American Heart Journal Plus: Cardiology Research and Practice 45 (2024) 100438

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

Protocol-driven approach to guideline-directed medical therapy optimization for heart failure: A real-world application to recovery

Crystal Lihong Yan [a,*], David Snipelisky [b], Mauricio Velez [b], David Baran [b], Jerry D. Estep [b], E. Joseph Bauerlein [c], Nina Thakkar Rivera [b]

[a] Divison of Internal Medicine, University of Miami Health System, Miami, FL, USA
[b] Heart, Vascular & Thoracic Institute, Cleveland Clinic Florida, Weston, FL, USA
[c] Miami Transplant Institute, Jackson Health System, Miami, FL, USA

ARTICLE INFO

Keywords:
Guideline-directed medical therapy
Heart failure
Reduced ejection fraction
Protocol
Titration

ABSTRACT

The objective of our study was to evaluate the real-world effects of an aggressive, personalized protocol for guideline-directed medical therapy (GDMT) titration in patients with heart failure (HF) with reduced ejection fraction (HFrEF). We conducted a two-center retrospective cohort study. Patients with HFrEF who presented to a HF clinic from January 2020 to December 2022 were placed on a GDMT protocol. 180 patients were included in the study. Mean GDMT score significantly increased from 4.7 to 5.9 ($p < 0.001$) between initial and final visits. Mean left ventricular ejection fraction (LVEF) significantly increased from 28 % to 33 % (+5 %, $p < 0.001$). 27 (15.7 %) of the 172 patients with complete New York Heart Association (NYHA) classification data had improvement by at least 1 class, while 2 (1.2 %) patients had worsening NYHA classification. 140 (77.8 %) patients had no unplanned hospitalizations between visits. 21 (11.7 %) patients had an unplanned hospitalization for acute HF during the study period with a mean time from first clinic visit to hospitalization of 183 days (range: 13–821 days). 2 (1.1 %) patients were hospitalized due to GDMT-associated adverse drug events (i.e. hypotension, hyperkalemia). 7 (3.9 %) patients died during the study period, which was lower than the predicted 1-year death rate for our cohort (12.3 %) using the MAGGIC score. In conclusion, an aggressive, personalized protocol for GDMT titration in patients with HFrEF led to significant improvements in LVEF, NYHA classification, hospitalization, and mortality in a real-world setting. This protocol may help serve as a road map to lessen the gap between clinical knowledge and practice surrounding optimization of GDMT and move HFrEF patients toward a path to recovery.

1. Introduction

Heart failure (HF) is a chronic, progressive disease that affects nearly 65 million people worldwide [1]. Guideline-directed medical therapy (GDMT) encompasses four pillars of medications that decrease mortality in patients with HF with reduced ejection fraction (HFrEF). The four pillars are beta blockers (BB); angiotensin receptor-neprilysin inhibitors (ARNI) or angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB); mineralocorticoid receptor antagonists (MRA); and sodium-glucose cotransporter-2 inhibitors (SGLT2I) [2]. Additionally, the combination of hydralazine and isosorbide dinitrate (H-ISDN) is recommended for HFrEF patients who are receiving optimal medical therapy and self-identify as African American [2]. While the mortality-sparing effects of these medications have been demonstrated in multiple randomized controlled trials, less is known about the impact of GDMT among HF patients in the real world.

Real-world application of GDMT is poor. Analysis of a large registry of chronic HFrEF patients in the United States found that 27 %, 33 %, and 67 % of eligible patients were not prescribed ARNI/ACEI/ARB, BB, or MRA therapy, respectively [3]. Only 14 %, 17 %, and 28 % were receiving target doses of ARNI, ACEI/ARB, and BB therapy [3]. Furthermore, only 1 % of patients were simultaneously receiving target doses of ARNI/ACEI/ARB, BB, and MRA therapy [3]. A common reason for the disconnect between clinical knowledge and practice is ambiguity surrounding how to achieve these known targets.

The objective of our study was to evaluate the effect of a personalized protocol for aggressive GDMT titration on clinical outcomes, specifically left ventricular ejection fraction (LVEF), New York Heart Association

* Corresponding author at: 1611 NW 12th Ave, C-600D, Miami, FL 33136, USA.
E-mail address: crystaly@med.miami.edu (C.L. Yan).

https://doi.org/10.1016/j.ahjo.2024.100438
Received 28 September 2023; Received in revised form 30 May 2024; Accepted 31 July 2024
Available online 3 August 2024

(NYHA) classification, hospitalization, and mortality in a real-world setting. Secondarily, we evaluated changes in GDMT prescription rates using this approach.

