients compared to the GCHFS clinic patients. The rate of appropriate use of β-blockers was calculated as the number of patients who received the β-blockers without any contraindications, divided by the denominator, which is the number of patients who should have actually received the β-blockers. The rate of the appropriate MTD use of β-blockers was calculated using a similar method like the MTDs of ACEIs as described above. There was a significant difference ($p < .001$) in contraindications for β-blockers use (5% v. 1%) in the MACS clinic patients compared to the GCHFS clinic patients. The use of target dose was significantly lower ($p < .01$) in the MACS clinic compared to those in the GCHFS clinic (22% v. 37%).

A significantly lower prescription of MRAs (32.1% v. 62.2%; $p < .01$) was noted in the MACS clinic patients compared to those for the GCHFS clinic patients. The effect size was small for ACEIs (Cramer's V = 0.113, degree of freedom = 1), but medium for the MTD of ACEIs (Cramer's V = 0.207, degree of freedom = 2) used without contraindications for the two clinics. A similar pattern of low effect size for β-blockers (Cramer's V = 0.161, degree of freedom = 1) and medium for the MTDs of β-blockers (Cramer's V = 0.200, degree of freedom = 2) was observed. In HFrEF patients, the effect size was also medium for MRAs (Cramer's V = 0.278, degree of freedom = 1) and for use of digoxin in chronic AF for the two clinics.

There was a significant difference ($p < .001$) in contraindications for MRAs use (16.1% v. 1%) in the MACS clinic patients compared to that in the GCHFS clinic patients. Further, the MACS clinic patients had similar rates of prescription for diuretics (84% v. 87%), but a significantly higher prescription for digoxin in chronic AF (82.5% v. 58.5%). Ivabradine was prescribed in only a few patients (MACS clinic = 2; GCHFS clinic = 11).

Table 4.10

Comparison of the use of medications between clinics with heart failure with reduced ejection fraction (EF < 50) patients.

Use of Medications	Total (n=489)	MACS (n=193)	GCHFS (n=296)	P-value
Contraindications for ACEIs	69 (14.11)	44 (23)	25 (8.4)	<.001
ACEIs prescribed without contraindications	280 (57.3)	97 (50.3)	183 (62)	.010
ACEIs not prescribed without contraindications	140 (29)	52 (27)	88 (30)	.474
Rate of appropriate use of ACEIs	280 (67)	97 (65.1)	183 (67.5)	.617
Contraindications for MTD of ACEIs	69 (14.1)	44 (23)	25 (8.4)	<.001
MTD of ACEIs prescribed without contraindications	193 (39.5)	64 (33.2)	129 (44)	.017
MTD of ACEIs not prescribed without contraindications	227 (46.4)	85 (44)	142 (48)	.386
Rate of appropriate use of MTD of ACEIs	193 (46)	64 (43)	129 (48)	.325
Target dose used for ACEIs	175 (36)	60 (31.1)	115 (39)	.080
Contraindications for ARBs	393 (80.4)	159 (82.4)	234 (79.1)	.37
ARBs prescribed without contraindications	17 (3.5)	5 (3)	12 (4.1)	.64
ARBs not prescribed without contraindications	12 (2.5)	7 (4)	5 (2)	.19
ARBs prescribed but no intolerance to ACEIs	67 (14)	22 (14.4)	45 (15.2)	.81
ARBs use or not	92 (19)	34 (18)	58 (20)	.583
Documented intolerance to ACEIs	37 (8)	16 (8.3)	21 (7.1)	.624
Rate of appropriate use of ARBs	17 (59)	5 (42)	12 (70.6)	-
Contraindications for MTD of ARBs	439 (90)	175 (91)	264 (89.2)	.518
MTD of ARBs prescribed without contraindications	7 (1.4)	3 (2)	4 (1.4)	.61
MTD of ARBs not prescribed without contraindications	24 (4.9)	9 (5)	15 (5.1)	.960
MTD of ARBs prescribed but no intolerance to ACEIs	19 (4)	6 (3.1)	13 (4.4)	.467
Rate of appropriate use of MTD of ARBs	7 (22.6)	3 (25)	4 (21)	-

The group difference was evaluated using Chi-square (χ^2) test. $p<.05$ is considered significant. MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; ACEIs: angiotensin-converting enzyme inhibitors; MTDs: maximum tolerated doses; ARBs: angiotensin receptor blockers; MRAs: mineralocorticoid receptor antagonists.

Use of Medications	Total (n=489)	MACS (n=193)	GCHFS (n=296)	P-value
Target dose used for ARBs	30 (6.1)	11 (6)	19 (6.4)	.746
Rate of appropriate use of ACEIs/ARBs	297 (71)	102 (68.4)	195 (72)	.438
Rate of appropriate use of MTD of ACEIs/ARBs	210 (50)	69 (46.3)	141 (52)	.264
Target dose of ACEIs/ARBs	203 (41.5)	71 (37)	132 (45)	.157
Contraindications for β-blockers	11 (2.2)	9 (5)	2 (1)	.006
β-blockers prescribed without contraindications	421 (86.1)	153 (79.3)	268 (90.5)	<.001
β-blockers not prescribed without contraindications	57 (12)	31 (16.1)	26 (8.8)	.014
Rate of appropriate use of β-blockers	421 (88.1)	153 (83.1)	268 (91.1)	.008
Contraindications for MTD of β-blockers	11 (2.2)	9 (5)	2 (1)	.006
MTD of β-blockers prescribed without contraindications	197 (40.3)	58 (30.1)	139 (47)	<.001
MTD of β-blockers not prescribed without contraindications	281 (57.5)	126 (65.3)	155 (52.4)	.005
Rate of appropriate use of MTD of β-blockers	197 (41.2)	58 (31.5)	139 (47.3)	<.001
Target dose used for β-blockers	151 (31)	42 (22)	109 (37)	<.001
MRA contraindications	34 (7)	31 (16.1)	3 (1)	<.001
MRA used without contraindications	246 (50.3)	62 (32.1)	184 (62.2)	<.001
Diuretics contraindications	2 (0.41)	2 (1)	0 (0)	-
Diuretics used without contraindications	419 (86)	162 (84)	257 (87)	.373
Digoxin contraindications	7 (6)	2 (1)	5 (1.7)	.552
Digoxin use without contraindications	112 (25)	57 (30)	65 (22)	.059
Use of digoxin in chronic atrial fibrillation	85 (70)	47 (82.5)	38 (58.5)	.004
Use of Ivabradine	13 (2.6)	2 (1)	11 (4)	.05

The group difference was evaluated using Chi-square ($\chi 2$) test. $P<0.05$ is considered significant. MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; ACEIs: angiotensin-converting enzyme inhibitors; MTDs: maximum tolerated doses; ARBs: angiotensin receptor blockers; MRAs: mineralocorticoid receptor antagonists.

d) Comparison of the use of medications between clinics with heart failure with preserved ejection fraction patients (EF>50)

Non-significant differences in the presence of hypertension (84% v. 75.3%), control of hypertension 69.3% v. 73%) and the prescription of ACEIs (43% v. 31.5%) and ARBs (28% v. 25%) were found between the two clinics (see Table 4.11). Additionally, a non-significant difference in the prescription of ACEIs/ARBs (70% v. 56.2%) was found in the MACS clinic patients compared to in the GCHFS clinic patients. However, the prescription of β-blockers (54% v. 68.5%; $p < .05$) and MRAs (30.1% v. 48%; $p < .01$) was significantly lower in the MACS clinic patients compared to those in the GCHFS clinic. Further, there was a significantly lower prescription of Furosemide (84% v. 94.5%), but a similar prescription rate for digoxin (25.3% v. 25%).

The prescription of anticoagulation for AF was significantly lower in the MACS patients ($p < .01$) compared to in the GCHFS clinic patients (27.1 % v. 48%). There was a significant difference ($p < .01$) in contraindications for anticoagulation in the presence of AF use (6% v. 3%) in the MACS clinic patients compared to the GCHFS patients. Ivabradine was used in only two patients in the GCHFS clinic but was not prescribed for any MACS patients. In HFpEF patients, the effect size was small for the use of ACEIs/ARBs (Cramer's V = 0.121, degree of freedom = 1), β-blockers (Cramer's V = 0.139, degree of freedom = 1) and MRAs (Cramer's V = 0.172, degree of freedom = 1) between the two clinics. However, there was a medium effect size for the prescription of anticoagulation in the presence of AF (Cramer's V = 0.207, degree of freedom = 2). The overall prescription of medications for HFpEF was lower compared to those of HFrEF patients; ACEIs/ARBs (56.2% v. 71%) and significantly lower ($p < .001$) for β-blockers (58.2% v. 88.1%) and MRAs (35.6% v. 50.3%) in HFpEF patients (see Table 4.12).

Table 4.11

Comparison of the use of medications between clinics with heart failure with preserved ejection fraction (EF > 50) patients.

Presence and control of hypertension	**Total (n=239)**	**MACS (n=166)**	**GCHFS (n=73)**	**P-value**
Presence of hypertension	194 (81.2)	139 (84)	55 (75.3)	.126
Control of hypertension	168 (70.3)	115 (69.3)	53 (73)	.604
ACEIs use	94 (39.3)	71 (43)	23 (31.5)	.101
ARB use	64 (27)	46 (28)	18 (25)	.623
ACEIs/ARBs	155 (65)	114 (69)	41 (56.2)	.062
β-blockers use	139 (58.2)	89 (54)	50 (68.5)	.032
MRA use	85 (35.6)	50 (30.1)	35 (48)	.008
Furosemide	208 (87)	139 (84)	69 (94.5)	.022
Ivabradine use	-	-	2 (2.3)	-
Digoxin used	60 (25.1)	42 (25.3)	18 (25)	.916
Contraindications for anticoagulation in AF	12 (5)	10 (6)	2 (3)	.006
Anticoagulated in presence of AF without contraindications	80 (33.5)	45 (27.1)	35 (48)	.002

The difference between the clinics was evaluated using Chi-square ($\chi 2$) test. Pearson Chi-square <.05 is considered significant. MACS: Multidisciplinary Ambulatory Consulting Service; GCHFS: General Cardiology Heart Failure Service; ACEIs: angiotensin-converting enzyme inhibitors; MTDs: maximum tolerated doses; ARBs: angiotensin receptor antagonists; MRAs: mineralocorticoid receptor blockers; AF: atrial fibrillation.

Table 4.12

Comparison of the use of medications between heart failure with preserved and reduced ejection fractions.

Medications category	**HFrEF (n=489)**	**HFpEF (n=239)**	**P-value**
ACEIs/ARBs	297 (71)	41 (56.2)	.0558
β-blockers use	421 (88.1)	139 (58.2)	<.001
MRA use	246 (50.3)	85 (35.6)	P<.001

HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor antagonists; MRAs: mineralocorticoid receptor antagonists. The difference between the groups was evaluated using Z test in Epi Tools. p<.05 is considered significant.

e) Binary logistic regression for the use of ACEIs/ARBs in heart failure with reduced ejection fraction (EF<50) patients.

Univariate binary logistic regression was performed for the use of ACEIs/ARBs in HFrEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Age, last clinic SBP, last clinic DBP, AF, anaemia, IHD, CRF, COPD, any cognitive impairment, any solid cancer, any CVA, falls, osteoarthritis, GORD, peripheral vascular disease (PVD), gout, ≥3 comorbidities and any thyroid disease were significant predictors ($p < .25$) in the univariate analysis (see Table 4.13). Therefore, these variables were included in the multivariate analysis.

According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant ($\chi^2 = 6.090$; $p = .637$) (see Table 4.14). The model explained 26.4% (Nagelkerke R^2) of the variance in the use of ACEIs. The Omnibus tests for the model coefficient showed that the model was statistically significant (χ^2 [88.383]; $p < .001$). Outpatients with chronic HF were 3.2% less likely to receive ACEIs/ARBs if they were older (OR = 0.968; 95% CI [0.944, 0.992]), 51% less likely if they had anaemia (OR = 0.493; 95% CI [0.267, 0.910]), 71% less likely if they had CRF (OR = 0.293; 95% CI [0.174, 0.492]), 46% less likely if they had gout (OR = 0.542; 95% CI [0.315, 0.952]) and 45.2% less likely if they had GORD (OR = 0.548; 95% CI [0.315, 0.952]). However, all patients were likely to be on ACEIs/ARBs if they had high SBP (see Table 4.15).

Table 4.13.

Univariate binary logistic regression for the use of ACEIs/ARBs in heart failure with reduced ejection fraction (EF < 50) patients.

				95% CI for Exp (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.047	.000	.954	.936	.972
Gender (male)	-.194	.371	.824	.539	1.260
Last clinic SBP	.008	.132	1.008	.998	1.019
last clinic DBP	.018	.035	1.018	1.001	1.036
Last clinic postural BP	-.012	.430	.988	.958	1.018
AF	-.272	.191	.762	.507	1.145
Anaemia	-1.195	.000	.303	.180	.510
IHD	-.494	.023	.610	.399	.933
Diabetes	-.208	.323	.812	.538	1.227
CRF	-1.497	.000	.224	.146	.344
Hypertension	-.241	.257	.786	.518	1.192
COPD	-.310	.218	.733	.448	1.201
Cognitive impairment	-.574	.165	.563	.251	1.265
Any solid cancer	-.503	.057	.605	.361	1.015
Lipids	-.168	.418	.845	.563	1.270
CVA	-.622	.022	.537	.315	.915
Falls	-.688	.201	.503	.175	1.442
Depression/anxiety	-.051	.862	.951	.538	1.679
Osteoarthritis	-.595	.024	.552	.329	.924
Osteoporosis	-.140	.731	.869	.391	1.933
GORD	-.640	.008	.527	.329	.845
PVD	-.522	.088	.594	.326	1.081
Gout	-1.004	.000	.367	.224	.601
≥3 Comorbidities	-1.428	.000	.240	.117	.492
Thyroid diseases	-.490	.108	.612	.337	1.113
Chronic liver disease	-.155	.854	.857	.164	4.471

SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: postural blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; CVA: cardiovascular accident; OA: osteoarthritis; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; COPD: chronic obstructive pulmonary diseases; MRAs: mineralocorticoid receptor antagonists, ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor antagonists.

Table 4.14
Model summary for the multivariate binary logistic regression for the use of ACEIs/ARBs in heart failure with reduced ejection fraction (EF < 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	57.241	16	.000
	Block	57.241	16	.000
	Model	88.383	18	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	422.500[a]	.181	.264

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	6.090	8	.637

Table 4.15
Multivariate binary logistic regression for the use of ACEIs/ARBs in heart failure with reduced ejection fraction (EF < 50) patients.

				95% CI for Exp (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.033	.010	.968	.944	.992
≥3 Comorbidities	-.069	.885	.934	.369	2.361
Last clinic SBP	.020	.020	1.020	1.003	1.037
Last clinic DBP	-.012	.377	.988	.961	1.015
Anaemia	-.707	.024	.493	.267	.910
CRF	-1.228	.000	.293	.174	.492
Gout	-.613	.044	.542	.298	.983
IHD	.069	.803	1.071	.624	1.837
GORD	-.602	.033	.548	.315	.952
Any solid cancer	-.552	.082	.576	.309	1.073
CVA	-.407	.222	.666	.346	1.279
PVD	-.185	.615	.831	.404	1.710
Osteoarthritis	-.410	.188	.664	.361	1.221
Falls	-.046	.939	.955	.293	3.114
Cognitive impairment	-.034	.943	.966	.376	2.481
COPD	-.346	.247	.708	.394	1.271
AF	.162	.538	1.176	.702	1.968
Thyroid diseases	-.384	.287	.681	.336	1.380

Variable (s) entered on step 1: last clinic SBP, last clinic DBP, any anaemia, CRF, gout, IHD, GORD, any solid cancer, any CVA, PVD, OA, falls, any cognitive impairment, COPD, AF and any thyroid.

SBP: systolic blood pressure; DBP: diastolic blood pressure; CRF: chronic renal failure; IHD: ischemic heart diseases; GORD: gastroesophageal reflux diseases; CVA: cardiovascular accident; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary diseases; AF: atrial fibrillation; ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor antagonists.

f) Binary logistic regression for the use of MTD of ACEIs/ARBs in heart failure with reduced ejection fraction (EF<50) patients.

Univariate binary logistic regression was performed for the use of MTD ACEIs/ARBs in HFrEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Age, AF, IHD, CRF, COPD, any solid cancer, osteoarthritis, GORD, gout and presence of ≥3 comorbidities were significant predictors (p <.25) in the univariate analysis (see Table 4.16). Therefore, these variables were included in the multivariate analysis. According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant (χ^2 =10.688; p = 0.220) (see Table 4.17). The model explained 13.4% (Nagelkerke R^2) of the variance in the use of ACEIs. The Omnibus tests for the model coefficient showed that the model was statistically significant (χ^2 [51.332]; p <.001). Outpatients with chronic HF were 3.2% less likely to receive ACEIs/ARBs if they were older (OR = 0.968; 95% CI [0.952, 0.984]), 45.2% less likely if they had CRF (OR = 0.548; 95% CI [0.346, 0.867]) (see Table 4.18).

Table 4.16
Univariate binary logistic regression for the use of MTD of ACEIs in heart failure with reduced ejection fraction (EF < 50) patients.

				95% CI for Exp (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.041	.000	.960	.946	.974
Gender (male)	-.117	.549	.889	.606	1.305
Last clinic SBP	.004	.347	1.004	.995	1.013
AF	-.455	.015	.634	.440	.916
Anaemia	-.354	.190	.702	.414	1.191
IHD	-.288	.121	.749	.521	1.079
Diabetes	.144	.445	1.154	.799	1.668
CRF	-.780	.000	.459	.306	.688
Hypertension	.099	.596	1.104	.766	1.592
COPD	-.324	.175	.723	.453	1.154
Cognitive impairment	-.172	.675	.842	.377	1.879
Any solid cancer	-.615	.021	.541	.320	.912
Lipids	-.059	.747	.942	.657	1.352
CVA	-.281	.293	.755	.447	1.275
Falls	-.662	.263	.516	.162	1.643
Depression/anxiety	.170	.508	1.186	.716	1.963
Osteoarthritis	-.593	.027	.553	.327	.934
Osteoporosis	-.448	.254	.639	.296	1.380
GORD	-.480	.044	.619	.389	.986
Gout	-.304	.227	.738	.451	1.208
≥3 Comorbidities	-.670	.003	.512	.327	.800
Thyroid diseases	.127	.661	1.135	.644	1.999

SBP: systolic blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; CVA: cardiovascular accident; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; MTD: maximum tolerated does; ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor antagonists.

Table 4.17
Model summary for the multivariate binary logistic regression for the use of MTD of ACEIs in heart failure with reduced ejection fraction (EF < 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	16.151	9	.064
	Block	16.151	9	.064
	Model	51.332	11	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	610.277[a]	.100	.134

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	10.688	8	.220

Table 4.18
Multivariate binary logistic regression for the use of MTD of ACEIs in heart failure with reduced ejection fraction (EF < 50) patients.

				95% CI for Exp (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.032	.000	.968	.952	.984
≥3 Comorbidities	.193	.511	1.213	.682	2.160
CRF	-.602	.010	.548	.346	.867
AF	-.273	.190	.761	.506	1.145
Anaemia	.152	.607	1.164	.653	2.075
IHD	-.049	.825	.953	.619	1.467
COPD	-.193	.446	.825	.502	1.354
Any solid cancer	-.507	.075	.602	.345	1.053
Osteoarthritis	-.351	.219	.704	.402	1.232
GORD	-.442	.080	.643	.392	1.055
Gout	-.073	.791	.930	.542	1.594

Variable(s) entered on step 1: CRF, AF, any anaemia, IHD, COPD, any solid cancer, Osteoarthritis, GORD and gout.

CRF: chronic renal failure; AF: atrial fibrillation; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary diseases; GORD: Gastroesophageal reflux dieses.

g) Binary logistic regression for the use of β-blockers in heart failure with reduced ejection fraction (EF<50) patients.

Univariate binary logistic regression was performed for the use of β-blockers in HFrEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Age, Gender (male), HR, COPD, any solid cancer, gout, any anaemia, IHD, any cognitive impairment, osteoporosis and any thyroid diseases were significant predictors ($p < .25$) in the univariate binary logistic regression (see Table 4.19). Therefore, these variables were included in the multivariate analysis.

