



# Impact of Pharmacist-Led Heart Failure Clinic on Optimization of Guideline-Directed Medical Therapy (PHARM-HF)

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## Abstract

This prospective study included patients with heart failure (HF) with reduced ejection fraction (HFrEF) with LVEF  $\leq 40\%$  to evaluate the impact of pharmacist on guideline directed medical therapy (GDMT). The primary outcome was to compare proportion of triple GDMT achieved for Angiotensin-Converting-Enzyme-Inhibitors (ACEI)/Angiotensin-Receptor-Blockers (ARB)/Angiotensin-Receptor-Nepriylsin-Inhibitors (ARNI), beta-blockers, aldosterone antagonists (AA), and quadruple GDMT which in addition to triple therapy, included Sodium glucose co-transporter 2 inhibitor (SGLT2i) at 90-day post-enrollment compared to baseline. Secondary endpoints included achieving target and/or maximally tolerated ACEI/ARB/ARNI and beta-blockers combined and individually as well as SGLT2i and AA GDMT at 90-day post-enrollment compared to baseline. We also compared combined and individual HF-related hospitalization/emergency room (ER) visits 90 days pre-/post-enrollment. Of the total 974 patients screened, 80 patients seen at least once in the heart failure medication titration clinic (HMTC) were included in the analysis. Median (IQR) age was 71 (57–69) years with majority white male. There was a significant improvement in the proportion of patients who achieved quadruple GDMT ( $p = 0.001$ ) and triple GDMT ( $p$ -value = 0.020) at 90-day post-enrollment compared to baseline. The secondary GDMT outcomes were also significantly increased at 90 days post-enrollment compared to baseline. Significant difference in mean as well as proportion of combined HF-related hospitalization/ER-visits was found 90 days pre-/post-enrollment ( $p = 0.047$ ). Our study found that pharmacist's intervention increased the proportion of patients who achieved GDMT at 90 days.

**Keywords** Congestive heart failure · Pharmacists · Veterans · Guideline-directed medical therapy (GDMT) · ACE inhibitor · B-adrenergic blockers · Aldosterone antagonist · Sodium glucose co-transporter 2 inhibitor · KCCQ-12 · Medication therapy management

## Highlights

- This pharmacist led heart failure medication titration clinic (HMTC) significantly increased the proportion of patients on quadruple and triple GDMT.
- This study also showed significant reduction in the combined heart failure-related hospitalizations and ER visit at 90 days post-enrollment compared to 90 days pre-enrollment and this was primarily driven by reduction in ER visits.
- Additionally, pharmacist interventions improved quality of life and patient adherence to self-care as measured by the KCCQ-12 and MOS-SAS questionnaire, respectively.

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## Introduction

Heart Failure (HF) impacts nearly 6.2 million adults in the USA with prevalence projected to increase by 46% in 2030 and a 5-year mortality rate approaching 50%, calling for strategies to improve medical management to reduce the

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health care burden associated with emergency room visits, hospitalizations, and mortality [1–3]. Guideline directed medical therapy (GDMT) in patients with heart failure with reduced ejection fraction (HFrEF) is recommended to reduce mortality and morbidity [4]. Pharmacotherapy options which have shown to improve survival in HFrEF patients include the following: angiotensin-converting-enzyme-inhibitor (ACEI), angiotensin-receptor-blockers (ARBs), angiotensin-receptor-neprilysin-inhibitors (ARNI), beta-blockers, aldosterone antagonists (AA), and more recently, sodium glucose co-transporter-2 inhibitors (SGLT2i) [4, 5].

Despite the range of available therapeutic options, clinical inertia along with medication intolerance and adherence remains a barrier to optimization of these medications [6]. Therefore an interdisciplinary approach which also includes a pharmacist as supported by the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) guidelines in managing HFrEF patients is invaluable given the complexity of the disease state and the medication burden [4, 5]. Pharmacist-led interventions have been shown to result in positive patient outcomes such as reducing hospitalizations and readmissions [7–9]. Previous studies support that pharmacist-led HF management improved patient outcomes by increasing the percentage of patients on GDMT [9, 10].

Previously our facility had inconsistent Clinical pharmacy specialist (CPS) involvement in the management of heart failure patients primarily limited to inpatient setting as part of clinical rounds with the team. This prospective quality improvement project was implemented with an aim of showing the impact of instituting a pharmacist-led heart failure medication-titration clinic (HMTc) in the management of HFrEF patients in an ambulatory setting on GDMT utilization, quality of life, clinical, and economic outcomes.

## Methods

This prospective observational study evaluated the impact of implementing pharmacist led HMTc. The study results were collected from November 1st 2020, through June 1st 2021. Patients at Salem Veterans Affairs (VA) Medical Center (SVAMC) greater than or equal to 18 years of age were included if they had a diagnosis of HFrEF recorded as of July 1, 2020, using national VHA heart failure dashboard which extracts patients with active heart failure diagnosis in their problem list, or two or more outpatient encounter diagnosis in past 2 years or one or more discharge diagnosis of heart failure (HF) in the past year. Data in this dashboard is extracted primarily using SQL (Structured Query Language) from

Corporate Data Warehouse. HFrEF in this report is defined as subgroup of heart failure patients with their lowest left ventricular ejection fraction (LVEF) documented in the past 3 years  $\leq 40\%$ . In cases where no LVEF is documented in the past 3 years, the most recent International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10) HF diagnosis codes are used to determine HFrEF vs. HFpEF (Supplemental file\_ICD codes\_HF). LVEF values utilized in this report are inferred based on the Veterans Affairs Informatics and Computing Infrastructure (VINCI) created validated natural language processing (NLP) tool to extract quantitative LVEF values from text notes and are updated quarterly [11]. This project was reviewed and exempt by the IRB as well as the P&T Committee of SVAMC and was conducted in accordance with the Helsinki's Declaration. Patient consent was waived as no patient identifiers were collected and this was within the clinical scope of practice for clinical pharmacy specialist within Veterans Health Administration. We followed the guidance provided by a tool designed to enhance pharmacist patient care intervention reporting (PaCIR) during the project design phase to increase the quality of the reporting of pharmacist-led intervention related outcomes [12].