2. Methods

We conducted a two-center retrospective cohort study. Patients with HFrEF, including established patients, new patient referrals, and treatment naïve patients, who presented to a HF cardiology clinic from January 2020 to December 2022 were placed on a GDMT protocol and included in the study. Patients were excluded if their follow-up period was <30 days or they underwent advanced HF therapies such as left ventricular assist device implantation or heart transplantation by their last visit. Approval for the study was obtained from our institution's review board. Outcomes of interest were clinical outcomes such as left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) classification, hospitalization, and mortality. The MAGGIC score was used to calculate the expected 1-year mortality for the cohort [4]. Medication prescription rates of HF-specific BBs, ARNIs, ACEIs, ARBs, MRAs, SGLT2I, and H-ISDN were also evaluated. Target doses were determined from prior clinical trials as outlined by the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) HF management guidelines [2]. If a patient reported taking a medication differently than prescribed, the reported medication usage was collected rather than the prescribed. We used a 5-group scoring system created by The Heart Failure Collaboratory to calculate a GDMT score for each patient to compare GDMT usage at initial versus final visit [5]. For BB use, 2 points were given for ≥50 % max daily dose and 1 point was given for <50 % max daily dose. For ARNI/ACEI/ARB use, 3 points were given for ARNI use at any dose, 2 points were given for ≥50 % max ACEI/ARB daily dose, and 1 point was given for <50 % max ACEI/ARB daily dose. For MRA and SGLT2I use, 2 points were given for any dose. For H-ISDN use, 1 point was given for any dose. Zero points were given per group if the patient was not taking that medication class.

2.1. Protocol

The protocol is fully described in Supplementary Fig. 1. The protocol was personalized according to the patient's home blood pressure and heart rate log, laboratory results (i.e. creatinine, potassium), and medication tolerance at the physician's discretion. However, medication doses were generally titrated in 2-week intervals by a physician during in-person or telehealth visits or subsequently via pre-specified instruction at a prior visit. Additionally, medication doses were titrated by a HF-trained nurse via telephone calls in between physician visits. All patients were offered a blood pressure kit to monitor their blood pressure and heart rate twice daily. Once patients reached 6.25 mg of carvedilol twice a day, sacubitril-valsartan was added at 24–26 mg daily. Carvedilol and sacubitril-valsartan were then alternately titrated until target doses of 25 mg twice a day and 97–103 mg twice a day, respectively. For those with CKD stage 3a and above, smaller and slower increases in sacubitril-valsartan were used and creatinine was monitored 2 weeks post initiation or up-titration of an ARNI/ACEI/ARB. Once sacubitril-valsartan was optimized, spironolactone was initiated at 12.5 mg daily and empagliflozin or dapagliflozin was considered for initiation at 10 mg daily. If labs were stable (K ≤ 5 mEq/L and Cr ≤ 2.5 mg/dL in men or Cr ≤ 2.0 mg/dL in women), spironolactone was titrated to a target dose of 25 mg daily. After spironolactone initiation, labs were checked at 1 week, 1 month, and then every 3 months. In general, a 30 % increase in creatinine was allowed during medication titration. Overdiuresis and hypotension were important factors that were considered as causes of creatinine increase as opposed to purely medication-induced. At this point, if the patient was still not at a mean arterial pressure goal of 65 mmHg, hydralazine and isosorbide dinitrate were initiated and titrated to target doses of 100 mg three times a day and 40 mg three times a day, respectively, regardless of whether the patient self-identified as African American.

2.2. Statistical analysis

Categorical variables were determined as frequencies and percentages. Continuous variables were determined as means and standard deviations. Differences between means from initial visit to final visit were analyzed using paired-samples *t*-test. Differences in prescription rates from initial visit to final visit were compared using the z-test. Statistical analysis was performed using IBM SPSS Statistics (version 27, 2020). A *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

180 patients were included in the study. Patient characteristics are described in Table 1. Mean age was 59.3 years, 37.8 % of patients were female, 54.4 % were White, 43.9 % were Black, and 43.9 % were Hispanic or Latino. Of the 79 Hispanic or Latino patients, 70 (88.6 %) were

Table 1
Patient characteristics ($n = 180$).

