A systematic review of the evidence in support of palliative care in people with persistently symptomatic heart failure

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Abstract

Background: Heart failure is common. People with advanced stages of the disease are symptomatic and have poor quality of life. Despite recommendations, this population have little access to palliative care. A barrier for people with heart failure accessing palliative care is clinicians' perceptions that there is little or no evidence to show that palliative care is beneficial in this patient group.

Aim: The thesis aims is to identify the evidence in support of palliative care in heart failure management.

Methods: A systematic review was conducted of the current evidence in support of palliative care in people with persistently symptomatic heart failure. Medline, Cochrane database, CINAHL, PsycINFO, HMIC, Care Search Grey Literature, reference lists, and citations were searched and experts were emailed for studies about 'persistently symptomatic heart failure' and 'palliative care'.

Results: Two researchers screened 7,005 titles and abstracts independently. Seven phase III trials, one phase II trial, one non-randomised quasi-experimental trial, five cohort studies, and one case-control study were included. Studies were heterogeneous in terms of population, intervention, comparator, and outcomes. However, study designs with adequate power and a multi-disciplinary palliative care intervention showed benefit for a variety of patient-reported outcomes such as symptom burden, depression, functional status, and quality of life, as well as, administrative outcomes such as resource use and costs of care.

Discussion: Overall, the results support the use of palliative care in managing patients with heart failure; however, findings were not consistent across all studies. Various methodological issues may contribute to discrepant results, and effect may have been under-estimated in several studies due to risk of contamination of controls. Further research is needed to understand which patients would benefit most from general and specialist palliative care.

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Author's Declaration

‘I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources.’

Chapter 1 – Introduction, Background and Rationale

Evidence based practice has developed into a cornerstone of modern medicine, where all interventions and service provisions are modelled and tested for safety, efficacy and efficiency in order to provide the best possible care for the public. As the emphasis on practising evidence-based medicine grows, this thesis aims to establish the current role of a palliative care approach in heart failure and assess the quality of the evidence supporting its use.

This chapter aims to lay the thesis' foundation by setting the scope of the terms 'palliative care' and 'heart failure'. It also covers the circumstances in which the two disciplines find common ground to improve the patients' quality of life and disease experience. The chapter will also attempt to summarise the current guidelines and policies available across the country, and the globe, that promote the merging of these two disciplines at relevant points of the disease course. Finally, it will aim to outline the barriers to people with chronic heart failure achieving equitable palliative care compared to patients with advanced cancer.

1.1 Palliative care

1.1.1 History

While the concept of palliation has been around for centuries, the speciality itself originated from care provided in hospices and research conducted in the latter half of the 20th century. In the 1950s, doctors, social workers, and social scientists around the world began to produce literature on the psychological, social, and medical aspects of dying, including the implications for the bereaved, in response to concerns of medical neglect among this population. [(1)] Among these researchers was Dame Cicely Saunders who coined the term 'total pain', encompassing the physical, mental, emotional and social aspects of the patient's distress. [(2)] The multidisciplinary approach in palliative care originates from such concepts.

The founding of St. Christopher's Hospice in 1967 by Dame Cicely Saunders is widely considered as the beginning of the modern hospice movement. This hospice, unlike those before it, allowed physicians to care for patients with incurable disease, as well as, conduct research and teach the principles of end-of-life care; a three stranded approach of clinical practice, education, and research. Due to the success of this hospice, other hospices mainly

funded by charity, community, and hospital palliative care teams, often NHS funded, with the same fundamental values began to emerge. The rapid expansion of this new field eventually led to palliative medicine being established as a subspecialty of general medicine in the late 1980s.

1.1.2 Definitions

The term palliate, meaning 'alleviate without curing' originates from Latin, *palliāre*, meaning to cover up or cloak. [3] While this term is easily defined, the scope of palliative care is constantly evolving and, consequently so is its definition. The World Health Organisation (WHO) definition of palliative care (Box 1) is most commonly used or adapted for guidelines both nationally and internationally. The most recent version (2002) [4] highlights the core aims of palliative care – early identification and assessment, and improving quality of life. Most importantly, it echoes the idea of 'total pain' by employing the multidisciplinary approach to address the physical, psychosocial, and spiritual needs of the patient as well as their family. In the context of this thesis, it is also important to note that the definition talks about 'an approach', which may be delivered by all clinicians using basic palliative care skills, or by a specialist multidisciplinary team. Specialist palliative care clinicians are those for whom palliative care is their core business and who have undertaken specialist training. During the inception of the subject it was aimed at those nearing the end of life, however, palliative care has since expanded its reach to earlier in the disease course where it has been shown to benefit patients when used 'in conjunction with other therapies intended to prolong life'. [4-8]

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;

- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Box 1: Adapted from the WHO definition of palliative care [4]

Unfortunately, difficulty arises when terms such as supportive care, holistic care, palliative care, and patient-centred care are used interchangeably. Misinterpreting these phrases to mean the same as 'care of the dying' often prevents physicians from referring patients appropriately and in a timely manner, if at all.

According to 'The Manual' developed by the National Institute for Health and Care Excellence (NICE) on Improving Supportive and Palliative Care, supportive care is thought of as an 'umbrella' term used to describe any form of support given to patients and their families from pre-diagnosis through to death and bereavement, aimed at maximising the benefits of treatment. It includes self-help, information given and symptom control, as well as palliative care. NICE also states that supportive care is a 'not a distinct speciality' but a shared responsibility. [9]

Patient-centred care is about the shared partnership between the physician and the patient in the management of the condition. It emphasises the importance of considering the patient's belief, background, preferences, and values when devising a tailored management plan.

Holistic or comprehensive care is often considered an essential component of supportive care, patient-centred care and palliative care where a multi-dimensional approach should be

taken, including the physical, emotional, social, psychological, economical, and spiritual needs of the patient.

While similar in ideology, these terms differ from palliative care in a few ways. Supportive, patient-centred, holistic care is designed to be provided to patients with any ailments from a painful toe to breast lump, however palliative care is aimed at chronic, progressive, life-threatening conditions with no cure. Additionally, unlike the others, specialist palliative care has 'well-defined areas of expertise... to which patients and carers may need access'. [9]

In contrast, terms such as end of life care or terminal care, which may be used interchangeably, [10] have a prognostic connotation associated. They may be provided as part of palliative care, or provided unaccompanied if there is a rapid and unexpected decline in health. Patients receiving such care are thought to have progressive decline of health with no hope of recovery. The nature of the terms implies a short prognosis, however, the expected survival duration varies among the literature. NICE and United Kingdom (UK) health policies often advocate the use of end of life care for those determined to be in the last 12 months of life. [11]

1.1.3 The evolving role of palliative care in modern medicine

The National Health Service (NHS) is under strain due to the high demands placed on it by the aging population. A growing number of patients are being rescued from sudden death following acute illnesses; however, the fragmented infrastructure of medical services and burdensome underlying disease process can lead to patients in need falling through the cracks. Palliative care is a multidisciplinary specialty of medicine dedicated to supporting patients and their families through the course of incurable diseases. Therefore, palliative care is well placed to bridge gaps between the care provided by general practitioners (GPs) and the hospital clinicians and thus maintain continuity of care.

Historically, palliative care was reserved for cancer patients who no longer responded to curative treatment and focused on pain management. The service has since broadened its scope and evolved to encompass the management of other physical symptoms, alongside providing emotional and spiritual support to truly target patients' 'total pain'. Additionally, patients and their families were given more information and played a more active role in the management, in order to preserve autonomy and instil feelings of preparedness.

Subsequently, palliative care extended beyond the terminal phase of illness due to the 'understanding that problems at the end of life have their origins at an earlier time in the trajectory of the disease' [12], so that it can preserve quality of life. Furthermore, towards the end of life, a greater focus was given to the concept of providing 'a good death' for patients.

Due to the evolving nature of palliative care, what is delivered (components) and how it is delivered (care model) has developed over time.

1.1.3.1 Components of care

Palliative care is comprised of services designed to enhance the patients' quality of life. Patients identified various factors that are important to them and contribute to their quality of life. These include symptom management, having a sense of control and feeling prepared, strengthening relationships, and having treatment decisions in place to avoid inappropriate prolongation of death. The consensus report for the national framework and preferred practices for palliative and hospice care quality recognises eight domains of care (Box 2) designed to address the issues important to patients. [13]

Domain 1	Structures and Processes of Care
Domain 2	Physical Aspects of Care
Domain 3	Psychological and Psychiatric Aspects of Care
Domain 4	Social Aspects of Care
Domain 5	Spiritual, Religious, and Existential Aspects of Care
Domain 6	Cultural Aspects of Care
Domain 7	Care if the Imminently Dying Patient
Domain 8	Ethical and Legal Aspects of Care

Box 2: 8 Domains of palliative and hospice care [13]

Adequate symptom management is at the forefront of palliation. The review conducted by Higginson *et al.* [14] identifies beneficial effects of palliative care in symptom management. Other studies have identified improvement in quality of life, mood, length of survival,

satisfaction with care, and reduction in hospital re-admissions and healthcare costs. [5, 7, 15-17]. Co-ordination of care and establishing goals of care early in the course of the disease is a vital principle of palliative care. With regards to care of the imminently dying patient, in the last few days of life it is important to keep the patient comfortable according to their wishes, in addition to maintaining dignity and protecting their human rights.

1.1.3.2 Models of care

Palliative medicine, unlike other specialties, offers a great deal of flexibility in service delivery. The important variables within the delivery of palliative care are where it is delivered, who delivers the care, and at what point along the disease course it is initiated.

Palliative care may be hospice, hospital, or community based. [18, 19] Depending on the local infrastructure available, hospital palliative care teams may provide consultation services as a secondary advisor to the referring physician or may have an inpatient unit, where they assume primary responsibility. Inpatient units are often reserved for patients with complex issues as other wards are less well equipped to these needs. Alternatively, palliative care can also be delivered in the community, in either patients' homes or other residential living settings such as nursing homes. An ambulatory palliative care team often responds to patients' needs and acts to prevent hospitalisation where possible and appropriate. The hospice model of palliative care is often a source of confusion. This confusion has arisen because, traditionally, it provided a comprehensive service for the terminally ill patients, but now the scope is extended to a problem-based approach whereby patients may also be admitted for symptom management much earlier on in the disease, and thereafter discharged home again. The term 'hospice' in the United States of America (USA) is also used specifically in relation to funded care in the last few months of life, often community based, which causes further confusion in the UK and elsewhere where 'hospice' and 'palliative care' are often used interchangeably.

Due to the evolving nature of palliative care and calls for access to palliative care to a wider range of patients, non-specialists take on a more prominent role in provision of palliation. GPs and other specialists are often required to screen and support the patient where possible, by providing appropriate information, addressing distressing symptoms and providing a holistic care program. Specialist palliative physicians and nurses are trained to

contend with cases that are more intricate and support front-line clinicians when needed. The multidisciplinary palliative care teams made up of physicians, nurses, social workers, and chaplaincy act as a tertiary level of care where issues are raised, discussed and resolved with the input of all members.

The point of access into palliative care is a much debated topic [20] and it is often linked to the trajectory of the disease. Murray *et al.* [21] describes the three iconic disease trajectories of chronic conditions (Box 3) and its implications for palliative care.

Trajectory 1	Steady progression with clear terminal phase
Trajectory 2	Gradual decline punctuated by episodes of acute decline and some recovery, followed by sudden, unexpected death
Trajectory 3	Prolonged gradual decline

Box 3: Typical illness trajectories [21]

The traditional model of palliative care was designed for cancer patients who followed trajectory 1. This model had a sharp transition point when the patient stops responding to curative treatment. Over time, as palliative care grew out of its identity as end of life treatment only, newer models have developed and the traditional cancer trajectory has changed for many cancers to one of chronic disease. Models of phased transition or simultaneous care approach better fit the trajectories 2 and 3 often experienced by those with organ failure. They promote partnership between curative and palliative medical teams and ensure continuity of care. Further down the disease course, if it is appropriate, palliative care takes on a bigger role to provide hospice and bereavement care in order to prepare patients and their families for the end.

1.2 Heart failure

1.2.1 Definition

The European Society of Cardiology (ESC) defines heart failure as a clinical syndrome caused by an abnormality of cardiac structure or function resulting in features of fluid overload such

as breathlessness, ankle swelling, and fatigue. [22] It worsens health status, shortens survival, and increases the risk of hospitalisation. [23]

Heart failure is an umbrella term most often used to describe patients with reduced left ventricular ejection fraction (LVEF). However, there are a subsection of patients with heart failure who have preserved ejection fraction (HF-PEF), and therefore, a normal LVEF. These patients have heart failure, as demonstrated by an elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP), due to diastolic dysfunction. Those with reduced LVEF, are better delineated in research and there is a better understanding of the pathophysiology and natural history of the disease process. There is therefore a greater emphasis on people with LVEF in this thesis, but this merely reflects the published literature, and this is not exclusive.

1.2.2 Epidemiology

It is estimated that over 23 million people worldwide are affected by heart failure. [24] However, the epidemiology of this condition is a much debated topic, as the data available on the subject varies depending on the population studied, with very little documented in developing countries. Some gaps in the data are attributed to the difficulty in diagnosing the condition, as the early symptoms are neither sensitive nor specific.

Heart failure has been categorised as an evolving epidemic, however the factors behind this are complex and hold the key to understanding the epidemiological trends of this condition. It is theorised that the increasing prevalence of heart failure may be due to a combination of the aging population and an improvement in medical management of heart failure, leading to increased survival and a shift from acute illness to chronic condition. Additionally, improved management of myocardial infarctions means that a greater number of people are surviving with a damaged left ventricle.

It is widely understood that the incidence of heart failure increases steadily with age. [25] Similarly, prevalence increases as age increases, as seen in a study in Rotterdam [26], with the overall prevalence of those over 55 years being approximately 3.9% and the prevalence among those aged 75 to 84 alone is 13%. Despite the rates above, a substantial proportion of the burden on health care services lie with rehospitalisation of patients, with just under 25% of heart failure patients being readmitted within 30 days in the US. [27]

1.2.2.1 Characteristics of the recorded heart failure population

Audits to describe the characteristics of patients suffering from heart failure in the general population have collected data on demographics, aetiology, treatment and other variables of interest are collected and used to shape guidelines and future practice. The large heart failure pilot survey (ESC-HF Pilot) conducted by the EURObservational Research Programme[28] recruited 5,118 patients across Europe. In this survey, 37% of the included patients were admitted for acute heart failure and 63% were outpatients with chronic heart failure. The average age of participants was 68.5 years and approximately 33.5% were female. Another survey of the western population, the British National Heart Failure Audit 2013-2014, [29] found the mean age of included participants on the index heart failure hospitalisation to be 78 years and approximately 56% of the included population were male. Among the population included in the audit, the majority of patients (approximately 80% on index hospitalisation and 85% on readmission) were in the New York Heart Association (NYHA) classification III/IV, which, as described below, is a measure of functional status and represents a high level of disease burden.

1.2.3 Pathophysiology

Heart failure is the final common pathway of most heart diseases. Identifying the underlying cause of the heart failure may help outline the likely progression of the disease. Coronary artery disease is the most commonly associated cause, accounting for about 36% of the cases in one study [25], however conditions such as hypertension and diabetes mellitus also play their role, co-existing with the primary cause.

Whether the cause is structural or functional, during heart failure the myocardial tissue undergoes specific changes and adapts in an attempt to compensate for the reduced cardiac output. The initial response is haemodynamic, through the Frank-Starling mechanism in an attempt to increase cardiac output. Following this, ventricular remodelling may manifest through left ventricular hypertrophy initially. However, eventually this pathological remodelling leads to ventricular dilatation, which may cause valvular regurgitation, and reduced contractility. The resulting mechanical and electrical dysynchrony reduces cardiac output. This temporary and maladaptive physiological response becomes fatal when perpetuated by neurohormonal activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, which vasoconstrict to aid organ perfusion in the short

term but promote ventricular remodelling in the long term. Inflammatory activation also plays a role in the development of heart failure; however, its role is less clear. [30]

1.2.4 Diagnosis

Diagnosis of a clinical syndrome, such as heart failure, relies on the accurate identification of the cardinal signs and symptoms, such as breathlessness and fatigue, and fluid overload, by the clinicians in primary care and emergency services. A thorough history and examination is vital, however, the diagnosis might be missed in early stages due to the non-specific symptoms. Once heart failure is suspected, evidence of abnormal cardiac structure or function must be sought. NICE guidelines [31] echo the ESC recommendations to perform a transthoracic Doppler 2D echocardiogram (echo) if there is history of myocardial infarction. If there is no such history, an additional investigation of serum natriuretic peptides (NP) is performed first. As NPs have a high negative predictive accuracy of approximately 98% [32], a normal value can be used to rule out heart failure and raised level requires an echo as it only has a specificity of 35%.

1.2.5 Classification

NYHA classification (Box 4) is the most widely used tool to measure functional status of the patient once the diagnosis is confirmed. However, a study by Goode *et al.* [33] showed the increasing misuse of the tool by physicians as a measure of disease severity. While the tool is a useful gauge to assess patients' ability to cope with the treatments available it, alone, is not a useful predictor of the disease trajectory. Furthermore, it may be less sensitive in detecting the changes in functional status in more advanced disease. [34]

NYHA Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea.
III	Marked limitation of physical activity. Comfortable at rest. Less than

	ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure are present at rest. Increased discomfort with any physical activity.

Box 4: NYHA functional classification of heart failure [35]

1.2.6 Prognosis

In the landmark population based study of Stewart *et al.* [36] comparing heart failure to commonly occurring cancers, heart failure was associated with a worse prognosis than most cancers in men and women with the notable exception of lung cancer. They estimated the five-year survival rate in heart failure to be approximately 25%. Also, Mosterd *et al.* stated that patients suffering from heart failure at any age are nearly five times more likely to die unexpectedly than those of similar ages not affected by heart failure. [37] There has since been an improvement in survival rates as treatments improve with six month mortality rate falling from 26% in 1995 to 14% in 2005. [38] Similarly the one year follow-up results of the ESC-HF Pilot Study found an all-cause mortality rate of 17.4% among patients who were hospitalised at the time of inclusion and 7.2% in patients who were ambulatory. [39] However, heart failure prognosis continues to be poor compared to the general population, with five year survival now estimated to at 53% compared to 93% among age and gender matched general population. [40]

1.2.7 Disease trajectory

Predicting the disease trajectory in heart failure is fraught with complex issues, for example the underlying disease characteristics such as systolic function greatly impact the progression of the condition, which may then be altered by a host of patient factors, such as co-morbidities. Goodlin *et al.* [41] illustrated the complexity of the disease trajectory of heart failure. It can be described as having five stages:

1. the onset of symptoms
2. stabilisation – where the compensatory mechanisms fall into play

3. periods of instability – where the compensatory mechanisms begin to fail and device therapy or heart transplant, if indicated, may return the patient to a stable condition

4. a steady decline – when functional status becomes gravely affected due to multiple organ involvement, and

5. the end of life.

The difficulty lies in estimating how long a patient may stay in any one of those stages or if they will stabilise following an acute episode of decompensation. Additionally, there is a risk of sudden death throughout the disease trajectory. As such, any intervention or approach to care, for example palliative and supportive care should be considered as early as possible and should be reviewed systematically.

1.2.8 Predictors of death

Identifying useful prognostic markers can help stratify the patients according to risk and can help with planning the management of their condition. Predictors of mortality include, but are not limited to, older age, low systolic blood pressure, high respiratory rate, poor creatinine clearance [42], hyponatraemia, abnormal T wave axis, and presence of co-morbidities. [37, 43] There are tools available to aid in the prediction of patient survival such as the Heart Failure Survival Score [44] or the Seattle Heart Failure Model. [45] However, a simple and useful indicator of disease severity, the NT-proBNP [46], can independently be monitored by clinicians due to its predictive response to treatment. However, the clinical utility in relation to identifying individual patients who are in the last year of life is limited. [47]

1.2.9 Management

The aim of heart failure management is to prevent disease progression and rehospitalisation while reducing morbidity and mortality. However, there is still a growing population with end-stage disease as β-adrenergic antagonists (β-blockers) and implantable cardioverter devices reduce the risk of sudden cardiac death. The precise mechanism of action is beyond the scope of this thesis; however, a brief synopsis of standard heart failure management is described below.