## Patient Selection and Data Source

Ambulatory patients seen by VA cardiology providers identified using the national dashboard were further manually screened for referral to HMTc. Patients were excluded if their most recently documented LVEF was  $\leq 40\%$  in the electronic medical record including any outside records available in the Joint Legacy Viewer (JLV) which may have been missed by the initial automated NLP process. Additionally, the LVEF on the dashboard was only updated every quarter and therefore prior to enrolling the patients, their most recent LVEF was validated via manual chart review. Patients with non-VA cardiologist, hospice, or palliative care enrollment, severe dementia, in nursing home/long term care facility, on investigational drug, Stage D/advanced heart failure on intravenous inotropic therapy were excluded. The computerized patient record system (CPRS) was reviewed for enrollment and referral (Fig. 2). Upon referral to the HMTc, a return to clinic order was placed by the HF CPS which alerted an advanced medical support assistant to schedule these patients within 2 weeks to be seen by the HF CPS. The HF CPS continued to monitor patients until maximum GDMT was achieved after which patients were discharged back to cardiology for routine follow up. Patients enrolled into HMTc with at least 1 visit with the HF CPS were included in the final analysis for outcomes described below.

## Environment and Care Delivery Mode

In anticipation for the need for flexibility in the care delivery mode in lieu of the COVID-19 pandemic, patient encounters were conducted as scheduled face-to-face, telephone, or clinical video tele-health visits. All face-to-face visits were conducted in the private patient examination room within the cardiology department with access to a weight scale and blood pressure monitors as well as cardiologists for immediate patient-related needs. Pharmacist provisioned devices for optimal outcomes (i.e., weight scales, Sphygmomanometer) to the patients for home use. Pharmacist could also enter home telehealth consults which allowed for a nurse to assist and work closely with the patients who were sent VA furnished devices. This data (weight, blood pressure, pulse) was documented by the nurse in CPRS without independently providing patient intervention and alerted to the CPS every 2 weeks for further evaluation. This allowed for efficient telehealth encounters without the need to see the patient face-to-face.

## Pharmacists' Responsibilities and Competency

The pharmacist-led HMTc was staffed by a PGY1 residency trained HF-CPS, who underwent additional training including 6-h presentations on pathophysiology, pharmacology, physical assessment, and 1 month once weekly hands-on training with Cardiology providers. A care coordination agreement was established between the pharmacy and cardiology services which allowed HF CPS to initiate, titrate, adjust, and discontinue dosages of the following HF medications: ACEI, ARB, ARNI, beta-blocker, loop diuretic, AA, hydralazine and isosorbide dinitrate, digoxin, and SGLT2i. The agreement allowed the HF CPS to order necessary laboratory tests, including but not limited to basic metabolic panel, liver function tests, and others as appropriate. Key components of patient interview by HF CPS are reported in Supplementary Table 1.

Quality of life was assessed via Kansas City Cardiomyopathy Questionnaire (KCCQ-12) score at initial visit and at 90 days. KCCQ-12, a validated Health Related Quality of Life measure specific to heart failure has shown to highly correlate with the original 23-item scale scores, incorporating physical limitations, symptom frequency, and overall quality of life. Higher scores indicated fewer physical limitations and symptom frequency (scaled 0 to 100). The use of this summary score has been used to determine impact of GDMT on patient's quality of life [4, 13, 14].

Medical Outcomes Study Specific Adherence Scale (MOS-SAS) questionnaire was administered at initial

encounter and 90 days. This 8-item questionnaire has been used to measure adherence to self-care behaviors such as regular exercise, taking medications as prescribed, consumption of one or less alcoholic beverage per day, decreasing smoking habits, following a low salt and low fat diet, checking weights daily, and monitoring and awareness to symptoms and has successfully demonstrated reliability and validity [15–17]. While there is no accepted standard to grade adherence for HF self-care, for medication adherence, 80% level has been used to define good adherence and therefore we used this as a threshold to define adherence using MOS-SAS. A cumulative score of greater than or equal to 80% (32/40 points derived from the 8 questions) regardless of the scores on individual questions was used to define adequate adherence [18]. As part of the documentation process, the HF CPS was required to capture interventions for each patient visit using Pharmacist Achieve Results with Medications Documentation (PhARMD) tool which is an electronic intervention tracking template within CPRS which allows for documentation of medication and disease state interventions by CPS [19].

## Follow up Frequency and Duration

The frequency of follow-up encounters depended on the medication specific changes.

Patients were followed for at least 90 days or until eligible for discharge. Patients were eligible for discharge if they achieved maximum GDMT and were stable for 2 consecutive encounters after last medication change, failed to keep appointment for 2 consecutive encounters (no shows), unable to benefit from HF medication management such as those with severe psychiatric disorders that may impede patient comprehension, refused to take medication, or no further pharmacological option existed within the scope of CPS or were subsequently enrolled into hospice or long-term care.