Demographics	
Age, years	59.33 (12.67)
Sex	
Female	68 (37.8 %)
Male	112 (62.2 %)
Race	
White	98 (54.4 %)
Black	79 (43.9 %)
Asian	2 (1.1 %)
Other	1 (0.6 %)
Ethnicity	
Hispanic or Latino	79 (43.9 %)
Non-Hispanic or Latino	100 (55.6 %)
Not reported	1 (0.5 %)
Body mass index, kg/m^2	29.50 (8.88)
Clinical history	
Cardiomyopathy	
Ischemic	26 (14.4 %)
Non-ischemic	57 (31.7 %)
Unknown	97 (53.9 %)
Obstructive CAD	48 (26.7 %)
Hypertension	131 (72.8 %)
Diabetes mellitus	67 (37.2 %)
Atrial fibrillation	64 (35.6 %)
Chronic kidney disease[a]	
Stage 3a (EGFR 45–59)	20 (11.1 %)
Stage 3b (EGFR 30–44)	27 (15.0 %)
Stage 4 (EGFR 15–29)	7 (3.9 %)
ESRD on hemodialysis	9 (5.0 %)
COPD	19 (10.6 %)
Current smoker	10 (5.6 %)
Cardiac device	
Pacemaker	6 (3.3 %)
AICD	62 (34.4 %)
CRT	20 (11.1 %)
Follow-up	
Number of clinic visits	5.29 (2.85)
Duration of follow-up, months	9.29 (5.95)

Data are number (percentage) or mean (standard deviation). Abbreviations: AICD automatic implantable cardioverter defibrillator; CAD coronary artery disease; COPD chronic obstructive pulmonary disease; CRT cardiac resynchronization therapy; EGFR estimated glomerular filtration rate; ESRD end stage renal disease.

[a] Stage based on calculated EGFR using 2021 CKD-EPI equation and creatinine at initial visit.

White and 9 (11.4 %) were Black. Mean body mass index was 29.5 kg/m^2. 72.8 % of patients had concomitant hypertension, 37.2 % had diabetes, 35.6 % had atrial fibrillation, and 34.4 % had chronic kidney disease. The average number of clinic visits and duration of follow-up was 5.3 visits and 9.3 months, respectively. For the 77 patients with a known initial HF diagnosis date, the mean time from diagnosis to first clinic visit was 4.7 years. Only 32 (17.8 %) patients were diagnosed with HF within 18 months prior to their initial clinic visit.

3.2. Medication changes

Medication prescription by frequency is shown in Fig. 1. There were statistically significant absolute increases in the number of patients taking a BB (+6.7 %, $p = 0.035$), ARNI/ACEI/ARB (+8.3 %, $p = 0.013$), and SGLT2I (+15.0 %, $p = 0.0005$). Prescription rates of MRAs and H-ISDN did not significantly change between visits. More specifically, there were statistically significant increases in the number of patients taking carvedilol (54.4 % to 78.3 %, $p < 0.00001$), sacubitril-valsartan (66.1 % to 86.7 %, $p < 0.00001$), empagliflozin (7.2 % to 14.4 %, $p = 0.028$), and dapagliflozin (6.1 % to 13.9 %, $p = 0.014$) from initial to final visit. There were also statistically significant decreases in the number of patients taking metoprolol succinate (31.3 % to 15.0 %, $p = 0.003$), lisinopril (7.2 % to 1.1 %, $p = 0.004$), and losartan (10.0 % to 4.4 %, $p = 0.041$) from initial visit to final visit. The mean number of GDMT medication classes prescribed per patient significantly increased from 2.3 to 2.7 ($p < 0.001$) between the first and last clinic visits. There was also a statistically significant increase in mean GDMT scores (4.7 vs. 5.9, $p < 0.001$) between visits.

Medication prescription by dosage is described in Supplemental Table 1. Pairwise comparison of dosages showed statistically significant increases in that of carvedilol (12.45 to 17.71, $p < 0.001$) and sacubitril-valsartan (43.73 to 57.82, $p < 0.001$) from initial to final visit. There were no significant dosage changes for the other medications.

