Heart failure disease management: a systematic review of effectiveness in heart failure with preserved ejection fraction

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Abstract

Aims  Heart failure with preserved ejection fraction (HFpEF) poses a substantial challenge for clinicians, but there is little guidance for effective management. The aim of this systematic review was to determine if there was evidence that disease management programmes (DMPs) improved outcomes for patients with HFpEF.

Methods and results  A systematic review of controlled studies in English or Greek of DMPs including patients with HFpEF from 2008 to 2018 was conducted using CINAHL, Cochrane, MEDLINE, and Embase. Interventions were assessed using a DMP taxonomy and scored for complexity and intensity. Bias was assessed using the Cochrane Collaboration tool. Initial and updated searches found 6089 titles once duplicates were removed. The final analysis included 18 studies with 5435 HF patients: 1866 patients (34%, study ranges 18–100%) had potential HFpEF (limited by variable definitions). Significant heterogeneity in terms of the population, intervention, comparisons, and outcomes prohibited meta-analysis. Statistically significant or positive trends were found in mortality, hospitalization rates, self-care ability, quality of life, anxiety, depression, and sleep, but findings were not robust or consistent. Four studies reported results separately for study-defined HFpEF, with two finding less positive effect on outcomes.

Conclusions  Varying definitions of HFpEF used in studies are a substantial limitation in interpretation of findings. The reduced efficacy noted in contemporary HF DMP studies may not only be due to improvements in usual care but may also reflect inclusion of heterogeneous patients with HFpEF or HF with mid-range EF who may not respond in the same way as HFrEF to individual components. Given that patients with HFpEF are older and multi-morbid, DMPs targeting HFpEF should not rely on a single-disease focus but provide care that addresses predisposing and presentation phenotypes and draws on the principles of comprehensive geriatric assessment. Other components could also be more targeted to HFpEF such as modification of lifestyle factors for which there is emerging evidence, rather than simply continuing the model of care used in HFrEF. Based on current evidence, HF DMPs may improve mortality, hospitalization rates, self-care, and quality of life in patients with HFpEF; however, further research specifically tailored to appropriately defined HFpEF is required.

Keywords  Heart failure; Heart failure with preserved ejection fraction; Disease management; Systematic review

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with HFrEF (n = 53 065) found a 30 day and 1 year all-cause readmission rate of 22% and 67% respectively and a composite all-cause readmission and mortality rate of 74.5% at 1 year. Current recommendations for management of HFrEF are to control cardiovascular and non-cardiovascular co-morbidities and use diuretics to manage fluid status. Although multi-disciplinary team (MDT) disease management programmes to reduce the risk of hospitalization and mortality are recommended for patients with HF, there is little information about their effectiveness specifically in HFrEF.

Disease management programmes (DMP) are designed to ‘improve outcomes through structured follow-up with patient education, optimization of medical treatment, psychosocial support and improved access to care’. Most HF DMPs in the 1990s–early 2000s focused on patients with HFrEF usually after an HF hospitalization. Outcomes for patients with HFrEF were improved through multi-component DMPs that included the following: optimization of evidence-based treatment (emphasis on medications for HFrEF), education, behaviour change, supported self-management, and clinician monitoring. In previous systematic reviews, HF DMPs were found to significantly reduce HF hospitalizations, and those with continued specialized follow-up reduced all-cause mortality and all-cause hospitalization. However, some reviews have found limited or no benefit, especially in studies after 2008, in studies with <3 months of follow-up, or in patients without a recent hospitalization.

In HF DMPs, it can be challenging to ascertain if the sample included patients with HFrEF, given relatively recent use of the term and controversies over diagnostic criteria. HFrEF is a more tempting target because of robust evidence for specific pharmacological therapies in reducing mortality and morbidity. Thus, little is known about the use and effectiveness of HF DMPs in patients with HFrEF in improving outcomes. The aim of this analysis was to determine if there was evidence that HF DMPs improved outcomes specifically for patients with HFrEF.

The review questions were as follows:

- Do MDT or nurse-led DMPs for patients with HFrEF result in greater outcomes for patients compared with usual care or another intervention?
- What are the components and processes of successful MDT or nurse-led DMPs for patients with HFrEF?

Methods

The review protocol was registered on Prospero (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017067980). The systematic review was conducted and reported in accordance to the PRISMA guidelines (http://www.prisma-statement.org/). The years 2008 to 2018 were chosen to reflect contemporary management of HF, increasing attention to HFrEF, and recommendations for HF DMPs in guidelines for management of HF. Language was restricted to English or Greek. Studies of community-dwelling adults with HFrEF were included, as were studies with a mixed HF population if the proportion of patients with HFrEF was discernible, and represented approximately 20% or greater of the total sample. The intervention had to be an MDT or nurse-led outpatient DMP with a minimum of 3 months of follow-up and a control group for comparison. Single interventions composed only of pharmacotherapy, exercise, invasive monitoring, end-of-life care, or telemonitoring alone were excluded. Interventions were assessed using a taxonomy of DMPs and scored for intensity and complexity. Final consensus on findings, interpretation, and text were agreed by all authors.

Information sources, search strategy, and study selection

The following databases were searched from January 2017 to May 2018: CINAHL through EBSCO, Cochrane, MEDLINE, and Embase through Ovid. References in included articles were hand searched. The following terms along with synonyms and relevant terms were applied: HF, primary care, randomized controlled trials, disease management, nurse, and multi-disciplinary. Titles and abstracts were reviewed by two authors (F. K. and C. D.), and full-text papers were reviewed by at least two of the authors.

Data process

The Cochrane data extraction form was revised to align with the aims of the current review and pilot tested. Data were abstracted and cross-checked by at least two authors independently. Bias was assessed using the Cochrane Collaboration tool by at least two authors on the following fields: (i) random sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinded outcome assessment, (v) selective outcome reporting, (vi) incomplete outcome data, and (vii) other bias.

