Review Article

Effectiveness of the Pharmacist-Involved Multidisciplinary Management of Heart Failure to Improve Hospitalizations and Mortality Rates in 4630 Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: There is evidence that heart failure (HF) patients who receive pharmacist care have better clinical outcomes.

Methods and Results: English-language peer-reviewed randomized controlled trials comparing the pharmacist-involved multidisciplinary intervention with usual care were included. We searched PubMed, MEDLINE, EMBASE, CINAHL, Web of Science, Scopus, and the Cochrane Library from inception through March 2017. Cochrane method for risk of bias was used to assess within and between studies. 18 RCTs (n = 4630) were included for systematic review, and 16 (n = 4447) for meta-analysis. Meta-analysis showed a significant reduction in HF hospitalizations {odds ratio (OR) 0.72 [95% confidence interval (CI) 0.55-0.93], P = .01, I2 = 39%} but no effect on HF mortality. Similarly, a significant reduction in all-cause hospitalizations [OR 0.76, 95% CI (0.60-0.96), P = .02, I2 = 52%] but no effect on all-cause mortality was revealed. The overall trend was an improvement in medication adherence. There were significant improvements in HF knowledge (P<.05), but no significant improvements were found on health care costs and self-care.

Conclusions: The pharmacist is a vital member of a multidisciplinary team in HF management to improve clinical outcomes. There was a great deal of variability about which specific intervention is most effective in improving clinical outcomes. (*J Cardiac Fail 2019;25:744−756*)

Key Words: Heart failure, Pharmacist, Multidisciplinary team, Meta-analysis, Hospitalization, Mortality.

Heart failure (HF) is an increasingly prevalent and debilitating disease.[1] An estimated 38 million people have been diagnosed worldwide.[2] HF is characterized by high rates of mortality and morbidity[3−6] and the readmission rate remains high.[4,7] HF limits functional capacity, is associated with impaired quality of life,[8,9] and imposes a high economic burden on health care.[10−13] Despite improved outcomes from medical therapy,[14] recent studies demonstrate that ∼25% of hospitalized patients with HF are readmitted within 30 days of discharge[15−17] and 50% are readmitted within 6 months.[18−21] Further, 50% of patients die within 5 years of diagnosis.[22−24] HF often coexists with polymorbidities and polypharmacy,

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highlighting the need for innovative pharmacist-involved multidisciplinary collaborative approaches.[25−29]

Introduction

Rationale

A previous systematic review of randomized controlled trials (RCTs) reported that pharmacist care significantly reduced the risk of all-cause and HF hospitalizations, and nonsignificantly reduced mortality, particularly if the pharmacist was a member of a multidisciplinary team.[30] The multidisciplinary approach for managing HF should incorporate the implementation of guideline-directed medical therapy (GDMT) advocated by Australian,[31] American,[25] and European professional societies.[32] Recently, pharmacist-involved multidisciplinary teams have demonstrated significant contributions to HF management, including optimization of GDMT for HF with reduced ejection fraction patients,[33,34] reduction in 30-day all-cause readmission,[35] reduction in time to initial follow-up,[36] safe transition of patient from hospital to ambulatory care,[37] and overall medication management.[38] Despite this evidence, knowledge gaps exist regarding the precise role of the pharmacist in a multidisciplinary team. Therefore, this study explores current and rigorous evidence regarding the role of the pharmacist within the multidisciplinary team for HF management to improve clinical outcomes.

Objective

The objective of this systematic review and meta-analysis was to comprehensively evaluate the role of pharmacist-involved multidisciplinary HF management, to determine its effect in relation to HF hospitalizations, HF mortality, all-cause hospitalizations, all-cause mortality, medication adherence (compliance), HF knowledge, health-care costs, self-care, and composite endpoint (all-cause hospitalizations, all-cause mortality).

Methods

This study was conducted in accordance with the Cochrane methodology,[39] and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[40] An explicit method of quality measurement, grading of recommendations, assessment, development, and evaluations (GRADE) approach was incorporated to draw a summary for each outcome.[41]

Protocol and Registration

Our protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42016052195).[42]

Eligibility Criteria

Studies were eligible if they included adults (≥18 years) with a confirmed diagnosis of HF according to diagnostic methods, such as the New York Heart Association (NYHA) classification, echocardiography, Framingham criteria, nuclear imaging, cardiac magnetic resonance imaging, physician notes in medical record, left ventricular ejection fraction, and American College of Cardiology Foundation and American Heart Association (ACC/AHF) classification. According to the ACC/AHF, ejection fraction (EF) is ≤40% in HF with reduced EF (HFrEF), whereas it is ≥50% in HF with preserved EF (HFpEF). RCTs which have enrolled patients with mid-range (EF 41−49)[32] or recovered EF (EF >40)[25] were not excluded in our review. We included English-language peer-reviewed RCTs (pharmacist-involved multidisciplinary interventions), full-text articles, and conference papers.

In the context of this review, a pharmacist-involved multidisciplinary intervention was defined as the condition of pharmacist(s) working in collaboration, at a minimum, with a physician within the intervention model. The intervention model may include interaction with other health-care professionals as needed. Eligible pharmacist interventions include medication reconciliation, discharge counselling, patient education, collaborative medication management, telephone follow-up, home medication review, self-adjustment of diuretic dose, prevention of medication errors, adverse drug reactions, and drug−drug interactions. Some of the duties—for example, patient education, telephone follow-up, home medication review and drug−drug interactions—could be offered to patients by physicians and nurse practitioners in different health-care settings without involving the typical work profile of a pharmacist. However, to be eligible for this meta-analysis, these interventions in RCTs must have been conducted within a multidisciplinary approach that did not exclude the pharmacist.

The intervention was compared with usual care, which involves either a follow-up by a cardiologist or general practitioner (GP) in a hospital, outpatient clinic, or family medical practice, or under multidisciplinary HF-specialist care, and care that did not include the pharmacist undertaking an active role.

Information Sources

Trials were identified through systematic searches of the databases recommended by the Cochrane Heart Group and other relevant databases from inception through March 2017. These included PubMed (NLM), MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), Web of Science (Thomson Reuters), Scopus (Elsevier), and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. The bibliographies of relevant studies and systematic reviews were searched manually. Corresponding authors were approached for further information regarding any missing, unreported, or ongoing trial data whenever relevant. Additionally, ongoing clinical trials and unpublished studies on the following clinical trial registers were searched:

1. ClinicalTrials.gov (www.ClinicalTrials.gov).
2. The WHO International Clinical Trial Registry Platform (ICTRP) (http://apps.who.int/trialsearch/).

Search

The search strategies used in this review are outlined in supplementary Table S1.

Study Selection

Two independent reviewers (D.R.P. and C.K.) identified studies based on inclusion and exclusion criteria. Reasons for the exclusion of the ineligible studies were identified and recorded. Disagreements regarding the study selection process were resolved by consensus with a third reviewer (J.F. and R.C.).

Data Collection Process

Data were extracted from included studies (D.R.P.) and checked for accuracy and completeness (C.K.). When sufficient data for meta-analysis was unavailable in the original RCTs, the corresponding authors were contacted.[43−47] We were unable to receive the required data for this meta-analysis from 3 RCTs.[48−50] In these instances, we used the data provided by the primary authors in previous meta-analysis.[30]

Data Items

The data from the eligible RCTs were extracted, including author, date of publication, setting and country, sample size, study populations, mean age of the patients, intervention groups, major outcome descriptions, endpoint measurements, and duration of follow-up.

