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Original article

Effectiveness and Factors Determining the Success of Management Programs for Patients With Heart Failure: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction and objectives: Heart failure management programs reduce hospitalizations. Some studies also show reduced mortality. The determinants of program success are unknown. The aim of the present study was to update our understanding of the reductions in mortality and readmissions produced by these programs, elucidate their components, and identify the factors determining program success.
Methods: Systematic literature review (1990-2014; PubMed, EMBASE, CINAHL, Cochrane Library) and manual search of relevant journals. The studies were selected by 3 independent reviewers. Methodological quality was evaluated in a blinded manner by an external researcher (Jadad scale). These results were pooled using random effects models. Heterogeneity was evaluated with the I^2 statistic, and its explanatory factors were determined using metaregression analysis.
Results: Of the 3914 studies identified, 66 randomized controlled clinical trials were selected (18 countries, 13 535 patients). We determined the relative risks to be 0.88 for death (95% confidence interval [95%CI], 0.81-0.96; $P < .002$; I^2, 6.1%), 0.92 for all-cause readmissions (95%CI, 0.86-0.98; $P < .011$; I^2, 58.7%), and 0.80 for heart failure readmissions (95%CI, 0.71-0.90; $P < .0001$; I^2, 52.7%). Factors associated with program success were implementation after 2001, program location outside the United States, greater baseline use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, a higher number of intervention team members and components, specialized heart failure cardiologists and nurses, protocol-driven education and its assessment, self-monitoring of signs and symptoms, detection of deterioration, flexible diuretic regimen, early care-seeking among patients and prompt health care response, psychosocial intervention, professional coordination, and program duration.
Conclusions: We confirm the reductions in mortality and readmissions with heart failure management programs. Their success is associated with various structural and intervention variables.

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Efectividad y determinantes del éxito de los programas de atención a pacientes con insuficiencia cardiaca: revisión sistemática y metanálisis

Palabras clave:
Insuficiencia cardiaca (tratamiento)
Programas de atención a la insuficiencia cardiaca (resultados)
Metanálisis
Equipo de trabajo
Organización
Método de provisión de cuidados

RESUMEN

Introducción y objetivos: Los programas de atención a pacientes de insuficiencia cardiaca reducen ingresos hospitalarios. Algunos estudios reducen mortalidad. Se desconocen los determinantes del éxito. El objetivo es actualizar el conocimiento sobre la reducción de mortalidad y reingresos de estos programas, describir sus componentes e identificar factores condicionantes de resultados.
Métodos: Revisión sistemática de la bibliografía (1990-2014) (PubMed, EMBASE, CINAHL, Cochrane Library) y búsqueda manual en revistas relevantes. Tres revisores independientes seleccionaron los estudios. La calidad metodológica fue evaluada a ciegas por una investigadora externa (escala Jadad). Los resultados se combinaron mediante modelos de efectos aleatorios. La heterogeneidad se evaluó con el estadístico I^2, y se determinaron sus factores explicativos mediante análisis de metarregresión.
Resultados: Se identificaron 3.914 estudios. Se seleccionaron 66 ensayos clínicos controlados y aleatorizados (18 países, 13.535 pacientes), y se observaron riesgos relativos de muerte de 0,88 (intervalo de confianza del 95% [IC95%], 0,81-0,96; $p < 0,002$; I^2, 6,1%), reingresos por todas las causas de

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0,92 (IC95%, 0,86-0,98; $p < 0,011$; I^2, 58,7%) y reingresos por insuficiencia cardiaca de 0,80 (IC95%, 0,71-0,90; $p < 0,0001$; I^2, 52,7%). Factores asociados al éxito: programas posteriores a 2001, no realizados en Estados Unidos, mayor uso basal de inhibidores de la enzima de conversión de la angiotensina/antagonistas del receptor de la angiotensina II, mayor número de profesionales y componentes de la intervención, especialización del cardiólogo y enfermera, educación protocolizada y evaluada, automonitorización de signos y síntomas, reconocimiento de descompensación, pauta flexible de diuréticos, aviso y atención precoz, intervención psicosocial, coordinación de profesionales y duración del programa.

Conclusiones: Se confirma la reducción de mortalidad y reingresos con los programas de insuficiencia cardiaca, cuyo éxito se asoció con diferentes variables de estructura e intervención.

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Abbreviations

HF: heart failure
LVEF: left ventricular ejection fraction
NYHA: New York Heart Association
RCT: randomized controlled trials
RR: relative risk

INTRODUCTION

The prevalence of heart failure (HF) is increasing, reaching > 10% in individuals older than 70 years.[1–3]

It is the main cause of hospitalization in persons older than 65 years.[1] Heart failure has a considerable impact on health care systems and comprises about 2.5% of overall health care expenditure,[1] mainly due to admissions. However, the cost attributable to informal care, typically provided by women in Spain, represents the largest part of the overall health care cost (59.1%-69.8%).[4] The disease has a marked impact on the quality of life of patients and their caregivers.[4,5]

Patients with HF are complex and of advanced age. Their considerable number of comorbidities and readmissions affect their clinical treatment and prognosis.[1,2]

Many of the admissions are considered avoidable.[1,2] Because numerous meta-analyses[6–23] and 1 metareview[24] have shown that HF management programs significantly reduce the number of readmissions, these approaches are recommended in European clinical practice guidelines (I-A).[2]

Nonetheless, these meta-analyses reviewed a limited number of studies, which were, moreover, heterogeneous in terms of populations studied, their characteristics and usual care, geographical area, and health care system. The extraordinarily complex interventions are frequently scarcely described. Thus, it is difficult to evaluate which characteristics and clinical contexts favor program success and could be used to guide the organization of the different health care systems when setting priorities. Some meta-analyses have studied certain characteristics indispensable for success[14,16] in a limited number of studies. Numerous meta-analyses[11,14–16,19–24] and recent articles[25–27] have mentioned the need to explore all of these elements in greater depth.

The objectives of this systematic review were the following: *a)* to update our understanding of the effectiveness of HF management programs not using remote monitoring while accurately describing the type of patient, the organization and contents of the intervention, and their ability to reduce mortality and readmissions, and *b)* to identify the determinants of program success.

METHODS

Design

The study design is detailed in the supplementary material (methodology and bibliographic references[1–10] in Appendix 1).

We performed a systematic review and meta-analysis of randomized controlled trials (RCT) assessing hospital admissions and/or mortality in HF management programs involving multifactorial interventions and not using remote monitoring methods apart from telephones.

Our methodology adopted the CONSORT (Consolidated Standards of Reporting Trials)[1] and AHA (American Heart Association) Taxonomy[2] guidelines to evaluate the sociodemographic and clinical characteristics of the population undergoing the intervention, organizational aspects of the health care team, program intensity, mode of health care delivery, and type of follow-up, and the precise contents of the interventions and usual care.

This meta-analysis adhered to the recommendations of the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement.[3]

Electronic databases—PubMed, EMBASE, CINAHL, and Cochrane Library—were searched from January 1990 to December 2014. In addition, we reviewed the main journals publishing articles on the topic of interest and the bibliography of the retrieved systematic reviews and meta-analyses. The databases consulted and the search strategy used are detailed in the supplementary material.

We included RCT published in English, Spanish, French, or German with data on mortality and/or all-cause readmissions or HF readmissions.

Telemedicine/telecare studies were excluded because they have been the subject of specific studies and their inclusion would increase heterogeneity; moreover, because of the high prevalence and high degree of clinical and psychosocial comorbidities in HF patients, this type of health care cannot be offered in a widespread manner. However, we included studies that only involved telephone contact because telephones are typically available to almost all types of patients.

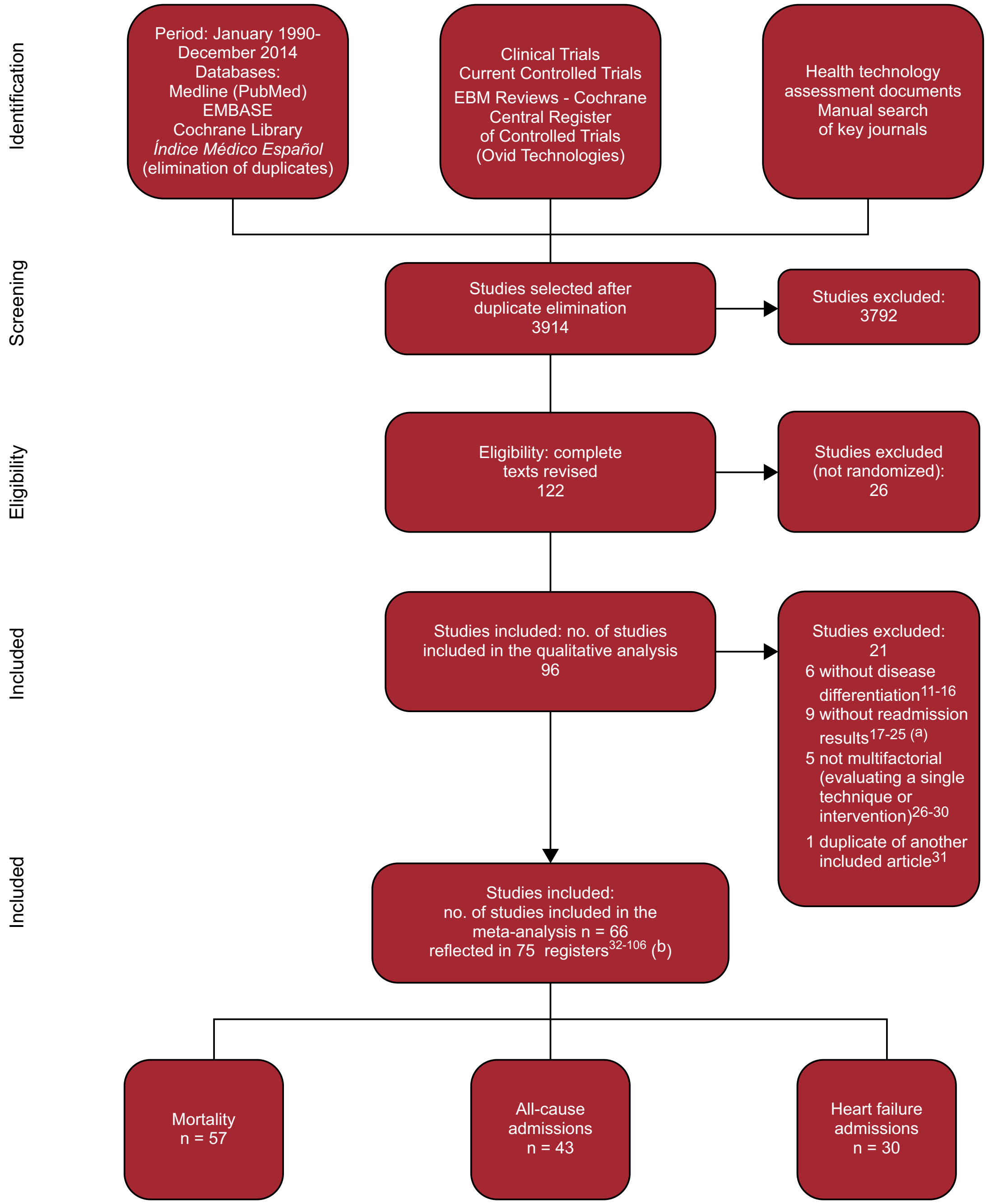
We also excluded medication studies (except for those analyzing drug titration and optimization), those studying multiple diseases, and those that were not multifactorial (eg, only examining exercise or a single technique). Nonetheless, we included 3 multifactorial studies whose intervention included cardiac rehabilitation of patients with HF.