Rates of target dose achievement are described in Fig. 2. There were statistically significant absolute increases in the number of patients on target doses of BBs (+16.7 %, $p = 0.0003$), ARNI/ACEI/ARBs (+15.0 %, $p = 0.0005$), and SGLT2Is (+13.4 %, $p = 0.001$). Prescription rates of MRAs and H-ISDN at target doses did not significantly change. More specifically, there were statistically significant increases in the number of patients on target doses of carvedilol (14.4 % to 32.8 %, $p < 0.00001$), sacubitril-valsartan (13.9 % to 28.9 %, $p = 0.0005$), empagliflozin (7.2 % to 14.4 %, $p = 0.028$), and dapagliflozin (5.0 % to 11.1 %, $p = 0.033$).

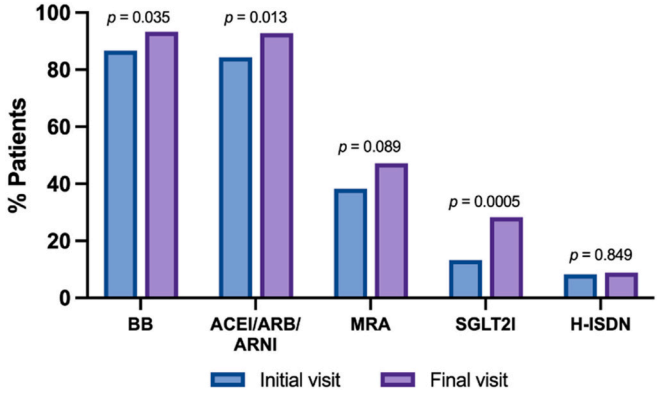

Fig. 1. Medication prescription rates by GDMT class ($n = 180$).
Bar graph showing the percent of patients on a medication class at initial visit compared to final visit. Abbreviations: ACEI angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; ARNI angiotensin receptor-neprilysin inhibitor; BB beta blocker; GDMT guideline-directed medical therapy; H-ISDN hydralazine and isosorbide dinitrate; MRA mineralocorticoid receptor antagonist; SGLT2I sodium-glucose cotransporter-2 inhibitor.

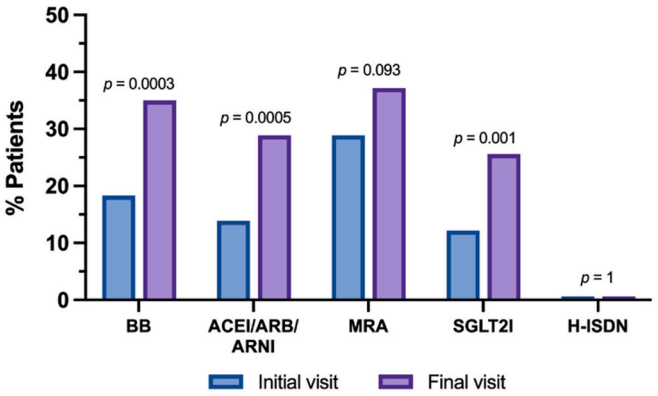

Fig. 2. Target dose achievement by GDMT class ($n = 180$).
Bar graph showing the percent of patients on the target dose of a medication by GDMT class at initial visit compared to final visit. Abbreviations as in Fig. 1.

3.3. Clinical parameters and outcomes

Changes in vital signs, biomarkers, functional classification, and imaging parameters are described using pairwise comparison in Fig. 3 and Supplementary Table 2. Mean heart rate decreased by 2.8 beats per minute ($p = 0.013$). Mean creatinine increased from 1.38 mg/dL to 1.45 mg/dL ($p = 0.043$); however, the difference was no longer statistically significant after removing outliers ($p = 0.469$). Mean NYHA classification significantly improved from 2.26 to 2.08 ($p < 0.001$). 27 (15.7 %) of the 172 patients with complete NYHA classification data had improvement by at least 1 class, while 2 (1.2 %) patients had worsening NYHA classification. Despite significant up-titration of GDMT, pairwise comparison showed no statistically significant differences in means of systolic blood pressure, diastolic blood pressure, mean arterial pressure, or NT-proBNP level between visits. Of the 110 patients with pairwise echocardiograms, 42 (38.2 %) had an absolute increase in LVEF of ≥10 % between visits. Mean LVEF significantly increased from 28 % to 33 % (+5 %, $p < 0.001$). Interventricular septal wall thickness at end-diastole (0.96 cm to 0.91 cm, $p = 0.079$), left ventricular posterior wall thickness at end-diastole (1.13 cm to 0.95 cm, $p = 0.054$), and left ventricular internal end-diastolic diameter (5.94 cm to 5.87 cm, $p = 0.465$) did not significantly change.