The following outcomes were considered:

- *Primary outcomes*, which included HF hospitalizations and HF mortality.
- *Secondary outcomes*, such as all-cause hospitalizations, all-cause mortality, medication adherence (compliance), HF knowledge, health-care costs, self-care, and composite endpoint. The composite endpoint is the combination of all-cause hospitalizations and all-cause mortality.[51] Mortality as a sole endpoint to determine the clinical benefit of the intervention requires larger and longer trials. Therefore, composite endpoints of death and hospitalizations are combined to amalgamate the overall efficacy by increasing statistical power.[52]

Risk of Bias in Individual Studies

The risk of bias assessment was performed using the Cochrane Risk of Bias Tool.[53] Two reviewers independently assessed the methodological quality and a consensus was achieved through discussion or referral to the third reviewer. The risk of bias assessment was performed at the study level.[54] RCTs were included in the meta-analysis, irrespective of the risk of bias results; however, the GRADE approach was used to generate a summary of each outcome.

Summary Measures

Forest plots were generated to estimate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the rates of HF hospitalizations, HF mortality, all-cause hospitalizations, all-cause mortality and composite endpoint. Meta-analysis was performed using RevMan 5.3 software.[55] To measure the outcomes, the random-effects model was selected if there were more than 5 studies and a fixed-effects model was used if there were fewer than 5 studies.[56] The weight of a single study in a forest plot indicates the impact of that particular study on an overall pooled estimate in a meta-analysis as calculated by the inverse of the variance.[57] The percentage value of the weight depends on the sample size and CI. A larger sample size and narrower CI means a higher weighting for a particular study.[58] Overall effects in the forest plots were considered significant at $P \leq .05$.

Synthesis of Results

Statistical heterogeneity was measured using the standard chi-squared test (χ^2; $P < .05$ was considered significant)[59] and Higgins I^2 test. The I^2 values of 25%, 50%, and 75% were considered low, moderate, and high variability, respectively.[60] When meta-analysis was not possible, a descriptive synthesis was undertaken to extract the evidence for the 4 secondary outcomes.

Publication bias was measured by the generation of funnel plots.[61] Reporting bias (selective reporting), poor reporting of certain outcomes due to negative results, was also measured.[62]

Additional Analysis

Sensitivity analysis was performed to determine the pooled estimate of HF hospitalizations, all-cause hospitalizations and all-cause mortality by including 4 RCTs with sufficient statistical power of ≥80%.[43,45,47,63] Meta-analysis was further undertaken by polling only RCTs with statistical power and 12 months of follow-up[43,45,47] to determine the effect on HF-related hospitalizations, all-cause hospitalizations and all-cause mortality.

Results

Study Selection

The initial search strategy identified 1294 potentially eligible studies from databases, and another 72 were found from clinical trial registers. After excluding duplicates, the remaining 786 studies were carefully screened by title and abstract. The full text of 55 publications was reviewed. Eighteen RCTs (n = 4630) were included for systematic review, and 16 (n = 4447) for meta-analysis. The PRISMA flow chart (Fig. 1) demonstrates the screening process for the eligible studies and the reasons for exclusion.

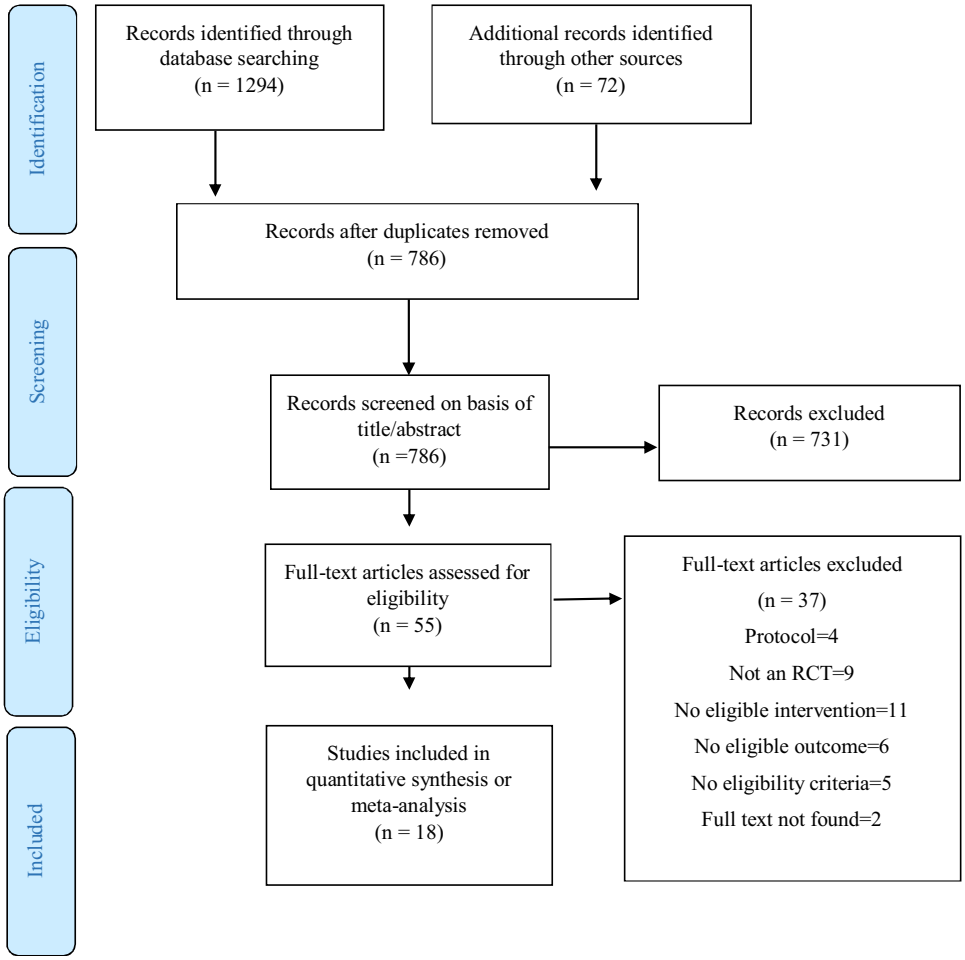

Fig. 1. PRISMA flow diagram: study screening and selection.

Study Characteristics

Eligible patients were those diagnosed with HF (≥18 years and mainly diagnosed with NYHA classes I−IV). Only 3 trials reported the value of EF in their eligibility criteria; EF ≤ 55 in 1 trial,[64] EF < 45 in 1 trial,[65] and EF ≤ 40 in 1 trial.[50] One RCT excluded patients who have preserved EF from recruitment.[63] Another RCT only included patients suffering from left ventricular systolic dysfunction.[43] The studies were conducted in the United States, Europe, the United Kingdom, Australia, Canada, and the United Arab Emirates. The mean age of the participants in the RCTs ranged from 58 to 84 years. The follow-up time ranged from 6 weeks to 12 months. The sample size for the RCTs ranged from a minimum of 34 to a maximum of 2169. Of the total participants (n = 4630), 61% were male and 39% were female. The settings for the RCTs included outpatient clinics, primary care centers, hospitals, patients' homes, and community pharmacies. Pharmacist-involved multidisciplinary intervention offered an integrated approach to educational counseling focusing on HF knowledge and medications, lifestyle modifications, self-care behaviors, medication management, and telephone follow-up. The characteristics of the 18 included studies are shown in Table 1.

Data for HF hospitalization (13 RCTs), HF mortality (2 RCTs), all-cause hospitalization (13 RCTs), all-cause mortality (15 RCTs), and composite endpoint (3 RCTs) were available to include in the meta-analysis. Additionally, data for medication adherence (10 RCTs), HF knowledge (2 RCTs), health-care costs (4 RCTs), self-care (1 RCT), and health-related quality of life (8 RCTs) were available for narrative synthesis to extract the overall effect on these outcomes.

