Multi-disciplinary palliative care is effective in people with symptomatic heart failure: a systematic review and narrative synthesis

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ABSTRACT

Background: Despite recommendations, people with heart failure have poor access to palliative care.

Aim: To identify the evidence in relation to palliative care for people with symptomatic heart failure.

Design: Systematic review and narrative synthesis. (PROSPERO CRD42016029911)

Data sources: Databases (Medline, Cochrane database, CINAHL, PsycINFO, HMIC, CareSearch Grey Literature), reference lists and citations were searched and experts contacted. Two independent reviewers screened titles, abstracts and retrieved papers against inclusion criteria. Data were extracted from included papers and studies were critically assessed using a risk of bias tool according to design.

Results: Thirteen interventional and ten observational studies were included. Studies were heterogeneous in terms of population, intervention, comparator, outcomes, and design rendering combination inappropriate. The evaluation phase studies, with lower risk of bias, using a multi-disciplinary specialist palliative care intervention showed statistically significant benefit for patient-reported outcomes (symptom burden, depression, functional status, quality of life), resource use and costs of care. Benefit was not seen in studies with a single component/discipline intervention or with higher risk of bias. Possible contamination in some studies may have caused under-estimation of effect and missing data may have introduced bias. There was no apparent effect on survival.

Conclusions: Overall, the results support the use of multi-disciplinary palliative care in people with advanced heart failure but trials do not identify *who* would benefit most from specialist palliative referral. There are no sufficiently robust multi-centre evaluation phase trials to provide generalisable findings. Use of common population, intervention and outcomes in future research would allow meta-analysis.

KEYWORDS: heart failure; palliative care; hospice; systematic review; quality of life

KEY STATEMENTS

What is already known about the topic?

People with advanced heart failure have poorer access to palliative care than people with cancer and the evidence base in support of heart failure palliative care is less developed.

What this paper adds

We have drawn together the current literature, both observational and experimental, investigating the use of palliative care in people with symptomatic heart failure.

Implications for practice, theory or policy

Our findings support the use of multi-disciplinary palliative care in this patient group, as distinct from single components only, but trials do not identify *who* would benefit most from specialist palliative referral. There are no sufficiently robust multi-centre evaluation phase trials to provide generalisable findings.

INTRODUCTION

The great advances in the management of heart failure(1) brings, as a consequence, more people living to experience advanced disease (New York Heart Association class III and IV)(2) where response to medical or device therapy is limited.(3) People with end-stage disease can have severe symptom burden, poor quality of life,(4) and social isolation. As prognostication is difficult,(5, 6) patients may receive invasive yet futile treatment in hospital during the last days of life, adding to stress for patients, families and the limited healthcare resources.(7)

Palliative care is a multi-disciplinary approach to care for people with life-limiting, progressive illness, aiming to maximise quality of life until death, and provide family support through to bereavement.(8) Evidence supports palliative care *integrated* into management of people with cancer,(9) and other chronic conditions.(10) Benefits include improved symptom burden and quality of life, decreased healthcare utilisation and costs,(11) autonomy in care at the end of life, and patient satisfaction.(12) Access to palliative care services *alongside* cardiac care for patients with advanced HF is recommended(13-15) but this is not reflected routinely in practice. Fewer people with HF are placed on the primary care palliative register in the United Kingdom than those with cancer (7% vs 48%),(16) and a similar proportion with advanced heart failure are referred for palliative care during hospital admissions.(17) Barriers to palliative care access include the unpredictable course of heart failure and a conflation of "palliative" and "dying" in the minds of clinicians, patients, and the public.(14, 18) Despite the well-established role of palliative care in other areas, this is not so for people with advanced heart failure, for whom heart failure management has one of the strongest evidence bases for any condition; this is likely to be an additional significant barrier in a specialty used to large trials which underpin practice.

The aim of this systematic review is to identify and analyse current available evidence which addresses the question of whether palliative care in people with advanced heart failure, is effective with regard to, patient-reported outcomes (symptom burden, depression, functional status, quality of life), resource use and costs of cares. The findings are discussed in the context of implications for clinical practice and gaps in knowledge are highlighted to help target future research.

METHODS

We conducted a systematic literature review and narrative synthesis. The protocol was registered on PROSPERO (ID=CRD42016029911) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The search was updated to March 31st 2019 using a rapid methodology (single reviewer, simplified search terms, one database [Medline]). The methods otherwise describe the original search.

Search strategy

Medline, Cochrane database, CINAHL, PsycINFO, HMIC, and Care Search Grey Literature were searched using free text and MeSH terms from 1995 to 2017 inclusive. The search strings represented the terms to identify the population (symptomatic heart failure) and the intervention of interest (palliative care) [supplementary table 1]. This was intentionally broad given the nature of the interventions sought. Reference lists and citations of included studies and key review articles were searched. Experts in the field were contacted. There were no language restrictions.

Eligibility criteria

Types of participants: Studies were included if participants had symptomatic heart failure (New York Heart Association class III & IV) or other evidence of advanced disease such as left ventricular ejection fraction <40%. Where only a subset were participants with symptomatic heart failure, studies were included if outcome data could be extracted for this subset.

