

# Effectiveness of comprehensive disease management programmes in improving clinical outcomes in heart failure patients. A meta-analysis

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## Abstract

**Background:** Disease management programmes (DMP) have been advocated to improve long term outcomes of heart failure (HF) patients.

**Aims:** To summarise the evidence supporting DMP effectiveness in improving HF clinical outcomes.

**Methods:** Eligible studies were located through a systematic literature search. Only randomised controlled trials (RCTs), enrolling HF patients, and allocating them to DMP or usual care (UC), were included. Information on study setting and design, participants' characteristics and interventions tested were collected. A study quality assessment was performed. Main clinical outcomes assessed were: all-cause mortality and (re)hospitalisations, HF-related (re)hospitalisations and mortality. Meta-analysis was performed according to both Yusuf–Peto method and random effects model.

**Results:** Thirty-three RCTs were included. Mortality was significantly reduced by DMP compared to UC: OR=0.80 (CI 0.69–0.93,  $p=0.003$ ). All-cause and HF-related hospitalisation rates were also significantly reduced: OR=0.76 (CI 0.69–0.94,  $p<0.00001$ ) and OR=0.58 (CI 0.50–0.67,  $p<0.00001$ ), respectively. Different DMP approaches appeared to be equally effective (sensitivity analyses).

**Conclusion:** DMP reduce mortality and hospitalisations in HF patients. Because various types of DMP appear to be similarly effective, the choice of a specific programme depends on local health services characteristics, patient population, and resources available.

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**Keywords:** Disease management programme; Heart failure; Hospitalisation; Mortality; Meta-analysis

## 1. Introduction

Heart failure (HF) is the leading cause of hospitalisation in many countries, and represents a huge economic burden [1]. About 40% of patients are readmitted within one year following their first hospital admission for HF [2–4]. Despite effective therapies, mortality for HF is still high, with 40% of patients dying within 4 years [3–5]. HF is predominantly a disease of the elderly: two thirds of patients admitted to hospital for HF are older than 65 years of age:

Patients frequently experience acute, recurrent episodes of decompensation, and are often affected by other significant co-morbidities [4,5], which lead to long, repeated hospitalisations [3,4].

The complexity of HF treatment has prompted the development and implementation of various disease management programmes (DMP) [6–8] in order to improve patients' long term outcomes. Several randomised controlled trials (RCTs) have compared DMP for HF to usual care. The results have been summarised in two previous meta-analyses, but these included a limited number of studies [9,10]. All-cause (re)hospitalisation rate was substantially reduced in patients allocated to DMP compared to usual care, but there appeared to be no effect on mortality, HF-related (re)hospitalisation, or length of hospital stay.

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We aimed to re-evaluate the evidence supporting the effectiveness of HF DM programmes in improving relevant clinical outcomes – mortality first – in a much larger sample of studies and patient populations. We also explored whether specific types of DMP, or different components, timing and duration of the programme, were likely to be most beneficial.

## 2. Methods

### 2.1. Literature search

RCTs were included if: (1) patients were enrolled with a diagnosis of HF, and were followed in an outpatient setting; (2) a comprehensive DMP was compared to usual care; (3) all-cause mortality and/or (re)hospitalisation rates, and HF-related (re)hospitalisation rates and/or HF-related mortality, were the outcomes assessed. Studies were excluded if the study population included patients with conditions other than HF, and if the data for those with HF could not be separated; the intervention tested was not a comprehensive programme; the comparison was between two “active” interventions without an usual care group; the study was performed in an inpatient setting only.

We developed a specific search strategy using a combination of keyword and free-text terms. The following text word terms and Medicine Subjects Headings (MeSH) were used: heart failure, congestive; disease management; case management; comprehensive health care; health services research; health services costs; home care services; clinical protocols; quality of health care; nurse-led clinics. Other key and text words were retrieved through the relevant articles. No language restriction was applied.

We searched the following databases in duplicate (R.R. and F.B.): PubMed — Medline and Pre-Medline (1980 — December 2004), EMBASE (1980 — December 2004); CINAHL (1982 — December 2004), the Cochrane Controlled Trial Registry (the “Central”, issue III 2004), and the Cochrane Effective Practice and Organisation of Care Study Registry. Internal medicine, cardiology and nursing journals from January 1990 to December 2004 were searched in printed or online editions by R.R. and F.B. All retrieved studies were carefully examined for references and related articles. We also used other sources, such as personal files on HF; contacts with experts of the disease and with the authors of retrieved articles, if deemed necessary to obtain study details. The authors of registered, but not yet published studies, or trials presented during scientific meetings as abstracts, were also contacted.

Study screening and assessment for eligibility was done in duplicate (by R.R. and F.B.), using standard forms. Agreement between the two screeners was calculated as percentage agreement and Cohen’s kappa, and disagreements were resolved by consensus.

Information on study setting and design, characteristics of trial participants, programme characteristics: time of initiation (in hospital, at discharge, after discharge, or in outpatient setting), type of intervention (educational, phone contacts, nurse visits, nurse and physician visits, nurse and pharmacist check-ups, multidisciplinary teams), duration of the intervention, patients’ compliance to intervention, were collected.

### 2.2. Study quality assessment

The quality of each study was evaluated according to the “component approach” [11], examining: (a) randomisation procedure (random sequence generation and allocation concealment) adequacy, (b) blinding of outcome assessors, (c) follow up completeness, and (d) intention-to-treat analysis. A sensitivity analysis [11] was performed, stratifying trials for the quality components considered: if all of them were present in a study, the study was deemed of “high” quality; otherwise, it was judged as being “not high”.

### 2.3. Statistical analysis

Our main outcomes were all-cause mortality and all-cause (re)hospitalisation rate, measured as number of patients ( $n$ ) allocated to intervention or usual care arms experiencing the outcome of interest at least once, over the total number of patients randomised to that arm ( $N$ ). Similarly, HF-related (re)hospitalisation rate and HF-related mortality (secondary outcomes) were measured as  $n$  of patients in the intervention or usual care groups experiencing the outcome at least once, over total  $N$  of patients allocated to that group. Hence, each patient could contribute to one event only for all these outcomes.