According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant ($\chi 2 = 7.988$; $p = 0435$) (see Table 4.20). The model explained 12.9% (Nagelkerke R^2) of the variance in the use of β-blockers. The Omnibus tests for the model coefficient showed that the model was statistically significant, χ^2 [33.123]; p=0.001). Outpatients with chronic HF were 3% less likely to receive β-blockers if they had high HR (OR = 0.973; 95% CI [0.953, 0.992]) and 59% less likely if they had gout (OR = 0.410; 95% CI [0.203, 0.828]). But, patients were nearly twice as likely to receive β-blockers if they had IHD (OR = 1.792; 95% CI [1.006, 3.191]) (see Table 4.21).

Table 4.19
Univariate logistic regression for the use of β-blockers use in heart failure with reduced ejection fraction (EF < 50) patients.

				95% C.I. for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.027	.016	.974	.953	.995
Gender (male)	-.525	.048	.591	.351	.996
Last clinic HR	-.029	.003	.971	.953	.990
AF	-.116	.658	.890	.533	1.488
Anaemia	-.392	.248	.676	.348	1.314
IHD	.429	.102	1.535	.919	2.566
Diabetes	-.083	.756	.921	.547	1.550
Hypertension	.104	.693	1.110	.662	1.860
COPD	-.565	.058	.568	.316	1.020
Asthma	-.385	.415	.680	.269	1.719
Cognitive impairment	-.612	.205	.543	.211	1.397
Any solid cancer	-.559	.078	.572	.307	1.064
Lipids	.153	.559	1.166	.697	1.949
CVA	-.017	.962	.983	.477	2.027
Falls	.050	.948	1.051	.232	4.766
Depression/anxiety	.002	.996	1.002	.486	2.064
Weight at first appointment	.006	.362	1.006	.993	1.019
Osteoarthritis	-.019	.956	.981	.489	1.968
Osteoporosis	-.598	.183	.550	.228	1.327
GORD	-.010	.976	.990	.525	1.866
PVD	-.243	.535	.785	.365	1.689
Gout	-.584	.060	.558	.303	1.025
≥3 Comorbidities	-.300	.392	.741	.373	1.473
Thyroid diseases	-.633	.076	.531	.264	1.068
Chronic liver disease	-.925	.275	.397	.075	2.087

SBP: systolic blood pressure; DBP: diastolic blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; CVA: cardiovascular accident; OA: osteoarthritis; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; COPD: chronic obstructive pulmonary diseases.

Table 4.20
Model summary for the multivariate binary logistic regression for the use of β-blockers in heart failure with reduced ejection fraction (EF < 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	27.257	9	.001
	Block	27.257	9	.001
	Model	33.123	11	.001

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	332.791[a]	.074	.129

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	7.988	8	.435

Table 4.21
Multivariate binary logistic regression for the use of β-blockers in heart failure with reduced ejection fraction (EF <50) patients.

				95% CI for Exp (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.016	.208	.984	.960	1.009
Gender (male)	-.576	.062	.562	.307	1.030
Last clinic HR	-.028	.007	.973	.953	.992
COPD	-.636	.056	.529	.276	1.017
Any solid cancer	-.628	.076	.534	.267	1.068
Gout	-.891	.013	.410	.203	.828
Any anaemia	-.209	.583	.811	.384	1.711
IHD	.583	.048	1.792	1.006	3.191
Any cognitive impairments	-.546	.299	.579	.207	1.624
Osteoporosis	-.083	.876	.920	.324	2.614
Any thyroid disease	-.567	.150	.567	.262	1.227

Variable (s) entered on step 1: last clinic HR, COPD, any solid cancer, gout, any anaemia, IHD, any cognitive impairment, Osteoporosis and any thyroid.

HR: heart rate; COPD: chronic obstructive pulmonary diseases; IHD.

h) Binary logistic regression for the use of MTD of β-blockers in heart failure with reduced ejection fraction (EF<50) patients.

Univariate binary logistic regression was performed for the use of MTD of β-blockers in HFrEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Age, Gender (male), HR, COPD, any solid cancer, gout, any anaemia, IHD, any cognitive impairment, osteoporosis and any thyroid diseases were significant predictors (p<.25) in the univariate analysis (see Table 4.22). Therefore, these variables were included in the multivariate analysis. According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant (χ^2 = 7.988; p = 0435) (see Table 4.23). The model explained 12.9% (Nagelkerke R^2) of the variance in the use of β-blockers. The Omnibus tests for the model coefficient showed that the model was statistically significant, χ2 [33.123]; p=0.001). Outpatients with chronic HF were 3% less likely to receive β-blockers if they had high HR (OR = 0.973; 95% CI [0.953, 0.992]) and 59% less likely if they havd gout (OR = 0.410; 95% CI [0.203, 0.828]). However, patients were nearly twice as likely to receive β-blockers if they had IHD (OR = 1.792; 95% CI [1.006, 3.191]) (see Table 4.24).

Table 4.22
Univariate logistic regression for the use of mtd of β-blockers use in heart failure with reduced ejection fraction (EF < 50) patients.

				95% CI for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.037	.000	.964	.950	.977
Gender (male)	-.273	.168	.761	.517	1.122
Last clinic HR	-.018	.019	.982	.967	.997
AF	-.201	.280	.818	.568	1.178
Anaemia	-.398	.144	.672	.394	1.146
IHD	-.125	.501	.882	.612	1.271
Diabetes	-.242	.203	.785	.541	1.139
Hypertension	-.084	.652	.919	.638	1.325
COPD	-.350	.145	.705	.441	1.128
Asthma	-.125	.740	.882	.421	1.848
Cognitive impairment	-.903	.056	.405	.161	1.023
Any solid cancer	-.445	.089	.641	.383	1.070
Lipids	-.146	.430	.864	.602	1.241
CVA	.027	.917	1.027	.616	1.715
Falls	-1.514	.048	.220	.049	.986
Depression/anxiety	.134	.604	1.143	.689	1.896
Osteoarthritis	-.354	.173	.702	.421	1.169
Osteoporosis	-.580	.152	.560	.253	1.237
GORD	.192	.396	1.212	.777	1.890
PVD	-.154	.606	.857	.478	1.538
Gout	-.401	.115	.669	.406	1.103
≥3 Comorbidities	-.392	.084	.675	.433	1.055
Thyroid diseases	-.187	.529	.830	.464	1.485
Chronic liver disease	.107	.889	1.113	.246	5.030

SBP: systolic blood pressure; DBP: diastolic blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; CVA: cardiovascular accident; OA: osteoarthritis; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; COPD: chronic obstructive pulmonary diseases.

Table 4.23
Model summary for the multivariate binary logistic regression for the use of mtd of β-blockers in heart failure with reduced ejection fraction (EF < 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	22.399	10	.013
	Block	22.399	10	.013
	Model	47.264	13	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	533.563[a]	.104	.140

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	10.780	8	.214

Table 4.24
Multivariate binary logistic regression for the use of MTD of β-blockers in heart failure with reduced ejection fraction (EF < 50) patients.

				95% CI for Exp (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.040	.000	.961	.943	.979
Gender (male)	-.145	.534	.865	.547	1.367
≥3 Comorbidities	.500	.117	1.649	.883	3.082
Any anaemia	-.262	.403	.769	.417	1.421
Diabetes	-.337	.138	.714	.457	1.114
COPD	-.303	.263	.739	.435	1.256
Any cognitive impairment	-.562	.267	.570	.211	1.537
Last clinic HR	-.026	.003	.974	.958	.991
Any solid cancer	-.318	.287	.727	.405	1.307
Falls	-1.043	.186	.352	.075	1.655
Osteoarthritis	.018	.952	1.018	.571	1.813
Osteoporosis	-.200	.658	.819	.338	1.985
Gout	-.556	.064	.573	.318	1.034

Variable(s) entered on step 1: any anaemia, diabetes, COPD, any cognitive impairment, last clinic HR, any solid cancer, falls, OA, Osteoporosis, and gout.

COPD: chronic obstructive pulmonary diseases; HR: heart rate.

i) Binary logistic regression for the use of MRAs in heart failure with reduced ejection fraction (EF<50) patients.

Univariate binary logistic regression was performed for the use of MRAs in HFrEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Age, Gender (male), last clinic SBP, last clinic DBP, last clinic postural BP, AF, anaemia, CRF, hypertension, any cognitive impairment, any solid cancer, hyperlipidaemia, falls, osteoarthritis, osteoporosis, PVD and ≥3 comorbidities were significant predictors ($p < 0.25$) in the univariate analysis (see Table 4.25). Therefore, these variables were included in the multivariate analysis. According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant ($\chi^2 = 13.105$; $p = .108$) (see Table 4.26). The model explained 26.4% (Nagelkerke R^2) of the variance in the use of ACEIs. The Omnibus tests for the model coefficient showed that the model was statistically significant (χ^2 [76.411]; $p < .001$). Outpatients with chronic HF were 4% less likely to receive MRAs if they were older (OR = 0.960; 95% CI [0.942, 0.979]) and 3.4% less likely if they had high SBP (OR = 0.966; 95% CI [0.955, 0.978]) (see Table 4.27).

Table 4.25
Univariate logistic regression for the use of MRAs use in heart failure with reduced ejection fraction (EF < 50) patients.

				95% C.I. for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.044	.000	.957	.943	.972
Gender (male)	-.436	.024	.646	.443	.943
Last clinic SBP	-.034	.000	.966	.956	.976
Last clinic DBP	-.018	.015	.982	.968	.996
Last clinic postural BP	-.024	.110	.976	.948	1.005
AF	.228	.210	1.256	.879	1.796
Anaemia	-.322	.213	.725	.437	1.203
IHD	-.048	.792	.953	.666	1.364
Diabetes	.189	.308	1.208	.840	1.737
CRF	-.670	.001	.512	.348	.752
Hypertension	-.454	.014	.635	.442	.912
COPD	-.209	.363	.812	.518	1.272
Asthma	.112	.760	1.119	.545	2.294
Cognitive impairment	-1.128	.012	.324	.134	.780
Any solid cancer	-.358	.148	.699	.430	1.136
Lipids	-.220	.224	.802	.562	1.144
CVA	-.255	.322	.775	.467	1.284
Falls	-1.445	.027	.236	.066	.846
Depression/anxiety	.172	.502	1.187	.719	1.961
Osteoarthritis	-.582	.021	.559	.340	.917
Osteoporosis	-1.021	.011	.360	.163	.795
GORD	-.076	.735	.927	.597	1.438
PVD	-.358	.219	.699	.395	1.237
Gout	-.170	.481	.844	.526	1.354
≥3 Comorbidities	-.651	.005	.521	.330	.823
Thyroid diseases	.018	.950	1.018	.581	1.784
Chronic liver disease	.908	.281	2.479	.476	12.904

SBP: systolic blood pressure; DBP: diastolic blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; CVA: cardiovascular accident; OA: osteoarthritis; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; COPD: chronic obstructive pulmonary diseases; MRAs: mineralocorticoid receptor antagonists.

Table 4.26
Model summary for the multivariate binary logistic regression for the use of MRAs in heart failure with reduced ejection fraction (EF < 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	76.411	17	.000
	Block	76.411	17	.000
	Model	76.411	17	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	401.862[a]	.197	.264

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	13.105	8	.108

Table 4.27
Multivariate binary logistic regression for the use of MRAs use in heart failure with reduced ejection fraction (EF < 50) patients.

				95% C.I. for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.040	.000	.960	.942	.979
Gender (male)	-.280	.233	.756	.477	1.197
≥3 Comorbidities	-.150	.675	.861	.426	1.737
Hypertension	.267	.298	1.306	.790	2.160
Last clinic SBP	-.034	.000	.966	.955	.978
CRF	-.467	.059	.627	.386	1.018
Any cognitive impairment	-.499	.328	.607	.224	1.648
Osteoarthritis	-.106	.725	.899	.497	1.627
Osteoporosis	-.419	.354	.658	.271	1.596
Falls	-.782	.269	.458	.114	1.832
Any solid cancer	-.059	.844	.943	.526	1.691
Lipids	.068	.778	1.070	.668	1.714
PVD	-.029	.934	.971	.490	1.925
AF	.405	.077	1.499	.957	2.350
Any anaemia	.207	.505	1.230	.669	2.262

Variable (s) entered on step 1: last clinic SBP, CRF, any cognitive impairment, OA, osteoporosis, falls, any solid cancer, lipids, PVD, AF and any anaemia.

SBP: systolic blood pressure; CRF: chronic renal failure; PVD: peripheral vascular diseases; AF: atrial fibrillation.

j) Binary logistic regression for the use of ACEIs/ARBs in heart failure with preserved ejection fraction (EF>50) patients.

Univariate binary logistic regression was performed for the use of ACEIs/ARBs in HFpEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Gender (male), hypertension, CRF, CVA, COPD, cognitive impairment, gout and falls were significant predictors (p <.25) in the univariate analysis (see Table 4.28). Therefore, these variables were included in the multivariate analysis. According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant (χ^2 = 2.983; p = 0.935) (see Table 4.29). The model explained 18.5% (Nagelkerke R^2) of the variance in the use of ACEIs/ARBs. The Omnibus tests for the model coefficient showed that the model was statistically significant (χ^2 [34.055]; p<.001). Outpatients with chronic HF were 50% less likely to receive ACEIs/ARBs if they had CRF (OR = 0.504; 95% CI [0.266, 0.955]) and 78% less likely if they had any cognitive impairment (OR = 0.221; 95% CI [0.068, 0.719]). But, patients were nearly three and half times likely to be prescribed on ACEI/ARBs if they had hypertension (OR = 30449; 95% CI [1.677, 7.095]) and nearly two and half times likely to be prescribed ACEIs/ARBs if they had COPD (OR = 2.389; 95% CI [1.129, 5.055]) (see Table 4.30).

Table 4.28
Univariate binary logistic regression for the use of ACEIs/ARBs in heart failure with preserved ejection fraction (EF >50) patients.

				95% C.I. for EXP(B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	.007	.617	1.007	.980	1.035
Gender (male)	-.360	.187	.698	.409	1.191
Last clinic SBP	-.003	.627	.997	.985	1.009
Low standing SBP (BP<115)	.061	.860	1.062	.543	2.080
Low postural BP (BP≥20)	-.452	.467	.636	.188	2.150
Last clinic DBP	-.011	.320	.989	.968	1.011
AF	.121	.657	1.128	.663	1.920
Anaemia	-.232	.427	.793	.447	1.405
IHD	-.216	.427	.806	.473	1.372
Diabetes	.104	.701	1.110	.652	1.890
CRF	-.522	.068	.593	.338	1.040
Hypertension	.941	.005	2.562	1.338	4.906
COPD	.620	.072	1.858	.947	3.648
Asthma	.254	.531	1.289	.582	2.856
Cognitive impairment	-1.092	.045	.336	.115	.978
Any solid cancer	-.155	.659	.857	.430	1.705
Hyperlipidaemia	-.049	.857	.952	.559	1.623
CVA	.697	.063	2.008	.962	4.189
Falls	.905	.167	2.472	.684	8.932
Depression/anxiety	-.371	.239	.690	.372	1.279
Osteoarthritis	.204	.496	1.226	.682	2.205
Osteoporosis	.405	.274	1.500	.725	3.103
GORD	.317	.276	1.373	.776	2.428
PVD	-.273	.456	.761	.371	1.560
Gout	-.730	.046	.482	.235	.986

SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: postural blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; CVA: cardiovascular accident; OA: osteoarthritis; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; COPD: chronic obstructive pulmonary diseases; MRAs: mineralocorticoid receptor antagonists, ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor blockers.

Table 4.29
Model summary for the multivariate binary logistic regression for the use of ACEIs/ARBs in heart failure with preserved ejection fraction (EF > 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	23.284	6	.001
	Block	23.284	6	.001
	Model	34.055	8	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	273.237[a]	.134	.185

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	2.983	8	.935

Table 4.30
Multivariate binary logistic regression for the use of ACEIs/ARBs in heart failure with preserved ejection fraction (EF >50) patients.

				95% C.I. for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Gender (male)	-.437	.143	.646	.360	1.159
Hypertension	1.238	.001	3.449	1.677	7.095
CRF	-.686	.036	.504	.266	.955
CVA	.705	.090	2.024	.895	4.577
COPD	.871	.023	2.389	1.129	5.055
Any cognitive impairment	-1.509	.012	.221	.068	.719
Gout	-.471	.254	.625	.278	1.402
Falls	.656	.360	1.928	.472	7.867

Variable (s) entered on step 1: CRF, any CVA, COPD, any cognitive impairment, gout, and falls.

CRF: chronic renal failure; CVA: cardiovascular accident; COPD: chronic obstructive pulmonary diseases; ACEIs/ARBs: angiotensin converting enzyme inhibitor/angiotensin receptor antagonists.

k) Binary logistic regression for the use of β-blockers in heart failure with preserved ejection fraction (EF>50) patients.

Univariate binary logistic regression was performed for the use of β-blockers in HFpEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Hypertension, last clinic HR, last clinic low heart rate (HR<60), anaemia, IHD, diabetes, COPD, cognitive impairment, hyperlipidaemia, osteoarthritis and GORD were significant predictors (p <.25) in the univariate analysis (see Table 4.31). Therefore, these variables were included in the multivariate analysis. According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant (χ^2 = 3.875; p = 0.868) (see Table 4.32). The model explained 30.1% (Nagelkerke R^2) of the variance in the use of ACEIs/ARBs. The Omnibus tests for the model coefficient showed that the model was statistically significant (χ^2 [56.469]; p <0.001). Outpatients with chronic HF were 4% less likely to receive β-blockers if they had high HR (OR = 961; 95% CI [0.933, 0.990]), 72% less likely to receive β-blockers if they had COPD (OR = 0.283; 95% CI [0.137, 0.584]) and 49.4% less likely to receive β-blockers if they had GORD (OR = 0.506; 95% CI [0.262, 0.980]). But, patients were two times more likely to be prescribed on β-blockers if they had IHD (OR = 2.096; 95% CI [1.106, 3.971]) (see Table 4.33).

Table 4.31
Univariate binary logistic regression for the use of β-blockers in heart failure with preserved ejection fraction (EF <50) patients.

				95% CI for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.013	.338	.987	.961	1.014
Gender (male)	.048	.858	1.049	.624	1.763
Last clinic HR	-.048	.000	.953	.932	.974
Last clinic low HR (HR<60)	.874	.011	2.396	1.219	4.706
AF	.286	.277	1.331	.795	2.229
Anaemia	.427	.144	1.533	.864	2.718
IHD	.677	.011	1.968	1.166	3.324
Diabetes	.635	.017	1.887	1.119	3.182
Hypertension	.573	.081	1.773	.933	3.369
COPD	-1.208	.000	.299	.160	.558
Asthma	-.313	.406	.732	.350	1.529
Cognitive impairment	-1.091	.053	.336	.111	1.015
Any solid cancer	.189	.588	1.208	.610	2.393
Hyperlipidaemia	.695	.009	2.003	1.189	3.376
CVA	.295	.380	1.344	.695	2.600
Falls	-.353	.495	.702	.254	1.939
Depression/anxiety	-.095	.758	.909	.495	1.670
Osteoarthritis	-.476	.094	.621	.356	1.085
Osteoporosis	.116	.735	1.123	.573	2.204
GORD	-.356	.196	.701	.409	1.201
PVD	.334	.370	1.397	.673	2.899
Gout	.008	.982	1.008	.491	2.070

SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: postural blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; CVA: cardiovascular accident; OA: osteoarthritis; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; COPD: chronic obstructive pulmonary diseases.

Table 4.32
Model summary for the multivariate binary logistic regression for the use of β-blockers in heart failure with preserved ejection fraction (EF < 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	53.309	10	.000
	Block	53.309	10	.000
	Model	56.469	11	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	247.747[a]	.225	.301

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	3.875	8	.868

Table 4.33
Multivariate binary logistic regression for the use of β-blockers in heart failure with preserved ejection fraction (EF < 50) patients.