Study Selection and Data Extraction

Three reviewers (M. J. Oyanguren Artola, J. Torcal Laguna, and P. M. Latorre García) independently analyzed the available information sources. At least 2 of the authors separately analyzed the full texts of the studies using predefined selection sheets. Any disagreements were resolved through discussion and, if the disagreement persisted, with the participation of the third author.

Article screening (Figure 1) identified a total of 96 publications on RCT, with 21 meeting at least 1 exclusion criterion (supplementary material[11–31]) and 75 corresponding to 66 randomized trials, reflected in 64 articles (supplementary material[32–95]), including 2 studies with 2 intervention arms, and a further 11 related articles (supplementary material[96–106]).

An external researcher and at least 2 members of the team conducted a blind evaluation of the methodological quality of the selected studies according to the Jadad criteria.[4] All of the selected studies scored at least 3 on the Jadad scale: 29 studies (43.9%) achieved 5 points; 23 (34.85%), 4 points; and 14 (21.21%), 3 points. The Jadad scale is described in the supplementary material.


Identification
Period: January 1990-December 2014
Databases:
Medline (PubMed)
EMBASE
Cochrane Library
Índice Médico Español
(elimination of duplicates)
Clinical Trials
Current Controlled Trials
EBM Reviews - Cochrane Central Register of Controlled Trials
(Ovid Technologies)
Health technology assessment documents
Manual search of key journals
Screening
Studies selected after duplicate elimination
3914
Studies excluded:
3792
Eligibility
Eligibility: complete texts revised
122
Studies excluded (not randomized):
26
Included
Studies included: no. of studies included in the qualitative analysis
96
Studies excluded:
21
6 without disease differentiation11-16
9 without readmission results17-25 (a)
5 not multifactorial (evaluating a single technique or intervention)26-30
1 duplicate of another included article31
Included
Studies included:
no. of studies included in the meta-analysis n = 66
reflected in 75 registers32-106 (b)
Mortality
n = 57
All-cause admissions
n = 43
Heart failure admissions
n = 30

([a]) One study[25] was excluded for not evaluating readmissions but it was a substudy of another included study[64] and provided baseline data on cognitive decline

([b]) Of the 75 registers, 64 were principal articles[32-95] representing 66 interventions (2 of these[53,85] had 2 intervention arms). Eleven are articles related to these research lines[96-106]

Figure 1. Flow diagram of study selection (supplementary material[11–106]).

Statistical Analysis

The STATA Metaprop[5] procedure was used for variables expressing proportions. This approach determined the pooled estimate of the proportion and its exact confidence intervals using the binomial test.

A random effects model (DerSimonian and Laird) was used to pool the results. This model takes into account variability among studies and within each study.[6] We also calculated the 95% confidence intervals (95%CIs) of the model. For the intervals, the relative risks (RRs) were calculated from the tabulated data of the individual studies selected, as well as the differences in the risks and their 95%CIs for mortality, all-cause admissions, and HF admissions. We also calculated the numbers of patients needed to treat (NNTs)[7] using the *metannt* procedure (STATA version 11).

To estimate and quantify the heterogeneity among the different studies, Cochran's Q test and I^2 statistic were used, with values of 25%, 50%, and 75% corresponding to low, moderate, and high degrees of heterogeneity, respectively.[8] The possible existence of a publication bias[9] was visually explored using a funnel plot comparing the effects of the studies (RRs) with their standard errors[10] (supplementary material).

Any studies containing more than 2 treatment arms were considered 2 studies with 2 separate arms and the values of the control group were halved to avoid its double weighting.[7]

A metaregression analysis was performed using the *metareg* procedure of STATA (version 11) to examine how much the different intervention components and study characteristics could explain the heterogeneity of the treatment effect between studies.

Two univariable metaregression analyses considering each factor separately were performed, as well as multivariable metaregressions considering all factors simultaneously. Both approaches gave similar results for the associations between treatment effects and study characteristics.

RESULTS

Description of the Programs

A description of the studies according to the study period, country, whether they were multicenter studies or not, sample size, place of recruitment, and inclusion and exclusion criteria is shown in Table 1 (Table 1 of the supplementary material[32–106]). In addition, we evaluated the sociodemographic, psychosocial, and clinical characteristics of the study patients (Table 2) (Table 2 and Table 3 of the supplementary material[32–106]). The patients were mainly older and male, with an advanced New York Heart Association (NYHA) functional class, reduced left ventricular ejection fraction (LVEF), and considerable cardiovascular and noncardiovascular comorbidity.

There was increased use over time of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) ($P < .012$) and beta-blockers ($P < .003$) and reduced use of digoxin ($P < .008$), with a wide variability in drug use among the different studies (Figure 2).

The intervention organization is shown in Table 3, and the definitions used are shown in the supplementary material (Table 4 of the supplementary material[32–106]). We analyzed the professionals dedicated to the programs and their degree of specialization, the mode of health care delivery, and the program intensity. In total, 83% of the programs were multidisciplinary, with interprofessional coordination and consensus-based/protocol-driven patient treatment. However, only 34.8% of the usual care involved 2 or more team members, and only 6% reported to coordination or planning systems. Nurses participated in 86% of the programs, cardiologists in 53%, and primary care physicians in 54%. The nurses were specialized in cardiology or HF in 48% of the programs and worked in a HF clinic or in the home setting in equal proportions; the cardiologists were specialized in HF in 33% (the professional duties are defined in the supplementary material). The program duration was proportionally distributed into < 3 months, 3-6 months, and > 6 months.

The intervention content during hospitalization was similar in the 2 groups, except in 10 studies. These latter studies included a supplementary evaluation that could involve medication, diet, exercise, or psychosocial aspects and postdischarge requirements. From this evaluation, a comprehensive discharge plan, as well as an appointment schedule and contact details, was frequently developed for the patient; this information was relayed to other

Table 1
Characteristics of the Studies of Heart Failure Management Programs*

	n (%)
Studies included	66
Period analyzed, 1993-2013	
After 2002	52 (78.8)
Patients	13 535
Multicenter setting	25 (37.9)
Region	
Europe	29 (43.9)
United States	23 (34.8)
Canada	4 (6.1)
South America	2 (3)
Asia	3 (4.5)
Australia-New Zealand	5 (7.6)
Setting of patient recruitment	
During hospitalization	50 (75.75)
In a clinic	9 (13.63)
Both	7 (10.6)
Inclusion criteria	
Admission for HF	36 (54.54)
Symptomatic HF	24 (36.36)
NYHA I	2 (3)
NYHA II	15 (22.7)
NYHA III	20 (30.3)
NYHA IV	17 (25.8)
Upper LVEF limit ≤ 55%	22 (33.33)
Lower age limit ≥ 65 y	10 (15.2)
Exclusion criteria	
Psychiatric disorder	43 (65.15)
End-stage disease	41 (62.12)
Residence in care home	34 (51.51)
Noncardiovascular disease possibly affecting results	26 (39.39)
Patient or physician refusal	19 (28.78)
Residence outside hospital area	23 (34.84)
Surgical intervention or transplant	17 (25.75)
Communication/adherence problems	19 (28.78)
Enrollment in another program	16 (24.24)
Severe renal disease or dialysis	13 (19.69)
Myocardial infarction or unstable angina	17 (25.8)
Lack of telephone	11 (16.66)

HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; %, the percentage of studies including the characteristic studied was calculated as n × 100/66 (total number of RCTs included in the meta-analysis).

[*] Table 1 of the supplementary material[32–106].

