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Heart Failure (W Tang, Section Editor)

The Impact of Pharmacist-Based Services Across the Spectrum of Outpatient Heart Failure Therapy

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Abstract

Purpose of review A multidisciplinary approach is vital to reduce mortality and hospitalizations in patients with heart failure. As members of the multidisciplinary team, pharmacists are uniquely positioned to care for patients across the spectrum of heart failure. This comprehensive review explores the different facets in which pharmacists can be utilized to impact the care for patients with heart failure, including those with cardiac transplant and left ventricular assist devices (LVADs), in the outpatient setting.
Recent findings Pharmacists can see heart failure patients in a variety of settings to reduce drug therapy–related issues, increase use of guideline-directed medical therapy (GDMT), and reduce hospitalizations. Although there is limited data available, pharmacists have also been described in aiding the therapeutic drug monitoring of warfarin for patients with LVADs and immunosuppression agents in the transplant population.
Summary Through collaborative practice agreements, pharmacists can provide progressive services such as titration of GDMT and lab monitoring, in addition to medication reconciliation, education, and review for potential drug-related problems. Pharmacists can increase access to patient care by providing services through distance-visits, shared medical appointments, and home visits.

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Introduction

In the USA, it is estimated that almost 1 million new cases of heart failure will be diagnosed annually, with a prevalence projected to increase by 46% by 2030. As of 2012, the economic burden of treating heart failure equates to 30.7 billion US dollars annually. The risk of heart failure increases as patients age, with those greater than 80 years of age having a 20% lifetime risk of developing new heart failure [1]. As a larger proportion of Americans age, more patients with heart failure will face increasingly complex treatment in the context of multiple comorbidities, which may include medications that can exacerbate or worsen heart failure [2].

Heart failure continues to be the leading cause of hospital admissions in patients who are 65 years of age or older, despite the number of medical therapies available to reduce morbidity and mortality for those with a reduced ejection fraction (HFrEF) [1, 3]. Since 2010, there have been many federal initiatives aimed to reduce the cost and burden of heart failure hospitalizations to the health care system. However, the progressive nature of heart failure may result in chronic guideline-directed medical therapy (GDMT) becoming intolerable over time, leading to more frequent hospitalizations.

As patients' progress toward end-stage heart failure and advanced therapies are considered, such as left ventricular assist devices (LVADs) or cardiac transplantation, drug therapies often include medications with narrow therapeutic indexes and drug interactions that require close monitoring. A statement from Heart Failure Society of America (HFSA) and American College of Clinical Pharmacy (ACCP), in addition to the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines, emphasizes the importance of a multidisciplinary approach, including physicians, nurses, pharmacists, dieticians, and social workers, across the spectrum of treating heart failure patients, including those with LVADs and heart transplants [3, 4••].

Cardiovascular and ambulatory trained clinical pharmacists are uniquely equipped to provide beneficial services to outpatients with heart failure, LVADs, and heart transplants. Most cardiovascular and ambulatory trained clinical pharmacists have received Doctor of Pharmacy (PharmD) degrees followed by completion of a post-graduate year one general pharmacy residency and post-graduate year two training that specializes solely on the treatment of cardiovascular diseases or ambulatory practice that includes treatment of cardiovascular diseases. Most clinically trained pharmacists will then pursue pharmacotherapy, ambulatory care, or cardiovascular specific board certifications [5••].

Two years ago, the Cleveland Clinic Kauffman Center for Heart Failure began to utilize cardiology trained clinical pharmacists to follow up patients between outpatient visits with their primary heart failure physician. Services offered at this clinic which may be provided by either in-person visits or virtually through distance health technologies provide examples of available pharmacist-based interventions including medication histories and

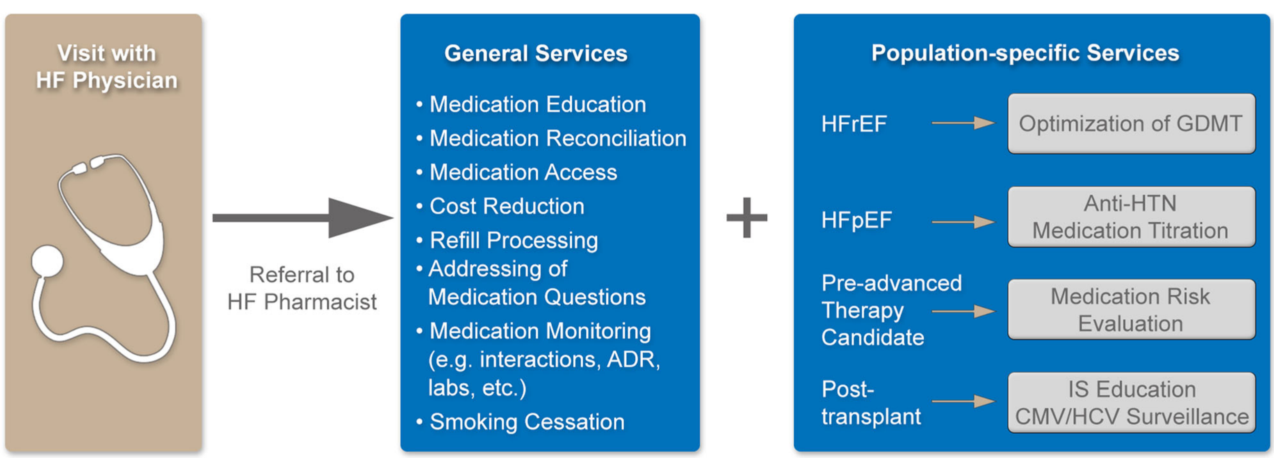

Fig. 1. Pharmacist-based services for heart failure and heart transplant patients at the Cleveland Clinic. HF, heart failure; ADR, adverse drug reactions; HFrEF, heart failure with a reduced ejection fraction; HFpEF, heart failure with a preserved ejection fraction; GDMT, guideline-directed medical therapy; HTN, hypertension; IS, immunosuppression; CMV, cytomegalovirus; HCV, hepatitis C virus

