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Pharmacist-led optimization of heart failure medications: A systematic review

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Abstract

Medications are a cornerstone of treatment of heart failure (HF) with reduced ejection fraction, thus pharmacists are valuable members of the multidisciplinary team approach to long-term patient management. As pharmacists' scope of practice has expanded, growing evidence shows an evolution in pharmacists' roles in the care of patients with HF. To synthesize the literature describing implementation of pharmacist-led medication titration and clinical assessments on outcomes in ambulatory patients with HF. MEDLINE, Embase, and Cochrane Controlled Register of Trials were searched from 2007 to March 18, 2020. English language articles that evaluated implementation of pharmacist-led medication titration in ambulatory patients with HF. Studies with interventions that involved pharmacists prescribing to initiate, modify, or discontinue medications with independent authority or under a collaborative practice agreement were considered. Ten retrospective studies from 718 identified articles were included. All studies incorporated pharmacist-led guideline-directed medical therapy (GDMT) titration, two with independent pharmacist prescribing in a multidisciplinary HF clinic, and seven in a pharmacist-only clinic. Patients were referred from both inpatient and outpatient settings and had an average reported range of 1–5.7 visits with pharmacists. While four studies exclusively included patients with HF and ejection fraction below 45%, the mean ejection fraction of all included patients ranged from 20% to 42%. Four studies showed an increased proportion of patients on GDMT or target doses after pharmacist prescribing. Four out of six studies showed a significant decrease in all-cause hospitalizations and one of two studies reported a significant decrease in all-cause mortality rate with intervention. This study found that pharmacist-led medication optimization increased the use of GDMT in ambulatory patients with HF, and may be associated with fewer hospitalizations and deaths. Future randomized controlled trials should evaluate the impact of adding pharmacist-led HF medication optimization to standard of care on clinical outcomes.

KEYWORDS

cardiology, heart failure, medication therapy management, pharmacy

1 | INTRODUCTION

Heart failure (HF) is associated with a poor long-term prognosis and has significant impacts on patient morbidity and mortality.[1] HF hospitalizations may lead to progression of disease and death, and nearly 25% of patients are readmitted within 30 days.[2] Despite robust evidence supporting the use of guideline-directed medical therapy (GDMT) in patients with HF with reduced ejection fraction (HFrEF), many patients receive suboptimal treatment. Contemporary registry data suggest that the majority of HFrEF patients are not on target therapy doses by 12 months, and less than 1% of patients are on concurrent target doses of triple therapy.[3] Including pharmacists in multidisciplinary approaches is imperative given that medications are the cornerstone of HF management.

Multidisciplinary ambulatory HF clinics have long been established and shown to improve patient outcomes, including decreasing hospitalizations.[2] Adding pharmacists to these teams has been shown to reduce HF hospitalizations, improve quality of life, and increase patients' knowledge of their condition and adherence to medications when compared with usual care.[4,5] The 2013 policy statement on the role of clinical pharmacy services in HF by the Heart Failure Society of America (HFSA) and American College of Clinical Pharmacy (ACCP) described traditional pharmacist roles as performing medication reconciliation, preventing adverse drug reactions and medication errors, therapeutic drug monitoring, and monitoring medication adherence.[6] However, the continued evolution of pharmacists' scope of practice has resulted in emerging evidence on pharmacists expanding their role in the care of patients with HF, including independent prescribing, ordering of laboratory tests, as well as advanced clinical assessment such as physical assessment and laboratory test interpretation.

The aim of this study was to synthesize the literature describing pharmacist-led HF medication titration on outcomes in ambulatory patients with HF.

2 | METHODS

This systematic review was conducted and reported according to the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) statement.[7]

2.1 | Search strategy

MEDLINE, Embase, and the Cochrane Controlled Register of Trials (CENTRAL) were searched from January 1, 2007 (year of search conducted in prior systematic review by one of the reviewers)[4] to March 18, 2020. The MEDLINE search query is available as an Appendix. Search terms were adapted according to the syntax of each database, restricted to studies reported in English. Bibliographies of included studies and relevant reviews were hand-searched.