## Data Parameters

Baseline patient characteristics collected include age, gender, race/ethnicity, weight, height, body mass index (BMI), left ventricular ejection fraction (LVEF), and pertinent laboratory parameters such as potassium, magnesium, serum creatinine, estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate. Values prior to and closest to the date of enrollment in HMTc were recorded. Concurrent medication use, baseline GDMT utilization, and other past medication history were also recorded.

## Outcomes

**Primary Outcome** was to compare the proportion of patients' who achieved triple and quadruple GDMT. Triple therapy was defined as the use of ACEI/ARB/ARNI, beta-blocker, and Aldosterone antagonist (AA) while quadruple therapy was defined as use of SGLT2i in addition to triple therapy as recommended by ACC/AHA guidelines [4, 5].

**Secondary outcomes** included comparing the following 90 days after clinic enrollment to the baseline: target or maximally tolerated GDMT achieved for ACEI/ARB/ARNI and Betablocker combined and individually; target GDMT for ACEI/ARB/ARNI and Betablocker individually, GDMT achieved for spironolactone and SGLT2i individually. Mean and proportion of combined HF-related hospitalizations and ER visit and each component separately, for 90-day post-enrollment period were compared to the 90-day pre-enrollment period.

Target GDMT was defined as achieving the target doses of ACEI/ARB/ARNI and Betablocker (HF-specific) as recommended in the guidelines [4, 5]. Maximally tolerated GDMT was defined as reaching maximum dose beyond which additional dose titrations cannot be safely achieved due to adverse effects such as low HR (< 50 bpm) or low SBP in absence of hypotension (< 90/50) or (< 100/60 with signs and symptoms of hypotension). GDMT for AA and SGLT2i were considered achieved if patient was prescribed these medications.

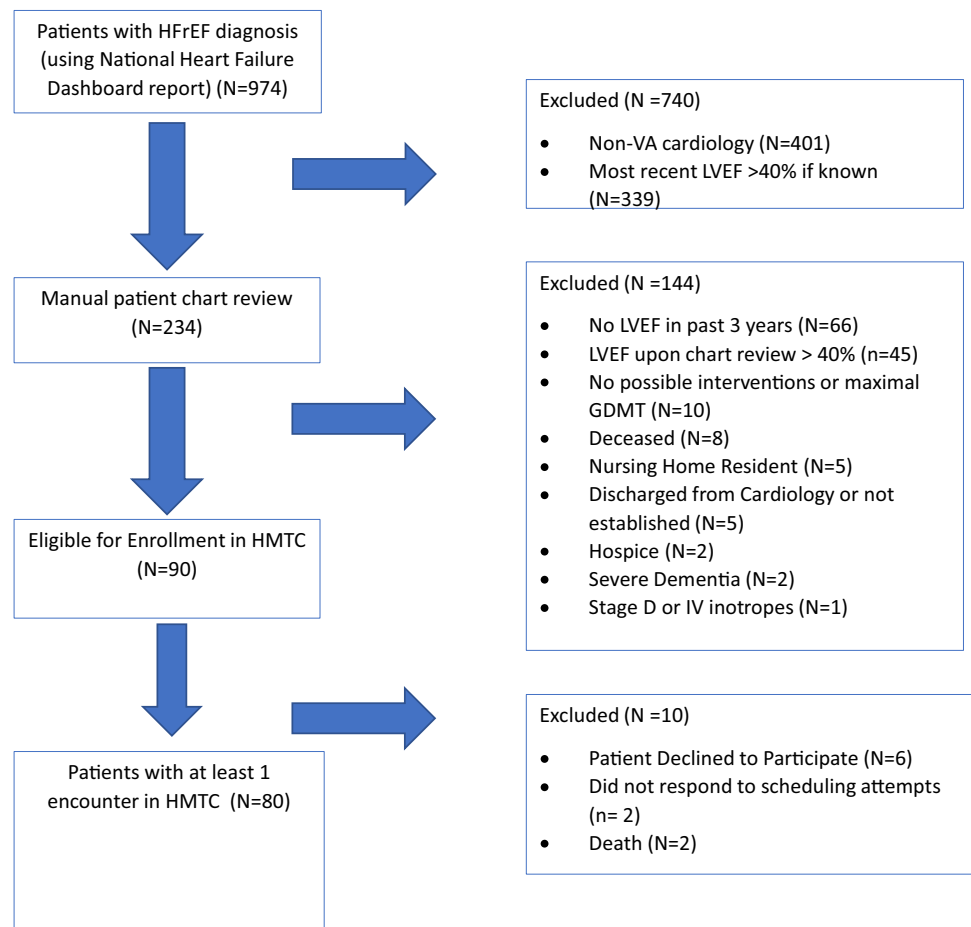
Additionally, we also compared mean and median KCCQ-12 scores as well as patient reported self-care adherence mean and median scores using MOS-SAS questionnaire at 90-day post-enrollment compared to the baseline. We also compared proportion of patient with acceptable adherence (32/40 points) measured using MOS-SAS questionnaire at 90 days compared to baseline. Pertinent laboratory parameters at 90 days compared to baseline included LVEF, potassium, magnesium, serum creatinine, SBP, DBP, and pulse. Baseline was defined as prior to the first clinic visit. Both KCCQ-12 and MOS-SAS questionnaires were administered to the patient via clinician on the first visit and at 90 days. We also calculated the GDMT optimization score defined as sum of positive therapeutic changes (+1 for new GDMT initiations or dose up-titration) and negative changes (-1 for GDMT discontinuation or dose down-titrations) by the end of 90 days post enrollment [20]. We also describe reasons for GDMT intolerance.