1.2.9.1 First line

Exercise, lifestyle advice, and education are the first line of management in conjunction with medical management. Such rehabilitation programmes are now recommended as part of standard treatment [22, 48], although implementation is poor. [49-51]

There are well-defined pharmacological treatments of heart failure that have had a major impact on both symptoms and survival. Angiotensin-converting-enzyme inhibitors (ACEIs) and β-blockers are started at a lose dose as first-line treatment and titrated up based on the patients' tolerance. [31] ACEIs and β-blockers are associated with reduced mortality [52-56], reduced progression of disease [57], lowered NYHA classes [55] and reduced hospitalisations. [56] If patients cannot tolerate ACEIs, angiotensin II receptor blockers (ARBs) are a non-inferior [58] alternative.

1.2.9.2 Second line

LCZ696 (brand name, Entresto), an angiotensin-receptor-neprilysin inhibitor (ARNI) containing an ARB, valsartan and a neprilysin inhibitor pro-drug sacubitril, is a novel heart failure treatment. A large randomised controlled trial (8399 patients with NYHA class II to IV chronic heart failure) found that LCZ696 reduces cardiovascular death by 20% compared to enalapril (median follow-up - 27 months) and is associated with reduced circulating NT-pro BNP. [59] Following the recent technology appraisal in April 2016 [60], NICE recommends sacubitril valsartan as a second-line treatment for patients with symptomatic chronic heart failure (NYHA II to IV) and reduced ejection fraction (<35%) who are on a stable dose of ACE inhibitors or ARBs.

Other treatments include ivabradine, aldosterone antagonists (spironolactone), hydralazine with nitrates and digoxin. For patients whose heart rate remains high (>75 beats per minute) despite treatment with β-blockers, ivabradine is shown to be beneficial [61] as a second line treatment but, it is associated with increased adverse effects in patients with a lower heart rate (<70 beats per minute). [62] Aldosterone antagonists may be used in addition to ACE inhibitors if symptoms persist to reduce hospitalisations [63], morbidity and mortality [64], especially following a myocardial infarction. [65] A combination of hydralazine and nitrates may be beneficial as first line treatment for patients intolerant to ACE inhibitors and ARBs, or as second line treatment [66], especially for patients of African descent. [67]

Digoxin, a positive inotrope and a negative chronotrope, may be prescribed as second line treatment, however it is thought to have no significant effect on mortality despite improving ventricular function and therefore reducing hospitalisations. [68] Patients require serum potassium monitoring if they are taking aldosterone antagonists or digoxin.

1.2.9.3 All patients

Diuretics are beneficial in maintaining fluid balance and have been shown to improve mortality, progression and exercise capacity. [69] Furosemide and bumetanide are the commonly used loop diuretics in the management of decompensated heart failure. A sequential nephron approach (targeting different parts of the nephron) with thiazide diuretics may be used for further effect. Finally, anti-thrombotics may be added as seen fit by the physician, as patients are at a higher risk of thromboembolic events. However, the risk and benefits should be individually assessed. [70]

1.2.9.4 Device therapy

Arrhythmias are an unheralded cause of death among patients with heart failure. The implantable cardioverter-defibrillator (ICD) is recommended by NICE [31] where clear indicators, such as documented ventricular arrhythmias or long QT syndromes, are present. Cardiac resynchronisation therapy (CRT) is a way of maximising stroke volume in people who have electrical dysynchrony and those with widening QRS interval (>120 milliseconds) should be considered. CRT with defibrillator or CRT with pacing alone may be appropriate, based on the patient's needs. Device insertion is associated with risks such as, haematoma, infection, smell (rare), lead displacement, dissection, perforation, pericardial effusion, tamponade or even device failure, so patient suitability and counselling (about life with the device) is important. Additionally, NICE guidance states that they should not be fitted in people with NYHA class IV disease, as there is no evidence that ICDs are cost-effective in this situation. [71]

1.2.9.5 Surgery

Invasive surgical procedures are considered when patients' clinical picture deteriorates despite optimising medical management. Coronary revascularisation may be indicated if the patient is experiencing refractory angina symptoms. Coronary artery bypass graft (CABG) is associated with a lower cardiovascular-related mortality rate over 10 years than medical

therapy alone in patients with underlying coronary disease. [72] The left ventricular assist device (LVAD) is a potential option for poor systolic function used only as a 'bridge to transplantation' or as destination therapy for those unsuitable for organ transplant. Finally, heart transplantation may be an option for heart failure patients with severe refractory symptoms or refractory cardiogenic shock.

1.3 Heart failure and palliative care

1.3.1 The need for palliative care in heart failure

Good treatment of heart failure and prevention of sudden cardiac death with device therapy reduces mortality at early stages of heart failure and increases length of survival. However, as the population survives longer with heart failure, their condition worsens (NYHA class III and IV) and a greater proportion experience persistently symptomatic heart failure associated with high morbidity. Quality of life is worse among those with a high NYHA class and a lower socio-economic status, and it is associated with hospitalisations that are more frequent. [73] Moreover, as prognostication in heart failure is fraught with complexity (mentioned above), patients may continue to receive aggressive medical treatment to the last days of life. Therefore, it is important to focus on what happens to the patients saved from death, but left suffering and discharged home.

While the long-term deterioration in heart failure can be observed, it is often noted retrospectively. One key sign is presence of refractory symptoms. Expectedly, patients closer to death have a more severe symptom burden. [74] Breathlessness, pain and fatigue are just a few of the symptoms heart failure patients are troubled within the last few months of life, with more men experiencing marked limitation in physical activity than women. [75]

In the late stages of heart failure, patients experience similar symptoms to those with advanced cancer and often the symptom burden and issues of mood and spiritual wellbeing are equal. [76] Patients with advanced cancer experiencing such complications are shown to benefit from a palliative care approach. [5, 7, 8] Furthermore, patients with advanced heart failure identified components of palliative care, such as managing physical symptoms, psychosocial stresses and lack of information, as being their key issues. The interviews of patients and carers by Murray *et al.* [77, 78] revealed that unlike patients suffering from

cancer, heart failure patients live with a more unpredictable course of illness and increasing limitation in activity which leads to social isolation. Therefore, arguably, access to palliative care that is individualised to their personal disease trajectories for patients suffering from heart failure is justifiable and potentially beneficial.

1.3.2 The role of palliative care in heart failure

Patients receive a thorough multifaceted initial assessment to identify key issues and establish goals of care. This first step sets up the relationship the patient can expect with the palliative care team.

Symptom burden is one of the most common reasons for a patient's referral. Therefore, each symptom is investigated for causes and where possible the underlying process is treated. Parallel to this, the symptom is palliated pharmacologically and behaviourally. Detailed description of palliative care interventions in heart failure are beyond the scope of this thesis but further details can be found elsewhere. [79, 80]

Due to the unpredictable nature of heart failure, palliative care teams promote early conversations about patients understanding of the disease, preferences in treatment and education in self-management. These conversations are also re-visited frequently to ensure that the patient stays involved with the management plan and the healthcare team remains updated on patients' wishes. However, these conversations are challenging and often do not happen. [81]

Palliative care also addresses end-of-life issues such as advance care planning and assists with decision-making. The patient, the physician, and the family and/or caregivers gather together to discuss and put into place advance decisions on treatment preferences in emergency and non-emergency situations. This ranges from decisions about resuscitation to place of care and level of invasive care the patient feels is acceptable. Patients are counselled about decisions regarding discontinuation of device therapy during the late stages of life to ensure patient comfort. Additionally, this opportunity allows patients to think about lasting power of attorney and organise their financial/ legal matters.

1.3.3 Heart failure patients' access to palliative care

The NICE Quality Standards for heart failure include the requirement for patients with severe heart failure to have access to palliative care services. [31] The Gold Standard Framework (GSF) [82] recommends the use of general and specific clinical indicators of decline, as well as an estimated prognosis of 12 months, as a point of access to palliative care for patients with heart failure. However, the paper by Haga *et al.* [47] illustrated the inaccuracy of tools such as GSF and Seattle Heart Failure Model at predicting the last year of life – a recommended trigger of palliative care. Additionally, by the time to death is recognised accurately, often it is too late for real intervention and consequent improvement of quality of life; approximately one third of people dying due to heart failure were recognised as needing a palliative care approach within a week of death. [83] Although predictors of death have been shown not to be helpful in predicting when patients should be referred to palliative care, the GSF Prognostic Indicator Guidance appears to be able to identify >80% of people with palliative care needs. Therefore, use of tools and clinical indicators should focus on identifying advanced disease and need rather than the time of death, and access to palliative care should be early, in addition to curative therapy, and in response to patients' need. [84]

1.4 Key literature

1.4.1 National guidelines and policies

Among other policies such as the 'Reduce Your Risk' campaign aimed at improving vascular risk, the NHS review in 2008 [85] highlighted the importance of personalised care among those with a long term condition and the need for dignity and respect at the end of life which is reliant upon complete access to palliative services.

NICE recommends the access to palliative care alongside specialist heart failure care for patients with moderate to severe heart failure (defined as NYHA class III and IV) who may benefit from such services. [31]

1.4.2 International guidelines

Similar recommendations are promoted by other organisations responsible for generating guidelines across the globe. This includes ESC which highlights the need for a 'shared-care

approach' between the 'specialist palliative care service and the heart failure team and/or the primary care physician'. [22] Likewise consideration for palliative care among patients with heart failure is advocated by the American Heart Association (AHA) [86], the Canadian Cardiovascular Society (CCS) [87] and the National Heart Foundation of Australia. [88]

1.4.3 Shortfalls

Despite the clear consensus recognising the need for palliative care in the management of heart failure, this is not reflected in common practice. The NHS Heart Failure Survey in 2008 found that less than 1% of patients were referred for rehabilitation or specialist palliative care. [89] A recent study examined the proportion of people who died from heart failure or cancer during 2009 who were also entered onto the Quality and Outcomes Framework palliative care register. Only 7% of patients with heart failure were entered into the register in comparison to the 48% of cancer patients. [83] While that study was looking at primary care referrals, another study preceding it by a few years found palliative care referrals among hospitalised patients to be very similar, where only 6% of patients deemed to have advanced heart failure were referred to palliative care during their hospitalisation. [90]

1.5 Barriers

The discordance between the apparent need for palliative care among patients with advanced heart failure and the lack of current provision is due to the numerous barriers currently in place. Notably, four overlapping factors at the root of the problem relate to the disease, the patient, the physician, and the services available, confounded by the complexities of communication around this subject.

1.5.1 Disease factors

The unpredictable course of the disease prevents the historical model of palliative care services provided to cancer patients from being simply extended to heart failure patients. Acute exacerbations may be temporary or terminal, making the judgement to refer to a palliative care team difficult under the 'prognosis dependent referral' model traditionally adopted in oncology. Additionally, the relapsing and remitting nature of the symptoms cause patients to overestimate their life expectancy (in comparison to model predicted expectancy) by 3 years on average [91] which may prevent them from seeking supportive or palliative care.

1.5.2 Patient factors

There is a consensus that most patients with heart failure do not believe they had a discussion with their doctors about the end of life, which is attributed to lack of open, forthcoming conversations about prognosis and death. [81, 92, 93] Patients often expect physicians to bring up the subject of end of life when they think it is appropriate and are often willing to discuss preferences of care even if the conversation may be challenging. [94] All in all, confused by their prognosis and feeling disempowered due to lack of information regarding available resources, patients may feel unprepared for the end of life. [92]

1.5.3 Physician factors

On the contrary, physicians may not initiate the dialogue regarding palliative care and end of life for many reasons, including fear of causing patients to lose hope, and prompting anxiety and stress, which, in turn, may increase demand for psychological support. Additionally, patients have diverse attitudes towards end of life conversations, where some patients would rather not think about death and accept that the disease is part of growing old and some patients feel that knowing about their prognosis and discussing their treatment and care options helps them to be organised. [81] This uncertainty leaves physicians more comfortable and confident in dealing with the biomedical aspects of the management plan.

Frontline healthcare staff and physicians not specialised in palliative care are often under-trained and under-equipped to best utilise any palliative care resources that may be available. An assessment conducted by Kavalieratos *et al.* [95] identified key gaps in knowledge regarding what palliative care is, when it is appropriate to refer, why it is important to patients, who delivers the care, where the referral should come from and how it can be accessed. Education and training, or lack thereof, underpins the majority of the reservations physicians hold on palliative care. Furthermore, although there are a few trials to confirm benefit of palliative care for people with other diagnoses (mainly cancer) [5-8, 96], there is concern that there is little or no evidence to support palliative care for people with heart failure which has restricted implementation of policy.

1.5.4 Service delivery factors

When there is a successful referral to palliative care, silos of care may develop due to the fragmented medical system and ambiguity over which providers are directly involved in a patient's care and in what capacity. Without partnership between different specialities and an agreed up on key worker, care cannot be co-ordinated effectively for patients requiring re-admissions and input from different teams simultaneously.

Such barriers can be overcome if there is better education among patients and carers, as well as front-line medical staff, regarding the role of palliative care, how to manage simple and straightforward issues early on and how to access specialist care if needed. Additionally, a more integrated approach to care with better communication between patient and physician as well as interdepartmental skill sharing can reduce the number of complicated cases presenting late, requiring high service input. [97] Above all, a clear and established infrastructure and protocols should be present to ensure that patients do not fall through the cracks, and are accounted for. Where there are more formal pathways of care between cardiology and palliative care, there are more referrals [98] and a reduction in deaths in acute hospital beds. [99]

1.6 Summary and purpose of the thesis

Heart failure is common. People with heart failure need good management of their heart failure to improve symptoms, quality of life and survival. However, problems and concerns often persist despite cardiac treatments, and people with heart failure may benefit from access to palliative care running alongside, delivered by the usual care team or specialists according to need, even from early on in their disease trajectory. People with advanced stages of the disease are particularly symptomatic and have poor quality of life. In spite of this, they have less understanding of their condition, less access to supportive and palliative care services and are less likely to die at home. There is a variety of barriers to people with heart failure accessing palliative care, but one is a perception that there is little or no evidence to show that palliative care is beneficial in this patient group. Therefore, the aim of this thesis is to identify the current knowledge regarding role of palliative care in heart failure management. A systematic review was conducted of the current evidence in support of palliative care in people with persistently symptomatic heart failure. The findings are

discussed in the context of implications for clinical practice and identified gaps in knowledge will be highlighted to help target future research in this area.

Chapter 2 – Methods

2.1 Protocol and registration

Details of the protocol for this systematic review were registered on PROSPERO, an international database of prospectively registered systematic reviews, and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016029911.

2.2 Search Strategy

In accordance with commonly used guidelines for systematic reviews [100, 101], a systematic search for studies was conducted using the following databases:

- Ovid Medline (R) 1946 to October Week 3 2015
- Cochrane Central Register of Controlled Trials (CENTRAL) Issue 11 of 12, November 2015
- EBSCO CINAHL 1982 to 2015
- PsycINFO 1987 to October Week 3 2015
- Health Management Information Consortium (HMIC) 1979 to October 2015
- CareSearch Grey Literature

Medline and CENTRAL databases were chosen as they collectively index medical and biomedical titles and abstracts. Initially, a search in the Embase 1974 to 2015 database also conducted, however this returned a high volume of results (19,045 records). Due to the strict time constraints associated with this project, a mutually agreed upon decision by the review team was made to exclude the results from the database - Embase. While there are drawbacks for this decision (see section 4.3), we were able to justify this deviation from the protocol due to the high level of overlap across Medline, CENTRAL and Embase.

CINAHL indexes nursing and allied health journals and PsycINFO contains records on psychology and the behavioural and social sciences. Both are vital due to the multidisciplinary nature of the palliative care approach. Moreover, HMIC was useful in identifying health management related articles. Finally, CareSearch Grey Literature was used to find unpublished literature, and titles and abstracts from non-indexed journals.

In addition, the reference lists and citations of all included studies and key review articles were searched. Finally, experts in the field were contacted, in order to identify and include all relevant papers. At each stage of the development of the search strategy, a librarian, Stuart Bentley, University of Hull, was consulted to ensure that all relevant studies can be identified.

2.2.1 Search terms

The search terms were designed to address the question according to the 'PICOS' framework. For each search string, both free text and medical subheading searches were used where possible. Synonyms and alternate search terms were identified with the aid of subject search filters for heart failure [102] and palliative care [103-105]. The three search strings represented the terms to identify the disease of interest (heart failure), the severity of the disease and the intervention of interest (palliative care) as seen in Table 1.

Table 1: Search terms used to conduct database searches

Search string	Search topic from the question	Search terms with Boolean operators
#1	'Heart failure'	Heart failure OR Cardiac failure OR Congestive heart failure OR Ventric* failure OR Systolic failure OR Myocardi* failure OR Ventric* dysfunction OR Cardiac dysfunction OR Systolic dysfunction OR Myocardi* dysfunction OR Ventric* insufficiency OR Cardiac insufficiency OR Systolic insufficiency OR

Table 1: Search terms used to conduct database searches

		Myocardi* insufficiency OR HF OR CHF OR CCF OR LVSD
#2	'Persistently symptomatic'	Advanced OR Chronic OR Terminal OR End stage OR Moderate OR Severe OR Progressive OR Persistent OR Fatal OR Limiting OR Incurable OR Unremitting OR Decompensated OR NYHA class III OR NYHA class IV
#3	Palliative care	Palliat* OR Terminal care OR Hospice* OR End of life care OR Holistic OR Respite OR Supportive care OR Care of the dying OR

Table 1: Search terms used to conduct database searches

		Patient centred care OR Advance* care OR Advance* directive
#4	Persistently symptomatic heart failure	**#1** AND **#2**
#5	Palliative care in persistently symptomatic heart failure	**#3** AND **#4**

The search string for Ovid Medline is included in Appendix 1 and it was adapted as needed for different databases.

2.3 Eligibility

2.3.1 Inclusion criteria

Studies were included if they met the following criteria:

2.3.1.1 Population

Patients over 18 years with persistently symptomatic heart failure (NYHA class III & IV) or other evidence of advanced disease such as poor quality of life, as defined by ESC or coded by International Classification of Diseases, can be included. Population where only a subset were patients with symptomatic heart failure may only be included if there was clear subset analysis of outcomes.

2.3.1.2 Intervention

Any study that states the use of palliative care, specialist or generalist, will be included. If certain vital components of palliative care intervention are present in the intervention given to the population, the study may be included.

2.3.1.3 Control

Any control will be included.

2.3.1.4 Study design

All randomised controlled trials (RCTs), quasi-randomised controlled trials, observational studies, qualitative studies, service evaluations, and national audits maybe included.

2.3.1.5 Restrictions

Time: 1995 to present day. Limited under expert advice as the concept of palliative care in heart failure is new.

Language: no restrictions. If any papers in other languages were found, they would be translated by members of the extended research group where possible.

2.3.2 Exclusion criteria

Studies were excluded if:

- they did not meet the inclusion criteria
- the methods section was not available or incomplete
- the design or other inclusion criteria could not be identified or
- they are duplicate publications, opinion pieces, narrative reviews, editorials, case histories or case series.

2.4 Study selection

The selection of studies from the search was conducted in two stages.

2.4.1 Stage 1

Titles and, where available, abstracts where compared to the predetermined inclusion criteria. Rejected studies were either clearly not relevant or were of interest but did not meet one or more of the inclusion criteria.

The first researcher screened all titles and abstracts. Due to pre-existing time constraints, the second researcher independently screened 20% of the results, initially. There was a high rate of agreement (approximately 98%), therefore, a 20% randomised selection of the remaining titles and abstracts were screened by the second researcher to minimize errors of screening.

2.4.2 Stage 2

Full papers of studies chosen for potential inclusion following stage 1 and those found through other search processes were obtained for a detailed assessment against the inclusion criteria. Two researchers independently screened all full papers for potential inclusion to avoid selection bias.

At both stages, any disagreements were resolved by discussion between the two researchers. For issues that could not be resolved in this manner, a third researcher was consulted.

2.5 Data extraction

A data extraction spreadsheet was created based on Centre for Reviews and Dissemination (CRD) guidance [100] and Cochrane Handbook for Systematic Reviews of Interventions. [101] The spreadsheet was piloted and amended as needed before two researchers independently extracted data from all included studies to minimise the risk of errors. Disagreements or discrepancies were resolved by mutual consent or by involvement of a third author.

Study identifiers, study characteristics, information regarding the population, intervention, comparators, and outcomes, including results were extracted from all included studies. Information was recorded on all reported outcomes including cost and satisfaction with care. Further information on the data items that were collected from papers is included in Appendix 2.

Where data was not reported or too ambiguous, attempts were made to contact the authors of the paper. If further information was available and provided, this was included in the review. However, if there was no further information, analysis was performed with only the information reported in the paper.