Table 2
Pooled Data of the Characteristics of the Patients in the Heart Failure Management Programs (Supplementary Material[32–106])

	RCT, n (%)	Mean (95%CI)	Proportion (95%CI)	Mean (range)	Proportion (range)
Sociodemographic characteristcs[a]					
Age, y (75% ≥ 70 y)	66 (100.0)	73.0 (43.0-81.0)			
Women (proportion)	66 (100.0)		42.0 (1.0-72.5)		
Caucasian (of the 19 studies, 16 were from the United States)	19 (28.8)		72.0		
Psychosocial characteristics,[a] proportion (range)					
Cognitive decline: various tests	10 (15.2)				
Cognitive decline	3 (4.5)				
Doubtful	1 (1.5)				
Within normal range	6 (9.1)				
Depression, %	5 (7.6)				3.0-35.0
Dependence: various tests	13 (19.7)				
Some type of dementia, %	10 (15.2)				10.0-50.0
Dementia (mean values close to normal)	3 (4.5)				
Living alone, %	25 (37.9)				12.0-60.0
Quality of life: diverse questionnaires. Moderate-severe deterioration					
Minnesota test (MLHFQ)	17 (25.8)	47.0 (23.0-64.0)			
MLHFQ and SF-36	4 (6.1)				
MLHFQ and EQ-5D	2 (3.0)				
MLHFQ and SF-12	1 (1.5)				
SF-36	2 (3.0)				
Clinical characteristics,[b] proportion (95%CI)					
Heart failure diagnosis prior to admission	20 (30.3)		66.0 (54.7-76.6)		
Ischemic etiology	30 (45.5)		50.2		
Hypertensive etiology	15 (22.7)		27.8		
Valvular heart disease etiology	11 (16.7)		16.0		
NYHA III-IV	46 (69.7)		55.0 (48.0-61.0)		
LVEF	45 (68.2)				
100% of patients with LVEF ≤ 50%-55%	20 (30.3)		43.8		
75%-100% of patients with preserved and reduced LVEF (LVEF 50%-55%)	24 (36.4)		56.2 (75.0-100.0)		
Preserved LVEF	1 (1.5)				
NT-proBNP, mean (range)	7 (9.1)			(320-9.335)	
6-min walk test	6 (9.1)			200.0 (120.0-321.0)	
Comorbidity: CV risk factors and CV and non-CV diseases, proportion (95%CI)					
Ischemic heart disease	51 (77.3)		50.0 (45.0-55.0)		
Atrial fibrillation	31 (47.0)		35.0 (29.5-40.0)		
Valvular heart disease	13 (19.7)		15.0 (11.0-20.0)		
Stroke	16 (24.2)		13.0 (11.0-15.0)		
Peripheral artery disease	3 (4.5)		17.0 (14.0-20.0)		
Pacemaker/implantable cardioverter-defibrillator	8 (12.1)		13.5 (9.0-18.0)		
Hypertension	44 (66.7)		57.0 (51.0-63.0)		
Diabetes mellitus	48 (72.7)		34.0 (30.5-37.0)		
Smoker/exsmoker	10 (15.2)		29.0 (16.0-41.0)		
Kidney failure	12 (18.2)		17.0 (10.0-24.0)		
Respiratory disease	30 (45.5)		26.0 (23.0-30.0)		
Anemia	1 (1.5)		16.0 (10.0-24.0)		
Laboratory results, mean (range)					
Creatinine, mg/dL	24 (36.4)			1.5	
Hemoglobin, means within the normal range	8 (12.1)				
Anemia	1 (1.5)			16.0 (10-24)	
Charlson index	8 (12.1)			3 (2.0-6.0)	
Number of comorbidities	4 (6.1)			4(2.0-6.0)	

Table 2 *(Continued)*
Pooled Data of the Characteristics of the Patients in the Heart Failure Management Programs (Supplementary Material[32–106])

	RCT, n (%)	Mean (95%CI)	Proportion (95%CI)	Mean (range)	Proportion (range)
Baseline drug therapy, proportion (95%CI)					
ACEI/ARB	53 (80.3)		74.5 (69.5-79.5)		
Beta-blockers	45 (68.2)		41.5 (35.0-48.5)		
Diuretics	41 (62.1)		89.0 (86.5-92)		
MRAs	20 (30.3)		29.0 (22.0-36.5)		
Digoxin	44 (66.7)		41.5 (37.0-46.5)		

95%CI, 95% confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CV, cardiovascular; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association functional class; RCT, randomized controlled trials.
The percentage of studies including the characteristic studied was calculated as n × 100 / 66 (total number of RCT included in the meta-analysis). Proportion: pooled estimate of the proportion; 95%CI: confidence interval of the proportion (exact values from the binomial test). Mean: pooled estimate of the mean of the numerical variables and 95%CI of the estimate or range, as appropriate.
[a] Table 2 of the supplementary material, data from original studies.
[b] Table 3 of the supplementary material, data from original studies.

community-based health care professionals and social workers. Nurses, and occasionally pharmacists, began educating the patients and family members during the patients' hospitalization. We analyzed postdischarge drug optimization and clinical monitoring, the content and mode of self-care education, psychosocial aspects, and program coordination are shown in Table 4 (definitions in the supplementary material, Table 4 of the supplementary material[32–106]).

Results of the Heart Failure Management Programs

Mortality

A total of 57 RCT evaluated mortality; of these, 4 showed a significantly positive result (Figure 3). Compared with 16.7% (95%CI, 14.3%-19.2%; I^2, 87.4%) of the control group, 13.7% (95%CI, 11.4%-15.9%; I^2, 89%) of the intervention group died, with a

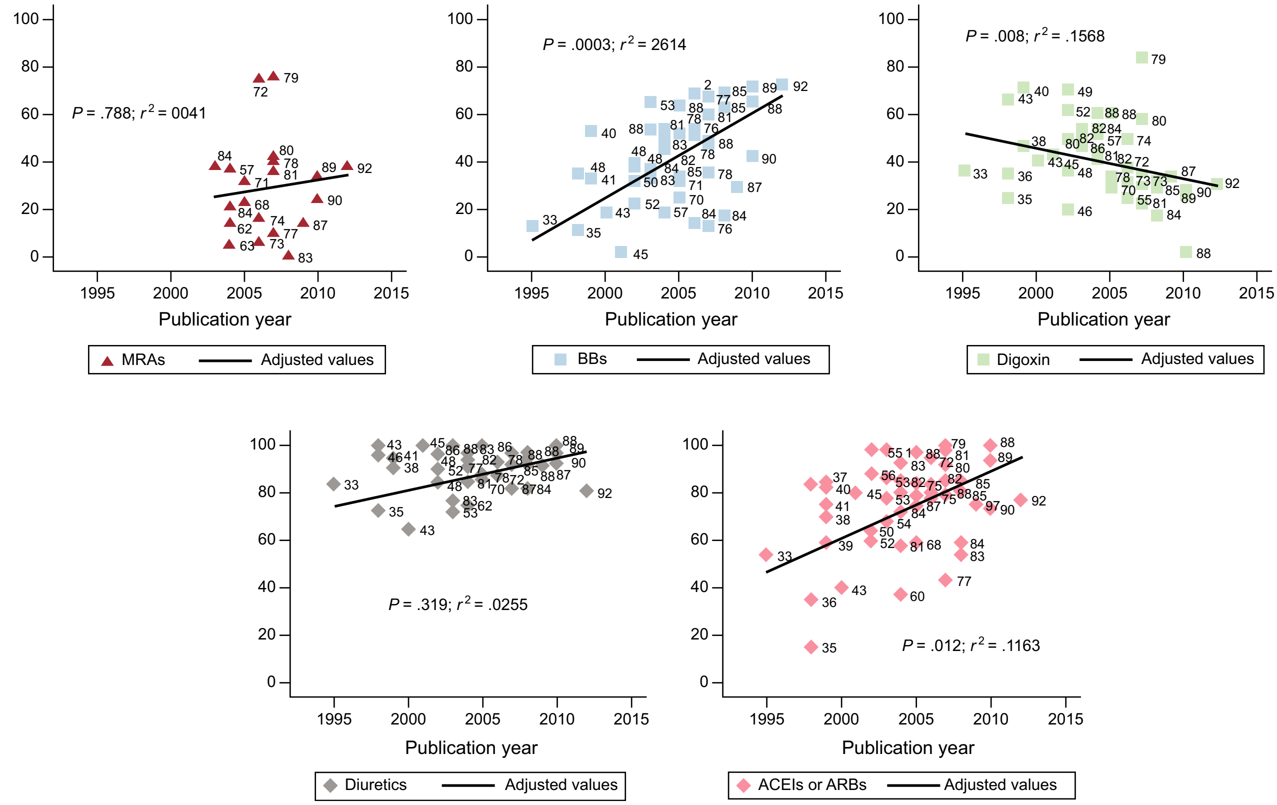


Figure 2. Percentage of drug use (BBs, ACEIs/ARBs, MRAs, diuretics, and digoxin) in the different studies according to the year of publication. Data reported by the publications at the start of the study. The straight line represents the mean value estimated from a regression model for each of the drugs. The numbers signify individual studies. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, beta-blockers; MRAs, mineralocorticoid receptor antagonists.

Table 3
Organizational Characteristics: Pooled Data of the Organization of the Heart Failure Management Programs

Organizational characteristics	RCT, n (%)	
	Intervention	Control (usual care)
Staff		
Multidisciplinary	55 (83.33)	23 (34.84)
Nurse	57 (86.36)	13 (19.69)
Cardiologist	35 (53.03)	22 (33.33)
Primary care physician	36 (54.54)	39 (59.09)
Dietitian	16 (24.24)	6 (9.09)
Pharmacist	16 (24.24)	4 (6.06)
Social worker	14 (21.21)	7 (10.60)
Specialization		
Specialist cardiology or HF nurse (at home or in HF clinic)	32 (48.48)	3 (4.54)
Study nurse (diverse experience and training)	12 (18.18)	1 (1.51)
Case manager (diverse experience and training)	6 (9.09)	0 (0.00)
General nurse	8 (12.12)	10 (15.15)
Cardiologist specialized in HF	22 (33.33)	4 (6.06)
General cardiologist	17 (25.75)	19 (28.78)
Team leader		
Nurse	39 (59.09)	
Shared by nurse and cardiologist or pharmacist	14 (21.21)	
Cardiologist	4 (6.06)	
Primary physician/internist	3 (4.54)	
Coordination between health care professionals	55 (83.33)	4 (6.06)
Care plan that includes caregiver	24 (36.36)	1 (1.51)
Mode of health care delivery		
In-hospital care	31 (46.96)	13 (19.69)
Discharge planning	15 (22.72)	6 (9.09)
Regular postdischarge follow-up	61 (92)	20 (30.30)
Telephone	42 (63.63)	
Home	27 (40.90)	
HF clinic	21 (31.81)	
Primary physician/internist	14 (21.21)	15 (22.72)
General cardiologist	6 (9.09)	9 (13.63)
General nurse clinic	2 (3.03)	
Group intervention	3 (4.54)	
Computer-guided program	9 (13.63)	
Combination of various modes of delivery (in-person and by telephone)	43 (65.15)	
Hot line (telephone nurse for emergencies or advice)	29 (43.93)	2 (3.03)
Program duration		
Up to 3 mo	23 (34.84)	
Up to 6 mo	20 (30.30)	
More than 6 mo	23 (34.84)	

HF, heart failure; RCT, randomized controlled trials.
The number (percentage) of the studies including the characteristic studied was calculated as n × 100 / 66 (total number of RCT included in the meta-analysis). Data from the original studies are in Table 4 of the supplementary material.[32–106]