## Economic Analysis (Supplementary file Fig. 5a–b)

Additional outcomes included estimating cost avoidance based on patient harm prevention. Each PHARMD tool interventions was converted to an indirect cost-saving

amount based on previously published estimates assigned to the outpatient VHA settings [21]. An important caveat to these estimations was that it did not screen individual interventions for their likelihood of preventing harm as reported in another study [22]. All cost estimates were adjusted using consumer price index [23]. These indirect cost estimates were obtained by multiplying costs avoided by total number of interventions. Aldridge et al. found in their study that 7% of the documented pharmacist interventions prevented serious harm; however, these estimates were based on chronic disease states such as hypertension, lipids, and diabetes and do not accurately reflect disease specific cost savings to account for the higher burden associated with HF morbidity and mortality. Furthermore, there are no cost estimates published to capture the impact of continual non-pharmacological interventions such as dietary and medication non-compliance which may have huge impact on the disease state outcomes and therefore no indirect cost saving amount was assigned for these interventions [21] (Supplementary file Fig. 1a–c). Cost estimates for heart failure related hospitalizations and ER visits were calculated using previously published data [24, 25]. Additional indirect cost savings were captured as cost avoided due to the difference in the combined HF hospitalization and ER visits at 90 days after clinic enrollment compared to 90 days prior to the enrollment. A cost benefit analysis was conducted to assess the benefit of pharmacist-led interventions compared to cost of patient care delivery. Cost of the pharmacist intervention was calculated as direct personnel cost based on VA salary for a typical CPS and included 30% fringe benefits (\$168,463). When divided by 2080 hours, this translated to \$80.99 per hour or \$1.35/min). Cost of pharmacist care was calculated as total number of visits X time per visit (minutes) × \$1.35. Any overheads such as patient education materials, office supplies, space, or electricity were assumed to be minimal and therefore were not included in this analysis. Results were reported as benefit-cost ratio for 90 days calculated as cost avoidance estimates from PharmD tool interventions plus cost avoidance from reduction in HF hospitalization and ER visits divided by total costs. Net benefit at 90 days was calculated as total cost savings minus total costs. We assumed a conservative 7% threshold for PharmD tool intervention related indirect cost saving to report adjusted benefit-cost ratio and net benefit at 90 days as sensitivity analysis.

**Statistics** Categorical data was represented as proportions and compared using chi-square test or Fisher's exact as appropriate. Continuous variables were represented as mean with standard deviation or median with interquartile range (for non-normal distribution), compared using Student *t*-test

**Fig. 1** Patient selection

(normal distribution) or Mann-Whitney U test (non-normal distribution). Dichotomous outcomes were compared using McNemar's test while paired *t*-test or Wilcoxon signed rank test was used for continuous data. Assuming 15% combined clinical GDMT at baseline, we calculated that a sample of 62 patients would be required to achieve 80% power at 0.05 two-sided alpha to detect difference of at least 20% with correlation of 0.2 in paired data. After accounting for 15% loss of patients, we calculated targeted sample size of 72 patients. All the data analysis was performed using the IBM® SPSS® Statistics version 26.

## Results

Using national heart failure dashboard, a total of 974 patients were identified with HFrEF diagnosis. Of these, 401 patients were being seen by outside cardiologist and 339 patients had LVEF > 40%. Remaining 234 patients were manually screened for additional exclusion as noted in Figs. 1 and 2 of which 90 patients were eligible for enrollment in HMTC (Fig. 1). Of these, 80 patients seen at least once in the HMTC were included in the final analysis (Fig. 1). The median age

(IQR) was 71 (63–74) years with most patients being white, male and NYHA Class II (Table 1). Common co-morbidities included hypertension, hyperlipidemia, diabetes, and coronary artery disease (Table 1).

### Primary Outcome (Table 2)

The proportion of patients who achieved both triple (29 (36.3%) vs. 15 (18.8%);  $p = 0.020$ ) and quadruple GDMT (17 (21.3%) vs. 2 (2.5%);  $p = 0.001$ ) were significantly higher at 90 days after clinic enrollment compared to baseline.

### Secondary Outcomes (Table 2)

There was significant increase in the proportion of patients who achieved target or maximally tolerated GDMT for ACEI/ARB/ARNI and betablockers combined ( $p$ -value < 0.001) and individually ( $p$ -value < 0.001 for both). Target GDMT doses achieved for ACEI/ARB/ARNI ( $p$ -value = 0.011) and betablocker ( $p$ -value < 0.001) were also significantly higher at 90-day post-enrollment compared to the baseline. Additionally,

**Table 1** Baseline patient characteristics

Data parameter	N = 80
Age [median (IQR)]	71 (63–74)
Sex-male	77 (96.3%)
Race (White)	62 (77.5%)
Race (African American)	17 (21.3%)
Baseline Left ventricular ejection fraction (LVEF)	
< 20%	3 (3.8%)
20–30%	27 (33.8%)
> 30 to 40%	50 (62.5%)
NYHA class	
I	3 (3.8%)
I–II	2 (2.5%)
II	35 (43.8%)
II–III	22 (27.5%)
III	18 (22.5%)
Duration of Heart failure at the time of enrollment	
6 months to 1 year	13 (16.3%)
1 year to 2 years	55 (68.8%)
Greater than 2 years	12 (15.0%)
Baseline GDMT	
ACEI/ARB/ARNI	61 (76.3%)
HF-specific betablocker	53 (66.3%)
Aldosterone antagonist	19 (23.8%)
Empagliflozin	6 (7.5%)
Hydralazine/Isosorbide Dinitrate	11 (13.8%)
Digoxin	9 (11.3%)
Ivabradine	1 (1.3%)
Chronic resynchronization therapy	9 (11.3%)
Implantable cardiac defibrillator	23 (28.8%)
Past medical history	
Hypertension	76 (95.0%)
Hyperlipidemia	66 (82.5%)
Diabetes	37 (46.3%)
Stable CAD	36 (45.0%)
Atrial fibrillation	29 (36.3%)
Chronic pulmonary disease	21 (26.3%)
Smoking	19 (23.8%)
CABG	17 (21.3%)
Myocardial infarction	2 (2.5%)
Venous thromboembolism	5 (6.3%)
Stroke/TIA	7 (8.8%)
Peripheral vascular disease	3 (3.8%)
Aspirin use	54 (67.5%)
Anticoagulant use	33 (41.3%)