2.2 | Eligibility criteria

Comparative randomized controlled trials and observational studies, as well as single-arm studies that evaluated the implementation of pharmacist-led medication optimization on outcomes in ambulatory patients with HF, focusing on patients with HFrEF when data was available separately for this subgroup, were included. For the intervention, studies were considered if pharmacists prescribed HF medications with independent authority or under a collaborative practice agreement (including initiation, modification, and discontinuation of medications). The comparator group, if present, could include usual care without pharmacist prescribing, or ambulatory team management without pharmacist inclusion.[6]

2.3 | Outcomes

Outcomes of interest included the proportion of HFrEF patients taking any GDMT and GDMT at target doses, as defined by contemporary guidelines referenced by included studies,[8-10] which included angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), or angiotensin receptor neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists. Additional outcomes of interest included death, all-cause hospitalization and HF hospitalization, adverse drug reactions, medication errors or discrepancies, and quality of life.

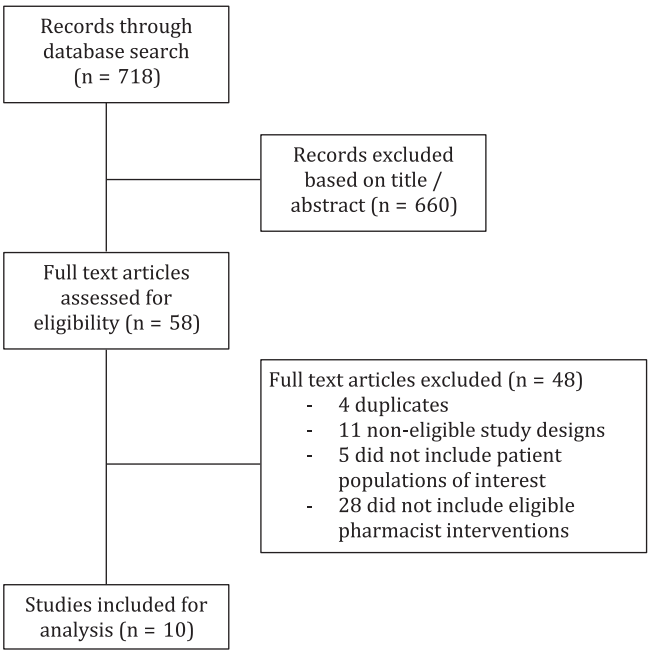
2.4 | Study selection and data extraction

Two reviewers (VC and RT) independently screened article titles and abstracts, reviewed full-text articles for inclusion, and extracted data using a standardized data collection form, including details on study design, participant demographics, baseline participant characteristics, clinic organization and pharmacist intervention, and outcomes.

3 | RESULTS

Of 718 identified articles, 10 observational studies were included with a total of 765 participants (Figure 1). Key characteristics are outlined in Table 1. Nine studies were conducted in the United States and one was conducted in the United Arab Emirates. All studies were retrospective, including five cohort studies comparing pharmacist-led medication titration to a control group without a pharmacist,[11-15] and four single-arm pre-post studies comparing pharmacist-led medication titration to care prior to implementing pharmacist-led medication titration.[16-19] One cohort study compared three groups: pharmacist-led medication titration, pharmacist providing usual care without medication optimization and a control group without a pharmacist.[20] The sample size within the pharmacist intervention group ranged from 51 to 144 patients. At baseline, the mean age was 65 years, 25.6% were women, and the mean ejection fraction ranged from 20% to 42%, with four studies restricted to patients with ejection fraction ≤40%-45%.[11,12,15,16]