Types of interventions: Any study with a palliative care, or component(s) of, intervention delivered by specialist or generalist services was included apart from advance care planning alone. Specialist palliative care services are those where palliative care is the core business and staff have additional specialist training. Generalist services refer to all other services where basic palliative care may be provided, but palliative care is not their primary purpose, such as primary care or hospital services such as cardiology. For this review, cardiac rehabilitation interventions are considered as "rehabilitative" rather than "palliative" services and were thus excluded.

Types of comparator: There was no restriction on the comparator arm or care setting.

Types of study design: Experimental or quasi-experimental, observational, and service evaluations, and national audits were included. Studies with unclear methods, duplicate publications (except where discreet outcomes were presented), opinion pieces, narrative reviews, editorials, case histories or case series were excluded.

Study selection

One reviewer (SD) screened all titles and abstracts against the eligibility criteria and a second reviewer (CV) independently reviewed a proportion (18%) and both screened retrieved full papers. Any disagreements were resolved by discussion between the two reviewers with access to a third reviewer (MJJ) where necessary.

Data extraction

A data extraction spreadsheet was designed and piloted. Two researchers (SD, CV) independently extracted the data. Disagreements or discrepancies were resolved by mutual consent or by involvement of a third author (MJJ). Study identifiers, study characteristics, information regarding the population, intervention, comparators, and outcomes, including results were extracted.

Where data was unreported or ambiguous, attempts were made to contact the authors of the paper.

Risk of bias assessment

SD and CV independently assessed the risk of bias and the disagreements were resolved by discussion and access to MJJ as needed. Randomised controlled trials were assessed with the use of the Cochrane Risk of Bias Tool and the Newcastle-Ottawa quality assessment Scale was used to judge the risk of bias in cohort and case control studies.

Synthesis of results

Descriptive narrative synthesis of the study design, the included population, the intervention, and comparator are presented in tabular format.

For the purpose of the review, randomised controlled trials, in accordance with the Medical Research Committee Framework for complex intervention development,(19) the terms "phase II/III" were not used. Trials were identified as feasibility and pilot phase trials and evaluation trials on the following basis. Studies with a stated aim to assess the efficacy or effectiveness of the intervention were classed as evaluation phase randomised controlled trials. Additionally, studies with power calculations aiming to design adequately powered trials to identify the effect of the intervention were also categorised as evaluation phase randomised controlled trials.

Outcomes and results were described; however, a meta-analysis was not conducted due to heterogeneity of outcomes, populations, and interventions.

RESULTS

The search process for the included studies is summarised in a flow chart (figure 1). The original database search identified 7,934 records after de-duplication, and a further 85 in the rapid update review. Overall, twenty-three studies met the inclusion criteria.
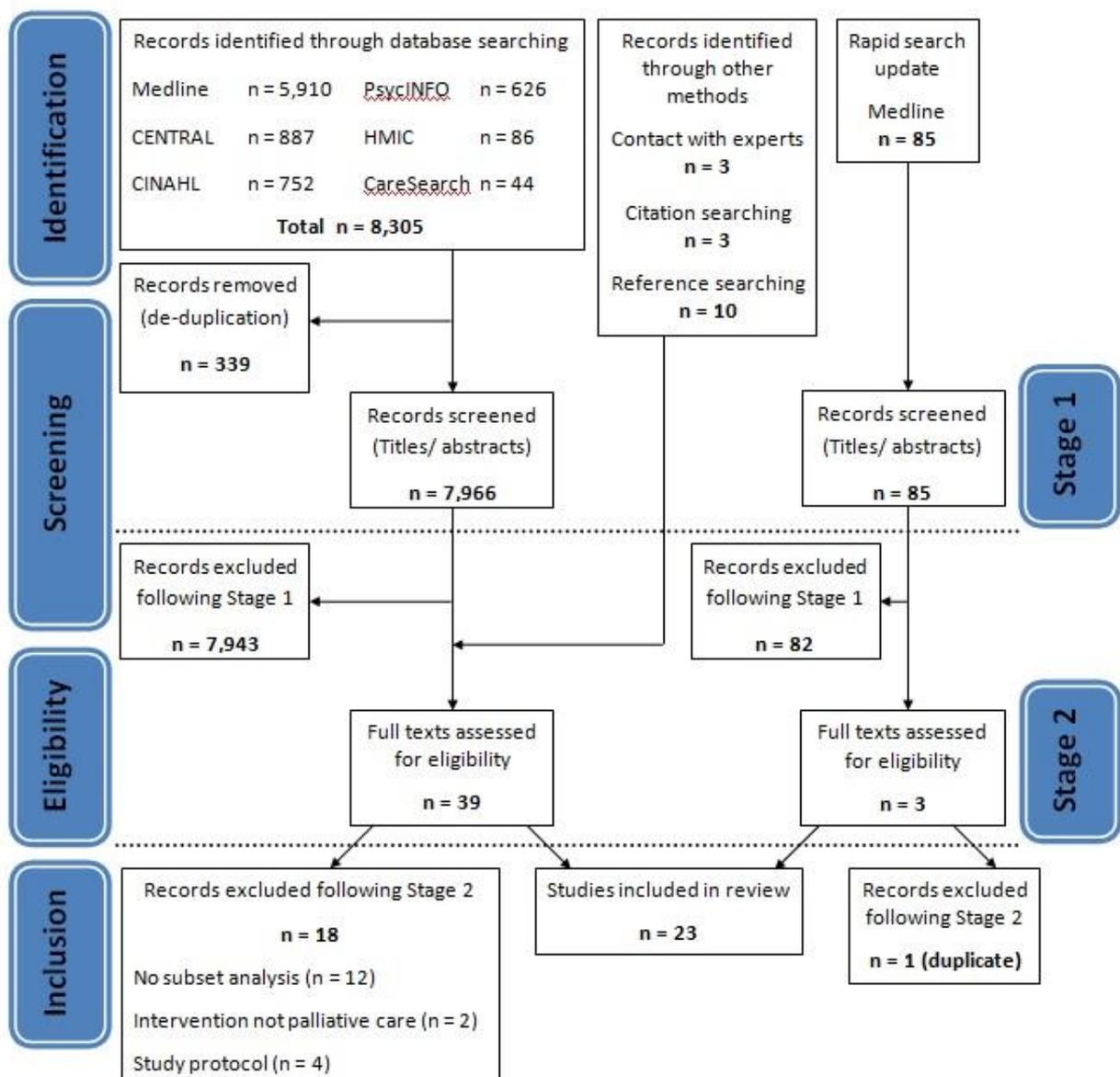