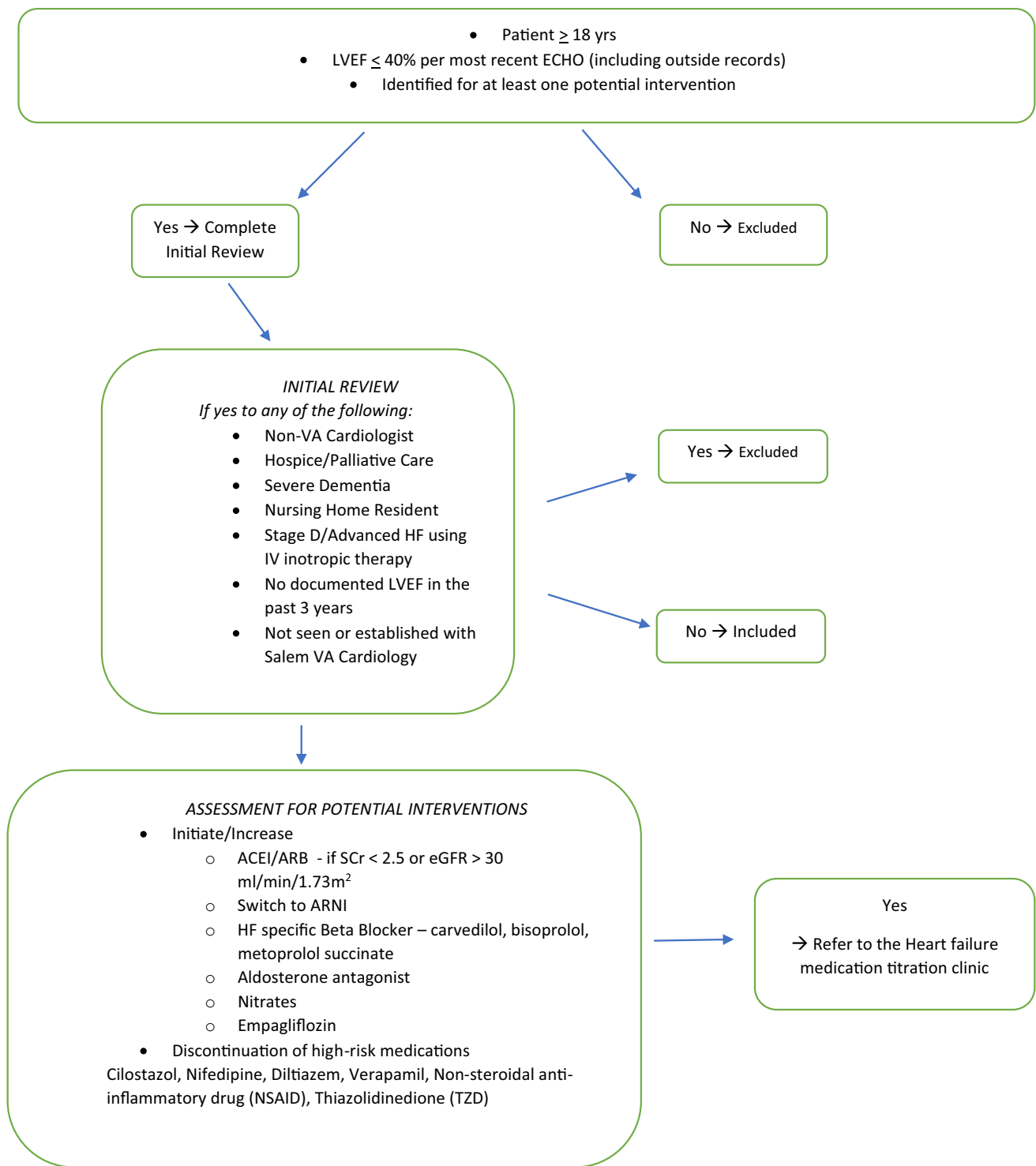
proportion of patients on AA ( $p$ -value = 0.041), ARNI (39 (48.8%) vs 18 (22.5%);  $p$ -value = 0.011), and SGLT2i (26 (32.5%) vs 6 (7.5%),  $p$ -value = 0.001), respectively, were significantly higher at 90-day post-enrollment compared to the baseline

There was a significant reduction in the overall mean combined HF-related hospitalization/ER visits 90-day post-enrollment as compared to 90-day pre-enrollment with a mean difference of 0.19 and 95% confidence interval ( $CI$ ) of 0.01 to 0.33 ( $p$  = 0.047) primarily driven by reduction in the HF-related ER visits ( $p$ -value: 0.042). The proportion of combined HF-related hospitalization and ER visits were significantly lower at 90-day post-enrollment compared to 90-day pre-enrollment ( $p$ -value = 0.008) mainly driven by reduction in the proportion of ER visits ( $p$ -value = 0.002).