2.6 Risk of bias assessment

The reliability and validity of a systematic review rests on the quality of the studies included. Intrinsic problems with design and flaws in methodology can call into question the strength of the evidence added by each study to the pool of current knowledge. Two researchers

independently assessed the risk of bias while simultaneously extracting data. Disagreements were resolved by discussion and inclusion of a third researcher if needed.

The Cochrane Collaboration recommends against using composite scores as this reduces the information available to judge the root cause of biases. Therefore, RCTs were assessed with the use of the 'Cochrane Risk of Bias Tool' [106], which is a domain based evaluation. This tool focuses on identifying selection bias (sequence generation and allocation concealment), performance bias (blinding of participants) and detection bias (blinding of assessors), attrition bias (addressing incomplete outcomes) and reporting bias (selective reporting).

The Newcastle-Ottawa quality assessment Scale (NOS) was used to judge the risk of bias in cohort and case control studies. The methodological quality of included observational studies was variable and the inclusion of single arm studies made the risk of bias assessment complex. Information was gathered on the selection of participants, the comparability of the study arms (where possible) and outcomes in cohort studies, or exposure, in case-control studies.

2.7 Synthesis of results

The characteristics of the 15 included studies were summarised in a table. Descriptive synthesis of the study design, the included population, the intervention, and comparator are presented.

Identifying and cataloguing the included studies by study design proved difficult, as this information was not always clear within the study methods. For the purpose of the review, randomised controlled trials were divided into phase II and phase III. Studies with a stated aim to assess the efficacy or effectiveness of the intervention were considered phase III RCTs. Additionally, studies that include power calculations aiming to design adequately powered trials to identify the effect of the intervention were also labelled phase III RCTs. Finally, underpowered trials were phase II RCTs.

Outcomes and results were described; however, a meta-analysis was not conducted.

Chapter 3 – Results

3.1 Study selection

The search process for the included studies is summarised in a flow chart (Figure 1) depicting the identification, screening, eligibility and inclusion as recommended by the Preferred Reporting Items for Systematic reviews (PRISMA) statement. [107]

The initial database search identified 26,050 papers. As previously mentioned, a decision was made at an early stage to exclude the results from the database 'Embase' (19,045) due to time constraints.

The searches from the remaining databases yielded 7,005 records. After removing duplicate records, one researcher screened 6,782 titles and abstracts and a second researcher independently screened approximately 40% of the results. 6,763 results were excluded due to ineligibility or duplication. The full texts of 19 studies identified from database searches, three studies identified through citation searching, two studies identified through searching references of included studies and three studies put forward by experts for inclusion were screened independently against the eligibility criteria by two researchers. 15 studies were chosen for inclusion. Of the 12 studies excluded, seven studies with mixed population had no subset analysis of patients with heart failure alone, one study had only an interview as the intervention, and four papers were study protocols, for which the completed studies were also screened and two were included.

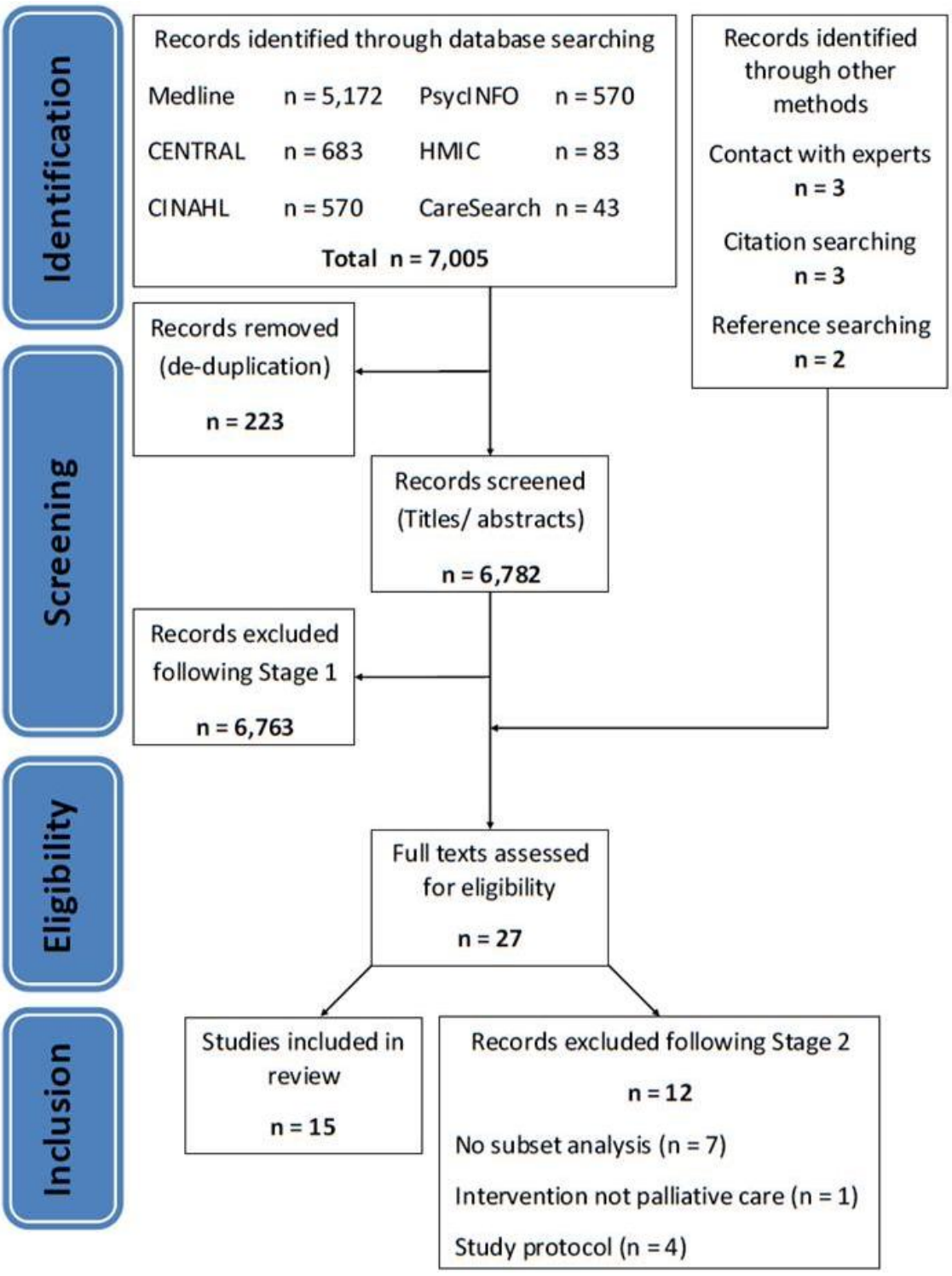

Figure 1: PRISMA flowchart depicting the search process and the study selection

3.2 Study characteristics

Characteristics of included studies are summarised in Table 2.

Table 2: Characteristics of included studies

First author, Year, Country	Study design and setting	Participants: Sample size (n), Age (years), Sex (%), Disease characteristics (NYHA Class, LVEF) where noted		Intervention and Comparator	Outcomes	Results
		Intervention	Comparator			
Interventional studies						
Aiken LS **(108)** **2006** **USA**	Phase III RCT Community based and Hospital based	Note: Mixed population study with subset analysis of CHF patients N = 100 (patients with CHF = 67) Mean Age (SD) = 68 (14) Sex: M = 42.0;	N = 90 (patients with CHF = 62) Mean Age (SD) = 70 (13) Sex: M = 30.0;	<u>PhoenixCare</u> Home-based palliative care focused on disease and symptom management, patient and care giver education on disease management, and social and psychological support. Providers: Registered nurse case manager (co-ordinator), primary care physician, health-plan case manager, and community agencies supported by a medical director, social worker, and pastoral counsellor.	1. Self management of illness and knowledge of resources 2. Preparation for end of life 3. Physical and mental functioning a. Participation in enjoyable activities b. Symptom control	1. No CHF subset analysis available for this variable. PhoenixCare participants reported a sense of having greater information for self-management, a greater appreciation of resources available to help with their illness and initially, better preparedness for daily experiences.

Table 2: Characteristics of included studies

		F = 58.0 No data on NYHA Class or LVEF	F = 70.0 No data on NYHA Class or LVEF	<u>Usual Care</u> Medical and disease orientated care included medication and technical treatment and other support service. Providers: Managed care organisations.	c. Trajectories of mental and physical functioning 4. Utilisation of medical service	2. No CHF subset analysis available for this variable. PhoenixCare participants showed a higher rate of having a living will or advance directive than controls. ($p < 0.05$). 3a. No effect seen in participants with CHF. 3b. PhoenixCare participants with CHF reported high symptom distress ($p < 0.05$). 3c. No difference in mental and physical functioning in PhoenixCare participants with CHF compared to a decline among CHF participants in the control arm. 4. Relatively unchanged

Table 2: Characteristics of included studies

						over time with no significant difference across arms.
Bekelman DB [109] 2015 USA	Phase III RCT with >80% power Community based with outpatient consultations	N = 187 Mean Age (SD) = 68.3 (9.6) Sex: M = 95.2; F = 4.8 NYHA class I = 16 (8.9%) NYHA class II = 77 (42.8%) NYHA class III = 82 (45.6%)	N = 197 Mean Age (SD) = 67.9 (10.6) Sex: M = 98.0; F = 2.0 NYHA class I = 16 (8.5%) NYHA class II = 85 (45.0%) NYHA class III = 82 (43.4%)	<u>Patient-Centred Disease Management</u> Multidisciplinary collaborative care of HF disease management, screening for and treatment of depression and telemonitoring with patient self-care support. Providers: Registered nurse (co-ordinator), primary care physician, psychiatrist. <u>Usual Care</u> Regular care at the discretion of health care provider. Information	1. HF-specific health status 2. Depression 3. Mortality 4. Hospitalisation	1. The intervention did not result in significantly greater improvement in the KCCQ overall score. 2. There was a greater improvement in PHQ-9 in the intervention arm (p = 0.01). 3. Fewer patients died in the intervention arm (p = 0.04). 4. No significant difference in hospitalisations between arms.

Table 2: Characteristics of included studies

		NYHA class IV = 5 (2.8%) LVEF: Normal = 78 (45.6%) Mild = 34 (19.9%) Moderate = 46 (26.9%) Severe = 13 (7.6%)	NYHA class IV = 6 (3.2%) LVEF: Normal = 84 (47.5%) Mild = 34 (19.2%) Moderate = 32 (18.1%) Severe = 27 (15.3%)	sheets for self-care given and if patients screened positive for depression at baseline, primary care physicians were notified. Providers: Regular health care professionals and nurses.		
Brännström M [110] 2014 Sweden	Phase III RCT with 80% power Community based with outpatient consultations	N = 36 Mean Age (SD) = 81.9 (7.2) Sex: M = 72.2; F = 27.8 NYHA class III	N = 36 Mean Age (SD) = 76.6 (10.2) Sex: M = 69.4; F = 30.6 NYHA class III	<u>Palliative advanced home care and heart failure care (PREFER) model</u> Person-centred care, total care including assessment of symptoms, quality of life, and risk, and registration into HF and palliative care registry. Providers: Specialised nurses,	1. Symptom burden 2. Health related quality of life 3. Disease-specific quality of life 4. Functional classes 5. Hospitalisation 6. Resource utilisation	1. No significant differences in overall score between the PREFER and control groups. 2. Age-adjusted health related quality of life was better in the PREFER group (p = 0.02).

Table 2: Characteristics of included studies

		= 28 (77.8%) NYHA class IV = 8 (22.2%) LVEF: 40-49 = 13 (36.1%) 30-39 = 16 (44.4%) <30 = 7 (19.4%)	= 23 (63.9%) NYHA class IV = 11 (30.6%) LVEF: 40-49 = 12 (33.3%) 30-39 = 21 (58.3%) <30 = 3 (8.3%)	palliative care nurses, cardiologist, palliative care physician, physiotherapist, and occupational therapist. <u>Usual care</u> No information. Providers: General practitioners or doctors and/ or the nurse-led heart failure clinic.		3. No significant difference in overall disease specific quality of life between groups. 4. There was a significant difference in mean NYHA class (p = 0.012) favouring the PREFER group, with more patients in the intervention experiencing an improvement in functional class (p = 0.015). 5. There were significantly fewer hospitalisations on average in the PREFER group compared to the control group (p = 0.009). This was accompanied with fewer

Table 2: Characteristics of included studies

						days spent in hospital on average in the PREFER group (p = 0.0011). There was no significant difference mortality between arms. 6. Utilisation of visits differed significantly between the two arms in favour of the intervention, but precise results are unclear.
Hopp FP (111) **2016** **USA**	Phase III RCT with approx. 80% power Hospital based	N = 43 Mean Age (SD) = 67.0 (11.0) Sex: M = 60.5; F = 39.5 No data on	N = 42 Mean Age (SD) = 68.0 (13.0) Sex: M = 42.9; F = 57.1 No data on	<u>Palliative Care Consultation</u> Clinical interviews to assess for uncontrolled symptoms, goals of care, advance care planning, code status, and desired post-treatment residential setting. Providers: Physician and advanced nurse practitioner. Other	1. Election vs non-election of comfort care a. Outpatient hospice b. Inpatient hospice c. A "Do Not Resuscitate"	1. No statistical difference was found in the primary end point. Additionally, there was no significant difference in mortality between arms.

Table 2: Characteristics of included studies

		NYHA Class Mean LVEF = 36.4 (16.7)	NYHA Class Mean LVEF = 38.1 (16.8)	professionals participated as needed – chaplains and social workers. <u>Usual Care</u> No information.	d. A "Do Not Resuscitate" order during hospitalisation d. A "Do Not Resuscitate" order at home or nursing home	
Sahlen KG (112) **2015** **Sweden**	Phase III RCT with 80% power Community based with outpatient consultations	N = 36 Mean Age (SD) = 81.9 (7.2) Sex: M = 72.2; F = 27.8 No data on NYHA Class or LVEF	N = 36 Mean Age (SD) = 76.6 (10.2) Sex: M = 69.4; F = 30.6 No data on NYHA Class or LVEF	Note: Same study as Brännström *et al.* [110] <u>PREFER model</u> Person-centred care, total care including assessment of symptoms, quality of life, and risk, and registration into HF and palliative care registry. Providers: Specialised nurses, palliative care nurses, cardiologist, palliative care physician, physiotherapist, and occupational therapist.	1. Quality adjusted life years 2. Costs of care	1. There was a small but significant difference in the weight of the quality adjusted life year (p = 0.026) favouring the PREFER model. 2. There is no overall significant difference in cost of care between the two arms.

Table 2: Characteristics of included studies

				<u>Usual care</u> No information. Providers: General practitioners or doctors and/ or the nurse-led heart failure clinic.		
Sidebottom AC [113] 2015 USA	Phase III RCT, but poor recruitment resulted in 47.5% power 1 Inpatient consultation	N = 116 Mean Age (SD) = 76.0 (11.9) Sex: M = 47.4; F = 52.6 No data on NYHA Class or LVEF	N = 116 Mean Age (SD) = 70.9 (13.6) Sex: M = 57.8; F = 42.2 No data on NYHA Class or LVEF	<u>Palliative care</u> Assessment of symptom burden, emotional, spiritual and psychosocial care, coordination of care orders, recommendation for change in current or future treatments. Providers: 4 physicians board certified in hospice and palliative medicine, 2 clinical nurse specialists board certified in advanced practice palliative care nursing, a social worker and a chaplain.	1. Symptom burden 2. Depression 3. Quality of life 4. Readmissions 5. Hospice use 6. ACP 7. Mortality	1. There was a statistically significant difference in symptom burden (favouring the intervention) in mean change from baseline between the intervention and the control ($p < 0.001$). 2. Similarly, there was a significant difference in depression in the intervention compared to the control ($p <$

Table 2: Characteristics of included studies

				<u>Control group</u> No information.		0.001). 3. The difference in improvement of quality of life in significantly better in the intervention arm (p < 0.001). 4. There was no significant difference in readmissions between arms. 5. There was no significant difference in hospice use between arms. 6. The intervention group was 2.87 time more likely to have completed the disease-specific ACP process. 7. There was no significant difference in death among patients in either

Table 2: Characteristics of included studies

						arm.
Wong FKY **(114)** **2016** **China**	Phase III RCT Community based	N = 43 Mean Age (SD) = 78.3 (16.8) Sex: M = 43.9; F = 56.1 NYHA class II = 6 (14.0%) NYHA class III = 31 (72.1%) NYHA class IV = 6 (14.0%) Mean LVEF = 39.0 (14.0)	N = 41 Mean Age (SD) = 78.4 (10.0) Sex: M = 61.0; F = 39.0 NYHA class II = 3 (7.3%) NYHA class III = 22 (53.7%) NYHA class IV = 16 (39.0 %) Mean LVEF = 37.0 (17.0)	<u>Transitional Care Palliative End-Stage Heart Failure</u> Pre-discharge assessment, patients' needs assessment (environmental, psychosocial, physiological and health-related behaviour) and intervention, goal setting and creating a mutually agree care plan. Providers: Nurse case managers (primary provider), trained volunteers, and nursing students. <u>Control group</u> Usual care – palliative care medical clinic, discharge advice on symptom management and medication, and referrals if appropriate. Also, control group received 2 attention control social calls.	1. Readmissions at 4 and 12 weeks 2. Symptom intensity 3. Functional status 4. Quality of life 5. Satisfaction with care	1. 4 week re-admission rate was not significantly different between groups, however there was significantly fewer 12 week readmissions among the patients in the intervention arm (p = 0.001). 2. No significant improvement in symptom burden across groups. 3. There was no difference in functional status between or within groups. 4. Both heart failure specific (p = 0.01) and palliative care specific (p

Table 2: Characteristics of included studies

						= 0.05) quality of life tools found significant improvement in the intervention compared to the control group. 5. The intervention group had significantly ($p < 0.001$) higher satisfaction with care.
Paes P [115] 2005 UK	Phase II RCT Outpatient consultations	N = 6 Mean Age (SD) = 73.2 (4.2) Sex: M = 100.0; F = 0.0 NYHA class III = 3 (50.0%) NYHA class IV = 3 (50%)	N = 7 Mean Age (SD) = 78.0 (7.0) Sex: M = 80.0; F = 20.0 NYHA class III = 3 (60.0%) NYHA class IV = 2 (40%)	<u>Palliative care consultation</u> 1 hour of palliative care medical outpatient consultation, followed by monthly 30-minute consultation for a total of 5 months. Provider: Palliative care physician. <u>Control group</u> Regular cardiology care.	1. Depression 2. Quality of life 3. Clinical evaluation	1. No statistically significant difference in depression between treatment arms. 2. No statistically significant difference in quality of life between treatment arms. 3. The evaluation forms were positive and found the format acceptable.

Table 2: Characteristics of included studies

		No data on LVEF	No data on LVEF			
Tadwalkar R [116] 2014 USA	Quasi-experimental trial Inpatient visits	N = 14 Mean Age (SD) = 58 (11) Sex: M = 42.9; F = 57.1 No data on NYHA Class or LVEF	N = 9 Mean Age (SD) = 57 (10) Sex: M = 55.6; F = 44.4 No data on NYHA Class or LVEF	<u>Religious support</u> Prayer, reading of religious text, religion-specific rituals, and other pastoral care. Provider: member of the chaplaincy. <u>Non-religious support</u> Personal discussions, recreational activities, undertaking social and spiritual support. Provider: in-house volunteer.	1. Depression 2. Spirituality 3. Symptom burden 4. Enjoyment and life satisfaction	1. There was a significant reduction in depression over time but there was no difference between the two groups. 2. There was no significant difference in spirituality between the two groups or over time. 3. There was no significant difference in symptom burden between groups or over time. 4. There was no significant difference in enjoyment and life satisfaction between groups or over time.