Results

Initial and updated searches found 7617 titles, with 6089 titles once duplicates were removed. The majority (5791) were excluded following title review. Abstracts (192) were screened in detail for eligibility, and 95 full-text papers were reviewed. Reasons for exclusion of papers can be found in Figure 1. An additional 20 papers from references were reviewed. The final analysis included 18 studies in 18 papers.
with 5435 patients with HF, 1866 of whom were considered by the study to have HFrEF (34%).

**Inclusion of patients with heart failure with preserved ejection fraction**

Only one study focused exclusively on patients with HFrEF; 17 other studies included and documented numbers of patients characterized as HFrEF based on study criteria. When studies stated that they included patients with HFrEF without documenting percentage or number, authors were contacted for information. The proportion of patients with HFrEF varied from 18% to 100% and was variably defined in the studies (Table J). No studies defined HFrEF in line with the current European Society of Cardiology (ESC) guidelines, which include the following criteria: signs and symptoms of HF, a left ventricular EF ≥ 50%, elevated levels of natriuretic peptides and either relevant structural heart disease (left ventricular hypertrophy and/or left atrial enlargement), and/or diastolic dysfunction on echocardiogram. Four studies included some analysis specific to patients with HFrEF, with three of these in comparison with HFrEF. Five studies had samples that were predominantly patients with HFrEF (64–84%) as defined by the study, although only one included discussion of issues specific to HFrEF.

**Heart failure with preserved ejection fraction definition**

The EF cut-off point for defining HFrEF ranged between ≥40% and ≥50%. It is noticeable that the ESC recommended cut-off point of EF ≥ 50% was used only in seven studies. Three
| Study                        | Country | Sample size | Identification of patients with HF | HFpEF definition/criteria                                                                 | Proportion HFpEF (%) | Separate results given for HFpEF |
|-----------------------------|---------|-------------|-----------------------------------|-------------------------------------------------------------------------------------------|---------------------|---------------------------------|
| Andryukhin et al. (2010)    | Russia  | N = 100     | Patients included if had signs and symptoms of HF, EF ≥ 50%, and echo evidence of DD, LV stiffness, or abnormal LV relaxation | Signs and symptoms of HF, EF ≥ 50%, and echo evidence of DD, LV stiffness, or abnormal LV relaxation | 100%                | Yes                             |
| Bekelman et al. (2015)      | USA     | N = 392     | Inpatient or outpatient diagnosis of HF, any type | EF ≥ 50%                                                                                   | 47% (163 of 348 patients with EF measured) | No                              |
| Bekelman et al. (2018)      | USA     | N = 314     | Symptomatic outpatients with HF, used dx + data on meds, EF, and BNP | EF ≥ 50%                                                                                   | 40% (n = 121)       | Intervention effect on KCCQ differed by EF, with less effect in HFpEF |
| Brotons et al. (2009)       | Spain   | N = 283     | Hospitalized for suspected HF, with HF as primary or second discharge diagnosis | EF ≥ 50%                                                                                   | 41% (n = 117)       | No                              |
| Chang et al. (2016)         | Taiwan  | N = 84      | Recruited from cardiology outpatient department, with cardiology confirmed dx of HF | EF ≥ 50%                                                                                   | 55% (n = 46)        | No                              |
| Dracup et al. (2014)        | USA     | N = 602     | Recruited from clinics and hospitals, needed hospitalization for HF within last 6 months | EF ≥ 40%                                                                                   | 49% (n = 295)       | HF group (by EF < 40% or ≥40%) added as a covariate; no difference between HFpEF and HFrEF |
| Freedland et al. (2015)     | USA     | N = 158     | Recruited from single medical centre, dx with HF within last 3 months | EF ≥ 45%                                                                                   | 46% (n = 73)        | No                              |
| Gonzalez-Guerrero et al.    | Spain   | N = 117     | Hospitalized with acute HF (ESC criteria) in a single centre | Not specifically defined                                                                  | 67% (n = 77)        | No                              |
| Jaarsma et al. (2008)       | The Netherlands | N = 1023 | Recruited during hospital admission for HF (signs and symptoms of HF, plus evidence of structural underlying heart disease on imaging) | Not specified in original paper, but secondary analysis used EF ≥ 40% for HFpEF | A secondary analysis of 661 patients found 33% with HFpEF (n = 218) | No                              |
| Kalter-Leibovici et al. (2017) | Israel  | N = 1360    | Recruited from public hospitals, primary care, and community cardiologists within 2 months after HF hospitalization; dx based on signs and symptoms, echo evidence | EF ≥ 50%                                                                                   | 18% (n = 247)       | Yes, less effect of DMP and very wide CI for HFpEF compared with HFrEF; no significant difference by composite outcome, HF hospitalization, or all-cause mortality |
| Kwok et al. (2008)          | China   | N = 105     | Recruited during hospital admission for HF | Differentiated between those with and without EF ≥ 40%                                      | 77% (n = 81)        | No                              |
| Leventhal et al. (2011)     | Switzerland | N = 42   | Recruited based on hospitalization for decompensated HF | EF ≥ 45%                                                                                   | 49% (n = 20)        | No                              |
| Masterson Creber et al. (2016) | USA     | N = 100     | Recruited during HF hospitalization at 1 urban hospital | Defined as ‘diastolic HF’ with no EF specified                                              | 25% (17 of the 67 who completed) | No                              |
| Shao et al. (2013)          | Taiwan  | N = 108     |                                           | EF > 40%                                                                                   | 22% (n = 24)        | No                              |

(Continues)
Table 1 (continued)

| Study | Country | Sample size | Identification of patients with HF | HFpEF definition/criteria | Proportion HFpEF (%) | Separate results given for HFpEF |
|-------|---------|-------------|-----------------------------------|---------------------------|----------------------|---------------------------------|
| Srisuk et al. (2015) | Thailand | N = 100 dyads | Patients attending heart clinics with dx HF | Not specifically defined; MD with objective evidence by mean EF was 50–51% ± 13 | 27% (n = 76) | No |
| Stewart et al. (2014) | Australia | N = 280 | Recruited from 3 cardiology hospitals | Cardiologist confirmed dx HF | EF > 45% | Yes, no difference in % with HFpEF by survived or died |
| Tsuchihashi-Makaya et al. (2013) | Japan | N = 168 | Recruited from 3 cardiology hospitals | EF > 40% | 64% (n = 107) | No |
| Young et al. (2016) | USA | N = 100 | Patients hospitalized with HF (HF discharge diagnosis) | EF ≥ 50% | 84% (n = 84) | No |

CI, confidence interval; DD, diastolic dysfunction; DMP, disease management programme; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricle.