Figure 1: PRISMA flowchart depicting the search process and the study selection

Study characteristics

Study design and setting

Eight papers reporting seven evaluation phase randomised controlled trials,(20-27) four feasibility and pilot phase studies/randomised controlled trials,(28, 29, 30, 31) one quasi-experimental study,(32) seven cohort studies,(33-39) two case-control studies,(40, 41) and one cross-sectional study(42) were included. The characteristics of included studies are summarised in table 1 (interventional studies) and table 2 (observational studies). Further details including outcomes and results are available in supplementary table 2. Sixteen studies were community-based,(21, 22, 25, 27-29, 35-42) two extended across community and hospitals,(21, 25) three were set in the hospital alone(24, 27, 32) and two in hospice.(33, 42)

Sample sizes ranged from 13(28) to 16,613.(42) Six studies(20-24, 26) provided sample size/power calculations. Bekelman *et al.*,(21) Brännström *et al.*,(22) and Hopp *et al.*(23) achieved adequate power to detect statistically significant differences in outcomes (90%, 80%, and 80% respectively). Aiken *et al.*,(20) Rogers *et al.*,(24) and Sidebottom *et al.*(26) were designed to reach adequate power however, due to difficulty in recruitment and high attrition rate, partly due to death, these studies did not reach their proposed sample size.

Table 1: Characteristics of included interventional studies

First author, year and country	Study setting	Participants: sample size (n), age (years), sex (%), disease characteristics (NYHA, LVEF)		Intervention	Comparator
		Intervention	**Comparator**		
Evaluation phase RCTs					
Aiken LS (20) **2006** **USA**	Community based and hospital based	N = 100 (CHF = 67) Mean Age (SD) = 68 (14) Sex: M = 42.0; F = 58.0	N = 90 (CHF = 62) Mean Age (SD) = 68 (14) Sex: M = 30.0; F = 70.0	PhoenixCare: Home-based palliative care	Usual care
Bekelman DB (21) **2015** **USA**	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%) class II = 77 (42.8%)	N = 197 Mean Age (SD) = 67.9 (10.6) Sex: M = 98.0; F = 2.0 NYHA: class I = 16 (8.5%) class II = 85 (45.0%)	Patient-centred disease management	Regular care

		class III = 82 (45.6%) class IV = 5 (2.8%) LVEF: Normal = 78 (45.6%) Mild = 34 (19.9%) Moderate = 46 (26.9%) Severe = 13 (7.6%)	class III = 82 (43.4%) class IV = 6 (3.2%) LVEF: Normal = 84 (47.5%) Mild = 34 (19.2%) Moderate = 32 (18.1%) Severe = 27 (15.3%)		
Brännström M (22) **2014** **Sweden**	Community based with outpatient consultations	N = 36 Mean Age (SD) = 81.9 (7.2) Sex: M = 72.2; F = 27.8 NYHA: class III = 28 (77.8%) class IV = 8 (22.2%) LVEF: 40-49% = 13 (36.1%) 30-39% = 16 (44.4%)	N = 36 Mean Age (SD) = 76.6 (10.2) Sex: M = 69.4; F = 30.6 NYHA: class III = 23 (63.9%) class IV = 11 (30.6%) LVEF: 40-49% = 12 (33.3%) 30-39% = 21 (58.3%)	PREFER: Palliative advanced home care and heart failure care	No information