Table 2: Characteristics of included studies

Observational studies						
Enguidanos SM [117] 2005 USA	Prospective Cohort Study Community based with outpatient consultations	Note: Mixed population study with subset analysis of CHF patients		Kaiser Permanente Home-based Palliative Care Program Extensive patient and family education on the disease/ condition; training in symptom control; psychosocial support aimed at assisting in making care choices in advance. Providers: Physicians, nurses, social workers, and other health care professionals. Usual Care Standard Kaiser Permanente TriCentrial Service Area care. Standard health care in response to needs and home care only when Medicare certified criteria is fulfilled. Access to psychosocial support and	1. Severity of illness 2. Service use 3. Site of death 4. Days on service 5. Costs of care	1. No CHF subset analysis available for this variable. Patients in the intervention group had significantly ($p < 0.001$) more severe illness at enrolment. 2. No CHF subset analysis available for this variable. There was no difference in obtaining hospice care between groups. 3. No CHF subset analysis available for this variable. Patients enrolled in palliative care were significantly more likely to die at home ($p < 0.001$).
		N = 159 (31) Mean Age (SD) = 70 (13.92) Sex: M = 49.1; F = 50.9 No data on NYHA Class or LVEF	N = 139 (51) Mean Age (SD) = 73 (13.29) Sex: M = 44.6; F = 55.4 No data on NYHA Class or LVEF			

Table 2: Characteristics of included studies

				social services is very limited.		4. Palliative care patients with heart failure had significantly fewer day on service ($p < 0.001$). 5. Patients diagnosed with heart failure in the palliative care group on average cost less than those in the control group.
Pattenden JF [118] 2013 UK	Prospective Cohort Study Community based	N = 99 Mean Age (SD) = 81.7 Sex: M = 60.6; F = 39.4 No data on NYHA Class or LVEF	N = 98 Mean Age (SD) = 78.85 Sex: M = 62.0; F = 37.8 No data on NYHA Class or LVEF	<u>Better Together Intervention</u> Self-management education and advice to patients and their carers, clinical assessment and regular monitoring and review, palliative nursing e.g. medication for symptoms and psychological support, respite care. Providers: British Heart Failure (BHF) Heart Failure Specialist Nurses	1. Resource use – admissions, length of stay 2. Costs of care 3. Benefits of care – death in preferred place of care 4. Cost-effectiveness	1. Significantly smaller proportion of patients in the intervention group in Bradford was admitted to hospital ($p < 0.01$), and there were significantly fewer admission per patient in the intervention in Poole ($p < 0.05$). There was no significant difference

Table 2: Characteristics of included studies

				(HFSN); Marie Curie Cancer Care Nurses (MCN), Marie Curie Cancer Care Healthcare Assistants (MCHCAs); district nurses and other support services. <u>Control patients</u> 'Convenience sample' historical sample.		between in length of stay between the intervention group and the control in either study site. 2. The costs of care were fewer in the Better Together intervention in both sites; however, the difference was only significant in Bradford. 3. The distribution of place of death was significantly different to the distribution of the control group ($p < 0.0001$). 4. There was considerable uncertainty around incremental cost-effectiveness. There was an additional cost per

Table 2: Characteristics of included studies

						admission averted in Bradford but the costs of the intervention were offset in Poole with an added saving.
Evangelista LS† [119] 2014 USA	Prospective Single-arm Cohort Study Outpatient consultations	N = 29 Mean Age (SD) = 53.3 (7.3) Sex: M = 75.9; F = 24.1 NYHA class II = 20 (69.0%) NYHA class III = 9 (31.0%) Mean LVEF = 23.1 (4.3)	N = 13 Mean Age (SD) = 52.5 (7.6) Sex: M = 61.5; F = 38.5 NYHA class II = 9 (69.2%) NYHA class III = 4 (30.8%) Mean LVEF = 30.5 (9.7)	<u>Palliative Care</u> Intake summary with current health status and treatment regimen, assessment of physical and psychological symptoms, determine illness understanding, establish goals of care, assist with treatment decision making and coordination of care. Providers: Palliative care specialist (e.g. physician or advance practice nurse). <u>'Intervention group'</u> Participants receiving > 2 palliative care consultations.	1. Perceived control 2. Patient activation 3. Symptom distress	1. Patients undergoing ongoing palliative care reported significantly greater improvement in perceived control ($p < 0.001$). 2. Patients undergoing ongoing palliative care reported significantly greater improvement in activation ($p < 0.001$). 3. Patients undergoing ongoing palliative care reported significantly greater reduction in symptom distress ($p <$

Table 2: Characteristics of included studies

				'Comparator group' Participants receiving ≤ 1 palliative care consultations.		0.001).
Evangelista LS* [120] 2014 USA	Prospective Single-arm Cohort Study Outpatient consultations	N = 29 Mean Age (SD) = 54.1 (8.4) Sex: M = 75.9; F = 24.1 NYHA class II = 20 (69.0%) NYHA class III = 9 (31.0%) Mean LVEF = 25.9 (5.3)	N = 7 Mean Age (SD) = 52.7 (6.3) Sex: M = 57.1; F = 42.9 NYHA class II = 5 (71.4%) NYHA class III = 2 (28.6%) Mean LVEF = 23.1 (4.3)	Palliative Care Comprehensive physical and psychosocial assessment, discussions about advance care planning, developed a treatment plan (with participants) and listing goals of care. Providers: Palliative care specialist (e.g. physician or advance practice nurse). 'Intervention group' Participants receiving palliative care consultation and follow up. 'Comparator group' Participants receiving initial palliative	1. Symptom rating 2. Type of palliative care, focus of care, medication use	1. Patients receiving follow up were more likely to show improvement in over symptom burden ($p < 0.001$). 2. Patients who chose to have additional palliative care input were referred to: • Pharmacist for new medication (69%) or changes to their medication (24% • social work support (69%) • physical and occupational

Table 2: Characteristics of included studies

				care consultation only.		therapists (66%) • psychiatrists (55%) • chaplain (45%) • home health (83%) • support groups (31%) and • hospice (7%).
Wong RC (121) **2013** **Singapore**	Prospective Single-arm Cohort Study Community based	N = 44 Mean Age (SD) = 79 (9) Sex: M = 38.6; F = 61.4 NYHA class III = 31 (70.0%) NYHA class IV = 13 (30.0%) No data on LVEF		<u>Home Palliative Care Program</u> Measure patient's physiological parameters, physical examination to elicit relevant signs and symptoms, medication modification or initiation to palliate patient's symptoms. Providers: Doctor, nurse and/ or counsellor. No control	1. HF hospitalisation 2. All cause hospitalisation 3. Time to death	1. Mean HF hospitalisation significantly improved from baseline ($p < 0.0001$). 2. Mean all-cause hospitalisation improved from baseline significantly ($p < 0.0001$). 3. Mean time to death was 5.5 months.
Evangelista LS (122)	Prospective Case-Control	N = 36	N = 36	<u>Palliative care consultation</u> Assessment of current medical status	1. Symptom burden 2. Depression	1. Patients who had a palliative care

Table 2: Characteristics of included studies

2012 **USA**	Study 1 Outpatient consultation	Mean Age (SD) = 53.9 (8.0) Sex: M = 72.2; F = 27.8 NYHA class II = 25 (69.4%) NYHA class III = 11 (30.6%) Mean LVEF = 25.4 (5.2)	Mean Age (SD) = 53.3 (8.7) Sex: M = 69.4; F = 30.6 NYHA class II = 26 (72.2%) NYHA class III = 10 (27.8%) Mean LVEF = 26.0 (6.2)	and screening intake, evaluation of patient's goals and preferences, assessment of areas of perceived needs and establish a treatment plan with co-ordination of care. Providers: Palliative care physician or advance practice nurse. <u>Control</u> No information.	3. Quality of life	consultation had significantly lower symptom burden (p = 0.031). 2. Patients who had a palliative care consultation had significantly lower depression (p = 0.034). 3. Quality of life significantly improved in those who had a palliative care consultation (p = 0.015).

Note: Evangelista LS 2014† is titled: On-going palliative care enhances perceived control and patient activation and reduces symptom distress in patients with symptomatic heart failure: A pilot study and Evangelista LS 2014 is titled: Does the Type and Frequency of Palliative Care Services Received by Patients with Advanced Heart Failure Impact Symptom Burden?*

Abbreviations: NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; RCT = Randomised Controlled Trial; CHF = Congestive Heart Failure; SD = Standard Deviation; HF = Heart Failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; PHQ-9 = Patient Health Questionnaire-9; ACP = Advance Care Planning.

3.3.1 Study design

Nine interventional studies are included in this review – seven phase III RCTs [108-114], one phase II RCT [115], and one non-randomised quasi-experimental trial. [116] Additionally, there are six observational studies included – five cohort studies [117-121] and one case-control study. [122] The design, population characteristics, study settings, comparator, and the interventions delivered, and outcomes measures varied among the included studies and are summarised in Table 2.

3.3.1.1 Sample sizes and power calculation

Sample sizes of the included studies vary from 13 [115] to 384. [109] While most studies did not publish sample size or power calculations, a few commented on being limited by its small number of participants. Five studies provided the calculations. Aiken *et al.* [108] discussed the difficulty in recruiting patients and subsequently losing those recruited due to death or transfer to hospice, which led to decreasing statistical power over time from 93% at baseline to 64% at 6 months into the study. Bekelman *et al.* [109] recruited and analysed data from 187 patients in the intervention arm and 197 patients in the usual care arm to detect a 5 point difference in the Kansas City Cardiomyopathy Questionnaire (KCCQ) mean summary score with predicted standard deviation (SD) of 15 and an α error probability of 0.05 giving a power calculation of approximately 90%. Brännström *et al.* [110] increased the number of participants recruited from 62 to 72 in order to maintain the power around 80% with a significance level of $p < 0.05$ due to the unforeseen high attrition rate, mostly attributed to death. Hopp *et al.* [111] recruited 85 participants in total despite a sample size calculation for power of 80% stating that 88 participants are needed to be included in the study to detect a 20% proportion difference with a significance of 0.05. However, the difference is small and unlikely to affect the power of the study. Finally, Sidebottom *et al.* [113] stated that the study was designed to achieve a statistical power of 80% with a prospective enrolment of 500 participants. However, with 232 recruited participants, the power to detect an effect size of 0.25 with statistical significance of 0.05 reduced to 47.5%.

3.3.2 Participants

The characteristics of the included population are described in Table 2. Across 15 studies, 1,495 heart failure patients were included (Sahlen *et al.* excluded as the results are from the same participants as those in Brännström *et al.*).

The age of the population in the included studies ranged from approximately 52.5 to 82 years. The average age of participants in the intervention groups was 69.64 years compared to 68.85 in the control groups. The age difference in the intervention and control groups at baseline reached significance in Brännström *et al.* [110] and Sahlen *et al.* [112] (as the report results from the same study) ($p = 0.012$), in Sidebottom *et al.* ($p = 0.003$), and among the Bradford participants in Pattenden *et al.* [118] ($p < 0.05$). However, differences of baseline characteristics in RCTs will be due to chance and the observed difference unlikely to be of clinical significance.

More men are represented in these studies than women (61.5% male vs 38.5% female inclusion).

3.3.2.1 Inclusion/ exclusion criteria

There is variability in the inclusion and exclusion criteria across the 15 studies.

Eleven out of the 15 studies included patients based on severity of their heart failure functional status. This is measured by NYHA classification (class II or III [120] and class III or IV [108, 110-112, 114-116, 118, 121]) or KCCQ (<60). [109] Two of the remaining studies [119, 122] measure NYHA class but did not require it as part of their inclusion criteria. Sidebottom *et al.* [113] included patients admitted with an acute episode of heart failure and Enguidanos *et al.* [117] recruited home-bound patients with congestive heart failure, however, neither measured functional status.

Additionally, eight studies also required the occurrence of a recent acute episode [108, 110-112, 114, 117, 118, 121] resulting in visits to the emergency department (ED), hospitalisation, or even symptoms of end of life. Of the eight studies, five studies [111, 114, 117, 118, 121] quantified an estimated life expectancy of >1 year as an inclusion criteria also.

Only five studies explicitly state an inclusion criterion of age over 18 years [108, 113, 116, 119, 122], however no study included patients below the age of 18.

Studies excluded patients with cognitive impairment [109-113, 119, 120], psychiatric impairment [109, 111, 114], other irreversible conditions affecting prognosis [109-112, 119, 122] and those undergoing or who underwent heart transplantation [109, 111, 113, 122] or insertion of a left ventricular assist device. [113, 119, 122]

3.3.2.2 Disease characteristics

Only eight studies described the functional status of the patients included by the NYHA classification. [109, 110, 114, 115, 119-122] Out of the 728 patients for whom NYHA class information was available 32 were classified as being NYHA class I, 276 as NYHA class II, 350 as NYHA class III and 70 as NYHA class IV, as seen in Figure 2.

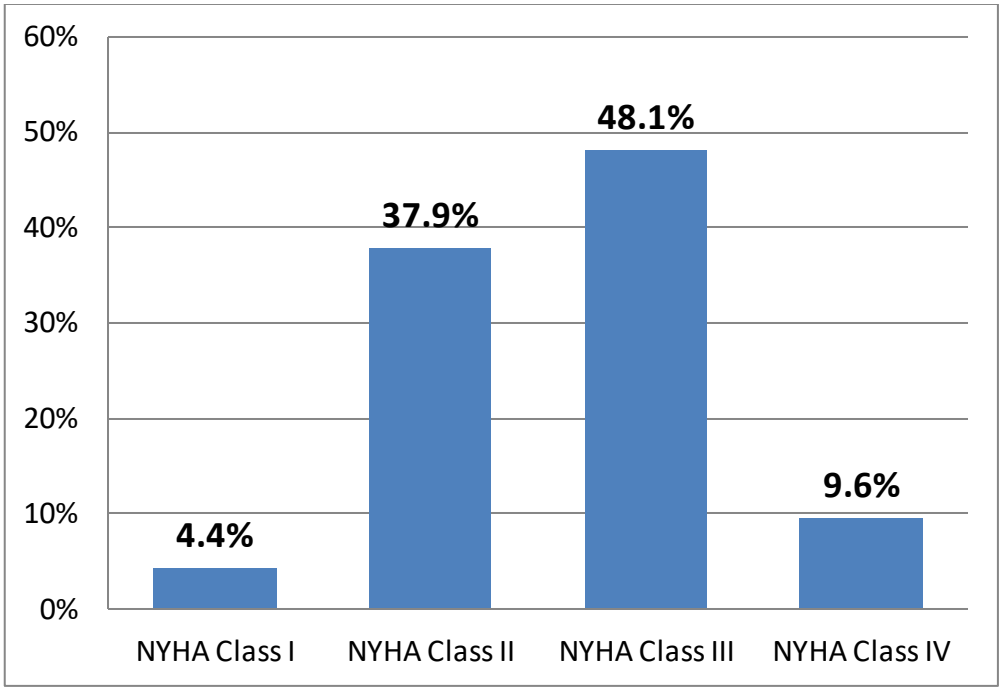

Figure 2: Distribution participants across the NYHA classes

Seven studies reported the severity of left ventricular function [109-111, 114, 119, 120, 122]. Bekelman *et al.* and Brännström *et al.* categorised a combined 420 patients into four categories - 'normal' (38.6%), 'mild' (22.1%), 'moderate' (27.4%) and 'severe' (11.9%) left ventricular functioning. The other five studies [111, 114, 119, 120, 122] provided the average LVEF for patients in each arm. The average LVEF of all patients in the intervention group of the five studies had a LVEF of 30% and those in the control group had 31%.

3.3.3 Intervention

As seen in Table 3, there is great variability in delivery of palliative care as an intervention across the participants studied. Most commonly included aspects of palliative care were assessment of current medical status and patients' needs, managing symptoms, providing formal and informal advance care planning with goal setting and care coordination. However, all studies included some form of multidisciplinary involvement in care.

Table 3: Breakdown of palliative care component delivered in the included studies

Study	Components of palliative care	Assessment of current status	Assessment of need	Assessment of quality of life	Symptom management	Psychological support	Social support	Spiritual support	Medication review and monitoring	Tele-health and monitoring	Patient education	Goal setting	Advance care planning	Coordination of care	Multidisciplinary involvement	Carer/ family support
Aiken LS [108]		✓	✓		✓	✓	✓		✓		✓		✓	✓	✓	✓
Bekelman DB [109]		✓	✓	✓	✓	✓			✓	✓	✓				✓	
Brännström M [110]		✓	✓	✓	✓					✓	✓	✓	✓	✓	✓	✓
Hopp FP [111]			✓									✓	✓		✓	
Sahlen KG [112]		✓	✓	✓	✓					✓	✓	✓	✓	✓	✓	✓
Sidebottom AC [113]		✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	
Wong FKY [114]		✓	✓	✓	✓					✓		✓	✓		✓	
Paes P [115]		✓	✓	✓	✓	✓			✓		✓		✓		✓	
Tadwalkar R [116]			✓	✓		✓		✓							✓	
Enguidanos SM [117]		✓	✓		✓	✓	✓	✓				✓	✓	✓	✓	
Pattenden JF [118]		✓	✓		✓	✓			✓		✓				✓	✓
Evangelista LS† [119]		✓	✓		✓	✓				✓	✓	✓	✓	✓	✓	
Evangelista LS* [120]		✓	✓		✓	✓	✓	✓	✓			✓	✓	✓	✓	
Wong RC [121]		✓	✓		✓				✓	✓			✓		✓	
Evangelista LS [122]		✓	✓	✓	✓	✓	✓		✓		✓	✓	✓		✓	

3.3.4 Comparator

Unfortunately, some studies do not give a description of the comparator. [110-113, 118, 122] Studies that do have some description of the comparator do not give details although they appear similar: regular care by their regular physicians and nurses. Bekelman *et al.* [109] screened for depression at baseline and reported screen-positive patients to their primary care physicians. Wong *et al.* [121] is a single arm study, and therefore did not have a comparator. The two observational studies by Evangelista et al. in 2014 [119, 120] are also single arm studies, however, they compare outcomes of patients who had follow-up care to patients who did not. Tadwalkar *et al.* [116] is looking at the impact of spiritual support on patients without a comparator, however, subgroup analysis of patients with religious and non-religious support is conducted.

3.4 Risk of bias assessment

3.4.1 Randomised Controlled Trials

The results of the assessment for risk of bias with the Cochrane Risk of Bias tool are presented in Table 4.

Table 4: Results of risk of bias assessment with the Cochrane Risk of Bias tool

Study	Adequate sequence generation?	Allocation concealment?	Blinding (participants and personnel)	Blinding (outcome assessors)	Incomplete outcome data addressed?	Free of selective reporting?
Aiken LS 2006 [108]	☑	☑	☒	☑	☒	☑
Bekelman DB 2015 [109]	☑	☑	☒	☑	☑	☑
Brännström M 2014 [110]	☑	☑	☒	☒	?	☑
Hopp FP 2016 [111]	?	?	☒	☒	☑	☒
Sahlen KG 2015 [112]	☑	☑	☒	☒	☑	☑
Sidebottom AC 2015 [113]	?	?	☒	☒	☑	☑
Wong FKY 2016 [114]	☑	☑	☒	☑	☑	☑
Paes P 2005◈ [115]	☑	☒	☒	☒	☒	☑
Tadwalkar R 2014 [116]	☒	☒	☒	☒	?	☑

◈ *Note that the risk of bias assessment for the study by Paes is derived from the full thesis on which the letter was based and not from the limited information in the published letter.*

Adequate randomisation and concealment of this process prevents selection bias or allocation bias, and therefore prevents introduction of uncontrolled confounders. Tadwalkar *et al.* [116] is designed as a non-randomised study where patients are in an intervention arm

based on personal preference, possibly due to the nature of the intervention. Unfortunately, the cause-effect relationship of the results from each arm cannot solely be attributed to the intervention, as there may be other influencing factors such as presence of co-morbidities. Other studies [111, 113, 115] provided insufficient information to assess the integrity of the sequence generation and the concealment of allocation, therefore, the risk of bias is unclear.

Mostly notably, the nature of the intervention – an approach to care – prevents blinding of participants and personnel delivering the intervention. Consequently, blinding of the assessors is important in maintaining impartiality in detecting true effect of the intervention. Brännström *et al.* [110] did not blind outcome assessment as some of the outcomes were patient reported, and physicians involved in the care assessed other outcomes such as functional classes. It is not completely clear that the assessor were or were not blinded in Sahlen *et al.* [112], however, as the results are from the same trial as Brännström *et al.* [110], it is likely that the same is true. Sidebottom *et al.* [113], Paes [115] and Tadwalkar *et al.* [116] use patient reported outcomes and therefore assessors could not blinded. However, Hopp *et al.* [111] also did not blind assessors as they conducted an open label trial.