Risk of Bias Within Studies

The overall risk of bias was judged as low in the included studies, as demonstrated by supplementary Fig. S1: Summary of risk of bias. Allocation concealment (selection bias) in 7 RCTs (39%), and blinding of outcome assessors

Table 1. Characteristics of Included Studies

Source	Setting (Country)	Sample Size (n)	Study Population	Mean Age (years)	Intervention Group and Major Outcome Description	Follow-Up (intervention frequency)
Goodyer (1995)[66]	Outpatient clinics (United Kingdom)	100	Chronic stable HF patients (>70 y) who required no alteration of medications.	84	Patient counseling about the use of medications. Significant improvement in medication compliance in intervention group.	3 months (2, 4 weeks)
Stewart (1998)[64]	Home visits (Australia)	97	HF patients (NYHA II, III or IV) discharged from hospital, high risk for unplanned readmission, LVEF≤ 55.	75	Discharge counseling, home visit, recommendation to visit community pharmacist and liaison with GPs. Reduced unplanned readmissions and death rates in intervention group.	6 months (1 week)
Gattis (1999)[65]	Outpatients clinics (United States)	181	HF patients undergoing evaluation in general cardiology clinics, and LVEF <45.	68	Therapeutic recommendations, counseling about medications and potential drug effects, and telephone follow-up. Significant reduction in all-cause mortality and HF clinical events in intervention group.	6 months (2, 12, and 24 weeks)
Rainville (1999)[67]	Hospital (United States)	34	Patients >50 y, diagnosed with HF, and with medical history of the disease.	70	Education about HF and self-care, medication review, and telephone follow-up. Lower readmissions rates in intervention group.	12 months (1, 4, 12, 48 weeks)
Varma (1999)[68]	Outpatients clinics (Northern Ireland)	83	Patients >65 y, diagnosed with HF (NYHA I–IV) and cognitive status score of >6. Recruited from hospital or those attending outpatient clinics.	76	Education on HF, medications and self-care, medication optimization, written information provided to GP or community pharmacist. Improved knowledge about drug therapy and lower hospital admissions in intervention group.	12 months (3 monthly)
Bouvy (2003)[46]	Community Pharmacy (Netherlands)	152	HF patients being treated with loop diuretics (NYHA class II/III), admitted to hospital or attended specialist HF clinic.	70	Structure interview, medication review, compliance measurement, and monthly follow-up. Improved medication compliance intervention group. No significant differences in re-hospitalization and mortality between groups.	6 months (monthly)
Tsuyuki (2004)[63]	Outpatient clinics (Canada)	276	Patients (>18 y) admitted to hospital due to HF (reduced systolic dysfunction).	74	Patient support program, medication optimization, education about HF, medication, and self-care behaviors. No difference in medication adherence between groups. Reduction in cost of care in intervention group.	6 months (2 and 4 weeks and monthly thereafter)
Sadik (2005)[45]	Outpatient clinics (United Arab Emirates)	208	Patients with diagnosed HF (NYHA class I–IV) and cognitive status score >6.	58	Education on HF, medication, self-care, and lifestyle modification. Pharmacist discussion with physician to optimize therapy. Improved compliance, and lower hospitalizations in the intervention group.	12 months (3, 6, 9, 12 months)
Gwardy-Sridhar (2005)[50]	Hospital (Canada)	134	Patients with HF (≥18 y), low left ventricular ejection fraction (LVEF ≤ 40%), under long-term treatment for HF or low LVEF.	67	Received 2 HF booklets, viewed video on congestive HF and multidisciplinary education medication compliance, diet and lifestyle modifications. Improved knowledge scores in intervention group.	12 months (2 to 4 days and every 3 months thereafter)
Lopez Cabezas (2006)[44]	Hospital (Spain)	134	Hospitalized patients for HF. Diagnosed using the Framingham criteria for HF. Majority in NYHA I, II.	76	Education on HF, diet, and medications. Telephone follow-up and clinical assessment. Reduced readmissions rates and improvement of medication compliance in intervention group.	12 months (1, 2, 3, 4, 5, 6, 8, 10, 12 months)
Holland (2007)[49]	Home visits (United Kingdom)	293	Patients (>18 y) admitted to ED due to HF as an ongoing condition, and (majority in NYHA class III), prescribed 2 or more drugs on discharge.	77	Home visit (within 2 weeks of discharge) and education on medications, life style modifications and self-care. Feedback was provided to GPs and the local pharmacist. One follow-up visit between 6–8 weeks. No reduction on hospital admissions in intervention group.	6 months (2 weeks, 6–8 weeks)

(*continued on next page*)

Table 1 (*Continued*)

Source	Setting (Country)	Sample Size (n)	Study Population	Mean Age (years)	Intervention Group and Major Outcome Description	Follow-Up (intervention frequency)
Murray (2007)[47]	Outpatient clinics (United States)	314	Patients (>50 y) diagnosed with HF (majority in NYHA II) and using at least 1 cardiovascular medication.	62	Medication reconciliation, education on medication adherence, and HF. Communicating with clinic nurses, and primary physicians. Improved adherence during intervention and decreased health-care cost in intervention group.	12 months (during, 3, 6, 9, 12 months)
Triller (2007)[69]	Home visits (United States)	154	Patients with primary or secondary diagnosis of HF (≥21 y) who were discharged and under home care.	80	Medication reconciliation, counseling on medication compliance and lifestyle modifications. Communication with nurses, and GPs. No significant difference in the composite endpoint between groups.	6 months (7 to 10 and 18 to 21 d)
Azad (2008)[70]	Outpatient clinics (Canada)	91	Patients diagnosed with chronic HF (older women, ≥63 y).	77	The interdisciplinary intervention pathway including 12 visits over a 6-week period. Exercise program, educational counseling and dietary management. No significant difference in mortality in intervention group.	6 months (biweekly visits)
Eggink (2010)[71]	Hospitals (Netherlands)	85	Adults (≥18 y) diagnosed with HF and prescribed 5 or more medications.	73	Medication review, discussion with cardiologists about prescribing errors, providing information to patients, providing written overview of the discharge medications, liaising with community pharmacy as well as with GPs. No difference in medication adherence between groups.	6 weeks (after discharge)
Korajkic (2011)[72]	Outpatient clinics (Australia)	70	Patients (≥18 y) diagnosed with HF with NYHA class II, III, and IV and were on a daily dose of furosemide (other medications allowed).	57	Education on self-care, dose adjustment of furosemide, HF and medications. Lower readmissions rates in the intervention group. Significant improvements in HF-related knowledge and medications in intervention group.	3 months (4, 8, and 12 weeks)
Lowrie (2012)[43]	Primary care center (United Kingdom)	2169	Patients (≥18 y) with left ventricular systolic dysfunction.	71	Training to pharmacist about HF and medications. Pharmacist collaborated with family doctors and patients for the optimization of treatment. No significant difference in death from any cause or hospital admissions for any cause between groups.	55 months (3−4 subsequent weekly or fortnightly).
Roblek (2016)[73]	Hospitals (Slovenia)	51	Patients diagnosed with HF, prescribed at least 2 medications during admission, and presence of at least 1 drug−drug interaction.	79	Evaluation of clinically relevant drug−drug interaction by the pharmacist. The relevancy of the drug−drug interactions was checked by a panel of 3 clinicians with help of electronic database. Lifestyle modifications information provided. No significant difference in composite endpoint, re-hospitalization and death, between groups.	6 months (During hospitalization, and at patient discharge.)

ED, emergency department; LVEF, left ventricular ejection fraction.