Table 4
Intervention Characteristics: Pooled Data of the Main Intervention Contents of the Heart Failure Management Programs

	RCT, n (%)	
	Intervention	Control (usual care)
Drug optimization (ACEI/ARB/MRA/others/ unspecified drugs)	32 (48.48)	9 (13.63)
Prescription	24 (36.36)	
Titration	14 (21.21)	
Nurse-led titration	10 (15.15)	1 (1.51)
Started by nurse with cardiologist supervision	7 (10.60)	0 (0.0)
Simplified drug regimen (reduced dosage or elimination of unnecessary drugs)	4 (6.06)	1 (1.51)
Other drug interventions		
Flexible diuretic regimen	21 (31.81)	1 (1.51)
Administration of intravenous diuretics	4 (6.06)	0 (0.00)
Review of drugs in home or clinic	14 (21.21)	0 (0.00)
Evaluation of drug optimization results	21 (31.81)	21 (31.81)
Clinical monitoring	49 (74.24)	5 (7.57)
Analytical monitoring	19 (28.78)	3 (4.54)
Facilitated telephone support	29 (43.93)	2 (3.03)
Early attention	27 (40.90)	2 (3.03)
Education (understanding of:)	63 (95.45)	17 (25.75)
The disease	50 (75.75)	10 (15.15)
Signs and symptoms	48 (72.72)	4 (6.06)
Treatment	50 (75.75)	11 (16.66)
Inappropriate drugs	2 (3.03)	0 (0.00)
Adherence	42 (63.63)	2 (3.03)
Life style and health habits, including sexual activity	23 (34.84)	7 (10.60)
Diet/low-sodium diet	47 (71.21)	9 (13.63)
Fluid restriction/balance	24 (36.36)	4 (6.06)
Exercise/rest advice	27 (40.90)	6 (9.09)
Cardiac rehabilitation	3 (4.54)	0 (0.00)
Discharge plan	4 (6.06)	0 (0.00)
Appointment scheduling/recording	2 (3.03)	4 (6.06)
Psychosocial support	2 (3.03)	4 (6.06)
Self-care includes:	39 (59.09)	3 (4.54)
Monitoring of signs and symptoms	41 (62.12)	8 (12.12)
Treatment with a flexible diuretic regimen	14 (21.21)	2 (3.03)
Knowing how and when to seek help	36 (54.54)	8 (12.12)
Daily weight monitoring	36 (54.54)	9 (13.63)
Abdominal circumference	1 (1.51)	0 (0.00)
Heart rate	2 (3.03)	0 (0.00)
Blood pressure	3 (4.54)	1 (1.51)
Respiratory rate	2 (3.03)	0 (0.00)
Self-care diary	23 (34.84)	5 (7.57)
Self-care assistance		
Provision of weighing scale	5 (7.57)	1 (1.51)
Provision of sphygmomanometer	1 (1.51)	1 (1.51)
Provision of pillbox	10 (15.15)	1 (1.51)
Provision of drug, analysis, and appointment calendars	4 (6.06)	1 (1.51)

Table 4 *(Continued)*

Intervention Characteristics: Pooled Data of the Main Intervention Contents of the Heart Failure Management Programs

	RCT, n (%)	
	Intervention	Control (usual care)
Mode of education		
Performed by nurse	Standard	
Performed by pharmacist	7 (10.60)	
Performed by primary care physician		4 (6.06)
Individual	62 (93.93)	11 (16.66)
Group	8 (12.12)	
In-person	58 (87.87)	12 (18.18)
Protocol-driven	48 (72.72)	5 (7.57)
Includes caregiver	29 (43.93)	
Provision of written information	49 (74.24)	13 (19.69)
Exclusively nonpersonalized education		10 (15.15)
Use of telephone	25 (37.87)	3 (4.54)
Assessment of education and/or self-care or adherence (any type)	25 (37.87)	
Psychosocial assessment and support (nurse, social worker, home care services; normally by nurses)	21 (31.81)	4 (6.06)
Nurses assess the home environment	5 (7.57)	0 (0.00)
Organization of care	22 (33.33)	8 (12.12)
Appointment scheduling/reminding	21 (31.81)	4 (6.06)
Submission of follow-up reports/advice	14 (21.21)	3 (4.54)
Coordination with other professionals	51 (77.27)	4 (6.06)

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists; RCT, randomized controlled trials.

The number (percentage) of studies including the characteristic studied is calculated by n × 100 / 66 (total number of RCT included in the meta-analysis). Data of the original studies are in Table 4 of the supplementary material.[32–106]

difference in risk of death of –2.1% (95%CI, –3.4% to –1.0%; $P < .0004$; I^2, 16.6%) attributable to the programs and RR = 0.88 (95%CI, 0.81-0.96; $P < .002$; I^2, 6.1%); in other words, there was a relative mortality reduction of 12% associated with the programs, with a NNT = 20 (95%CI, 14-36) for programs longer than 6 months (NNT Table of the supplementary material). Heterogeneity was low.

All-cause Admissions

A total of 43 RCT evaluated all-cause admissions, with 9 obtaining a significantly positive result (Figure 4). Compared with 49.5% (95%CI, 45.1%-51.3%; I^2, 89.9%) of the control group, 44.5% (95%CI, 37.9%-51.1%; I^2, 96.7%) of the patients in the intervention group were admitted at least once, with a difference in risk of admission of –4.8% (95%CI, –8% to –1.5%; $P < .004$; I^2, 63.5%) attributable to the programs and RR = 0.92 (95%CI, 0.86-0.98; $P < .011$; I^2, 58.7%); this corresponded to a relative reduction in all-cause admission of 8% associated with the programs, with NNT = 29 in studies longer than 6 months. Heterogeneity was moderate.

Heart Failure Admissions

A total of 30 RCT recorded HF admissions, with 8 obtaining a significantly positive result (Figure 5). Compared with 30% (95%CI, 24%-35.9%; I^2, 95.10%) of the controls, 23.5% (95%CI, 18.9%-28.1%; I^2, 93.7%) of the patients of the intervention group were admitted at least once, with a difference in risk of admission of –5.6% (95%CI, –9% to –2.2%; $P < .001$; I^2, 67.8%) attributable to the programs and RR = 0.80 (95%CI, 0.71-0.90; $P < .0001$; I^2, 52.7%); this comprised a relative reduction in HF admissions of 20% associated with the programs, with NNT = 11 (95%CI, 8-20) in studies shorter than 3 months and NNT = 17 (95%CI, 12-35) in those longer than 6 months. Heterogeneity was moderate.

Analyses of the effects of the programs according to the setting of the intervention are shown in Table 5 of the supplementary material and indicate that the programs were effective in both the clinic and in the home setting or in a combination of these.

Determinants of the Results

The main characteristics of the HF management programs significantly associated with reduced mortality and/or reduced all-cause or HF admissions (Table 5) (Table 6 of the supplementary material[32–106]) were the following: year of performance 2002 or later, a country other than the United States, main baseline use of ACEI/ARB, and an inverse relationship between patient age and mortality.

Regarding the organizational characteristics, the number of members of the multidisciplinary team, specialist HF cardiologist and nurse, and a duration > 6 months were significantly associated with positive outcomes, although an intervention < 3 months was significant.

Finally, the intervention contents were associated with reduced mortality and/or fewer admissions for all-causes and for HF: the number of components evaluated in this meta-analysis, including the flexible diuretic regimen, early treatment of deterioration, psychosocial aspects, care organization and coordination, self-monitoring of signs and symptoms and early care-seeking if there was deterioration, keeping a self-care diary, understanding of the treatment, exercise, psychosocial aspects, and coordination of care, as well as appropriate evaluation of education and self-care and inclusion of caregivers.

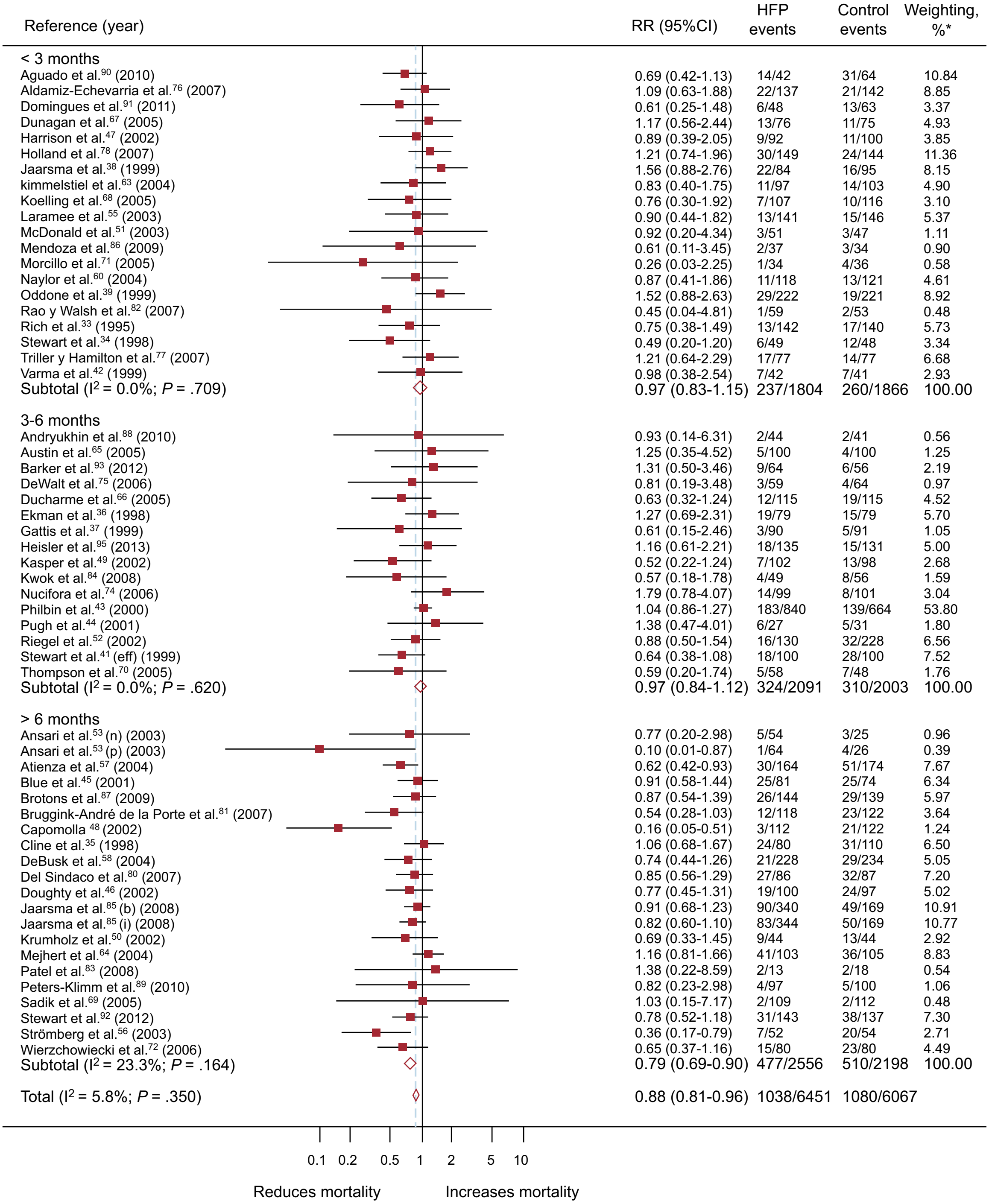
The following also reduced the risk of mortality and/or readmissions, without reaching statistical significance: drug optimization, titration, administration of intravenous diuretics, and clinical and analytical monitoring.