There was significant reduction in SBP, DBP and pulse rate at 90-day post-enrollment compared to baseline (Table 3). Improvement in LVEF was captured as mean difference of 5.01% (95%  $CI$  0.37 to 12.63%;  $p$ -value:0.041) at 90-day post-enrollment compared to baseline in 25 patients. There was a significant improvement in the median KCCQ-12 score ( $p$  < 0.001; Table 3) and the mean difference of 6.31 (95%  $CI$  of 4.09 to 8.52;  $p$ -value < 0.001) was observed when comparing 90-day post-enrollment to baseline. There was a non-significant improvement in the proportion of patients deemed as adherent per MOS-SAS score ( $p$ -value: 0.075). However, significant difference was found in the median MOS-SAS score 90-day post-enrollment ( $p$ -value: < 0.001, Table 3) and the mean difference of 2.77 (95%  $CI$  1.40 to 4.22;  $p$ -value: < 0.001) was observed post-enrollment as compared to baseline.

Mean ( $\pm$  SD) encounter by CPS in the HMTc clinic at 90-day post-enrollment were  $3.65 \pm 1.53$  as compared to  $1.22 \pm 1.13$  cardiology encounters during the same timeframe. A total of 289 CPS encounters of 30 min each for 80 patients were captured with 38 face-to-face and 251 telephone based resulting in a total of 144.5 hours of physician time saved. Dose of ACEi/ARB/ARNI were increased 66 times, betablockers were increase 71 times during the study period while diuretics were adjusted 46 times. Potassium supplement was initiated in 4 patients while adjusted 5 times. Additionally, 8 patients were on digoxin and CPS checked levels on 7 patients overdue for monitoring and adjusted dose in 3 patients. Reasons for not reaching target GDMT were drug intolerance including hypotension ( $n$  = 18), hyperkalemia ( $n$  = 2), acute kidney injury ( $n$  = 5), and low heart rate ( $n$  = 9). The process of titration was not yet complete at 90 days in 46 patients (57.5%). The average GDMT optimization score at 90 days after enrollment in the clinic was  $+1.98 \pm 1.06$ .

Cost avoidance associated with CPS intervention assessed using PhARMD Tool Interventions resulted in estimates ranging from a conservative \$34,488.93 (based on 7% assumption) to best case scenario where all interventions were likely to prevent harm, of about



**Fig. 2** Enrollment flowchart and possible interventions evaluated

\$492,698.95. Benefit-cost ratio was 51.82 and net benefit estimate was \$592,862.45 in the best-case scenario. Adjusted benefit-cost ratio and net benefit was 12.68 and \$136,652.43, respectively, at 90 days (Supplementary file Fig. 1a–c).

## Discussion

This study showed that significantly higher proportion of HFrEF patients enrolled in a pharmacist-led HMTC achieved quadruple and triple GDMT at 90-day post-enrollment

**Table 2** Primary and secondary outcomes

<i>N</i> = 80	Baseline	90-day post-enrollment	<i>P</i> -value
<b>Primary Outcome</b>			
Quadruple therapy <sup>#</sup>	2 (2.5%)	17 (21.3%)	0.001
Triple therapy <sup>#</sup>	15 (18.8%)	29 (36.3%)	0.020
<b>Secondary Outcomes</b>			
Target or maximally tolerated GDMT achieved for both ACEI/ARB/ARNI and Betablocker <sup>#</sup>	3 (3.8%)	26 (32.5%)	< 0.001
Target GDMT for both ACEI/ARB/ARNI and Betablocker <sup>#</sup>	2 (2.5%)	10 (12.5%)	0.021
Target or maximally tolerated GDMT for ACEI/ARB/ARNI <sup>#</sup>	19 (23.8%)	38 (48.8%)	< 0.001
Target GDMT for ACEI/ARB/ARNI <sup>#</sup>	19 (23.8%)	32 (40.0%)	0.011
Target or maximally tolerated GDMT for HF-specific Betablocker <sup>#</sup>	5 (6.3%)	35 (43.8%)	< 0.001
Target GDMT for HF-specific Betablocker <sup>#</sup>	5 (6.3%)	24 (30.0%)	< 0.001
ARNI	18 (22.5%)	39 (48.8%)	0.011
Aldosterone antagonists <sup>#</sup>	18 (22.5%)	31 (38.8%)	0.041
SGLT2 inhibitors <sup>#</sup>	6 (7.5%)	26 (32.5%)	0.001
<b>Health care utilization</b>			
	<b>90-day pre-enrollment</b>	<b>90-day post-enrollment</b>	<i>P</i> -value
Combined HF-related hospitalization and ER visits <sup>#</sup>	30 (37.5%)	14 (17.5%)	0.008
HF hospitalization <sup>#</sup>	12 (15.0%)	6 (7.5%)	0.210
ER visits <sup>#</sup>	18 (22.5%)	8 (10.0%)	0.002
Combined HF-related hospitalization and ER visits *(mean ± SD)	0.32 ± 0.64 ( <i>n</i> = 23)	0.13 ± 0.46 ( <i>n</i> = 11)	0.047
HF-hospitalization*	0.16 ± 0.37 ( <i>n</i> = 12)	0.07 ± 0.27 ( <i>n</i> = 6)	0.134
HF- ER visits*	0.16 ± 0.35 ( <i>n</i> = 11)	0.06 ± 0.24 ( <i>n</i> = 5)	0.042

\*Analyzed using paired *t*-test<sup>#</sup>Proportions in paired sample were analyzed using McNemar's Test