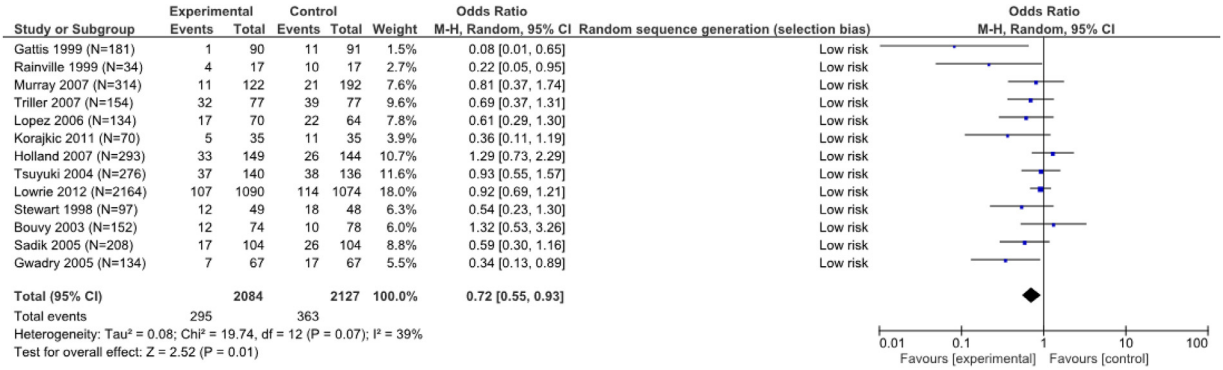

Fig. 2. Forest plot of heart failure hospitalizations (random-effects model). Test of overall effect, $P < .05$ is considered significant.

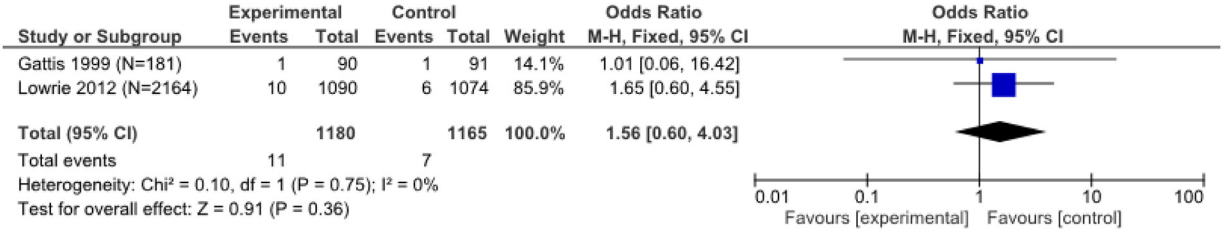

Fig. 3. Forest plot of heart failure mortality (fixed-effects model). Test of overall effect, $P < .05$ is considered significant.

(detection bias) in 3 RCTs (17%) were unclear. Although the performance bias (blinding of participants and personnel) was found to be 100%, given the nature of the interventions in the included studies, it is not valid in this review (supplementary Table S2). The open nature of the interventions prohibited true blinding in the trials.

Synthesis of Results

Effect on HF Hospitalizations. Thirteen RCTs (4211 patients) reported HF hospitalizations (patients hospitalized at least once).[43–47,49,50,63–65,67,69,72] Of these, 8 RCTs[44,45,50,64,65,67,69,72] showed a reduction in HF hospitalization, but 5 had no effect.[43,46,47,49,63] Only 4 had sufficient statistical power to detect effect on HF hospitalizations.[43,45,47,63] A pooled estimate of the 13 RCTs showed a significant reduction in HF hospitalizations (OR 0.72, 95% CI [0.55–0.93], $P = .01$, $I^2 = 39\%$) in a random-effects model (Fig. 2). The χ^2 test showed that the P value is not significant ($P = .07$) for heterogeneity. The heterogeneity for the pooled effect on HF hospitalizations was medium ($I^2 = 39\%$). In the meta-analysis of 4 RCTs with sufficient statistical power, there was no significant reduction in HF hospitalizations (OR 0.87, 95% CI [0.69–1.08], $P = .20$, $I^2 = 0\%$). In addition, there was no statistically significant difference in the net effect on HF hospitalizations when the meta-analysis was restricted to 3 RCTs with statistical power and 12 months of follow-up.[43,45,47]

Effect on HF Mortality. Only 2 RCTs (2345 patients)[43,65] reported HF mortality. Only 1 included RCT had statistical power to detect effect on HF mortality.[43] A pooled

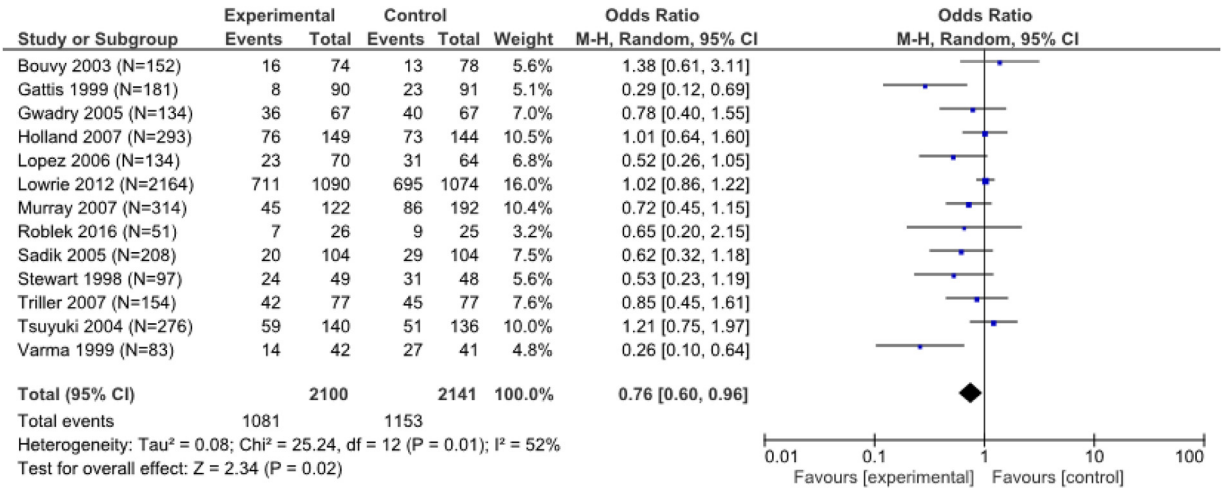

Fig. 4. Forest plot of all-cause hospitalizations (random-effects model). Test of overall effect, $P < .05$ is considered significant.