		<30% = 7 (19.4%)	<30% = 3 (8.3%)		
Hopp FP (23) 2016 USA	Hospital based	N = 43 Mean Age (SD) = 67.0 (11.0) Sex: M = 60.5; F = 39.5 Mean LVEF = 36.4% (16.7)	N = 42 Mean Age (SD) = 68.0 (13.0) Sex: M = 42.9; F = 57.1 Mean LVEF = 38.1% (16.8)	Palliative care consultation	No information
Rogers JG (24) 2017 USA	Community based and hospital based	N = 75 Mean Age (SD) = 71.9 (12.4) Sex: M = 56.0; F = 44.0 NYHA: class III = 54 (72.0%) class IV = 15 (20.0%) LVEF: >55% = 21 (28.0%) 40-55% = 14 (18.7%) 25-40% = 17 (22.7%)	N = 75 Mean Age (SD) = 69.8 (13.4) Sex: M = 49.3; F = 50.7 NYHA: class III = 58 (77.3%) class IV = 5 (6.7%) LVEF: >55% = 14 (18.7%) 40-55% = 19 (25.3%) 25-40% = 14 (18.7%)	PAL-HF: Multi-component palliative care	Usual care

		<25 = 23 (30.7%)	<25 = 28 (37.3%)		
Sahlen KG (25); 2015; Sweden: Details are the same as Brännström *et al.* (23)					
Sidebottom AC (26) **2015** **USA**	Inpatient consultation	N = 116 Mean Age (SD) = 76.0 (11.9) Sex: M = 47.4; F = 52.6	N = 116 Mean Age (SD) = 70.9 (13.6) Sex: M = 57.8; F = 42.2	Palliative care consultation	No information
Wong FKY (27) **2016** **China**	Community based	N = 43 Mean Age (SD) = 78.3 (16.8) Sex: M = 43.9; F = 56.1 NYHA: class II = 6 (14.0%) class III = 31 (72.0%) 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%) class III = 22 (53.7%) class IV = 16 (39.0%) Mean LVEF = 37.0% (17.0)	Transitional palliative care	Usual care

Feasibility and pilot phase RCTs					
Paes P (28) **2005** **UK**	Outpatient consultations	N = 6 Mean Age (SD) = 73.2 (4.2) Sex: M = 100.0; F = 0.0 NYHA: class III = 3 (50.0%) 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%) class IV = 2 (40%)	Palliative care consultation	Regular care
Bakitas M (29) **2017** **USA**	Community based with outpatient consultations	N = 61 Mean Age (SD) = 70.59 (10.7) Sex: M = 50.8; F = 49.2 NYHA: class I = 1 (1.6%) class II = 3 (4.9%) class III = 43 (70.5%) class IV = 12 (19.7%)	Single-arm study ENABLE CHF-PC: Early palliative care intervention		

		Unknown = 2 (3.3%) Mean LVEF = 37.86% (16.3)			
O'Donnell A (30) USA	In-patient and/or recent discharged to community from admission for acute decompensated heart failure	N = 26 Mean Age (SD) = 74.7 (11.2) Sex: M 53.9, F = 46.1 NYHA class 1 or 2 = 10 (38.5%) NYHA class 3 or 4 = 16 (61.5%) Mean LVEF = 30% (14)	N = 24 Mean Age (SD) = 69.2 (10.2) Sex: M = 62.5, F = 37.5 NYHA class 1 or 2 = 8 (33.3%) NYHA class 3 or 4 = 16 (66.7%) Mean LVEF = 36% (17)	Social worker consultation for care planning Palliative care physician consultation	Usual care and printed materials about palliative care and advance care planning
Johnson MJ (31) UK	Community based with out-patient consultations	Cohort 1: palliative cardiology N = 43 Mean Age (SD) = 75.8 (12.3) Sex: M 55.8, F = 44.2 NYHA: class I = 0	Cohort 2: usual care N = 34 Mean Age (SD) = 78.4 (11.3) Sex: M 50.0, F = 50.0 NYHA: class I = 0	Cohort 1: palliative care clinic conducted by consultant cardiologist with special interest, and heart failure nurse consultant	Cohort 2: usual care

		class II = 0 class III = 40 (93.0) class IV = 3 (7.0)	class II = 3 (8.8) class III = 30 (88.2) class IV = 1 (2.9)		
Quasi-experimental study					
Tadwalkar R **(32)** **2014** **USA**	Inpatient visits	N = 14 Mean Age (SD) = 58 (11) Sex: M = 42.9; F = 57.1	N = 9 Mean Age (SD) = 57 (10) Sex: M = 55.6; F = 44.4	Religious support	Non-religious support

| First author, year and country | Study setting | Participants: sample size (n), age (years), sex (%), disease characteristics (NYHA, LVEF) | | Intervention | Comparator |
		Intervention	Comparator		
Cohort studies					
Connor SR (33) **2007** **USA**	Hospice care (Retrospective)	N = 2095 (CHF = 83) Mean Age = 73.5 Sex: M = 55; F = 45	N = 2260 (CHF = 457) Mean Age = 73.9 Sex: M = 59; F = 41	Hospice care	No claims for hospice care
Enguidanos SM (34) **2005** **USA**	Community based with outpatient consultations (Prospective)	N = 159 (CHF = 31) Mean Age (SD) = 70 (13.92) Sex: M = 49.1; F = 50.9	N = 139 (CHF = 51) Mean Age (SD) = 73 (13.29) Sex: M = 44.6; F = 55.4	Home-based palliative care program	Standard health care