				95% C.I. for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Hypertension	.614	.124	1.848	.845	4.042
Last clinic HR	-.040	.009	.961	.933	.990
Low HR (HR<60)	.408	.410	1.504	.569	3.974
Anaemia	.531	.137	1.700	.845	3.422
IHD	.740	.023	2.096	1.106	3.971
Diabetes	.062	.856	1.064	.547	2.067
COPD	-1.262	.001	.283	.137	.584
Cognitive impairment	-.812	.221	.444	.121	1.631
Hyperlipidaemia	.492	.134	1.636	.859	3.116
Osteoarthritis	-.638	.072	.528	.264	1.058
GORD	-.681	.043	.506	.262	.980

Variable (s) entered on step 1: last clinic HR, LOW_HR, any anaemia, IHD, diabetes, COPD, cognitive impairment, lipids, OA and GORD.

HR: heart rate; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary diseases; CVA: cardiovascular disease; GORD: gastroesophageal reflux diseases.

l) Binary logistic regression for the use of MRAs in heart failure with preserved ejection fraction (EF>50) patients.

Univariate binary logistic regression was performed for the use of MRAs in HFpEF patients to ascertain the important predictors needed for the multivariate binary logistic regression. Gender (male), hypertension, AF, IHD, diabetes, CRF, asthma, hyperlipidaemia, osteoporosis and low standing SBP (BP<115) were significant predictors (p <.25) in the univariate analysis (see Table 4.34). Therefore, these variables were included in the multivariate analysis. According to the Hosmer and Lemeshow test, the binary logistic regression model was not statistically significant (χ^2 = 9.506; p = 0.301) (see Table 4.35). The model explained 15.5% (Nagelkerke R^2) of the variance in the use of MRAs. The Omnibus tests for the model coefficient showed that the model was statistically significant (χ^2 [28.233]; p <0.01). Outpatients with chronic HF were two times more likely to receive MRAs if they had low standing SBP of <115 mm Hg (OR = 2.105; 96% CI [1.044, 4.244]) (see Table 4.36).

Table 4.34
Univariate binary logistic regression for the use of MRAs in heart failure with preserved ejection fraction (EF > 50) patients.

				95% C.I. for EXP(B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Age	-.013	.359	.987	.961	1.014
Gender (male)	.435	.112	1.544	.904	2.639
Last clinic SBP	-.029	.000	.972	.958	.986
Last clinic DBP	-.034	.005	.966	.944	.990
Low standing SBP (BP<115)	.916	.006	2.500	1.306	4.785
Low postural BP (BP≥20)	-.404	.559	.668	.172	2.586
AF	.507	.065	1.660	.969	2.844
Anaemia	.120	.682	1.128	.635	2.001
IHD	-.559	.042	.572	.334	.980
Diabetes	-.585	.033	.557	.325	.955
CRF	-.714	.021	.490	.267	.898
Hypertension	-.480	.147	.619	.324	1.184
COPD	-.094	.770	.910	.485	1.709
Asthma	.482	.204	1.619	.770	3.405
Cognitive impairment	-.105	.852	.900	.297	2.725
Any solid cancer	.375	.278	1.455	.738	2.868
Hyperlipidaemia	-.432	.112	.649	.381	1.106
CVA	.259	.438	1.295	.673	2.492
Falls	.369	.481	1.446	.519	4.031
Depression/anxiety	-.058	.857	.944	.501	1.776
Osteoarthritis	-.320	.289	.726	.402	1.312
Osteoporosis	-.872	.030	.418	.190	.920
GORD	-.013	.963	.987	.565	1.725
PVD	-.022	.953	.978	.470	2.037
Gout	.028	.941	1.028	.491	2.152

SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: postural blood pressure; AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; CVA: cardiovascular accident; OA: osteoarthritis; GORD: gastroesophageal reflux diseases; PVD: peripheral vascular diseases; COPD: chronic obstructive pulmonary diseases; MRAs: mineralocorticoid receptor antagonists.

Table 4.35
Model summary for the multivariate binary logistic regression for the use of MRAs in heart failure with preserved ejection fraction (EF > 50) patients.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	24.003	8	.002
	Block	24.003	8	.002
	Model	28.233	10	.002

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	279.059[a]	.113	.155

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	9.506	8	.301

Table 4.36
Multivariate binary logistic regression for the use of MRAs in heart failure with preserved ejection fraction (EF < 50) patients.

				95% C.I. for EXP (B)	
Variables	**B**	**Sig.**	**Exp (B)**	**Lower**	**Upper**
Gender (male)	.317	.305	1.373	.749	2.515
Hypertension	-.202	.593	.817	.390	1.713
AF	.359	.231	1.432	.796	2.575
IHD	-.571	.057	.565	.314	1.017
Diabetes	-.465	.143	.628	.337	1.171
CRF	-.526	.113	.591	.308	1.132
Asthma	.433	.294	1.541	.687	3.459
Hyperlipidaemia	-.086	.781	.917	.500	1.684
Osteoporosis	-.855	.059	.425	.175	1.032
Low standing SBP (BP<115)	.744	.037	2.105	1.044	4.244

Variable (s) entered on step 1: AF, IHD, diabetes, CRF, asthma, lipids, osteoporosis and low standing SBP.

AF: atrial fibrillation; IHD: ischemic heart diseases; CRF: chronic renal failure; SBP: systolic blood pressure; MRAs: mineralocorticoid receptor antagonists.

Chapter 5: Discussion

5.1 Discussion of systematic review and meta-analysis: Phase I

5.1.1 Summary of evidence

The findings of this study indicate that pharmacist-involved multidisciplinary HF management resulted in a significant reduction in HF hospitalisation (28%) but had no effect on reducing HF mortality. Similarly, a significant reduction in all-cause hospitalisation (24%) and no effect on all-cause mortality was observed. When the meta-analysis was limited to four RCTs with sufficient statistical power in an attempted sensitivity analysis, none of the primary or secondary outcomes were significant. Three RCTs showed significant improvement, six found a non-significant improvement, and one RCT found no difference in medication adherence. Interestingly, three RCTs had statistical power, but only one had statistically significant improvement and was sufficiently powered (Sadik et al., 2005). The overall trend was an improvement in medication adherence. There was also evidence to support significant improvements in HF knowledge, but no significant improvements in health care costs, self-care, and composite endpoint.

Two RCTs that measured HF knowledge and the one RCT measuring self-care lacked statistical power. However, two RCTs that measured health care costs had sufficient statistical power (Murray et al., 2007; Tsuyuki et al., 2004), but there was no statistically significant difference between the intervention and control group in both RCTs. The results for HF mortality and self-care reflect evidence from only two and one RCTs, respectively. Thus, the net effect is very likely to change with further research. The overall trend was an improvement in health-related quality of life. The most common instruments to measure health-related quality of life were

MLHF and SF-36. There was a great deal of variability regarding which specific intervention is most effective in improving clinical outcomes because pharmacist-involved multidisciplinary intervention offered an integrated approach including multiple interventions. Our study has identified a knowledge gap of evidence from an RCT of pharmacist-involved multidisciplinary intervention for the effective management of HF to improve clinical outcomes.

While significant and convincing evidence has been available for HFrEF, little evidence exists regarding effective therapies for HFpEF; the result is a cohort of patients with significant unmet clinical needs. Our results should be interpreted with caution because we are not confident how many patients with HFpEF were enrolled in the 18 RCTs included in our study. However, it is known that very few patients with HFpEF have been recruited in clinical trials (Pothineni et al., 2018). There was no heterogeneity for HF mortality, all-cause mortality and composite endpoint (I^2=0). However, we observed low heterogeneity (I^2=39%) for HF hospitalisations and slightly higher than medium level of heterogeneity (I^2=52%) for all-cause hospitalisations. Potential sources of heterogeneity may be due to the settings where the studies were conducted, sample size, patients' characteristics, risk of bias, type of intervention delivered and a difference in healthcare systems among countries where the studies were conducted.

Our results should be interpreted with caution because only three of the included RCTs mentioned the value of EF in their eligibility criteria for participants. The remaining 15 RCTs did not restrict HFpEF patients from enrolment. Further, significant methodological heterogeneity exists regarding the setting, the patients'

age, follow-up times and sample sizes. In addition, only four of the 18 included RCTs (22.22%) achieved sufficient statistical power. It is often argued that the grading of bias risk into low, unclear, and high demarcations is likely to be subjective (Jordan, Lensen, & Farquhar, 2017). Thus, in the current meta-analysis, we contacted the primary authors and evaluated the risk of bias using the well-known Cochrane risk of bias assessment tool to minimize the impact of subjective bias. The overall risk of bias in the included trials in the current meta-analysis was low. Selective reporting was negligible due to the open nature of the interventions. We observed some degree of publication bias especially for HF hospitalisations and all-cause mortality as demonstrated by the asymmetry of the funnel plots. There was no reporting bias in the included trials. Therefore, to extract an explicit summary of each outcome from those heterogeneous trials included in our study, the GRADE approach was used. To the best of our knowledge, this is the most up-to-date systematic review and meta-analysis to comprehensively evaluate the benefits of pharmacist inclusion in a multidisciplinary team in HF management.

5.1.2 Comparison with previous meta-analysis

Two earlier relevant meta-analyses of RCTs in multidisciplinary HF management suggested a significant reduction in hospital readmissions (Gwadry-Sridhar et al., 2004; Holland et al., 2005) and all-cause mortality (Gwadry-Sridhar et al., 2004). However, pharmacists were not involved within the multidisciplinary team in the majority of the included trials. Koshman *et al* conducted a systematic review and meta-analysis (12 RCTs, 2060 patients) to determine the effect of pharmacist care on patient outcomes for HF (Koshman et al., 2008). This study demonstrated significant reductions in the rate of all-cause hospitalisations [OR 0.71, 95% CI

(0.54–0.94)] and HF hospitalizations [OR 0.69, 95% CI (0.51–0.94)], and a non-significant reduction in mortality. Further, pharmacist-involved collaborative care led to greater reductions in the rate of HF hospitalisations [OR 0.42; 95% CI (0.24–0.74)] than pharmacist-directed care [OR 0.89; 95% CI (0.68–1.17)]. Findings in the current meta-analysis are similar regarding the effect on HF hospitalizations, all-cause hospitalisations and all-cause mortality compared to the above meta-analysis. The current study extends the earlier work by including data from six recent RCTs to strengthen the available scientific evidence to for an expanded role of the pharmacist in HF management.

Despite having similar results to the above highlighted meta-analysis, the current study includes more stringent eligibility criteria for RCTs of pharmacist-involved multidisciplinary HF management. The above meta-analysis (Koshman et al., 2008) included RCTs that evaluated the impact of pharmacist care activities on patients with HF; however, for an RCT to be included in current meta-analysis, pharmacists needed to be working in collaboration with at least a physician within the intervention model. For example, one RCT conducted in Australia was excluded as home medication review by a pharmacist had no effect on mortality or health care utilization due to the fact that the pharmacist worked in isolation as highlighted in the limitation of the study by the authors (Barker et al., 2012). However, this RCT met the eligibility criteria of the earlier meta-analysis. The current meta-analysis also evaluated the impact of pharmacist-involved multidisciplinary HF management on a more extensive range of clinical outcomes, including HF knowledge, health care costs and self-care. Further, we performed a sensitivity analysis to check whether reductions in hospitalisations and mortality rates are still

retained in sufficiently powered studies (4 RCTs). The optimal practice of EBM and improvement of clinical outcomes is facilitated by embedding pharmacists within a multidisciplinary team for effective HF management (Stough & Patterson, 2017). The current meta-analysis focuses on the role of the pharmacist within the multidisciplinary team in the management of HF.

Two recent meta-analyses have been more restricted in focus, examining pharmacist-involved care for patients with HF and acute coronary syndrome (Kang et al., 2016), and the effect of multidisciplinary clinics on readmission and mortality without pharmacist-involved multidisciplinary HF management (Gandhi et al., 2017). The meta-analysis conducted by Kang *et.al* found reductions in all-cause hospitalization [OR 0.74; 95% CI (0.58–0.94)]. In contrast, the meta-analysis performed by Gandhi *et al* reported no significant difference in all-cause hospitalization (OR, 1.04, P = 0.33), however reduced HF hospitalisation (OR, 0.68, P = 0.003) and all-cause mortality (OR, 0.71, P = 0.006). The findings in the current meta-analysis are mixed compared to the results of these two meta-analyses.

Transitional care interventions increase patients' independence and aim to focus on patients' safety during the transition between healthcare settings. Two earlier meta-analyses were conducted to evaluate the impact of different transitional care interventions in HF management (Feltner et al., 2014; Van Spall et al., 2017). However, they are not solely focused on determining the role of a pharmacist-involved multidisciplinary team. The meta-analysis conducted by Feltner et al. found that home visit programs and multidisciplinary HF clinic interventions reduced readmission and mortality (Feltner et al., 2014). However, of the 47

included RCTs, only four were pharmacist-involved multidisciplinary interventions. The meta-analysis conducted by Van Spall *et al.* reported no significant improvement in mortality and readmissions. Interestingly, this meta-analysis included only three pharmacist-involved multidisciplinary interventions out of 57 RCTs to determine the overall effect. Moreover, the above study included one RCT (Barker et al., 2012) that was excluded in current meta-analysis. Therefore, the results of these two meta-analyses explained above cannot be directly correlated to determine the effect of pharmacist-involved multidisciplinary interventions in the management of HF.

5.1.3 Comparisons with previous findings

A retrospective study of hospitalized HF patients in rural Japan to determine the effect of pharmacist-involved multidisciplinary inpatient education found a significant reduction in the composite endpoint of HF hospitalisations and all-cause mortality ($p<0.001$) (Kinugasa et al., 2014). This contrasts with the findings of the current study. The reduction in all-cause mortality and composite endpointobserved in the current meta-analysis may be mediated by EBT optimization attributed to having a clinical pharmacist in the multidisciplinary team (Milfred-Laforest et al., 2013). There is also growing evidence for a reduction in mortality rates among HF patients due to better use of EBM (Burnett et al., 2017; Khan, Fonarow, Ahmed, et al., 2017; Shen et al., 2017).

The largest trial included in our review (n=2164) with the longest follow-up (4.7 years) did not find an improvement in the primary composite endpoint of death from any cause or hospital admission for worsening HF (Lowrie et al., 2012). A limitation of this study was that the intervention was delivered by non-specialist

pharmacists in collaboration with family doctors. The Heart Failure Society of America and the American College of Clinical Pharmacy cardiology practice and research network both highlighted that to improve the clinical outcomes of HF patients, pharmacists should have completed specialized postdoctoral training in the form of residencies and/or fellowships in cardiovascular pharmacotherapy (Milfred-Laforest et al., 2013). Addressing the lack of appropriately trained pharmacists within multidisciplinary teams may offer a better service in overall HF management to improve clinical outcomes.

A systematic review previously found a significant reduction in readmission and mortality rates through the implementation of interventions to improve medication adherence among HF patients (Ruppar et al., 2016). Another study by Davis et al. also reported the pharmacist's role in improving medication adherence (Davis et al., 2014). An overall improvement in medication adherence was observed in current study. Therefore, the reduction in HF and all-cause hospitalisations in the current study may have been contributed to by improvement in medication adherence. One pharmacist-involved multidisciplinary RCT of ambulatory chronic HF patients is ongoing: the PHARMacy-based interdisciplinary trial (Laufs et al., 2018). This trial aims to determine the effect of pharmacist-involved multidisciplinary care on medication adherence, hospitalizations and mortality. The intervention components are medication review, regular dose dispensing of medications, and counselling on medication and HF symptoms. This trial is rigorous, expecting to recruit 248 patients to achieve 85% power with a long follow-up of 12 months. The trial's recruitment has been completed, and the results of the

pilot study suggest a positive impact on control of blood pressure and lipids and improvement of the quality of life of HF patients.

An educational intervention targeting HF knowledge improvement led to a clinically significant reduction in HF readmissions, and health care costs (Krumholz et al., 2002). The reduction in HF readmissions may lead to improved cost-effectiveness according to evidence from an earlier systematic review (Maru et al., 2016). The current study found that HF knowledge was significantly improved, hospitalizations were reduced, and a non-significant reduction in health care costs was observed. The presence of a pharmacist within a multidisciplinary team is essential for the best practice of EBT, which ultimately may affect the reduction of HF hospitalizations (Motiejunaite, Chouihed, & Mebazaa, 2017; Stough & Patterson, 2017). The significant reduction in HF hospitalization and all-cause hospitalizations observed in the current meta-analysis also would be expected to reduce health care costs. Poor knowledge is a strong predictor of poor self-care in HF patients (Dracup et al., 2014). Importantly, HF self-care leads to a reduction of clinical events (all-cause mortality, emergency room visits and hospitalizations) (Lee et al., 2017). The current study found a non-significant improvement in self-care, although this is based on evidence from a single RCT and may not be clinically relevant. There was no effect on the composite endpoint of all-cause mortality and all-cause hospitalization in current study from the pooled results from three RCTs. A recent retrospective chart review had observed a significant reduction (adjusted hazard ratio = 0.44; 95% CI [0.22, 0.88]; p = .02) for the composite end point of 30 days of all-cause readmission and death (Hale et al., 2017).

It is noteworthy that in our earlier literature review (Parajuli et al., 2017), we found that engagement of pharmacists in HF management improved medication adherence, medication management, self-care ability, patient satisfaction, HF knowledge, and reduction in HF readmission rates. These findings were heavily derived from observational studies. However, the findings from current meta-analysis are solely from RCTs. Therefore, it can be strongly argued that there is a substantial increasing evidence for a pharmacist to be a key member of a multidisciplinary HF management team. A recent study highlighted that pharmacist-involved collaborative management of HF had beneficial effects for the implementation of a transition of care program (Boykin et al., 2018). Another recent review (24 clinical trials and systematic reviews) found that the pharmacist should be involved as a member of a multidisciplinary team in HF management. The most reliable role of the pharmacist-involved multidisciplinary is in medication management (Cheng, 2017). The ongoing PHARMacy-based randomized controlled interdisciplinary trial (Laufs et al., 2018) may provide additional evidence for the importance of the pharmacist-involved multidisciplinary model of care in the management of HF patients to improve clinical outcomes in the near future.

5.2 Discussion of retrospective cohort study-Phase II

This study is a snapshot of demographics, clinical characteristics and the use of EBTs and an evaluation of the predictors for the use of EBTs in CHF outpatients in a large tertiary hospital in Australia. The similarities and differences in the demographics and clinical characteristics and the use of EBTs in CHF outpatients were compared between two multidisciplinary clinics with and without pharmacist

involvement. Importantly, the two clinics (MACS and GCHFS) have different characteristics; for example, patient demographics and clinical characteristics, clinicians, exposure to a pharmacist and the eventual model of care. CHF patients in the pharmacist-involved multidisciplinary clinic (MACS) were significantly older, less likely to be female, had higher SBP and DBP, were under polypharmacy and had a high prevalence of multiple comorbidities; thus they represent a complex group of individuals compared with the GCHFS clinic patients.

Despite the active involvement of the pharmacist in the MACS clinic, underutilisation of EBT was observed for use of ACEIs, the MTD of ACEIs, β-blockers, the MTD of β-blockers and MRAs in HFrEF patients. There was a low effect size for ACEIs and β-blockers but a medium effect for the MTD of ACEIs and the MTD of β-blockers, MRAs and digoxin use in chronic AF. However, the effect size was small for the use of ACEIs/ARBs, β-blockers and MRAs in HFpEF patients. Notably, the effect size was medium for the use of anticoagulants in the presence of AF. The statistical significance difference ($p < .05$) alone does not sufficiently explain the actual difference between the two groups (Sullivan & Feinn, 2012). One must estimate the value of effect size that describes the magnitude of the true treatment effect between the two groups (Kalinowski & Fidler, 2010). The underutilisation of EBTs in the MACS clinic was associated with contraindications, patient age, blood pressure, heart rate and comorbidities. Other potential reasons may be polypharmacy, side effects and adverse effects, adherence problem in patients, patient preference and non-responsiveness to the medications.

