

Medication Adherence Interventions Improve Heart Failure Mortality and Readmission Rates: Systematic Review and Meta-Analysis of Controlled Trials

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Background—Poor adherence to medications is a common problem among heart failure (HF) patients. Inadequate adherence leads to increased HF exacerbations, reduced physical function, and higher risk for hospital admission and death. Many interventions have been tested to improve adherence to HF medications, but the overall impact of such interventions on readmissions and mortality is unknown.

Methods and Results—We conducted a comprehensive search and systematic review of intervention studies testing interventions to improve adherence to HF medications. Mortality and readmission outcome effect sizes (ESs) were calculated from the reported data. ESs were combined using random-effects model meta-analysis methods, because differences in true between-study effects were expected from variation in study populations and interventions. ES differences attributed to study design, sample, and intervention characteristics were assessed using moderator analyses when sufficient data were available. We assessed publication bias using funnel plots. Comprehensive searches yielded 6665 individual citations, which ultimately yielded 57 eligible studies. Overall, medication adherence interventions were found to significantly reduce mortality risk among HF patients (relative risk, 0.89; 95% CI, 0.81, 0.99), and decrease the odds for hospital readmission (odds ratio, 0.79; 95% CI, 0.71, 0.89). Heterogeneity was low. Moderator analyses did not detect differences in ES from common sources of potential study bias.

Conclusions—Interventions to improve medication adherence among HF patients have significant effects on reducing readmissions and decreasing mortality. Medication adherence should be addressed in regular follow-up visits with HF patients, and interventions to improve adherence should be a key part of HF self-care programs. (*J Am Heart Assoc.* 2016;5:e002606 doi: 10.1161/JAHA.115.002606)

Key Words: heart failure • hospitalization • intervention • medication adherence • meta-analysis • mortality • readmission • systematic review

Over 5.7 million persons in the United States and at least 23 million people worldwide live with heart failure (HF),^{1–3} which is associated with considerable morbidity, mortality, and health care costs. Cardiovascular disease remains the leading cause of death in the United States.^{4,5} Mortality rates among HF patients, in particular, are high. Of all deaths in the United States in 2009 (from any cause), 11% listed HF as a cause or contributing factor.⁶ HF hospitalization rates also remain high,

with over 1 million hospital discharges for HF in 2010, a rate essentially unchanged since 2000.^{3,7} Whereas HF is often considered a problem of the elderly, the rate of hospitalizations for HF patients under age 65 has significantly increased as well,⁸ and despite efforts to prevent or delay the onset of cardiovascular disease, the prevalence of HF continues to rise.^{2,3}

HF patients are taught self-care strategies to help manage symptoms, maintain physical functioning, and prevent symptom exacerbations and worsening of disease that could lead to hospitalization or death. Medication is a critical part of HF treatment, and adhering to medication regimens is a key behavior in HF self-care. Unfortunately, adherence among patients with HF is low, negatively affecting clinical outcomes and leading to increased HF exacerbations, reduced physical function, and higher risk for hospital admission and death.^{9–11}

Many interventions have been tested to improve adherence to medication among HF patients, but the overall impact of these interventions on patient mortality and hospital readmissions is not known. Previous reviews have only

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Table 1. Search Strategy for Medline

1.	patient compliance/
2.	medication adherence/
3.	1 or 2
4.	exp Vaccines/
5.	immunization/or immunization schedule/or immunotherapy, active/or vaccination/or mass vaccination/
6.	exp Contraceptive Agents/
7.	Contraception Behavior/
8.	exp Contraception/
9.	(viagra or sildenafil).mp.
10.	exp antipsychotic agents/
11.	exp Mental Retardation/
12.	exp "schizophrenia and disorders with psychotic features"/
13.	exp Substance-Related Disorders/
14.	Mental Disorders/
15.	exp Psychiatry/
16.	Probiotics/
17.	disabled children/or mentally disabled persons/or mentally ill persons/
18.	Prisoners/
19.	group homes/or exp nursing homes/
20.	Institutionalization/
21.	Military Personnel/
22.	Disulfiram/
23.	antabuse.mp.
24.	exp Methadone/
25.	or/5-24
26.	((improv\$ or promot\$ or enhanc\$ or encourag\$ or foster\$ or advocat\$ or influenc\$ or incentiv\$ or ensur\$ or remind\$ or optimiz\$ or optimis\$ or increas\$ or impact\$) adj5 (complan\$ or adheren\$)).mp.
27.	((prevent\$ or address\$ or decreas\$) adj5 (noncomplan\$ or nonadher\$ or non complian\$ or non adher\$)).mp.
28.	3 not 25
29.	(medicat\$ or regimen\$ or prescription\$ or prescribed or drug\$ or pill or pills or tablet\$ or chemotherap\$).mp.
30.	dt.fs.
31.	pharmaceutical preparations/or exp dosage forms/or drugs, generic/or prescription drugs/
32.	agents.hw.
33.	meds.tw.
34.	(regimen or regimens).tw.
35.	or/29-34
36.	28 and 35
37.	*patient compliance/
38.	(complan\$ or adher\$ or noncomplan\$ or nonadher).ti.

Continued

Table 1. Continued

39.	(complan\$ or adher\$).ab. /freq=2
40.	26 or 27 or 37 or 38 or 39
41.	exp heart failure
42.	(CHF or HF or heart failure).af.
43.	cardiac.mp.
44.	41 or 42 or 43
45.	36 or 40
46.	44 and 45

synthesized very few studies and may not accurately reflect the overall state of the literature. This article reports the results of a comprehensive systematic review and meta-analysis of mortality and hospitalization outcomes from HF medication adherence (MA) intervention studies.

Methods

This research synthesis used well-established systematic review and meta-analysis methods, with reporting according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹²⁻¹⁴ The project protocol is available from the primary author upon request.

Study Eligibility

Studies of adults (age ≥ 18 years) testing interventions to improve adherence to medications among patients with a diagnosis of HF were eligible for inclusion in the meta-analysis. Studies of patients who were institutionalized or otherwise not involved with administering their own medications were excluded. Both published and unpublished studies were included in order to analyze as comprehensive a sample of studies as possible. Searches were not limited by language; potentially eligible studies warranting further review were translated into English as necessary. Studies were not initially excluded based on study design or any a priori measure of study quality. In meta-analyses, two-group studies are analyzed separately from any single-group (pre-post) studies. Only 1 single-group study met the eligibility and outcome criteria for this project. As a result, this analysis focuses only on those studies with 2-group (ie, intervention vs control) comparisons.