All studies included patients labelled as HFpEF but without explicitly defining this population. The remaining nine studies used either >45% or 40% as EF criterion to differentiate patients with HFpEF. The percentage of patients with HFpEF defined by the studies ranged between 22% and 77%. By ESC criteria, these would be samples of patients with both HF with mid-range EF (HFmrEF, EF 40–49%) and HFpEF, which are considered two distinct clinical entities in the guidelines.

### Interventions and study characteristics

Interventions varied by components, duration, methods of delivery, intensity, complexity, and outcomes (Tables 2 and 3). All of the interventions were directed to patients, with three including carers. Eleven of the study interventions were delivered primarily by nurses with relevant experience or additional training, delivered primarily by nurses with relevant experience or additional training, although advice or referral for increasing physical activity was frequently a component in other studies. Telemonitoring was included in the intervention in two studies, and five provided medication adjustment by nurses or via general practitioners. Patient assessment was included in all but two studies, although the extent, frequency, and type of assessment varied.

The duration of the interventions ranged from 3 months to over 2 years, and interventions in seven of the studies were ≥12 months. All studies included at least one face-to-face encounter with patients, but telephone contact was used in all to deliver some of the intervention. Home visits were used in 11 studies. Outpatient or clinical visits were included in all but two studies. The majority of studies were judged to be high in intensity and complexity based on delivery of multiple components using different methods of delivery and high frequency of contact, and five were judged to be moderate.

### Comparison

Seventeen of the 18 studies compared an intervention with usual care, although two of these also included two intervention arms varying by intensity and complexity. Usual care was variably described across studies, and efforts to standardize usual care were made in only four studies. Controlling for patient contact as a confounding variable was only described in one study. Stewart et al. tested multi-disciplinary comprehensive care delivered by either outpatient clinic or home visits.
| Study | Components | Mode of delivery | Complexity, duration, intensity |
|-------|------------|------------------|---------------------------------|
|       | Education/ >behavioural/ >SM | Exercise | Telemonitoring | Clinician >review | Medication >adjustment | Education/ >assessment/ >DC plan | Home >visits | Telephone | Outpatient >or clinic >session | Multi- >resources | Complexity | Duration | Frequency of contact |
|       | Assessment |                   |                      |                   |                      |                   |                      |          |          |                      |                |            |          |                              |
| Andryukhin et al. (2010) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | High | 6 months | Weekly F2F education/ skills sessions × 4; weekly exercise × 4; weekly phone calls, Months 2–6 |
| Bekelman et al. (2015) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | High | 12 months | Monthly × 12 |
| Bekelman et al. (2018) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | High | 3 months | 1–2 phone calls per month planned; mean calls by RN 13 (5.7), SW 10 (4) |
| Brotons et al. (2009) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | High | 12 months+ | Home 1× per month × 12; phone 2× per month × 12 |
| Chang et al. (2016) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | Mod | 12 weeks | x1 monthly face to face and x6 biweekly phone calls |
| Dracup et al. (2014) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | Mod | 1 month then PRN | LITE: 2 phone calls biweekly PLUS: biweekly 1 phone call |
| Freedland et al. (2015) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | Not >specified | | | |
| Gonzalez-Guerrero et al. (2015) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | High | 12 months | Comprehensive hospital DC planning and close follow-up at a geriatric day hospital (GDH), from a multidisciplinary team; phone contacts and face-to-face visits at the GDH |
| Jaarsma et al. (2008) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | High | 18 months | Basic support group received UC + 9 HFSN clinic visits. Intensive support was UC + 18 HFSN clinic visits, phone calls weekly first month, MDT support, 2 home visits |
| Kalter-Lebovic et al. (2017) | ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ | | | | | | | | | | High | Mean = 2.7 years | Initial remote contact 1× per week, adjusted based on need. Clinic every 6 months or more if needed |