Most patients (140, 77.8 %) had zero unplanned hospitalizations between visits (Fig. 4A), while some had one (25, 13.9 %), two (9, 5.0 %), or three or more (6, 3.3 %) unplanned hospitalizations between visits. For the 40 patients (22.2 %) with an unplanned all-cause hospitalization during the study period, the mean time from first clinic visit to hospitalization was 146 days (range: 13–821 days). Twenty-one patients (11.7 %) had an unplanned hospitalization for acute HF during the study period with a mean time from first clinic visit to hospitalization of 183 days (range: 13–821 days). Two patients (1.1 %) were hospitalized due to GDMT-associated adverse drug events (i.e. hypotension, hyperkalemia).

Seven patients (3.9 %) died during the study period (Fig. 4B). Three patients died of septic shock, two patients suffered cardiac arrest (one with pulseless ventricular tachycardia and one with pulseless electrical activity) shortly after arrival to the emergency department from unclear causes, one patient died of complications of a malfunctioning arteriovenous fistula, and one patient died outside of our health system for an unknown reason. The predicted 1-year death rate for our cohort using the MAGGIC score was 12.3 %. Patients who died had worse mean NYHA classification at baseline (2.86 vs. 2.24, $p = 0.018$) and lower LVEF at follow-up (21.07 vs. 34.66, $p = 0.032$). There were no statistically significant differences in mean duration of follow-up on the protocol, number of clinic visits, number of GDMT classes at first or last clinic visit, age at first clinic visit, LVEF at first clinic visit, or NYHA classification at last clinic visit.

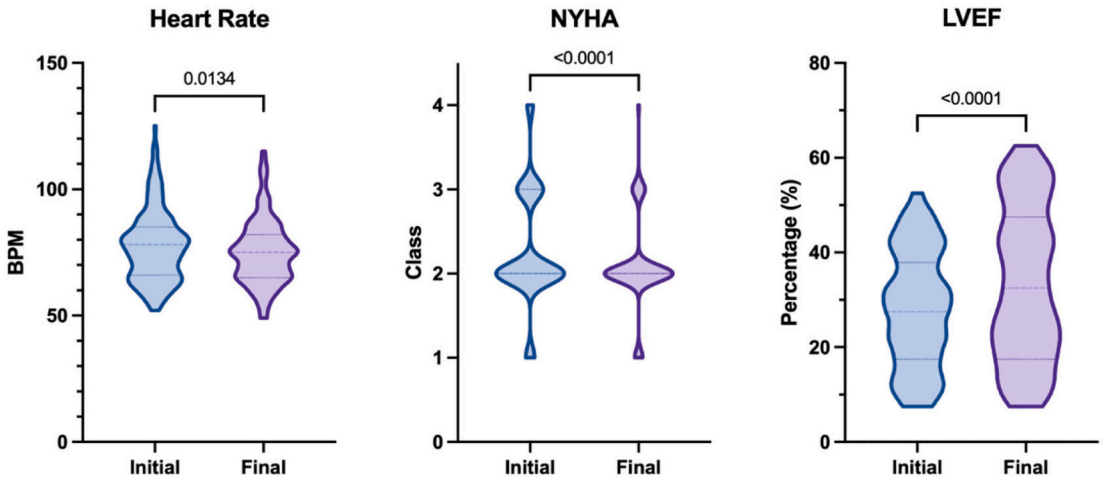

Fig. 3. Improvements in clinical parameters following GDMT.
Violin plots showing the distribution of data for heart rate, NYHA classification, and LVEF at initial visit compared to final visit. The width of each curve corresponds to the frequency of data points in that region. The middle dashed line represents the median. The upper and lower dotted lines represent the first and third quartiles. Abbreviations: BPM beats per minute; LVEF left ventricular ejection fraction; NYHA New York Heart Association.