Table 1. Outcomes of pharmacist-based interventions in heart failure, mechanical circulatory support, and heart transplant patients

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
Pharmacist-Conducted Medication Reviews and Patient Education				
Varma (1999)	HFrEF; elderly ($n = 83$)	RCT	Education on disease state, treatment, lifestyle modifications, and self-monitoring vs. standard care	Improved 2-min walk test at 6 months (90.3 ± 39.2 m vs. 64.2 ± 29.4 m; $p = 0.03$), MLHF questionnaire scores at 9 months (15.6 ± 14.6 vs. 25.7 ± 18.5; $p = 0.04$), knowledge of medications ($p = 0.0026$), and readmission rates (14 vs. 27; $p = 0.006$)
Bucci (2003)	HFrEF, HFpEF ($n = 79$)	RCT	Medication education and distribution of adherence tools vs. standard care	Improved medication appropriateness index score (0.74 vs. 0.49; $p = 0.605$)
Singh-Franco (2005)	HFrEF, HFpEF ($n = 29$)	Pre/post intervention analysis	Education on medications, adherence, lifestyle modifications, and self-monitoring	Reduction in the total number of hospitalizations (23 vs.50; $p < 0.018$) and LOS (108 days vs. 263 days; $p < 0.03$) No significant reduction in HF hospitalizations, LOS for HF hospitalizations, and total number of HF signs and symptoms
Murray (2007)	HFrEF, HFpEF; low-income ($n = 314$)	RCT	Medication history and reconciliation, assessment of patients' medication knowledge, and patient-tailored education vs. standard care	Improved adherence during 3 month intervention period (78.8% vs. 67.9%; 95% CI 5.0–16.7%) Reduction in emergency department visits and hospital admissions by 19.4%
Gastelurrutia (2011)	HFrEF, HFpEF ($n = 97$)	C	Medication reviews to identify DNO or rDNO	87 DNO identified, 60 rDNO identified, 94% of which were preventable
Elman (2016)	HFrEF ($n = 48$)	RR	Pharmacist educated providers on GDMT for HF and developed protocols for transitioning to or initiating evidence-based BB therapy	46% of patients switched to or initiated on evidence-based BB therapy
Dempsey (2017)	HFrEF, HFpEF ($n = 60$)	RR	Medication and allergy reconciliation, assess for medication optimization,	304 drug therapy-related issues identified, 43% due to untreated

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
			education, and ensured appropriate dosing of IV diuretics	indications and 55% due to suboptimal therapeutic choices
Dempsey (2018)	HF or ACS; elderly ($n = 118$)	Quality improvement pilot study	Medication history and reconciliation, medication education, distribution of adherence tools, and triage/ resolution of medication access issues Follow-up phone calls conducted on an as-needed basis	Primary: Reduced rates of readmission for HF or ACS by 20% compared to institutions baseline rates ($p = 0.596$) Other: 244 recommendations for therapeutic optimization were provided with an 81% provider acceptance rate and 100% patient satisfaction rate
Yates (2019)	HFrEF, HFpEF ($n = 128$)	RR	Medication profile review including HF medication optimization, as well as comorbidity management, including diabetes, hypertension, hyperlipidemia, iron deficiency anemia, and tobacco use	Primary: reduction in average DRPs identified 2 weeks after initial visit (2.55 vs. 1.95; $p = 0.016$) Other: most common interventions were in HF disease management, followed by drug interactions, and dyslipidemia management
Turner (2000)	HFrEF ($n = 156$)	RCT	Identified patients with HF either not on ACE-I or on suboptimal doses of ACE-I and educated providers on GDMT vs. standard care	No significant increase in prescribing of ACE-I or doses of ACE-I prescribed
Bouvy (2003)	HF ($n = 152$)	RCT	Interviewed patient on medication use and identified and helped resolve medication adherence issues Pharmacist followed-up with the patient via telephone monthly vs. standard care	Primary: improved adherence to loop diuretics (140/7656 days without loop diuretic vs. 337/6196 days; RR 0.33 [95% CI 0.24–0.38]) Other: no difference in hospitalizations, mortality, or QoL
Ziman (2012)	HFrEF ($n = 80$)	Retrospective pilot study	Pharmacist ordered TSH and free T4 labs for patients overdue for these labs If abnormal results, pharmacists coordinated drug therapy and follow-up labs	90% of patients previously delinquent on thyroid function testing received relevant thyroid labs 10 patients (12.5%) with abnormal thyroid function tests not on prior drug therapy received treatment