The mean age of patients in this study was 79 ± 10 years for HFpEF, 76.5 ± 11 years for HFmrEF and 71 ± 13.4 years for HFrEF patients. These cohorts are much

older compared to the mean age of the ESC Heart Failure Long-Term (ESC-HF-LT) registry (Chioncel et al., 2017) in which the age was 68 ± 13.7 years for HFpEF, 64.2 ± 14.2 years for HFmrEF and 64 ± 12.6 years for HFrEF patients. Patients in the current sutdy were 11 years older for HFpEF, 12 years older for HFmrEF and 7 years older than the European registry. HFpEF patients in the current study were 2 years older compared with the age of patients in a NSW snapshot study (79 ± 10 years v. 77 ± 13 years) (Newton et al., 2016). The Korean National Health Insurance claims database showed that those patients were two years younger than the HFpEF patients in the current study (77.5 ± 7 years v. 79 ± 10 years) (Kim et al., 2012). However, regarding the mean age of the HFrEF patients, the current study revealed that patients were younger than those in a more recent Australian study of chronic HFrEF patient data from a large teaching hospital (71 ± 13.45 years v. 78.9 ± 11.7 years) (Khalil et al., 2017).

The analysis of the same demographic and clinical characteristics stratified by EF in the current study showed similarities in the epidemiology of patients as those in the ESC-HF-LT registry (Chioncel et al., 2017). According to the ESC-HF-LT registry, compared with HFpEF individuals, patients with HFrEF were younger (64 years v. 68 years) and more likely to be male (78% v. 52%). Our study revealed a similar trend of individuals being younger (71 years v. 78 years) and a higher proportion of males (64% v. 43%) for HFrEF patients compared to HFpEF patients. Likewise, in the ESC-HF-LT registry, compared with HFpEF patients, HFrEF patients were more likely to have ischemic aetiology (57% v. 51%) but less likely to have hypertension (55.4% v. 82%) and AF (44% v. 53%). AF prevalence is in ascending order with the increasing value of EF (Sartipy et al., 2017). The

observation regarding the prevalence of AF in the current study concurs with previous findings that found it to be highest in HFpEF patients.

The prevalence of HFpEF, HFmrEF and HFrEF was 31%, 13% and 56%, respectively, in the current study. The prevalence of HFmrEF has been reported previously as being between 10% and 20% (Andronic, Mihaila, & Cinteza, 2016; Lam & Solomon, 2014). Despite this grey area, HFmrEF (EF = 41–49) is well accepted and we are yet to discover the characteristics of the patients in this HF category (Nadar & Tariq, 2018). Further, it has a poorly understood prognosis (Lam & Solomon, 2014). It was recognised that HFmrEF is a distinct group of intermediate HF patient characteristics between the HFrEF and HFpEF group (Tsuji et al., 2017). There was no significant difference in all-cause mortality between the three HF groups (Farré et al., 2017).

Uncertainty exists regarding the profile of HFmrEF patients whether it is more towards HFrEF and HFpEF as evidence exists on both sides that it is a heterogeneous group (Rastogi et al., 2017). The HFmrEF cohort in the current study resembled the HFpEF cohort regarding mean age (79 ± 10 v. 76.5 ± 11), HR (70.7 ± 16 v. 70.6 ± 15.6 beats/min) and being under polypharmacy. However, the HFmrEF cohort resembles the HFrEF cohort for the proportion of male gender distribution (58% v. 64.1%) and epidemiology of IHD (64% v. 57%) in line with the ESC-HF-LT registry. Similar findings to the HFmrEF group, resembling HFrEF for male gender and ischemic aetiology, were reported in another study (Gomez-Otero et al., 2017).

The prevalence of IHD is more prominent in HFmrEF compared to in HFrEF and HFpEF (Koh et al., 2017; Vedin et al., 2017). The observation in the current study

was in line with a previous study for highest prevalence of IHD in HFmrEF compared to all other groups. Conversely, another study found that the presence of IHD was more common in HFrEF than in HFmrEF (Guisado-Espartero et al., 2018). This study also found that the blood pressure of HFmrEF was closer to the HFpEF group; however, the SBP of the HFmrEF patients in the current study was intermediate between the HFrEF patients and HFpEF patients. The mean weights were similar in the HFpEF, HFmrEF and HFrEF cohorts. Compared with the HFmrEF and HFrEF patients, the MACS clinic patients in HFpEF were older, had higher weights, high SBP and DBP, were under polypharmacy and had a higher prevalence of multiple comorbidities. The current study found a notable difference in demographics and comorbidities with the different cut-offs for EF.

Comparing patients with reduced to mid-range and preserved ejection fraction, patients were at least seven years older and much more likely to be female, have higher SBP, more polypharmacy, higher prevalence of diabetes, COPD, hyperlipidaemia, GORD, osteoarthritis, worse renal function and be more anemic. Unfortunately, little evidence exists regarding how to effectively manage HFpEF and HFmrEF groups of HF patients (Ponikowski et al., 2016; Redfield, 2016). A recent review demonstrated that pharmacists are capable of contributing in the medication management and eventually a reduction in hospitalisations by embedding a counselling approach in HF management while working within a multidisciplinary team (Cheng, 2017). Therefore, one strategy would be an expert multidisciplinary team, including a pharmacist, for optimal management of those complex and heterogeneous HF patients.

Although the MACS clinic had similar rates of guideline-based prescriptions of ACEIs/ARBs (68.4% v. 72%) and their MTDs (46.3% v. 52%), they had surprisingly significantly lower β-blockers (83.1% v. 91.1%), and their MTDs (31.5% v. 47.3%) and MRA (32.1% v. 62.2%) prescriptions were noted in HFrEF patients compared to GCHFS clinic patients. The effect size was low for β-blockers, but medium for MTDs of β-blockers and use of MRAs between the two clinics in HFrEF patients. Further, for HFrEF patients, there were similar rates of diuretic prescriptions (84% v. 87%), but significantly higher digoxin prescription rates in chronic AF (82.5% v. 58.5%) in the MACS clinic compared to in the GCHFS clinic. EBT use was higher in the current study compared to the NSW HF snapshot study with β-blockers (88% v. 78%) and MRAs (50.3% v. 45%) in HFrEF patients (Newton et al., 2016). Similar patterns of better use of ACEIs/ARBs (71% v. 52%), β-blockers (88% v. 49%) and MRAs (50.3% v. 15%) were evident, but there were slightly lower rates of prescription of diuretics (86% v. 90%) and digoxin (25% v. 29%) found in current study compared to a recent Australian study on chronic HFrEF patients from a large metropolitan hospital (Khalil et al., 2017). Khalil et al.'s study had compared their findings with a previous study in Australia: the CHART 2003 (Wlodarczyk et al., 2003).

In the CHART 2003 study, regarding patients hospitalised with HF, ACEIs/ARBs were prescribed in 87.7% of patients (1220), β-blockers in 24% of patients (499) and MRAs in 12.7% of patients (264). The prescription of ACEIs/ARBs, β-blockers and MRA in current study were superior to all three studies in Australia (Khalil et al., 2017; Newton et al., 2016; Wlodarczyk et al., 2003). However, a recent retrospective study from US revealed that the prescription rate for the β-blockers in

patients hospitalised with HF had significantly increased from 73.3% to 96.3% (p = .027) from admission to discharge (Suzuki et al., 2018). Underutilisation of EBTs in real life is a well-known issue in HF management (Lenzen et al., 2005). Compelling evidence exists regarding poor adherence to guideline-based recommendations for the use of EBTs in HF; the barriers include: clinician knowledge, up-titration reluctance, patient preference and time and availability of human resources (Cabana et al., 1999; Swennen et al., 2013; Williamson et al., 2012). In certain instances, the underlying reason for the underutilisation of EBTs may also be unknown. Low heart rate and poor adherence to prescriptions is associated with use of lower use of β-blockers (Kalra et al., 2013).

Age, anaemia, CRF, gout and GORD were significant predictors for the lower utilisation of ACEI/ARBs in the current study's multivariate analysis. Patients were older, and the presence of these comorbidities was significantly higher in the MACS clinic compared to in the GCHFS clinic. In contrast to the current study's findings, presence of hyperlipidaemia and IHD have been reported as significant predictors to receiving a higher prescription of ACEIs/ARBs in HF patients (Ibrahim et al., 2016). A previous study found that age, presence of comorbidities and renal function were significant predictors for ACEI prescriptions (Komajda, Follath, et al., 2003).

Older age (>70 years), and presence and increase of respiratory disease were the significant predictors for the higher prescription of β-blockers in a previous study (Komajda, Follath, et al., 2003). Last clinic HR and the presence of IHD were significant predictors in the reduction of β-blocker prescriptions whereas presence of IHD increased β-blocker prescriptions in HFrEF patients in the current study's

multivariate analysis. Gout prevalence was significantly higher and IHD prevalence was significantly lower in the MACS clinic in HFrEF patients. In a qualitative study in the US, a side effect (hypotension) and polypharmacy were the major barriers to β-blocker use and its titration (Levitan et al., 2017). Another qualitative study from Australia reported that burden of side effect for ACEIs, and concern of side effects, contraindications, the comorbidities and poor experience of GPs were the critical barriers to underutilisation of β-blockers in HF patients (Phillips, Tofler, & Marton, 2004). The diversity of patient characteristics, presence of comorbidities and polypharmacy between two clinics was the underlying cause for the lower prescription of β-blockers in the MACS clinic despite of active involvemtn of the pharmacist in HF management.

A critical reason behind the underutilisation of MRAs in HF is due to associated hyperkalaemia and the detrimental effect on renal function (Cooper et al., 2017; Eschalier et al., 2013; Juurlink et al., 2004). Patient age and last clinic SBP were significant predictors for the lower utilisation of MRAs in the current study's multivariate analysis. As observed in this study regarding the prescribing of MRAs, age contributes 4% and SBP contributes 3.4% for predicting the utilisation of MRAs. Therefore, one potential reason for the lower prescription of MRAs in the MACS clinic was the presence of contraindicating conditions (16% v. 1%; MACS v. GCHFS clinics). Further research is needed to confirm other relevant reasons for example the occurance of hyperkalemia. Digoxin is useful to improve morbidity in HF patients who have AF as a comorbidity (Fauchier et al., 2016; Reis et al., 1997; van Veldhuisen et al., 2013). A total of 70% (85) of patients received digoxin in chronic AF in the current study (82.5% v. 58.5%; MACS v. GCHFS; $p < .001$).

Patient age, HR, SBP and presence of comorbidities were the critical predictors of EBTs in the current study, as reported in a recent Australian study (Khalil et al., 2017).

Despite established guidelines and recommendations for the treatment of HFrEF patients, up to 80% of patients received doses lower than the target doses (Komajda, The Study Group of Diagnosis of the Working Group on Heart Failure of the European Society of, et al., 2003). The prescription of doses lower than the targets for EBTs in clinical practice is associated with higher hospitalisations and mortality (Fonarow et al., 2011). The current study found that 41.5% of patients were given the recommended dose for ACEIs/ARBs and 31% of β-blockers. There was a similar rate of guideline-based prescription of the target dose of ACEIs/ARBs (37% v. 45%; MACS v. GCHFS clinic in the current study). However, significantly lower (31% v. 21%) ($p < .001$) prescriptions of the target dose of β-blockers were observed. In a recent European prospective study, patients received 22% of the target doses for ACEIs/ARBs and 17% of the target doses for β-blocker (Ouwerkerk et al., 2017). In that European study, the underlying reasons for the failure to titrate to maximum doses were not explained.

Although the target doses of ACEIs/ARBs (37%) and β-blockers (22%) in the MACS clinic patients in the HFrEF group were lower compared to the GCHFS clinic, these values were higher compared to the European Prospective study (Ouwerkerk et al., 2017). In a previous study, the recommended target dose for β-blockers was achieved in only 10–30% of HF patients (Atherton & Hickey, 2017) whereas it was 31% in the current study. High prescription rates for ACEIs/ARBs (92%) and β-blockers (93%) were reported in the 2013 ESC-HF LT registry

(Maggioni, Anker, et al., 2013). However, the target doses in this registry were still lower than those in current study (29% v. 41.5% for ACEIs/ARBs and 18% v. 31% for β-blockers).

A previous study successfully implemented a medication titration plan that had improved the prescription of target doses of ACEIs/ARBs and β-blockers in HFrEF patients (EF < 50) in Australia (Hickey et al., 2016). The target dose for ACEIs/ARBs increased from 37% to 55% (p = .051) and from 38% to 51% for β-blockers (p = .045). The prescription of the target doses of ACEIs/ARBs and β-blockers in the HFrEF patients in the current study are slightly lower than they are in a previous Australian study (Hickey et al., 2016).

It is well known that chronic HF patients do not receive guideline-recommended target doses of EBTs in routine clinical practice (Cleland, 2002; Kalra et al., 2013). Evidence is emerging that higher doses of ACEIs/ARBs and β-blockers have a more potent effect of reducing mortality and hospitalisations in chronic HF patients compared to lower doses (Bristow et al., 1996; Konstam et al., 2009; Ouwerkerk et al., 2017; Packer et al., 1999). Therefore, an opportunity exists to prescribe MTD in chronic HF patients unless they are tolerated or have specific contraindications (Ponikowski et al., 2016). The rates of appropriate use of MTD of ACEIs/ARBs and β-blockers were 50% and 41.2%, respectively. A significant predictor for the use of MTD of ACEIs/ARBs in the current study was age and CRF whereas it was age and last clinic heart rate for β-blockers. The tolerability of specific doses of β-blockers in individual patients with multiple comorbidities and polypharmacy

should be closely monitored rather than just an approach to reach the target doses in real life (Mehta et al., 2004).

In reality, patients enrolled in RCTs are substantially older and have more complex conditions compared to patients who are enrolled (Fonarow et al., 2008). It is argued that failure to prescribe doses lower than the target dose may not always be clinically wrong due to tolerability; therefore, it is crucial that the emphasis for up-titration is adopted based on an individualised dose approach (Follath, 2009). According to a systematic review, the widely recognised definition of polypharmacy is a condition that requires the use of five or more medications daily (range = 2 to 11) (Masnoon et al., 2017). The mean number of medications used in the MACS patients was 11.25 ± 4, indicating that there was substantial polypharmacy in MACS clinic patients. Polypharmacy is associated with a significant burden of poor medication adherence, drug–drug interactions and adverse effects in HF patients (Mastromarino et al., 2014). Elderly HF patients suffer from multiple chronic diseases, which ultimately leads to higher polypharmacy prevalence (Shakib & Clark, 2016).

The older age of the patients and presence of polypharmacy may have accounted for the lower utilisation of EBTs in the MACS clinic patients compared to those in the GCHFS clinic. Lower EBT use in HFrEF patients due to contraindications have been reported previously (Atwater et al., 2012). The contraindications for use of ACEIs and their MTDs was 22.8% v. 8.4% (MACS v. GCHFS clinic patients); for β-blockers, it was 4.7% v. 0.7% (MACS v. GCHFS clinic patients). These findings highlighted that contraindications may be one potential reason for lower EBT and MTD prescriptions in the MACS clinic in the current study despite the pharmasist's

active involvement. Overall, the current findings demonstrated that the prescription of EBT and target doses were satisfactory compared with recent data from Australian studies and other international studies.

In a previous Australian study, a lower prescription of ACEIs (61.9% v. 72.5%; $p < .01$) was found among HFpEF patients compared to those in HFrEF patients (Wong et al., 2010). In the current study, the prescription of ACEIs/ARBs was lower in the HFpEF patients compared to in the HFrEF patients (56.2% v. 71%) without a significant difference ($p = .0558$). However, the prescription of β-blockers and MRA was significantly lower ($p < .001$) in HFpEF patients compared to HFrEF patients (58.2% v. 88.1%; 35.6% v. 50.3%, respectively). There remains a lack of evidence regarding the effectiveness of currently available medications for HFpEF and the most widely accepted strategy is to manage underlying symptoms (Ponikowski et al., 2016).

It is well known that a lack of evidence exists for the effective management of HFpEF (Nanayakkara & Kaye, 2015). This may be attributed to an incomplete understanding of the epidemiology and pathophysiology of the condition (From & Borlaug, 2011). However, expert groups have highlighted that the dilemma for HFpEF management has been partly addressed due to the possible benefits of currently available medications (Polsinelli & Shah, 2017). Likewise, in HFrEF patients, a non-significant prescription of ACEIs/ARBs (70% v. 56.2%) was observed in HFpEF patients in the MACS clinic compared to the GCHFS clinic.

However, a significantly lower ($p < .001$) prescription of β-blockers and MRAs in the MACS clinic patients with HFpEF was revealed. A significantly lower prescription of MRAs ($p < .001$) and furosemide ($p < .05$), but similar prescription

rates for digoxin (25.3% v. 25%) were also observed. The effect size was low for the differences in the prescription of β-blockers, MRAs, furosemide and digoxin between the two clinics for HFpEF patients. However, a medium effect size was found for the prescription of anticoagulations in the presence of AF. There were more patients with contraindications for anticoagulation in the presence of chronic AF in the MACS clinic compared to in the GCHFS clinic (six patients vs. two patients) with no significant statistical difference.

Recently, two meta-analyses were published to determine the effectiveness of ACEIs/ARBs and β-blockers in HFpEF patients (Khan, Fonarow, Khan, et al., 2017; Zheng et al., 2018). The first study (25 RCTs) in HFpEF patients (LVEF ≥ 40%) showed a reduction in all-cause and cardiovascular mortality by β-blockers (Zheng et al., 2018). The second study (six RCTs and seven observational studies) reported a significant reduction in all-cause mortality by ACEIs/ARBs, which was only mediated by observational studies. However, the pooled analysis was unable to reduce cardiovascular mortality (Khan, Fonarow, Khan, et al., 2017). These findings have shed new light on the effectiveness of existing medications in HFpEF, but there is still a lack of consensus over this.

A significantly higher percentage of patients have low HR (< 60) ($p < .001$) and low standing SBP (<115) without a significant group difference ($p = .124$) as well as low postural BP was observed in 6.6% (11) patients in the MACS clinic compared to in the GCHFS clinic. No patients had low postural blood pressure in the GCHFS clinic. The overall prescription of medications for HFpEF was lower compared to those of HFrEF patients—ACEIs/ARBs (56.2% v. 71%)—and significantly lower ($p < .001$) for β-blockers (58.2% v. 88.1%) and MRAs (35.6%

v. 50.3% in HFpEF patients. These findings indicate that patients in the HFpEF category were not over treated.

A systematic review and meta-analysis (15 RCTs) revealed that the use of MRAs in HFpEF was associated with ADRs including hyperkalaemia and gynecomastia compared with HFrEF patients (Berbenetz & Mrkobrada, 2016). The MACS clinic, being a holistic model of care, may have considered these ADRs in prescribing MRAs in HFpEF patients, which is a potential reason for a significantly lower prescription of MRAs in the MACS clinic compared with in the GCHFS clinic. The exact benefits of MRAs in HFpEF patients is still poorly understood (Vizzardi et al., 2014); therefore, the generalisation of the role of currently available medications may not be clinically relevant.

Some cases of inappropriate prescribing were also noticed; for example, two patients were on two β-blockers simultaneously, two patients were on both ACEIs and ARBs and one patient received the wrong dose for apixaban. Similarly, some patients were on contraindicated medications. The benefit of having a pharmacist in the multidisciplinary team is that pharmacists can easily detect cases of inappropriate prescribing and contraindicated medications under usage. The presence of comorbidities including hypertension, CRF, COPD, cognitive impairment and gout were the significant predictors of lower prescription of ACEIs/ARBs in HFpEF patients in the multivariate analysis undertaken in the current study. However, presence of CVA was associated with higher prescription numbers of these medications. The lower utilise of these medications in the MACS clinic was because of the higher prevalence of those comorbidities compared with the GCHFS clinic in the current study.

It has also been reported that age is a strong predictor of the lower prescription of β-blockers in the elderly (Muntwyler et al., 2004). The presence of COPD, gout and last clinic HR were significant predictors for the lower use of β-blockers in HFpEF in the current study's multivariate analysis. However, the presence of IHD is associated with significantly higher prescribing of β-blockers. Again, the differential prevalence of these comorbidities between the MACS and GCHFS clinics explains why MACS patients have significantly lower prescriptions of β-blockers in the current study. The only significant predictor for MRA use in the multivariate analysis was low standing SBP. This predictor was associated with a higher prescription of MRAs in HFpEF patients.