Search Strategies and Information Sources

Multiple search strategies were employed to identify as many eligible studies as possible. Electronic database searches were developed and carried out by a health sciences research librarian on the research team. Databases searched included

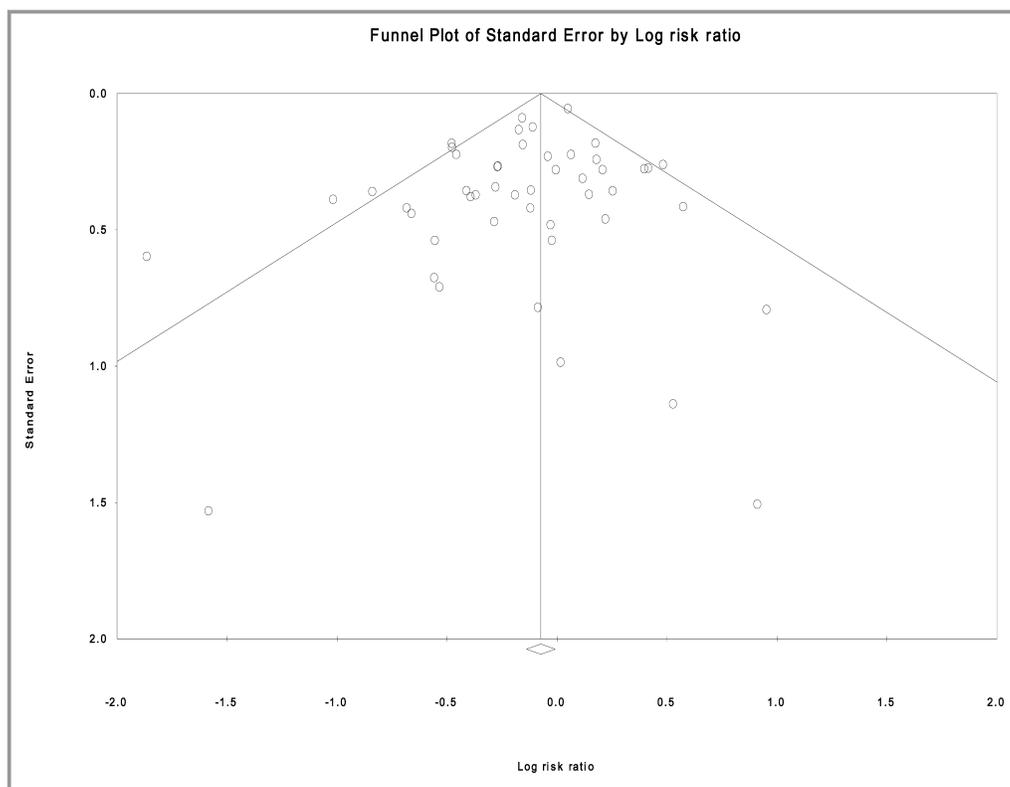


Figure 1. Funnel plot for mortality outcomes.

MEDLINE, CINAHL, PsycINFO, Cochrane Central Register of Controlled Trials, Scopus, ProQuest, International Pharmaceutical Abstracts, DARE, and Highwire. All databases were searched from inception through 2013. Search terms were developed for each database, including both indexed search terms (eg, MeSH terms) and free-text keywords. For example, the MeSH and free text keyword search terms included medication adherence, patient compliance, adherent, adherence, non-compliant, noncompliance, nonadherent, nonadherence, prescription drugs, dosage forms, generic, prescription (s), prescribed, drug(s), medications, pill(s), tablet(s), regimen (s), improve, promote, enhance, encourage, foster, advocate, influence, incentive, ensure, remind, optimize, increase, impact, address, decrease, heart failure, congestive heart failure, CHF, and HF. See Table 1 for a sample search strategy.

Further search methods included hand searching of selected journals for the previous 10 years to identify studies that may not have been located through electronic database searching. Reference lists of review articles were searched to identify further studies, and author searches were conducted on the names of primary investigators of eligible studies. Research registries, such as clinicaltrials.gov, and conference proceedings were also searched to identify studies that had been conducted but not reported in an indexed source.

Each search result was evaluated for eligibility by 2 research staff. The full text of any studies deemed potentially

eligible in the initial screening were evaluated to determine final eligibility. Every eligible study was independently coded and entered into separate databases by 2 trained research staff. Data were compared to reach 100% agreement on all coding items to ensure data accuracy. If a study report did not include sufficient data for calculating an effect size (ES), the study authors were contacted and asked to provide the necessary information.

Risk of Bias

Studies were not evaluated a priori for study quality or risk of bias, because no validated tools for this exist and require subjective evaluation by evaluators. Rather, the research team coded study characteristics that are typically considered to be quality indicators (eg, randomization, use of intention-to-treat, blinding of data collectors, study attrition, etc) and analyzed them empirically by moderator analyses. In this way, rather than excluding studies for perceived methodological flaws, we could determine whether indicators of risk for bias actually affected ES.

Statistical Analyses

Analyses were performed using Comprehensive Meta-Analysis software (Biostat, Inc., Englewood, NJ). A relative risk (RR) ES

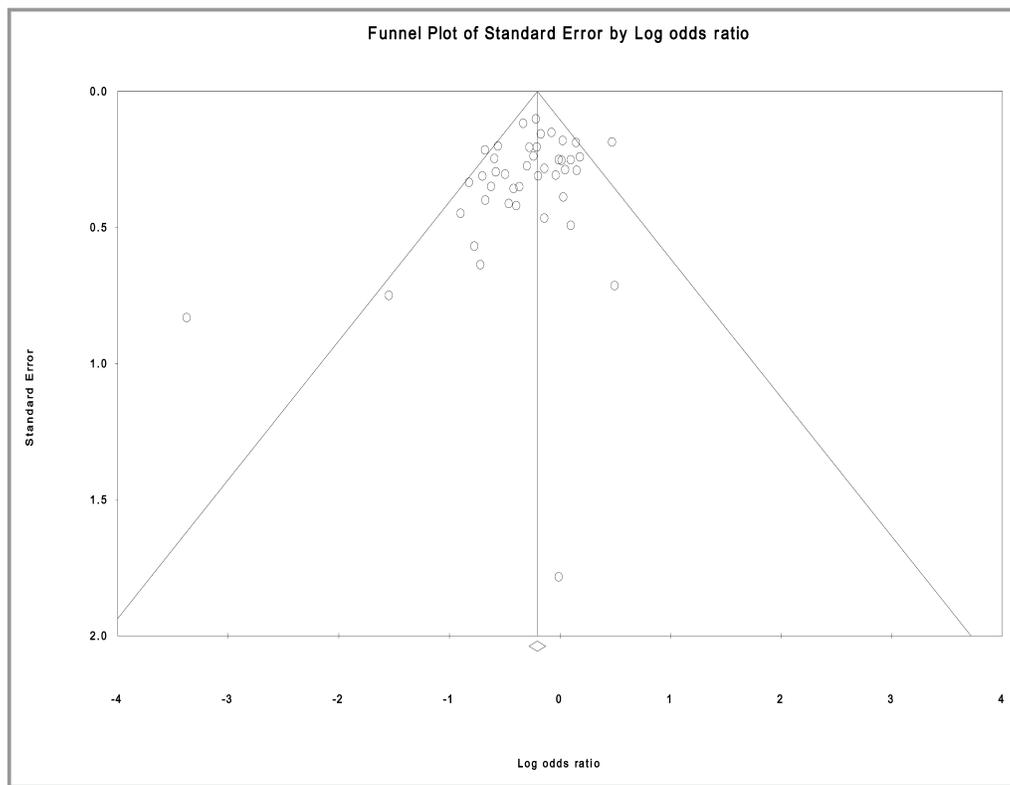


Figure 2. Funnel plot for readmission outcomes.

was calculated for each study reporting mortality outcomes. Whereas we are reporting RR for hospitalization outcomes, not all studies provided sufficient data for calculating RR, but all studies did report sufficient data for calculating an odds ratio (OR). Therefore, we are reporting both RR and OR ES measures for hospitalization outcomes.

For studies testing more than 1 intervention and sharing the same control group, we followed procedures established by the Cochrane Collaboration as well as Borenstein, Cooper,

and colleagues by merging intervention groups to avoid dependency among comparisons in the meta-analysis.^{13–15}

Study ESs were pooled using a random-effects model. The random-effects model was chosen because of the expected heterogeneity across samples and across studies testing different types of adherence interventions. Substantial heterogeneity is expected in health behavior research. Each individual study ES was weighted by the inverse of its total variance (the study's sampling variance plus the calculated between-study variance, or T^2). Studies with significant standardized residuals were examined as potential outliers. Heterogeneity across the studies was assessed using the heterogeneity statistic, Q , as well as I^2 , which is a "signal-to-noise" ratio indicating the proportion of between-study heterogeneity in the meta-analysis. We assessed for publication bias by visual examination of funnel plots (see Figures 1 and 2).