The pooled effect estimates for binary variables were expressed as odds ratio (OR) and risk ratio (RR); 95% confidence intervals (CI) were calculated, and the analysis was performed according to the Yusuf–Peto’s method and random effects model (DerSimonian and Laird). For continuous variables, such as length of hospital stay and total number of days spent in hospital, we calculated means and standard deviations, and combined them in a weighted mean difference (WMD) [12].

We used the software RevMan 4.2.7 statistical package (Review Manager version 4.2.7, May 2004; [www.cochrane.org](http://www.cochrane.org)).

Statistical heterogeneity in each outcome considered was evaluated applying the Cochran  $Q$  test [12], considering a  $p$  value  $<0.05$  as statistically significant. Sensitivity analyses were performed to test differences in interventions, duration of follow up, year of publication and study country, as possible source of heterogeneity.

The presence of publication and other biases was assessed by means of funnel plots [13].

### 3. Results

#### 3.1. Literature search

Our search strategy located 804 titles, of which 750 were deemed ineligible on the basis of title and abstract, and 54 were retrieved as full text (Fig. 1). Thirty-three out of 54 met the eligibility criteria, and were included in the analysis [14–46]. The remaining 21 trials (list available on request) were excluded for various reasons: they were not original papers (1 study), were sub-study reports ( $n=7$ ); failed to provide separate data for HF patients ( $n=4$ ); the intervention was not a comprehensive DMP ( $n=2$ ), the study compared two active interventions ( $n=2$ ), or they did not measure outcomes we were interested in ( $n=2$ ). One study was completed in the 1960s, and was excluded because the study population, co-interventions and the patient characteristics are likely to have been very different from recent trials. Another study was excluded because it utilised a cluster randomisation design, with hospitals as the units of randomisation, and the intervention was mostly delivered in an inpatient setting. A third study randomised nurses to provide DMP or usual care to HF patients: nurses were therefore the units of randomisation.

The percentage agreement for study screening and eligibility between two reviewers (R.R. and F.B.) was 80%; kappa was 0.83 (CI 0.61–1.00).

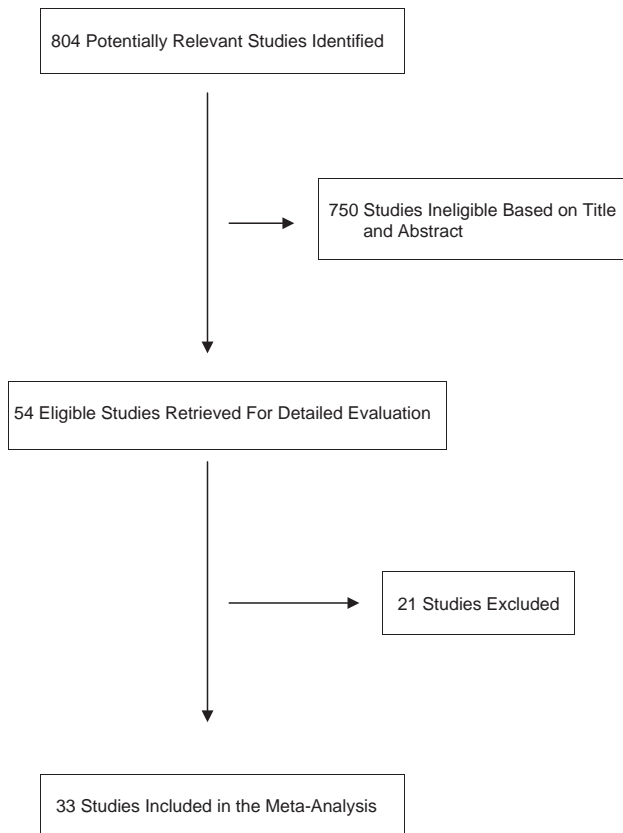


Fig. 1. Flow diagram of study inclusion and exclusion process.

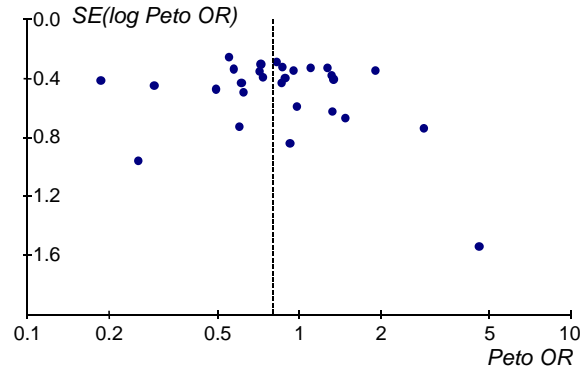


Fig. 2. Funnel plot of included studies, constructed around the common effect estimate of all-cause mortality. OR calculated with the YusufPeto method. The individual data points represent the included studies; the vertical line indicates the common effect estimate.

The possible presence of publication and other biases in the literature search was explored with funnel plots constructed around the combined effect estimate for all-cause mortality (main outcome). The graph showed a fairly symmetrical distribution of the included studies around the pooled effect estimate, indicating little evidence of publication bias (Fig. 2).

#### 3.2. Study characteristics

Table 1 summarises the characteristics of the included studies. They were published between 1993 and 2004; 15 trials were performed in the US, 12 in Europe, 2 in Australia, two in Canada and one each in New Zealand and Argentina. Most studies were performed in academic centres or tertiary referral hospitals; several, however, involved community hospitals or primary care physicians [17,26,29,34,37–40,42,44–46].

The majority of patients were older than 65 years (73 years on average), women were well represented (58%), and 75% of patients were whites. The diagnosis of HF was usually based on typical symptoms and clinical and radiological signs of pulmonary congestion. Only in the most recent trials was the presence of left ventricular systolic dysfunction on echocardiography required for a patient to be included in the study [16,20,22,23,30–32,34–36,41,44,46]. Many trials enrolled patients with New York Heart Association (NYHA) functional class III and IV symptoms [19–24,26,27,29,31–33,36–38,41], who were at high risk for re-hospitalisation for HF or other chronic conditions. However, only two studies [14,16] explicitly excluded low risk patients.