(Continues)
| Study                        | Components | Mode of delivery | Complexity, duration, intensity |
|-----------------------------|------------|-----------------|----------------------------------|
|                             | Assessment | Exercise | Telemonitoring | Clinician review | Medication adjustment | Education/assessment >DC plan | Home visits | Telephone | Outpatient >or clinic session | Multi-media >resources |
| Kwok et al. (2008)          | ✓          | ✓         |               | ✓                 | ✓                    | ✓          | ✓            | ✓          | ✓          | ✓          | ✓          |
| Leventhal et al. (2011)     | ✓          | ✓         |               |                   |                      |            | ✓            | ✓          | ✓          | High 6 months Weekly × 4 first month and then monthly for 6 months Initially home visit, followed by 17 structured telephone calls (weekly × 4, bi-monthly × 4, monthly × 6) plus additional calls when needed |
| Masterson Creber et al. (2016) | ✓          | ✓         |               |                   |                      |            | ✓            | ✓          | ✓          | ✓          | ✓          |
| Shao et al. (2013)          | ✓          | ✓         |               |                   |                      |            | ✓            | ✓          | ✓          | Moderate 3 months 1 F2F contact and 3–4 phone calls over 90 days |
| Srisuk et al. (2017)        | ✓          | ✓         |               |                   |                      |            | ✓            | ✓          | ✓          | Moderate 6 months 1 F2F education/ counselling session. Phone calls 15 min/ week in first month, per fortnight in the second month and once a month in Months 3–6 |
| Stewart et al. (2014)       | ✓          | ✓         |               |                   |                      | ✓          | ✓            | ✓          | ✓          | High 6 months MDT comprehensive care by clinic or home visits |
| Tsuchihashi et al. (2013)   | ✓          | ✓         |               |                   |                      |            | ✓            | ✓          | ✓          | High 6 months Home visits by nurse within 14 days post-DC, then q 2 weeks for 2 months. Then monthly telephone until 6 months |
| Young et al. (2016)         | ✓          | ✓         |               |                   |                      |            | ✓            | ✓          | ✓          | High 3 months Telephone contact twice a week, Weeks 1–2; once weekly, Weeks 3–6; every other week, Weeks 7–12 |
| STUDY | TPs | OM | MORT. | HOSP. | HF-QOL | GENERIC | ANKH/ DEPR. | SELF-CARE | ACTIV. | BIOCHEM | ECHO | OTHER | RESULTS (impact of intervention on outcome measure) |
|-------|-----|----|-------|-------|--------|---------|-------------|------------|--------|---------|------|-------|--------------------------------------------------|
| 1. Brotons et al. 2009 | Monthly for 12 months | USED YES-AC* | YES – Ac* | YES – HF* | YES | MLHFQ | NR | NR | YES | MMAS-8 | NR | NR | Positive Neutral/ Negative |
|          | DETAILS | Assessed by review of hospital discharge records | Assessed by review of hospital discharge records | | | | | | | | | | The aggregate of all-cause mortality and HF hospital readmissions improved but not significantly in the intervention arm. There was a significant improvement in QoL between the control and intervention group at 1 year. |
| 2. Chang et al. 2016 | BL, 4wks, 8wks, 12wks | USED NR | NR | NR | NR | YES | HADS | NR | NR | NR | YES* | Sleep quality measured by: Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale |
|          | DETAILS NR | | | | | | | | | | | Neutral/ Negative Anxiety and depression scores unchanged, when compared with controls, the intervention arm had a significantly greater improvement in both anxiety and depression. |
| 3. Dracup et al. 2014 | BL, 3, 12, 24 months | USED YES-AC* | YES – CV* | YES – HF* | YES | NHFSCBQ | NR | NR | NR | YES | Heart Failure Knowledge Scale, Short Test of Functional Health Literacy in Adults |
|          | DETAILS | Assessed by medical record review, family/physician interview, death certificate and Social Security Death Index check | Assessed by questioning patients and physicians and medical record review | | | | | | | | | Neutral/ Negative Self-care improvement observed in the intervention groups were no longer significantly different from the control group. |

(Continues)
| STUDY                        | TPs  | OM             | MORT. | HOSP. | HF-QOL | GENERIC QOL | ANX/DEPR | SELF-CARE | ACTIV. | BIOCHEM | ECHO | OTHER | RESULTS (impact of intervention on outcome measure)                                      |
|-----------------------------|------|----------------|-------|-------|--------|-------------|-----------|------------|--------|---------|------|-------|--------------------------------------------------|
| 4. Freedland et al. 2015    | BL, 3, 6, 9, DETAILS Not defined | Not defined | KCCQ  | SF-12  | BDI-II, BAI, Depression Interview, Structured Hamilton Rating Scale | SCHFI     | 6MMTV, average daily activity level on Actigraphy (1wk wear) | NR      | NR      | NIH PROMIS Measures | Six-month depression scores were lower in the CBT than the usual care arm on the BDI-II. Six-month outcomes were superior in the CBT relative to the usual care arm on secondary measures of depression, anxiety, HF-related quality of life, mental health-related quality of life, fatigue and social functioning. The groups did not differ on any of the physical functioning measures. There was no statistically significant difference in the time to the first all-cause hospitalization or death between the usual care and CBT groups. |
| 5. Gonzalez-Guerrero et al. 2014 | BL, 12 mts | YES-AC* | YES-AC* | MLHQ   | YES EQ-SD | NR   | NR | NR | YES Hb, urea, creatinine, uric acid, Na⁺, K⁺, albumin, TC, troponin T, CRP, NT-proBNP | NR | YES Global Deterioration Scale | Positive In the intervention group, the probability of having an event (either hospitalisation or mortality) between BL and 1 year was significantly lower. Those receiving the intervention had a significant reduction in mortality risk. Neutral/Negative Those receiving the intervention had a non-significant reduction in HF readmissions but an increase in non-HF related hospitalisations. |
| 9. Jaarsma et al. 2008      | BL, 18 mts | YES – AC* | YES – HF* | NR   | NR | NR | NR | NR | YES Number of days lost due to death or hospitalisation | NR | NR | NR | Neutral/Negative Neither the moderate nor intensive intervention reduced the combined end points of HF related death and hospitalization compared with standard follow-up. |

(Continues)
| STUDY | TPs | OM | MOR.T. | HOSP. | HF-QOL | GENERIC QOL | ANX / DEPR | SELF-CARE | ACTIV. | BIOCHEM | ECHO | OTHER | RESULTS (impact of intervention on outcome measure) |
|-------|-----|----|--------|-------|--------|-------------|------------|-----------|--------|---------|------|-------|-----------------------------------------------|
| 10. Kalter-Leibovici et al. 2017 | BL, 6, 12, 18, 24 mts | USED | YES – AC* | YES – HF* | ASSESSED by review of discharge summaries. | NR | YES | NR | YES | SF-36 | YES | PHQ-9 | YES | PURCHASE of recommended medications | NR | YES | NR | TOTAL number of hospital admissions and in-hospital days for heart failure and for all causes | POSITIVE | NEUTRAL/NEGATIVE |
|           | DETAILS | NR | ASSSESSED by review of discharge summaries. | NR | YES | SF-36 | YES | PHQ-9 | YES | SF-36 | YES | PHQ-9 | YES | PURCHASE of recommended medications | NR | YES | NR | TOTAL number of hospital admissions and in-hospital days for heart failure and for all causes | POSITIVE | NEUTRAL/NEGATIVE |
| 11. Kwok et al. 2007 | BL, 6 mts | USED | NR | NR | YES – AC* | Electronic database review; readmission reason assessed by geriatrician or cardiologist and categorized | NR | NR | NR | YES | General Health Questionnaire | NR | NR | YES | 6MWT | NR | NR | YES | LHS, Abbreviated Mental Test | POSITIVE | NEUTRAL/NEGATIVE |
|           | DETAILS | NR | ELECTRONIC database review; readmission reason assessed by geriatrician or cardiologist and categorized | NR | NR | YES | General Health Questionnaire | NR | NR | YES | 6MWT | NR | NR | YES | LHS, Abbreviated Mental Test | POSITIVE | NEUTRAL/NEGATIVE |
| 12. Leventhal et al. 2011 | BL, 3, 6, 9, 12 mts | USED | YES AC* | YES HF & AC* | ASSESSED by review of medical records by blinded researcher | YES | MLHFQ | YES | EQ-SD | YES | Geriatric Depression Scale | NR | NR | NR | NR | NR | NR | YES | Specific Activity Scale | POSITIVE | NEUTRAL/NEGATIVE |
|           | DETAILS | NR | ASSESSED by review of medical records by blinded researcher | YES | MLHFQ | YES | EQ-SD | YES | Geriatric Depression Scale | NR | NR | NR | NR | NR | NR | YES | Specific Activity Scale | POSITIVE | NEUTRAL/NEGATIVE |
| 13. Masterson- | BL, 90 days | USED | NR | NR | YES | KCCQ | NR | NR | NR | YES* | SCHFI | NR | NR | NR | YES | HF Symptoms via Heart Failure | POSITIVE | ALTHOUGH not statistically |
|           | DETAILS | NR | YES | KCCQ | NR | NR | NR | YES | SCHFI | NR | NR | NR | YES | HF Symptoms via Heart Failure | POSITIVE | ALTHOUGH not statistically |