Pattenden JF (35) **2013** **UK**	Community based (Prospective)	N = 99 Mean Age (SD) = 81.7 Sex: M = 60.6; F = 39.4	N = 98 Mean Age (SD) = 78.85 Sex: M = 62.0; F = 37.8	"Better Together" intervention: education and palliative nursing	'Convenience sample' - historical
Evangelista LS (36) **2014** **USA**	Outpatient consultations (Prospective)	N = 29 Mean Age (SD) = 53.3 (7.3) Sex: M = 75.9; F = 24.1 NYHA: class II = 20 (69.0%) 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%) class III = 4 (30.8%) Mean LVEF = 30.5% (9.7)	Single arm study Palliative care consultations: 'Intervention group' Participants receiving > 2 palliative care consultations 'Comparator group' Participants receiving ≤ 1 palliative care consultations	
Evangelista LS (37) **2014**	Outpatient consultations (Prospective)	N = 29 Mean Age (SD) = 54.1 (8.4) Sex: M = 75.9; F = 24.1	N = 7 Mean Age (SD) = 52.7 (6.3) Sex: M = 57.1; F = 42.9	Single arm study Palliative care consultations: 'Intervention group'	

USA		NYHA: class II = 20 (69.0%) class III = 9 (31.0%) Mean LVEF = 25.9% (5.3)	NYHA: class II = 5 (71.4%) class III = 2 (28.6%) Mean LVEF = 23.1% (4.3)	Participants receiving palliative care consultation and follow up. 'Comparator group' Participants receiving initial palliative care consultation only.
Taylor GJ (38) 2017 USA	Community based (Retrospective)	N = 32 Age Range (Median) = 48-94 (70) Sex: M = 100; F = 0 NYHA: class III = 2 (6.7%) class IV = 28 (93.3%) 23 patients had HFrEF (LVEF <30%); 7 had HFpEF.		Single arm study Home delivered palliative care
Wong RC (39) 2013	Community based (Prospective)	N = 44 Mean Age (SD) = 79 (9)		Single arm study Home palliative care program

Singapore		Sex: M = 38.6; F = 61.4 NYHA: class III = 31 (70.0%) class IV = 13 (30.0%)			
Case-control studies					
Cassel JB (40) **2016** **USA**	Community based (Retrospective)	N = 174 Mean Age (SD) = 87.5 (6.6) Sex: M = 44.3; F = 55.7	N = 499 Mean Age (SD) = 87.1 (6.4) Sex: M = 43.7; F = 56.3	Transitions: Concurrent medical and palliative care	No information
Evangelista LS (41) **2012** **USA**	Outpatient consultation (Prospective)	N = 36 Mean Age (SD) = 53.9 (8.0) Sex: M = 72.2; F = 27.8 NYHA: class II = 25 (69.4%) class III = 11 (30.6%) Mean LVEF = 25.4% (5.2)	N = 36 Mean Age (SD) = 53.3 (8.7) Sex: M = 69.4; F = 30.6 NYHA: class II = 26 (72.2%) class III = 10 (27.8%) Mean LVEF = 26.0% (6.2)	Palliative care consultation	No information

Cross-sectional study					
Blecker S (42) **2011** **USA**	Hospice care	N = 6,436 Mean Age (SD) = 85.0 (7.6) Sex: M = 39.5; F = 60.5	N = 10,177 Mean Age (SD) = 83.6 (7.9) Sex: M = 44.5; F = 55.5	Hospice care	No claims for hospice care

Abbreviations: NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; RCT = randomised controlled trial; CHF = congestive heart failure; SD = standard deviation; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction

Participants

Across 23 studies, 19,891 participants (average age range 52.5 to 87.5; men = 59.3%) were included. Severity of heart failure was indicated by New York Heart Association classification(21, 22, 24, 27, 28, 30, 31, 36-39, 41) (figure 2), Kansas City Cardiomyopathy Questionnaire,(21, 30, 31) recent acute episode resulting in visits to the emergency department, hospitalisation or symptoms of end of life.(20, 22-25, 27, 30, 31, 34, 35, 38) In four studies,(21, 22, 24, 38) the data on left ventricular ejection fraction were presented in categories – 'normal' (34.6%), 'mild' (19.7%), 'moderate' (24.7%) and 'severe' (21.0%) left ventricular ejection fraction. The average left ventricular ejection fraction of the patients included in seven other studies(23, 27, 29 -31, 36, 37, 41) was 32%.
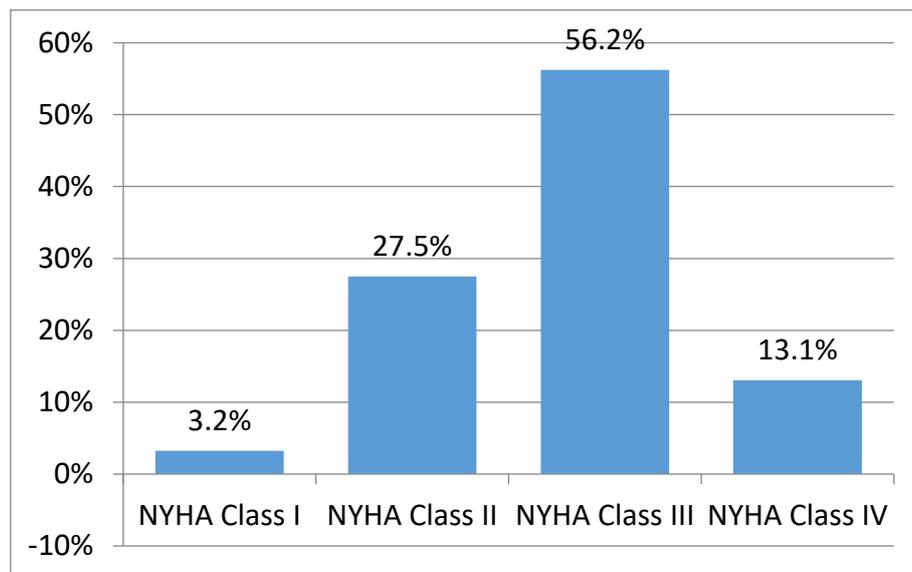
Figure 2: Distribution of participants across the NYHA classes reported in 13 studies; reported here for the 12 studies where all four classes are reported separately

Intervention

The intervention varied in terms of components and delivery (supplementary table 3) and details were missing in Connor *et al.*(33) and Blecker *et al.*(42) Most common aspects of palliative care included were symptom management, psychological support and advance care

planning. All studies included an assessment of current medical status and patients' needs, and were provided by a multidisciplinary team.

Comparator

In general description of the comparator was absent(22, 23, 25, 26, 30, 33, 35, 39-42) or minimal(20, 21, 24, 27, 28, 34). Six of the included studies were single arm studies, with no comparator.(29, 32, 36-39) One feasibility study reported two cohorts,(31) one from a palliative cardiology clinic, and one from usual care, but the study was not designed as quasi-experimental although descriptive comparisons were made. This study is reported as a feasibility study, but as the methods fit best with observational design, the quality was assessed as a cohort study.

Risk of bias

Evaluation phase studies

The risk of bias of the evaluation phase studies is summarised in supplementary table 4 using the Cochrane Risk of Bias tool. The main source of bias was the lack of blinding, but this was inherently impossible. Three trials attempted to blind outcome assessors.(20, 21, 27) There were a number of other issues relating to risk of bias. Missing data, particularly of patient-reported primary outcomes was significant, but details on pattern of missingness or how this was handled were not provided apart from Rogers *et al.*(24) (used a mixed effects model for the primary outcomes). Wong *et al.*(27) used the generalised estimating equation which is able to take missing data into account, but this was not made explicit as a method of handling missing data.(20, 28) Other biases include the risk of type 1 errors due to multiple statistical testing on small participant samples,(20) statistically significant differences in New York Heart Association classes between arms at baseline,(27) and poor fidelity to allocated arms

with some participants accessing palliative care as part of usual care in the comparator arms.(24, 26)

Observational studies – cohort studies

The Newcastle-Ottawa Scale risk of bias assessment for the seven cohort studies is summarised in supplementary table 5. The four single-arm cohort studies could not be assessed fully as there is no non-exposed group. Most cohort studies had representative samples, however, Taylor *et al.*(38) recruited male veterans only and the second cohort in Johnson *et al* used a convenience sample only.(31) None of the included studies measured the outcome of interest at baseline, but these were expected to improve or worsen based on exposure rather than appear or disappear. Comparability could be assessed through the baseline characteristics of the included participants, but analyses did not control for confounding factors. The primary objective for Johnson *et al* was to test the feasibility of a subsequent trial with regard to recruitment, attrition and data quality from these two settings, and was not designed to compare the two groups in any way other than descriptively.(31)

Observational studies – case-control studies

The Newcastle-Ottawa Scale risk of bias assessment for the two case-control studies is summarised in supplementary table 6. The case definition, case representativeness, and selection of controls was appropriate in both studies, however the controls are poorly defined. The comparison groups were matched for age, sex, and race. Evangelista *et al.*(41) provided no information on how the exposure was measured and neither study provided information on non-response rates.

Observational studies – Cross-sectional study

Cross-sectional design has inherent flaws, e.g. the exposure and outcome are measured at the same time-period. The summary quality rating for Blecker *et al.*(42) is fair, but the sample is not justified, no weight is given to level of exposure to intervention or repeat exposure in the analysis and the outcome measurement relied significantly on coding.

Outcomes

The salient results of the outcomes from the included studies are summarised in table 3.