While Aiken *et al.* [108] made significant efforts to contact patients for follow up and conducted attrition analysis in an attempt to assess the impact of missing data, no plan to manage missing data was described in the statistical methods. The attrition analysis revealed that patients who were eliminated from outcome analysis had worse functioning i.e. death, admission to hospice of skilled nursing facilities. This exclusion of patients reduced the power of the study and may have biased results as differential attrition based on allocation to a certain arm was found. Paes [115] had an uneven drop-out rate (all from control group), which exacerbated the issue of the small sample size. Wong *et al.* [114] conducted intention to treat analysis, despite the high dropout rate. In Brännström *et al.* [110] there were missing questionnaires (loss to follow up), however there is no information on which arm the non-responding patients belonged to and so the risk of bias is unclear. While, Tadwalkar *et al.* [116] conducted a modified intention to treat analysis, whereby they excluded patients who dropped out following randomisation, prior to intervention, it is unclear if excluding these patients would have a significant impact.

Hopp *et al.* [111] gives a results summary of patients who met the primary endpoint, however to ensure transparency, all results should have been reported clearly. Additionally, they do not state their plans to conduct qualitative interviews in the methods, however the data is reported on in the results section. As the intervention centred around a clinical interview, if the qualitative interview was conducted at the beginning of the study, this could have had a beneficial effect and diluted their results. [123]

3.4.1.1 Other biases

Sample size

While some studies found significant differences among some outcomes, it is important to note that almost all studies (except Bekelman *et al.*) comment on the small sample sizes included and its effects such as difficulty detecting small effects and generalisability of results.

Furthermore, Aiken *et al.* [108] has a high risk of type 1 errors as they conducted multiple statistical tests. The sample in Bekelman *et al.* [109] is chosen from a population of US veterans which may impact its generalisability.

Baseline differences

The average age of patients in each arm was not equal in Brännström *et al.* [110] and consequently in Sahlen *et al.* [112], however the authors adjusted for age in the analysis of results. Similarly Sidebottom *et al.* had a significant difference in ages in each arm and was addressed by controlling for age in the analyses. Wong *et al.* [114] also had some significant differences in baseline characteristics, most significantly, patients assigned to the control arm had a higher NYHA class, which does not seem to be accounted for although this should have underestimated benefit if anything in this positive trial.

Quality assurance of intervention

The intervention in Tadwalkar *et al.* [116] did not appear to be well-regulated and no efforts were made to ensure the comparability of the intervention to control while maintaining a clear distinction. Similarly, the effect of the intervention may be underestimated in Sidebottom *et al.* (another positive trial) as not all patients who were assigned to the

intervention received palliative care (due to withdrawal or high work load among the providers) and eight control patients received palliative care through their standard care as it could not be ethically withheld.

3.4.2 Cohort studies

The NOS risk of bias assessment for the five cohort studies is included in Table 5. This assessment is complicated due to the nature of the included studies i.e. single arm studies [119-121] and studies with a historical comparison. [118] Single group studies are less methodologically robust, however may still provide valuable results. For this analysis, the two single-arm cohort studies by Evangelista *et al.* [119, 120] are assessed as though the less exposed arm is the control and the arm with higher palliative care follow ups as the exposed group. Additionally Wong *et al.* could not be assessed completely as there is no non-exposed group.

Table 5: Results of NOS risk of bias assessment for cohort studies

Study	Selection	Comparability	Outcome
Enguidanos SM 2005 [117]	★★★☆	☆☆	☆★★
Pattenden JF 2013 [118]	★★★☆	☆☆	☆★★
Evangelista LS 2014† [119]	★★★☆	☆☆	☆★★
Evangelista LS 2014* [120]	★★★☆	☆☆	☆★★
Wong RC 2013 [121]	★★★☆	☆☆	☆★★

All cohort studies had representative samples and confirmed exposure to palliative care. Demonstrating that the outcome of interest was not present at the start of the study is of less use in an intervention such as this, because outcomes such as hospitalisations, symptom distress, and quality of life are expected to improve or worsen based on exposure, not appear or disappear. Comparability could be assessed with the help of baseline characteristics however, none of the studies controlled for confounding factors as part of their plan for the analysis. Therefore, comparability was not assured through the methodology. Outcome assessment was often self-reported and therefore could not be blinded. Determining adequate follow-up length is difficult as the study design varied with some studies looking at time to death as an outcome while others compared patients with and without follow-up for outcome difference.

3.4.3 Case-control study

The NOS quality assessment for case-control is summarised in Table 6. For selection of cases and controls, Evangelista *et al.* [122] scored 3 stars out of a possible 4. The case definition is adequate with independent validation from hospital records and all patients referred by their heart failure (HF) care providers were consented and assessed for eligibility, therefore the cases are representative of those would receive palliative care referrals among the general population. The manual for NOS scale gives the third star in 'Selection' for controls from the community it order to ensure that the controls are derived from the same population as the cases, however in this study both the cases and the controls were hospitalised for HF exacerbation. Therefore, this star was awarded, nonetheless. No definition of the controls was available and therefore history of the outcome among the controls could not be ascertained. The comparison group was matched by sex, age, race, and NYHA class with the cases. Additionally, to control for differences at baseline, the analysis included time 1 values as covariates. The exposure was measured with the use of secure hospital records among the cases however no such information is available for controls. There was no information available on non-response rate among controls also.

Table 6: Results of NOS risk of bias assessment for case-control studies

Study	Selection	Comparability	Exposure
Evangelista LS 2012 [122]	★★★☆	★★	★☆☆

3.5 Outcomes

3.5.1 Symptom burden

Eight studies reported on the effect of palliative care on the patients' symptom burden [108, 110, 113, 114, 116, 119, 120, 122]. Three randomised controlled trials [110, 113, 114] measured symptom burden with the use of the tool Edmonton Symptom Assessment Scale (ESAS). ESAS is a valid and reliable [124], self administered tool that assesses the severity of nine commonly occurring symptoms on a scale of 0 to 10 – pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well being and shortness of breath.

Brännström *et al.* [110] observed a significant improvement ($p = 0.02$) in nausea in the intervention arm compared to the control arm, but no significant difference was found in the total scores. Additionally, eight out of the nine sub categories improved in the intervention compared to four out of nine in the control arm; however, the differences between the two arms were not significant. Sidebottom *et al.* [113] found significant difference in improvement of the total ESAS score between the intervention and the control group at 1 month (3.69 points, $p < 0.001$) and at 3 months (4.31 points, $p < 0.001$) from baseline. In total, there was an 11% improvement in the ESAS score in the intervention arm. Wong *et al.* [114] showed no significant difference in improvement of total symptom intensity between groups. However, there was significant improvement ($p < 0.01$) in depression and anxiety over time in the intervention arm compared to the control.

Three observational studies also used ESAS [119, 120, 122]. In the 2012 observational study by Evangelista *et al.* [122] patients in both groups demonstrated significantly lower levels of symptom burden ($p < 0.001$). The group-time interactions were also significant ($p = 0.031$)

with patients in the intervention arm experiencing lower symptom interference. While patients who received a PC consultation have more significant improvements in fatigue ($p < 0.001$), pain ($p = 0.044$), well-being ($p = 0.035$), depression ($p = 0.029$), dyspnoea ($p = 0.008$), and nausea ($p = 0.045$), patients in the matched control group had worsening symptoms of fatigue ($p < 0.001$) and pain ($p = 0.044$). Evangelista *et al.* [119] observed a significant reduction in symptom distress ($p = 0.04$) among patients who received ongoing palliative care compared to those who received one or fewer palliative care consultations. Evangelista *et al.* [120] reported a significant improvement ($p < 0.001$) in the symptom burden experienced by all participants. Additionally, patients receiving further palliative care services following the initial consultation showed significant improvement in fatigue ($p < 0.001$), pain ($p = 0.044$), anxiety ($p = 0.029$), sense of well-being ($p = 0.035$), dyspnoea ($p = 0.008$) and nausea ($p = 0.045$) compared to those who only completed the initial consultation.

As part of assessing the patients physical and mental functioning, Aiken *et al.* [108] incorporated the Memorial Symptom Assessment Scale (MSAS) into the questionnaires used to measure the outcomes. MSAS is another valid patient rated tool for symptom assessment measuring frequency, severity, and distress of individual symptoms on a Likert scale. [125, 126] PhoenixCare participants in the study with congestive heart failure (CHF) experienced significantly higher symptom distress ($p < 0.05$) than those in the control arm. Tadwalkar *et al.* [116] also utilised MSAS to assess symptom prevalence and distress, however found no significant difference in the score over time in either arm.

3.5.2 Depression

Five studies investigated the symptom of depression in its own merit. [109, 113, 115, 116, 122] Two RCTs and a case-control study use the self-administered Patient Health Questionnaire-9 (PHQ-9) to measure depression based on the physical and mood symptoms rated on a scale of 0 to 3. [109, 113, 122] PHQ-9 is widely used to screen for, diagnose and monitor depression and it severity. [127] Bekelman *et al.* [109] identified a significantly ($p = 0.01$) greater improvement in PHQ-9 score in the intervention arm compared to the usual arm after one year. Also, Sidebottom *et al.* [113] found a significant difference in the improvement of PHQ-9 scores between the intervention and the control arms at 1 month (1.42 points, $p < 0.001$) and at 3 months (0.72 points, $p < 0.001$) with a 17% improvement in PHQ-9 score from

baseline in the intervention group. Evangelista *et al.* [122] found a significant improvement in depression over time (p = 0.002). In addition, the group-time interaction was also significant (p = 0.034) with lower levels of depression in the palliative care group compared to the standard care. In a pilot study by Paes [115] depression was measured with the Hospital Anxiety and Depression Scale (HADS), a self assessment scale validated to detect states of anxiety, depression and emotional distress rated on a scale of 0 to 3. [128] While there was a decrease in the depression score in the intervention arm and an increase in the control, this difference was not statistically significant. The trial by Tadwalkar *et al.* [116] found a significant difference (p = 0.04) in the Quick Inventory of Depressive Symptomatology (QIDS-SR16) score from baseline to two weeks for all included patients, however there was no significant difference over time in either arm.

3.5.3 Functional status

Patients in Brännström *et al.* [110] had a significant difference (p = 0.012) in change of mean NYHA classes from baseline. On average more patients experienced an improvement in functional status in the PREFER arm compared to the control (p = 0.015). Wong *et al.* [114] measured functional status with the use of the Palliative Performance Scale (PPS), adopted from the Karnofsky Performance Scale, to quantify ambulation, activities, self-care, intake and consciousness level. There was no significant difference in functional status at baseline or at the end-point.

3.5.4 Quality of life

Five phase III RCTs [109, 110, 112-114], one phase II RCT [115], one quasi-experimental trial [116] and a case-control study [122] measure quality of life. There are multitudes of tools available to measure quality of life. In the included studies the following were used: KCCQ [109, 110], EuroQol (EQ-5D) [110, 112], Minnesota Living with Heart Failure Questionnaire (MLHFQ) [113, 122], Chronic Heart Failure Questionnaire (CHQ) [114], McGill Quality of Life Questionnaire (MQOL) [114], the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) [115], and Quality of Life Enjoyment and Satisfaction (Q-LES-Q-SF)[116]. KCCQ quantifies physical function, social function, symptom burden, self-efficacy and knowledge and quality of life through a validated self-administered tool.[129] The scores are transformed onto a scale on 0 – 100. EQ-5D is also a validated [130] self-completed tool designed to measure health related quality of life (HRQL) quantifying five dimensions

(mobility, self-care, usual activities, pain/ discomfort , anxiety/ depression) on a 5 point scale. MLHFQ was designed to represent the physical, emotional, social, and mental domains of quality of life. It assesses the effect 21 items over the past months on a scale of 0 to 5. CHQ, a 20-item tool representing dyspnoea, fatigue, emotional status, and mastery with a 7 point Likert scale, and MQOL, a heart failure specific scale focusing on physical, emotional, existential and support domains rated from 0 to 10, are also validated tools to assess quality of life. [131, 132] On the contrary EORTC QLQ-C30 was designed and validated [133] to measure physical, social and psychological functions among cancer patients. Q-LES-Q-SF assesses satisfaction across 16 physical and psychological characteristics.

Bekelman *et al.* [109] stated that the KCCQ score in both the intervention and control arm increased by 13.5 points. However, neither the difference between groups not over time (3-month, 6-month, and 12-month data) was significant. Brännström *et al.* [110] also found no significant differences in total KCCQ score between the two arms. However, 19 summary scores improved in the PREFER arm, with significant improvements in total symptom burden (18%, $p = 0.035$), self-efficacy (17%, $p = 0.041$), and disease-specific quality of life (24%, $p = 0.047$). In contrast, there were improvements in 11 summary scores in the control arm, none of which were significant. Additionally, the age-adjusted HRQL, measured by EQ-5D, was significantly better in patients in the intervention arm compared to the controls (baseline to 6 months 28% vs. 3% increase, $p = 0.02$ and baseline to last measurement 20% vs. 1% increase, $p = 0.04$). Sahlen *et al.* [112] assessed quality of life with the use of EQ-5D and reported it in the quality assessed life years (QALY) format. They noted that the change in QALY weight was small but significant ($p = 0.026$) with patients in the intervention group gaining weight. Sidebottom *et al.* [113] identified a significant 4.92 point difference between intervention group and control group at 1 month ($p < 0.001$) and 3.06 point difference at 3 months ($p < 0.001$) in MLHFQ. Wong *et al.* [114] found significant improvement in both the palliative-specific scale MQOL-HK ($p < 0.05$) and the heart failure specific CHQ Chinese version ($p < 0.01$). Paes [115] found differences in scores between groups (favouring the intervention) and over time, however, none of the results reached significance. Evangelista *et al.* [122] demonstrated a significantly ($p = 0.015$) better quality of life according to the MLHFQ in the palliative care group compared to the standard heart failure care group.

However, Tadwalkar *et al.* [116] found no significant difference in quality of life enjoyment or satisfaction between groups or over time.

3.5.5 Resource use

Nine studies [108-110, 113, 114, 117, 118, 120, 121] use a variety of measure to quantify resource use, including, visits to the ED, hospitalisations, length of stay (LOS) in hospitals, re-admission rate, hospice care, and referrals to additional services (i.e. physical or occupation therapy). Aiken *et al.* [108] measured service utilisation by counting number of stand-alone emergency department visits prior to inclusion in study (to establish a normative pattern) and then comparing the number of visits to the emergency department by participants in each arm. There was no significant change in pattern seen in either arm. The authors also hoped to report length of stay in hospital, however there was no reliable source of data. Bekelman *et al.* [109] found no significant difference between the two arms in 1 year hospitalisation rates or time to hospitalisation. Brännström *et al.* [110] found that the mean number of hospitalisations and mean number of days spent in hospital were significantly higher in the control arm ($p = 0.009$ and $p = 0.011$ respectively). Additionally, they found significant differences between visits and phone calls between the two groups. However, there is reporting of results in the text conflicts with the table. The authors were not available for clarification. While there were no significant differences in election of hospice care between arm in Hopp *et al.* [111], two patients in the palliative care group elected hospice care. Sidebottom *et al.* [113] found no significant association between 30-day inpatient readmission or hospice use and assignment to intervention or control group when adjusting for age, gender and marital status. Conversely, the authors found that the intervention group was significantly more likely (2.87 times, $p = 0.033$) to have completed the disease-specific advance care planning (ACP) process within 6 months. Wong *et al.* [114] found no significant difference between the two arms in the 4-week readmission rate or the mean number of readmission although the trend favoured the intervention. However, the difference in the readmission rate and mean number of readmissions between the two arms at 12 weeks was significant ($p = 0.009$ and $p = 0.001$, respectively). Enguidanos *et al.* [117] investigated service use as well as site of death of participants. On average, the palliative care group had fewer days on service ($p < 0.001$), however there is no statistical difference in obtaining hospice care between the two groups. Patients with congestive heart failure in

palliative care group were more likely to die at home ($p < 0.001$) than those in usual care. Fewer patients in the intervention arm of both sites of the Pattenden *et al.* [118] study were admitted to hospital, however the difference only significant among the Bradford sample ($p < 0.01$). Mean number of all-cause hospitalisations per patient were significantly lower in the intervention group of the Poole patients ($p < 0.05$) and the proportion of patients admitted with heart failure was significantly lower in the intervention group in both Bradford ($p < 0.05$) and Poole ($p < 0.01$). There was no significant difference between the intervention and the control in length of stay in either site. In Evangelista *et al.* [120] all patients who chose to have additional palliative care input were referred to a pharmacist to develop a treatment regimen, 69% had new medication prescribed and 24% had changes to their medication. 69% of patients who had further palliative care following the initial consultation also sought social work support. 66% were referred to physical and occupational therapists, 55% were referred to psychiatrists and 45% met with the chaplain. Additionally patients were referred to community health services such as home health (83%), support groups (31%) and hospice (7%). Mean number of follow up visits for those who chose to have continued palliative care was 2.21. Mean all cause hospitalisation and HF hospitalisations improved after recruitment into palliative home care ($p < 0.0001$) in Wong *et al.* [121]

3.5.6 Mortality

Six included studies [108-111, 113, 121] identified, and reported mortality among their participants. In Aiken *et al.* [108], 16% of patients in the intervention arm died compared to 13% in the control, however they do not include a significance calculation. Bekelman *et al.* [109] found that fewer patients died in the intervention arm over time ($p = 0.04$). No statistical difference in mortality between the two arms in Brännström *et al.* [110] In Hopp *et al.*[111] 23.8% of patients died 3 to 6 months after randomisation, but there was no significant difference between groups. Sidebottom *et al.* [113] found no significant difference in death within 6 months of enrolment between the intervention and the control. 68% of patients recruited by Wong *et al.* [121] died within programme and the mean time to death was 5.5 months.

3.5.7 Cost

Three studies [112, 117, 118] measures costs incurred due to the intervention and the control. Sahlen *et al.* [112] set out to assess cost-effectiveness and therefore conducted an assessment of costs incurred due to the intervention in comparison to the control with the help of a purpose built model. This model calculates the cost with the help of known or assumed staffing costs and time spent at a service by a patient, which, if not known was also assumed based on recommendations. The study found that there were no significant differences in average cost over a 6-month period per participant as the high staffing costs in the intervention group are balanced by the reduced costs for hospital care and emergency transport. Similarly, Enguidanos *et al.* [117] calculated costs generated by multiplying number of visits of service days by the costs of staff time associated with care in 1999. Unlike Sahlen *et al.* [112], this study did not include administrative or overhead costs. The results showed a 52% decrease in the cost of the intervention compared to the usual care, of which 19% can be attributed to enrolment into palliative care and number of days on service. Pattenden *et al.* [118] collected data on costs of procedures undergone and inpatient costs for both arms. While the cost of the intervention was lower in both sites, the mean difference in patient cost was significant in Bradford but not in Poole.

3.5.8 Satisfaction with care

Wong *et al.* [114] measured satisfaction with care using an 11-item questionnaire and there was significantly more satisfaction with care among the palliative care group. Paes [115] distributed clinical evaluation forms to patients in the intervention group for feedback which was positive, with patients feeling that they understand more about their condition and found the communication about their condition helpful.

Table 7 provides a summary of the results in the included studies categorised by the outcome of interest and is supported by information regarding the adequacy of the study methodology.