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
Bleske (2014)	HFrEF, HFpEF ($n = 121$)	Interventional study	Conducted clinical assessment to evaluate for signs and symptoms of HF, including fluid overload and low cardiac output using The One Minute Clinic for Heart Failure (TOM-C) tool Patients were instructed to follow up their provider based on responses	62% of patients had one or more signs or symptoms of worsening HF, 39% of patients reported edema, and 17% of patients reported shortness of breath
Schulz (2019)	HFrEF, HFpEF; elderly ($n = 237$)	RCT	Conducted comprehensive medication review, provided a supply of medicines in dosing aids filled by the pharmacist, education on medications, adherence, and signs/symptoms of worsening HF, and checked vitals vs standard care Recommendations for regimen alteration made to clinician	Primary: improved rates of adherence at 1 year (mean difference 5.7%; $p = 0.007$) Other: larger proportion of patients adherent to their medications at 1 year (44 to 86% vs. 42 to 68%; $p = 0.005$), and improved QoL after 2 years (difference in MLHFQ scores − 7.8 points; $p = 0.02$). No significant difference in hospitalizations or deaths
Pharmacist-led medication optimization clinics				
Gattis (1999)	HFrEF ($n = 180$)	RCT	Medication optimization Medication education Follow-up telephone at weeks 2, 12, and 24 to identify problems and answer questions vs. standard care	Primary: lower rates of all-cause mortality and HF events (4 vs 16; $p = 0.005$) Other: higher doses of ACE-I achieved ($p < 0.001$) and more ACE-I intolerant patients on other vasodilators (75% vs. 26%; $p = 0.02$)
Jain (2005)	HFrEF ($n = 234$)	Pre/post intervention analysis	Protocol-driven medication optimization	57% of patients on none or only one GDMT agent prior to initial visit, decreased to 11% by last follow-up visit Improvement in the percentage of patients on “medium” or “high doses” of BB (18 to 57%) and ACE-I (55 to 86%)

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
Lowrie (2012)	HFrEF ($n = 2164$)	Cluster randomized trial	Medication review and optimization completed weekly	Primary: no significant difference in death from any cause or hospital admission for HF (35.8% vs. 35.4%; $p = 0.72$) Other: GDMT started or dose increased in more patients (33.1% vs. 18.5%; $p < 0.001$)
Martinez (2013)	HFrEF; veterans ($n = 144$)	Pre/post intervention analysis	Medication optimization completed by telephone encounters	Primary: more patients reached target doses of ACE-I/ARB (52.9% vs. 31%; $p = 0.007$) and BB (49% vs. 24.7%; $p = 0.012$)
Jackevicius (2015)	HFrEF, HFpEF ($n = 277$)	RC	Medication optimization and education during two of six HF Post-Discharge Management visits vs. historical controls	Primary: decrease in 90-day HF readmissions (7.6% vs. 23.3%; $p < 0.001$) Other: decrease in time-to-first HF readmission at 90 days or all-cause mortality (0% vs. 28.6%; $p < 0.001$)
Donaho (2015)	HFrEF, HFpEF ($n = 169$)	RC	Two post-discharge visits with NP and pharmacist (at 1 week and 4 weeks) for per protocol medication titration, medication reconciliation, and medication and disease state education	Average of 1.7 HF medications were altered per person during the first visit 44.3% reduction in rates of all-cause readmissions compared to hospital average
Milfred-LaForest (2017)	HFrEF, HFpEF; veterans ($n = 135$)	Retrospective quality assurance analysis	Medication and allergy reconciliation Medication review and optimization completed 7 days after discharge Medication education Scheduled follow-up appointment with a physician	Medication discrepancies identified in 53% of patients and medications optimized for 70% of patients BB doses were higher among patients with HFrEF after the clinic visit (152 ± 109 mg/day vs. 165 ± 108 mg/day; $p = 0.005$) ACE-I doses were higher among patients with HFrEF after the clinic visit (30 ± 20 mg/day vs. 31 ± 19 mg/day; $p = 0.044$)

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
Hale (2017)	HFrEF, HFpEF; veterans ($n = 244$)	RC	Medication review and optimization completed 7–10 days after discharge Medication education Scheduled follow-up with the patient until care established with cardiology provider vs. standard care	Primary: no difference in 90-day death and all-cause readmission (adjusted hazard ratio [HR] = 0.64; 95% CI = 0.40–1.02; $P = 0.06$) Other: time to first follow-up shorter (11 ± 6 vs 20 ± 23 days; $p < 0.001$) and lower 30-day death and all-cause readmission rates (adjusted HR = 0.44; 95% CI = 0.22–0.88; $p = 0.02$)
Noschese (2017)	HFrEF; veterans ($n = 48$)	Retrospective case control	Medication optimization vs. standard care	Primary: more patients achieved ACE-I/ARB target doses (79.2% vs. 50%; $p = 0.07$) and BB target doses (87.5% vs. 20.8%; $p = 0.01$) Other: reduced rates of HF readmissions within 30 days (0% vs. 8.3%; $p = 0.49$), emergency department visits for HF (20.8% vs. 37.5%; $p = 0.34$), and mortality (0% vs. 12.5%; $p = 0.23$) in intervention group
Bhat (2018)	HFrEF ($n = 148$)	RR	Protocol-driven medication optimization, with co-signature of prescriptions by referring physicians Medication education vs. standard care	Primary: 95% vs 87% of patients were prescribed ACE-I/ARB and BB. Of these, more patients reached the target or maximum tolerated doses in the intervention group (64% vs. 40%; $p = 0.01$) Other: no difference in CV-related hospitalizations (0.45 vs. 0.35; $p = 0.38$) or HF exacerbations (0.18 vs. 0.11; $p = 0.42$)
Schumacher (2018)	HFrEF ($n = 111$)	Pre/post intervention analysis	Medication optimization and education	50% reduction in HF hospitalizations Increase in percent of a patient prescribed ACE-I/ARB (94% vs. 74%) and BB (84% vs. 82%) within the first year

Table 1. (Continued)