Moderator analyses were conducted for potential moderator variables that were present in a sufficient number of studies to further explain heterogeneity across studies, compare effects between different subgroups, and evaluate the impact of potential sources of bias. We used metaregression for continuous variables and a meta-analytic analogue of ANOVA for categorical variables. Moderator analyses were conducted on study characteristics (such as year of publication or whether a study reported a funding source), sample characteristics (mean age, sex, and race/ethnicity), and intervention characteristics.

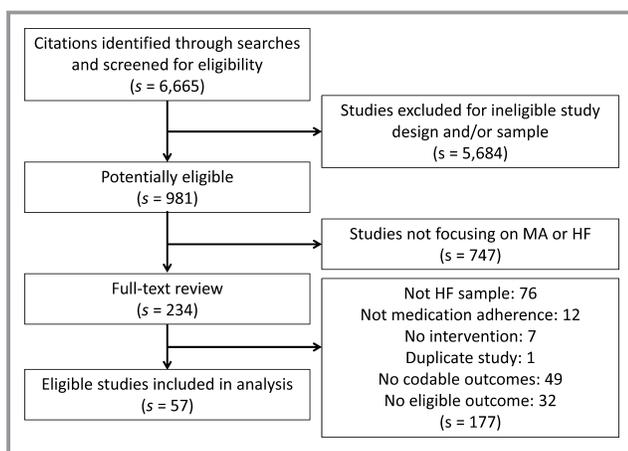


Figure 3. Flow diagram of study selection. s=number of studies. HF indicates heart failure; MA, medication adherence.

Table 2. Characteristics of Heart Failure Medication Adherence Trials Reporting Mortality or Readmission Outcomes

Study (Year)	Country	NYHA Class, %* Mean LVEF, %	Mean Age, yr % Female	No. of Subjects Randomized	Data Collectors Blinded	Outcomes
Antonicelli (2008, 2010) ^{16,17}	Italy	NR/58/37/5 LVEF: 36%	78 39%	Tx: 28 Co: 29	NR	Mortality RR: 0.58 Readmission OR: 0.04
	Intervention:	Weekly telemonitoring assessing adherence and HF symptoms, adjusting treatment as needed				
	Control:	Usual care				
Assyag (2009) ¹⁸	France	NR/NR/44/55 LVEF: NR	72.9 41.7%	Tx: 218 Co: 211	NR	Mortality RR: 0.86 Readmission OR: 1.17
	Intervention:	Multidisciplinary HF management and patient education, and symptom monitoring				
	Control:	Usual care				
Atienza (2004) ¹⁹	Spain	10.5/39.5/40/10 LVEF: 36%†	68 40%	Tx: 164 Co: 174	NR	Mortality RR: 0.62 Readmission OR: 0.51
	Intervention:	Inpatient education about HF, self-monitoring, and medications; Postdischarge clinic follow-up and telemonitoring				
	Control:	Usual care				
Azad (2008) ²⁰	Canada	25/45/27/NR LVEF: NR	75 100%	Tx: 45 Co: 46	Y	Mortality RR: 0.21 Readmission OR: NR
	Intervention:	Multidisciplinary HF clinical pathway program (12 visits over 6 weeks) including education and counseling				
	Control:	Usual care				
Balk (2008) ²¹	Netherlands	7/40/48/2 LVEF: 31%	66 30%	Tx: 101 Co: 113	NR	Mortality RR: 1.25 Readmission OR: NR
	Intervention:	Video-based patient education, adherence reminders, and motivational messages				
	Control:	Usual care				
Bisharat (2012) ²²	Israel	NR	69.4 32.4%	Tx: 33 Co: 41	NR	Mortality RR: NR Readmission OR: 0.68
	Intervention:	Patient counseling by nurse (pre-discharge) and pharmacist (post-discharge)				
	Control:	Usual care				
Blue (2001) ²³	UK	NR/21.5/38/40.5 LVEF: NR	75 42%	Tx: 84 Co: 81	Y	Mortality RR: 0.96 Readmission OR: 0.83
	Intervention:	Nursing home visits and telephone contacts for medication and disease education, self-monitoring, and psychological support				
	Control:	Usual care				
Bocchi (2008) ²⁴	Brazil	20/41/26/12 81% had LVEF ≤ 45%	50.7 31%	Tx: 233 Co: 117	Y	Mortality RR: 0.85 Readmission OR: 0.58
	Intervention:	Disease management program including education and telephone monitoring				
	Control:	Usual care				
Bouvy (2003) ²⁵	Netherlands	9/34/51/6 LVEF: NR	69.7 34%	Tx: 74 Co: 78	NR	Mortality RR: 0.67 Readmission OR: NR
	Intervention:	Pharmacists conducted structured interviews about medication use, reasons for nonadherence, and reinforcing adherence. Patients contacted monthly for follow-up				
	Control:	Usual care				
Capomolla (2002) ²⁶	Italy	NYHA III to IV: 35% LVEF: 29%	56 16%	Tx: 112 Co: 122	NR	Mortality RR: 0.16 Readmission OR: NR
	Intervention:	Day-hospital multidisciplinary HF management program including education, counseling, and nurse telephone follow-up				
	Control:	Usual care				

Continued

Table 2. Continued

Study (Year)	Country	NYHA Class, %* Mean LVEF, %	Mean Age, yr % Female	No. of Subjects Randomized	Data Collectors Blinded	Outcomes
Cleland (2005) ²⁷	UK, Germany, Netherlands	19.6/43.2/29.6/7.6 LVEF: 25%	67.2 23%	Tx A: 173 Tx B: 168 Co: 85	NR	Mortality RR: 0.62 Readmission OR: 0.80
	Intervention:	A: Nurse telephone support B: Nurse telephone support plus home telemonitoring				
	Control:	Usual care				
Cline (1998) ²⁸	Sweden	NR/NR/62/NR LVEF: 34%	75.6 47%	Tx: 80 Co: 110	NR	Mortality RR: 1.07 Readmission OR: 0.54
	Intervention:	Patient and family disease and medication education, pill organizers, symptom diaries				
	Control:	Usual care				
Dahl (2001) ²⁹	USA	NR	73.5 NR	Tx: 609 Co: 583	NR	Mortality RR: 0.64 Readmission OR: 0.73
	Intervention:	Advanced practice nurse delivered HF self-care education to hospitalized patients. Follow-up phone calls to high-risk patients				
	Control:	Usual care				
Dawson (1998) ³⁰	USA	NR	70.6 50%	Tx: 8 Co: 2	NR	Mortality RR: NR Readmission OR: 1.00
	Intervention:	Advanced practice nurse conducted patient education and goal setting regarding HF pathophysiology, medications (effects and side effects), diet, exercise, symptom monitoring, and follow-up appointments				
	Control:	Usual care				
DeBusk (2004) ³¹	USA	I to II: 49% III to IV: 51% LVEF: NR	72 49%	Tx: 228 Co: 234	Y	Mortality RR: 0.77 Readmission OR: 1.04
	Intervention:	Home-based nurse case management including patient education, self-management skills, and care coordination				
	Control:	Usual care				
DeWalt (2012) ³²	USA	19/50/20/11 59% had LVEF <45%	60.7 48%	Tx: 303 Co: 302	Y	Mortality RR: 0.68 Readmission OR: NR
	Intervention:	Single session of self-care training, then telephone-delivered self-care training (5–8 calls over 4 weeks, then every 2 weeks, tapering to monthly) by health educators, including daily weights, symptom assessment, medication adherence, diuretic titration, low-sodium diet, and exercise				
	Control:	Single session of self-care training plus usual care				
Doughty (2002) ³³	New Zealand	0/0/24/76 LVEF: 32%	73 40.1%	Tx: 100 Co: 97	NR	Mortality RR: 0.77 Readmission OR: 1.18
	Intervention:	Postdischarge clinical review, patient education, medication and weight diaries, and regular clinic follow-up				
	Control:	Usual care				
Dunagan (2005) ³⁴	USA	NR/20/71/9 LVEF: NR	70 56%	Tx: 76 Co: 75	Y	Mortality RR: 1.16 Readmission OR: 0.70
	Intervention:	Telephone monitoring by nurses including HF education, self-management skills, diet, and adherence, plus screening for symptom changes and exacerbations				
	Control:	Usual care				
Ekman (1998) ³⁵	Sweden	NYHA III to IV: 100% LVEF: 40.5%	80.3 42%	Tx: 79 Co: 79	NR	Mortality RR: 1.24 Readmission OR: 0.88
	Intervention:	Nurse-monitored structured care program in an outpatient clinic including setting goals for medication adherence, weight, diet, or symptom monitoring				
	Control:	Usual care				