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
Symptom burden	Brännström M [110]		✓		Yes	Yes	Yes	Unlikely
	Sidebottom AC [113]	✓			Yes	Yes	Yes	Possibly
	Wong FKY [114]		✓		Yes	Yes	Yes	Unlikely
	Evangelista LS 2012 [122]	✓			No	Yes	Yes	Possibly
	Evangelista LS 2014† [119]	✓			No	Yes	Yes	No control
	Evangelista LS 2014* [120]	✓			No	Yes	Yes	No control

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Aiken LS [108]			✓	Yes	Yes	No	Likely
	Tadwalkar R [116]		✓		No	Yes	No	Unlikely
Depression	Bekelman DB [109]	✓			Yes	No	No	Likely
Depression	Sidebottom AC [113]	✓			Yes	Yes	Yes	Possibly
Depression	Evangelista LS 2012 [122]	✓			No	Yes	Yes	Possibly
Depression	Paes P [115]		✓		No	Yes	Yes	Unclear

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Tadwalkar R [116]		✓		No	Yes	No	Unlikely
Functional status	Brännström M [110]	✓			Yes	Yes	Yes	Unlikely
	Wong FKY [114]		✓		Yes	Yes	Yes	Unlikely
Quality of life	Bekelman DB [109]		✓		Yes	No	No	Likely
	Brännström M [110] (disease-specific)		✓		Yes	Yes	Yes	Unlikely
	Brännström M [110] (HRQL)	✓			Yes	Yes	Yes	Unlikely

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Sahlen KG [112]	✓			Yes	Yes	Yes	Unlikely
	Sidebottom AC [113]	✓			Yes	Yes	Yes	Possibly
	Wong FKY [114] (palliative-specific scale)	✓			Yes	Yes	Yes	Unlikely
	Wong FKY [114] (HF-specific)	✓			Yes	Yes	Yes	Unlikely
	Paes P [115]		✓		No	Yes	Yes	Unclear
	Evangelista LS 2012 [122]	✓			No	Yes	Yes	Possibly

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Tadwalkar R [116]		✓		No	Yes	No	Unlikely
Resource use	Aiken LS [108] (ED visits)		✓		Yes	Yes	No	Likely
	Bekelman DB [109] (hospitalisations)		✓		Yes	No	No	Likely
	Brännström M [110] (hospitalisations)	✓			Yes	Yes	Yes	Unlikely
	Brännström M [110] (LOS)	✓			Yes	Yes	Yes	Unlikely
	Hopp FP [111] (hospice care)		✓		Yes	Yes	Yes	Unclear

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Sidebottom AC [113] (re-admissions)		✓		Yes	Yes	Yes	Possibly
	Sidebottom AC [113] (ACP)	✓			Yes	Yes	Yes	Possibly
	Wong FKY [114] (re-admissions)	✓			Yes	Yes	Yes	Unlikely
	Enguidanos SM [117] (days on service)	✓			No	Unclear	Yes	Unlikely
	Enguidanos SM [117] (hospice care)		✓		No	Unclear	Yes	Unlikely
	Enguidanos SM [117] (place of death)	✓			No	Unclear	Yes	Unlikely

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Pattenden JF [118] (hospitalisations)	✓			No	Yes	No	Unlikely
	Pattenden JF [118] (LOS)		✓		No	Yes	No	Unlikely
	Evangelista LS 2014* [120]	N/A			No	Yes	Yes	No control
	Wong RC [121] (hospitalisations)	✓			No	Yes	Yes	No control
Mortality	Aiken LS [108]		✓		Yes	Yes	No	Likely
Mortality	Bekelman DB [109]	✓			Yes	No	No	Likely

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Brännström M [110]		✓		Yes	Yes	Yes	Unlikely
	Hopp FP [111]		✓		Yes	Yes	Yes	Unclear
	Sidebottom AC [113]		✓		Yes	Yes	Yes	Possibly
	Wong RC [121]	N/A			No	Yes	Yes	No control
Cost	Sahlen KG [112]		✓		Yes	Yes	Yes	Unlikely
	Enguidanos SM [117]	✓			No	Yes	Yes	Unlikely

Table 7: Summary of outcome results

Outcome	Study	Results			Adequacy of study methodology			
					Study design	Population	Intervention	Control
		Significantly in favour of intervention	No significant difference	Significantly in favour of control	Phase III RCT	Advanced heart failure	Specialist palliative care	Risk of contamination by intervention
	Pattenden JF [118]	✓			No	Yes	No	Unlikely
Satisfaction	Wong FKY [114]	✓			Yes	Yes	Yes	Unlikely
	Paes P [115]	✓			No	Yes	Yes	Unclear

Chapter 4 – Discussion

This thesis set out to answer the question of whether there was any evidence to support the use of palliative care interventions in people with advanced heart failure. Historically, a palliative care approach and access to palliative care services has only been available for patients with cancer, however, more recent recognition that people with advanced heart failure also have palliative care needs [36, 73-76] has led to a call for people with heart failure to have similar access. Despite this, utilisation of a palliative care approach or access to palliative care services in heart failure has been sparse. [83, 89, 90] One of the barriers to accessing palliative care for these patients is the perceived or real lack of good quality evidence of benefit to the patient. Therefore, this review has collated the current body of evidence examining the effects of palliative care on patients with heart failure with the intent to guide future clinical and research priorities for the management of advanced chronic heart failure.

4.1 Summary findings

Overall, (see Table 7 in Chapter 3) the results from the included studies support the use of palliative care in managing patients with heart failure. Participants in the observational studies and those in RCTs allocated to care from a specialist palliative multi-disciplinary team benefited with regard to patient-related outcomes such as symptom burden, depression, functional status, and quality of life, as well as, administrative outcomes such as resource use and costs of care. However, findings were not consistent across all studies. In this chapter, methodological factors relating to study design, study population, and outcome measures, which might explain the variation in results, will be discussed. Implications for clinical practice and priorities for future research will be presented.

4.2 Factors which could contribute to mixed results

As seen in Table 7, some outcomes assessed by the included studies either were not improved (either before/after, or between group depending on design) or benefit was better in the control arm. Various factors may contribute to this variability in results seen across studies. While clinical heterogeneity across studies has an effect on the accuracy of

the summary findings in this review, methodological factors (as described in Table 7 and below) are also likely to play a part.

4.2.1 Study design

4.2.1.1 Observational or experimental

Some authorities consider that observational studies will over-estimate effect. [134, 135] Surprisingly, a recent systematic literature review by Anglemeyer *et al.* [136] did not find a significant difference in effect size between observational and RCT outcomes. Nevertheless, the well-accepted consensus supports that RCTs provide higher levels of evidence from which stronger recommendations for clinical practice can be made. Trials without randomised allocation such as Tadwalkar *et al.* [116] and the observational studies [117-122] present a difficulty in assessing the precise impact of an intervention on a population. It is not clear whether this association is influenced by bias (i.e. selection bias), chance, or due to a causal relationship.

All of the RCTs [108-115] randomised patients individually (unit of randomisation – individual patients); none were cluster RCTs where the unit of randomisation may be the institution or the clinic. As such, a risk of contamination of the control group by the intervention is possible depending on how the intervention was delivered and by whom and is discussed further in the 'Delivery and fidelity to allocation' section below.

4.2.1.2 Statistical power

Difficulties in recruitment and retention are seen in most of the included studies [108, 110-122], leaving some underpowered or only powered to detect moderate to large effects of the intervention. Due to the nature of these patients and their health status, it may be valuable to detect even small effects of an intervention as this may translate into a substantially positive individual experience in the late stages of a disease course. Small sample sizes increase the probability of type 2 errors, where the study mistakenly fails to reject a null hypothesis of no difference in effect – that is, a real effect is missed. This is seen in the phase II RCT by Paes [115], where no significant differences in outcomes were found between arms as it was not designed with sufficient power. Some studies, however, did reach adequate power [109-112] to find benefit, which they did, and others found benefit despite being underpowered. [113]

4.2.1.3 Blinding

Blinding of the investigator and the subject reduces biased reporting, which is especially pertinent with subjective outcome. [137] As previously mentioned (in the risk of bias assessment in Chapter 3), patients could not be blinded to the intervention they were receiving due to the nature of the intervention. This could affect retention rates because if the patient is not receiving their preferred intervention, they may be less motivated to take part in follow-up. Additionally, patient-reported outcomes are complicated by the potential for reporting bias and patients allocated to control may not fully understand the purpose of the trial. [138] However, this is unavoidable due to the nature of the intervention. There is an even greater risk of bias in open-label trials where both the participant and the outcome assessors are not blinded. Moreover, even where assessors are blinded, disclosure by participants which break the blind is common. [96]

4.2.1.4 Setting

Most studies were conducted in developed western countries; nine in the USA [108, 109, 111, 113, 116, 117, 119, 120, 122], two in the UK [115, 118], two in Sweden [110, 112] and two studies in Asia – one in China [114] and one in Singapore. [121] Health care systems across these countries are quite different, which may impact patients' health seeking behaviour. In some studies such as, Sidebottom *et al.* [113], patients were only funded for the single session and the burden of costs incurred in follow-up appointments would fall on the patient themselves or their medical insurance, which may dissuade patients to continue with care. Additionally, patients raised in different countries may behave differently when seeking further assistance in response to advice given by the intervention team, with some being reluctant due to their cultural and regional influences. This lack of compliance, resulting in high attrition [108] may diminish the effect the intervention has on the patient.

4.2.2 Population

A proportion of the clinical heterogeneity arises from the demographics of the population included in studies. It is, therefore, important to consider if the population included in the reviewed studies a) reflect the population with heart failure in the general population and b) represent those who might benefit most from palliative care. The need for palliative care is likely to be higher in patients with more advanced disease, older and with co-morbid

disease. Inclusion of patients who are less likely to need palliative care could reduce the benefit of the effect seen.

4.2.2.1 Age

Figure 3 shows the average age distribution of patients across included studies. While the average age of all patients in this review are similar to the ESC-HF pilot survey [28] (continental European data), the British data [29] suggests a higher average age of patients suffering with heart failure during their index hospitalisation. The average age of patients included in 4 of the 15 studies [116, 119, 120, 122] is lower than in the other studies and lower than the average within this review and compared to the external populace.

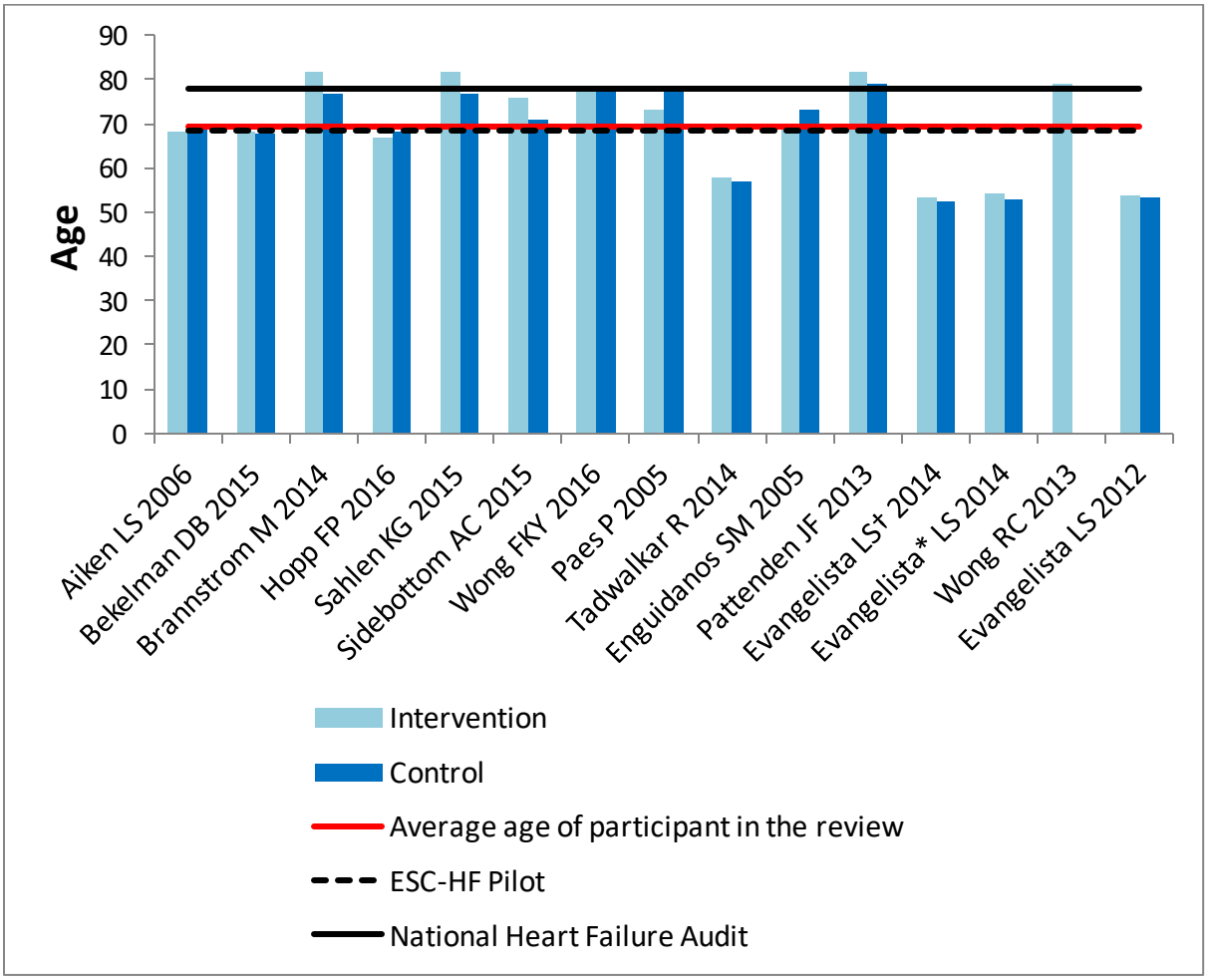

Figure 3: Bar chart showing the age distribution of patients across included studies

As the inclusion criterion was 18 or over; all patients attending adult services would be eligible. The inclusion criterion likely to be of most importance is therefore the severity of disease, not the patients' age.

4.2.2.2 Severity of heart failure

The management of distressing symptoms is defined by the WHO as a pillar of palliative care (described in Chapter 1). [4] Patients in NYHA class III and IV have, by definition, a higher symptom burden and worse functional status than those with class I or II symptoms. It could be argued that they have a greater need for additional support, and patients in class II and especially class I, may not benefit to the same extent. Nine studies [108, 110-112, 114-116, 118, 121] included patients with NYHA class III or IV only and patients in 3 studies [119, 120, 122] have NYHA class II or III disease. Two studies [113, 117] give no indication as to the stage of the disease or nature of the disease burden on the patients. Therefore it is difficult to ascertain if this patient population will benefit from palliative care intervention, although patients in Sidebottom *et al.* [113] were recruited during a hospital admission for acute decompensation and on average at baseline had had a previous admission within the previous six months indicating unstable disease. Bekelman *et al.* [109] included any patient with a heart failure diagnosis code in the electronic record and so consists of patients with NYHA I to IV and LVEF normal to severe. Although they excluded patients with a KCCQ score over 60, most participants, nonetheless, had NYHA class I and II and normal to mild LVEF. Therefore, it is unclear if these patients had sufficient need for palliative care to be able to demonstrate benefit – at least in physical domains. This could explain why depression was the only symptom that had greater improvement than controls in Bekelman's study.

Palliative care is designed to 'positively influence the course of the illness' [4], therefore assessing its impact on functional status would be helpful. Unfortunately, only two studies measured the impact of palliative care on the functional status, and one found palliative care to be positively associated with functional status [110] and the other found no significance. [114] Therefore, this needs to be investigated further.

4.2.2.3 Ethnicity

Ethnicity of participants is depicted in the pie chart below and is useful regarding the generalisability of the results. There are great inequalities in access to health due to ethnicity and race [139] and socio-economic status. [140, 141] Ethnicity is sometimes used as a proxy for societal factors [142], however, race and genetic composition play a more important role in influencing the natural history of the disease, response to treatment and help-seeking behaviour.

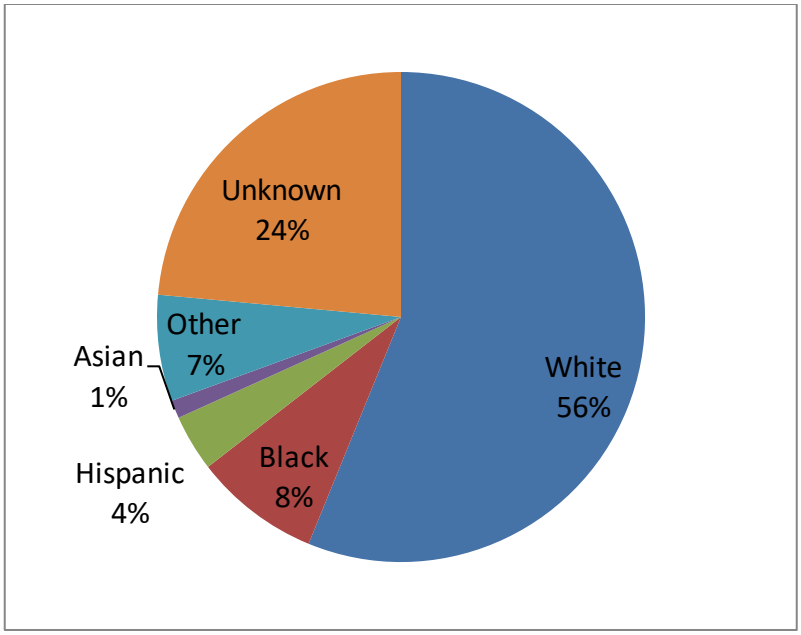

Figure 4: Pie chart showing the ethnic composition of the patients included in the review

4.2.2.4 Co-morbidity

In addition to disease burden, patients' co-morbidities can be a source of need for palliative care. Seven out of 15 studies do not report on patients' co-morbidities. [108, 111, 113, 115-118] Where reported in the studies [109, 110, 112, 114, 119-122], the most common co-morbidities were coronary artery disease, atrial fibrillation and hypertension, which could all cause or worsen heart failure. Within the data available, some studies [109, 110, 112, 114] have a higher proportion of the population reporting the presence of a number of co-morbidities. It is difficult to estimate the severity of patients' co-morbidities and, therefore, the relationship between the presence of co-morbidities and outcomes, as there appears to be no clear trend.

Overall, it is likely that the factors mentioned above contribute to a proportion of the variance.

4.2.3 Intervention and comparator

4.2.3.1 Components of care

As discussed previously (in Chapter 1), palliative care is a multi-faceted approach to care and it consists of multiple components which can be tailored to the needs of the patient. Referring back to Table 3, it is clear that there are many studies that address numerous elements of patient management, however, Tadwalkar *et al.* [116] focused on solely on

spiritual counselling and its effects. As detailed above (in Chapter 3), Tadwalkar *et al.* [116] and Hopp *et al.* [111] found no significant differences in outcomes within and between groups. While these are important components of palliative care, exploring the effects of only a single aspect of general palliative care could be a major contributor to conflicting results seen in this review.

In contrast, studies investigating the effect of palliative care as a more comprehensive intervention [108, 110, 112, 113, 120, 122] distinct from control tended to have more evident results in favour of palliative care (see Table 7). In studies where a specialist palliative care physician, specialist nurse and additional team members were involved [110-115, 117, 119-122] patients were more likely to have better outcomes than in studies with 'generalist' provision or only aspects of specialist care. [108, 109, 116, 118]

4.2.3.2 Frequency of consultations

Two studies [113, 122] assessed the effect of a single palliative care consultation on outcomes over time. However, if a patients' assessment of need indicates a need for palliative care, the benefits from one consultation alone cannot fully represent the potential benefit of ongoing palliative care and does not represent usual palliative practice. Continuity of care fosters good doctor-patient relationships [143] which may be more likely to enhance the benefits of palliative care. Therefore, it would appear plausible that studies with more tailored input, in terms of frequency, from the intervention would show an even greater benefit to patients.

4.2.3.3 Delivery and fidelity to allocation

Adequate delivery of the intervention and patients' fidelity to allocation is likely to have been compromised in some studies, thus underestimating any effect that may be seen. Some patients did not receive the intervention as prescribed either due to limited availability of providers [113] or due to the model of advance booking (limiting access to care if patients deteriorate rapidly). [118] Meanwhile other patients received palliative care despite their allocation into the control arm [113], as it would be unethical to turn patients away from care. Therefore, arguably, these studies under estimate the effect of the intervention.

Furthermore, none of the RCTs were cluster trials, and it is possible that the control group could have been contaminated by the intervention. Based on the study methods described in the papers, some studies are at a greater risk of 'contamination of control' by the intervention. In some studies, there were opportunities for usual care providers to learn from the intervention team either by being involved in implementing aspects of palliative care or through observation. [108, 109, 113, 122]

In some studies, the intervention and comparator were too similar to detect significant effect of palliative care. This may have been due to over-attentive comparator with regular access to well-trained providers that may not represent true current practice. [108, 109, 117]

Analysis of variance in Aiken *et al.* [108] between treatment arms, controlling for time and patient diagnosis, suggested that patients with heart failure in the intervention arm suffered a greater increase in symptom distress compared to the control arm. The reasons above could explain this unexpected result as the intervention in

For example, the intervention in Aiken *et al.* [108] was delivered by registered nurse case managers with access to generalist physicians (primary care physicians) and a medical director (unclear whether this is a specialist palliative physician). Part of the intervention included communication of plans and education with the 'multiple care organisation' and attending physician involved in usual care. The comparator was quite similar with high intensity of frequent care and increased access to additional services such as psychological counselling with providers having knowledge and involvement of the intervention. This may increase the risk of contamination of controls as outlined above.

4.2.3.4 Underlying level of heart failure therapy

The underlying level of heart failure therapy of patients in each study is unclear. This factor is unlikely to influence the results of the outcomes in RCTs as the patients are randomly allocated to each arm. However, this may be a limitation, especially in observational studies, as patients on optimal heart failure treatment are perhaps more likely to exhibit positive outcomes.