FIGURE 1 PRISMA flow diagram



3.1 | Clinic organization and pharmacist-led medication titration

Seven studies evaluated pharmacist-only clinics[11,13,15-18,20] and two studies incorporated a pharmacist with prescribing authority into a multidisciplinary HF clinic.[14,19] Six studies reported that pharmacists in intervention groups had extra training or specialized in cardiology or HF therapy (Table 1).[11,12,16,18-20] Patients were referred to the clinics for the purposes of addressing medication discrepancies and medication titration (N = 5),[12,13,16,17,19] transition of care from inpatient to outpatient settings (N = 7),[11-14,18-20] and/or for clinical deterioration (N = 1).[18] Referrals originated from the hospital discharge team in three studies,[13,14,20] from outpatient cardiologists in one study,[12] from both inpatient and outpatient clinicians in five studies,[11,15,16,18,19] and from a specialty HF clinic in one study.[17] Six studies reported average number of appointments, ranging from 1 to 5.7 visits.[12-14,16,18,19] Of the eight studies that reported clinic structures, three had appointment lengths of 60 minutes,[11,13,18] and the rest had appointments lasting ≤30 minutes.[12,14,16,19] Five studies had in-person visits,[11-14,16,19,20] two studies described in-person clinics with telephone follow-ups as needed,[17,18] and one study reported implementing exclusively telephone-based clinic encounters.[15] Seven studies reported concurrent care by cardiologists during pharmacist-led medication titration,[11,12,14,15,17-19] though it is unclear if they made adjustments to medication regimens, whereas the remaining studies did not describe the involvement of other clinicians.[13,16,20] After pharmacist led-titration, patients were discharged to their primary care providers or primary cardiologists in four studies,[11-13,20] to the HF clinic in one study,[17] and to an unspecified provider in the remaining studies.[14,15,18-20]

The intervention arm of all included studies incorporated pharmacist prescribing, including initiation and titration of GDMT and discontinuation of contraindicated or unnecessary medications. Two studies further incorporated both pharmacist-performed physical assessment and ordering and interpretation of laboratory tests,[14,16] six studies implemented laboratory monitoring without physical assessment,[12,13,15,17,18,20] and two studies did not report pharmacist-performed physical assessment or laboratory monitoring.[11,19] In addition to medication optimization, pharmacist interventions also included regimen simplification, patient education, and self-management tools.[18]

3.2 | Impact of pharmacist-led medication titration on guideline-directed medication use

Four studies reported the proportion of patients receiving GDMT both before and after pharmacist-led optimization (Table 2).[11,12,17,19]

TABLE 1 Summary of study characteristics

Study Enrolment date Location	n Pharmacist/ control group	Patient population	Intervention and details of care						
			Pharmacist training or designation	Reason for referral	Appointment length, min	Number of visits Duration of pharmacist intervention	Independent/ collaborative pharmacist prescribing	Pharmacist orders labs	Pharmacist performs physical assessment
Retrospective cohort studies									
Martinez et al[15] 2011-2012 Florida	51/93	Mean age: 68 Women: 0% Mean LVEF: 27% NYHA: NR Comorbidities: NR	Clinical pharmacist	Medication optimization	20-25	NR NR	Yes	Yes	No
Jackevicius et al[14] 2010-2012 California	144/133	Mean age: 72 Women: 2% Mean LVEF: 37% NYHA: NR Comorbidities: CKD (44% vs 31%). CAD, CA, COPD, DM, HTN, Hx MI, stroke: NSS	Clinical pharmacist	Transition of care	30	NR NR	Yes	Yes	Yes
Hale et al[13] 2010-2013 Michigan	122/122	Mean age: 68 Women: 0% Mean LVEF: 35% NYHA: NR Comorbidities: CAD, PVD, arrhythmia, DM, stroke, CKD, COPD NSS	Clinical pharmacist	Transition of care	60	NR NR	Yes	Yes	NR
Bhat et al[12] 2011-2013 Illinois	51/97	Mean age: 60 Women: 34% LVEF <40% (mean NR) NYHA: I (39% vs 37%), II (47% vs 50%), III (14% vs 13%) Comorbidities: CAD (47% vs 70%). DM, HTN, DLD, Stroke, COPD, CKD: NSS	Cardiology residency training	Medication optimization Transition of care	30	Mean 5.7 visits (SD 2.9) NR	Yes	Yes	NR
Al-Bawardy et al[11] 2012-2014 New York	109/45	Mean age: 64 Women: 45% Mean LVEF: 28% NYHA: NR Comorbidities: NR	PharmD, HF therapy training by the National Heart Failure Training Program	Transition of care	60	Total 1 visit without further follow-up	Yes	NR	NR

(Continues)

TABLE 1 (Continued)