Continued

Table 2. Continued

Study (Year)	Country	NYHA Class, %* Mean LVEF, %	Mean Age, yr % Female	No. of Subjects Randomized	Data Collectors Blinded	Outcomes
Falces (2008) ³⁶	Spain	II: 86% III to IV: 14% LVEF: 52%	79.5 58.3%	Tx: 53 Co: 50	NR	Mortality RR: 0.51 Readmission OR: 0.52
	Intervention:	Education about HF, medication, and diet with telephone follow-up				
	Control:	Control type not specified				
Ferrante (2010) ³⁷	Argentina	I to II: 50.6% III to IV: 49.4% 79.6% had LVEF <40%	65 29.2%	Tx: 760 Co: 758	NR	Mortality RR: 1.06 Readmission OR: 0.81
	Intervention:	Educational booklet and nurse-delivered telephone education and monitoring focusing on improving adherence, exercise, symptom monitoring, weight, and edema				
	Control:	Usual care				
Gattis (1999) ³⁸	USA	13/54/30/3 LVEF: 30% [†]	67.3 32%	Tx: 90 Co: 91	N	Mortality RR: 0.59 Readmission OR: NR
	Intervention:	Clinical pharmacist provided therapy optimization recommendations to physician and medication education to patients. Patients also received medication calendars and telephone follow-up				
	Control:	Usual care				
Harrison (2002) ³⁹	Canada	1/22/67/10 LVEF: NR	75.6 45%	Tx: 92 Co: 100	NR	Mortality RR: 0.89 Readmission OR: 0.67
	Intervention:	Transitional care intervention to provide education and closer monitoring at and after discharge from hospital				
	Control:	Usual care with similar number of provider contacts				
Holland (2007) ⁴⁰	UK	6/27/34/33 LVEF: NR	77 53.5%	Tx: 149 Co: 144	NR	Mortality RR: 1.20 Readmission OR: NR
	Intervention:	Home visits by pharmacists to provide education on HF, self-care, and medication. Medication organizers provided when deemed necessary				
	Control:	Usual care				
Jaarsma (1999) ⁴¹	Netherlands	III: 17% III to IV: 21% IV: 61% LVEF: 34.4%	73 42%	Tx: 89 Co: 97	Y	Mortality RR: 1.63 Readmission OR: 0.57
	Intervention:	HF education provided by a nurse, including symptom recognition, sodium restriction, fluid management, and adherence				
	Control:	Usual care				
Jerant (2003) ⁴²	USA	NR/65/32/3 LVEF: NR	70.1 54%	Tx A: 13 Tx B: 12 Co: 12	N	Mortality RR: 2.50 Readmission OR: 0.49
	Intervention:	A: Home video-based telecare visits B: Telephone contact by a nurse				
	Control:	Usual care				
Kasper (2002) ⁴³	USA	NR/35.5/58.5/NR LVEF: 27.3%	62 39.5%	Tx: 102 Co: 98	Y	Mortality RR: 0.52 Readmission OR: 0.62
	Intervention:	Team-based approach with algorithm-based treatment plans with postdischarge clinic and telephone contacts, pill sorters, dietary support, and education				
	Control:	Usual care by primary physicians				
Kimmelstiel (2004) ⁴⁴	USA	1/54.5/42.5/2 LVEF: 30.5%	72.1 42%	Tx: 97 Co: 103	Y	Mortality RR: 0.83 Readmission OR: 1.11
	Intervention:	Home visit by a nurse focusing on medication adherence, barriers, and HF self-care; written educational materials provided; telephone follow-up				
	Control:	Usual care				

Continued

Table 2. Continued

Study (Year)	Country	NYHA Class, %* Mean LVEF, %	Mean Age, yr % Female	No. of Subjects Randomized	Data Collectors Blinded	Outcomes
Koelling (2005) ⁴⁵	USA	NYHA: NR LVEF: 26.5%	64.8 42%	Tx: 107 Co: 116	NR	Mortality RR: 0.76 Readmission OR: 0.45
	Intervention:	Predischarge HF, self-care, and medication education session with a nurse educator; patients given a copy of treatment guidelines in lay language				
	Control:	Usual care				
Krumholz (2002) ⁴⁶	USA	NYHA: NR LVEF: 37.5%	73.8 43%	Tx: 44 Co: 44	NR	Mortality RR: 0.70 Readmission OR: 0.41
	Intervention:	HF patient education by nurse within 2 weeks of hospital discharge; telephone follow-up for 12 months				
	Control:	Usual care				
Laramée (2003) ⁴⁷	USA	17/45/35/3 LVEF: NR	70.7 46%	Tx: 141 Co: 146	NR	Mortality RR: 0.89 Readmission OR: 1.03
	Intervention:	Inpatient care coordination by a nurse case manager; patient and family education; 12 weeks of telephone follow-up; HF medications adjusted to optimal regimen per guidelines				
	Control:	Usual care				
Lopez-Cabezas (2006) ⁴⁸	Spain	I to II: 86% III to IV: 14% LVEF: 51%	75.7 56%	Tx: 70 Co: 64	N	Mortality RR: 0.43 Readmission OR: 0.50
	Intervention:	Education about HF, diet, medications, and MA with telephone follow-up				
	Control:	Usual care				
McDonald (2002) ⁴⁹	Ireland	NYHA: NR LVEF: 37%	70.8 33.7%	Tx: 51 Co: 47	NR	Mortality RR: 0.92 Readmission OR: NR
	Intervention:	Inpatient education consults by specialist nurse and dietician; postdischarge telephone follow-up and HF clinic visits				
	Control:	Usual care				
Mejhert (2004) ⁵⁰	Sweden	NR/62/37/1 LVEF: 34%	75.8 42%	Tx: 103 Co: 105	NR	Mortality RR: 1.20 Readmission OR: 1.06
	Intervention:	Nurse-monitored management program including symptom and laboratory monitoring, medication adjustment, and patient education; written educational materials				
	Control:	Usual care				
Murray (2007) ⁵¹	USA	19.5/41/35/4.5 LVEF: 49.6%	62.1 66.9%	Tx: 122 Co: 192	Y	Mortality RR: 1.50 Readmission OR: 0.82
	Intervention:	Pharmacist-delivered medication education, health literacy tools, and medication calendar; MA and weight monitoring				
	Control:	Usual care				
Nimpitakpong (2002) ⁵²	Thailand	NR	61.4 47.5%	Tx A: 38 Tx B: 42 Co: 45	NR	Mortality RR: 1.71 Readmission OR: 1.12
	Intervention:	A: Discharge consultation with a nurse; written materials with education, behavioral, and support strategies; consultation with a pharmacist B: All of elements of (A) plus follow-up home visit for to monitor patient, problem solve, and reinforce MA				
	Control:	Usual care				
Nucifora (2006) ⁵³	Italy	1/35/62/2 LVEF: 43%	73 38%	Tx: 99 Co: 101	NR	Mortality RR: 1.79 Readmission OR: 1.00
	Intervention:	Predischarge HF and treatment education by a cardiovascular nurse; telephone follow-up; MA and symptoms assessment				
	Control:	Usual care				