4.2.3.5 Co-ordination of care

It could be argued that the benefits experienced by patients are a result of better co-ordinated care, which is indeed a key component of palliative care, but may also be provided by non-palliative services. Several issues would indicate that this is not the whole story. Firstly, patients can have a better outcome by simply participating in trials because of the additional co-ordination of care and meticulous follow up that is inherent in trial process. Thus, all patients are likely to have received better co-ordination of care even in the control arm. Secondly, in Sidebottom *et al.* [113], all HF patients were referred to an ACP facilitator, making it less likely that improved coordination is the sole reason for the benefit seen. In the Wong *et al.* [114] trial, the participants allocated to usual care had access to palliative care clinic consults if needed, and thus, good co-ordination of care, and the participants in the intervention arm received home-based and more frequent palliative care i.e. could be argued that they had a higher "dose" of palliative care. The usual care arm also received phone calls, which were in addition to usual care, and could have triggered better co-ordinated care. Finally, palliative care is care which aims to improve quality of life by meticulous holistic assessment and management of symptoms. [4] Quality of life improved in all three adequately powered studies in favour of the intervention group that included explicit management of symptoms. [110, 112-114] Studies where the intervention did not include these aspects [108, 109, 116] did not result in a greater benefit for quality of life or symptoms, despite the additional co-ordination of care. Therefore, it seems reasonable to infer then that better co-ordination of care *along with* measures to address symptoms and quality of life is the key to the benefit seen.

4.2.4 Outcomes

Hopp *et al.* [111] assessed the impact of a palliative care consultation on 'comfort-orientated care' measured by election of outpatient or inpatient hospice care and presence of a do not attempt cardiopulmonary resuscitation (DNACPR) order. Although DNACPR status is often increased in successful studies of advance care planning, [144, 145] that is not necessarily the quality marker of care any more than death at home is a quality marker of good care. For that reason, even though DNACPR may be measured, and may increase in palliative care studies, the aim of palliative care is not to convince patients to place DNACPR orders *per se*. Instead, it is to inform patients of the choices available and communicate the benefits and drawbacks. Indeed, an appropriate and successful outcome of palliative care may be excellent symptom control, improved functional status and a decision to retain DNACPR status with ongoing review. Therefore, although the study by Hopp *et al.* [111] was negative, the outcome is not clinically meaningful in the setting of a palliative care intervention.

4.3 Limitations of the review

Following the initial search, the strategy for identifying studies for potential inclusion had to be modified to exclude results from the database Embase. This was a pragmatic decision due to time constraints, and some studies may have been missed. Additionally, the second researcher, due to their time-constraints, reviewed only a proportion (approximately 40%) of the titles and abstracts; therefore, there is still some risk of selection bias.

Despite the heterogeneity of the treatment and comparator groups and the population, a meta-analysis may still provide a deeper understanding of the effect of palliative care on outcomes. This is because the heterogeneity more truly reflects the variability of palliative care implementation around the world. Although outcomes were measured with a variety of tools, there are a number of studies that use the ESAS score and PHQ-9 questionnaire. Unfortunately, few of these studies reported the raw data and despite attempts to contact authors, insufficient information to conduct the meta-analysis as part of this thesis could be gathered within the time available. Therefore, this is planned as a post-thesis exercise.

4.4 Implications for clinical practice

Current national [31] and international [22, 86-88] guidelines recommend that palliative care play a role in heart failure management. The evidence collated in this review supports this recommendation. Palliative care is beneficial to patients, but it is most likely to be effective only when used as a comprehensive intervention with regular assessment of patients' needs and a tailored management. However, it is unlikely that all patients with heart failure require specialist palliative care even if this was a sustainable option (as specialist palliative care is a scarce resource). [146] There is no consensus as to which patients suffering from heart failure will benefit most from specialist palliative care. Therefore, good interconnection between the cardiology teams, their local palliative care and primary care teams with information and knowledge sharing would be best practice.

Despite limited resources, there is a case to be made here for upstream prevention through an early integration of palliative care into the management of heart failure. Early training in self-management and communication about the condition, goals of care and role of palliative care in patients' management with the support of a multi-disciplinary team can in turn reduce the burden on the healthcare system. Patients receiving palliative care are more

aware of available resources [108], feel better prepared for life events [108], have a greater chance of undergoing advance care planning [108, 113] and so can be care for and die in their preferred place of care. [99, 117] Additionally, patients feel more satisfied with the care they receive. [114, 115]

Although the WHO definition states that palliative care 'intends neither to hasten or postpone death' [4], a concern remains about palliative care involvement – that it is seen as "giving up" on the patient, and even hastening death. Most of the included studies [108, 110, 111, 113] do not show significant differences in mortality rates between intervention groups and control groups which should be reassuring. Indeed, the mortality rate in one study [109] favoured the intervention significantly indicating that whilst improved survival may not be a primary goal of palliative care, it may result from good symptom control and improvement in functional status. Increased survival has also been shown in some other palliative care trials. [6, 7]

In addition to the improvement of patients' wellbeing, palliative care was found to reduce costs. [117, 118] However, this was variable depending on record keeping and which aspects of the care were calculated for costs (reported in Chapter 3). These results, may be credited to the comprehensive care provided which in turn reduced hospitalisations [110, 118, 121], readmissions [114], and length of stay. [110]

Referring back to purpose of the thesis (in Chapter 1), the perception that there is little or no evidence in support of palliative care for patients with heart failure was thought be a barrier to implementation. However, as seen in this review, there is such evidence, yet, there is still no change in practice. It has been estimated that translation of research in to practice takes an average of 17 years. [147, 148] Little is known about the reason for this delay [149], however clinicians' preconceptions may be a source of delay. [150] Clinicians' lack of knowledge, firmly held attitudes and behaviour may act as barriers to uptake of evidence. [151, 152] Therefore it may be that the concern put forward about "lack of evidence" are much more complex than at first sight, and is, in reality, masking a fear, in clinicians, of having difficult conversations, of managing patients in distress, and feeling under-skilled and prepared to deal with complex situations, particularly within the constraints of current service models. Therefore, better education, [153] review of service configurations and

delivery and dissemination of this research in cardiology may be needed in order to alter clinical practice.

4.5 Future research

This review is the first to bring together quantitative studies conducted to investigate palliative care for people with heart failure. This review is vital in showing the evidence in support of palliative care in heart failure despite the methodological concerns in some studies. It also highlights the areas in which future research should focus. Box 5 summaries these areas.

1. Which patients require involvement of specialist palliative care services and who can be managed under the usual care team?
2. What are the key transferable components of general palliative care and specialist palliative care? How does each one impact or influence outcomes?
3. Who should be involved in the delivery of care? What skills or training do they need?
4. What service configuration changes need to be implemented to ensure that there are no gaps in the service?

Box 5: Gaps in evidence for use of palliative care in heart failure

Although it is useful to identify the general areas in which future research should focus, it is perhaps more useful to identify specific methodologies that may be used to answer the questions in Box 5. Table 8 shows a few of the methodologies that may be most appropriate to improve our knowledge of the effectiveness of palliative care.

Table 8: Suggested methodology for future research

Study design	Randomised controlled study to have a true comparison of effects and reduce concerns of bias.
	Adequate sample size powered to detect an effect size, which represents a clinically important difference, and allowing for subset analyses if needed despite high attrition rates.
	Community and hospital based setting to encompass all aspects of care
	Blinding is not possible given the nature of the intervention. Use of cluster designs to prevent contamination of control group.
Population	Representative sample of heart failure patients with advanced disease with detailed demographic data and planned analyses to identify patient characteristics that predict a beneficial response to palliative care.
Intervention	Clarification of key components of palliative care. Sufficiently detailed description of intervention delivery to allow an assessment of the feasibility of administration of care and to identify infidelity to treatment arm if unjustified gaps are present.
Comparator	Well described comparator of usual care distinct from intervention.
Outcomes	Primary outcome should be quality of life. Other outcomes to investigate include symptom burden; change in functional status, disease severity or survival; satisfaction with care; health care providers attitudes and experiences of delivering care (to modify future delivery if need); resource use; and costs of care for policy makers.
Follow-up	Short and long-term follow-up appointments to see the immediate effects and the long-term consequences of the intervention.

Chapter 5 – Conclusions

In conclusion, palliative care is beneficial to patients with heart failure in addressing various part of a patient's life. However, there are several methodological issues, which increase the risk of bias and therefore, reduce the strength of evidence presented in some studies. Studies that showed most benefit to patients from palliative care were adequately powered, with the inclusion of appropriate patients, comparing the effect of a comprehensive and appropriate palliative care intervention to a true comparator on outcomes relevant to patient care. While there are gaps in evidence, there are clear pointers for implementation in current practice such as early integration of palliative care with an approach that focuses on problems rather than prognosis.

References

1. Clark D. From margins to centre: a review of the history of palliative care in cancer. The Lancet Oncology. 2007;8(5):430-8.

2. Saunders C. Care of the dying 3. Control of pain in terminal cancer. Nursing Times. 1959:1031-2.

3. Dictionary.com2015. Collins English Dictionary - Complete & Unabridged 10th Edition 2015 [cited 2015 14 September]. Available from: http://dictionary.reference.com/browse/palliate.

4. World Health Organization. WHO definition of palliative care. 2002. World Health Organization: Geneva. 2011.

5. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA. 2009;302(7):741-9.

6. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. The Lancet Respiratory Medicine. 2014;2(12):979-87.

7. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non–small-cell lung cancer. New England Journal of Medicine. 2010;363(8):733-42.

8. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. The Lancet. 2014;383(9930):1721-30.

9. NICE. Improving supportive and palliative care for adults with cancer: the manual: National Institute for Clinical Excellence; 2004 [cited 2016 April]. Available from: https://www.nice.org.uk/guidance/csg4/resources/improving-supportive-and-palliative-care-for-adults-with-cancer-773375005.

10. Hui D, Nooruddin Z, Didwaniya N, Dev R, De La Cruz M, Kim SH, et al. Concepts and definitions for “actively dying,”“end of life,”“terminally ill,”“terminal care,” and “transition of care”: a systematic review. Journal of Pain and Symptom Management. 2014;47(1):77-89.

11. National Institute of Clinical Excellence. End of life care for adults. NICE Quality Standard [QS13]. 2011.

12. Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative care: the World Health Organization's global perspective. Journal of Pain and Symptom Management. 2002;24(2):91-6.

13. National Quality Forum. A National Framework and Preferred Practices for Palliative and Hospice Care: A Consensus Report: National Quality Forum; 2006 [cited 2016 12 March]. Available from: http://www.qualityforum.org/Publications/2006/12/A_National_Framework_and_Preferred_Practices_for_Palliative_and_Hospice_Care_Quality.aspx.

14. Higginson IJ, Finlay IG, Goodwin DM, Hood K, Edwards AG, Cook A, et al. Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers? Journal of Pain and Symptom Management. 2003;25(2):150-68.

15. Gade G, Venohr I, Conner D, McGrady K, Beane J, Richardson RH, et al. Impact of an inpatient palliative care team: a randomized controlled trial. Journal of Palliative Medicine. 2008;11(2):180-90.

16. Morrison RS, Penrod JD, Cassel JB, Caust-Ellenbogen M, Litke A, Spragens L, et al. Cost savings associated with US hospital palliative care consultation programs. Archives of Internal Medicine. 2008;168(16):1783-90.

17. Smith S, Brick A, O’Hara S, Normand C. Evidence on the cost and cost-effectiveness of palliative care: A literature review. Palliative Medicine. 2014;28(2):130-50.

18. Center to Advance Palliative Care. Palliative Care Definitions and Delivery Models Center to Advance Palliative Care [cited 2016 March]. Available from: https://www.capc.org/payers/palliative-care-definitions/.

19. Salisbury C, Bosanquet N, Wilkinson E, Franks P, Kite S, Lorentzon M, et al. The impact of different models of specialist palliative care on patients' quality of life: a systematic literature review. Palliative Medicine. 1999;13(1):3-17.

20. Gardiner C, Ingleton C, Gott M, Ryan T. Exploring the transition from curative care to palliative care: a systematic review of the literature. BMJ Supportive & Palliative Care. 2011;1(1):56-63.

21. Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. BMJ. 2005 2005-04-28 21:57:37;330(7498):1007-11.

22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2016 2015-05-20 00:00:00;37(27):2129-200.

23. Bekelman DB, Hutt E, Masoudi FA, Kutner JS, Rumsfeld JS. Defining the role of palliative care in older adults with heart failure. International Journal of Cardiology. 2008;125(2):183-90.

24. McMurray J, Petrie M, Murdoch D, Davie A. Clinical epidemiology of heart failure: public and private health burden. European Heart Journal. 1998;19:P9-16.

25. Cowie M, Wood D, Coats A, Thompson S, Poole-Wilson P, Suresh V, et al. Incidence and aetiology of heart failure. European Heart Journal. 1999;20(6):421-8.

26. Mosterd A, Hoes A, De Bruyne M, Deckers J, Linker D, Hofman A, et al. Prevalence of heart failure and left ventricular dysfunction in the general population. European Heart Journal. 1999;20(6):447-55.

27. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA. 2013;309(4):355-63.

28. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). European Journal of Heart Failure. 2010;12(10):1076-84.

29. Mitchell P, Marle D, Donkor A, Shote A, McDonagh T, Hardman S, et al. National Heart Failure Audit, April 2013-March 2014. NICOR (National Institute for Cardiovascular Outcomes Research) and The British Society for Heart Failure (BSH). 2015.

30. McDonagh TA, Gardner RS, Clark AL, Dargie H. Oxford textbook of heart failure: Oxford University Press; 2011.

31. National Institute of Clinical Excellence. Chronic Heart Failure in Adults. NICE Quality Standard [QS9]. 2011.

32. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. European Journal of Heart Failure. 2005;7(4):537-41.

33. Goode KM, Nabb S, Cleland JG, Clark AL. A comparison of patient and physician-rated New York Heart Association class in a community-based heart failure clinic. Journal of Cardiac Failure. 2008;14(5):379-87.

34. Johnson MJ, Bland JM, Davidson PM, Newton PJ, Oxberry SG, Abernethy AP, et al. The relationship between two performance scales: new york heart association classification and karnofsky performance status scale. Journal of Pain and Symptom Management. 2014;47(3):652-8.

35. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 6th ed: Little, Brown Medical Division; 1994.

36. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant'than cancer? Five-year survival following a first admission for heart failure. European Journal of Heart Failure. 2001;3(3):315-22.

37. Mosterd A, Cost B, Hoes A, De Bruijne M, Deckers J, Hofman A, et al. The prognosis of heart failure in the general population. European Heart Journal. 2001;22:1318-27.

38. Mehta PA, Dubrey SW, McIntyre HF, Walker DM, Hardman SM, Sutton GC, et al. Improving survival in the 6 months after diagnosis of heart failure in the past decade: population-based data from the UK. Heart. 2009;95(22):1851-6.

39. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the heart failure pilot survey (ESC-HF Pilot). European Journal of Heart Failure. 2013;15(7):808-17.

40. Hobbs FR, Roalfe AK, Davis RC, Davies MK, Hare R. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). European Heart Journal. 2007.

41. Goodlin SJ, Hauptman PJ, Arnold R, Grady K, Hershberger RE, Kutner J, et al. Consensus statement: palliative and supportive care in advanced heart failure. Journal of Cardiac Failure. 2004;10(3):200-9.

42. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? Journal of Cardiac Failure. 2003;9(1):13-25.

43. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290(19):2581-7.

44. Aaronson KD, Schwartz JS, Chen T-M, Wong K-L, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997;95(12):2660-7.

45. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The seattle heart failure model prediction of survival in heart failure. Circulation. 2006;113(11):1424-33.

46. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ. 2005;330(7492):625.

47. Haga K, Murray S, Reid J, Ness A, O'Donnell M, Yellowlees D, et al. Identifying community based chronic heart failure patients in the last year of life: a comparison of the Gold Standards Framework Prognostic Indicator Guide and the Seattle Heart Failure Model. Heart. 2012;98(7):579-83.

48. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ. 2004;328(7433):189.

49. Golwala H, Pandey A, Ju C, Butler J, Yancy C, Bhatt DL, et al. Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: findings from Get With the Guidelines–Heart Failure Registry. Journal of the American College of Cardiology. 2015;66(8):917-26.

50. Piepoli MF, Binno S, Corrà U, Seferovic P, Conraads V, Jaarsma T, et al. ExtraHF survey: the first European survey on implementation of exercise training in heart failure patients. European Journal of Heart Failure. 2015;17(6):631-8.

51. Buttery AK, Carr-White G, Martin FC, Glaser K, Lowton K. Limited availability of cardiac rehabilitation for heart failure patients in the United Kingdom: findings from a national survey. European Journal of Preventive Cardiology. 2013:2047487313482286.

52. Doughty Rea, Rodgers A, Sharpe N, MacMahon S. Effects of beta-blocker therapy on mortality in patients with heart failure. European Heart Journal. 1997;18(4):560-5.

53. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart

failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. The Lancet. 2003;362(9377):7-13.

54. Merit-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in-congestive heart failure (MERIT-HF). The Lancet. 1999;353(9169):2001-7.

55. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). New England Journal of Medicine. 1987;316:1429-35.

56. Solvd Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. New England Journal of Medicine. 1991;1991(325):293-302.

57. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation. 1996;94(11):2800-6.

58. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. The Lancet. 2000;355(9215):1582-7.

59. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. European Heart Journal. 2015:ehv186.

60. National Institute of Clinical Excellence. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. NICE Technology Appraisal Guidance [TA388]. 2016.

61. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. The Lancet. 2010;376(9744):875-85.

62. Štulc T, Češka R. Ivabradine, coronary heart disease, and heart failure: time for reappraisal. Current Atherosclerosis Reports. 2014;16(12):1-4.

63. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. New England Journal of Medicine. 2011;364(1):11-21.

64. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New England Journal of Medicine. 1999;341(10):709-17.

65. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New England Journal of Medicine. 2003;348(14):1309-21.

66. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. New England Journal of Medicine. 1991;325(5):303-10.

67. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino Jr R, Ferdinand K, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. New England Journal of Medicine. 2004;351(20):2049-57.

68. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. New England Journal of Medicine. 1997;1997(336):525-33.

69. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. The Cochrane Library. 2012.

70. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. New England Journal of Medicine. 2012;366(20):1859-69.

71. National Institute of Clinical Excellence. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrythmias and heart failure. NICE Technology Appraisal Guidance [TA314]. 2014.

72. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. New England Journal of Medicine. 2016;374(16):1511-20.

73. Iqbal J, Francis L, Reid J, Murray S, Denvir M. Quality of life in patients with chronic heart failure and their carers: a 3-year follow-up study assessing hospitalization and mortality. European Journal of Heart Failure. 2010;12(9):1002-8.

74. Levenson JW, McCarthy EP, Lynn J, Davis RB, Phillips RS. The last six months of life for patients with congestive heart failure. Journal of the American Geriatrics Society. 2000;48(S1):S101-S9.

75. Nordgren L, Sörensen S. Symptoms experienced in the last six months of life in patients with end-stage heart failure. European Journal of Cardiovascular Nursing. 2003;2(3):213-7.

76. Bekelman DB, Rumsfeld JS, Havranek EP, Yamashita TE, Hutt E, Gottlieb SH, et al. Symptom burden, depression, and spiritual well-being: a comparison of heart failure and advanced cancer patients. Journal of General Internal Medicine. 2009;24(5):592-8.

77. Murray SA, Boyd K, Kendall M, Worth A, Benton TF, Clausen H. Dying of lung cancer or cardiac failure: prospective qualitative interview study of patients and their carers in the community. BMJ. 2002;325(7370):929.

78. Murray SA, Kendall M, Grant E, Boyd K, Barclay S, Sheikh A. Patterns of social, psychological, and spiritual decline toward the end of life in lung cancer and heart failure. Journal of Pain and Symptom Management. 2007;34(4):393-402.

79. Johnson M, Hogg K, Beattie J, Watson M. Heart Failure: From Advanced Disease to Bereavement: OUP Oxford; 2012.

80. Johnson M, Lehman R, Hogg K. Heart failure and palliative care: a team approach. 2nd ed: Taylor & Francis Group LLC; 2015.

81. Barclay S, Momen N, Case-Upton S, Kuhn I, Smith E. End-of-life care conversations with heart failure patients: a systematic literature review and narrative synthesis. British Journal of General Practice. 2011;61(582):e49-e62.