DMP interventions varied widely: (1) multidisciplinary approach ( $N_o.$  of trials=7) [14,16,31,32,34,35,41], as defined by the primary investigators, always started during the index hospitalisation, carried out for 2–12 weeks up to one year after discharge, and delivered by various health professionals, (2) interventions centred on specific health professionals, usually HF specialist nurses (but also case

Table 1  
Characteristics of included studies

Study	Participants	DMP characteristics	FU duration (months)
Atienza, 2004 [41]	Setting: Spain, academic centre; 338 pts; age 59–74 yrs; 50% NYHA class III–IV	Multidisciplinary, in hospital→1 year (education, discharge plan, pre-planned outpatient clinic visits)	22
Blue, 2001 [27]	Setting: UK, academic centre; 165 pts; age 75 (8) yrs; >70% NYHA class III–IV	Nurse-led, post discharge→1 year (home visits, phone calls)	12
Bouvy, 2003 [39]	Setting: The Netherlands; 152 pts; age 70 (10) yrs; >40% NYHA class III–IV	Pharmacist-led, after discharge→6 months (drug education and counselling)	6
Capomolla, 2002 [35]	Setting: Italy, tertiary care centre; 234 pts; age 56 (10) yrs; 35% class III–IV	Multidisciplinary, post-discharge→1 year (risk stratification, therapy optimisation, clinical visits+phone calls)	12
Cline, 1998 [20]	Setting: Sweden, academic centre; 206 pts; age 75 (5) yrs; 62% NYHA class III	Nurse-led, in hospital→8 months (clinical visits, phone calls)	12
DeBusk, 2004 [45]	Setting: US, community hospitals; 462 pts; age 72 (11) yrs; 50% class III–IV	Nurse-led, in hospital→1 year (education, therapy counselling, medical advice)	12
Dial, 2003 [42]	Setting: Argentina, academic and community hospitals; 1518 pts; age 65 (12) yrs; 52% NYHA class I–II	Nurse-led, telephone intervention, after discharge→1 year (education, therapy counselling, clinical status monitoring)	14
Doughty, 2002 [31]	Setting: New Zealand, academic centre; 197 pts; age 73 (11) yrs; all NYHA class III–IV	Multidisciplinary, after discharge→6 months (education, clinical visits, phone calls)	12
Ekman, 1998 [19]	Setting: Sweden, academic centre; 158 pts; age >65 yrs; NYHA class III–IV	Nurse-led, post discharge→6 months (education and counselling)	6
Harrison, 2002 [33]	Setting: Canada, academic centre; 157 pts; age 75 (9) yrs; 77% NYHA class III–IV	Nurse-led, in hospital→3 months (education, counselling, home visits)	3
Jaarsma, 1999 [21]	Setting: The Netherlands, academic centre; 179 pts; age >50 yrs	Nurse-led, in hospital→10 days (1 home visit only)	9
Jerant, 2001 [28]	Setting: US, academic centre; 37 pts; age >40 yrs; >30% NYHA class III–IV	Nurse-led, post-discharge→2 months (phone consultations+home telemonitoring devices)	6
Kasper, 2002 [32]	Setting: US, academic centre; 200 pts; age 60 (14) yrs; 60% class III	Multidisciplinary, after discharge→6 months (clinical visits by nurses and cardiologist, nurse home visits)	6
Krumholtz, 2002 [30]	Setting: US, academic centre; 88 pts; age 72 (10) yrs	Nurse-led, post discharge→1 year (educational sessions; phone calls for further education and medical advice)	12
Laramee, 2003 [37]	Setting: US, academic and community centres; 256 pts; age 78 (12) yrs; 38% NYHA class III–IV	Case manager-led, in hospital→3 months (discharge planning, clinical visits, phone calls)	3
McDonald, 2002 [34]	Setting: Ireland, academic centre; 98 pts; age 71 (10) yrs; all NYHA classes	Multidisciplinary, in hospital→3 months (therapy optimisation, outpatient clinic visits, phone calls)	3
Mejhert, 2004 [44]	Setting: Sweden, secondary referral centre; 208 pts; age 76 (7) yrs; 62% NYHA class II	Nurse-led, after discharge→18 months (education, medical advice, clinical status monitoring)	
Naylor, 1994 [15]	Setting: US, academic centre; 142 pts; age >65 yrs	Nurse-led, in hospital→2 weeks (discharge planning phone calls)	3
Naylor, 1999 [24]	Setting: US, academic centre; 108 pts; age >65 yrs	Nurse-led, in hospital→4 weeks (discharge plan; 2 home visits, phone calls)	6
Naylor, 2004 [40]	Setting: US, academic centre; 239 pts; age >65 yrs	Nurse-led, in hospital→3 months (discharge plan, education, counselling, frequent home visits)	12
Pharm, 1999 [22]	Setting: US, university hospital; 181 pts; age >55 yrs; >50% NYHA class II	Pharmacist-led, post discharge→6 months (clinical assessment, therapy optimisation, visits+phone calls)	6
Pugh, 2001 [29]	Setting: US, academic centre; 58 pts; age 74.4 (6.8) yrs; NYHA class III–IV	Case manager-led, in hospital→6 months (discharge planning, clinical visits, phone calls)	6
Rainville, 1999 [25]	Setting: US, university hospital; 34 pts; age 69 (9.7) yrs; 68% NYHA class III	Pharmacist and nurse-led, at discharge→6 months (discharge planning, 2 phone calls, further contact only if needed)	12
React, 2004 [46]	Setting: Canada, academic and urban hospitals; 276 pts; age 74 (12) yrs; 57% NYHA class I–II	Pharmacist/nurse-led, at discharge→6 months (education, therapy counselling)	
Rich, 1993 [14]	Setting: US, university centre; 98 pts; at high and intermediate risk of re-hospitalisation	Multidisciplinary, in hospital→3 months (education, medical advice, close follow up)	3
Rich, 1995 [16]	Setting: US, academic centre; 282 pts; NYHA class II–III	Multidisciplinary, in hospital→3 months (counselling, frequent home visits, phone calls)	3
Riegel, 2002 [36]	Setting: US, academic centre; 358 pts; age 72 (12) yrs; 97% NYHA class III–IV (62% class IV)	Case manager, in-hospital→6 months (education, medical advice; phone calls)	6