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; HF, heart failure; GDMT, guideline-directed medical therapy; ER, emergency room

**Table 3** Post-90-day patient demographics as compared to baseline

Parameter ( <i>n</i> )	Baseline ( <i>n</i> = 80)	90-day post-enrollment ( <i>n</i> = 80)	<i>P</i> -value
LVEF ( <i>n</i> = 25)	31.53 + 6.26	36.54 + 10.37	0.041
Potassium ( <i>n</i> = 78)	4.11 + 0.47	4.18 + 0.42	0.245
Magnesium ( <i>n</i> = 42)	2.11 + 0.28	2.19 + 0.29	0.349
Serum creatinine ( <i>n</i> = 78)	1.22 + 0.45	1.30 + 0.50	0.066
Systolic blood pressure	128.44 + 14.79	112.31 + 18.82	< 0.001
Diastolic Blood pressure	76.83 + 8.43	70.87 + 8.24	0.018
Pulse rate	76.92 + 10.95	71.05 + 10.74	0.009
Adherence assessed by MOS-SAS** ( <i>n</i> = 72)	38 (50.7%)	48 (64%)	0.075
KCCQ-12 score ( <i>n</i> = 72)* Median (IQR)	36 (27–36)	44 (29–49)	< 0.001
MOS-SAS score ( <i>n</i> = 72)* Median (IQR)	32 (27–39)	35 (29–38)	< 0.001

\*Analyzed using Wilcoxon signed rank test for non-parametric data

\*\*Proportions in paired sample were analyzed using McNemar's Test

Abbreviations: MOS-SAS, medical outcomes study specific adherence scale; LVEF, left ventricular ejection fraction; KCCQ-12, Kansas City Cardiomyopathy Questionnaire; IQR, interquartile range



compared to the baseline. Additionally, significantly higher proportion of patients achieved GDMT for ACEI/ARB/ARNI, beta-blocker, AA, and SGLT2i, therapy at 90-day post-enrollment. Pharmacist intervention in HMTc also significantly reduced mean as well as proportion of combined HF-related hospitalization/ER visits at 90-days post-enrollment as compared to 90-days pre-enrollment primarily driven by reduction in HF-related ER visits.

In previously published VA study, a pharmacy medication titration clinic (PMTC) aimed at preventing readmissions by targeting patients discharged after HF exacerbations showed that in the PMTC group, achievement of beta-blocker target doses ( $p = 0.01$ ) and composite clinical GDMT ( $P = 0.02$ ) were significantly higher; however, achieved target doses of ACE/ARB were non-significant ( $P = 0.07$ ) [26]. This study showed trend in reduction of readmission rate for HF at 30 and 90 days as well as ER visits however did not reach statistical significance unlike our study. This study had an average age of 66 and majorly male African American population as opposed to median age of 71 years with largely white male patients in our study. Additionally, our study lacked comparator group, however, showed significant difference in the achieved GDMT for quadruple and triple GDMT as well as combined ACEI/ARB/ARNI and Betablocker with pharmacist intervention. Of note, our patients were stable patients with average duration of CHF diagnosis of 1.2 years. This highlighted the lack of close monitoring and dedicated clinical staff for this patient population at our facility. Another VA study similarly showed that implementation of pharmacist managed HMTc increased the percentage of patients achieving optimal ACEI, ARB, and Beta-blocker dosages [27]. We found that the aggressive rapid sequential strategy endorsed by Greene SJ et al., published 3 months after our clinical enrollment begun would have been difficult to implement in our clinical practice owing to the patient demographics observed in our study and therefore, this strategy was not tested [28]. Previously published study by Wilenheimer R et al. did not show any difference between the bisoprolol first versus enalapril first treatment strategy and our study did not adhere to a specific preferential sequence of initiating GDMT [29].

A retrospective study from a large academic hospital showed that implementation of outpatient pharmacist managed HFREF medication-titration-assistance-clinic (MTAC) resulted in a greater proportion of patients achieving targeted or maximally tolerated doses as compared to those managed by general cardiology in an average of 60-year-old patients with higher proportion of female patients and African Americans [30]. This study had a follow-up of 12 months as compared to only 90 days in our study; however, given that most of the current GDMT has showed to have mortality benefit as early at 4 weeks, rapid initiation and titration is pertinent and therefore, we feel that 90 days

provides a good insight on what can practically be achieved in our veteran patients. In contrast were the results of the HOOPS study by Lowrie et al. resulting in only modest improvement in the prescribing of ACE/ARB and beta-blockers [31]. One important distinction in the study design was the lack of independent prescriptive authority allowing physicians to reject the recommendations made by pharmacist. This really highlights the importance of incorporating pharmacist with provider privileges in the HF management in face of the growing pharmacotherapeutic options and disease burden.