Reference (author, year)	Population (*n*)	Trial design	Intervention	Outcomes
Pogge (2018)	HFrEF ($n = 52$)	RR	Initiation and titration of sacubitril/valsartan and adjustment of diuretic regimens Medication education Recommendations made to cardiology for optimization of other GDMT	86.5% of patients achieved target-dose sacubitril/valsartan 73% increase in number of patients achieving target-dose RAAS inhibition therapy compared to baseline pre-intervention
Al-Bawardy (2019)	HFrEF ($n = 154$)	C	Medication review and optimization completed 7–10 days post-discharge Medication and lifestyle modification education	Primary: lower rates of readmissions at 30 days (9.2% vs 20%; $p = 0.063$) and 90 days (24.8% vs. 48.9%; $p = 0.003$)
Transitions of care telepharmacy interventions				
Rainville (1999)	HFrEF ($n = 34$)	RCT	Identification of risk factors of readmission with corrective action and education provided prior to discharge Follow-up phone calls conducted at 3 and 7 days post-discharge, as well as 30, 90, and 120 days to reinforce education provided vs standard care	Reduction in readmissions (23.5% vs. 58.8%; $p < 0.05$), as well as composite of readmission and death (29.4% vs. 82.3%; $p < 0.01$) at 12 months
Lopez Cabezas (2006)	HFrEF, HFpEF ($n = 134$)	RCT	Telephone calls monthly for the first 6 months and every 2 months thereafter to address patient concerns and reinforce education provided to the patient prior to discharge vs standard care	Reduced number of patients readmitted and the total number of readmissions at 2 months (11.4% vs. 25%; $p = 0.041$ and 9 vs. 26; $p = 0.034$) and 6 months (24.3% vs. 42.2%; $p = 0.028$ and 25 vs. 54; $p = 0.023$) Significantly decreased mortality at 12 months (12.9% vs. 29.7%; $p = 0.017$) but not at other time points
Salas (2015)	HF ($n = 30$)	Prospective pilot study	Telephone calls within 5 days of discharge to address patient concerns and remind the patient of follow-up appointments, and monthly thereafter up to 6 months post-discharge	Reduced 30-day HF readmission rate (16.6% vs. 28.1%) compared to baseline institutional Medicare and Medicaid patient readmission rates

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
			At first follow-up appointment, pharmacist-conducted medication history and provided recommendations for adherence improvements	
Truong (2015)	HF ($n = 632$)	RR	Telephone calls made within 5 days post-discharge to identify medication access issues, assess for side effects, and evaluate medication adherence Home visits conducted on an as-needed basis vs. standard care	Reduced all-cause 30-day readmission rates (12.3% vs. 23.8%; $p = 0.005$)
McKinley (2018)	HFrEF, HFpEF ($n = 132$)	RR	Telephone calls at 15 and 30 days to reinforce education provided prior to discharge and address patient concerns vs. standard care	Reduced 30-day readmission rates (21.6% vs. 37.9%; $p = 0.04$)
Moye (2018)	HFrEF, HFpEF ($n = 177$)	C	Telephone calls at 14 and 30 days to reinforce education provided prior to discharge and address patient concerns	Reduced 30-day all-cause readmissions (12% vs. 25%; $p = 0.03$) compared to the historical control group
Murphy (2019)	HFrEF ($n = 100$)	C	Telephone calls made by NP by 72 h post-discharge and another call made by pharmacist between days 4 and 7 to ensure understanding of and adherence to medication regimens Patient scheduled with the pharmacist in clinic 1–2 weeks post-discharge for a medication review and medication and disease state education	Reduced 30-day readmission rates compared to historical institutional rates (18.2% vs. 24%; $p = 0.238$)
Home visits				
Stewart (1998)	HFrEF, HFpEF (total $n = 97$)	RCT	Home visit conducted by nurse and pharmacist 1-week post-discharge vs. standard care Assessed patients' understanding of medications and adherence and	Primary: reduced unplanned readmissions (36 vs. 63; $p = 0.03$) and out-of-hospital deaths (1 vs 5; $p = 0.11$)

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
			reinforced education and provided adherence tools as needed	Other: fewer days of hospitalization (261 vs 452; $p = 0.05$) and total deaths (6 vs 12; $p = 0.11$)
Triller (2007)	HFrEF ($n = 154$)	RCT	Medication history and reconciliation, and medication, self-monitoring, and lifestyle modification education Pharmacist followed up 7–10 and 18–21 days to reinforce information and assess concerns vs. standard care	No difference in composite 6-month all-cause hospitalization or death (61% vs. 62%; $p = 1.0$), mortality (22% vs. 18%; $p = 0.67$), all-cause hospitalization (55% vs. 58%; $p = 0.63$), or HF hospitalization (42% vs. 51%; $p = 0.26$)
Holland (2007)	HF ($n = 293$)	RCT	Home visit within 2 weeks post-discharge and again at 6–8 weeks post-discharge Provided education on medications, adherence, lifestyle modification, and self-monitoring vs. standard care	Primary: no difference in emergency readmissions (134 vs. 112; $p = 0.28$) Other: no difference in mortality (30 vs. 24; $p = 0.54$)
Roughead (2009)	HFrEF; veterans ($n = 5717$)	RC	In-home medication assessment, including identification of drug-related problems and medication knowledge deficits, and adherence evaluation Recommendations for regimen alteration made to a clinician who was responsible for follow-up with the patient vs. standard care	45% reduction in the rate of hospitalization for HF at any time ($p = 0.0007$)
Barker (2012)	HFrEF, HFpEF ($n = 120$)	RCT	In-home medication assessment, including appropriateness of medication regimen and adequate supply of non-expired medications, provided patient with medication education, and ensured appropriate follow-up vs. standard care	No difference in mortality (HR 1.41, 0.50–3.97; $p = 0.514$), or hospitalizations (IRR = 1.74, 0.85–3.60; $p = 0.131$) Longer LOS for HF exacerbation in the 6-month follow-up in intervention group (IRR = 2.34, 1.80–3.05; $p = 0.000$)
Lee (2015)	HF; elderly ($n = 103$)	C	Home visits twice every 3 to 4 months to assess blood pressure, blood glucose, and cholesterol levels, and	31.8% increase in number of subjects free of symptoms of HF from baseline to last follow-up visit ($p < 0.001$)