Patient-centred outcomes

Symptom burden was measured with the use of Edmonton Symptom Assessment Scale(22, 26, 27, 31, 36, 37, 41) and Memorial Symptom Assessment Scale.(20, 29, 32) Five(26, 29, 36, 37, 41) out of the nine studies investigating the change in symptom burden found significant improvement in symptoms such as breathlessness, pain and fatigue. Participants in the intervention arm of Aiken *et al.*(20) experienced significantly higher symptom distress than their counter-parts in the control arm, and in Johnson *et al,* symptoms improved more in the usual care cohort.(31) Nine studies investigated depression using the Patient Health Questionnaire-9,(21, 26, 30, 41) Hospital Anxiety and Depression Scale,(24, 25, 29, 31) and Quick Inventory of Depressive Symptomatology.(32) Five studies(21, 24, 25, 30, 41) found significant improvement in depression with the intervention. There was a significant improvement in New York Heart Association classes from baseline following the intervention,(22, 38) but no change in functional status measured by Palliative Performance Scale(27) or Australian-modified Karnofsky Performance Scale.(31)

Various measures were used to assess quality of life, including, Kansas City Cardiomyopathy Questionnaire and EuroQol-5D. Some studies used a combination to assess disease- or intervention-specific and health-related quality of life. Seven(24-27, 29, 30, 41) out of 11

studies found significant improvement in quality of life, with one other(22) noting a significant improvement in health-related quality of life but not in disease-specific quality of life. Five studies investigated the effect on survival, while others(20, 24, 27, 29, 30, 31) commented on attrition due to death. Four studies(22, 23, 26, 31) found no significant difference in mortality between the intervention and comparator arm. There were significantly fewer deaths in the intervention arm in Bekelman *et al.*(21) and the participants survived significantly longer in Connor *et al.*(33)

Resource use

Thirteen studies evaluated use of resources in different ways. Seven(22, 27, 31, 35, 39, 40, 42) out of ten studies found significant reduction in hospitalisations and re-admissions, and five(29, 31, 34, 40, 42) out of six studies had significant reduction in length of stay in hospital or service use. There was no significant difference in hospice use among the participants. Patients in the intervention arm were more likely to complete advance care planning(26, 30, 31) and less likely to die in hospital.(34, 40) Three studies(34, 35, 40) found a statistically significant drop in costs in the intervention arm, one feasibility study found preliminary cost savings in the intervention group (31), however one found no significant difference and the expenditure of the intervention arm in Blecker *et al.*(42) was significantly higher when adjusted for covariates.

Table 3: Summary of salient outcome results

Study	Patient-centred outcomes					Resource use				
	Symptom burden	Depression	Quality of life*	Functional status	Mortality	Hospital visits	Length of service use	Hospice care	Place of death & ACP	Costs
Aiken LS [20]	✗					◇?				
Bekelman DB [21]		✓	◇?		✓	◇?				
Brännström M [22]	◇?		✓ ◇?	✓	✓	✓				
Hopp FP [23]					◇?			◇?		
Rogers JG [24]		✓	✓							
Sahlen KG [25]			✓							◇?
Sidebottom AC [26]	✓	✓	✓		◇?	◇?		◇?	✓	
Wong FKY [27]	◇?		✓ ✓	◇?		✓				
Paes P [28]		◇?	◇?							
Bakitas M [29]	✓	◇?	✓				✓	◇?		
Tadwalkar R [32]	◇?	◇?	◇?							
O'Donnell A [30]		◇?	◇?		◇?				✓	
Johnson MJ [31]	✗	◇?	◇?	◇?	◇?	✓			✓	✓
Connor SR [33]					✓					
Enguidanos SM [34]							✓	◇?	✓	✓
Pattenden JF [35]						✓	◇?			✓

Study	Patient-centred outcomes					Resource use				
	Symptom burden	Depression	Quality of life*	Functional status	Mortality	Hospital visits	Length of service use	Hospice care	Place of death & ACP	Costs
Evangelista LS† [36]	☑	☑								
Evangelista LS* [37]	☑									
Taylor GJ [38]				☑						
Wong RC [39]						☑				
Cassel JB [40]						☑	☑		☑	☑
Evangelista LS [41]	☑		☑							
Blecker S [42]						☑	☑			☒

***Note that the quality of life assessment was conducted separately in some studies for disease-specific/ health-related/ palliative care-specific data therefore may have multiple entries.*

ACP = Advance care planning

Key: ☑ = results significantly in favour of intervention, ☒ = results significantly in favour of control, ◇ = no significant difference

DISCUSSION

This review collated the current body of evidence from a range of countries examining the effects of palliative care on patients with advanced heart failure with the intent to guide future clinical and research priorities for this population.

The results from evaluation phase studies support the use of multi-component, multi-disciplinary palliative care interventions. Benefits were improvement in patient-centred outcomes including symptom burden, depression, quality of life, functional status, and reduced use of healthcare resources and costs of care.

Findings were inconsistent across all studies, likely due to the significant clinical and methodological heterogeneity between studies, across all aspects: study design, study population and setting, components of the intervention and control and choice of outcome measures.