One unique feature of our study was the prospective implementation planned a priori, allowing us to design the study to meet the power and collect appropriate data parameters. Our study is unique in which the results achieved in our study are reflective of the post COVID-19 pandemic clinical setting where telehealth is increasingly gaining popularity. This study exemplifies that by utilizing home telehealth consults that enable patients to directly report blood pressure, heart rate, and weight can deliver similar results as those observed in the previously published studies with in-person visits [26, 30]. We also incorporated assessment of KCCQ-12 and MOS-SAS questionnaires into CPS visit. To the best of our knowledge, this is the first study reporting impact of pharmacist-led-HMTc on quality of life which is an important goal of the treating HF and objectively assessing patient adherence to disease state management including medication adherence in veteran patients. A randomized control multicenter trial PHARM-CHF evaluating impact of involvement of community pharmacist on medication adherence and QOL in 258 HF patients, showed significant improvement in the primary endpoint of medication adherence within 365 days in the pharmacy group compared to usual care group [mean difference 5.7%; (1.6 to 9.8;  $p = 0.007$ )] [32]. Additionally, pharmacy care which included medication counseling and review also improved quality of life after 2 years as evaluated by Minnesota Living with Heart Failure Questionnaire scores [mean difference  $-7.8$  ( $-14.5$  to  $-1.1$ ;  $p = 0.02$ )]. In our study, the impact on QOL was significant at 90-day post-enrollment as measured by KCCQ-12 scores [mean difference 6.31 (4.09 to 8.52;  $p$ -value  $< 0.001$ )]. Published data have shown that an improvement of 5 or more points in KCCQ-12 score is independently associated with decreased mortality (hazard ratio, 0.59; 95% CI, 0.44–0.80;  $p < 0.001$ ) [33].

In prospective pilot study by Bhatt A et al., implementation of virtual multidisciplinary GDMT team improved utilization of GDMT prescription at discharge in 118 HFREF patients hospitalized for non-cardiovascular reasons and had an mean GDMT optimization score of  $+0.62 \pm 1.11$  in the intervention group at hospital discharge compared to  $+1.98 \pm 1.06$  at 90 days in our study [20]. This study was not able to assess adherence or impact on quality of life and post

discharge data was collected based on passive patient chart review. In comparison, our study did not have a comparator group; however, we showed the use of this simple score in ambulatory care clinic led by pharmacist for a much longer duration of follow up of 90 days. Additionally, our study was able to further evaluate the impact on patient adherence and quality of life using MOS-SAS and KCCQ-12 questionnaire.

The study was small sample with non-randomized study design. Large proportion of white male patients in our study limits the generalizability. The observed results can be limited by the accuracy of documentation in medical records leading to incomplete data with possible misclassification. Reduction in the need to see a physician or mid-level practitioners as opposed to CPS clinic implementation cost was not accounted in the reported cost estimates limiting the interpretation of observed cost savings. One caveat was that administration of KCCQ-12 and MOS-SAS questionnaire via health care provider given that primary mode of care delivery was telehealth which may have introduced bias in the observed results. Study was not powered to detect difference in the combined HF related hospitalizations and ER-visit outcomes. Only 25 patients had LVEF available at 90 days and this may have underestimated the observed benefit in our study. Additional therapies proven to reduce morbidity such as digoxin, Ivabradine and vericiguat were not evaluated in this study. Finally, the lack of control group may limit the interpretation of the study results and its comparisons to previously published studies [26, 30].

Given, the method of LVEF utilized in the dashboard, there seemed to be discrepancy in the initial LVEF, and one observed most recently in the medical chart. The original business rules for data extraction also focused on the lowest LVEF in the last 3 years in order to be more sensitive for patients that may have HFpEF, and these values were only updated every 3 months. This resulted in significant exclusions after manually reviewing patient charts as patients either may have had ECHO done outside our facility or have an updated ECHO available since the time dashboard last updated or their most recently updated ECHO indicated LVEF > 40%. The old business rules for LVEF utilized in the NLP were very sensitive for HFpEF and very specific for HFrEF; however, these had low overall accuracy (~54%). New business rules recently implemented balance sensitivity and specificity and have an improved overall accuracy (~88%). This should address this limitation for any subsequent studies conducted using the VHA National HF Dashboard.

Future randomized controlled trials and real-world implementation studies should focus on comparing the pharmacist-led intervention to a control group along with evaluating the optimal strategy for sequence of initiation and titration of GDMT. CPS integration in the management

of HF may reduce the burden of other providers and potentially increase access for new patients while simultaneously improving clinical and economic outcomes. There is growing evidence supporting role of pharmacist in this setting; however, the impact of CPS working with an advanced scope of practice making independent clinical decision continues to be limited. In conclusion, this study found that pharmacist-led HMTC significantly increased the proportion of patients who achieved triple and quadruple GDMT at 90 days, reduced hospitalization and ER visits related to heart failure and improved quality of life as measured by KCCQ-12 questionnaire.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s12265-022-10262-9>.

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**Author Contribution** Primary and second author have made substantial contributions to the conception and design of the research project as well as the acquisition, analysis, and interpretation of data. All authors have contributed towards the drafting of the initial manuscript and offered comments to the previous versions for important intellectual content. The final draft of manuscript was written by Tanvi Patil (Primary author). All authors have agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Availability of data and material** Aggregated data has been provided with this study. No additional patient specific data can be disclosed given the VHA patient privacy policy.

**Code availability** Not Applicable

## Declarations

**Ethics approval** Please refer to the “Methods” section.

**Consent to participate** Not applicable as this was a quality improvement study implemented as part of routine clinical care and waived by IRB.

**Consent for publication** Approved by appropriate institution IRB and Privacy Officer to proceed with the publication of this material.

**Conflict of Interest** Tanvi Patil, Salihah Ali, Alamdeep Kaur, Meghan Akridge, Davida Eppes, James Paarlberg, and Amitabh Parashar have nothing to disclose.

Nabil Jarmukli has the following conflict of interest to disclose pertaining to one of the drugs utilized in this study:

2017–2021: Principal Investigator BI Salem VA Medical Center, EM-PEROR-Reduced Study

2017–2021: Principal Investigator BI Salem VA Medical Center, EM-PEROR-Preserved Study

KCCQ-12 Instrument for Clinical Users was purchased for use during the study duration.

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