Study Enrolment date Location	n Pharmacist/ control group	Patient population	Intervention and details of care						
			Pharmacist training or designation	Reason for referral	Appointment length, min	Number of visits Duration of pharmacist intervention	Independent/ collaborative pharmacist prescribing	Pharmacist orders labs	Pharmacist performs physical assessment
Hahn et al[20] 2015-2017 Texas	35/35	Mean age: 60 Women: 63% Mean LVEF: 42% NYHA II-III: 72% vs 42% vs 63% Comorbidities: DM, HTN, DLD, COPD, CKD, atherosclerotic disease: NSS	Clinical pharmacy specialist	Transition of care	NR	≤2 NR	Yes	Yes	NR
Single-arm retrospective cohort studies									
Milfred-LaForest et al[18] 2008-2009 Ohio	71 with LVEF ≤40%	Mean age: 69 Women: 1% Mean LVEF: NR NYHA: NR Comorbidities: N/A	Staff pharmacists supervised by clinical pharmacist specializing in HF. All completed HF continuing education program	Transition of care Clinical deterioration	60	Total 1 visit for 93% patients Mean 1.4 weeks (SD 0.8) follow-up	Yes	Yes	No
Pogge and Davis[17] 2015-2017 Arizona	52 analyzed	Mean age: 69 Women: 25% Mean LVEF: 26% NYHA: II-III (100%) Comorbidities: NR	NR	Medication optimization	NR	NR Median 8 weeks follow-up from initiation to final dose change	Yes	Yes	NR
Atallah et al[19] 2017-2019 United Arab Emirates	94 analyzed	Mean age: 58 Women: 33% Mean LVEF: NR NYHA: I (13%), II (63%), III (21%), IV (3%) Comorbidities: N/A	Cardiology pharmacotherapy specialist	Medication optimization Transition of care	30	Mean 1.9 visits (SD 1.4) Mean 7.3 weeks (SD 5.1) follow-up	Yes	No	No
Ingram et al[16] 2016 Ohio	36	Mean age: 63 Women: 52% Mean LVEF: 30.5% NYHA: I (10.5%), II (53%), III (17%), unknown (10.5%) Comorbidities: NR	Training with HF cardiologists to develop and maintain physical assessment skills	Medication optimization	30	Mean 4.9 visits Mean 12.7 weeks follow-up	Yes	Yes	Yes

Abbreviations: CA, cancer; CAD, cardiovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DLD, dyslipidemia; DM, diabetes mellitus; HF, heart failure; LVEF, left ventricular ejection fraction; N/A, not applicable; NR, not reported; NSS, not statistically significant; NYHA, New York Heart Association [class]; PharmD, Doctor of Pharmacy (degree); PVD, peripheral vascular disease.

TABLE 2 Guideline-directed medical therapy use among patients with heart failure with reduced ejection fraction before and after pharmacist-led medication titration

	ACEI/ARB, % (% on target dose)			Angiotensin receptor-neprilysin inhibitor, % (% on target dose)			Beta-blocker, % (% on target dose)			Mineralocorticoid receptor antagonist, % (% on target dose)		
Study identifier	Before	After	*P*-value	Before	After	*P*-value	Before	After	*P*-value	Before	After	*P*-value
Pogge and Davis[17]	73.0 (13.5)	100[a] (86.5[a])	<.001 (<.001)	0	100 (86.5)	–	86.5 (23.1)	94.2 (25.0)	1.0 (1.0)	30.8	23.1	.125
Bhat et al[12]	92 (39)	95 (80)	–	NR	NR	–	90 (16)	100 (75)	–	10	NR	–
Al-Bawardy et al[11]	60/17.9	72.6/12.6	–	NR	NR	–	94.7	97.9	–	47.4	47.4	–
Atallah et al[19]	83.0[b] (7.4[b])	88.3[b] (25.5[b])	.003 (<.001)	17.0	50 (46.8)	–	98.9 (31.9)	98.9 (40.4)	1.0 (.032)	51.1	59.6	.043 (.46)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NR, not reported.
[a]Switched to angiotensin receptor-neprilysin inhibitor.
[b]Including angiotensin receptor-neprilysin inhibitor.