Table 2. Summary of Secondary Outcomes

Study	Medication Adherence (compliance)	*P* Value
Goodyer (1995)[66]	Mean compliance score after the intervention was 93% (SD, 11.7) for the intervention group, and 51% (SD 31.5) for usual care.	<.001
Varma (1999)[68]	A total of 10 patients were compliant and 3 were noncompliant in the intervention whereas 3 were compliant and 7 noncompliant in the usual care group.	<.05
Sadik (2005)[45]	The number of patients having self-reported compliance for prescribed medication was 85 for treatment and 35 for usual care group. Similarly, the compliance for lifestyle adjustment was 75 for treatment group and 29 for usual care group at 12 months.	<.05
Gwadry (2005)[50]	Noncompliance for intervention and usual care group for different medications class; ACEIs: 13% (4.1−22.5), 17% (7.2−26.8); β-blockers: 13% (1.8−24.5), 15% (2.7−26.7); digoxin: 15% (2.9−25.7), 19% (3.5−27.8); and diuretics 23% (11.1−35.8), 23% (10.7−35.1).	NS
Lopez (2006)[44]	The degree of compliance was 85% vs 73.9% in the intervention and usual care group respectively at 12 months.	NS
Bouvy (2003)[46]	The intervention group had 140/7656 days without diuretics vs 337/6196 for usual care, relative risk (0.33, 0.24−0.38, CI 95%).	NS
Tsuyuki (2004)[63]	Nonsignificant improvement of ACE inhibitors adherence over the 6 months; 83.5 ±29% in the intervention group vs 86.2 ±29% in the usual care group.	NS
Holland (2007)[49]	Nonsignificant improvement of drug adherence in the intervention group (adjusted mean difference=0.12 units, −0.48 to 0.73 units).	.68
Murray (2007)[47]	Nonsignificant improvement on drug adherence during the 9-month intervention period; 67.9% and 78.8% in the usual care and intervention groups, respectively (difference, 10.9 percentage points [95% CI, 5.0 to 16.7 percentage points]). However, this effect disappeared in the 3-month post-intervention follow-up period; adherence was 66.7% and 70.6% for usual care and intervention group respectively (difference, 3.9 percentage points [CI, 5.9 to 6.5 percentage points]).	NS
Eggink (2010)[71]	No difference on drug adherence; 79.5% in the usual care group vs 78.0% in the intervention group (RR: 1.07 [95% CI 0.47−2.44]).	NS
Study	**Heart Failure Knowledge**	**P value**
Gwardy-Sridhar (2005)[50]	The change in knowledge score was 2.24 ± 2.46 (95% CI 1.63−2.85) in the intervention and 1.38 ± 2.16 (95% CI 0.85−1.91) in the usual care group, respectively.	<.02 (immediate), and 0.05 (over 1 year)
Korajkic (2011)[72]	Significant improvement in HF knowledge; 94% intervention vs 71% usual care.	.01
Health-care costs		
Stewart (1998)[64]	The mean cost of hospital-based care was ($3200 [95 % CI, $ 1800−$4600]) for intervention group and ($5400 [95 % CI, $3200−$6800]) for usual care group The cost for community-based health care was $620 per patient to intervention group and $680 per patient for control group. The costs were estimated in Australian dollars.	NS
Tsuyuki et al (2004)[63]	Reduction in cost of care for intervention group (2531 Canadian dollar less per patient). This amount is equivalent to current estimate of $1902.	NS
Murray et al (2007)[47]	The annual direct health-care costs for intervention group was lower by $2960 (CI, $-7603 to $1338) per patient.	NS
Triller et al (2007)[69]	Nonsignificant reduction in cost (total health system cost, hospital costs, and home care agency cost).	NS
Self-care		
Holland et al (2007)[49]	Nonsignificant improvements of self-care score in the intervention group 26.58 vs 28.27 (low scores imply better self-care behavior).	NS

ACEIs, angiotensin converting enzyme inhibitors; NS, Nonsignificant; SD, standard deviation; RR, relative risk. $P \leq .05$ is considered significant.

estimate of the 2 RCTs showed no reduction in HF mortality (OR 1.56, 95% CI [0.6−4.03], $P = .36$, $I^2 = 0\%$; Fig. 3). There was no heterogeneity for net effect ($I^2 = 0\%$).

Effect on All-Cause Hospitalizations. Thirteen RCTs (4241 patients) reported all-cause hospitalizations.[43−47,49,63-66,68,69,73] Of these, only 4 had sufficient statistical power to detect effect on all-cause hospitalizations.[43,45,47,63] Nine RCTs[44−47,64−66,68,69] reported reduced all-cause hospitalizations, with 4 showing no effect.[43,49,63,73] A pooled estimate of the 13 RCTs showed a significant reduction in all-cause hospitalizations (OR 0.76, 95% CI [0.60−0.96], $P = .02$, $I^2 = 52\%$; Fig. 4). The χ^2 test showed that the P value was significant ($P = .01$) for heterogeneity. The heterogeneity for the pooled effect on all-cause hospitalizations was slightly higher than medium ($I^2 = 52\%$). In the meta-analysis of 4 RCTs with sufficient statistical power, there was no significant reduction in all-cause hospitalizations (OR 0.97, 95% CI [0.84−1.13], $P = .73$, $I^2 = 35\%$). In addition, there was no statistically significant difference in the net effect on all-cause hospitalizations when the meta-analysis was restricted to 3 RCTs with statistical power and 12 months of follow-up.[45,47,49]

Effect on All-Cause Mortality. Fifteen RCTs (4366 patients) reported all-cause mortality.[43−47,49,50,63−65,67−70,73] Among them, only 4 had sufficient statistical power to detect effect on all-cause mortality.[43,45,47,63] Six RCTs showed a significant reduction in all-cause mortality.[44,46,50,64,65,67] A pooled estimate of the 15 RCTs showed no significant reduction in all-cause mortality (OR 0.92, 95% CI [0.74−1.13], $P = .41$, $I^2 = 9\%$; figure not included). The heterogeneity for net effect was low ($I^2 = 9\%$). In the meta-analysis of 4 RCTs with sufficient statistical power, there was no significant

reduction in all-cause hospitalizations (OR 1.03, 95% CI [0.87−1.23], $P = .73$, $I^2 = 0\%$). In addition, there was no statistically significant difference in the net effect on all-cause mortality when the meta-analysis was restricted to 3 RCTs with statistical power and 12 months of follow-up.[45,47,49]

Effect on Medication Adherence (Compliance). Medication adherence was reported in 10 RCTs (Table 2).[44−47,49,50,63,66,68,71] The interventions in these RCTs focused on education about HF and medications, self-care, medication review, medication optimization, adverse drug reactions, providing written information, exposure to a video about HF, collaboration with GPs, and telephone follow-up. Among the 10 RCTs, only 3 had sufficient statistical power to detect effect on medication adherence.[45,47,63] Three RCTs[45,66,68] showed significant improvement, 6[44,46,47,49,50,63] found nonsignificant improvement, and 1[71] found no difference in medication adherence.

Effect on HF Knowledge. HF knowledge was reported in 2 studies (Table 2).[50,72] These interventions mainly focused on educational sessions to improve knowledge of HF and self-care behaviors, provide booklets and show a video on congestive HF. Both of the included RCTs lacked statistical power. However, both RCTs found a significant improvement ($P < .05$) in knowledge of HF.[50,72]

Effect on Health-Care Costs. The effect on health-care costs was measured in 4 RCTs (Table 2).[47,63,64,69] Of them, 2 had sufficient statistical power.[47,63] Cost-effectiveness was measured in different ways: mean cost of hospital-based care, health-care cost, total health-care cost, and composite cost (total health-system cost, hospital cost, home care agency cost). All 4 RCTs reported a nonsignificant reduction in health-care costs. The reduction in cost per patient in intervention group was not mentioned in 2 RCTs.[64,69] One study, conducted in the U.S., reduced the cost in the intervention group by $2960 (CI: $−7603 to $1338) per patient.[47] A Canadian study reduced the cost by $1902 (current estimate of $CDN) per patient.[63]

Effect on Self-Care. The impact on self-care was reported in 1 RCT (Table 2),[49] which found a nonsignificant improvement. This RCT lacks statistical power. The intervention consisted of a home visit by a pharmacist within 2 weeks of discharge, focused on patient/career education regarding medications, exercise, diet, smoking cessation, and providing feedback recommendations to GPs and the local pharmacist afterward. Self-care was measured using the European HF self-care behavior scale.[74]

Effect on Composite Endpoint. Three RCTs (2369 patients) reported a composite endpoint.[43,69,73] Of the 3 RCTs, only 1 had sufficient statistical power to detect the effect on composite endpoint.[43] A pooled estimate of the 3 RCTs showed no significant reduction in composite endpoint (OR 0.97, 95% CI [0.82−1.16], $P = .74$, $I^2 = 0\%$; figure not included).

Effect on Health-Related Quality Of Life. Health-related quality of life was measured in 9 RCTs.[44-47,49,50,68,70,72] Of them, 2 had sufficient statistical power to detect the effect on health-related quality of life.[45,47] Among the 9 RCTs, only 4 studies reported a significant improvement and difference in health-related quality of life in HF patients. The quality of life was measured by different instruments: the Chronic Heart Failure Questionnaire,[47] EuroQol- 5 Dimension,[44,49] the Minnesota Living With Heart Failure (MLHF),[45,46,49,50,68,70,72] the 36-Item Short Form Health Survey (SF-36),[45,50,68,70] the Dartmouth Primary Care Cooperative Information Project/World Organizations of National Colleges, Academics, Academic Associations of General Practice/Family Physicians,[46] and the 15-item Geriatric Depression Scale.[70]

Risk of Bias Across Studies

There are no small studies on the bottom right of the funnel plot of HF hospitalizations so that the typical inverted funnel-like shape was not observed indicating the presence of some degree of publication bias (supplementary Fig. S2a). The studies in funnel plot for all-cause hospitalizations are more closely clustered and equally distributed (supplementary Fig. S2b). A degree of asymmetry and absence of small studies on the bottom right side of the plot was also observed in funnel plot of all-cause mortality (supplementary Fig. S2c).