DISCUSSION

The present study of 66 RCT performed in 18 countries and including 13 553 patients is the largest study of this type so far. Previous comparable meta-analyses published between 2004 and 2012 (19 in total) evaluated between 6 and 35 RCT. Our study included 16 trials published between 2005 and 2013 not included in the previous meta-analyses (supplementary material[59,71,72,76,77,82,83,86–91,93–95]).

This meta-analysis confirmed the reduction in all-cause and HF admissions and showed that HF programs reduce mortality.

Our results on mortality reduction agree with those of 6 previous meta-analyses[6,11,13,14,17,21]; another 6 studies[9,10,15,18,19,23] showed favorable nonsignificant tendencies and another[8] showed neutral results, although the trials included in this last analysis were performed before 2001. One meta-analysis[7] showed a reduction in the combination of mortality and readmissions, another 3 studies[12,16,20] did not analyze pooled mortality and found a significant reduction in 3, 4, and 1 studies, respectively, and 1 study[22] did not evaluate mortality. The metareview by Savard et al.[24] did not combine meta-analyses but found significant reductions in 6 of 13 meta-analyses and nonsignificant but favorable tendencies in the remainder.



Reference (year)	RR (95%CI)	HFP events	Control events	Weighting, %*
< 3 months				
Aguado et al.[90] (2010)	0.69 (0.42-1.13)	14/42	31/64	10.84
Aldamiz-Echevarria et al.[76] (2007)	1.09 (0.63-1.88)	22/137	21/142	8.85
Domingues et al.[91] (2011)	0.61 (0.25-1.48)	6/48	13/63	3.37
Dunagan et al.[67] (2005)	1.17 (0.56-2.44)	13/76	11/75	4.93
Harrison et al.[47] (2002)	0.89 (0.39-2.05)	9/92	11/100	3.85
Holland et al.[78] (2007)	1.21 (0.74-1.96)	30/149	24/144	11.36
Jaarsma et al.[38] (1999)	1.56 (0.88-2.76)	22/84	16/95	8.15
kimmelstiel et al.[63] (2004)	0.83 (0.40-1.75)	11/97	14/103	4.90
Koelling et al.[68] (2005)	0.76 (0.30-1.92)	7/107	10/116	3.10
Laramee et al.[55] (2003)	0.90 (0.44-1.82)	13/141	15/146	5.37
McDonald et al.[51] (2003)	0.92 (0.20-4.34)	3/51	3/47	1.11
Mendoza et al.[86] (2009)	0.61 (0.11-3.45)	2/37	3/34	0.90
Morcillo et al.[71] (2005)	0.26 (0.03-2.25)	1/34	4/36	0.58
Naylor et al.[60] (2004)	0.87 (0.41-1.86)	11/118	13/121	4.61
Oddone et al.[39] (1999)	1.52 (0.88-2.63)	29/222	19/221	8.92
Rao y Walsh et al.[82] (2007)	0.45 (0.04-4.81)	1/59	2/53	0.48
Rich et al.[33] (1995)	0.75 (0.38-1.49)	13/142	17/140	5.73
Stewart et al.[34] (1998)	0.49 (0.20-1.20)	6/49	12/48	3.34
Triller y Hamilton et al.[77] (2007)	1.21 (0.64-2.29)	17/77	14/77	6.68
Varma et al.[42] (1999)	0.98 (0.38-2.54)	7/42	7/41	2.93
Subtotal (I^2 = 0.0%; *P* = .709)	0.97 (0.83-1.15)	237/1804	260/1866	100.00
3-6 months				
Andryukhin et al.[88] (2010)	0.93 (0.14-6.31)	2/44	2/41	0.56
Austin et al.[65] (2005)	1.25 (0.35-4.52)	5/100	4/100	1.25
Barker et al.[93] (2012)	1.31 (0.50-3.46)	9/64	6/56	2.19
DeWalt et al.[75] (2006)	0.81 (0.19-3.48)	3/59	4/64	0.97
Ducharme et al.[66] (2005)	0.63 (0.32-1.24)	12/115	19/115	4.52
Ekman et al.[36] (1998)	1.27 (0.69-2.31)	19/79	15/79	5.70
Gattis et al.[37] (1999)	0.61 (0.15-2.46)	3/90	5/91	1.05
Heisler et al.[95] (2013)	1.16 (0.61-2.21)	18/135	15/131	5.00
Kasper et al.[49] (2002)	0.52 (0.22-1.24)	7/102	13/98	2.68
Kwok et al.[84] (2008)	0.57 (0.18-1.78)	4/49	8/56	1.59
Nucifora et al.[74] (2006)	1.79 (0.78-4.07)	14/99	8/101	3.04
Philbin et al.[43] (2000)	1.04 (0.86-1.27)	183/840	139/664	53.80
Pugh et al.[44] (2001)	1.38 (0.47-4.01)	6/27	5/31	1.80
Riegel et al.[52] (2002)	0.88 (0.50-1.54)	16/130	32/228	6.56
Stewart et al.[41] (eff) (1999)	0.64 (0.38-1.08)	18/100	28/100	7.52
Thompson et al.[70] (2005)	0.59 (0.20-1.74)	5/58	7/48	1.76
Subtotal (I^2 = 0.0%; *P* = .620)	0.97 (0.84-1.12)	324/2091	310/2003	100.00
> 6 months				
Ansari et al.[53] (n) (2003)	0.77 (0.20-2.98)	5/54	3/25	0.96
Ansari et al.[53] (p) (2003)	0.10 (0.01-0.87)	1/64	4/26	0.39
Atienza et al.[57] (2004)	0.62 (0.42-0.93)	30/164	51/174	7.67
Blue et al.[45] (2001)	0.91 (0.58-1.44)	25/81	25/74	6.34
Brotons et al.[87] (2009)	0.87 (0.54-1.39)	26/144	29/139	5.97
Bruggink-André de la Porte et al.[81] (2007)	0.54 (0.28-1.03)	12/118	23/122	3.64
Capomolla [48] (2002)	0.16 (0.05-0.51)	3/112	21/122	1.24
Cline et al.[35] (1998)	1.06 (0.68-1.67)	24/80	31/110	6.50
DeBusk et al.[58] (2004)	0.74 (0.44-1.26)	21/228	29/234	5.05
Del Sindaco et al.[80] (2007)	0.85 (0.56-1.29)	27/86	32/87	7.20
Doughty et al.[46] (2002)	0.77 (0.45-1.31)	19/100	24/97	5.02
Jaarsma et al.[85] (b) (2008)	0.91 (0.68-1.23)	90/340	49/169	10.91
Jaarsma et al.[85] (i) (2008)	0.82 (0.60-1.10)	83/344	50/169	10.77
Krumholz et al.[50] (2002)	0.69 (0.33-1.45)	9/44	13/44	2.92
Mejhert et al.[64] (2004)	1.16 (0.81-1.66)	41/103	36/105	8.83
Patel et al.[83] (2008)	1.38 (0.22-8.59)	2/13	2/18	0.54
Peters-Klimm et al.[89] (2010)	0.82 (0.23-2.98)	4/97	5/100	1.06
Sadik et al.[69] (2005)	1.03 (0.15-7.17)	2/109	2/112	0.48
Stewart et al.[92] (2012)	0.78 (0.52-1.18)	31/143	38/137	7.30
Strömberg et al.[56] (2003)	0.36 (0.17-0.79)	7/52	20/54	2.71
Wierzchowiecki et al.[72] (2006)	0.65 (0.37-1.16)	15/80	23/80	4.49
Subtotal (I^2 = 23.3%; *P* = .164)	0.79 (0.69-0.90)	477/2556	510/2198	100.00
Total (I^2 = 5.8%; *P* = .350)	0.88 (0.81-0.96)	1038/6451	1080/6067	

Figure 3. Forest plot showing the results of a random effects (DerSimonian and Laird) meta-analysis on the effects of heart failure management programs on mortality stratified by intervention duration. 95%CI, 95% confidence interval; HFP, heart failure program; RR, relative risk. *Study weight, random effects model.

The reduction in all-cause readmissions concurs with the results of 13 meta-analyses.[6–9,11–15,18,21–23] Another meta-analysis[10] (which only included 6 trials from 1998 to 2003) showed a nonsignificant tendency toward a reduction, and another[20] only found significant differences in reduced admissions in 2 of 8 studies due to their heterogeneity. Four meta-analyses[12,16,19,20] did not provide pooled data, with 1 of these[16] showing a reduction in the combination of readmissions and mortality in 8 management programs and, finally, 1 meta-analysis[17] did not measure all-cause readmissions. In the metareview by Savard et al.,[24] 10 of the 13 meta-analyses found reductions in all-cause readmissions.