A number of possibilities behind the underutilisation of EBT in elderly patients have been proposed; for example, the presence of comorbidities, frailty, cognitive impairment, lack of social support, polypharmacy, symptom management and maintaining the quality of life of patients (Wang et al., 2012). The presence of multiple comorbidities, cognitive impairment and polypharmacy were very common in MACS patients in our study compared to in GCHFS clinic patients. The effect of these variables on the use of EBT requires further investigation to ascertain their effect on poor utilisation of EBT in our MACS clinic.

A physician-targeted intervention to promote the prescribing behaviours in Australia improved the prescription of EBTs and was associated with a reduction in hospital admissions (Chua et al., 2018). These findings were in line with an earlier meta-analysis in which there was an improvement in prescribing rates of EBTs by embedding an audit and feedback approach (Ivers et al., 2014). As physicians work to collaborate with pharmacists and other health professionals in

multidisciplinary clinics in HF management, better prescribing of EBTs, MTD and target doses could be anticipated if such an audit and feedback approach is implemented. Involving pharmacists in the multidisciplinary team and implementation of the individual-tailored intervention and embedding audit and feedback strategies could potentially be successful strategies for the better practice of EBTs and target dose recommendations (Atherton & Hickey, 2017).

Chapter 6: Conclusions

6.1 Conclusions from systematic review and meta-analysis: phase I

The findings of this study indicated that pharmacist-involved multidisciplinary HF management resulted in a significant reduction in HF hospitalisation but had no effect on reducing HF mortality. A significant reduction in all-cause hospitalisation and no effect on all-cause mortality was also observed. There was a great deal of variability regarding which specific intervention is most effective in improving clinical outcomes, because pharmacist-involved multidisciplinary intervention offered an integrated approach including multiple interventions.

The GRADE assessment indicated moderate-quality evidence for significant reduction of HF hospitalisations, all-cause hospitalisations and overall improvement in medication adherence. Significant improvement in HF knowledge and non-significant reduction in health care costs were also of moderate quality. Non-significant reduction in HF mortality, all-cause mortality and composite endpoint were of low quality. The evidence for non-significant improvement in self-care was found to be of very low quality. The results for HF mortality and self-care reflect evidence from only two and one RCTs, respectively. Thus, the net effect is very likely to change with further research. This study highlights a persistent gap of evidence from an RCT of pharmacist-involved multidisciplinary intervention (having sufficient statistical power and longer follow-ups) for the effective management of HF to improve clinical outcomes. The pharmacist would seem to

be an essential member of a multidisciplinary team and should be included in HF management irrespective of any setting.

Strength and limitations -Phase I

The major strength of this study is that it includes the largest number of RCTs in any such meta-analysis. In addition, this is the first study to comprehensively evaluate the potential benefits of pharmacist involvement in multidisciplinary HF management teams on such a large number of outcome measures. The outcome summary represents an explicit measure of quality of evidence for each outcome following the GRADE approach, which is another strength.

The limitations of the current study include the inclusion of only English-language RCTs and the diversity of interventions, settings and health care systems in which the studies were conducted, and their follow-up times, sample heterogeneity, and statistical power.

Recommendation for practice and policy-Phase I

A strong recommendation can be made for including a pharmacist within multidisciplinary teams to improve the effectiveness of HF management. Multidisciplinary interventions offer an integrated approach to educational counseling about diseases and medications, enhancing lifestyle modifications, and self-care behaviors, medication optimization, and telephone follow-ups. Embedding a pharmacist within a multidisciplinary team provides various clinical benefits in the management of HF. Appropriate use of medications is an essential factor in improving HF outcomes, and the inclusion of a pharmacist in a multidisciplinary team may contribute significantly to achieving this. There is room for future trials of pharmacist-involved multidisciplinary interventions to

investigate the impact on clinical outcomes with long follow-ups and sufficient statistical power.

6.2 Conclusions from retrospective cohort study-Phase II

Patients are seven years older, much more likely to be female, have a higher SBP, be experiencing more polypharmacy, have a higher prevalence of diabetes, COPD, hyperlipidaemia, GORD, osteoarthritis, worse renal impairment and worse anaemia when comparing reduced to mid-range and preserved ejection fraction. Therefore, a proper strategy for successful management of HF needs to be designed based on these factors. CHF patients in the MACS clinic were significantly older, less likely to be female, had higher SBP and DBP, were under polypharmacy and had a high prevalence of multiple comorbidities. The necessity of pharmacist involvement in the pharmacist involved multidisciplinary clinic, the MACS clinic, can be justified due to the underlying complex nature of the patients than in GCHFS clinic. Older age of patients, heart rate, blood pressures, contraindications, comorbidities and polypharmacy were the potential reasons for lower prescription of β-blockers and MRAs in MACS clinic in HFrEF and HFpEF patients. The other roles of the pharmacist within a multidisciplinary team, including continuity of care, medication compliance, prevention of adverse reactions and education need further research.

Strengths and limitations-Phase II

The major strength of this study is that it includes a large number of participants. In addition, this retrospective study represents the data of CHF patients from 12 years from a large tertiary hospital. The patient's demographics and clinical characterstics

was compared among HFrEF, HFmrEF and HFpEF. The individual data of 723 patients were reviewed, and the utilisation of EBTs and their predictors for both HFrEF and HFpEF was compared. Only the patients who have echocardiography were included in the evaluation of utilisation of EBTs. Coding for each group of medications was performed by two independent researchers and checked for discrepancies. Any disagreements were resolved by consensus with a third researcher to increase the robustness of the research.

There are some limitations of this retrospective study that need to be noted. The two clinics (MACS and GCHFS) have different characteristics; for example, patient demographics and clinical characteristics, clinicians, exposure to a pharmacist and the eventual model of care. Therefore, a direct comparision of utilisation of EBTs between MACS and GCHFS clinic and concluding the role of the pharmacist HF management is not relevant. The impact of qualifications, experiences and expertise of the pharmacists in the MACS group and that of all of the nurses and clinicians in both groups was not considered in this study. Despite the large sample size, this study represents the patients' data from a single tertiary care center, and the results can not be heavily generalised to the Australian population. The intolerance of medications, side effects during titration, non-responsiveness of medications and patient's preference may have been poorly documented which may have some influence on the overall findings from this study.

Recommendations for practice and policy-Phase II

There is a notable difference in demographics and comorbidities with the different cut-offs for EF. Patients are on average 7 years older, much more likely to be female, have higher SBP, more polypharmacy, a higher prevalence of diabetes,

COPD, hyperlipidaemia, GORD, osteoarthritis, worse renal impairment and worse anaemia while going from reduced to mid-range and preserved. There is an emerging role for the pharmacist in the HF management particularly due to polypharmacy associated with underlying multiple comorbidities, and diversity in patient's characterstics in HFrEF, HFmrEF and HFpEF. The role of the pharmacist-involved multidisciplinary team in medication optimisation, particularly the recommendation of EBT, needs to be investigated in a well designed RCT. The other roles of the pharmacist within a multidisciplinary team, including continuity of care, improving medication adherence, prevention of adverse reactions and patient education require further research. Age, renal function, the presence of comorbidities, blood pressure, heart rate and presence of contraindications need to be considered while prescribing maximum tolerated doses and target doses.

6.3 Overall conclusion of this thesis

The pharmacist-involved multidisciplinary team in HF management significantly reduced HF and all-cause hospitalisations and improved medication adherence as well as HF knowledge. No effect was observed on HF mortality, all-cause mortality, and composite endpoint of all-cause hospitalisations and all-cause mortality, health care costs and self-care. CHF patients in the pharmacist-involved multidisciplinary clinic (MACS) were significantly older, less likely to be female, had higher SBP and DBP, were under polypharmacy and had a high prevalence of multiple comorbidities; thus they represented a complex group of individuals compared with the GCHFS clinic patients. Older age of patients, heart rate, blood pressures, contraindications, comorbidities and polypharmacy were the potential reasons for lower prescription of β-blockers and MRAs in MACS clinic in HFrEF and HFpEF

patients. The pharmacist is an essential member of the multidisciplinary team and should be included in HF management irrespective of setting.

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List of appendix

Appendix I: Outcomes of the thesis

1. **Parajuli DR**, Franzon J, McKinnon R, Shakib S, Clark R. Role of the pharmacist for improving self-care and outcomes in heart failure. Curr Heart Fail Rep. 2017 Apr; 14(2):78-86. doi: 10.1007/s11897-017-0323-2.
2. **Parajuli DR**, Kourbelis C, Franzon J, Newman P, McKinnon R, Shakib S, Whitehead D, Clark R. Effectiveness of the pharmacist-involved multidisciplinary management of heart failure compared to usual care to improve hospitalizations and mortality rates in 4630 patients: a systematic review and meta-analysis of randomized controlled trials. Submitted, under minor review (Journal of Cardiac Failure).
3. **Parajuli DR**, Shakib S, Eng-Frost J, Caughey Gillian, McKinnon R, Whitehead D, Clark R. Comparison of the demographics, clinical characteristics and utilization of evidence-based therapies in chronic heart failure outpatients in multidisciplinary clinics with and without the involvement of a pharmacist: a retrospective cohort study. PLOS One. 2018, in progress.

Conference abstracts from thesis accepted and published in national and international conferences

1. **D Parajuli,** J Franzon, R McKinnon, S Shakib, R Clark. Comparison of the Demographics and Clinical Characteristics of Heart Failure Patients in Multidisciplinary Clinics with and Without a Pharmacist Involvement. Heart, Lung and Circulation 2017; 26(Suppl 2): S131. DOI: https://doi.org/10.1016/j.hlc.2017.06.201

2. **Parajuli DR**, Kourbelis C, Franzon J, Newman P, McKinnon R, Shakib S, Clark R. Effectiveness of the Pharmacist-involved Multidisciplinary Management of Heart Failure to Improve Readmission and Mortality Rates: Systematic Review and Meta-analysis of Randomized Controlled Trials. The 2017 South Australian Cardiovascular Research Showcase, 27th October 2017, South Australia, Australia.
3. **Parajuli DR**, Kourbelis C, Franzon J, Newman P, McKinnon R, Shakib S, Clark R. Effectiveness of the pharmacist-involved multidisciplinary management of heart failure to improve readmission and mortality rates: systematic review and meta-analysis of randomized controlled trials. European Society of Cardiology Congress 2018, 24-29 August, Munich Germany.
4. **Parajuli DR**, Shakib S, Eng-Frost J, Franzon J, Caughey G, McKinnon R, Whitehead D, Clark R. Comparison of the utilization of evidence-based medicines in patients with chronic heart failure in multidisciplinary clinics with and without a pharmacist. Pharmaceutical Society of Australia 2018 Annual Conference, 27-29th July, Sydney, Australia.

National and international conferences attended during the candidature.

1. Attended the 26th annual scientific meeting of the Australian Cardiovascular Health and Rehabilitation Association (ACRA), 1-3 Aug 2016, South Australia, Australia.
2. Attended 2017 SA Nurses & Midwives Research Symposium South Australian Health & Medical Research Institute on 17th May 2017, SAHMRI Auditorium, South Australia, Australia.

3. Attended a scientific conference **(poster presentation),** The Cardiac Society of Australia and New Zealand (CSANZ) on Aug 10-13, Perth Western Australia, Australia.
4. Attended, 2017 South Australian Cardiovascular Research Showcase (poster presentation), Friday 27th October, SAHMRI Auditorium, South Australia, Australia.
5. Attended 13th Quality in Postgraduate Research Conference. Impact, Engagement, and Doctoral Education, 17-19 April, 2018. National Wine Centre, Hackney Road, Adelaide.
6. Attended European Society of Cardiology Congress **(oral presentation)** 2018, 24-29 August, Munich Germany.
7. Pharmaceutical Society of Australia 2018 Annual Conference **(poster presentation)**, 27-29th July, Sydney, Australia.

Appendix II. Critical Appraisal Skilled Programme for Systematic Review and Meta-Analysis

Author of the study	**Q1. Did the review address a clearly focused question?**	**Q2. Did the authors look for the right type of papers?**	**Q3. Do you think all the important relevant studies were included?**	**Q4. Did the review's authors do enough to assess quality of the included studies?**	**Q5. If the results of the review have been combined, was it reasonable to do so?**	**Q6. What are the overall results of the review?**	**Q7. How precise are the results?**	**Q8. Can the results be applied to the local population?**	**Q9. Were all important outcomes considered?**	**Q10. Are the benefits worth the harms and costs?**
Koshman et al 2008	Yes	Yes	Yes	Yes	Yes	Significant reductions in the rate of all-cause and HF hospitalisations. Results are expressed as Odds Ratio (OD).	All-cause hospitalisation: (OR, 0.71; 95% CI, 0.54-0.94), HF hospitalisations (OR, 0.69; 95% CI, 0.51-0.94).	Yes	Yes	Yes
Kang et al. 2016	Yes	Yes	Yes	Yes	Yes	Significant reduction in all-cause hospitalisations	All-cause hospitalisations: (OR, 0.74; 95% CI, 0.58-0.94)	Yes	Yes	Yes

Critical Appraisal Skilled Programme for RCTs

Author of the study	Q1. Did the trial address a clearly focused issue?	Q2. Was the assignment of patients to treatments randomized?	Q3. Were all of the patients who entered the trial prosperity accounted for at its conclusion?	Q4. Were patients, health works and study personnel blind to treatment ?	Q5. Were the groups similar at the start of the trial?	Q6. Aside from the experimental intervention, were the groups treated equally?	Q7. How large was the treatment effect?	Q8. How precise was the estimate of the treatment effect?	Q9. Can the results be applied to the local population, or in your context?	Q10. Were all clinically important outcomes considered?	Q11. Are the benefits worth the harms and costs?
Barker et al. 2012	Yes	Yes	Yes	No	Yes	Yes	No-significant	Precise results	Yes	Yes	Yes
Korajkic et al 2011	Yes	Yes	Yes	No	Yes	Yes	Significant	Precise results	Yes	Yes	Yes
Lowrie et al. 2012	Yes	Yes	Yes	No	Yes	Yes	Significant	Precise results	Yes	Yes	Yes
Roblek et al. 2016	Yes	Yes	Yes	No	Yes	Yes	Significant	Precise results	Yes	Yes	Yes
Vinulan et al 2014	Yes	Yes	Yes	No	Yes	Yes	Significant	Precise results	Yes	Yes	Yes

Appendixes

Critical Appraisal Skilled Programme for Cohort Study

Author of the study	Q1. Did the study address a clearly focused issue?	Q2. Was the cohort recruited in an acceptable way?	Q3. Was the exposure accurately measured to minimize bias?	Q4. Was the outcome accurately measured to minimize bias?	Q5. Have the authors identified and considered all important confounding factors?	Q6. Was the follow up of subjects complete and long enough?	Q7. What are the results of the study?	Q8. How precise are the results?	Q9. Do you believe the results?	Q10. Can the results be applied to the local population?	Q11. Do the results of this study fit with other available evidence?	Q. 12 What are the implications of this study for practice?
Salas et al. 2015	Yes	Yes	Yes	Yes	Not clear	No	Significant	Precise	Yes	Yes	Yes	Reduction in readmission

Appendixes

Critical Appraisal Skilled Programme for Case Control Study

Author of the study	Q1. Did the study address a clearly focused issue?	Q2. Did the authors use an appropriate method to answer their question?	Q3. Were the cases recruited in an acceptable way?	Q4. Were the controls selected in an acceptable way?	Q5. Were the exposure accurately measured to minimize bias?	Q6a Aside from the experimental intervention, were the groups treated equally? Q6b. Consideration of potential confounders?	Q7. How large was the treatment effect?	Q8. How precise was the estimate of the treatment effect?	Q9. Do you believe the results ?	Q10. Can the results be applied to the local population?	Q11. Do the results of this study fit with other available evidence?
Szkiladz et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Not-significant	Precise	Yes	Yes	Yes

Appendixes

Critical Appraisal Skilled Programme for Interventional Study

Author of the study	Q1. Were participants randomized?	Q2. Was randomization concealed?	Q3. Were participants analyzed in the groups to which they were randomized?	Q4. Were participant in each group similar with regard to known prognostic variables?	Q5. Were participants aware of group allocation?	Q6. Were clinicians aware of group allocation?	Q7. Were outcome assessors aware of group allocation?	Q8. Was follow-up complete?	Q9. How large was the treatment effect?	Q10. How precise was the estimate of the treatment effect?	Q11. Were study participants similar to my own situation?	Q. 12 Were clinically-important outcomes considered?
Anderegg et al. 2014	Not clear	Not clear	Yes	No	Yes	Yes	Yes	Yes	Not significant	Precise	Yes	Yes
Andhuvan et al. 2014	No	No	NA	NA	Yes	Yes	Not clear	Not clear	Significant	Precise	Yes	Yes
Donhao et a. 2015	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Significant	Precise	Yes	Yes
Fera et al. 2014	No	No	NA	NA	Yes	Yes	Yes	Not clear	Significant	Precise	Yes	Yes
Herring et al. 2014	No	No	Yes	NA	Yes	Yes	Yes	Not clear	Non-significant	Not-precise	Yes	Yes
Kalista et al. 2015	No	No	NA	NA	Yes	Yes	Yes	No	Significant	Precise	Yes	Yes
Kinugasa et al. 2015	No	No	Yes	Yes	Yes	Yes	Yes	Not clear	Significant	Precise	Yes	Yes
Lee et al. 2015	No	No	Yes	No	Yes	Yes	Yes	Yes	Significant	Not-precise	No	Yes

Appendixes

Critical Appraisal Skilled Programme for Interventional Study

Author of the study	Q1. Were participants randomized?	Q2. Was randomization concealed?	Q3. Were participants analyzed in the groups to which they were randomized?	Q4. Were participant in each group similar with regard to known prognostic variables?	Q5. Were participants aware of group allocation?	Q6. Were clinicians aware of group allocation?	Q7. Were outcome assessors aware of group allocation?	Q8. Was follow-up complete?	Q9. How large was the treatment effect?	Q10. How precise was the estimate of the treatment effect?	Q11. Were study participants similar to my own situation?	Q. 12 Were clinically-important outcomes considered?
Martinez et al. 2013	No	No	Yes	Yes	Yes	Yes	Yes	Not clear	Significant	Precise	Yes	Yes
Shepherd et al. 2015	No	No	Yes	Yes	Yes	Yes	Yes	Not clear	Significant	Precise	Yes	Yes
Turong et al. 2015	No	No	NA	NA	Yes	Yes	Not clear	Not clear	Significant	Precise	Yes	Yes
Warden et a. 2014	Not clear	Not clear	Yes	No	Yes	Yes	Yes	Yes	Significant	Precise	Yes	Yes

Appendixes

Critical Appraisal Skilled Programme for Qualitative Study

Author of the study	Q1. Was there a clear statement of the aims of the research?	Q2. Is a qualitative methodology appropriate?	Q3. Was the research design appropriate to address the aims of the research?	Q4. Was the recruitment strategy appropriate to the aims of the research?	Q5. Was the data collected in way that addressed the research issue?	Q6. Has the relationship between researcher and participants been adequately considered?	Q7. Have ethical issues been taken into consideration?	Q8. Was the data analysis sufficiently rigorous?	Q9. Is there a clear statement of findings?	Q10. How valuable is the research?
Lowrie et al. 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Valuable

Appendix III: Systematic review protocol registration.

Role of the pharmacist-involved multidisciplinary management of heart failure to improve readmission and mortality rates: systematic review protocol of randomized controlled trials

Daya Ram Parajuli, Constance Kourbelis, Julie Franzon, Peter Newman, Ross McKinnon, Sepehr Shakib, Robyn Clark

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Citation

Daya Ram Parajuli, Constance Kourbelis, Julie Franzon, Peter Newman, Ross McKinnon, Sepehr Shakib, Robyn Clark. Role of the pharmacist-involved multidisciplinary management of heart failure to improve readmission and mortality rates: systematic review protocol of randomized controlled trials. PROSPERO 2016:CRD42016052195 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016052195

Review question (s)

Review question:

What is the evidence from randomized controlled trials (RCTs) for efficacy of a pharmacist-involved in the multidisciplinary management of heart failure (HF) patients to improve HF mortality, HF-related re-hospitalization, medication compliance, HF knowledge and self-care, and cost effectiveness?