(Continues)
| STUDY | TPs | OM | MORT. | HOSP. | HF-QOL | GENERIC | QOL | ANX / DEPR | SELF-CARE | ACTIV. | BIOCHEM | ECHO | OTHER |
|-------|-----|----|-------|-------|--------|---------|-----|-----------|-----------|--------|---------|------|-------|
| Creber et al. 2015 | | | | | | | | | | | | | |

| RESULTS (impact of intervention on outcome measure) |
|--------------------------------------------------|
| Somatic Perception Scale |
| significant, the improvement in self-care maintenance was numerically greater in the intervention group and a statistical and clinically significant 8.7-point increase in SCHFI was observed when adjusting for confounding factors. |

| 14. Shao et al. 2013 | BL, 4, 12 wks | USED NR | YES AC | YES | YES | NR | NR | YES* | NR | NR | NR | NR | YES |
|----------------------|----------------|----------|--------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|
| DETAILS NR | | Assessed by review of medical records. | | | | | | Self-Efficacy for Salt & Fluid Control & modified EHFS CBS | | | | |
| participant's perception of the ability to control salt and fluid intake. |
| Positive |
| Neutral/Positive |
| There was no reduction in health service use between the groups. |

| 15. Srisuk et al. 2014 | BL, 3, 6 mth | USED NR | YES | NR | NR | YES | NR | NR | YES | NR | NR | NR | NR |
|----------------------|---------------|----------|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|
| DETAILS NR | | | Patients: MLHPQ | | | | | | | | | | |
| Carers: SF12 |
| Positive |
| Neutral/Negative |
| Negative or neutral results not reported. |
| STUDY                        | TPs                 | OM    | MORT.                      | HOSP. | HF-QOL | GENERIC QOL | ANX / DEPR. | SELF-CARE | ACTIV. | BIOCHEM | ECHO | OTHER | RESULTS (impact of intervention on outcome measure) |
|-----------------------------|---------------------|-------|----------------------------|-------|--------|-------------|--------------|------------|--------|---------|------|-------|--------------------------------------------------|
| 16. Stewart et al. 2014     | BL, 12 - 18 mth, 3-4 yrs | USED AC* | YES AC* A blinded endpoint committee adjudicated on the type and cause of mortality | YES MLHFQ | YES EQ-5D | NR          | YES SCHFI    | NR        | NR      | NR      | NR   | NR    | YES Length of hospital stay; uptake of gold-standard pharmacotherapy. Positive. Home-based intervention was associated with significantly fewer all-cause deaths and significantly fewer days of hospital stay. Favourable trends towards home-based intervention were strengthened in the long-term (16% fewer deaths and reduction in AC mortality.) |
| 17. Tsuchihashi-Makaya et al. 2013 | BL, 2, 6, 12 mths | USED AC | YES HF Not defined | NR      | NR      | YES SF-8 | YES* HADS | NR        | NR      | NR      | NR   | NR    | Neutral/ Negative There was no difference in AC mortality between the groups. The physical and mental health QOL score significantly increased from baseline at all follow-up time points in the intervention but not in the control. HF hospitalizations were reduced in the intervention group. |
| 18. Young et al. 2016       | BL, 3 and 6 mths   | USED NR | YES - AC All-cause readmission and emergency department visits at 30, 90 and 180 days assessed by | NR      | NR      | NR       | NR          | NR        | NR      | YES Atlanta HF Knowledge Test | Neutral/ Negative No significant differences were observed between groups in the pattern of change across time on any of |
| STUDY | TPs | OM | MORT. | HOSP. | HF-QOL | GENERIC | QOL | ANX. / DEPR. | SELF-CARE | ACTIV. | BIOCHEM | ECHO | OTHER |
|-------|-----|----|-------|-------|--------|---------|-----|-------------|-----------|--------|---------|------|-------|
|       | both self-report and primary care provider record review | | | | | | | | | | | | |
|       | 2 x Medication Adherence Scales | expended | energy, | estimated | | | | | | | | | |
|       | SCHRI Energy expenditure | | | | | | | | | | | | |
|       | Actiwatch average activity | | | | | | | | | | | | |
|       | SF-6D intensity | | | | | | | | | | | | |
|       | EHFSCBS assessed by | | | | | | | | | | | | |

RESULTS (impact of intervention on outcome measure)

- Patient-reported SM adherence at 3 and 6 months after discharge.
- On average, the intervention group had a significantly greater increase in self-efficacy for heart failure self-management, self-management strategies and patient activation.
- The actigraphy variables collected. There was no significant difference in clinical biomarkers. The 30-day readmission rate was significantly higher in the intervention group than in the control group with no difference between groups at 90 and 180 days. No group differences were found for self-management knowledge.