Our HF readmission results agree with those of the 9 meta-analyses evaluating this variable[6,7,11,13,15,17,22] and with controlled trials evaluating the impact of pharmacist collaborative care in patients with HF by Koshman et al.[18] The case management programs reported by Taylor et al.[19] showed tendencies toward a reduction. Koshman et al.[18] showed that pharmacist-directed care (without collaborative care) failed to reduce admissions. In the metareview by Savard et al.,[24] the 9 meta-analyses measuring changes in HF-related hospitalization found significantly fewer HF readmissions.

Regarding the determinants of readmission and/or mortality reductions produced by the programs, our meta-analysis indicates

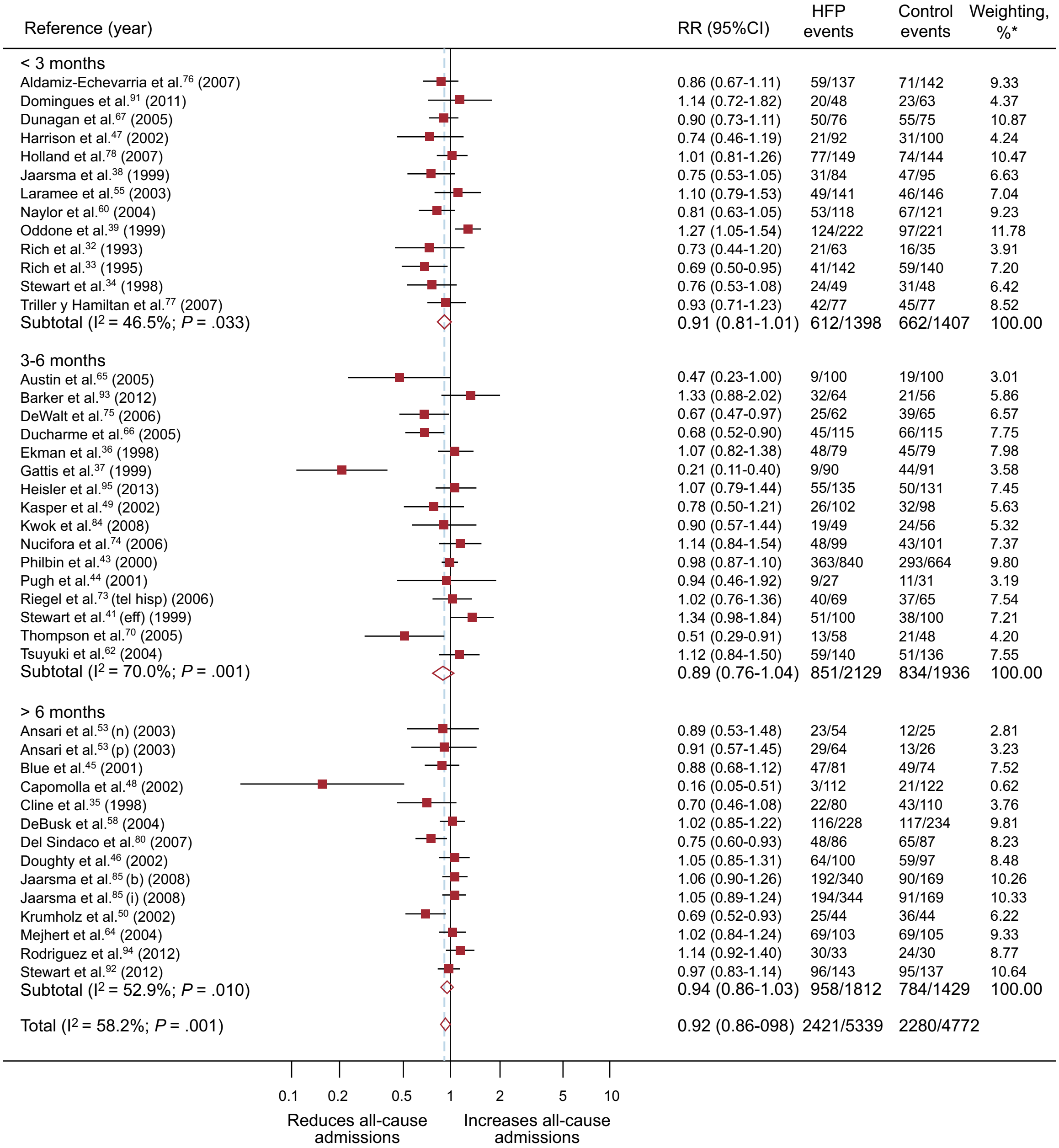
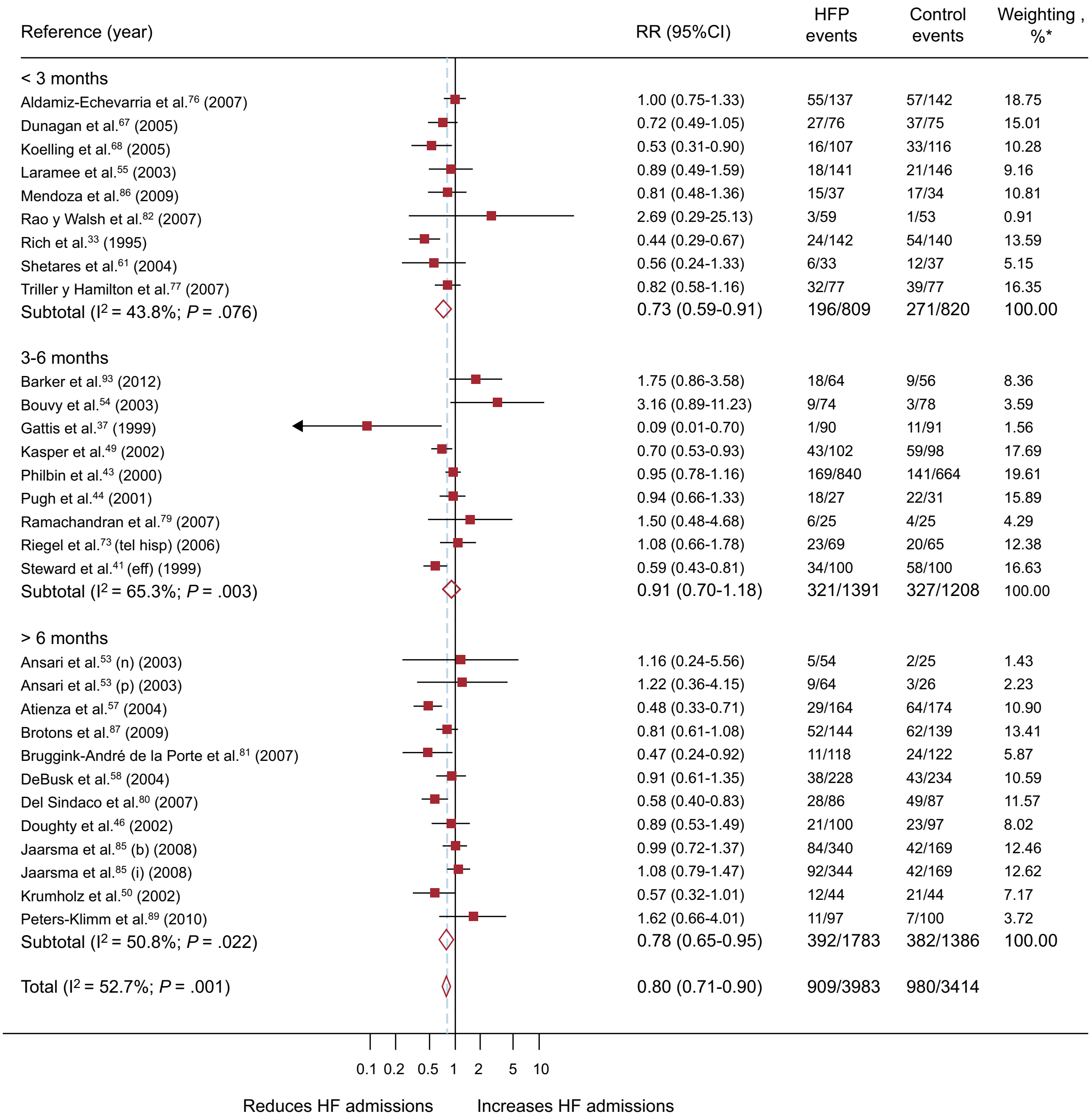


Figure 4. Forest plot showing the results of a random effects (DerSimonian and Laird) meta-analysis on the effects of heart failure management programs on all-cause admissions stratified by intervention duration. 95%CI, 95% confidence interval; HFP, heart failure program; RR, relative risk. *Study weight, random effects model.

that study performance in 2002 or later improved the morbidity and mortality results, as in the meta-analysis by Göhler et al.[14] The improved results of programs from 2002 onward were associated with greater baseline use of ACEIs and beta-blockers: greater baseline use of ACEIs was a significant determinant of the results, a finding previously reported by Phillips et al.[10] and Göhler et al.,[14] whereas greater use of beta-blockers was a nonsignificant determinant of the results. Programs performed in the United States also showed worse results than those conducted in other countries. American programs are associated with predominantly home-based care—possibly due to fewer HF clinics or units—a lower proportion of specialist HF cardiologists and nurses, a higher frequency of case managers, and lower percentage of drug optimization, as well as added coordination difficulties due to US health care being delivered almost exclusively by private sector providers.

Most patient characteristics were not significantly associated with the results, as expected, given that the studies comprised RCT with usual care and comparable intervention groups and as previously reported for NYHA and LVEF[16] and HF with ischemic etiology or diabetes mellitus.[14] In contrast, Göhler et al.[14] linked a lower NYHA class to a greater mortality reduction. Similar to these authors, we found an inverse relationship between age and mortality,[14] contradicting the analysis by Yu et al.,[16] which reported that demographic factors had no effect.