Limitations of the included studies

Although we searched the international literature, 16/23 studies were conducted in the United States which may limit generalisability.

Patients in randomised controlled trials were randomised individually and intervention was delivered in the same site as the control arm; therefore, there is a risk of control group contamination.(20, 21, 26, 30, 41) Also, some patients did not receive the prescribed intervention either due to limited availability of providers(26) or limited access to care if patients deteriorated rapidly.(35) Meanwhile, other patients received palliative care despite allocation to control in response to clinical need.(24, 26) Therefore, the effect of the intervention may be under-estimated. Further, in one study (20) heart failure participants

were a subgroup only. Baseline differences in symptom distress (higher in the intervention group) were therefore not adjusted for, which may have affected the findings.

Conclusions from the non-randomised trials(32) and observational studies regarding the precise impact of the intervention, should be cautious due to risk of selection bias and effect of confounders which were either not reported, or, if they were, adjusted findings were not presented.

Eleven studies(20-25, 27-28, 32, 35, 39) included only patients with New York Heart Association class III and IV, consistent with the population most likely to benefit from palliative care. Other studies did not provide New York Heart Association classification or also included patients with New York Heart Association class I and II but without subgroup-analysis. This may have led to an underestimation of effect.

Palliative care is a multi-component intervention, but was variably delivered across included studies. Studies investigating the effects of limited aspects of palliative care (32) (23) found no significant difference in outcomes between the intervention and the comparator, unlike studies investigating a more comprehensive intervention. Two studies(26, 41) assessed the effect of a single palliative care consultation – which does not represent usual palliative care practice. Hopp *et al.*(324) chose completed "do not resuscitate" orders as the primary outcome which is inconsistent with the defined aim of palliative care (improvement in quality of life and symptom control).(8)

Apart from the risk of contamination, the quality of the studies designed to evaluate effectiveness(20-27) was good, accepting that blinding was not possible. However, as expected with palliative care studies, there were missing data in patient-report primary outcomes at levels associated with bias. Rogers *et al.*(24) addressed this explicitly for their primary outcomes using a linear mixed models with an indicator variable for the treatment

group and Wong *et al.*(27) used generalized estimating equations. As with previously noted poor reporting of missing data,(43) neither described the pattern of missingness to confirm that this approach was appropriate.(44) However, Rogers *et al.*(24) did note the significant levels of missing data and made the reasonable comment that bias should be limited because the attrition was similar in both arms.

Strengths and limitations of the review

This review was not restricted to randomised controlled trials, to allow an understanding of the breadth and gaps in the published literature relating to palliative care for people with heart failure. However, as with any systematic review, some studies with potential for inclusion may have been missed. Due to the clinical and methodological heterogeneity between the included studies, we were unable to conduct a meta-analysis. This heterogeneity reflects the variation in palliative care implementation around the world.

Implications for clinical practice and research

Palliative care delivered as comprehensive intervention with regular assessments of patients' needs and a tailored management appears to be beneficial for patients with symptomatic heart failure. However, in practice, referral of all patients with New York Heart Association III and IV heart failure to specialist palliative care seems both unnecessary and unsustainable. Current recommendations(13, 14, 15, 5) support an integrated approach where usual care teams (in cardiology, elderly care or primary care) provide general palliative care for identified needs but involve specialist palliative care for complex or persistent concerns.(46) Although the study of a palliative care intervention led by the cardiology team was not designed to show effectiveness,(31) it demonstrates that it is possible to deliver in clinical practice.

Future trials of specialist palliative care should focus on the patients with heart failure most likely to benefit from specialist intervention. A recent cohort study of people admitted to hospital for heart failure identified that those most likely to have specialist palliative care needs (defined as those with "persistently severe impairment of any patient reported outcome") as those with a Kansas City Cardiomyopathy Questionnaire summary score of <29 on admission.(47) This moves away from the question of "when is the right time to refer", which assumes proximity to death as the primary criterion.

Well-designed studies which minimise contamination (for example, cluster design) are also needed to test the effectiveness and cost-effectiveness of interventions whereby the usual care team provide most palliative care, supported by specialists as needed. Consensus around core components of palliative care, configuration of palliative care teams, the most effective model of service provision to ensure tailored generalist and/or specialist palliative care, core outcome sets and careful thought and agreement about how to both minimise and manage missing data would facilitate both quality of results and the ability to conduct meta-analysis.

Conclusions

Multi-component, multi-disciplinary palliative care interventions appear to provide patient-centred benefit and reduce use of healthcare resources and costs. However, there are no sufficiently robust multi-centre evaluation phase trials to provide generalizable findings. Consensus is needed for regarding core intervention components, study population, outcome sets, management strategies for missing data and optimum design to inform multi-centre trials for use in future meta-analysis.

CONTRIBUTIONS

SD and MJJ conceived the question; SD, MJJ and AH designed the protocol; SD conducted the search; SD and CV selected the studies and extracted data; SD wrote the first draft; all authors contributed to critical revision and agree the final manuscript.

DATA SHARING

All data are presented in this manuscript.

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