Objectives:

The objective of this study is to review RCTs of the pharmacist-involved in the multidisciplinary management of HF to determine the impact in relation to HF mortality, HF-related re-hospitalization, medication compliance, HF knowledge and self-care, and cost effectiveness.

Searches

Electronic search:

An appropriate search strategy will be developed in collaboration with the senior librarian from the University. We will identify trials through systematic searches of the following bibliographic databases and recommended by the Cochrane Heart Group.

The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library

MEDLINE (Ovid)

EMBASE (Ovid)

CINAHL (EBSCO)

PubMed (Ovid)

Web of Science (Thomson Reuters)

Scopus (Ovid)

IEEE Xplore

LILACS (Bireme)

The Cochrane sensitivity-maximizing RCT filter will be applied to MEDLINE (Ovid), and adaptations of the filter will be applied to the other databases, except CENTRAL.

We will search all databases from their inception through March 2017 for all the articles published in English.

Searching other resources:

The references of the retrieved articles and relevant systematic reviews will be hand searched to identify additional relevant articles. We will contact corresponding authors of studies to seek further information on any missed, unreported or ongoing trials. We will search for ongoing clinical trials and unpublished studies on the following clinical trial registers:

ClinicalTrials.gov (www.ClinicalTrials.gov), and

The WHO International Clinical Trial Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)

Types of study to be included

A pharmacist-involved multidisciplinary management model is one where the pharmacist works within the multi-disciplinary team. We will include RCTs (including cluster RCTs and cross-over) of pharmacist-involved multidisciplinary management of HF only. We will include only peer reviewed published studies reported as full-text or peer reviewed conference abstracts.

Condition or domain being studied

Heart failure (HF) is a chronic and debilitating condition resulting from the reduced capacity of the heart to circulate sufficient blood around the body. HF is characterized by poor prognosis, high rates of mortality and morbidity, increasing prevalence, and readmission remains unacceptably high especially in the elderly. The impaired quality of life and heavy economic burden imposed by HF signal the need for improved approaches to HF management to address this high and increasing burden of disease.

As such, alternative models of care are important for HF management. The disease trajectory of HF underlined by poly-morbidities and associated polypharmacy, especially in the elderly population, have driven the development of pharmacist-involved multidisciplinary collaborative approaches. Multidisciplinary team management for HF which incorporates the implementation of evidence based guidelines including pharmacological and non-pharmacological approaches has been recommended by Australian, American and European guidelines; however, this approach has not been comprehensively evaluated in recent years. Therefore, we plan to perform a systematic review to provide up to date, rigorous evidence of the impact of pharmacist-involved multidisciplinary management of HF.

Participants/ population

Inclusion criteria:

Adults (>18 years);

Confirmed diagnosis of chronic heart failure according to NYHA class or any other diagnostic methods predominantly by echocardiography, nuclear imaging, and cardiac magnetic resonance imaging (MRI).

Exclusion criteria:

We will exclude all the RCTs where the pharmacist has not worked in the team for the management of HF;

Non-randomized controlled trials (non-RCTs) and systematic reviews.

Intervention(s), exposure(s)

The pharmacist-involved multidisciplinary intervention could be medication reconciliation, patient education, and collaborative medication management, discharge counseling, pharmaceutical care, telephone follow-up by care transition pharmacist, pharmacist-initiated education to increase HF knowledge, home medication teaching by a community pharmacy, pharmacist managed heart failure clinic, recommendation of disease-modifying medications, reduction of mediation errors and clinically relevant drug-drug adverse drug reactions,and self-adjustment of diuretic dose. However, only the RCTs of pharmacist-involved multidisciplinary management of HF with any kind of above interventions measuring the impact on HF mortality, HF-related re-hospitalization, medication compliance, HF knowledge and self-care, and cost effectiveness as their primary or secondary outcomes will be included in our review.

Comparator(s)/ control

Usual care includes either follow-up by a cardiologist and/or general practitioner in outpatient clinics, as inpatients, in family medical practices or under multidisciplinary heart failure specialist care which does not include a pharmacist in the team.

Context

We will include all studies conducted in outpatient's clinics, involving inpatients, telemonitoring, or home visiting that includes a multidisciplinary approach and involves a pharmacist in the team.

Outcomes (s)

Primary outcomes

Heart failure mortality

Heart failure-hospitalizations

Secondary outcomes

Medication compliance

HF knowledge and self-care

Cost-effectiveness

Data extraction, (selection and coding)

Selection of studies:

Two independent reviewers (P DR and CK) will initially screen the titles and abstracts of the identified publications for inclusion of all the potential studies. Full-text screening will be undertaken where insufficient information ascertained from the title or abstract of a paper. A final list of articles will be identified for inclusion in the review. We will also identify and record reasons for exclusion of the ineligible studies. Disagreements

regarding study selection at any stage will be solved by discussion or if required, we will consult a third person (RC). We will identify and exclude duplicates. We will record the selection process in sufficient detail to complete preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram and characteristics of excluded studies.

Data extraction and management:

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. We will extract the following study characteristics.

Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals, and date of study.

Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline left ventricular ejection fraction, inclusion criteria, and exclusion criteria.

Interventions: intervention, comparison.

Outcomes: primary and secondary outcomes specified and collected, and time points reported.

Notes: funding for trial, and notable conflicts of interest of trial authors.

Two authors (P DR and CK) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (RC).

Both the primary and secondary review authors will transfer data into the Review Manager 5.3 file and will cross check.

Risk of bias (quality) assessment

Two reviewers (P DR and CK) will independently assess the methodological quality of the eligible trials using the domain-based approach to study quality assessment recommended by the Cochrane handbook for systematic reviews of interventions. In cases of disagreement, consensus will be achieved through referral to the third reviewer (RC). Selection bias (randomization and allocation concealment), performance bias (blinding of participants and investigators), detection bias (blinding of outcome adjudicators), attrition bias (differential loss to follow-up), and reporting bias (selective outcome reporting) will be judged to be of low, unclear, or high risk for each trial. We will then judge each trial as a whole to ascertain whether there was low, unclear, or high risk of bias based on Cochrane guidelines. We will summarise the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that have contributed to that outcome.

Strategy for data synthesis

We will analyse dichotomous data as risk ratios with 95% confidence intervals, and continuous data as mean differences or standardized mean differences with 95% confidence intervals. We will enter data presented as a scale with a consistent direction

of effect. We will narratively describe skewed data reported as medians and interquartile ranges.

We will use the I-squared statistic to measure heterogeneity among the trials in each analysis. If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible study biases for the primary outcomes. We will undertake meta-analyses only where this is meaningful, i.e. if the interventions are similar enough for pooling to make sense. We will use a random-effects model, as we expect some heterogeneity in the interventions. We will use the grading of recommendations assessments, development and evaluation working group (GRADE) approach to rate the quality of body of evidence.

Analysis of subgroups or subsets

We will undertake subgroup analysis for our primary outcomes as follows if sufficient number of included studies will be available:

All-cause mortality and HF-related mortality.

All-cause readmission and HF-related readmission.

Dissemination plans

This study is a part of a PhD thesis by publication so a paper for presentation and publication in a relevant scientific journal with the highest impact factor will be the outcome.

Contact details for further information

Daya Ram Parajuli

para0067@flinders.edu.au

Organisational affiliation of the review

Flinders University

http://www.flinders.edu.au/

Review team

Mr Daya Ram Parajuli, Flinders University

Dr Constance Kourbelis, Flinders University

Dr Julie Franzon, Flinders University

Mr Peter Newman, Flinders University

Professor Ross McKinnon, Flinders University

Professor Sepehr Shakib, Royal Adelaide Hospital

Professor Robyn Clark, Flinders University

Anticipated or actual start date

30 March 2017

Anticipated completion date

17 July 2017

Funding sources/sponsors

Heart Foundation Future Fellowship

Conflicts of interest

None known

Language

English

Country

Australia

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Death; Heart Failure; Humans; Interdisciplinary Communication; Medication Adherence; Mortality; Patient Care Management; Patient Readmission; Pharmacists; Treatment Outcome

Stage of review

Ongoing

Date of registration in PROSPERO

01 December 2016

Date of publication of this revision

01 December 2016

age of review at time of this submission	**Started**	**Complet**
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

PROSPERO

This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites

Appendix IV: Search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

#	**Searches**
1	heart failure/ or heart failure, diastolic/ or heart failure, systolic/
2	ventricular dysfunction/ or ventricular dysfunction, left/
3	Cardiomyopathies/
4	((heart or cardiac or myocard*) adj2 (fail* or insufficien* or decomp*)).tw.
5	ventricular dysfunction.tw.
6	(HFpEF or HFrEF or left ventricular ejection fraction or ((preserved or reduced) adj ejection fraction)).tw.
7	(LV dysfunction or (diastolic adj (dysfunction* or failure*)) or (systolic adj (dysfunction* or failure*))).tw.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Pharmacists/ or Pharmacies/ or Pharmacy/ or community pharmacy services/ or pharmacy service, hospital/
10	(pharmacist* or pharmacy or pharmacies or (pharmaceutical adj (service* or care or support))).tw.
11	9 or 10
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	randomi#ed.ab.
15	clinical trials as topic.sh.
16	randomly.ab.
17	trial.ti.

18	12 or 13 or 14 or 15 or 16 or 17
19	exp animals/ not humans.sh.
20	18 not 19
21	8 and 11 and 20

Embase <1974 to 2017 March 20>

#	**Searches**
1	exp heart failure/
2	heart left ventricle function/ or ventricular dysfunction/
3	Cardiomyopathies/
4	((heart or cardiac or myocard*) adj2 (fail* or insufficien* or decomp*)).mp.
5	ventricular dysfunction.mp.
6	(HFpEF or HFrEF or left ventricular ejection fraction or ((preserved or reduced) adj ejection fraction)).mp.
7	(LV dysfunction or (diastolic adj (dysfunction* or failure*)) or (systolic adj (dysfunction* or failure*))).mp.
8	or/1-7
9	Pharmacists/ or Pharmacy/ or hospital pharmacy/ or clinical pharmacy/
10	(pharmacist* or pharmacy or pharmacies or (pharmaceutical adj (service* or care or support))).mp.
11	9 or 10
12	randomized controlled trial/
13	controlled clinical trial/
14	randomi#ed.ab.
15	clinical trial/
16	randomly.ab.
17	trial.ti.
18	or/12-17
19	8 and 11 and 18

CINAHL

#	**Query**
S1	(MH "Heart Failure")
S2	(MH "Ventricular Dysfunction") OR (MH "Ventricular Dysfunction, Left")
S3	TI (((heart or cardiac or myocard*) N2 (fail* or insufficien* or decomp*))) OR AB (((heart or cardiac or myocard*) N2 (fail* or insufficien* or decomp*)))
S4	TI ventricular dysfunction OR AB ventricular dysfunction
S5	TI (HFpEF or HFrEF or left ventricular ejection fraction or ((preserved or reduced) N ejection fraction))
S6	TI ((LV dysfunction or (diastolic N (dysfunction* or failure*)) or (systolic N (dysfunction* or failure*)))) OR AB ((LV dysfunction or (diastolic N (dysfunction* or failure*)) or (systolic N (dysfunction* or failure*))))
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	(MH "Pharmacists") OR (MH "Pharmacy Service") OR (MH "Pharmacy, Retail")
S9	TI ((pharmacist* or pharmacy or pharmacies or (pharmaceutical N1 (service* or care or support)))) OR AB ((pharmacist* or pharmacy or pharmacies or (pharmaceutical N1 (service* or care or support))))
S10	S8 OR S9
S11	(MH "Randomized Controlled Trials") or (MH "Random Assignment") or (MH "Random Sample+")
S12	(MH "Clinical Trials") or (MH "Intervention Trials") or (MH "Therapeutic Trials")
S13	(MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies")
S14	(PT randomized controlled trial) OR (PT clinical trial)
S15	TI (random* or RCT or RCTs) or AB (random* or RCT or RCT*)
S16	TI (clinical* N5 trial*) or AB (clinical* N5 trial*)
S17	TI (controlled N3 (trial* or stud*)) or AB (controlled N3 (trial* or stud*))
S18	TI (clinical* N3 trial*) or AB (clinical* N3 trial*)

S19	TI ((control or treatment or experiment* or intervention) N3 (group* or subject* or patient*)) or AB ((control or treatment or experiment* or intervention) N3 (group* or subject* or patient*))
S20	TI ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*)) or AB ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*))
S21	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S22	S7 AND S10 AND S21

Scopus

(((TITLE-ABS-KEY(((heart or cardiac or myocard*) W/2 (fail* or insufficien* or decomp*)))) OR (TITLE-ABS-KEY((HFpEF or HFrEF or "left ventricular ejection fraction" or ((preserved or reduced) W/1 "ejection fraction")))) OR (TITLE-ABS-KEY(("LV dysfunction" or (diastolic W/1 (dysfunction* or failure*)) or (systolic W/1 (dysfunction* or failure*)))))) AND (TITLE-ABS-KEY((pharmacist* or pharmacy or pharmacies or (pharmaceutical W/1 (service* or care or support)))))) AND ((ABS (randomi?ed OR randomly)) OR (TITLE(trial)))

Cochrane

((heart or cardiac or myocard*) NEAR/2 (fail* or insufficien* or decomp*)) or (HFpEF or HFrEF or left ventricular ejection fraction or ((preserved or reduced) NEAR/1 ejection fraction)) or (LV dysfunction or (diastolic NEAR/1 (dysfunction* or failure*)) or (systolic NEAR/1 (dysfunction* or failure*))) in Title, Abstract, Keywords and pharmacist* or pharmacy or pharmacies or (pharmaceutical NEAR/1 (service* or care or support)) in Title, Abstract, Keywords and (self-care or self-management or self-monitoring or self-efficacy) in Title, Abstract, Keywords , Publication Year from 2013 to 2016 in Trials'

PUBMED

(((((((pharmacist*[tiab] OR "pharmaceutical care"[tiab] OR "pharmaceutical service*"[tiab])))) AND (((("heart failure"[tiab] OR "left ventricular dysfunction"[tiab] OR cardiomyopathy[tiab] OR "left ventricular ejection fraction"[tiab] OR "LV dysfunction"[tiab] OR "systolic dysfunction"[tiab] OR "diastolic dysfunction"[tiab] OR "cardiac failure"[tiab] OR "preserved ejection fraction"[tiab] OR HFpEF[tiab] OR "reduced ejection fraction"[tiab] OR HFref[tiab])))) NOT Medline[SB]))) AND (trial[tiab] OR trials[tiab])

Web of Science

# 1	TOPIC: (((heart or cardiac or myocard*) NEAR/2 (fail* or insufficien* or decomp*)))
# 2	TOPIC: ((HFpEF or HFrEF or “left ventricular ejection fraction”))
# 3	TOPIC: ((preserved or reduced) NEAR/1 "ejection fraction")
# 4	TOPIC: ((“LV dysfunction” or (diastolic NEAR/1 (dysfunction* or failure*)) or (systolic NEAR/1 (dysfunction* or failure*))))
# 5	#4 OR #3 OR #2 OR #1
# 6	TOPIC: ((pharmacist* or pharmacy or pharmacies or (pharmaceutical NEAR/1 (service* or care or support))))
# 7	#6 AND #5
# 8	TI=(trial) OR TS=(randomi?ed OR randomly)
# 9	#8 AND #7

Appendix V: Coding and data analysis guidelines (Phase II)

S1 Table. Method for analysis of evidence-based medicines

This criteria was developed based on 2016 European Society of Cardiology guidelines for indications, and contraindications. However, the dose of each individual drugs was based on Australian Medicine Handbook. Data coding was done by two independent researchers (DRP and Joanne) and discrepancies were resolved in consultation with third researcher (SS). Standard criteria for evaluation of use of different medications in HFrEF and HFpEF are described below.

A. Standard criteria for heart failure with reduced ejection fraction (HFrEF)

Angiotensin converting enzyme inhibitors (ACEIs) inhibitors use or not

3= where there is no indication for ACEIs, or there is contraindication to its use

1= where there is indication and any ACEIs dose is prescribed

0= where there is indication and no contraindication and ACEIs are not prescribed

2= where there is use of ACEIs in presence of clear contraindication such as angioedema, pregnancy, intolerance or hypersensitivity to ACEIs

Indication for ACEIs is EF<40%

Contraindications to ACEIs inhibitors are:

- *Bilateral renal artery stenosis
- Angioedema
- Pregnancy
- Presence of intolerance or hypersensitivity to ACEIs
- *Significant renal dysfunction; serum creatinine >221μ mol/L or 2.5 mg/dL or eGFR<30 mL/min/1.73m^2

- *Systolic BP on sitting or standing of <90 (whichever is less)
  *=Doesn't apply to patients already on ACEIs

ACEIs dose maximum tolerated dose (MTD) (only for those who are on ACEIs)

3= where there is no indication for maximum tolerated dose of ACEIs, or there is contraindication for maximum tolerated dose.
1= where there is indication, and maximum tolerated dose of ACEIs are prescribed
0= where there is indication, no contraindication and maximum tolerated dose of ACEIs are not prescribed.
2= where there is use of MTD of ACEIs in presence of clear contraindication such as angioedema, pregnancy, intolerance or hypersensitivity to ACEIs.

% of maximum tolerated dose who are on ACEIs

- Calculated as the dose given as percentage of lower target dose
- Should be calculated for all cases where ACEIs or not is not blank
- Although the daily dose used is greater than target dose, the maximum % of MTD is 100%

Starting dose and Target dose for Angiotensin converting enzyme inhibitors (ACEIs) inhibitors

	Starting dose (mg)	Target dose (mg)
ACEIS		
Captopril	6.25 t.i.d.	50 t.i.d.
Enalapril	2.5 o.d.	10-20 o. d.
Lisonopril	2.5 o.d.	20-40 o.d.
Ramipril	2.5 b.d.	10 o.d.
Trandolapril	1 o.d.	4 o.d.
Perindopril arginine salt	2.5 o.d.	5 o.d.
Perindopril erbumin salt	2 o.d.	4 o.d.
Fosinopril	5-10 o.d.	10-40 o.d.

β –blockers use or not

2= where there is no indication for β –blockers, or there is contraindication to its use

1= where there is indication and any β –blockers dose are prescribed

0= where there is indication and no contraindication and β –blockers are not prescribed

Indication for β –blockers is EF<40%

Contraindications to β –blockers are:

- Second- or third-degree AV block (in the absence of a pacemaker).
- Critical limb ischemia
- Severe or poorly controlled asthma
- Known allergic reactions/other adverse reaction (drug specific)
- *severe hypotension; systemic blood pressure <90mm Hg (lower of sitting or standing)
- *Heart rate <50 beats/minute (bpm; unless a pacemaker is present).
  *=Doesn't apply to patients already on β –blockers

Whether β –blockers dose maximum tolerated dose (MTD)

2= where there is no indication for maximum tolerated dose of β –blockers, or there is contraindication for maximum tolerated dose
1= where there is indication, and maximum tolerated dose of β –blockers are prescribed
0= where there is indication, no contraindication and maximum tolerated dose of β –blockers are not prescribed.

% of maximum tolerated β –blockers dose

- Calculated as the dose given as percentage of lower target dose
- Should be calculated for all cases where β –blockers or not is not blank
- If actual daily dose is >100% of target dose, then only put in 100%
-

Starting dose and target dose of β –blockers

	Starting dose (mg)	Target dose (mg)
β –blocker		
Bisoprolol	1.25.o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25 b.i.d.
Metoprolol succinate (CR/XL)	23.75 o.d.	190 o.d.
Metoprolol	12.5 b.d.	100 b.d.
Nebivolol	1.25 o.d.	10 o.d.
Atenolol	20 o.d.	100 o.d.