TABLE 3 Clinical outcomes among patients with heart failure with reduced ejection fraction with pharmacist-led medication titration vs control group

Study identifier	Outcome	Pharmacist intervention group, %	Control, %	*P*-value
Retrospective cohort studies (control = group with no pharmacist-led titration)				
Al-Bawardy et al[11]	All-cause hospitalization at 30 days	9.2	20.0	.06
	All-cause hospitalization at 90 days	24.8	48.9	.003
	All-cause hospitalization at 1 year	59.6	55.6	.64
	All-cause death at 1 year	5.2	11.1	.29
Bhat et al[12]	Cardiovascular hospitalization	Mean 0.45/patient	Mean 0.35/patient	.38
	Heart failure exacerbation	Mean 0.18/patient	Mean 0.11/patient	.42
Hahn et al[20]	All-cause hospitalization at 30 days	8.6	25.7	.046
Hale et al[13]	All-cause death or hospitalization at 30 days	9.8	18.9	.02
	All-cause death or hospitalization at 90 days	25.4	34.4	.06
Jackevicius et al[14]	Heart failure hospitalization at 90 days	7.6	23.3	<.001
	All-cause death at 90 days	1.4	5.3	.043
Single-arm retrospective cohort studies (control = period before pharmacist-led titration)				
Ingram et al[16]	All-cause hospitalization at 13 weeks	3 admissions	12 admissions	.041
Milfred-LaForest et al[18]	All-cause hospitalization at 30 days	19	9	NR

Abbreviation: NR, not reported.

Overall, these studies found higher use of ACEI/ARB (ranging from 88% to 98%),[11,12,19] beta-blockers (ranging from 94% to 100%)[12,17,19] and mineralocorticoid receptor antagonists (ranging from 13% to 60%),[12,17,19] and greater attainment of target doses of ACEI/ARB/ARNI and beta-blockers after pharmacist-led optimization.[12,17,19] Two studies reported on ARNI use: one study described a dedicated pharmacist-led ARNI titration clinic, which initiated an ARNI in 100% of patients who were referred (from 73% previously on ACEI/ARB) and titrated 86.5% to the target dose.[17] In the second study, pharmacist-led optimization increased the percentage of HFrEF patients on an ARNI by the end of follow-up increased from 37% to 50%, with 46.8% of them achieving target doses.[19]

3.3 | Association of pharmacist-led medication optimization with hospitalizations and mortality

Seven included studies described hospitalizations and/or mortality at various time points (Table 3).[11-14,16,18,20] From these studies, hospitalizations and deaths were numerically lower in the pharmacist-led optimization group, though the comparisons and results were varied (Table 3). Six studies reported the rate of hospitalizations, four of which were statistically significantly lower in favor of the pharmacist intervention.[11,12,14,16,18,20] All-cause hospitalizations at 30 days were significantly lower in one study with pharmacist-led medication optimization compared with a control group without pharmacist care

(8.6% vs 25.7%, $P = .046$), whereas pharmacist usual care compared with control group was not significantly different (7.1% vs 25.7%, $P = .057$).[20] Another study did not find significant differences between pharmacist-led medication titration and usual care in all-cause hospitalizations at 30 days (9.2% vs 20%, $P = .06$) or 1 year (59.6% vs 55.6%, $P = .64$), the difference was significant at 90 days (24.8% vs 48.9%, $P = .003$).[11] Two studies reported all-cause mortality: death at 90 days was 1.4% in the pharmacist-led medication optimization group versus 5.3% in the group without pharmacist care ($P = .043$) in one study, and death at 1 year was 5.2% in the pharmacist-led medication optimization group versus 11.1% in the group without pharmacist care ($P = .29$).[11,14]

3.4 | Other outcomes

None of the included studies described adverse drug reactions or quality of life as outcomes. Two studies reported identification of medication discrepancies, which were commonly identified by the pharmacists.[10,16]

4 | DISCUSSION

In this systematic review of 10 observational studies, pharmacist-led medication optimization added to usual care was associated with greater use of HFrEF GDMT. Furthermore, pharmacist-led HFrEF medication optimization was associated with fewer all-cause hospitalizations and deaths in some studies. Overall, we found significant variation in the structure of delivering pharmacist-led medication optimization, including differences in encounter type, length, frequency, and monitoring. This is in part due to the fact that the studies included were single-center and observational in design.