GRADE Assessment of Quality of Evidence

The GRADE summary table (supplementary Table S3) illustrates the summary of each outcome along with a description of the quality of the evidence. The grading of each outcome is based on potential risk of bias, impression, CI, and number of studies measuring that particular outcome. We found moderate-quality evidence for significant reduction of HF hospitalizations, all-cause hospitalizations, and overall improvement in medication adherence. Significant improvement in HF knowledge and nonsignificant reduction in health-care costs were also of medium quality. Nonsignificant reduction in HF mortality, all-cause mortality, and composite endpoint were of low quality. The evidence for nonsignificant improvement in self-care was found to be of very low quality.

Discussion

Summary of Evidence

The findings of this study indicated that pharmacist-involved multidisciplinary HF management resulted in a significant reduction in HF hospitalizations (28%) and all-cause hospitalizations (24%) but had no effect on reducing HF mortality and all-cause mortality. The overall trend was an improvement in medication adherence. There was also evidence to support significant improvements in HF knowledge, but no significant improvements in health-care costs, self-care, and composite endpoint. The results for HF mortality and self-care reflect evidence from only 2 and a single RCT, respectively. The net effect is likely to change with further research. The overall trend was an improvement in health-related quality of life. The most common instruments

used to measure health-related quality of life were MLHF and SF-36.

Although significant and convincing evidence has been available for HFrEF, little evidence exists regarding effective therapies for HFpEF; the result is a cohort of patients with significant unmet clinical needs.[75–78] We are not confident in the number of patients with HFpEF that were included in the 18 RCTs included in our analysis. Therefore, whether the observed improved outcomes apply to patients with HFpEF remains undefined. There was no noted heterogeneity for HF mortality, all-cause mortality, and composite endpoint ($I^2 = 0$). However, we observed low heterogeneity ($I^2 = 39\%$) for HF hospitalizations and slightly higher than medium level of heterogeneity ($I^2 = 52\%$) for all-cause hospitalizations. Potential sources of heterogeneity may be because of the settings where the studies were conducted, sample size, patients' characteristics, risk of bias, type of intervention delivered, and a difference in health-care systems among countries where the RCTs were conducted.

It is often argued that the grading of bias risk into low, unclear, and high demarcations is likely to be subjective.[79] We contacted the primary authors and evaluated the risk of bias using the Cochrane risk of bias assessment tool to minimize the impact of subjective bias. The overall risk of bias in the included trials in the current meta-analysis was low. Selective reporting was negligible due to the open nature of the interventions. We observed some degree of publication bias especially for HF hospitalizations and all-cause mortality, as demonstrated by the asymmetry of the funnel plots. To extract an explicit summary of each outcome from those heterogeneous trials included in our study, the GRADE approach was used.

In 2008, Koshman et al[30] conducted a systematic review (12 RCTs covering, 2060 patients) to determine the effect of pharmacist care on patient outcomes for HF. A significant reduction in the rate of all-cause hospitalizations and HF hospitalizations, and a nonsignificant reduction in mortality was found. Further, pharmacist-involved collaborative care led to greater reductions in the rate of HF hospitalizations compared with pharmacist-directed care. After the Koshman (2008) study, we noted a gap in evidence from systematic review and meta-analysis specifically focused on the role of the pharmacist in HF management. Our findings are consistent regarding the effect on HF hospitalizations, all-cause hospitalizations, and all-cause mortality compared with Koshman's previous meta-analysis.[30] However, our study extends this earlier work by including data from 6 recent RCTs to strengthen the available scientific evidence.

Furthermore, despite having similar results to the previous meta-analysis by Koshman et al, 2008,[30] our analysis includes more stringent eligibility criteria particularly, pharmacists needed to be working in collaboration with at least a physician within the intervention model. Koshman et al[30] highlighted the optimal practice of GDMT and improvement of clinical outcomes facilitated by embedding pharmacists within a multidisciplinary team for the most effective HF management. We excluded 1 RCT conducted in Australia in which home medication review by a pharmacist had no effect on mortality or health-care utilization[80] but that trial meets the eligibility criteria of the previous meta-analysis.[30]

A retrospective study of hospitalized HF patients in rural Japan, to determine the effect of pharmacist-involved multidisciplinary inpatient education, found a significant reduction in the composite endpoint of HF hospitalizations and all-cause mortality ($P < .001$).[81] However, our meta-analysis showed a nonsignificant reduction in the composite endpoint of all-cause hospitalizations and all-cause mortality. There is growing evidence for reduction in mortality rates among HF patients due to better use of GDMT.[82–84] Pharmacist initiated multidisciplinary intervention leads to a significant increase in prescription of GDMT as well as a reduction in 30-day all-cause readmission rate.[85] Likewise, a reduction in 90-day readmission rate is recently reported where HF patients visited a pharmacist-led post-discharge clinic.[86]

A review article by Davis et al[87] reported an improvement in medication adherence by pharmacist-delivered interventions in HF patients as long as the intervention was provided. Although an overall trend of an improvement in medication adherence was observed, we remain unsure if the improvement in medication adherence had direct impact on reduction of hospitalizations and mortality rates in HF patients in our study. Importantly, a very recent RCT of the pharmacist-involved multidisciplinary intervention found an improvement in medication adherence and quality of life but no effect on hospitalizations and mortality in ambulatory chronic HF patients.[88]

An included pilot RCT educational tailored-intervention consisting of providing HF booklets and showing a video on HF, assisting patients to improve medication adherence as well as promoting healthy diet and life-style modifications, resulted in a significant improvement in HF knowledge.[52] Another RCT on ambulatory HF patients found a similar significant improvement in HF knowledge after diuretic dose adjustment offered by the pharmacist-involved multidisciplinary intervention.[76] The ultimate impact of improved HF knowledge on hospitalizations and mortality rates by pharmacist-involved multidisciplinary interventions required further investigation. The major economic burden in HF is the cost associated with hospitalizations.[89,90] Despite of overall nonsignificant reduction in health-care costs, a significant reduction in hospitalizations in our study is worth noting.

We observed a nonsignificant improvement in self-care based on evidence from a single RCT warranting a further research to extract clinically relevant answer. It is noteworthy that in our earlier literature review,[91] the engagement of pharmacists in HF management improved medication adherence, medication management, self-care ability, patient satisfaction, HF knowledge, and the reduction in HF readmission rates. These findings were heavily derived from observational studies. The findings from this meta-analysis are solely from RCTs. Therefore, we hypothesize that there is a substantial increasing opportunity for

pharmacists as a key members of the multidisciplinary HF management team to improve clinical outcomes.

There was a great deal of variability, in the reported RCTs, regarding which specific intervention is most effective in improving clinical outcomes, because pharmacist-involved multidisciplinary intervention offered an integrated approach of multiple interventions. Our study highlights a persistent gap in evidence from RCTs of pharmacist-involved multidisciplinary interventions (having sufficient statistical power and longer follow-up) for the effective management of HF in improving overall clinical outcomes. This study is the first study to comprehensively evaluate the potential benefits of pharmacist involvement in multidisciplinary HF management teams related to the widest variety of outcome measures. The use of the GRADE approach is another strength.