Angiotensin receptor blockers (ARBs) use or not

1= ARB used

0=ARB not used

ARBs EBM use or not

3= where there is no indication for ARBs, or there is contraindication to its use

1= where there is indication, no contraindication and any ARBs dose is prescribed

0= where there is indication, no contraindication and ARBs are not prescribed

2= where the patient is on an ARB but really there is no contraindication to ACEIs and they should be on that instead

Indication for ARBs is EF<40%, and there is documented intolerance to ACEIs

Contraindications to ARBs inhibitors:

- Pregnancy
- Bilateral renal artery stenosis
- previous intolerance or hypersensitivity to ARBs
- Significant renal dysfunction; serum creatinine >221µ mol/L or 2.5 mg/dL or eGFR<30 mL/min/1.73m^2
- Systolic BP on sitting or standing of <90 (whichever is less)

Whether ARBs dose maximum tolerated dose (MTD)

3= where there is no indication for maximum tolerated dose of ARBs, or there is contraindication for maximum tolerated dose
1= where there is indication and maximum tolerated dose of ARBs are prescribed
0= where there is indication and no contraindication and maximum tolerated dose of ARBs are not prescribed.
2= where the patient is on an ARB at maximum tolerated dose without documented intolerance to ACEIs

% of maximum tolerated ARBs dose

- Calculated as the dose given as percentage of lower target dose
- Should be calculated for all cases where ARBs or not is not blank
- If actual daily dose is >100% of target dose, then only put in 100%

Starting dose and target dose for ARBs

	Starting dose (mg)	Target dose (mg)
ARBs		
Candesartan	4 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Losartan	50 o.d.	100.o.d
Telmisartan	40 o.d.	80 o.d.
eprosartan	400 o.d.	600 o.d.
irbesartan	75 o.d.	300 o.d.

Mineralocorticoid/aldosterone receptor antagonists (MRAs) use or not

1= no contraindication and any MRAs dose prescribed
0= no contraindication and MRAs are not prescribed

Contraindications

- Known allergic/other adverse reaction including hyperkalemia (K^+ >5 mmol/L)
- Significant renal dysfunction; serum creatinine >221µ mol/L or 2.5 mg/dL or eGFR<30 mL/min/1.73m2

Presence of MRA contraindications

1= any contraindication for MRA

0= no contraindication for MRAs

Diuretic use or not

1= no contraindication and any diuretic dose prescribed
0= no contraindication and diuretic are not prescribed

Contraindications to diuretics: Drug specific adverse drug reactions.

Presence of diuretics contraindications

1= any contraindication for diuretics
0= no contraindication for diuretics

Digoxin use or not (Which includes if just documented as atrial fibrillation or chronic atrial fibrillation, but not Paroxysmal AF)

1= no contraindication and any digoxin prescribed
0= no contraindication and digoxin is not prescribed

Contraindications to digoxin

- Significant sinus or atrioventricular block (unless the block has been addressed with a permanent pacemaker).
- Trifascicular block if no report of permanent pacemaker
- Contraindicated in second‐ or third-degree heart block (without pacemaker),
- SVT involving accessory pathway (Wolff-Parkinson-White syndrome)
- Ventricular tachycardia or fibrillation (if patient has AICD in situ, then by itself is not a contraindication- is only a contraindication if there is documented history of VT or VF)
- VT and VF if no report of implantable cardioverter defibrillator (ICD) device
- Hypertrophic obstructive cardiomyopathy
- Cor pulmonale (acute and chronic) or constrictive pericarditis.
- Previous intolerance

Digoxin contraindications

- **1=** any contraindication for digoxin
- **0=** no contraindication for digoxin

Digoxin use in presence or absence of atrial fibrillation (AF)

1= used in presence chronic of AF
2= used in absence of chronic AF

B. Standard criteria for heart failure with preserved ejection fraction (HFpEF)

Presence of hypertension or not

1= where hypertension reported in comorbidity list

0= where hypertension has not been reported in comorbidity list

Control of hypertension or not

1= where systolic blood pressure (SBP) is less than 140 (sitting position) and diastolic blood pressure (DBP) less than 90 mm Hg

0= where SBP is > 140 or DBP > 90 mm Hg

Angiotensin converting enzyme inhibitors (ACEIs) inhibitors use or not

1= where any ACEIs has been prescribed

0= where any ACEIs has not been prescribed

β –blockers use or not

1= where any β –blockers has been prescribed

0= where any β –blockers has not been prescribed

Angiotensin receptor blockers (ARBs) use or not

1= where any ARB has been prescribed

0= where any ARB has not been prescribed

Mineralocorticoid/aldosterone receptor antagonists (MRAs) use or not

1= where any MRAs has been prescribed
0= where any MRAs has not been prescribed

Loop diuretic (Furosemide) use or not

1= where any loop diuretic has been prescribed
0= where any diuretic has not been prescribed

Use of thiazide diuretics or not
1= where any thiazide diuretics has been prescribed
0= where any thiazide diuretics has not been prescribed
2= renal function is abnormal (creatinine >221 µ mol/L) and thiazide is not used

Digoxin use or not

1= where digoxin has been prescribed
0= where digoxin has not been prescribed

Presence of Atrial fibrillation (AF)

1= presence of AF
0= no AF

Anticoagulation in Atrial fibrillation

1= patients anticoagulated in presence of AF
0= patients not anticoagulated in presence of AF
2= patients not anticoagulated in presence of contraindications or where there is clear documentation of reason or patient preference.

Contraindications to use of any anticoagulant in AF:

- Patients with increased risk of bleeding such as severe uncontrolled hypertension, recent gastrointestinal bleeding, genitourinary bleeding, active ulceration, or severe thrombocytopenia (platelet count <50,000).
- Patient after intracranial haemorrhage.

Contraindications for use of Warfarin in AF

- Same contraindication applicable for any anticoagulation.
- People non-adherence as well as lack of access to international normalized ratio (INR) monitoring.

Contraindications for use of new oral anticoagulants

- *Dabigatran:* If creatinine clearance <30 mL/min.
- *Rivaroxaban:* If creatinine clearance 30ml/min (as dose is 20mg once daily).

Apixaban: If creatinine clearance <25 mL/minute.

Appendix VI: Ethics approval

From: Health:CALHN Research LNR [mailto:Health.CALHNResearchLNR@sa.gov.au]

Sent: Tuesday, 8 November 2016 2:10 PM
To: Daya Ram Parajuli <para0067@uni.flinders.edu.au>

Cc: Shakib, Sepehr (Health) <Sepehr.Shakib@sa.gov.au>; Robyn Clark <robyn.clark@flinders.edu.au>; Ross McKinnon <ross.mckinnon@flinders.edu.au>; julie.franzon@flinders.edu.au; Scherer, Daniel (Health) <Daniel.Scherer@sa.gov.au> **Subject:** APPROVED LNR: R20161105 - Low/Negligible Risk Research Ethics Application

Dear Daya,

RAH Protocol: R20161105

Project Title: Comparison of the pharmacist-involved multidisciplinary care model with a similar multidisciplinary heart failure team without a pharmacist to determine different clinical outcomes in heart failure patients

Thank you for the email below with attached documentation for the above study for review, including:

- Cover letter dated 28 October 2016
- Study protocol
- CALHN LNR Ethics and Governance Form
- CVs

I have reviewed the document(s) and the study is **APPROVED**, effective **from the date of this email.**

Please accept this e-mail as **Acknowledgement of Receipt, Review and APPROVAL** of the document(s), **on behalf of RAH Human Research Ethics** and retain a copy for your records.

For multi-centre studies a copy of this email must be forwarded to Principal Investigators at every site approved by the RAH HREC for submission to the relevant Research Governance Officer along with a copy of the approved documents.

Your application will be reviewed by the CALHN Research Office who will advise if you need to address any additional issues.

A formal letter will follow in due course. You should not commence the study until you receive this letter.

A/Prof Andrew Thornton
Chairman, Research Ethics Committee
Royal
Adelaide
Hospital ph
(08) 8222
4139 mob:
0418 832
346

Government of South Australia
SA Health

Central Adelaide Local Health Network
Royal Adelaide Hospital Human Research Ethics Committee
Level 4, Women's Health Centre
Royal Adelaide Hospital
North Terrace
Adelaide, South Australia, 5000
Telephone: +61 8 8222 4139
Email: Health.CALHNResearchEthics@sa.gov.au

Approval Date: 08 November 2016

HREC Reference number: HREC/16/RAH/462

CALHN reference number: R20161105
please quote this number in all future correspondence

Prof Sepehr Shakib
Clinical Pharmacology
ROYAL ADELAIDE HOSPITAL

Dear Prof Sepehr Shakib

Project title: Comparison of the pharmacist-involved multidisciplinary care model with a similar multidisciplinary heart failure team without a pharmacist to determine different clinical outcomes in heart failure patients

RE: Audit APPROVAL

Thank you for submitting the above project for ethical review. This project was considered under the expedited approval process of the Royal Adelaide Hospital Human Research Ethics Committee and deemed to be an audit according to the requirements of the National Statement on Ethical Conduct in Human Research. I also note that you have identified an appropriate strategy for review by the Medical Administration of the Institution of any publications arising from the activity prior to their submission.

The documents reviewed and approved include:

- Cover letter dated 28 October 2016
- Study protocol
- CALHN LNR Ethics and Governance Form

GENERAL TERMS AND CONDITIONS OF APPROVAL OF AUDIT:

- Adequate record-keeping and data security is important. The duration of record retention for all clinical research data is 15 years.
- Confidentiality is important. The data collected should as much as possible protect the identity of individuals. Where this is not possible, a separate file of subject identifiers should be maintained such that clinical information is kept separately from subject identifiers.
- You must notify the Research Ethics Committee of any changes which might warrant review of the approval.
- Approval is ongoing. Annual or final reports are ***not*** required.
- The REC must be advised within 30 days of completion so that the file can be closed.

Should you have any queries about the HREC's consideration of your project, please contact Ms Heather O'Dea on 08 8222 4139, or Health.CALHNResearchEthics@sa.gov.au.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until governance authorisation at that site has been obtained. Please contact the CALHN Research Office Health.CALHNResearchLNR@sa.gov.au

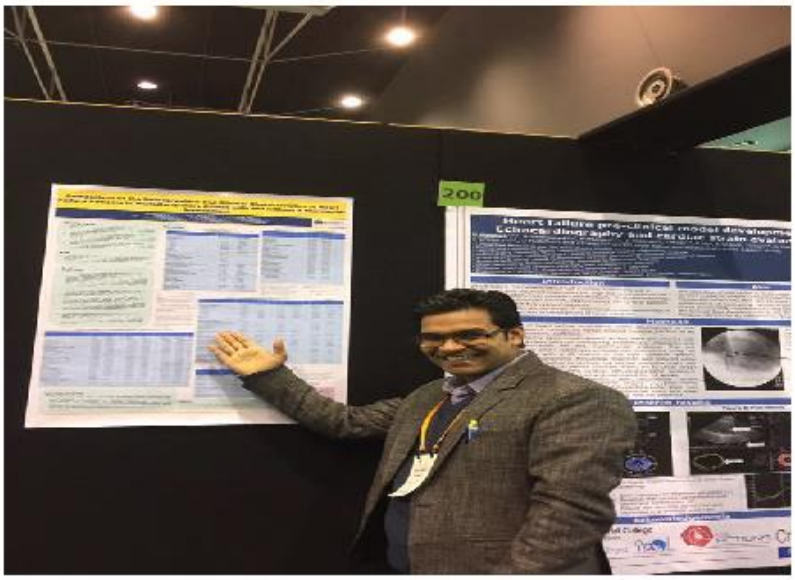
This Committee is constituted in accordance with the NHMRC *National Statement on the Ethical Conduct of Human Research (2007) and incorporating all updates.*

The HREC wishes you every success in your research.

Yours sincerely,

A/Prof A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

Appendix VII. Poster presentation in the 2017 CSANZ Annual Scientific Meeting. 10-13, August, Perth, WA.

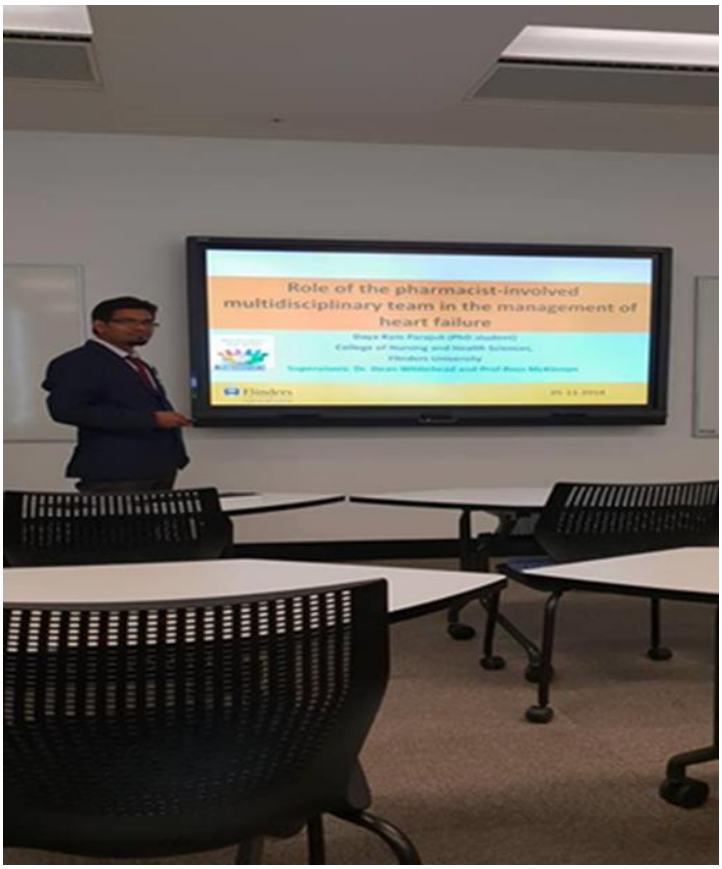


Appendix VIII. Oral presentation in the European Society of Cardiology Congress 2018, 24-29 August, Munich Germany.

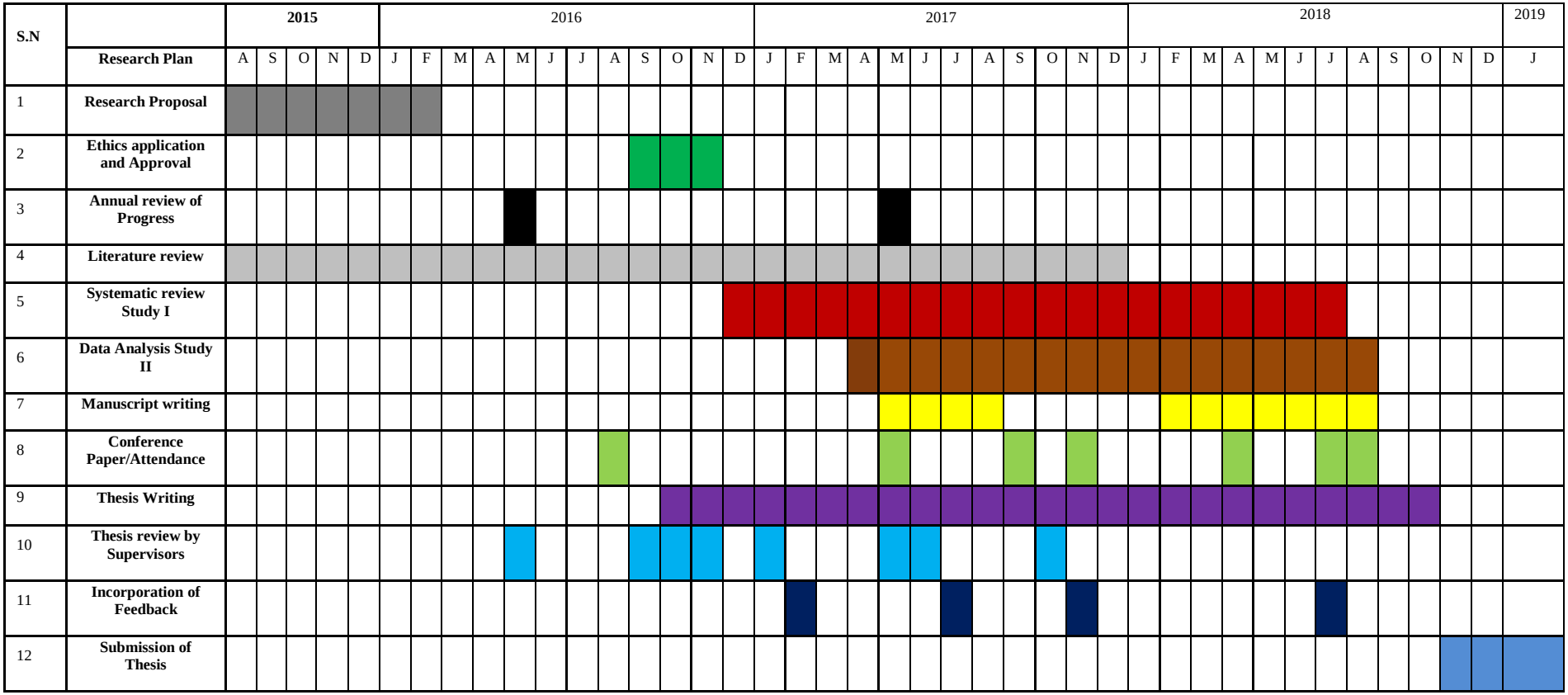
Appendix IX: Poster presentation in Pharmaceutical Society of Australia 2018 Annual Conference, 27-29th July, Sydney, Australia.

Appendix X. Poster presentation in the 2017 South Australian Cardiovascular Research Showcase, 27th October 2017, South Australia, Australia.

Appendix XI: Final PhD presentation



Appendix XII: Gantt chart of the thesis completion.



Appendix XIII. Publication of literature review chapter

Curr Heart Fail Rep (2017) 14:78–86
DOI 10.1007/s11897-017-0323-2

SELF-CARE AND HEALTH OUTCOMES (R GALLAGHER AND R CLARK, SECTION EDITORS)

Role of the Pharmacist for Improving Self-care and Outcomes in Heart Failure

Daya Ram Parajuli[1] & Julie Franzon[1] & Ross A. McKinnon[2] & Sepehr Shakib[3] &

Robyn A Clark[1]

Published online: 23 February 2017

Abstract
Purpose of Review This review highlights the current and emerging approaches for the role of the pharmacist for improving self-care and outcomes in heart failure management. Recent Findings Pharmacists are contributing to heart failure management in a variety of settings, including hospitals, clinics, and communities. Different interventions which may be mediated by the pharmacist include drug adherence, discharge counseling, medication reconciliation, telephone follow-up, and recommendation of evidence-based medicines. Summary Pharmacist engagement in heart failure management has demonstrated improved drug adherence, readmission rates, medication management, self-care ability, patient satisfaction, and heart failure knowledge. Some findings are mixed, especially for readmission rates. Improved medication management was reported in nearly all studies, despite significant heterogeneity in the models of care, patient populations, and study designs. This review highlights the requirement for large randomized trials with extended follow-up to confirm the impact of the role of the pharmacist in HF self-care, particularly through multidisciplinary-based interventions.

This article is part of the Topical Collection on Self-Care and Health Outcomes

Keywords Heartfailure .Self-care .Pharmacist .Medication adherence. Dischargecounseling. Readmission

Introduction

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest

or during stress" [1•]. It is often complicated by multiple comorbidities and is characterized by poor prognosis [2] and high rates of morbidity and mortality [3–5], with hospital readmission rates unacceptably high [6, 7]. Overall prevalence is high and increasing [8–10], and there is a substantial burden of disease in the elderly [9, 11–13]. As such, it represents a rapidly growing public health burden with an estimated 38 million people currently living with heart failure worldwide [14–16].

As with any chronic condition, patient self-care is essential to minimize the impacts and progression of the disease. HF self-care covers a wide range of behaviors including medication adherence and recognition of symptoms as well as management strategies such as daily weighing, exercise, cessation of smoking, healthy diet, and the ability to seek timely help [17–23].