Abbreviations: NR = Not reported, CV = Cardiovascular, AC = All cause, HF = heart Failure, MLHFQ = Minnesota Living with Heart Failure Questionnaire, KCCQ = Kansas City Cardiomyopathy Questionnaire, PHQ-9 = Patient Health Questionnaire 9-item, GAD-7 = Generalised Anxiety and Depression Scale 7-item, HDAS = Hospital Anxiety and Depression Scale, 6MWT = Six Minute Walk Test, TC = Total Cholesterol, LDL = Low Density Lipoprotein, HS-CRP = High Specificity CRP, NTproBNP = N-terminal pro b-type natriuretic peptide, LA = Left Atrium, LVEDV = Left ventricular end-diastolic volume, LV = Left ventricle, Hb = Haemoglobin, K+ = potassium, Na+ = Sodium, NYHA = New York Heart Association, BMI = Body Mass Index, WC = waist circumference, SF = Short Form, MMAS-8 Morisky Medication Adherence Scale, EHFSCBQ = European Heart Failure Self-Care Behaviour Questionnaire, BDI = Beck Depression Inventory, BAI = Brief Anxiety Index, LHS = London Handicap Scale, SCHFI = Self Care of Heart Failure Index.
Outcomes

The effect of disease management programmes on mortality
The most common primary outcome measure employed was a composite of mortality and hospitalization, either all-cause/all-cause (n = 4), all-cause/HF (n = 3), cardiovascular/cardiovascular (n = 1), or cardiovascular/HF (n = 1). All-cause mortality and/or all-cause hospitalizations were secondary outcome measures in four studies respectively, and one study employed an all-cause/HF composite as a secondary objective. In the studies measuring mortality, three reported a significant improvement. The proportion of HFpEF patients in these studies was 67%, 47%, and 27%, respectively. Of these studies, only Stewart et al. reported separate HFpEF statistics (HFpEF defined as those with EF > 45%) and found no difference in percentage with HFpEF by survived or died. Nine studies reported no significant difference of their respective interventions on mortality between either intervention groups or intervention and usual care. Kalter-Leibovici and colleagues dichotomized findings by HF group and found no significant difference by composite outcome (all-cause mortality/HF hospitalization), or all-cause mortality alone, and much wider confidence intervals in those with EF ≥ 50%. Four of these nine studies without statistical significance did report positive trends in mortality in favour of the intervention. Dracup et al. added HF group (by EF < 40% or >40%) as a covariate and found no difference in outcomes between groups.

The effect of disease management programmes on hospitalizations
Most studies (88%) employed hospitalization(s) as an outcome measure; the most common was all-cause hospitalizations (n = 8), HF-only hospitalizations (n = 5), HF and all-cause (n = 2), or cardiovascular (n = 1). Only three reported a statistically significant result. The remainder reported either no impact or prolonged time to hospitalization, and lower total numbers hospitalized; or trends towards higher hospitalizations in intervention groups.

The effect of disease management programmes on self-care
Nine studies evaluated the effect of the intervention on self-care. There was significant variability in the self-care outcome measures employed: the most frequently employed (n = 5) was the Self-Care of Heart Failure Index followed by the European Heart Failure Self-Care Behaviours Questionnaire (n = 3). Of the studies assessing effect on self-care (n = 9), four reported a statistically significant positive effect, two reported improvements that were not significant, and one reported no impact, and in two studies, the effect could not be ascertained from the publication.

The effect of disease management programmes on condition-specific quality of life
Heart failure quality of life was measured by either the Minnesota Living with Heart Failure Questionnaire (n = 5) or the Kansas City Cardiomyopathy Questionnaire (KCCQ) (n = 4). Three studies failed to demonstrate significant improvement, one study did not reach statistical significance but demonstrated a clinically meaningful improvement in quality of life as measured by KCCQ; and five studies reported a statistically significant improvement in the intervention arm.

The effect of disease management programmes on anxiety, depression, and sleep quality
Anxiety and depression were commonly measured and featured in nine of the 18 studies, and these were the primary outcome in two studies. Freedland et al. demonstrated that cognitive behavioural therapy plus an HF education programme was superior to usual care plus an HF education programme only, and this improvement was sustained over time. Tsuchiashi-Makaya et al. similarly found that their home-based DMP significantly improved psychological status compared with usual care and was also sustained over time. Of the seven studies examining anxiety or depression as a secondary outcome measure, impact of the intervention on either variable, anxiety or depression, was undeterminable in two publications and improved either significantly or clinically in the intervention arm in five studies. One study specifically focussed on improving sleep in HF patients and found both sleep quality and day-time sleepiness levels significantly improved in the intervention arm.

Outcomes by heart failure with preserved ejection fraction with ejection fraction ≥50%
If we use the ESC criterion that HFpEF includes an EF ≥ 50%, then seven studies are of interest. The outcomes of mortality and/or hospitalization were measured in six studies. Of these, only one had significantly fewer events in the intervention group, specifically in all-cause mortality. Kalter-Leibovici et al. did not find a significant difference in outcomes for DMP vs. control, and as noted previously, the confidence intervals around the hazard ratios for HF hospitalization and all-cause mortality were much wider for patients with HFpEF.