The limitations of the current study include the inclusion of only English-language RCTs and the diversity of interventions, settings, and health-care systems in which the studies were conducted, and their follow-up times, sample heterogeneity, and statistical power. Despite the stated beneficial contribution of the pharmacist-involved multidisciplinary team, the exact (magnitude) contribution of the role, to the overall effect seen with the multidisciplinary teams remains unclear and forms the basis for further research.

Conclusions

The pharmacist is a vital member of a multidisciplinary HF management team to improve clinical outcomes. There was a great deal of variability regarding which specific intervention is most effective in improving clinical outcomes. This study highlights a persistent gap of evidence from a RCT of pharmacist-involved multidisciplinary intervention (having sufficient statistical power and longer follow-up) for the effective management of HF to improve clinical outcomes.

Disclosures

No conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.07.455.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J-P, Fullerton HJ. Executive summary: heart disease and stroke statistics−2016 update: a report from the American Heart Association. Circulation 2016;133:447–54.
2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016;13:368–78.
3. Al-Khazaali A, Arora R, Helu HK. Effective strategies in reducing rehospitalizations in patients with heart failure. Am J Ther 2016;23:e799–804.
4. Inamdar AA, Inamdar AC. Heart failure: diagnosis, management and utilization. J Clin Med 2016;5:E62.
5. Jessup M, Marwick TH, Ponikowski P, Voors AA, Yancy CW. 2016 ESC and ACC/AHA/HFSA heart failure guideline update:- what is new and why is it important? Nat Rev Cardiol 2016;13:623–8.
6. Mazurek JA, Jessup M. Understanding heart failure. Card Electrophysiol Clin 2015;7:557–75.
7. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure-associated hospitalizations in the United States. J Am Coll Cardiol 2013;61:1259–67.
8. Fry M, McLachlan S, Purdy S, Sanders T, Kadam UT, Chew-Graham CA. The implications of living with heart failure; the impact on everyday life, family support, co-morbidities and access to healthcare: a secondary qualitative analysis. BMC Fam Pract 2016;17:139.
9. Hoekstra T, Lesman-Leegte I, van Veldhuisen DJ, Sanderman R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. Eur J Heart Fail 2011;13:1013–8.
10. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Pina IL, Trogdon JG. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6:606–19.
11. Rohde LE, Bertoldi EG, Goldraich L, Polanczyk CA. Cost-effectiveness of heart failure therapies. Nat Rev Cardiol 2013;10:338–54.
12. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol 2013;61:391–403.
13. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2017;14:591–602.
14. Loudon BL, Noordali H, Gollop ND, Frenneaux MP, Madhani M. Present and future pharmacotherapeutic agents in heart failure: an evolving paradigm. Br J Pharmacol 2016;173:1911–24.
15. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 2013;309:355–63.
16. Curtis LH, Greiner MA, Hammill BG, Kramer JM, Whellan DJ, Schulman KA, Hernandez AF. Early and long-term outcomes of heart failure in elderly persons, 2001−2005. Arch Intern Med 2008;168:2481–8.
17. Krumholz HM, Merrill AR, Schone EM, Schreiner GC, Chen J, Bradley EH, Wang Y, Wang Y, Lin Z, Straube BM, Rapp MT, Normand SL, Drye EE. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cardiovasc Qual Outcomes 2009;2:407–13.
18. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? Circulation 2012;126:501–6.
19. Joynt KE, Jha AK. Who has higher readmission rates for heart failure, and why? Implications for efforts to improve care using financial incentives. Circ Cardiovasc Qual Outcomes 2011;4:53–9.
20. Chun S, Tu JV, Wijeysundera HC, Austin PC, Wang X, Levy D, Lee DS. Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. Circ Heart Fail 2012;5:414–21.

21. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, Laskar S, Smith AL, Dunbar S, Triposkiadis F, Butler J. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. J Card Fail 2011;17:54–75.
22. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics−2014 update: a report from the American Heart Association. Circulation 2014;129:e28–e292.
23. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics−2012 update: a report from the American Heart Association. Circulation 2012;125:e2–e220.
24. Halushka MK, Mitchell RN, Padera RF. Heart failure therapies: new strategies for old treatments and new treatments for old strategies. Cardiovasc Pathol 2016;25:503–11.
25. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey D.E. Jr., et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.
26. Chong VH, Singh J, Parry H, Saunders J, Chowdhury F, Mancini DM, Lang CC. Management of noncardiac comorbidities in chronic heart failure. Cardiovasc Ther 2015;33:300–15.
27. Azad N, Lemay G. Management of chronic heart failure in the older population. J Geriatr Cardiol 2014;11:329–37.
28. Hopper I, Kotecha D, Chin KL, Mentz RJ, von Lueder TG. Comorbidities in heart failure: are there gender differences? Curr Heart Fail Rep 2016;13:1–12.
29. Youn J-C, Han S, Ryu K-H. Temporal trends of hospitalized patients with heart failure in korea. Korean Circ J 2017;47:16–24.
30. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. Arch Intern Med 2008;168:687–94.
31. Krum H, Jelinek MV, Stewart S, Sindone A, Atherton JJ. 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Med J Aust 2011;194:405–9.
32. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
33. Bhat S, Kansal M, Kondos GT, Groo V. Outcomes of a pharmacist-managed heart failure medication titration assistance clinic. Ann Pharmacother 2018;52:724–32.
34. Suzuki M, Matsue Y, Izumi S, Kimura A, Hashimoto T, Otomo K, Saito H, Suzuki M, Kato Y, Funakoshi R. Pharmacist-led intervention in the multidisciplinary team approach optimizes heart failure medication. Heart Vessels 2018;33:615–22.
35. Moye PM, Chu PS, Pounds T, Thurston MM. Impact of a pharmacy team-led intervention program on the readmission rate of elderly patients with heart failure. Am J Health Syst Pharm 2018;75:183–90.
36. Hale GM, Hassan SL, Hummel SL, Lewis C, Ratz D, Brenner M. Impact of a pharmacist-managed heart failure postdischarge (bridge) clinic for veterans. Ann Pharmacother 2017;51:555–62.
37. Boykin A, Wright D, Stevens L, Gardner L. Interprofessional care collaboration for patients with heart failure. Am J Health Syst Pharm 2018;75:e45–9.
38. Cheng JW. Current perspectives on the role of the pharmacist in heart failure management. Integr Pharm Res Pract 2017;7:1–11.
39. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Chichester, UK: John Wiley & Sons; 2011.
40. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.
41. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW. Jr., Atkins D, Meerpohl J, Schunemann HJ. GRADE guidelines: 4. Rating the quality of evidence−study limitations (risk of bias). J Clin Epidemiol 2011;64:407–15.
42. Parajuli DR, Kourbelis C, Franzon J, PN, McKinnon R, Shakib S, Clark R. Role of the pharmacist-involved multidisciplinary management of heart failure to improve readmission and mortality rates: systematic review protocol of randomized controlled trials 2016: Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=52195.
43. Lowrie R, Mair FS, Greenlaw N, Forsyth P, Jhund PS, McConnachie A, Rae B, McMurray JJ. Pharmacist intervention in primary care to improve outcomes in patients with left ventricular systolic dysfunction. Eur Heart J 2012;33:314–24.
44. Lopez Cabezas C, Falces Salvador C, Cubi Quadrada D, Arnau Bartes A, Ylla Bore M, Muro Perea N, Homs Peipoch E. Randomized clinical trial of a postdischarge pharmaceutical care program vs. regular follow-up in patients with heart failure. [Spanish, English]. Farmacia Hospitalaria 2006;30:328–42.
45. Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol 2005;60:183–93.
46. Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoes AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study [erratum]. J Card Fail 2003;9:481.
47. Murray MD, Young J, Hoke S, Tu W, Weiner M, Morrow D, Stroupe KT, Wu JW, Clark D, Smith F, Gradus-Pizlo I, Weinberger M, Brater DC. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. Ann Intern Med 2007;146:714–25.
48. Azad N, Molnar F, Byszewski A. Lessons learned from a multidisciplinary heart failure clinic for older women: a randomised controlled trial. Age Ageing 2008;37:282–7.
49. Holland R, Brooksby I, Lenaghan E, Ashton K, Hay L, Smith R, Shepstone L, Lipp A, Daly C, Howe A, Hall R, Harvey I. Effectiveness of visits from community pharmacists for patients with heart failure: HeartMed randomised controlled trial. BMJ 2007;334:1098.
50. Gwadry-Sridhar FH, Arnold JM, Zhang Y, Brown JE, Marchiori G, Guyatt G. Pilot study to determine the impact of a multidisciplinary educational intervention in patients hospitalized with heart failure. Am Heart J 2005;150:982.
51. Packer M. Development and evolution of a hierarchical clinical composite end point for the evaluation of drugs and devices for acute and chronic heart failure: a 20-year perspective. Circulation 2016;134:1664–78.
52. Anker SD, Schroeder S, Atar D, Bax JJ, Ceconi C, Cowie MR, et al. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. Eur J Heart Fail 2016;18:482–9.
53. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
54. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
55. Collaboration C. RevMan 5.3 user guide. The Cochrane Collaboration. Available with RevMan 2014.

56. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evid Based Healthc 2015;13:196–207.
57. Ried K. Interpreting and understanding meta-analysis graphs: a practical guide. Aust Fam Physician 2006;35:635–8.
58. Perera R, Heneghan C. Interpreting meta-analysis in systematic reviews. Evid Based Med 2008;13:67–9.
59. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
60. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
61. Sedgwick P, Marston L. How to read a funnel plot in a meta-analysis. BMJ 2015;351:h4718.
62. Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. BMJ 2014;349:g6501.
63. Tsuyuki RT, Fradette M, Johnson JA, Bungard TJ, Eurich DT, Ashton T, Gordon W, Ikuta R, Kornder J, Mackay E, Manyari D, O'Reilly K, Semchuk W. A multicenter disease management program for hospitalized patients with heart failure. J Card Fail 2004;10:473–80.
64. Stewart S, Pearson S, Horowitz JD. Effects of a home-based intervention among patients with congestive heart failure discharged from acute hospital care. Arch Intern Med 1998;158:1067–72.
65. Gattis WA, Hasselblad V, Whellan DJ, O'Connor CM. Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. Arch Intern Med 1999;159:1939–45.
66. Goodyer LI, Miskelly F, Milligan P. Does encouraging good compliance improve patients' clinical condition in heart failure? Br J Clin Pract 1995;49:173–6.
67. Rainville EC. Impact of pharmacist interventions on hospital readmissions for heart failure. Am J Health Syst Pharm 1999;56:1339–42.
68. Varma S, McElnay JC, Hughes CM, Passmore AP, Varma M. Pharmaceutical care of patients with congestive heart failure: interventions and outcomes. Pharmacotherapy 1999;19:860–9.
69. Triller DM, Hamilton RA. Effect of pharmaceutical care services on outcomes for home care patients with heart failure. Am J Health Syst Pharm 2007;64:2244–9.
70. Azad N, Molnar F, Byszewski A. Lessons learned from a multidisciplinary heart failure clinic for older women: a randomised controlled trial. Age Ageing 2008;37:282–7.
71. Eggink RN, Lenderink AW, Widdershoven JWMG, van den Bemt PMLA. The effect of a clinical pharmacist discharge service on medication discrepancies in patients with heart failure. Pharm World Sci 2010;32:759–66.
72. Korajkic A, Poole SG, MacFarlane LM, Bergin PJ, Dooley MJ. Impact of a pharmacist intervention on ambulatory patients with heart failure: a randomised controlled study. J Pharm Pract Res 2011;41:126–31.
73. Roblek T, Deticek A, Leskovar B, Suskovic S, Horvat M, Belic A, Mrhar A, Lainscak M. Clinical-pharmacist intervention reduces clinically relevant drug-drug interactions in patients with heart failure: a randomized, double-blind, controlled trial. Int J Cardiol 2016;203:647–52.
74. Jaarsma T, Arestedt KF, Martensson J, Dracup K, Stromberg A. The European Heart Failure Self-care Behaviour scale revised into a nine-item scale (EHFScB-9): a reliable and valid international instrument. Eur J Heart Fail 2009;11:99–105.
75. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med 2016;375:1868–77.
76. Plitt GD, Spring JT, Moulton MJ, Agrawal DK. Mechanisms, diagnosis, and treatment of heart failure with preserved ejection fraction and diastolic dysfunction. Expert Rev Cardiovasc Ther 2018;16:579–89.
77. Parikh KS, Sharma K, Fiuzat M, Surks HK, George JT, Honarpour N, et al. Heart failure with preserved ejection fraction expert panel report: current controversies and implications for clinical trials. JACC Heart Fail 2018;6:619–32.
78. Sharma K, Kass DA. Heart failure with preserved ejection fraction. Circ Res 2014;115:79–96.
79. Jordan VM, Lensen SF, Farquhar CM. There were large discrepancies in risk of bias tool judgments when a randomized controlled trial appeared in more than one systematic review. J Clin Epidemiol 2017;81:72–6.
80. Barker A, Barlis P, Berlowitz D, Page K, Jackson B, Lim WK. Pharmacist directed home medication reviews in patients with chronic heart failure: a randomised clinical trial. Int J Cardiol 2012;159:139–43.
81. Kinugasa Y, Kato M, Sugihara S, Yanagihara K, Yamada K, Hirai M, Yamamoto K. Multidisciplinary intensive education in the hospital improves outcomes for hospitalized heart failure patients in a Japanese rural setting. BMC Health Serv Res 2014;14:351.
82. Khan MS, Fonarow GC, Ahmed A, Greene SJ, Vaduganathan M, Khan H, Marti C, Gheorghiade M, Butler J. Dose of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and outcomes in heart failure: a meta-analysis. Circ Heart Fail 2017;10:e003956.
83. Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, Cope S. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. Circ Heart Fail 2017;10:e003529.
84. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, et al. Declining risk of sudden death in heart failure. N Engl J Med 2017;377:41–51.
85. Sandison K, Marsh M, Lizza B, Yancy CW, Mutharasan RK. Pharmacist education at discharge correlates with reduced 30-day readmissions in heart failure patients. J Card Fail 2017;23:S113.
86. Al-Bawardy R, Cheng-Lai A, Prlesi L, Assafin M, Xu S, Chen K, Tandan S, Aneke CS, Murthy S, Pina IL. Heart failure postdischarge clinic: a pharmacist-led approach to reduce readmissions. Curr Probl Cardiol 2019;44:100407.
87. Davis EM, Packard KA, Jackevicius CA. The pharmacist role in predicting and improving medication adherence in heart failure patients. J Manag Care Spec Pharm 2014;20:741–55.
88. Schulz M, Griese-Mammen N, Anker SD, Koehler F, Ihle P, Ruckes C, Schumacher PM, Trenk D, Bohm M, Laufs U. Pharmacy-based interdisciplinary intervention for patients with chronic heart failure: results of the PHARM-CHF randomized controlled trial [e-pub ahead of print]. Eur J Heart Fail 2019;21:1012–21.
89. Dunlay Shannon M, Shah Nilay D, Shi Q, Morlan B, VanHouten H, Hall Long K, Roger Véronique L. Lifetime costs of medical care after heart failure diagnosis. Circ Cardiovasc Qual Outcomes 2011;4:68–75.
90. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? EP Europace 2011;13:ii13–7.
91. Parajuli DR, Franzon J, McKinnon RA, Shakib S, Clark RA. Role of the Pharmacist for Improving Self-care and Outcomes in Heart Failure. Curr Heart Fail Rep 2017;14:78–86.