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
			conduct a medication and adherence review	Reduction in mean Morisky Medication Adherence Score (− 0.54 ± 1.50; $p = 0.005$)
Kalista (2015)	HF (n = 10)	Prospective pilot project	Home visits within 1 week of discharge to complete medication history and reconciliation, and provide patient with medication and disease state education	Improvement in adherence questionnaire scores from initial visit to final follow-up (1.0, 0.5–1.5; $p = 0.004$) Lower rates of readmissions compared to other patients enrolled in visiting nurse services (10% vs. 38%)
Heart transplant and mechanical circulatory support				
Bishop (2014)	CF-LVAD patients (HM2, HVAD) ($n = 55$ (1:4))	RC	Patient self-testing INR with pharmacist management vs. usual care	TTR: 44% vs 31%, $p = 0.026$ No difference in major bleeds or thrombotic events
Borden (2015)	LVAD patients with supratherapeutic INRs ($n = 18$)	C	Enoxaparin bridging when INR < 1.6 by MDS team (pharmacist phone call within 24 h to confirm access and provide education)	26 of 27 courses of successful bridging (single failed course not related to anticoagulation), no major bleeding, no thrombotic events within 30 days
Kuyumjian (2016)	CF-LVAD patients ($n = 33$)	C	MDS INR management (protocols, clinical pharmacist consultant) vs. historical management (LVAD coordinators, CT surgeons, cardiologists)	TTR: 60% vs. 29.7%, $p < 0.001$ Similar rates of bleeding and thromboembolic complications
Cajita (2017)	Heart transplant centers ($n = 36$)	Secondary data analysis	Descriptive data review	80.6% of heart transplant centers utilized MDS teams (44.4% included a pharmacist) Use of MDS associated with higher levels of CIM, $p = 0.042$
Thrall (2017)	Solid organ transplant recipients ($n = 110$ (11 heart transplant recipients))	RC	Clinical pharmacist to monitor minimum monitoring requirements and coordinate follow-up vs. no formal transplant follow-up	Increased percentage of patients meeting minimal immunosuppression monitoring requirements, $p < 0.001$

Table 1. (Continued)

Reference (author, year)	Population (n)	Trial design	Intervention	Outcomes
				Increase in patients meeting drug concentration monitoring requirements for tacrolimus (51%, $p < 0.001$) and cyclosporine (22%, $p = 0.034$)
Wang (2018)	Solid organ transplant recipients ($n = 100$ pre-interventions (23 heart transplant patients) vs. 85 intervention (7 heart transplant patients))	Retrospective quasi-experimental	Pharmacist reviewed automated CMV DNA results and provided treatment recommendations vs. usual care by the primary team	Increased rate of CMV eradication at day 21: 83.5% vs. 71.0%, $p = 0.038$ Fewer patients reached pretreatment viral load of ≥ 10,000 IU/mL: 10.6% vs. 27.3%, $p = 0.004$ More patients initiated on therapy within 5 days of first quantifiable viral load: 62.4% vs. 55.0%, $p = 0.02$
Gellalty (2015) (abstract)	Heart transplant or LVAD ($n = 86$ patient encounters; 67 unique patients [10 LVAD encounters, 6 LVAD patients])	Descriptive	Specialist pharmacist incorporated into an outpatient clinic	46 actual or potential drug-related problems identified in 25 patient encounters

CF-LVAD, continuous flow left ventricular assist device*HF*, heart failure; *HFrEF*, heart failure with reduced ejection fraction; *HFpEF*, heart failure with preserved ejection fraction; *MLHFQ*, Minnesota Living with Heart Failure Questionnaire; *LOS*, length of stay; *ACS*, acute coronary syndrome; *ACE-I*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker; *BB*, beta blocker; *QoL*, quality of life; *LVAD*, left ventricular assist device; *RCT*, randomized controlled trial; *RR*, retrospective review; *RC*, retrospective cohort; *C*, cohort; *DNO*, drug-related negative outcome; *rDNO*, risk of developing drug-related negative outcome; *PA*, physician assistant; *NP*, nurse practitioner; *CI*, confidence interval; *MDS*, multidisciplinary; *CMV*, cytomegalovirus reconciliations, medication and disease state education, ensuring access to medications, identification of drug-drug interactions, therapeutic drug monitoring, and optimization of GDMT (Fig. 1). This comprehensive review will focus on the outcomes of pharmacist-led interventions for the spectrum of patients with heart failure, including LVADs and cardiac transplantation (Table 1).