Despite consensus from international guidelines regarding the importance of GDMT to improve outcomes in patients with HFrEF, only a minority of patients with HFrEF receive all classes of medications with proven benefit in HFrEF, and even fewer receive these medications at target doses.[21-23] Suboptimal use of HFrEF GDMT is associated with therapeutic inertia and perceived stable condition.[21-23] Previous data have shown that approximately 25% of patients are readmitted to hospital within 30 days after an index HF hospitalization,[2] which is in keeping with the control groups of included studies.[11,13,20] Several studies have established that independent prescribing by pharmacists increases use of evidence-based medications, adherence and target attainment across a range of other chronic conditions including stroke, hypertension, diabetes, and dyslipidemia.[24-26] The addition of a pharmacist as part of the multidisciplinary HF team has been demonstrated in several randomized trials and meta-analyses to have significant improvement in outcomes, including a reduction in hospitalizations.[4,27] The role of pharmacists in these prior HF studies generally consisted of medication reconciliation, patient education, monitoring, and therapeutic recommendations, which formed the evidence base for the clinical pharmacy services described in the HFSA/ACCP policy statement.[6] Newer HF care models recognize pharmacists as care providers and have endorsed independent prescribing and monitoring of patients with HF.[13,28-30] This study builds upon the scope of interventions described in past studies such as the PHARM trial[27] by enhancing the identification of drug-related problems with active optimization of GDMT by pharmacists with prescribing authority. This enhanced intervention would be anticipated to further improve outcomes beyond the current standard of care by pharmacists. Randomized controlled trials are needed to confirm the clinical benefit of these advanced interventions. Furthermore, while the proportion of patients on GDMT at baseline are comparable to contemporary registry data, pharmacist-led medication initiation and titration resulted in higher use of GDMT post-intervention.[3] The present review extends previous work, demonstrating that newer HF care models with pharmacists independently initiating and titrating HF medications can improve the use of GDMT, which in turn improves clinical outcomes.

The studies included in this review differed in patient inclusion criteria, format of the clinic and delivery of interventions, as well as outcomes. Although this renders it difficult to assess the contribution of individual components of the intervention on outcomes, several common themes emerged across studies. First, most studies focused on recently discharged HFrEF patients not receiving GDMT, and therefore identified a high risk population in whom pharmacist-led titration may have the greatest impact. Second, some studies implemented serial encounters with pharmacist-ordered laboratory testing, which allows for multiple titrations and prospective monitoring for adverse drug events.[12,16,19] Third, few studies reported using an explicit GDMT titration protocol, and most of them preceded the advent of use of ARNI-based regimens and SGLT2 inhibitors for heart failure. Sacubitril–valsartan, the only marketed ARNI, was approved for use in 2015. In aggregate, these studies suggest a need for a prospective, randomized trial to evaluate enhanced care with pharmacist-led titration of modern HFrEF pharmacotherapy delivered over multiple in-person and virtual/telehealth encounters compared with standard pharmacy care on GDMT attainment, adherence, patient health-related quality of life, and other clinical outcomes in patients with HFrEF with recent hospitalization or other risk factors.

4.1 | Limitations

This review has several limitations inherent to the included studies. First, none of the included studies were randomized controlled trials, and therefore prone to bias and confounding when comparing outcomes between pharmacist-led titration and comparator groups. Second, included studies were not generally designed nor powered to demonstrate differences in clinical outcomes such as hospitalizations and mortality. There were several differences between studies in the delivery of pharmacist-led

titration, including frequency of encounters and follow-up duration, and the optimal strategy for implementation remains uncertain. However, the descriptions of interventions employed in this review can aid in the future design of studies comparing various strategies. Our review did not identify any studies that reported medication errors, discrepancies or adverse drug reactions in detail. This should remain an area of interest as these interventions are likely under-reported and an opportunity for pharmacists caring for patients with HF.

5 | CONCLUSION

Pharmacist-led optimization of medications for ambulatory HFrEF patients increases use of guideline-directed medical therapy, which may be associated with fewer hospitalizations and deaths. Future randomized controlled trials should evaluate the impact of adding pharmacist-led HFrEF medication optimization to standard of care on clinical outcomes.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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APPENDIX

MEDLINE search query

1. pharmacist.mp or Pharmacists/
2. Community Pharmacy Services/or Pharmacy Service, Hospital/or Pharmacy/
3. Pharmaceutical Services/
4. Clinical pharmacy services$.mp
5. Pharmacist expertise.mp
6. Heart failure.mp or Heart Failure/
7. Congestive heart failure.mp
8. Heart function.mp
9. Cardiomyopathy.mp or Cardiomyopathies/
10. 1 or 2 or 3 or 4 or 5
11. 6 or 7 or 8 or 9
12. 10 and 11
13. Limit 12 to (English language and yr="2007-current")