The single study that assessed self-care reported significant improvement favouring the intervention group. The intervention was efficacious in terms of health-related quality of life (HRQoL) in two studies. In two studies, there was no significant difference between intervention and control groups in 3 and 6 months of HRQoL measured by the KCCQ. Additionally, Bekelman et al. reported a lower effect size of the intervention on the KCCQ for HFpEF.
compared with HFrEF (−0.03 vs. 0.28). All five studies measuring the outcomes of anxiety and/or depression demonstrated significant improvement in favour of the intervention arm. 17–19,21,22

Outcomes by intervention provider

Six of the 11 studies with mainly nurse-led interventions had outcomes related to mortality and/or hospitalization; one of them demonstrated significant improvement in all-cause mortality 26 and another one in HF hospitalizations. 34 Half of the six nurse-led studies that assessed HRQoL reported improved HRQoL in the intervention group as compared with control. 17,26,29 The majority of the nurse-led studies evaluating self-care changes achieved a significantly positive result at least once during follow-up (including adjusted results) when comparing the intervention to the control group. 25,26,30,33 Among the nurse-led studies, the intervention group yielded superior results in relation to anxiety and/or depression in three out of five studies. 17,21,34 Five studies employed a multidisciplinary approach in their intervention: two reduced mortality and/or hospitalization 18,35 in the intervention group vs. control group, one improved HRQoL 25 in comparison with control group, and all three studies measuring depression and/or anxiety had better results in the intervention group in this regard. 18,19,22 None of the multidisciplinary studies assessed self-care. In the study of Freedland et al., 27 the intervention was delivered by behavioural therapists and was effective in improving HF quality of life, anxiety, and depression. One study did not specify the provider of the intervention. 23

**Assessment of bias**

Most studies were rated as low risk in terms of random sequence generation. However, bias varied considerably across other aspects with most studies being unable to conceal allocation to intervention or usual care arms after randomization from research team and patients. Almost all studies had blinded outcome assessment, and most reported complete outcome results (Table 4).

**Discussion**

In this systematic review, we found a limited number of contemporary studies of DMPs in HF that included or sufficiently described patients with HFrEF and only one that was specifically designed for this group. Across the studies, there was significant heterogeneity in terms of the population, intervention, comparisons, and outcomes that prohibited meta-analysis. Definitions for HFrEF were variable with only seven of the 18 studies employing an EF of ≥50%. This reflects the lack of a universal approach in defining HFrEF even among recent trials, 39 despite the guidance provided by the ESC. Interventions were similarly heterogeneous with extensive variability in the components included, mode of delivery, complexity, and duration. Comparison groups received scant attention; few studies sufficiently described attempts to standardize or account for potential confounding in ‘usual care’ control arms. In terms of outcomes, the most commonly measured were hospitalizations (83%) and mortality (66%),

| Table 4 Bias |
| --- |
| First author and year | Random sequence generation | Allocation concealment | Blinded investigators/patients | Blinded outcome assessment | Selective outcome reporting | Incomplete outcome data | Other bias |
| Andryukhin (2010) | Unclear | Low | High | Low | High | High | Higha |
| Bekelman (2015) | Low | Low | High | Lowb | Low | Low | Low |
| Bekelman (2018) | Low | Low | High | Low | Low | High | Low |
| Brotons (2009) | Low | Low | High | Low | Low | Low | Low |
| Chang (2016) | Unclear | Low | High | Low | Low | Low | High |
| Dracup (2014) | Low | Low | Low | Low | Low | Low | Low |
| Freedland (2015) | Unclear | Low | High | Low | Low | Low | Low |
| González-Guerrero (2014) | Low | Low | High | Lowc | Low | Low | Low |
| Jaarsma (2008) | Low | Unclear | High | Low | Low | Low | Low |
| Kalter-Leibovici (2017) | Low | Unclear | High | Low | Low | Low | Low |
| Kwok (2008) | Low | Low | High | Low | Low | Low | Low |
| Leventhal (2011) | Low | Low | High | Low | Low | Low | High |
| Masterson Creber (2016) | Unclear | Unclear | High | Low | Low | High | Low |
| Shao (2013) | Low | Low | High | Low | Low | Low | Low |
| Srisuk (2015) | Low | Low | High | Low | Low | Low | Low |
| Stewart (2014) | Low | Unclear | High | Low | Low | Low | Low |
| Tsuchihashi-Makaya (2014) | Unclear | Unclear | Unclear | Unclear | Low | Low | Low |
| Young (2016) | Low | Low | High | Low | Low | Low | High |

Source: Freedland et al. 27

aPositive change included no change from baseline.
bPositive change included improvement for 3 and 6 months.
cPositive change included improvement for primary outcome.
and a minority demonstrated that the DMP had a statistically significant impact on either outcome.

Four studies with both HFrEF and HFrEF reported results separately for patients identified as HFrEF in the study, but only two defined HFrEF using the recommended ESC criterion of EF > 50%.²⁻²² Bekelman et al.²⁹ (40% HFrEF, n = 121) found that the intervention had less effect on quality of life in those with HFrEF compared with HFrEF. Kater-Leibovici et al.³² (18% HFrEF, n = 247) also found less effect of the DMP and wide confidence intervals for HFrEF compared with HFrEF; however, overall, there was no significant difference by composite outcome, HF hospitalization, or all-cause mortality by HF group. In the study exclusively HFrEF (using EF ≥ 50%), fifteen the intervention group had improvement or no deterioration in several cardiovascular risk factors, quality of life, depression, and left ventricular end-diastolic volume index compared with control. There was no statistically significant difference between intervention and control on cardiovascular events or mortality at 6 and 18 months. This trial was innovative in including exercise sessions and measuring specific echocardiographic parameters but nonetheless included recommendations for HFrEF medications that have not been shown to improve event-free survival in patients with HFrEF. Bias was also assessed as high on some components (Table 4).

Programme components offer a useful framework to explore reasons for variable impact on outcomes assessed in included studies.

**Clinical assessment**

Sixteen studies included either MDT or nurse-led clinical assessment that then formed the basis of individualized HF specific treatment plans. None detailed exploration of co-morbidity, clinical phenotyping, or comprehensive geriatric assessment, although one DMP was delivered through a geriatric day-care hospital.³⁵ Data from clinical trials have clearly demonstrated the high incidence of co-morbidities in HFrEF and effects of this has on outcome. The CHARM trial found that demographic risk factors (age and sex) and non-cardiac risk factors contributed more to mortality and morbidity outcomes in patients with HFrEF (n = 1086 defined as EF > 40%), while cardiac disease burden contributed more to outcomes in those with HFrEF.⁴⁰ If co-morbidities drive the development of HFrEF through a systemic pro-inflammatory state as currently postulated,⁴¹ then the focus on appropriate control of cardiovascular and non-cardiovascular co-morbid conditions is essential.³,⁸,⁴²

The ARISE-HF investigators recently presented a pragmatic framework that includes profiling to determine concurrent co-morbidities, identifying individualized priorities and patient-centred goals, supporting multi-professional home-based case management, coordinating care, and emphasizing self-care.⁴³ Shah et al.³ devised an HFrEF treatment grid organized by predisposition phenotype (e.g. hypertension and metabolic syndromes) and clinical presentation phenotype (e.g. lung congestion and atrial fibrillation) to determine management based on the patient’s phenotypic features and co-morbid conditions. Upadhyya et al.⁴⁴ have called for HFrEF to be recognized as a true geriatric condition and suggested that geriatric principles should be used in the treatment of HFrEF.