Continued

Table 2. Continued

Study (Year)	Country	NYHA Class, %* Mean LVEF, %	Mean Age, yr % Female	No. of Subjects Randomized	Data Collectors Blinded	Outcomes
Oddone (1999) ⁵⁴	USA	11/36.5/33.5/19 65% had LVEF <40%	64.5 1%	Tx: 222 Co: 221	Y	Mortality RR: 1.52 Readmission OR: 1.62
	Intervention:	Inpatient education provided by RN using AHA guidelines; Treatment plan developed with patient, physician, and nurse; postdischarge telephone and clinic follow-up				
	Control:	Usual care				
Powell (2010) ⁵⁵	USA	III: 31.6% LVEF: NR	63.6 47.3%	Tx: 451 Co: 451	Y	Mortality RR: 0.90 Readmission OR: 0.85
	Intervention:	Group-based self-management counseling and skills training				
	Control:	Usual care with HF education alone				
Rainville (1999) ⁵⁶	USA	NR/14.7/67.7/17.7 LVEF: NR	69.9 50%	Tx: 17 Co: 17	NR	Mortality RR: NR Readmission OR: 0.22
	Intervention:	Pharmacist and clinical nurse specialist identified and addressed patients' readmission risk factors; pharmacist-delivered HF education, medication education; recommended medication changes				
	Control:	Usual care				
Ramachandran (2007) ⁵⁷	India	I to II: 74% III: 14% IV: 12% LVEF: 21.8%	44.6 22%	Tx: 25 Co: 25	NR	Mortality RR: NR Readmission OR: 1.66
	Intervention:	Face-to-face and telephone HF self-management education; patient education manual with self-monitoring charts				
	Control:	Usual care				
Rich (1995) ⁵⁸	USA	Mean NYHA class: 2.4 LVEF: 42%	79.3 63%	Tx: 142 Co: 140	Y	Mortality RR: 0.76 Readmission OR: 0.56
	Intervention:	Inpatient HF education by a nurse, dietary and social service consultations; medication review by a geriatric cardiologist; postdischarge nurse follow-up				
	Control:	Usual care				
Riegel (2006) ⁵⁹	USA	NR/18.7/46.3/35.1 LVEF: 43.2%	72 53.7%	Tx: 70 Co: 65	NR	Mortality RR: 0.58 Readmission OR: 0.97
	Intervention:	Telephone nurse case management to teach self-care knowledge and skills and monitor symptoms				
	Control:	Usual care				
Ross (2004) ⁶⁰	USA	NR	56 23%	Tx: 54 Co: 53	NR	Mortality RR: 0.98 Readmission OR: 0.88
	Intervention:	Web access to medical record, educational guide, and messaging system				
	Control:	Usual care				
Sadik (2005) ⁶¹	UK	29.5/50.5/16/4 LVEF: NR	58.7 50%	Tx: 109 Co: 112	Y	Mortality RR: 1.02 Readmission OR: NR
	Intervention:	Regimen simplification (where possible); pharmacist-provided HF, medication, and symptom management education; HF symptom and MA self-monitoring				
	Control:	Usual care				
Sethares (2004) ⁶²	USA	NR	76.2 100%	Tx: 33 Co: 37	NR	Mortality RR: NR Readmission OR: 0.47
	Intervention:	Tailored educational messages chosen based on responses to questions about treatment benefits and barriers				
	Control:	Usual care				
Shively (2013) ⁶³	USA	3.6/33/52.4/NR LVEF: NR	66.1 1.2%	Tx: 43 Co: 41	NR	Mortality RR: NR Readmission OR: 0.64
	Intervention:	6-month intervention delivered by advanced practice nurses; Content included goal setting, HF education, medication education, and barrier identification, symptom/weight monitoring, and planning responses to situations				
	Control:	Usual care				

Continued

Table 2. Continued

Study (Year)	Country	NYHA Class, %* Mean LVEF, %	Mean Age, yr % Female	No. of Subjects Randomized	Data Collectors Blinded	Outcomes
Sisk (2006) ⁶⁴	USA	18.5/22.4/14/45.1 LVEF: NR	59.4 46.3%	Tx: 203 Co: 203	Y	Mortality RR: 1.00 Readmission OR: 0.77
	Intervention:	Nurses counseled patients on HF self-care, symptoms, and medications; care management team met to discuss patients regularly				
	Control:	Usual care				
Stewart (2002) ⁶⁵	Australia	NR/45.5/45/9.5 LVEF: 38%	75 43.8%	Tx: 149 Co: 148	Y	Mortality RR: 0.86 Readmission OR: 0.75
	Intervention:	Postdischarge home visit; review of patient's adherence to and knowledge of treatment; assessment of available social support and risk factors				
	Control:	Usual care				
Strömberg (2003) ⁶⁶	Sweden	NR/18/71/11 LVEF: NR	77.5 38.7%	Tx: 52 Co: 54	Y	Mortality RR: 0.36 Readmission OR: NR
	Intervention:	Nurse-led HF clinic; medications optimized, HF and social support education given; telephone follow-up				
	Control:	Usual care				
Strömberg (2006) ⁶⁷	Sweden	NR	70 29.2%	Tx: 82 Co: 72	Y	Mortality RR: 2.61 Readmission OR: NR
	Intervention:	7-module computer-based multimedia HF education program				
	Control:	Usual care				
Tierney (2003) ⁶⁸	USA	NR	60 66%	Tx A: 197 Tx B: 158 Tx C: 170 Co: 181	Y	Mortality RR: NR Readmission OR: 0.94
	Intervention:	A: Automated guideline-based care suggestions provided to physicians B: Prompts to pharmacist to review guideline-based cardiac care suggestions C: Includes content of both treatments A and B				
	Control:	Usual care				
Tsuyuki (2004) ⁶⁹	Canada	8/49/38/5 LVEF: 31%	72 42%	Tx: 140 Co: 136	NR	Mortality RR: 1.30 Readmission OR: 1.21
	Intervention:	Predischarge medication and HF education, adherence aids, written materials, and event diary provided; postdischarge follow-up telephone contact for 6 months				
	Control:	Usual care				
Udelson (2009) ⁷⁰	USA	18.7/65.9/15.4/NR LVEF: 29.5%	65.3 26.2%	Tx: 136 Co: 133	N	Mortality RR: NR Readmission OR: 1.04
	Intervention:	Once-daily dosing regimen				
	Control:	Twice-daily dosing regimen				
Varma (1999) ⁷¹	UK	Mean NYHA class: 2.12 LVEF: NR	75.9 59%	Tx: 42 Co: 41	NR	Mortality RR: 0.98 Readmission OR: NR
	Intervention:	HF, medication, and symptom management education by a pharmacist; self-monitoring diaries				
	Control:	Usual care				
Wakefield (2009) ⁷²	USA	NR/28/65/7 LVEF: 41.4%	69.5 1%	Tx A: 47 Tx B: 52 Co: 49	Y	Mortality RR: 1.13 Readmission OR: NR
	Intervention:	A: Telephone contacts for symptom monitoring and reinforcement of treatment plan by a nurse for 3 months postdischarge B: Same as A, but using a videophone instead of telephone				
	Control:	Usual care				

AHA indicates American Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction; MA, medication adherence; NR, information not reported or not available; NYHA, New York Heart Association; OR, odds ratio; RN, registered nurse; RR, relative risk.