Pharmacist-based heart failure clinics

Pharmacist-conducted medication reviews and patient education

Pharmacists are fundamental members of the multidisciplinary team who are trained to provide medication education and conduct medication reviews with a goal of reducing polypharmacy and the number of drug-related problems (DRPs) [6]. Patients aged 65 years or older and diagnosed with heart failure are prescribed an average of 6.8 medications [7]. Several studies have evaluated the benefit of pharmacist-conducted medication reviews, usually in conjunction with education on medications and adherence, lifestyle modifications, and self-monitoring for symptoms of heart failure (Table 1). Three studies found that such interventions resulted in the identification of DRPs, such as untreated disease states or suboptimal therapeutic choices in both patients with HFrEF and heart failure with a preserved ejection fraction (HFpEF) [8–10]. Furthermore, medication reviews and patient education may improve exercise tolerance, quality of life, and adherence to medication regimens [11, 12]. Importantly, several studies demonstrated that the optimization of medication regimens may reduce hospital length of stay and admission rates. Interventions to optimize medication regimens included recommendations to initiate or titrate GDMT, ensuring appropriate laboratory monitoring, identification and resolution of drug-drug interactions and adverse drug events, and ensuring medication access [11, 13–16]. In most studies, pharmacists identified a way to optimize drug therapy and provided recommendations to a physician or advanced practice provider for consideration.

Pharmacists in community settings are distinctively positioned to provide medication review services and education, as they are easily accessible to both patients and caregivers. In addition to identifying patients who are not on optimized GDMT, community pharmacists can ensure appropriate monitoring and follow-up and aid in improving medication adherence [17–19]. The One Minute Clinic for Heart Failure tool was created by Bleske and colleagues to aid community-based pharmacists in conducting clinical assessments to evaluate for signs and symptoms of worsening heart failure [20]. This tool may allow for the early identification of worsening heart failure so that the patient can follow-up with their provider. In fact, both pharmacists and patients believe that community pharmacists–provided medication reviews and education met an unmet need in their care [21]. Based on pilot study results revealing positive feedback from physician offices, pharmacists, and patients, a recent randomized control trial was completed to assess outcomes of a community pharmacist–led intervention, including a comprehensive medication review, procurement of adherence aids, medication and disease state education, and vital sign measurements at bi-weekly follow-up visits to the pharmacy [22]. The patients randomized to the pharmacist intervention arm resulted in an increase of the primary outcome of medication adherence at 1 year (mean difference of proportion of days covered by prescription claims = 5.7% [95% confidence interval (CI) 1.6–9.8]; $p = 0.007$) and improved quality of life after 2 years (difference in MLHFQ scores − 7.8 points [95% CI − 14.5 to − 1.1], $p = 0.02$), when compared to standard of care [23•].

Medication optimization clinics

The ACC/AHA/HFSA guidelines for the treatment of HFrEF recommend GDMT prescribed at target doses to decrease hospitalizations and prolong survival [3, 24]. Unfortunately, a large percentage of patients are discharged from the hospital on suboptimal doses and lack of subsequent optimization may lead to preventable heart failure deaths [25, 26]. Most recently, the CHAMP-HF Registry identified significant gaps in the use and dose of GDMT [27, 28]. As pharmacotherapy specialists, clinical pharmacists can be utilized to see patients at frequent intervals to titrate GDMT and monitor for adverse drug effects.

A randomized controlled trial conducted by Gattis et al. first described a pharmacist's role in optimizing medication regimens. The pharmacist assessed the patients and created drug therapy plans independently, prior to discussing their plan with a physician. If agreed upon by the physician, the plan was implemented and monitored by the pharmacist. Patients randomized to receive the pharmacist-based intervention, as compared to standard care, demonstrated lower rates of all-cause mortality and heart failure events (4 vs. 16 events; odds ratio (OR) 0.22 [95% CI 0.07–0.65; $p = 0.005$]), which was driven by the reduction in hospitalizations and emergency room visits for heart failure [29]. Further studies describe pharmacist-led medication optimization clinics, in which pharmacists titrate medications per protocol or independently (Table 1) [30–41]. While differences exist in how pharmacists optimized heart failure medications, all studies resulted in higher percentages of patients on optimal doses of GDMT [31•, 32, 35–41]. However, outcomes related to mortality and hospitalizations were not consistent in the available literature, with seven studies showing a reduction in these outcomes [30, 31•, 32, 33•, 34, 36, 38, 39, 41].

Interestingly, four studies included medication optimization for patients with HFpEF; however, the specific interventions were not described [32, 33•, 34, 38]. While the incidence of patients hospitalized with HFpEF is almost equal to those with HFrEF, unlike HFrEF, a paucity of data exists for medications to reduce mortality and morbidity in patients with HFpEF [1]. As a result, the ACC/AHA/HFSA guidelines focus on the treatment of comorbid conditions, such as hypertension, in this population [24]. Pharmacists can be utilized to treat blood pressure and potentially other common comorbid conditions that affect patients with HFpEF.

Pharmacist's role in transitions of care

Telepharmacy interventions

Effective transitions of care (TOC) programs are critical to facilitate safe, smooth, and efficient shifts from one setting of care to another [42]. These programs often incorporate bundled interventions, such as inpatient education and post-discharge follow-up, including telepharmacy interventions. The American Society of Health System Pharmacists defines telepharmacy as "a method used in pharmacy practice in which a pharmacist utilizes telecommunications technology to oversee aspects of pharmacy operations or provide patient-care services." These services may include medication therapy management, patient assessment, patient counseling, and outcomes assessments [43].