Table 1 (continued)

Study	Participants	DMP characteristics	FU duration (months)
Stewart, 1998 [18]	Setting: Australia, academic centre; 97 pts; age 35–91yrs	Nurse-led, at discharge→1 week (1 home visit only by pharmacist and nurse)	6
Stewart, 1999 [23]	Setting: Australia, academic centre; 200 pts; age >55 yrs	Nurse-led, at discharge→2 weeks (1 home visit only; phone calls for further visits, if needed)	6
Stromberg, 2003 [38]	Setting: Sweden, academic centre; 106 pts; age 77 (7) yrs; 80% NYHA class III–IV	Nurse-led, at discharge→3 weeks (1 visit only at the outpatient clinic; phone calls thereafter, if pt stable)	12
Trochu, 2005 [43]	Setting: France, university centre; 202 pts; age 77 (10) yrs	Multidisciplinary, in hospital→1 year (education, home visits and phone contacts, psychological support)	12
Varma, 1999 [26]	Setting: UK, academic hospital; 83 pts; age 75.5 (5.6) yrs; 60% NYHA class III–IV	Pharmacist-led, at discharge→1 year (therapy optimisation, pharmacist or outpatient clinic visits)	12
Weinberger, 1996 [17]	Setting: US, tertiary and community hospitals; 504 pts; age >50 yrs	Nurse-led, in hospital→6 months (discharge plan, follow up by family physicians, 3 planned nurse phone calls)	6

Pts: patients.

Age: mean (standard deviation), in years, when available.

NYHA: New York Heart Association.

managers, or pharmacists), focused on some components of care, such as patient and family education [20,21,30,33,46], or improvement in patient adherence to drug therapy [21,24,25,38,46]. The intervention could be initiated in hospital, at discharge, or immediately afterwards. It could last from a few weeks to one year, and could consist of a series of planned home/outpatient clinic visits supplemented by regular phone contacts [19,20,22,26–30,33,36,37,39,45,46], or 1–2 home/outpatient visits by the specialist nurse

or pharmacist, and, in case of need, phone calls [15,17,18,21,23–25,38,44].

Usual care (UC) was less defined and only briefly described, or not described at all, by the investigators. Patients allocated to usual care were generally referred to their family physicians and home care nurses, or other home care services, after discharge following the index hospitalisation.

Patients were followed for 3 to 22 months (average of 6 months).

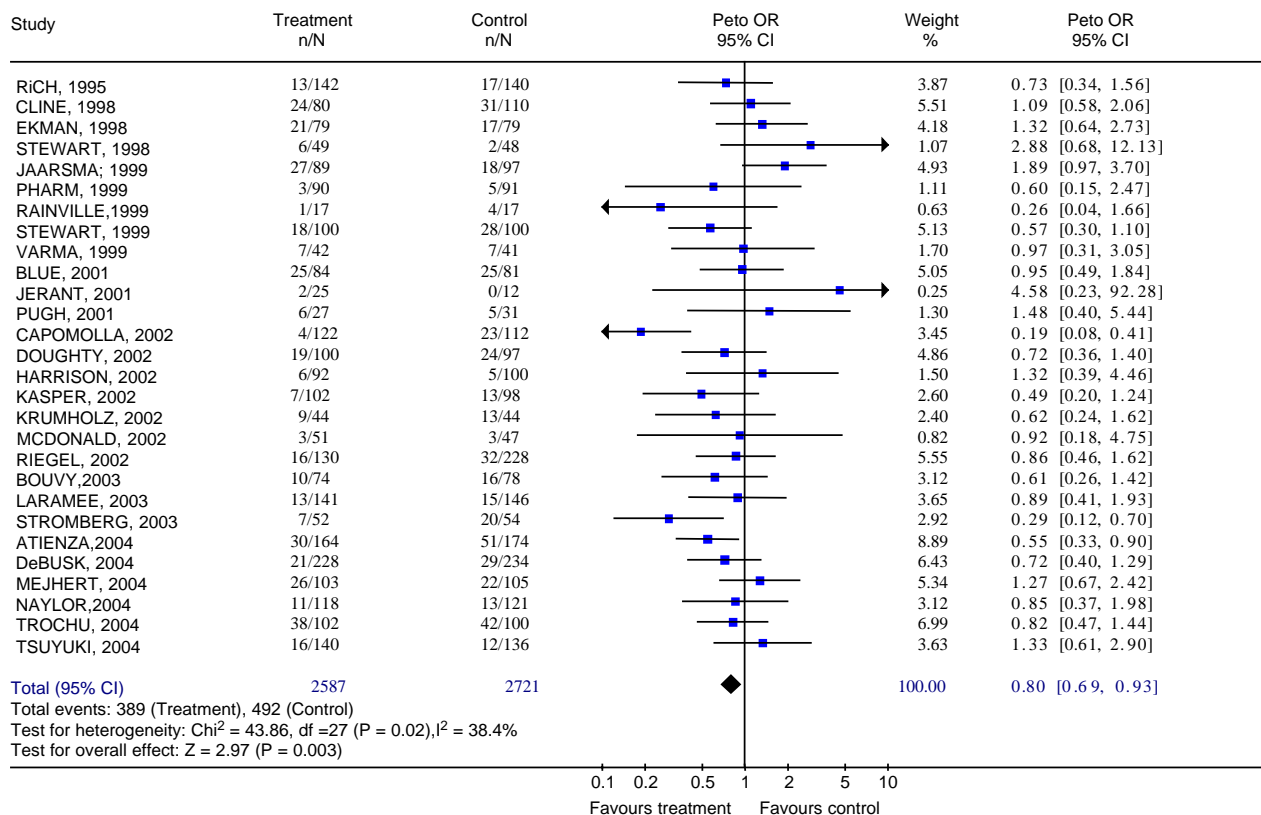


Fig. 3. All-cause mortality. OR calculated with the Yusuf-Peto method. n: number of patients experiencing the outcome of interest in the DMP (treatment) group or in the usual care (control) group. N: total number of patients allocated to treatment (DMP) or to control (usual care) group.