*NYHA classification reported as percentage of subjects rated as class I/II/III/IV unless otherwise specified.

[†]Median.

Results

Literature searching resulted in 6665 citations of potentially eligible studies. Of those, 234 were screened as being eligible for full-text review, and 57 studies fulfilled the inclusion criteria for this meta-analysis (see Figure 3). Mortality outcomes were reported for 48 studies. Hospitalization/readmission outcomes were reported for 43 studies.

Primary Study Characteristics

Studies in the sample were published between 1996 and 2013. Attributes for each study are reported in Table 2,^{16–72} and study demographics are summarized in Table 3. Study participants were largely older, with mean sample ages ranging from 45 to 80 years (median, 70.4). Information on type of HF was inconsistently reported in the primary studies. In those studies that did report the type of HF, the sample consisted entirely or predominantly of patients with reduced ejection fraction. Studies had a median sample size of 197. Whereas many of the studies reported some degree of attrition between randomization and final follow-up, all but 3 reported mortality and/or hospitalization outcomes for all randomized subjects, even if other measures were not collected for subjects lost to follow-up.^{62,63,70}

Interventions in the Reviewed Studies

Intervention descriptions across the eligible studies varied widely in degree of detail. A bulk of the interventions utilized medication education (s=50) and disease education (s=48) as components of their interventions. In addition to using educational approaches, 14 interventions improved integration of care for HF patients and 11 attempted to get patients to incorporate self-management strategies in some manner. Another common intervention strategy was self-monitoring. Eight interventions had patients self-monitor their medication-

taking behavior by using a medication diary or other means, whereas 28 interventions encouraged patient self-monitoring of HF signs or symptoms. All but 4 interventions used multiple intervention strategies to improve adherence. The single-strategy approaches involved disease education (s=2), dose modification (s=1), and a patient web portal (s=1). Although most studies used medication education in combination with other strategies, no other distinct patterns of intervention component combinations emerged.

Fifty-two interventions involved some degree of face-to-face contact with an interventionist. Many interventions involved interventionists from more than 1 discipline. Of those that specified the interventionist profession, 40 used nurses (including 5 using advanced practice nurses), 14 used pharmacists, 15 used physicians, 7 had dietitians, 6 had social workers, 1 had a case manager, and 4 employed unspecified health care providers. Only 4 studies had interventions delivered by the patients' regular health care providers.

Information about intervention dose was poorly reported across the studies. Only 28 studies clearly reported the number of intervention sessions (median=6.5 sessions; range, 1–52). Six studies reported the number of minutes per session (median=48.75; range, 10–120). Interventions were delivered over a median of 181 days (s=48; range, 1–901).

Nearly all interventions incorporated some form of verbal interaction in which interventionists talked to patients about their HF or HF medication. Thirty-eight interventions were delivered partly over the telephone. Fewer used telehealth (s=2), text messaging (s=2), computer delivery (s=4), video (s=6), or mailed intervention materials (s=4).

Meta-Analysis of Study Outcomes

Forty-eight studies reported sufficient data for calculating mortality outcome ESs (see Figure 4). Random-effects meta-analysis found that mortality risk was 10.6% lower among HF patients who received MA interventions when compared to control groups (RR, 0.89; 95% CI, 0.81, 0.99). The pooled analysis yielded low, but significant, heterogeneity, with a Q -statistic of 67.46 ($P=0.027$) and an I^2 of 30.33. When 2 studies with significant residuals were removed to test for potential outliers, RR was essentially unchanged (RR, 0.92; 95% CI, 0.85, 1.00), but the heterogeneity was reduced ($Q=52.88$; $P=0.196$; $I^2=14.90$).

MA interventions also reduced HF patients' risk of hospitalization (RR=0.89; 95% CI, 0.81, 0.97). However, only 32 treatment versus control studies contributed to the pooled estimate of RR. In order to include a larger number of studies in the hospitalization meta-analysis, we used the OR metric because 43 studies could provide data for the calculation of the overall effect (see Figure 5). The pooled random-effects

Table 3. Descriptive Statistics of Eligible Studies

	s	Min	Q ₁	Median	Q ₃	Max
Year of publication	57	1996	2002	2004	2007	2013
Mean age (y)	56	44.6	64.9	70.4	75	80.3
Total post-test sample size per study	57	10	107	197	306	3902
Percentage attrition	57	0	0	0	0	9.5
Percentage female	55	1	32.4	42	50	100
Percentage from under-represented racial/ethnic groups	23	4.5	19	26.5	54	100

s=number of studies.