Current literature varies by the types of pharmacists' interventions prior to discharge, as well as the number of phone calls and length of follow-up. In general, pharmacists conducted medication reviews with or without medication reconciliation prior to discharge. Discharge education was incorporated in all cases, but the method by which the education was provided differed, including the mode of education (verbal, written, video), as well as the number of educational sessions provided. In some cases, a pharmacist ensured adequate access and supplies of medications before the patient left the hospital. The follow-up phone calls took place anywhere between 5 days and 1 month following discharge and were conducted in order to address questions or concerns, reinforce education previously provided, and assess adherence. While it is difficult to distinguish the impact of individual interventions, the bundled nature of the described interventions in all studies demonstrated a reduction in readmission rates [44–50].

Shared Medical Appointments

Shared Medical Appointments (SMA), or Group Clinic Appointments, were developed in an attempt to provide patients with safe and effective healthcare from one or more healthcare professionals in a group setting, while simultaneously reducing healthcare costs and improving patient engagement. These visits often include history taking, physical examination, clinical management, and patient education [51]. Pharmacists have been integrated into SMAs to enhance the management of patients with various chronic diseases, including diabetes, hypertension, and dyslipidemia [52, 53]. In one systematic review evaluating a variety of SMA models, there were more positive intervention effects, including appropriate medication initiation and titration, in the studies describing SMAs led by clinical pharmacists [54].

Involvement of pharmacists in heart failure SMAs is not well described. However, this is a potential opportunity for expansion of clinical pharmacy services. Singrey et al. described their heart failure SMA as a combination of a medical group visit and mindfulness-based stress reduction (MBSR) visit for patients recently discharged from the hospital with a primary diagnosis of acute decompensated heart failure. During the medical group visit, patients were provided education on lifestyle modification, medications, and pertinent lab test values. During the MBSR portion of the visit, an evaluation of the patient's emotional distress, self-compassion, and social isolation was completed. In addition to receiving this valuable healthcare service, patients were able to develop relationships with one another and develop group support. Pharmacists led two of the eight visits, focusing on medication education and conducting medication reviews [55]. Although no heart failure outcomes were reported, the authors noted the positive reception from other members of the multidisciplinary team. A multicenter, randomized controlled trial is currently underway to assess the efficacy of SMAs, which includes a clinical pharmacist, to improve health and decrease hospitalizations and death for patients recently discharged from the hospital with heart failure [56].

Home visits

Conducting home visits removes the barrier of patient transportation and allows pharmacists to visually assess a patient's medication regimen, including prescribed and over the counter medications, easily identify access or adherence issues, and consider overall lifestyle. Several different models of home visits have been described in the literature: conducted independently by a pharmacist, in collaboration with a nurse, or in combination with an advanced practice provider and paramedic [57–64]. In the latter model, the pharmacist's role focused on medication care coordination, including resolving medication-related issues or discrepancies, and assessing adherence barriers. The paramedic conducted physical and mental health assessments, provided disease state and diet education, and administered IV diuretics as needed, and the advanced practice provider provided close clinic follow-up. The benefits of this type of intervention on outcomes such as unplanned readmissions, time spent out of the hospital, quality of life, and mortality are not consistently reported in current literature. Although three studies saw a significant reduction in hospitalizations, time to hospitalizations, and/or deaths, the same number of studies found no difference in similar outcomes [57, 59, 60, 62–64].

Pharmacist interventions in advanced heart failure therapies

Cardiac transplantation

The Centers for Medicare and Medicaid Services mandate that a qualified expert in transplant pharmacology, preferably a pharmacist, should be involved in all phases of a transplant program's care, including postoperative outpatient care, in order to be reimbursed for their services [65]. Clinical pharmacists' role in this setting is further supported by the American Society of Transplantation and the United Network for Organ Sharing which provide specific recommendations on how clinical pharmacists should be utilized within heart transplant teams [66, 67].

The involvement of a clinical pharmacist within the transplant team is presumed beneficial, as successful outcomes depend on optimal use of immunosuppressive therapy and the prevention and treatment of opportunistic infectious diseases. Pharmacists are well equipped to recognize potential drug-drug and drug-food interactions and provide assistance in dosing and interpreting drug therapy levels, especially in the context of patient-specific characteristics (e.g., renal dysfunction, age, body habitus). Despite this, studies evaluating the role of the clinical pharmacist within ambulatory heart transplantation clinics are limited. Only three studies and an abstract evaluated the incorporation of a clinical pharmacist in the care of outpatients who had previously undergone heart transplantation and of those, heart transplant recipients were typically only a subset of the total population (Table 1).

Available literature demonstrates that incorporation of clinical pharmacists into the care of patients who had received solid organ transplants, including heart transplantation, leads to the identification of potential drug-related problems, improved therapeutic monitoring, and more efficient and effective treatment of cytomegalovirus (CMV) [68–70]. Additionally, the utilization of a multidisciplinary team, which included a pharmacist 44.4% of the time, was associated with higher levels of "chronic illness management," defined as a system of care that focuses on access, continuity of care, and patient self-involvement that has been associated with improved clinical outcomes, including reduced hospital admissions and emergency room visits, and decreased costs for transplant populations [71–73].