**Educational/behavioural/self-management interventions**

Self-management interventions have previously been found to reduce risk of the composite endpoint of HF-related hospitalization and all-cause death, HF-related hospitalization alone, and result in a small improvement in HRQoL compared with usual care.⁴⁵ In this review, all studies incorporated educational, behavioural, or self-care components designed to improve self-management. Only three of nine studies measuring self-care as an outcome demonstrated a statistically significant improvement in self-care. Programme characteristics, mechanisms of effect, and evidence for efficacy may explain this finding. In an individual patient data meta-analysis of 20 trials of self-management support in patients with HF (n = 5624), no specific programme characteristics were identified that consistently had a positive effect on multiple outcomes. A 2016 systematic review and realist synthesis of the main mechanisms of HF DMPs found that to be effective, programmes should contain components that increase patient understanding of HF, self-care, self-efficacy, family/caregiver involvement, psychosocial well-being, health professional support, and technology use.⁴⁶ Although many studies encompassed components that harnessed one or more of these mechanisms, no single programme comprehensively covered all. Finally, our knowledge of optimal lifestyle behaviours and self-care in HFrEF is limited, and self-care interventions for patients with HFrEF lack evidence of effectiveness.

**Exercise**

Being physically active was advocated in most studies, but only one study delivered an exercise intervention.¹⁷ Other studies encouraged exercise as part of self-management education and support, referred to formal exercise programmes (although uptake not reported), and one measured activity as part of a primarily telephone-delivered self-management intervention. No significant difference between the groups was found in activity, which was low in both groups. Exercise is a promising but underutilized intervention in patients with HFrEF. While data are limited, a meta-analysis of six trials (n = 276 patients) showed that cardiorespiratory fitness
and quality of life were significantly improved with exercise compared with control. Clinical outcomes were not reported, and the studies were of short duration (12–24 weeks). A small study tested the effect of a calorie restricted diet, aerobic exercise training (primarily walking), a combination of diet and exercise, or an attention control on 100 obese patients with HFpEF. At 24 weeks, the diet, exercise, and diet + exercise groups had significant improvements in exercise capacity by peak VO₂ (greatest increase in diet + exercise) but no significant improvement on quality of life measured by the MLHFQ. Diet significantly improved KCCQ scores, and diet and exercise decreased body weight and improved New York Heart Association class.

**Telemonitoring**

Two studies in this review included telemonitoring as a component of a DMP. Multiple studies of non-invasive telemonitoring as the primary intervention in HF have been conducted with inconsistent results. The latest guidelines on management of HF have no recommendations for non-invasive telemonitoring in management. A recent paper tested a holistic and structured remote management intervention involving a multi-disciplinary team (nurses, primary care physicians, cardiologists, other providers, and the patient), telemonitoring, risk assessment, and tailored support and management available 24 h or 7 days/week. The intervention resulted in fewer days lost to unplanned cardiovascular hospitalizations and all-cause mortality compared with usual care over 1 year. However, the sub-group analysis of patients with EF > 45% (n = 537) showed no benefit between intervention and usual care.

**Limitations**

This systematic review has a number of limitations. Importantly, the varying and inconsistent definitions of HFpEF (some samples included HFmrEF), heterogeneity of studies with significant variation in the aims, interventions and outcomes measured, ascertainment of the condition, and proportion of patients with HFpEF limited our ability to compare the studies directly, employ a meta-analysis, and draw clear conclusions for this group of patients. In only six studies, the percentage of patients with HFpEF exceeded 50%, and just four studies reported separate results for patients with HFpEF (including patients not meeting ESC guideline criteria for HFpEF). The search strategy may have failed to retrieve relevant studies, as grey literature or reports in languages other than English and Greek were not included. Time restrictions were applied, and the search was not extended to all available databases. In DMPs, blinding of the research team and participants is not feasible, which may bias results in favour of the intervention group. Caution should be used in the interpretation of findings and the results of the current review especially given the lack of data for appropriately defined HFpEF.

**Conclusions**

Varying definitions of HFpEF (including patients with HFmrEF) used in studies are a substantial limitation in interpretation of findings, which may not reflect the effect of DMPs in HFpEF patients. Although statistically significant or positive trends in the primary outcomes were found in mortality, hospitalization rates, self-care ability, HF knowledge, quality of life, anxiety, depression, and sleep, the evidence is not sufficiently robust or consistent to draw substantive conclusions. We have used programme components as a way of exploring how impact may have been attenuated. Given that patients with HFpEF are older and multi-morbid, DMPs targeting HFpEF should not rely on a single-disease focus but provide care that addresses predisposing and presentation phenotypes of well-defined HFpEF and draws on the principles of comprehensive geriatric assessment. Other components could also be more targeted to HFpEF such as modification of lifestyle factors for which there is emerging evidence, rather than simply continuing the model of care used in HFrEF. The reduced efficacy noted in contemporary HF DMP studies may not only be due to improvements in usual care but may reflect inclusion of heterogeneous patients with HFmrEF and HFpEF who may not respond in the same way as HFrEF to individual components. Based on current evidence, HF DMPs may improve mortality, hospitalization rates, self-care, and quality of life in patients with HFpEF; however, further research specifically tailored to appropriately defined HFpEF is required.

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**Conflict of interest**

None declared.
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