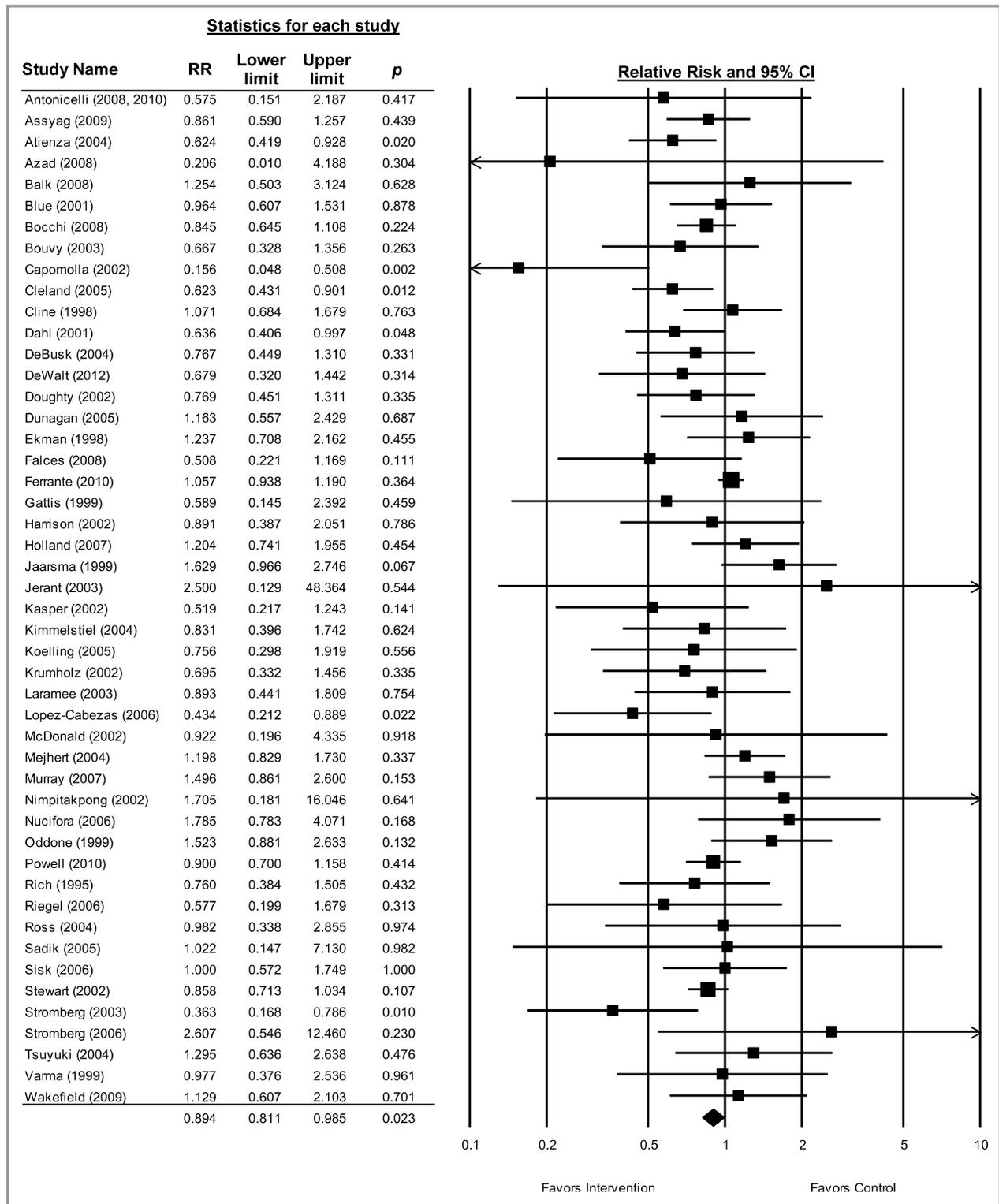


Figure 4. Forest plot for mortality outcome. RR indicates relative risk.

OR was 0.79 (95% CI, 0.71, 0.89). Again, the studies contained significant heterogeneity ($Q=72.00$; $P=0.003$; $I^2=41.66$). In this analysis, 2 studies had significant residuals. Removing those studies from the analysis gave an OR of 0.79

(95% CI, 0.73, 0.87) and reduced heterogeneity ($Q=44.54$; $P=0.287$; $I^2=10.19$). Pooled analysis statistics for both mortality and hospitalization outcomes are reported in Table 4.

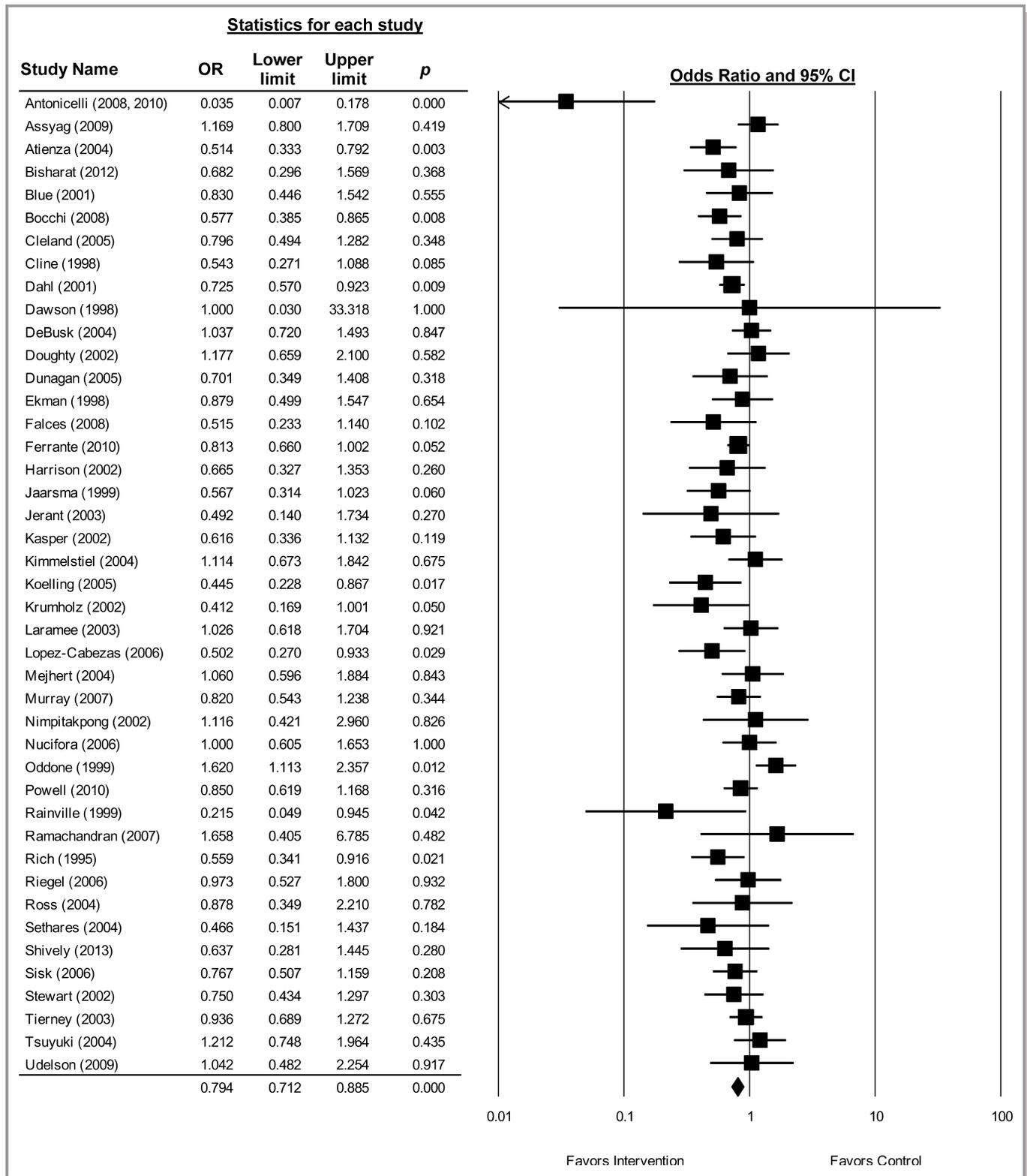


Figure 5. Forest plot for readmissions outcome. OR indicates odds ratio.

Risk of Bias Sensitivity Analyses

We conducted moderator analyses to evaluate whether ESs were different based on factors such as year of publication,

presence of funding, study location, type of control group, randomization procedures, blinding, and use of intent-to-treat analyses (see Table 5 for list of report and methodological moderators analyzed). No significant ES differences were

Table 4. Meta-Analysis Summary Statistics

Outcome	Relative Risk			Odds Ratio			Q	I ²
	k _{RR}	RR	95% CI	k _{OR}	OR	95% CI		
Mortality	48	0.89*	0.81, 0.99	48	0.86*	0.76, 0.98	67.46*	30.33
Readmissions	32	0.89*	0.81, 0.97	43	0.79***	0.71, 0.89	72.00**	41.66

I² indicates heterogeneity index; k, number of comparisons; Q, heterogeneity statistic.

*P<0.05; **P<0.01; ***P<0.001.

detected from any of the risk of bias analyses for either mortality or hospitalization outcomes.

Intervention and Sample Moderators

Although the studies tested many different types of interventions, only 2 intervention components showed significant ES differences in our moderator analyses (Table 6). For mortality outcomes, interventions that included components to improve health care providers' skills for addressing MA with their patients had a greater risk for mortality than did interventions not trying to improve health care provider adherence skills (RR, 1.50 vs 0.87; P=0.007). However, because only 4 studies' interventions included content to improve health care providers' adherence management skills, this finding must be interpreted carefully.