Durable mechanical circulatory support

A joint opinion paper from HFSA and ACCP recommends the involvement of clinical pharmacists in the care of both heart transplant and advanced heart failure patients requiring durable mechanical circulatory support (MCS) with an LVAD [4••]. Similar to the care of patients having undergone heart transplantation, the care of patients with LVADs is also heavily reliant on the optimal use of drug therapy. Examples include prevention of pump thrombosis and cerebrovascular accidents (CVAs) with vitamin K antagonists (VKAs) and antiplatelet therapy, minimization of gastrointestinal bleeding that may be exacerbated by such therapies, appropriate antibiotic use for the treatment of driveline infections, and potential medical treatment of LVAD thrombosis. Despite this, there are minimal published studies evaluating outpatient pharmacy services for patients with LVADs, which focus solely on anticoagulation. Nevertheless, the utilization of pharmacists in this setting has proven beneficial. Involvement of pharmacists, whether directly managing patients' VKA therapy or acting in a consolatory capacity, is associated with increased time in therapeutic range (TTR; 44–60% vs. 29.7–31.0%) [74, 75]. With the aid of a multidisciplinary team including a pharmacist to confirm drug access and provide education, the use of enoxaparin to bridge patients with a subtherapeutic INR has also been shown to be effective with 26 of 27 patients successfully completing a bridge in the absence of major bleeding or thrombotic events within 30 days [76].

Incorporating pharmacists into outpatient heart failure clinics

Collaborative practice agreements

Evolving health care initiatives, such as the Hospital Readmission Reduction Program created by the Centers for Medicare and Medicaid Services in 2012, inspired the need to focus on creative approaches to reduce hospital readmissions for patients with certain conditions, including heart failure. A consortium statement from the American Pharmacists Association recognized that the utilization of pharmacists through collaborative practice agreements (CPAs) can improve health care outcomes and reduce the cost of care [77]. Pharmacists may work under CPAs, which formalize the pharmacist-prescriber relationship and protocolize autonomous patient-care services that may be provided by a pharmacist. With the exception of Alabama and Delaware, most states have laws and regulations in place, as defined by the boards of pharmacy and medicine, which authorize pharmacists to practice under CPAs [78••].

Pharmacist-based services are often tailored to each institution to align with the needs of patient care. Services such as reviewing medication profiles for drug interactions and providing medication education already fall under the purview of a pharmacist's scope of practice. However, a pharmacist may provide services such as initiating, modification, and discontinuing medications through the use of CPAs [77, 78••]. CPAs, created in conjunction with a local prescribing group, provide a framework for the relationship between the diagnosing prescriber, pharmacist, and services offered to the patient. Details covered in a CPA may include which patients may be referred to a pharmacist, how often the patient must be seen by the referring physician, a protocol for services rendered by a pharmacist, and qualification of the pharmacists who are providing the outlined services [78••].

Using the clinic established at the Cleveland Clinic, Kauffman Center for Heart Failure, as an example, there are several services offered to patients (Fig. 1). Working under a CPA, pharmacists may independently provide progressive services, such as titration of GDMT in patients with HFrEF, laboratory monitoring, and optimization of anti-hypertensive agents in patients with HFpEF. All patients who are seen by a pharmacist will have their medication profile reviewed and reconciled, in addition to medication and disease state education. Through expanded pharmacist-based services, patients have increased access to healthcare which in turn, relieves physicians to see new or more complex patient cases [5••].

Revenue for pharmacists-based services

State legislation varies with regard to recognizing pharmacists as providers and permitting pharmacists' prescriptive authority. While several states have legislation allowing pharmacists to have prescriptive authority, it does not always correspond to appropriate compensation for services provided [79, 80]. Most states are now pursuing legislation to recognize pharmacists as health care providers, however federal regulations remain unchanged and prohibit pharmacists from directly billing for services [79]. In hospital-based clinics or physician offices, pharmacists may serve as mid-level providers and must work under a supervising physician to bill for services. Depending on the type of clinic, for example, hospital-based vs. physician-based, facility-fee billing or incident-to billing may be utilized where the pharmacist may see patients under the direct supervision of a physician [81–83].

Because the frequency of which pharmacists receive compensation for services varies widely across the nation and even within institutions, justifications for full-time equivalent (FTE) pharmacists in the outpatient setting heavily rely on institutional savings by indirect costs. Previously reviewed literature suggests that pharmacist-based interventions in the ambulatory care setting may reduce hospitalizations for chronic disease states, like heart failure, which may indirectly influence costs and rehospitalization penalties [11]. Pharmacists may also increase revenue for other providers by participating in post-discharge follow-up phone calls permitting other health care providers, such as advanced practice providers and physicians, to capture TOC billing post-hospital discharge. Finally, there are some opportunities to charge cash for services. For example, all healthcare providers at the Cleveland Clinic have the ability to see patients through a virtual encounter using a web-based platform. Tiered cash pricing for such services is based on the duration of visit and provider type.

Conclusion

The growing prevalence of heart failure in the USA is straining the current healthcare system. Pharmacists are uniquely situated to reduce the burden on traditional providers through the provision of services that may increase medication adherence, decrease adverse drug reactions, and reduce time spent hospitalized for heart failure [1, 29, 33•, 34, 38, 39]. Pharmacist-based services can help empower patients with heart failure to understand and manage their complex medication regimens through medication review and reconciliation, identification of drug-drug interactions, and medication education. Pharmacists may also work independently under CPA's to initiate, modify, or discontinue medications and order laboratory monitoring. Such services increase patient access directly by allowing for more frequent follow-up between physician visits and indirectly by allowing physicians a greater opportunity to see new and/or more complex patients. Compensation for pharmacist-based services varies across the nation and may change as states begin to adopt legislation that recognizes pharmacists as providers. However, in the absence of direct compensation, pharmacist-based interventions may still offset costs of readmissions and emergency room visits. As such, pharmacists provide an opportunity by which consistent levels of patient care can be maintained through either traditional face-to-face visits or via telephone or video appointments, SMAs, and home visits to improve overall care delivered to patients with heart failure.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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