### 3.3. Quality assessment

Twelve out of 33 study reports [17–20,24,25,30,33,34,39,41,45] provided enough details on randomisation procedure to be judged as adequate. As expected, due to the nature of intervention, blinding was not feasible. Patients were masked regarding which group they had been allocated to in 3 studies only [17,22,37]; care providers and outcome assessors were blinded in 8 trials [17,23,24,28,31,33,41,45]. All but one [23] studies achieved more than 75% complete follow up. Eighteen studies [17–20,24,25,28,29,31–35,39–42,45] performed an intention-to-treat analysis, as stated by the investigators. According to the quality criteria chosen, 10 out of 33 trials were deemed to be of “high” quality [17,19,23,24,28,29,33,39,41,45].

### 3.4. Main analysis

#### 3.4.1. All-cause mortality rate

Twenty eight studies [16–23,25–46] provided data on mortality (total  $N_o.$  of patients 5308, total  $N_o.$  of events 881) (Fig. 3). Only 3 studies [35,38,41] found a statistically significant reduction in death rate in patients allocated to the intervention group compared to usual care. The pooled OR (Yusuf–Peto method) was 0.80 (CI 0.69–0.93,  $p=0.003$ ) with some degree of heterogeneity ( $\chi^2_{27}=43.86$ ,

$p=0.02$ ), which was totally accounted for by one study only [35]. It did not appear to be different from the other trials with respect to design, patients enrolled, type of intervention.

The combined RR was 0.84 (CI 0.74–0.94;  $p=0.003$ , no heterogeneity); the pooled OR calculated with the random effect was 0.81 (CI 0.67–0.98,  $p=0.03$ , test for heterogeneity:  $\chi^2_{27}=40.20$ ,  $p=0.05$ ).

#### 3.4.2. All-cause (re)hospitalisation rates

In 32 studies [14–38,40–45], which reported all-cause (re)hospitalisation rates in 7387 patients, there were 3220 events (Fig. 4). Seven trials [20,29,30,34,38,39,41] found a significant reduction in (re)hospitalisation rates in patients allocated to the intervention group compared to usual care. Only one study [17], which was directed at facilitating patients’ access to primary care, found an increased rate of hospital (re)admissions following the intervention. The combined OR (Yusuf–Peto method) was 0.76 (CI 0.69–0.94,  $p<0.00001$ ) with a significant degree of heterogeneity ( $\chi^2_{31}=71.01$ ,  $p<0.00001$ ); the pooled RR was 0.86 (CI 0.82–0.91,  $p<0.00001$ ); the random effect OR was 0.70 (CI 0.60–0.82,  $p<0.00001$ ), both highly heterogeneous. Most of the observed heterogeneity was attributable to a single study [17]: when excluded, heterogeneity was substantially reduced ( $p<0.04$ ).

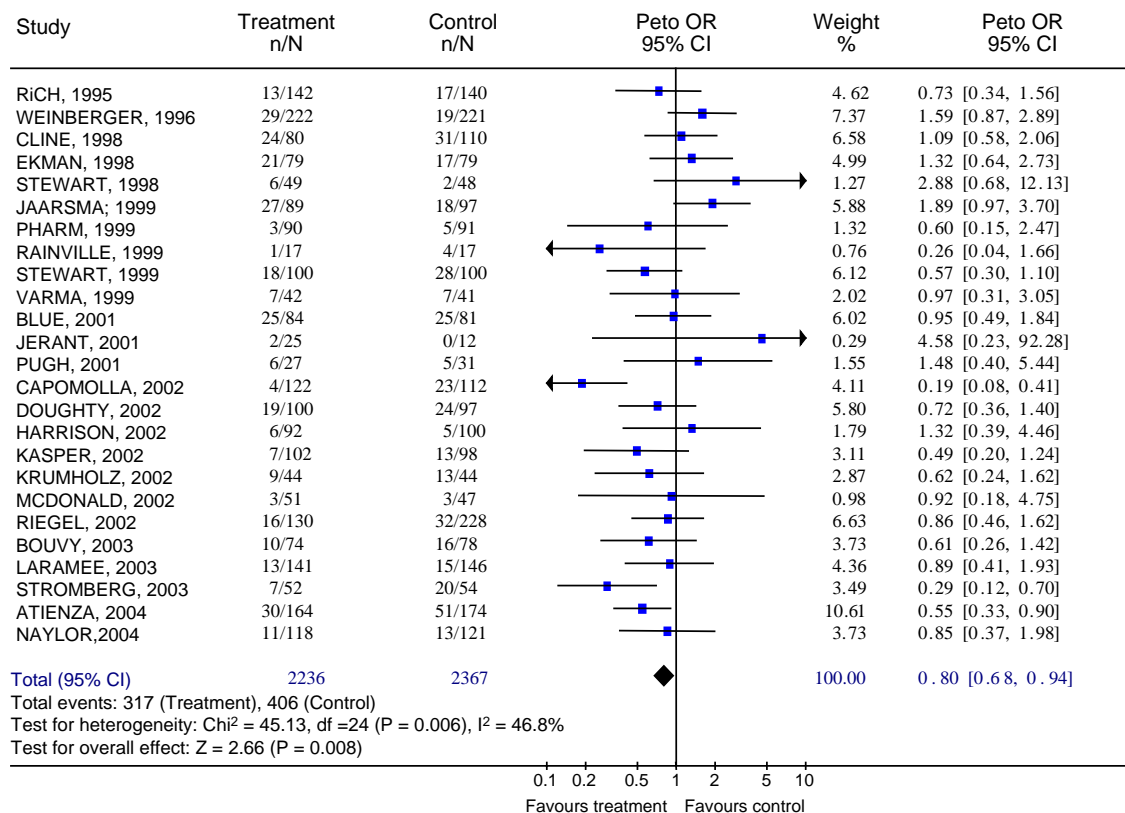


Fig. 4. All-cause (re)hospitalisation rate. OR calculated with the Yusuf–Peto method.  $n$ : number of patients experiencing the outcome of interest in the treatment (DMP) or in the control (usual care) group.  $N$ : total number of patients allocated to DMP (treatment) or usual care (control).