For hospitalization outcomes, interventions that did not include self-monitoring of patients' medication taking had a lower mean OR than did interventions using self-monitoring (OR, 0.76 vs 1.03; P=0.016). Other intervention components as well as sample moderators, such as sex, age, and race/ethnicity, were tested for their influence on ES (see Table 5), but no significant differences were found.

Discussion

Our analyses found that interventions to improve adherence to medications for HF significantly reduce the risk for both hospitalization and death. The ESs for these outcomes were largely consistent across studies, with little heterogeneity in the overall ES estimates. In performing this analysis, we conducted a comprehensive search to include a broad spectrum of intervention studies. Previous meta-analyses of HF management programs have been more restricted in focus, examining distance-mediated interventions using telephone support or telemonitoring⁷³ or outpatient disease management programs.⁷⁴ Another meta-analysis by Feltner et al.⁷⁵ examined transitional care interventions to prevent HF readmissions, but did not report overall ES estimates across intervention types.

Comparison With Past Meta-Analyses

ESs in this meta-analysis are largely consistent with ESs in previous meta-analyses reporting results across far fewer primary studies. For mortality, our RR of 0.89 was lower than Gwady-Sridhar et al.'s⁷⁶ finding of 0.98 and similar to Inglis et al.'s⁷³ findings for structured telephone support interventions (RR=0.88). The RR of mortality we calculated is somewhat greater than what Inglis et al. found for telemonitoring interventions (RR=0.66).⁷³ In their meta-analysis of HF care management programs, Wakefield et al.⁷⁴ found a mortality outcome OR of 0.79 (converted from the reported standardized mean difference [d]), which is comparable to our mortality OR of 0.86.

Looking at readmission outcomes, we found an OR of 0.79 and RR of 0.89. Wakefield et al. identified an OR of 0.75 (converted from d),⁷⁴ whereas Gwady-Sridhar et al. reported a RR of 0.79⁷⁶ and Inglis et al. reported RRs of 0.92 and 0.91 for structured telephone support and telemonitoring interventions, respectively.⁷³

Previous meta-analyses did not conduct moderator analyses to determine which intervention components were associated with larger ESs. In our project, we found that readmission outcomes were actually better when adherence interventions did not have patients self-monitoring their medication-taking behavior. A previous meta-analysis looking at adherence interventions among older adults found that self-monitoring interventions were associated with increased MA ESs.⁷⁷ It is possible that for HF patients, self-monitoring of disease symptoms, such as daily weight measurement, may be more useful than monitoring medication taking to prevent hospital readmission.

An interesting finding in this project was that interventions designed to train health care providers to have better skills for addressing MA actually resulted in a greater mortality risk for patients than did interventions not focusing on health care providers. This finding must be interpreted cautiously, given that only 4 studies included improving health care providers' skills for addressing adherence. Each of these 4 interventions also included a variety of other types of intervention components. Whereas health care provider skills and health

Table 5. List of Tested Moderators

Report and methodological moderators
Allocation concealment
Blinding of data collectors
Location where study was conducted
Presence of funding
Publication method (eg, journal article, dissertation)
Randomization method
Type of control group (true control vs attention-control)
Use of intent-to-treat analyses
Year of publication
Sample moderators
Sex (% of women in sample)
Mean sample age
Presence of comorbidities
Race/ethnicity
Intervention moderators
Disease education
Dose modification
Duration of intervention
Goal setting
Improving health care provider skills to address adherence
Improved integration of health care services
Increasing health care providers' time with patients
Institutional system change
Mediated intervention
Computer-mediated intervention
Telephone-mediated intervention
Medication education/counseling
No. of intervention sessions
Problem solving
Review of medications for appropriateness
Self-management skills
Self-monitoring of medication
Self-monitoring of signs or symptoms of heart failure
Social support
Type of interventionist
Written materials to improve adherence

care system interventions are important, interventions to improve MA must be patient centered. It is very difficult to modify patient behavior simply by modifying health care provider behavior, and a broader meta-analysis of health care provider interventions to improve MA found that whereas health care provider interventions are modestly

Table 6. Selected Intervention Moderators for Mortality and Readmission Outcomes

Moderator	k	RR	95% CI	I ² , %	Q	P Value
Mortality						
Intervention included disease education						
Yes	42	0.91	0.82, 1.01	32.35	2.59	0.107
No	6	0.72	0.55, 0.94	0.00		
Intervention included medication education						
Yes	41	0.89	0.81, 0.98	26.28	0.00	0.995
No	7	0.89	0.57, 1.41	54.49		
Intervention designed to improve health care providers' skills for addressing MA						
Yes	4	1.50	1.02, 2.19	0.00	7.34	0.007
No	44	0.87	0.79, 0.96	29.39		
Intervention included patient self-monitoring of medication-taking						
Yes	7	0.93	0.73, 1.18	0.00	0.14	0.711
No	41	0.89	0.79, 0.99	38.68		
Readmissions						
Intervention included disease education						
Yes	38	0.81	0.73, 0.90	35.21	0.80	0.372
No	5	0.58	0.29, 1.18	72.24		
Intervention included medication education						
Yes	38	0.81	0.73, 0.90	33.55	1.15	0.283
No	5	0.57	0.30, 1.08	73.03		
Intervention designed to improve health care providers' skills for addressing MA						
Yes	4	0.99	0.76, 1.27	0.00	2.86	0.091
No	39	0.772	0.69, 0.87	44.25		
Self-monitoring of medication taking						
Yes	6	1.03	0.83, 1.28	0.00	5.81	0.016
No	37	0.76	0.68, 0.86	42.38		

k indicates the number of comparisons; MA, medication adherence; OR, odds ratio; RR, relative risk.

effective, interventions must also include patient-centered approaches.⁷⁸

Limitations

Any meta-analysis project is subject to certain limitations. First, it is always possible that some eligible studies may have not been identified through our searches. We used comprehensive search methods to identify as many eligible studies as possible and employed careful study-tracking procedures to avoid excluding any eligible studies. Meta-analyses are limited, however, by the primary research that has been conducted, methodological quality of the primary research, and quality of reporting of the primary studies. It is unknown whether

otherwise eligible studies that were excluded because of inadequate data for calculating ESs might have impacted the overall ES.

Recommendations for Future Research

Room exists to develop interventions that further improve mortality and readmission risk for HF patients. Many MA interventions for HF patients are conducted as part of broader HF self-care interventions. No quantitative synthesis has yet summarized and compared effectiveness across HF self-care interventions to identify the most effective approach to improve HF outcomes. Furthermore, it is likely that the most effective approaches may differ for specific patient populations, a research question that may be further explored through meta-analysis.

The lack of heterogeneity in mortality and readmission outcomes indicates that any intervention that successfully improves HF medication adherence is likely to improve mortality and readmission outcomes. Future research should investigate methods to assess adherence in clinical practice settings and integrate MA interventions into practice to improve clinical outcomes, and whether any type of additional attention may improve HF mortality and readmission rates.

Conclusion

Overall, interventions to improve adherence to HF medications lower risk for hospital readmission and overall mortality. MA is a key component of HF self-care and should be addressed as part of any HF self-care program. Room may exist for further improving MA interventions for HF patients, but the existing data show that the standard of care for addressing adherence in clinical practice can be improved to reduce HF morbidity and mortality.

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Disclosures

None.

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