82. Gold Standards Framework. Prognostic Indicator Guidance The Gold Standards Framework Centre In End of Life Care; 2011 [cited 2015 13th Oct 2015]. 4:[Available from: http://www.goldstandardsframework.org.uk/cd-content/uploads/files/General%20Files/Prognostic%20Indicator%20Guidance%20October%202011.pdf.

83. Gadoud A, Kane E, Macleod U, Ansell P, Oliver S, Johnson M. Palliative Care among Heart Failure Patients in Primary Care: A Comparison to Cancer Patients Using English Family Practice Data. PLoS One. 2014;9(11):e113188.

84. Hogg KJ, Jenkins SM. Prognostication or identification of palliative needs in advanced heart failure: where should the focus lie? Heart. 2012;98(7):523-4.

85. Darzi A. High quality care for all: NHS next stage review final report. London: Department of Health. 2008;2009.

86. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;62(16):e147-e239.

87. McKelvie RS, Moe GW, Cheung A, Costigan J, Ducharme A, Estrella-Holder E, et al. The 2011 Canadian Cardiovascular Society heart failure management guidelines update: focus on sleep apnea, renal dysfunction, mechanical circulatory support, and palliative care. Canadian Journal of Cardiology. 2011;27(3):319-38.

88. National Heart Foundation of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011.

89. Nicol ED, Fittall B, Roughton M, Cleland JG, Dargie H, Cowie MR. NHS heart failure survey: a survey of acute heart failure admissions in England, Wales and Northern Ireland. Heart. 2008;94(2):172-7.

90. Greener DT, Quill T, Amir O, Szydlowski J, Gramling RE. Palliative care referral among patients hospitalized with advanced heart failure. Journal of Palliative Medicine. 2014;17(10):1115-20.

91. Allen LA, Yager JE, Funk MJ, Levy WC, Tulsky JA, Bowers MT, et al. Discordance between patient-predicted and model-predicted life expectancy among ambulatory patients with heart failure. JAMA. 2008;299(21):2533-42.

92. Rogers AE, Addington-Hall J, Abery A, McCoy A, Bulpitt C, Coats A, et al. Knowledge and communication difficulties for patients with chronic heart failure: qualitative study. BMJ. 2000;321(7261):605-7.

93. Barnes S, Gott M, Payne S, Seamark D, Parker C, Gariballa S, et al. Communication in heart failure: perspectives from older people and primary care professionals. Health & Social Care in the Community. 2006;14(6):482-90.

94. Formiga F, Chivite D, Ortega C, Casas S, Ramon J, Pujol R. End-of-life preferences in elderly patients admitted for heart failure. QJM. 2004;97(12):803-8.

95. Kavalieratos D, Mitchell EM, Carey TS, Dev S, Biddle AK, Reeve BB, et al. “Not the ‘grim reaper service’”: an assessment of provider knowledge, attitudes, and perceptions regarding palliative care referral barriers in heart failure. Journal of the American Heart Association. 2014;3(1):e000544.

96. Farquhar MC, Prevost AT, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, et al. Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. BMC Medicine. 2014;12(1):1.

97. Johnson MJ, Gadoud A. Palliative care for people with chronic heart failure: when is it time? Journal of Palliative Care. 2011;27(1):37.

98. Johnson MJ, MacCallum A, Butler J, Rogers A, Sam E, Fuller A, et al. Heart failure specialist nurses' use of palliative care services: a comparison of surveys across England in 2005 and 2010. European Journal of Cardiovascular Nursing. 2012;11(2):190-6.

99. Johnson M, Nunn A, Hawkes T, Stockdale S, Daley A. Planning for end-of-life care in heart failure: experience of two integrated cardiology-palliative care teams. British Journal of Cardiology. 2012;19(2):71.

100. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care: Centre for Reviews and Dissemination; 2009.

101. Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions 5.1.0: Cochrane Collaboration; 2011.

102. Damarell RA, Tieman J, Sladek RM, Davidson PM. Development of a heart failure filter for Medline: an objective approach using evidence-based clinical practice guidelines as an alternative to hand searching. BMC Medical Research Methodology. 2011;11(1):1.

103. Cochrane. Palliative Care Search Strategy Cochrane; Pain, Palliative and Supportive Care [cited 2015 06 September]. Available from: http://papas.cochrane.org/searching-studies.

104. CareSeach. Palliative Care Filter [cited 2015 06 September]. Available from: http://www.caresearch.com.au/caresearch/tabid/322/Default.aspx.

105. Sladek R, Tieman J, Fazekas BS, Abernethy AP, Currow DC. Development of a subject search filter to find information relevant to palliative care in the general medical literature*. Journal of the Medical Library Association. 2006;94(4):394.

106. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

107. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 2009-07-21 10:46:49;339.

108. Aiken LS, Butner J, Lockhart CA, Volk-Craft BE, Hamilton G, Williams FG. Outcome evaluation of a randomized trial of the PhoenixCare intervention: program of case management and coordinated care for the seriously chronically ill. Journal of Palliative Medicine. 2006;9(1):111-26.

109. Bekelman DB, Plomondon ME, Carey EP, Sullivan MD, Nelson KM, Hattler B, et al. Primary results of the Patient-Centered Disease Management (PCDM) for heart failure study: a randomized clinical trial. JAMA Internal Medicine. 2015;175(5):725-32.

110. Brännström M, Boman K. Effects of person-centred and integrated chronic heart failure and palliative home care. PREFER: a randomized controlled study. European Journal of Heart Failure. 2014;16(10):1142-51.

111. Hopp FP, Zalenski RJ, Waselewsky D, Burn J, Camp J, Welch RD, et al. Results of a Hospital-Based Palliative Care Intervention for Patients With an Acute Exacerbation of Chronic Heart Failure. Journal of Cardiac Failure. 2016.

112. Sahlen K-G, Boman K, Brännström M. A cost-effectiveness study of person-centered integrated heart failure and palliative home care: Based on a randomized controlled trial. Palliative Medicine. 2015:0269216315618544.

113. Sidebottom AC, Jorgenson A, Richards H, Kirven J, Sillah A. Inpatient palliative care for patients with acute heart failure: outcomes from a randomized trial. Journal of Palliative Medicine. 2015;18(2):134-42.

114. Wong FKY, Ng AYM, Lee PH, Lam P-t, Ng JSC, Ng NHY, et al. Effects of a transitional palliative care model on patients with end-stage heart failure: a randomised controlled trial. Heart. 2016:heartjnl-2015-308638.

115. Paes P. A pilot study to assess the effectiveness of a palliative care clinic in improving the quality of life for patients with severe heart failure. Palliative Medicine. 2005;19(6):505-6.

116. Tadwalkar R, Udeoji DU, Weiner RJ, Avestruz FL, LaChance D, Phan A, et al. The beneficial role of spiritual counseling in heart failure patients. Journal of Religion and Health. 2014;53(5):1575-85.

117. Enguidanos SM, Cherin D, Brumley R. Home-based palliative care study: site of death, and costs of medical care for patients with congestive heart failure, chronic obstructive pulmonary disease, and cancer. Journal of Social Work in End-Of-Life & Palliative Care. 2005;1(3):37-56.

118. Pattenden JF, Mason AR, Lewin R. Collaborative palliative care for advanced heart failure: outcomes and costs from the 'Better Together'pilot study. BMJ Supportive & Palliative Care. 2013;3(1):69-76.

119. Evangelista LS, Liao S, Motie M, De Michelis N, Lombardo D. On-going palliative care enhances perceived control and patient activation and reduces symptom distress in patients with symptomatic heart failure: a pilot study. European Journal of Cardiovascular Nursing. 2014;13(2):116-23.

120. Evangelista LS, Liao S, Motie M, De Michelis N, Ballard-Hernandez J, Lombardo D. Does the type and frequency of palliative care services received by patients with advanced heart failure impact symptom burden? Journal of Palliative Medicine. 2014;17(1):75-9.

121. Wong R, Tan PT, Seow YH, Aziz S, Oo N, Seow SC, et al. Home-based advance care programme is effective in reducing hospitalisations of advanced heart failure patients: a clinical and healthcare cost study. Annals of Academic Medicine Singapore. 2013;42(9):466-71.

122. Evangelista LS, Lombardo D, Malik S, Ballard-Hernandez J, Motie M, Liao S. Examining the effects of an outpatient palliative care consultation on symptom burden, depression, and quality of life in patients with symptomatic heart failure. Journal of Cardiac Failure. 2012;18(12):894-9.

123. Farquhar MC, Prevost AT, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, et al. The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with

advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial. Trials. 2016;17(1):1.

124. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton symptom assessment scale. Cancer. 2000;88(9):2164-71.

125. Chang VT, Hwang SS, Feuerman M, Kasimis BS, Thaler HT. The Memorial Symptom Assessment Scale Short Form (MSAS-SF). Cancer. 2000;89(5):1162-71.

126. Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Kiyasu E, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. European Journal of Cancer. 1994;30(9):1326-36.

127. Kroenke K, Spitzer RL, Williams JB. The PHQ-9. Journal of General Internal Medicine. 2001;16(9):606-13.

128. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. Journal of Psychosomatic Research. 2002;52(2):69-77.

129. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. Journal of the American College of Cardiology. 2000;35(5):1245-55.

130. Ravens-Sieberer U, Wille N, Badia X, Bonsel G, Burström K, Cavrini G, et al. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. Quality of Life Research. 2010;19(6):887-97.

131. Lee DT, Doris S, Woo J. Validation of the chronic heart failure questionnaire (Chinese version). Quality of Life Research. 2005;14(5):1421-6.

132. Cohen SR, Mount BM, Bruera E, Provost M, Rowe J, Tong K. Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. Palliative Medicine. 1997;11(1):3-20.

133. Kaasa S, Bjordal K, Aaronson N, Moum T, Wist E, Hagen S, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. European Journal of Cancer. 1995;31(13):2260-3.

134. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ. 1998;317(7167):1185-90.

135. Odgaard-Jensen J, Vist GE, Timmer A, Kunz R, Akl EA, Schünemann H, et al. Randomisation to protect against selection bias in healthcare trials. The Cochrane Library. 2011.

136. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. The Cochrane Library. 2014.

137. Furberg BD, Furberg CD. Why is blinding/masking so important? Evaluating Clinical Research: Springer; 2007. p. 49-52.

138. Harrop E, Noble S, Edwards M, Sivell S, Moore B, Nelson A. "I didn't really understand it, I just thought it'd help": exploring the motivations, understandings and experiences of patients with advanced lung cancer participating in a non-placebo clinical IMP trial. Trials. 2016;17(1):1-12.

139. Scambler G. Sociology as applied to medicine: Elsevier Health Sciences; 2008.

140. Black D, Morris J, Smith C, Townsend P. Inequalities in health: report of a Research Working Group. London: Department of Health and Social Security. 1980;19.

141. Bartley M, Blane D. Inequality and social class. Sociology as applied to medicine Elsevier Limited. 2008.

142. Chin MH, Humikowski CA. When is risk stratification by race or ethnicity justified in medical care? Academic Medicine. 2002;77(3):202-8.

143. Ridd M, Shaw A, Lewis G, Salisbury C. The patient–doctor relationship: a synthesis of the qualitative literature on patients' perspectives. British Journal of General Practice. 2009;59(561):e116-e33.

144. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. BMJ. 2010;340:c1345.

145. Brinkman-Stoppelenburg A, Rietjens JA, van der Heide A. The effects of advance care planning on end-of-life care: a systematic review. Palliative Medicine. 2014:0269216314526272.

146. Quill TE, Abernethy AP. Generalist plus specialist palliative care—creating a more sustainable model. New England Journal of Medicine. 2013;368(13):1173-5.

147. Balas EA, Boren SA. Managing clinical knowledge for health care improvement. Yearbook of Medical Informatics2000. 65-70 p.

148. Trochim W, editor Translation won't happen without dissemination and implementation: Some measurement and evaluation issues. 3rd Annual Conference on the Science of Dissemination and Implementation Bethesda, MD: NIH Office of Behavioral and Social Sciences Research; 2010.

149. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. Journal of the Royal Society of Medicine. 2011;104(12):510-20.

150. Johnson MJ, Noble SI. Challenging Previously Held Beliefs About Clinical Practice: Evidence or Experience? Journal of Pain and Symptom Management. 2015;50(1):e1-e2.

151. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-AC, et al. Why don't physicians follow clinical practice guidelines?: A framework for improvement. JAMA. 1999;282(15):1458-65.

152. Lang ES, Wyer PC, Haynes RB. Knowledge translation: closing the evidence-to-practice gap. Annals of Emergency Medicine. 2007;49(3):355-63.

153. Davis D, Davis ME, Jadad A, Perrier L, Rath D, Ryan D, et al. The case for knowledge translation: shortening the journey from evidence to effect. BMJ. 2003;327(7405):33-5.

Appendices

Appendix 1

Search string for Ovid Medline

Search string	Search term	Number of search results	Subject headings
Free text search			
1	Heart failure.mp.	141613	
2	Cardiac failure.mp.	10003	
3	Congestive heart failure.mp.	32950	
4	Ventric* dysfunction.mp.	34653	
5	Cardiac dysfunction.mp.	6488	
6	Systolic dysfunction.mp.	5381	
7	Cardiac insufficiency.mp.	3758	
8	Myocardi* insufficiency.mp.	266	
9	Ventric* insufficiency.mp.	264	
10	Myocardi* dysfunction.mp.	3560	
11	Myocardi* failure.mp.	711	
12	Ventric* failure.mp.	3924	
13	HF.mp.	22094	
14	CHF.mp.	10529	
15	CCF.mp.	999	
16	LVSD.mp.	334	
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or	194756	

Search string for Ovid Medline

Search string	Search term	Number of search results	Subject headings
	13 or 14 or 15 or 16		
Medical Subject Heading search			
18	exp Heart failure/	94085	Heart failure
19	exp Ventricular dysfunction/ or exp Stroke Volume/ or exp Heart diseases	955905	Ventricular Dysfunction Coronary Disease Heart Heart Ventricles Myocardial Infarction Middle Aged Adult Stroke Volume Exercise Test Heart Diseases Mitral Valve Stenosis
20	18 or 19	955905	
Free text search			
21	Advanced.mp.	264404	
22	Chronic.mp.	980181	
23	Terminal.mp.	356046	
24	End stage.mp.	45354	
25	Moderate.mp.	288616	
26	Severe.mp.	652156	
27	Progressive.mp.	206313	
28	Persisitent.mp.	158718	

Search string for Ovid Medline

Search string	Search term	Number of search results	Subject headings
29	Fatal.mp.	133029	
30	Limiting.mp.	109378	
31	Incurable.mp.	6613	
32	Unremitting.mp.	943	
33	Decompensated.mp.	6573	
34	NYHA class III.mp.	1388	
35	NYHA class IV.mp.	495	
36	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2771584	
Free text search			
37	Palliat*.mp.	67709	
38	Terminal care.mp.	23095	
39	Hospice*.mp.	11867	
40	End of life care.mp.	5188	
41	Holistic.mp.	18366	
42	Respite.mp.	1643	
43	Supportive care.mp.	9097	
44	Care of the dying.mp.	1581	
45	Patient centred care.mp.	641	
46	Advance* care	2185	
47	Advance* directive	1284	

Search string for Ovid Medline

Search string	Search term	Number of search results	Subject headings
48	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	119531	
Medical Subject Heading search			
49	exp Palliative care	43258	Palliative care
50	exp "Quality of Life"/ or exp Palliative Medicine/ or exp Terminal Care	172355	Palliative medicine Palliative care Neoplasms Terminal care Adult Pain Education, Medical Aged "Quality of Life" Analgesics Depression
51	exp Hospices/ or exp Hospice Care/	9228	Hospice Care Hospices Terminal care Hospitals, Special Insurance, Health, Reimbursement United States Attitude to death Insurance, Health Hospital Planning

Search string for Ovid Medline

Search string	Search term	Number of search results	Subject headings
			Neoplasms Palliative Care
52	exp Holistic Health	7226	Neoplasms Holistic health Family practice Adult Vomiting "Delivery of Health Care" Nurse- Patient Relations Social Work Endometriosis Drug therapy
53	exp Home Nursing/ or exp Respite Care/ or Home Care Services/	41546	Respite Care Parents Child Care Disabled persons Adolescent Home Care Services Home Nursing Intellectual Disability Forensic Psychiatry Parental Consent Pilot Projects
54	exp Patient-Centred Care/	12693	Patient-centred care Physician patient relations Aged

Search string for Ovid Medline

Search string	Search term	Number of search results	Subject headings
			Patient participation "Attitude of Health personnel" Nursing care Chronic disease Family practise HIV infections Middle aged
55	exp Advance Care planning/	7349	Advance care planning United states Family planning services Emergency service, hospital "Delivery of Health Care" Developing Countries Contraception Evaluation Studies as Topic Hospital Administration Resuscitation Community Health Services
56	exp Advance directives/	6263	Advance directives
57	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56	264044	
Drawing search terms together			
58	17 or 20	996475	
59	36 and 58	199876	
60	48 or 57	305382	

Search string for Ovid Medline

Search string	Search term	Number of search results	Subject headings
61	59 and 60	5172	

Note:

In Ovid Medline

- mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
- exp means explode

Drawing search terms together:

- Search string 58 represents free text and medical subject heading searches of 'heart failure'.
- Search string 36 represents free text and medical subject heading searches of 'persistently symptomatic'.
- Search string 59 represents free text and medical subject heading searches of 'persistently symptomatic heart failure'.
- Search string 60 represents free text and medical subject heading searches of 'palliative care'.
- Search string 61 represents free text and medical subject heading searches of 'palliative care in persistently symptomatic heart failure'.

Appendix 2

List of data items collected from studies as part of the data extraction tool:

- Study identifiers
    - First author
    - Title
    - Year Published
    - Type of publication (e.g. journal article/ conference abstract)
    - Country of origin
    - Source of funding
- Study characteristics
    - Aims/ objectives of the study
    - Study design
    - Study inclusion and exclusion criteria
    - Recruitment procedure (details of randomisation, blinding etc)
- Participants
    - Sample size
    - Age
    - Sex
    - Ethnicity
    - Socio-economic status
    - Disease characteristics

    - Co-morbidities

- Intervention
    - Setting
    - Description
    - Number of participants
    - Number included in the analysis
    - Number of withdrawals
    - Number of exclusions
    - Number lost to follow up
- Comparator
    - Setting
    - Description
    - Number of participants
    - Number included in the analysis
    - Number of withdrawals
    - Number of exclusions
    - Number lost to follow up
- Outcomes and results (for each outcome)
    - Outcome
    - Definition in the study
    - Measurement tool
    - Unit of measurement

    - Result
    - Length of follow-up
- Additional information

Glossary

Abbreviations	Terms in full
ACE inhibitor	Angiotensin-Converting-Enzyme Inhibitor
ACP	Advance Care Planning
AHA	American Heart Association
ARB	Angiotensin II Receptor Blockers
ARNI	Angiotensin-Receptor-Neprilysin Inhibitor
CABG	Coronary Artery Bypass Graft
CCS	Canadian Cardiovascular Society
CENTRAL	Cochrane Central Register of Controlled Trials
CHF	Congestive Heart Failure
CHQ	Chronic Heart Failure Questionnaire
CRT	Cardiac Resynchronisation Therapy
echo	Echocardiography
ED	Emergency Department
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EQ-5D	EuroQol 5 Dimensions questionnaire
ESAS	Edmonton Symptom Assessment Score
ESC	European Society of Cardiology
ESC-HF Pilot	Heart Failure Pilot survey
GP	General Practitioner

Abbreviations	Terms in full
GSF	Gold Standards Framework
HADS	Hospital Anxiety and Depression Scale
HF	Heart Failure
HF-PEF	Heart Failure with Preserved Ejection Fraction
HMIC	Health Management Information Consortium
HRQL	Health-Related Quality of Life
ICD	Implantable Cardioverter-Defibrillator
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOS	Length of Stay
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MQOL	McGill Quality of Life Questionnaire
MSAS	Memorial Symptom Assessment Scale
NOS	Newcastle-Ottawa quality assessment Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
NP	Natriuretic Peptide
NT-proBNP	N-Terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association

Abbreviations	Terms in full
PHQ-9	Patient Health Questionnaire-9
PPS	Palliative Performance Scale
PREFER	Palliative advanced home caRE and heart FailurE caRe
PRISMA	Preferred Reporting Items for Systematic reviews
QALY	Quality Adjusted Life Years
QIDS-SR16	Quick Inventory of Depressive Symptomatology
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction
RCT	Randomised Controlled Trial
SD	Standard Deviation
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
β-blocker	β-Adrenergic Antagonists