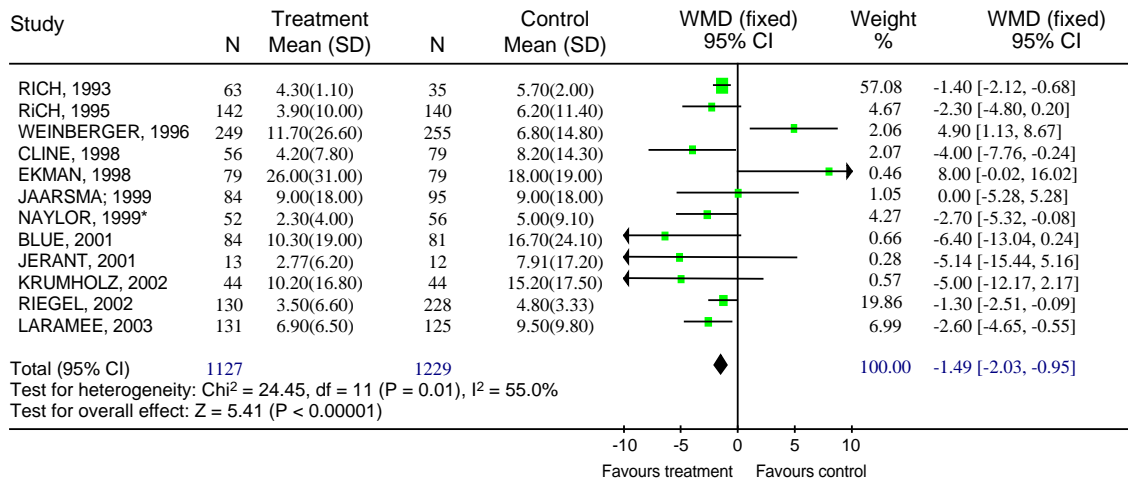


Fig. 5. Total number of days spent in hospital for any reason during follow up. WMD, weight mean difference, calculated with the fixed method. *n* and *N*: see legend of previous figures.

HF-specific (re)hospitalisation rates were assessed in 20 studies [19–33,36–38,41,43,45,46] ( $N_o$ . of patients=3817,  $N_o$ . of events=1060). Eight trials [22,23,27,30,34,36,43] showed a statistically significant reduction in the intervention group compared to usual care; none demonstrated an increase. The combined OR (Yusuf–Peto method) was 0.58 (CI 0.50–0.67,  $p < 0.00001$ ). Again the test for heterogeneity was statistically significant ( $\chi^2_{19} = 39.82$ ,  $p < 0.003$ ), without identifying any study as the likely source of heterogeneity. The combined RR was 0.69 (CI 0.63–0.77,  $p < 0.00001$ , no heterogeneity) and the random effect OR was 0.56 (CI 0.45–0.71,  $p < 0.00001$ , with some degree of heterogeneity).

Seven studies [16,22,28,37,40,41,45] reported data on (re)hospitalisation rates for conditions other than HF. None demonstrated a statistically significant reduction in this outcome in the intervention group compared to usual care. The combined OR was 1.06 (CI 0.84–1.34).

Data on HF-specific mortality rate as available in 4 trials only [21,22,35,38]. There was a statistically significant reduction in the intervention group compared to usual care ( $N_o$ . of patients=700; OR 0.37, CI 0.21–0.73,  $p < 0.0002$ ) with no heterogeneity. This OR value was much lower than the pooled OR computed on all studies

reporting mortality data (see above). However the data were so sparse that the combined results should be deemed unreliable.

3.5. Other outcomes

The total number of days spent in hospital for any cause during the follow up after the index hospitalisation (measured as mean±standard deviation) was significantly reduced in the intervention group compared to usual care: WMD=−1.49, CI −2.03 to −0.95,  $p < 0.00001$  (12 studies,  $N_o$ . of patients=2356) (Fig. 5, Table 2). The number of days in hospital for worsening HF, the length of hospital stay during hospital re-admissions (for any cause and for worsening HF), the total number of all-cause and HF-related multiple re-admissions were similarly reduced in the intervention arm compared to usual care (Table 2). The data, i.e. number of patients and number of events, were however relatively few, and any combined analysis results may be somewhat unreliable.

Several studies ( $N_o$ .=11;  $N_o$ . of patients=2038) [23,24,26,31,35,36,37,40,41,44–46] assessed the use of angiotensin converting enzyme inhibitors (ACE-I) at base-

Table 2  
Other clinically relevant outcomes

Outcome	$N_o$ studies	$N_o$ pts	OR	CI	WMD	CI
$N_o$ days in hospital (all-cause)	12	2356			−1.49	−2.03 to −0.95
$N_o$ days in hospital (HF-related)	5	815			−1.25	−1.99 to −0.50 •
Length of hospital stay	4	582			−1.89	−2.81 to −0.97
$N_o$ multiple hospital re-admissions (all-cause)	6	1590	0.51	0.40–0.86		
$N_o$ multiple hospital re-admissions (HF-related)	5	1256	0.65	0.51–0.83		

$N_o$ : total number.

OR: odds ratio (calculated with the Yusuf–Peto method).

CI: 95% confidence intervals.

WMD: weight mean difference.

•: no heterogeneity.