Self-care is a process of learning over time from experience, and an individualized management approach that emphasizes self-care behaviors that must be adopted for HF patients to develop the necessary skills required [24, 25•, 26]. The ability to implement effective self-care practices into daily life, including integrating family into the care process and responding to HF symptoms, are the cornerstones to optimize the outcomes of individual patients [25•, 27••, 28, 29]. Despite this knowledge, self-care in HF patients is poor worldwide [30]. HF patients with multiple comorbidities have been shown to have poor self-efficacy, eventually contributing to low self-care maintenance [31, 32]. Improving self-care management is one of the most promising strategies in HF management [33–35]. In addition, consensus guidelines from Australia [36], Europe [1•], and America [37] have advocated self-care as a critical component of HF management. Incorporation of self-care strategies in the management of HF patients eventually leads to better clinical outcomes, particularly reductions in all-cause and HF-related hospitalization [38–40].

HF patients are optimally supported by a multidisciplinary team, which may include any combination of clinicians appropriate to oversee the ongoing management of the condition. Counseling about self-care in HF has been recommended as a best practice guideline for the clinical pharmacist [41]. When deliberately engaged with HF patients, pharmacists have been successful in the reduction of all-cause and HFrelated hospitalization [42], appropriate medication prescribing [43], reduction of medication discrepancies and prescription errors [44], appropriate use of evidence-based medicines [45••], and the reduction of clinically relevant drug-drug interactions [46••].

To date, the specific benefits of pharmacist involvement in HF management for improving self-care and clinical outcomes have not been thoroughly reported. Therefore, this review focuses on literature published within the past 4 years and examines the issue with regard to the findings of previous studies, aiming to highlight the current and emerging approaches in the contemporary management of HF. A summary of the studies reviewed can be found in Table 1.

Methods

We searched different databases; Medline (Ovid), PubMed (Ovid), Scopus (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO), Cochrane library, and Web of Science (Thomson Reuters) encompassing the period from 2013 through to October 2016 for all relevant articles published in English. We applied the following keywords as a search strategy for all the databases mentioned above: “heart failure” OR “left ventricular dysfunction” OR “cardiomyopathy” OR “left ventricular ejection fraction” OR “LV dysfunction” OR “systolic dysfunction” OR “diastolic dysfunction” OR “cardiac failure” OR “preserved ejection fraction” OR “HFpEF” OR “reduced ejection fraction” OR “HFrEF” AND pharmacist* OR “pharmaceutical care” OR “pharmaceutical service*” AND “*self-care” OR “self-management” OR “self-monitoring” OR “self-efficacy*”.

We also searched the references ofretrieved studies to identify additional relevant articles.

Results

Our preliminary search yielded 82 articles published between 2013 and 2016. After excluding duplicates, 49 articles remained. They were further reviewed by title and abstract as well as full text to remove irrelevant articles. A total of four articles were included. The manual search of the references cited in each publication identified helped us to identify an additional ten relevant articles. The resulting 14 articles were retained for review.

Description of Extracted Evidence

The included studies have been grouped into themes based on the nature of the intervention carried out by the pharmacist. These are as follows:

Discharge Counseling, Medication Reconciliation, and Educational Intervention

These types of interventions are most often initiated atthe time of discharge from hospital, and sometimes throughout the hospital stay. Pharmacists can be involved in general counseling about disease, medicines, and self-care behaviors as well as specific tasks such as medication reconciliation and patient education. The major objective of medication reconciliation is to check whether the patients are receiving the actual list of medicines as prescribed, while educational interventions are targeted to provide information about HF, medications, and self-care management.

Pharmacist-Managed Heart Failure Medication Titration Clinic-Based Intervention

In pharmacist-managed HF clinics, pharmacists are engaged particularly in the optimization of the prescription of current medications. This is generally an ongoing role.

Community Pharmacist Intervention

Community pharmacists provide services to HF patients about disease, medications, and self-care management either in a community pharmacy setting, or in their homes.

Pharmacist-Led Transition of Care Intervention

Pharmacists may have a specific role during the transition of patients from hospital to home to provide optimal care. While

Table 1 Characteristics of included studies

Source	Study design	Sample size	Study population (country)	Mean age of patients (years)	Key components of pharmacist intervention (setting)	Usual care description	Duration of follow-up (months)
Anderegg et al. 2014 [47]	Observational pre-post analysis	3316	Hospital patients (USA)	54	Medication reconciliation on discharge for high risk patients (hospital)	No/limited medication reconciliation	1
Andhuvan et al. 2014 [48]	Prospective interventional study	83	HF patients (India)	–	Counseling for medication adherence (hospital)	–	6
Donaho et al. 2015 [49]	Retrospective chart review	169	HF patients (USA)	59	Medication education and reconciliation, medication up-titration, discharge planning (clinic)	–	1
Fera et al 2014 [50]	Retrospective observational	175	HF/COPD patients (USA)	175	Medication therapy review, patient education, telephone follow-up (hospital/clinic)	–	1
Kalista et.al 2015 [51]	Observational	10	Recently discharged HF patients (USA)	81	A community pharmacist-provided in-home medication reconciliation and teaching service for patients within 1 week of admission, 2 follow-up telephone calls 1 week and 4 weeks after the visit (outpatients)	–	1
Kinugasa et al. 2014 [52]	Retrospective review	277	Hospitalized HF patients (Japan)	–	Intensive medication education and medication adherence review on admission and discharge	–	–
Lowrie et al. 2014 [53]	Focus groups and interviews	65	Chronic HF patients (Scotland)	67	Community pharmacy-based cognitive services (Community)	–	–
Martinez et al. 2013 [54•]	Retrospective chart review	28	HF patients (USA)	79	Prescribing privileges, adjust medication dosages under specific protocols jointly established by cardiology and pharmacy staff (Outpatient HF clinic)	Nurse or physician runs the titration clinic without pharmacist	6
Salas et al. 2015 [55••]	Prospective pilot study	30	HF patients (USA)	57	Tailored medication and disease counseling, discharge medications, telephone follow-up (hospital/outpatients)	–	1
Shepherd et al. 2015 [56]	Prospective interventional	48	HF patients (USA)	69	Education on HF pathophysiology and its pharmacologic and non-pharmacologic treatment (Community hospital)	–	1
Szkiladz et al. 2013 [57]	Non-randomized intervention	180	HF patients (USA)	71	Discharge counseling (hospital)	Standard discharge counseling by nurse	1
Truong et al. 2015 [58]	Retrospective review	632	HF patients (USA)	68	Medication reviews, daily monitoring, discharge counseling, post-discharge follow up (hospital/outpatients)	Usual inpatient and discharge care—usually written instructions or educational material	1
Vinluan et al. 2015 [59]	RCT—pilot	16	HF patients (USA)	–	Individualized inpatient counseling (disease, medications, self-care) and telephone call follow-up	Standard discharge counseling by nurse	3
Warden et al. 2014 [60]	Quasi-experimental pre-post analysis	115	HF patients (USA)	56	Data collection, admission monitoring, discharge medication reconciliation, recommendations, instructions, and advice. Telephone follow-up	Admission medication reconciliation by physicians. Discharge counseling by nursing staff	1

this caremay cover some of the same aspects asthe in-hospital counseling, education, and medication reconciliation described in the first theme, care transition pharmacists are focused on the continuum of care from hospital to home, and will usually provide follow up care for a period of time.

Discharge Counseling, Medication Reconciliation, and Educational Intervention

A small randomized control trial (RCT), which was the only RCT identified, conducted by Vinluan et al. [61] assessed the impact of pharmacist vs nurse discharge counseling on medication adherence and hospital readmission rates in a very small sample of elderly HF patients (n=16) in the USA. They found evidence to suggest that pharmacist intervention resulted in improved medication adherence within the first 2 months after discharge, but that this effect disappeared after 3 months. Mortality was lower, but readmissions were higher in the pharmacist intervention group. This study was significantly limited by a high rate of attrition on an already small initial sample, and the authors do suggest that longer term and/ or more intense follow-up may be necessary to maintain the improvement in medication adherence.

While the RCT provides the highest level of evidence, other types of studies are also valuable to illustrate the types of interventions which are being adopted, and the results which are being obtained. A number of non-RCTstudies have investigated the effects of pharmacist participation in education for HF patients either during hospitalization or at discharge [48, 56, 57, 59, 60]. Improvements in medication adherence and/or patient knowledge about their medications were reported in all cases, and this is likely to translate into improved self-care capability and more positive clinical outcomes.

Hospital readmission rates are the frequently reported outcome of pharmacist involvement in HF patient management. Patient education by a pharmacist has been shown to reduce both all-cause [47, 57, 58, 60] and HF-specific [50, 52] readmission rates in a number of studies. However, results are not entirely consistent, with several studies—including the RCT discussed earlier—finding either no difference or a higher rate of readmissions [48, 56, 61].

Mortality rates are also of particular interest as a clinical outcome of HF management strategies. While the duration of the majority of studies reviewed was limited to a 30-day follow-up, two studies did report all-cause mortality. Results were mixed, with one study

reporting lower mortality [61] and one reporting no effect [50]. It is likely that a longer follow up time is needed to detect any significant mortality patterns.

Readmission and mortality rates are important statistics for demonstrating the efficacy of interventions; however, many studies report additional findings which both inform and support the importance of pharmacist involvement in the management of HF. A study conducted in India additionally identified some of the main barriers to effective medication adherence in their study population, including forgetfulness (63.0%), being reliant on others to purchase medication (39.7%), and polypharmacy (27.7%) [59]. Based on these results, the authors also concluded that continuous follow-up was an important factor in ongoing medication adherence. Further to this, a review of HF self-management interventions in general concluded that patient characteristics such as low income, poor literacy, and low education levels were more likely to be associated with poor self-management capacity than characteristics such as age, gender, and ethnicity (among others) [51]. While the barriers are likely to change in different settings, pharmacist awareness of these constraints is essential for them to effectively contribute to and monitor selfcare behavior.

There can also be additional economic benefits beyond hospitalization costs. A study by Skiladz et al. [56] reported that, despite no significant difference in readmission rates being observed in the intervention group (n = 86), a total of 34 medication errors were documented and it was estimated that the detection of these resulted in a cost avoidance of over $4,000. Donaho et al. [62] also reported a high rate of medication errors detected.

The proportion of HF patients receiving optimal care—for example, all facets of discharge planning and instruction completed—has also been shown to improve with the inclusion of a pharmacist in the care team [49, 50, 60]; while overall patient satisfaction with their care, and confidence in their level of knowledge, has also been an important outcome for some studies [54•, 57]. The majority of clinical studies do not include a qualitative component, or even administrative assessments, but measures of adherence to best practice and the level of patient satisfaction may reflect improved engagement with both professional and self-care HF management, and may be an important component of improved clinical outcomes.

The majority of the studies discussed above have reported on the role of the pharmacist in a hospital setting, particularly their involvement in discharge procedures and education. Some also report some level of post-discharge follow up—usually by telephone [48, 60]. However, pharmacists operate in many different settings, and can contribute to the management of HF through different models of care. The following sections discuss some

specific examples where pharmacists operate in unique settings to deliver medication expertise and advice, either directly to HF patients or to support the wider clinical team.

Pharmacist-Managed Heart Failure Medication Titration Clinic-Based Intervention

Pharmacists are often involved in HF management in a clinic setting, usually as part of a multidisciplinary team. Martinez et al. [49] described the impact of a pharmacist-managed medication titration clinic in the USA, operating as an adjunct to the regular care multidisciplinary clinic, on the percentage of HF patients (n=28) achieving optimal dosages of critical medications. The pharmacists used patient telephone interviews and tele-monitoring technology to track patient's clinical measurements on a daily basis and were able to adjust medication dosages in line with specific protocols as well as offering education and advice during each telephone contact.

Outcomes for these patients were compared to those whose dosage titrations were carried out by other clinicians in a multidisciplinary clinic setting only. The results of this study found that target medication doses were achieved in a significantly higher percentage of pharmacist-managed titration clinic enrollees for the evidence-based medications prescribed. The outcomes of this study did not include mortality rates or HF-related hospital readmissions.

This intervention is unique among those reviewed for the high intensity of engagement and the subsequent dosage control, as well as the innovative use of technology. It is hoped that readmission and/or mortality rates will be reported in the future.

Community Pharmacist Intervention

Pharmacists can also contribute to HF management in a community setting, often as part of a community pharmacy practice. Lowrie et al. [54•] investigated the impact of a community pharmacist HF service in the UK on medication adherence and self-care management in chronic HF patients (n=65), using a focus group with pharmacists and semistructured interviews with individual patients. The results suggested that the community pharmacists felt confident in providing adequate information to improve adherence and selfcarein HF patients, and valuedthe opportunity to contribute to this program. In addition, patients welcomed the opportunity for discussion with the pharmacist to supplement the care and information they received from their general practitioner. Expressed views indicated that patients generally had an increased understanding of their condition and its treatment, and that participating in this service improved medication adherence for at least some patients.

In another UK-based study, in conjunction with the visiting nurse service, a community pharmacist-provided in-home medication teaching service was initiated and evaluated for medication adherence and hospital readmission rates for HF patients following recent hospital discharge [52]. Each patient received one in-home visit followed up by telephone calls at 1 and 4 weeksafter the pharmacist's visit.Although only a small study (n=10), the results showed that this type of support helped facilitate the successful transition of care from an inpatient to outpatient setting, improved medication adherence, and reduced hospital readmission rates. The expansion of this service to reach a wider range of patients would serve to augment these benefits.

Pharmacist-Led Transition of Care Intervention

The engagement of pharmacists to support the transition of patients from hospital to home is an emerging area of research in HF management. A recent systematic review [53] of transitional care strategies, while not specifically evaluating pharmacist contributions, stresses the importance of medication reconciliation and adherence and does recommend that pharmacists be involved in medication reconciliation as part of a transitional care team.

Fera et al. [47] describe a USA-based case study about the contribution of the care transition pharmacist (CTP) in a primarycareresourcecenter. The CTP reviewedmedications and provided patient education and support during admission, and provided follow-up support via telephone within 3 days of discharge. The likelihood of 30-day hospital presentation was reduced among the patients receiving a follow-up telephone call from a CTP.

Similarly, a prospective, single-center pilot study in the USA was conducted where a pharmacy resident ran a transition of care service to determine its impact on readmission rates in patients (n=30) with HF [63]. Pharmacists were engaged in counseling about medications and diseases, medication reconciliation, and follow up appointment reminder telephone calls. Overall, the 30-day HF readmission rate decreased from 28.1 to 16.6%, and the majority of patients (88%) attended their follow up appointments.

In a third study from the USA, Donaho et al. [62] performed a retrospective chart review to determine the effect of a pharmacist-involved multidisciplinary clinic on 30-day hospital readmissions in newly discharged congestive HF patients (n=169). The team monitored physical and clinical signs and performed education, medication adjustment and titration, care coordination, and referral recommendations as warranted. This approach showed a 44.3% reduction compared to the hospital's average 30- day readmission rates.

Discussion

There has been a large range of interventions studied across diverse countries addressing different potential contributions which pharmacists can make. This is because the role of pharmacists in different countries and different healthcare settings is not standardized, hence it is difficult to make any specific conclusions. However, there are some overall trends evident.

This review suggests that pharmacist involvement in HF self-care generally leads to positive clinical outcomes, although there are some exceptions. Evidence for the current review has come from a number of settings and several countries over the past 4 years. To our knowledge, this study is the first to comprehensively summarize the specific role of the pharmacist in improving self-care and outcomes in HF patients over this time period.

The pilot RCT by Vinluan et al. [61] showed improved drug adherence as well as a decrease in readmission rates in the first month after discharge. However, the outcomes were not maintained in successive months. This result agrees with earlier findings that improved medication adherence in the pharmacist-involved management of HF were not sustained after the end of the intervention [55••] and that only longer duration interventions in self-management can bring improvement in clinical outcomes in HF [64]. In this context, we can hypothesize that pharmacist-mediated drug interventionto improve long-term adherence must be ongoing to result in improved clinical outcomes.

Although the RCT by Vinulan et al. used a very small sample size and a significant proportion of participants were lost to follow up, these results are important in demonstrating the potential of pharmacist contributions to improved drug adherence in HF management. This is supported by the results of the observational studies, which also found improvements in drug adherence [52, 54•, 57, 59], as well as reduction of 30day readmission rates, and improved patient satisfaction with information provided by pharmacists regarding self-care [52, 54•, 57, 58].

A recent systematic review identified a significant reduction of readmission and mortality rates associated with the implementation of interventions to improve medication adherence among HF patients [65]. The results of the studies reported here support these findings. Reduction of 30-day all-cause readmission rates has been found to be mediated by pharmacist-involved medication reconciliation, and discharge education [58] as well as

pharmacist led-transition of care intervention [47, 62, 63]. Similarly, improved 30-day HF-specific readmission rates have been found [44, 45••, 46••, 47, 48, 50, 56–61, 63].

However, we also found some contrasting results on the impact of the pharmacist on readmission rates. Despite other benefits (increased knowledge, detection of medication errors), no significant change in readmission rates was found in several studies [48, 56, 61].

Despite these anomalies, the trends reported here generally support the findings of Koshman et al. [42] who conducted an early systematic review (2008), including only RCTs, to assess the role of pharmacists in the care of patients with HF. In this review, pharmacist care was associated with significant reductions in the rate of all-cause hospitalizations (11 studies [2026 patients]; OR=0.71; 95% CI=0.54–0.94) and HF hospitalizations (11 studies [1977 patients]; OR=0.69; 95% CI=0.51–0.94) and a non-significant reduction in mortality (12 studies [2060 patients]; OR=0.84; 95% CI=0.61–1.15). Pharmacist-collaborative care (pharmacist role is a component of a multidisciplinary intervention) led to greater reductions in the rate of HF hospitalizations (OR=0.42; 95% CI=0.24–0.74) than pharmacist-directed care (pharmacist initiates, and manages the intervention) (OR = 0.89; 95% CI=0.68–1.17). The findingsof this review indicatethat pharmacist care in the management of patients with HF greatly reduces the risk of all-cause and HF-specific hospitalization, particularly if the pharmacist was a member of a multidisciplinary team, and this finding is supported by the more recent evidence gathered here.

A more recent systematic review performed by Kang et al., which included both RCTs and non-RCTS, of pharmacist involvement in care for HF and acute coronary syndrome (ACS) also reported beneficial outcomes [45••]. Reductions in allcause hospitalization and increased prescription rates of angiotensin converting enzyme inhibitors (ACEIs) and βblockers were found in the pharmaceutical care group, but the authors concluded that the strength of evidence for other outcomes was insufficient or low. They suggested that the diversity of care and the heterogeneity of patient populations and clinical settings likely contributed to the inconclusive results, and these same effects could also explain the mixed findings in these areas in our review.

The strongest evidence of the benefits of pharmacist involvement in HF management and self-care from both the recent systematic review [45••] and our current review is around medication management, including medication reconciliation, use of evidence-based medicines, appropriate prescribing, dose-titration, and patient adherence. This finding is

also in accordance with earlier studies, where pharmacist counseling in self-care in HF patients has been reported to support the appropriate adjustment of diuretic dose [66]; and the use of evidenced-based medicines improved after the incorporation of a pharmacist-involved multidisciplinary team despite a high number of comorbid conditions and the resulting complexity of management [67••].

Conclusion

Pharmacist involvement in HF self-care has demonstrated specific benefits, particularly around improvements in drug adherence, decreased 30-day readmission, HFhospitalization, better utilization of evidence-based medicines, increased self-care management ability, increased patient satisfaction, and increase in HF knowledge. However, the results are mixed especially for improvement in readmission rates, and this is probably driven by the heterogeneity of the studies reviewed and the relatively short length offollow up in most studies.

Despite these mixed results, we found consistent evidence for the benefits of pharmacist involvement in HF management around medication management, and improving self-care behaviors, particularly drug adherence. These benefits are likely to translate into improved clinical outcomes, but interventions may have to include extended patient contact and longer term follow-up measurement to observe related improvements in hospital admission and mortality rates. This review highlights the importance of large randomized trials with extended follow-up time to definitively measure the impact of the role of the pharmacist in HF self-care, particularly through multidisciplinary-based interventions.

Acknowledgements

The authors would like to acknowledge the assistance of Mr. Peter Newman, Senior Librarian, Flinders University. Prof Robyn Clark is support by a Heart Foundation Future Leader Fellowship (APP100847-2016-2019).

Compliance with Ethical Standards

Conflict of Interest Daya Ram Parajuli, Julie Franzon, Ross A. McKinnon, Sepehr Shakib, and Robyn A Clark declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance' •• Of major importance

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