As mentioned in previous meta-analyses, the care team is the main organizational characteristic associated with significantly reduced morbidity and mortality, specifically, the number of members[6,13,14] and the specialization of the multidisciplinary team, and the inclusion of specialist HF cardiologists and nurses.[6,10,11,13,14,16] Our study also adds dieticians and social workers, although the inclusion of the latter was only nearly



Reference (year)	RR (95%CI)	HFP events	Control events	Weighting , %*
< 3 months				
Aldamiz-Echevarria et al.[76] (2007)	1.00 (0.75-1.33)	55/137	57/142	18.75
Dunagan et al.[67] (2005)	0.72 (0.49-1.05)	27/76	37/75	15.01
Koelling et al.[68] (2005)	0.53 (0.31-0.90)	16/107	33/116	10.28
Laramee et al.[55] (2003)	0.89 (0.49-1.59)	18/141	21/146	9.16
Mendoza et al.[86] (2009)	0.81 (0.48-1.36)	15/37	17/34	10.81
Rao y Walsh et al.[82] (2007)	2.69 (0.29-25.13)	3/59	1/53	0.91
Rich et al.[33] (1995)	0.44 (0.29-0.67)	24/142	54/140	13.59
Shetares et al.[61] (2004)	0.56 (0.24-1.33)	6/33	12/37	5.15
Triller y Hamilton et al.[77] (2007)	0.82 (0.58-1.16)	32/77	39/77	16.35
Subtotal ($I^2 = 43.8\%$; *P* = .076)	0.73 (0.59-0.91)	196/809	271/820	100.00
3-6 months				
Barker et al.[93] (2012)	1.75 (0.86-3.58)	18/64	9/56	8.36
Bouvy et al.[54] (2003)	3.16 (0.89-11.23)	9/74	3/78	3.59
Gattis et al.[37] (1999)	0.09 (0.01-0.70)	1/90	11/91	1.56
Kasper et al.[49] (2002)	0.70 (0.53-0.93)	43/102	59/98	17.69
Philbin et al.[43] (2000)	0.95 (0.78-1.16)	169/840	141/664	19.61
Pugh et al.[44] (2001)	0.94 (0.66-1.33)	18/27	22/31	15.89
Ramachandran et al.[79] (2007)	1.50 (0.48-4.68)	6/25	4/25	4.29
Riegel et al.[73] (tel hisp) (2006)	1.08 (0.66-1.78)	23/69	20/65	12.38
Steward et al.[41] (eff) (1999)	0.59 (0.43-0.81)	34/100	58/100	16.63
Subtotal ($I^2 = 65.3\%$; *P* = .003)	0.91 (0.70-1.18)	321/1391	327/1208	100.00
> 6 months				
Ansari et al.[53] (n) (2003)	1.16 (0.24-5.56)	5/54	2/25	1.43
Ansari et al.[53] (p) (2003)	1.22 (0.36-4.15)	9/64	3/26	2.23
Atienza et al.[57] (2004)	0.48 (0.33-0.71)	29/164	64/174	10.90
Brotons et al.[87] (2009)	0.81 (0.61-1.08)	52/144	62/139	13.41
Bruggink-André de la Porte et al.[81] (2007)	0.47 (0.24-0.92)	11/118	24/122	5.87
DeBusk et al.[58] (2004)	0.91 (0.61-1.35)	38/228	43/234	10.59
Del Sindaco et al.[80] (2007)	0.58 (0.40-0.83)	28/86	49/87	11.57
Doughty et al.[46] (2002)	0.89 (0.53-1.49)	21/100	23/97	8.02
Jaarsma et al.[85] (b) (2008)	0.99 (0.72-1.37)	84/340	42/169	12.46
Jaarsma et al.[85] (i) (2008)	1.08 (0.79-1.47)	92/344	42/169	12.62
Krumholz et al.[50] (2002)	0.57 (0.32-1.01)	12/44	21/44	7.17
Peters-Klimm et al.[89] (2010)	1.62 (0.66-4.01)	11/97	7/100	3.72
Subtotal ($I^2 = 50.8\%$; *P* = .022)	0.78 (0.65-0.95)	392/1783	382/1386	100.00
Total ($I^2 = 52.7\%$; *P* = .001)	0.80 (0.71-0.90)	909/3983	980/3414	

Figure 5. Forest plot showing the results of a random effects (DerSimonian and Laird) meta-analysis on the effects of heart failure management programs on heart failure admissions stratified by intervention duration. 95%CI, 95% confidence interval; HF, heart failure; HFP, heart failure program; RR, relative risk. *Study weight, random effects model.

significant. A cardiologist not specialized in HF and pharmacist nonsignificantly reduced the risk. Our meta-analysis agrees with the observation of Yu et al.[16] that the incorporation of the primary care physician to the specialized HF cardiologist and nurse team could be beneficial and, like the present authors, Whellan et al.[12] questioned whether the participation of primary care physicians in these programs could be effective without the participation of specialized HF cardiologist and nurse team.

Programs with home- and clinic-based follow-up significantly reduced admissions for HF, unlike those with telephone care alone.

Our study agrees with previous studies identifying a duration > 6 months as a factor with a significant effect on readmission reduction,[14,17,21] although an intervention < 3 months was also significant (this period typically shows more admissions, which may explain its stronger influence). These findings differ from those of Roccaforte et al.,[11] who found an association with studies lasting 3-6 months. Similar to Holland et al.,[13] we conclude that the study quality does not affect the results, in contrast to Roccaforte et al.,[11] who contend that the higher the study quality, the greater the mortality reduction.

Regarding the intervention, we agree with other meta-analyses[10,16,21] in finding that the number of intervention components evaluated in our study significantly reduced readmissions or mortality.

The elements of the intervention significantly reducing the risk of mortality and/or readmissions in our meta-analysis were identified in previous studies: flexible diuretic regimen,[16] early treatment of deterioration,[6,12,16] psychosocial aspects, and care organization and coordination.[16]

Other elements of the intervention evaluated in this meta-analysis reduced the risk of morbidity and mortality to a greater or lesser extent, although nonsignificantly: clinical and analytical monitoring, easy access to care, intravenous diuretic administration, and drug optimization and titration.[16]

Although patient education and self-care are considered positive elements of the intervention in numerous meta-analyses,[6,15–17,23] our meta-analysis showed that the reduction

Table 5
Factors Related to the Success of Heart Failure Management Programs. Results of the Metaregression Analysis[a]

	Mortality (57 RCT)				All-cause admissions (43 RCT)				HF admissions (30 RCT)			
	n	Δ	*P* > t		n	Δ	*P* > t		n	Δ	*P* > t	
Jadad scale	57	↓	0.110	NS	43	↓	0.202	NS	30	↓	0.276	NS
Year performed ≤ 2001, 2002[b]	57	↓	0.016	[b]	43	↑	0.622	NS	30	↑	0.023	[b]
3-, 6-9-, 12-, and > 12-mo follow-up	57	↓	0.132	NS	43	↓	0.764	NS	30		0.826	NS
Age, y	57	↑	0.015	[b]	43	↓	0.724	NS	30	↓	0.492	NS
Country of performance: *1, Australia/New Zealand/Hong Kong;* *2, Canada/South America/other;* *3, Europe; 4, United States*	57	↑	0.034	[b]	43	↓	0.578	NS	30	↓	0.646	
Women, %	57		0.102	NS	43	↓	0.501	NS	30	↓	0.586	
NYHA I-II patients, %	39		0.996	NS	21		0.948	NS	20		0.678	NS
NYHA III-IV patients, %	41	↓	0.799	NS	27		0.868	NS	22	↓	0.997	NS
Patients with depressed ejection fraction, %	40	↓	0.134	NS	28	↓	0.494	NS	19	↓	0.095	NS
Patients with ischemic heart disease, %	45		0.989	NS	33		0.919	NS	24	↓	0.160	NS
Patients with atrial fibrillation, %	28		0.534	NS	20		0.541	NS	14	↓	0.652	NS
Patients with hypertension, %	37	↓	0.279	NS	27		0.868	NS	20	↓	0.622	NS
Patients with DM, %	42	↓	0.847	NS	31		0.727	NS	23		0.841	NS
% of patients with COPD	27	↓	0.626	NS	20	↓	0.177	NS	17	↓	0.101	NS
Drugs at time of inclusion												
Patients taking diuretics ≤ 84; 84-95; > 95, %	36	↓	0.342	NS	26		0.913	NS	18		0.561	NS
Patients taking BBs ≤ 22.80; 22.81-52.00; ≥ 52,01, %	39	↓	0.167	NS	23		0.424	NS	22		0.460	NS
Patients taking ACEIs/ARBs ≤ 64.00; 64.01-82.00; ≥ 82,01, %	47	↓	0.007	[b]	35	↓	0.512	NS	25		0.252	NS
Patients taking MRAs ≤ 17.00; 17.01-37.00; ≥ 37,01, %	16	↓	0.461	NS	8	↓	0.196	NS	10	↓	0.958	NS
Patients taking digoxin ≤ 34.00; 34.01-42.00; ≥ 42,01, %	38	↓	0.945	NS	28	↓	0.371	NS	21	↓	0.081	NS
Staff dedicated to the program												
Cardiologist specialized in HF	22	↓	0.018	[b]	12	↓	0.355	NS	13	↓	0.149	NS
General cardiologist	17	↓	0.124	NS	12	↓	0.632	NS	9	↓	0.149	NS
HF nurse	31	↓	0.011	[b]	21	↓	0.373	NS	14	↓	0.005	[b]
Case manager nurse	6	↓	0.901	NS	4		0.801	NS	4		0.150	NS
Nurse hired for study	13		0.082	NS	9		0.612	NS	4		0.709	NS
Other nurses	7		0.187	NS	6		0.635	NS	4	↓	0458	NS
Family physician/internist	32	↓	0.906	NS	24	↓	0.782	NS	17	↓	0.239	NS
Dietitian	14	↓	0.023	[b]	13	↓	0.518	NS	7	↓	0.328	NS
Pharmacist	16	↓	0.767	NS	11	↓	0.639	NS	5		0.780	NS
Social worker	14	↓	0.056	[c]	12	↓	0.519	NS	7	↓	0.632	NS
Number of team members	57	↓	0.004	[b]	43	↓	0.483	NS	30	↓	0.007	[b]
Mode of health care delivery												
Hospital care	25		0.408	NS			0.400	NS	13	↓	0.268	NS
Discharge planning	13		0.570	NS		↓	0.997	NS	8	↓	0.051	[c]
Type of follow-up												
HF clinic		↓	0.138	NS	13	↓	0.561	NS	9	↓	0.598	NS
Cardiology clinic		↓	0.161	NS	5		0.903	NS	4	↓	0.499	NS
Non-HF nurse clinic		↓	0.414	NS	1		0.508	NS	6	↓	0.147	NS
Primary care clinic	14	↓	0.232	NS	7	↓	0.508	NS	5	↓	0.094	NS
Home	28		0.764	NS	22	↓	0.355	NS	15		0.963	NS
Telephone		↓	0.579	NS	30		0.741	NS	19	↓	0.389	NS
Hot line		↓	0.285	NS	19	↓	0.104	NS	12	↓	0.281	NS
Duration of intervention (1-3)	56	↓	0.053	[c]	42		0.567	NS	30		0.873	NS
Intervention components												
Optimization	29	↓	0.450	NS	21	↓	0.177	NS	16	↓	0.159	NS
Titration	14	↓	0.206	NS	10		0.530	NS	6	↓	0.754	NS
Flexible diuretic regimen	18	↓	0.124	NS	12	↓	0.380	NS	6	↓	0.004	[b]
Intravenous diuretics	4	↓	0.068	[c]	2	↓	0.055	[c]	0			NS
Clinical monitoring	45	↓	0.075	[c]	35	↓	0.198	NS	21	↓	0.364	NS
Analytics	19	↓	0.375	NS	13	↓	0.639	NS	9	↓	0.309	NS