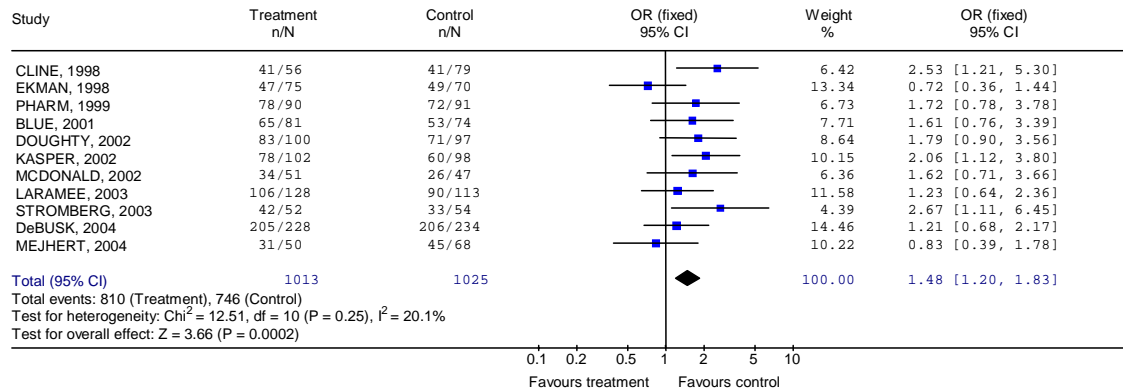


Fig. 6. Proportion of patients on ACE-I therapy at the end of follow up in the two allocation groups. OR calculated with the Yusuf–Peto method. *n* and *N*: see legends of previous figures.

line and at the end of follow up, both in term of proportion of patients receiving these drugs, and of recommended doses. Pre- and post-intervention comparisons and between-group comparisons were performed. The adequacy of the drug regimen compared to that recommended by guidelines, or tested in RCTs, was evaluated in very different ways, so that it was not possible to identify a common effect measure to be combined in the analysis. As for the proportion of patients receiving any ACE-I at the end of follow up, all studies showed a significantly higher proportion of patients on ACE-I in the usual care group compared to the intervention group, with no heterogeneity: OR=1.48 (CI 1.20–1.83) (Fig. 6).

It was not possible to analyse beta-adrenoceptor blocker use in a reliable way, as data were only available in three studies [20,37,42].

### 3.6. Sensitivity analyses

Overall, similar results for the main outcomes of interest (mortality, all-cause and HF-related (re)hospitalisation rates) were observed across several sensitivity analyses performed according to pre-defined hypotheses (Table 3). In particular, “high quality” studies and programmes lasting 3–6 months were those most consistently associated with a significant reduction in all outcomes considered.

Table 3  
Sensitivity analysis results

Sensitivity analysis	Mortality		All-cause readmission rate		HF-related readmission rate	
	OR	CI	OR	CI	OR	CI
High quality studies	0.70 ( <i>N<sub>o.</sub></i> = 10)	0.53–0.91 •	0.75 ( <i>N<sub>o.</sub></i> = 10)	0.63–0.80 •	0.58 ( <i>N<sub>o.</sub></i> = 8)	0.45–0.75 •
Low quality studies	0.85 ( <i>N<sub>o.</sub></i> = 20)	0.71–1.03	0.75 ( <i>N<sub>o.</sub></i> = 20)	0.66–0.86	0.58 ( <i>N<sub>o.</sub></i> = 11)	0.46–0.70
Multidisciplinary	0.58 ( <i>N<sub>o.</sub></i> = 7)	0.44–0.75 •	0.58 ( <i>N<sub>o.</sub></i> = 8)	0.47–0.71	0.51 ( <i>N<sub>o.</sub></i> = 5)	0.39–0.66 •
Nurse	0.93 ( <i>N<sub>o.</sub></i> = 21)	0.77–1.11 •	0.82 ( <i>N<sub>o.</sub></i> = 24)	0.74–0.91	0.61 ( <i>N<sub>o.</sub></i> = 15)	0.51–0.73
Short intervention (0–3 months)	0.88 ( <i>N<sub>o.</sub></i> = 10)	0.66–1.16	0.61 ( <i>N<sub>o.</sub></i> = 13)	0.51–0.74 •	0.61 ( <i>N<sub>o.</sub></i> = 7)	0.46–0.82 •
Medium intervention (3–6 months)	0.84 ( <i>N<sub>o.</sub></i> = 9)	0.63–1.12 •	1.05 ( <i>N<sub>o.</sub></i> = 9)	0.88–1.26 •	0.68 ( <i>N<sub>o.</sub></i> = 7)	0.53–0.86 •
Long intervention (>6 months)	0.73 ( <i>N<sub>o.</sub></i> = 10)	0.59–0.91	0.71 ( <i>N<sub>o.</sub></i> = 10)	0.62–0.82	0.47 ( <i>N<sub>o.</sub></i> = 5)	0.37–0.61

OR and CI: odds ratio and 95% confidence intervals for the outcome considered (Yusuf–Peto method).

Multidisciplinary, nurse: types of disease management programmes.

Short, medium, long intervention: disease management programme duration.

*N<sub>o.</sub>*: total number of studies in each subgroup.

•: no heterogeneity.

Nurse-led interventions did not appear to affect all-cause mortality (21 trials,  $N_o.$  of patients=3757, OR=0.93, CI 0.77–1.11, no heterogeneity).

### 3.7. Quality of life

Several investigators evaluated quality of life (QOL) as an outcome [14,15,17,18,21,23,26,28,29,31,32,35,39–41,44]. Different scales were used, principally The Minnesota Living With Heart Failure Questionnaire, and/or the Short Form-36 Questionnaire. In some studies the results were presented as mean scores with standard deviations, in others as median scores with range. It was therefore not possible to combine them in a summary measure. Eight studies [14,15,28,31,33,40,41] reported statistically significant differences (improvement) in QOL scores, both between the two allocation groups, and before and after the intervention. Four investigators found discordant results: QOL improvement in the short term (within 6 months), but not at the end of the follow up (one year) [23,26,40], or improvement in some QOL components (symptoms, distress), but not in others (functional and psychological components) [21]. Finally, 4 studies [17,29,39,44] did not report any statistically significant differences between the two groups of patients and/or between pre- and post-intervention period.

## 4. Discussion

### 4.1. Main findings

Our meta-analysis confirms, extends, and updates findings previously published [9,10] — that comprehensive DM programmes for HF are effective in reducing (re)hospitalisation rates for all causes and for worsening HF. Unlike previous analyses [9,10], which included fewer studies and patients, we have also demonstrated a statistically and clinically significant risk reduction of 16% in total mortality. This translates into one life saved for 34 patients treated, and compares quite favourably with those reported for various pharmacological treatments widely applied in clinical practice [47]. There was a high proportion of elderly patients (60% of the total sample), patients in NYHA class III–IV (45%), and patients with an ejection fraction <0.35 (39%). The observed control event rate (18%), however, was quite similar to that reported in less selected patient populations in several epidemiological studies [2,48,49]. In these types of patients, 90% of the deaths are attributable to cardiovascular causes, and about 30% to progressive heart failure [50]. Therefore, even if DMP were effective in reducing HF-related mortality only, this would be expected to translate into an overall benefit.

We found a substantial reduction in the rates of all-cause hospital re-admissions (14%), and HF-related (re)hospitalisations (31%), which was highly significant, and comparable in magnitude with those demonstrated with the use of

ACE-inhibitors and beta-blockers in HF patients [51,52]. Other clinically important outcomes, which are considered useful markers of HF burden on health care systems [53,54] — cumulative number of days spent in hospital during follow up, length of hospital stay during subsequent re-admissions, and total number of multiple (re)hospitalisations — were all reduced by these strategies. Patients allocated to the intervention group were not only re-admitted less frequently, but spent less and less time in hospital.

The results on quality of life were less conclusive, partly because of the relatively small sample size of the trials evaluating this outcome, and partly because of the different measurement tools used. However, an improvement in at least some QOL components was observed by several investigators, and none reported a deterioration in the patients allocated to intervention compared to usual care.

Eleven trials reported data on ACE-inhibitor therapy. The number of patients receiving these drugs at the end of follow up was surprisingly higher — and statistically different — in the usual care than in the intervention group. It should be noted that three studies [27,34,46] randomised patients to intervention or usual care only after optimisation of ACE-I treatment, hence no further increase in ACE-I use might be expected. In other trials, patients allocated to usual care might have been prescribed ACE-I by their own physicians, aware of their participation in a HF management trial and their allocation to the control group. In this regard, it was not possible to analyse beta-adrenoceptor blocker use in a reliable way, as data were only available in three studies [20,37,42].

### 4.2. Heterogeneity and sensitivity analyses

A certain degree of heterogeneity was present in the main analyses, depending on the summary measure or the pooling method used. It was expected because of the various types of interventions examined, and was explored through sensitivity analyses according to a priori defined hypotheses (differences in study quality, intervention main characteristics, length of follow up, year of publication, etc.). A relevant component of the observed heterogeneity was identified in the study quality, as “high quality” trials formed a homogeneous group of studies, which appeared to be significantly and consistently associated with a reduction in all outcomes considered. This finding stresses the importance of assessing primary study quality when performing a meta-analysis.

Multidisciplinary programmes and interventions of medium duration (3–6 months) appeared to be more consistently associated with a beneficial effect on mortality and HF-related (re)hospitalisation rates than nurse-led interventions and short (less than 3 months) or long (more than 6 months) duration programmes.

Usual care (the comparator) was poorly defined and described, or not described at all, by most investigators. This represents a limitation of the studies included in our

analysis, and may be a source of heterogeneity: usual care varied from simple referral to specialist follow up in academic centres. In the first case, any type of structured disease management programme would appear more effective in improving HF clinical outcomes; in the latter, it might be quite difficult to observe a difference, if any.

Residual heterogeneity, if present, was difficult to explain on clinical grounds, and might be due to the play of chance.

#### 4.3. Strengths and limitations

The use of multiple data bases, without any language restriction, and the development of a specific search strategy allowed for a large number of citations to be retrieved. Contacts with experts provided the opportunity to include studies not otherwise located, helping minimise publication and other biases. The literature search was continuously updated while the review was in progress.

The presence of publication and other biases was assessed with funnel plots [13]. Empirical studies [13,55] have demonstrated funnel plot results are fairly consistent with those derived from various statistical tests. In our meta-analysis, the funnel plot constructed around the common effect estimate for all-cause mortality was quite symmetric, indicating the likely absence of publication bias.

Some authors have raised concerns that these management strategies, while aimed to improve HF clinical course, may impair the provision of other medical care and necessary medications [9]. We chose all-cause mortality and all-cause (re)hospitalisation rate as our primary outcomes for this very reason.

It was not possible to demonstrate whether DM programmes for HF were effective in all clinical settings, because most studies included were performed in academic, tertiary, or urban hospital centres. We were unable to obtain individual patient data, which could have allowed us to identify which type of HF patients may benefit mostly from these strategies, regardless of the degree of disease severity, the presence of multiple co-morbidities, and a previous history of frequent hospital re-admissions.

While preparing our manuscript for submission, another meta-analysis on the same topic has been published by McAlister et al. [56]. Our results are relatively similar, although their analysis was performed grouping studies according to four different types of intervention. We identified only two types of intervention, broadly categorised as “multidisciplinary” and “nurse-led” interventions, according to the definition provided by the primary investigators themselves in their published reports. We preferred to perform sensitivity analyses based on some objective criteria differentiating the various types of programmes, such as intervention duration, or length of follow up. Overall, similar results for the main outcomes of interest (mortality, all-cause and HF-related (re)hospitalisation rates) were observed across the various groups of studies so identified.

## 5. Conclusions

Comprehensive DM programmes for HF patients reduce mortality and hospitalisations, may improve quality of life, and are potentially cost-saving, in moderate to high risk populations.

Ongoing [57] and future trials assessing the relative effectiveness of different types of intervention will provide answers about which programmes to adopt in practice. The final choice will rest on a careful evaluation of the characteristics of the local health services, patient population, barriers to the access to optimal medical care, human and financial resources.

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