Table 5 *(Continued)*

Factors Related to the Success of Heart Failure Management Programs. Results of the Metaregression Analysis[a]

	Mortality (57 RCT)				All-cause admissions (43 RCT)				HF admissions (30 RCT)			
	n	Δ	$P > t$		n	Δ	$P > t$		n	Δ	$P > t$	
Facilitated access to care	19	↓	0.073	[c]	23	↓	0.080	[c]	14	↓	0.151	NS
Early treatment of deterioration	26	↓	0.003	[b]	20	↓	0.526	NS	12	↓	0.049	[b]
Protocol-driven education	54		0.222	NS	41		0.928	NS	27	↓	0.668	NS
Self-care	33	↓	0.125	NS	27		0.025	[b]	15		0.604	NS
Psychosocial support	18	↓	0.016	[b]	16	↓	0.914	NS	9	↓	0.312	NS
Care organization/coordination	18	↓	0.020	[b]	15	↓	0.724	NS	19	↓	0.266	NS
Nurse-led drug optimization	10	↓	0.213	NS	7		0.553	NS	5	↓	0.638	NS
Number of intervention components (1-12)	57	↓	0.004	[b]	43	↓	0.569	NS	30	↓	0.036	[b]
Understanding												
Of the disease	44	↓	0.132	NS	32		0.882	NS	19	↓	0.233	NS
Signs and symptoms	43	↓	0.067	[c]	31	↓	0.977	NS	19	↓	0.283	NS
Treatment	44	↓	0.068	[c]	31	↓	0.040	[b]	21	↓	0.007	[b]
Inappropriate drugs	2		0.529	NS	1		0.944	NS	2	↓	0.536	NS
Treatment adherence	36	↓	0.725	NS	27	↓	0.672	NS	20	↓	0.523	NS
Life style	20		0.302	NS	11		0.814	NS	7	↓	0.835	NS
Diet	40	↓	0.725	NS	30		0.264	NS	21	↓	0.172	NS
Fluid	21	↓	0.283	NS	15		0.659	NS	8	↓	0.317	NS
Exercise/rest	23	↓	0.003	[b]	18		0.747	NS	11	↓	0.075	[c]
Rehabilitation	3	↓	0.534	NS	2	↓	0.180	NS	1			
Discharge plan	4	↓	0.712	NS	3	↓	0.263	NS	1		0.429	NS
Appointment scheduling	0				0				0			
Psychosocial aspects	17	↓	0.225	NS	16	↓	0.443	NS	6	↓	0.672	NS
Self-care												
Signs and symptoms	37	↓	0.026	[b]	27	↓	0.420	NS	16	↓	0.341	NS
Flexible diuretic regimen	13	↓	0.176	NS	5	↓	0.435	NS	2	↓	0.271	NS
Care-seeking if there is deterioration	32	↓	0.017	[b]	26		0.432	NS	15	↓	0.178	NS
Weight control	31	↓	0.462	NS	25		0.076	NS	14		0.981	NS
Abdominal circumference	0				0				0			
Heart rate	2	↓	0.353	NS	0			NS	1		0.213	NS
Blood pressure	3	↓	0.489	NS	1	↓	0.353	NS	2	↓	0.775	NS
Respiratory rate	2	↓	0.047	[b]	0			NS	1	↓	0.100	NS
Self-care diary	18	↓	0.047	[b]	16			NS	10	↓	0.100	NS
Provision of weighing scale	4		0.478	NS	5		0.334	NS	3		0.334	NS
Provision of blood pressure monitor	1	↓	0.913	NS	1	↓	0.353	NS	1	↓	0.296	NS
Provision of pillbox	7		0.825	NS	1		0.783	NS	3		0.709	NS
Provision of calendars	7		0.917	NS	6		0.521	NS	6	↓	0.938	NS
Appointments	0			NS	0			NS	0			NS
Self-care contents	0			NS	0			NS	0			NS
Mode of education												
Individual	53		0.987	NS	40	↓	0.730	NS	27	↓	0.668	NS
Group	6		0.792	NS	5		0.626	NS	2		0.489	NS
With caregiver	24	↓	0.034	[b]	18	↓	0.404	NS	8	↓	0.164	NS
Protocol-driven	42	↓	0.064	[c]	32	↓	0.605	NS	18	↓	0.296	NS
In-person	50	↓	0.096	[c]	37	↓	0.594	NS	24	↓	0.387	NS
Exclusively not in-person	2		0.645	NS	2		0.839	NS	2		0.752	NS
Telephone	21	↓	0.632	NS	15	↓	0.405	NS	10		0.724	NS
Evaluation of education	8	↓	0.006	[b]	3	↓	0.391	NS	4	↓	0.006	[b]
Evaluation of self-care	8	↓	0.006	[b]	3	↓	0.391	NS	4	↓	0.006	[b]

↓, reduced relative risk between the RCT that refer to the factor and those that do not; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, beta-blockers; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; MRAs, mineralocorticoid receptor antagonists; NS, not significant; NYHA, New York Heart Association; RCT, randomized controlled trials.

In the case of drugs, the variable was collected in the percentage of patients using the medication; the tertiles have been considered for the analysis.

[a] Table 6 of the supplementary material.[32–106]

[b] $P < .05$ in metaregression analysis.

[c] Almost significant in metaregression analysis.

was generally nonsignificant, despite reducing the risk of morbidity and mortality. However, some education and self-care components were essential for a significant risk reduction: self-monitoring of signs and symptoms and early care-seeking, keeping a self-care diary, understanding of treatment and exercise, psychosocial aspects, and care coordination, as well as education and self-care evaluation and caregiver inclusion. In-person and protocol-driven education was nearly significant. Other education and self-care elements reduced the risk but nonsignificantly, such as understanding of diet and fluid intake and inappropriate drugs, the importance of adherence, the discharge plan, weight control, and use of pillboxes.

The clinical implications of this study are as follows: *a)* specific programs should be universally introduced for patients with HF, at least for those who have had a hospital admission, because there is sufficient evidence for the implementation of successful programs, which can also be cost-effective by reducing hospital admissions and relieving the social burden of informal care; *b)* these programs should be implemented in hospital-based HF units, community-based HF clinics, and in the home setting; *c)* the program design should include at least the factors shown in this meta-analysis to significantly reduce admissions and mortality and those reducing the risk, which are converted into management quality criteria, and *d)* before the widespread introduction of programs, they should be contextualized, adapted, and tested in each health care system, and their efficacy and manner of implementation should be studied, in conjunction with continual reevaluation with quality indicators.

New high-quality primary studies are required to explore in greater depth the key factors for the success of the programs and their intervention and organizational characteristics through a description of the characteristics of the patients, health care system, and social and geographic context of the programs. Their application should be studied in subgroups with preserved LVEF, women, patients with psychiatric disorders or important comorbidities, and the manner and content of the participation of the primary care physician in the specialized HF cardiologist and nurse teams. Programs including telemonitoring should be studied with the same degree of precision mentioned and their cost-effectiveness should be contrasted with those of programs omitting such methods.

Limitations

The interventions required interpretation because the studies poorly describe the interventions implemented, their contents, the organization and patient characteristics, and usual care. Most studies also failed to evaluate the direct results of their interventions (eg, degree of drug optimization achieved, knowledge acquired by patients and family members, degree of adherence, and the results of early treatment of decompensations). The education intervention of the HF programs is scarcely described and almost entirely overlooked in the control groups.

The definition of depressed LVEF in some studies is currently obsolete. The definition of admission is imprecise in numerous studies as to whether planned admissions or emergency department visits were included and their minimum duration.

The multifactorial nature of the programs regarding their contents, intensity, type of organization, and patients and the geographical and health care system differences make it difficult to draw definitive conclusions on the characteristics guaranteeing the success of HF management programs in all health care systems.

CONCLUSIONS

The present meta-analysis corroborates in December 2014 the reduction in all-cause and HF admissions of most previous meta-analyses but includes many more RCT (66 in total) and is more up-to-date, in addition to including RCT from Spain. Our work also consolidates the reduced mortality reported in some of these meta-analyses and identifies the determinants of readmission and mortality results.

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CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- Overall, HF management programs reduce admissions.
- Some programs do not obtain such results, for unclear reasons.
- Some programs also reduce mortality but others do not, and there are no conclusive general results.
- The need to implement HF management programs is undeniable but precise elucidation is required of the determinants of success, specifically, the patient characteristics, intervention contents, and the social, geographical, and health care system organization and program setting.

WHAT DOES THIS STUDY ADD?

- The present study ratifies in December 2014 the reduction in all-cause and HF admissions and confirms the reduction in mortality with multifactorial programs without telemonitoring.
- The study identifies the following significant determinants of readmissions and mortality: multidisciplinary teams with specialist HF nurses and cardiologists; self-monitoring of signs and symptoms; prompt care-seeking and understanding of treatment; protocol-driven education in and self-care and its assessment; flexible diuretic regimen; early treatment of deteriorations; psychosocial intervention; coordination of hospital- and community-based professionals; clinic- and home-based follow-up after discharge; and a duration longer than 6 months.
- The following also nonsignificantly reduce the risk of readmissions and mortality: drug optimization, titration, intravenous diuretic administration, and clinical and analytical monitoring.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2016.05.012.

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