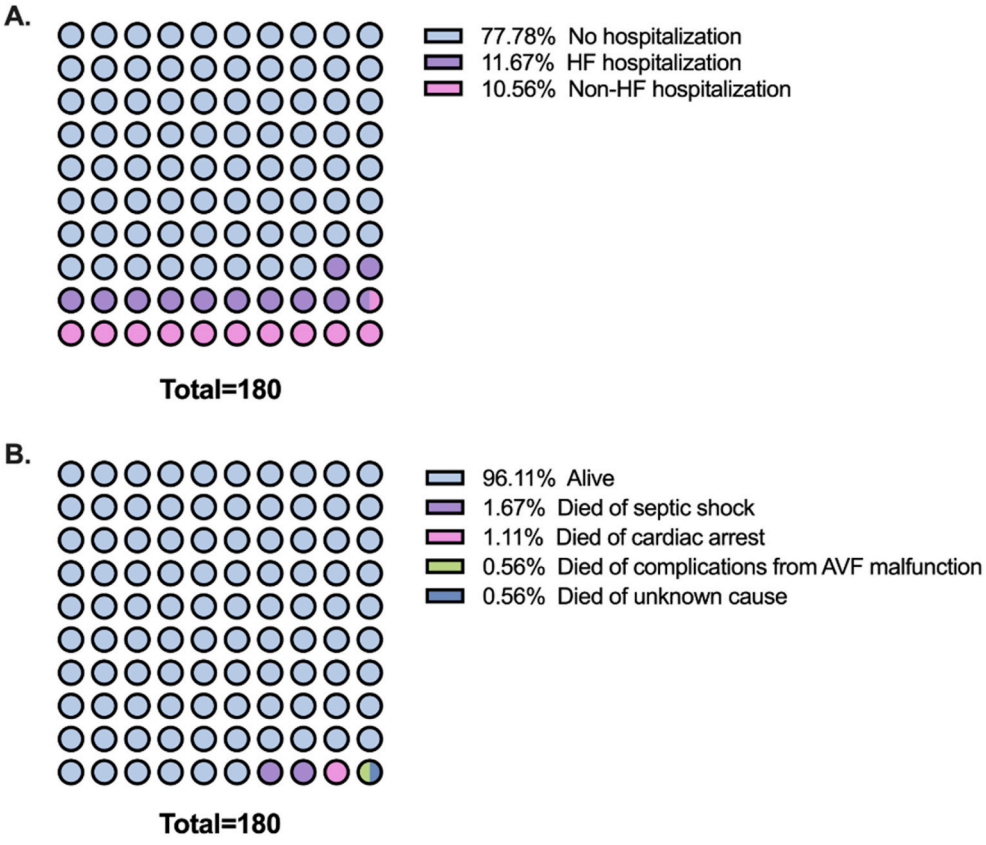

Fig. 4. Hospitalization and mortality rates.
Dot plots of 100 dots showing an approximation of the percent of patients (180 patients total) who were hospitalized and died during the study period. Abbreviation: AVF arteriovenous fistula; HF heart failure.

4. Discussion

In this retrospective multi-center cohort study of 180 HFrEF patients, we sought to determine the clinical impact of a protocol-driven approach to GDMT up-titration in a real-world setting. Our main findings were: 1) mean LVEF, NYHA classification, and heart rate significantly improved between visits; 2) a small proportion of patients had an unplanned hospitalization for acute HF during the study period and not until a mean follow up time of >6 months; 3) only 1 patient died of cardiac-related causes; and 4) the number of GDMT classes prescribed per patient significantly increased between clinic visits.

Mortality rates were low in our cohort. The observed all-cause mortality rate in our cohort (3.9 %) was considerably lower than the predicted 1-year mortality rate (12.3 %) generated from a clinical risk

score accounting for 13 highly significant independent predictors of mortality in HF patients [4]. Furthermore, the 1-year all-cause and cardiac mortality rates were 11 % and 8 %, respectively among HFrEF patients enrolled in a large prospective study [6]. Personalization of our protocol and frequent patient visits (on average every 7 weeks) likely contributed to improved GDMT adherence in our cohort, as evidenced by increased GDMT prescription rates, and translated into improved mortality.

Comparable data for hospitalization rates among HFrEF cohorts treated with GDMT is sparse. All-cause hospitalization and HF hospitalization rates were 22.2 % and 11.7 %, respectively in our cohort with a mean follow-up time of 9 months. In comparison, HF hospitalization was 5.2 % in the DAPA-HF trial at 9 months [7]. Prevention of HF hospitalization is crucial as the mean survival time among HF patients after first hospitalization is only 2.6 years, with even worse outcomes after subsequent hospitalizations [8]. Moreover, once hospitalized for acute HF, about one third of HF patients are readmitted within 3 months [9]. Our cohort had a considerably low readmission rate as only 15 (10.7 %) patients had two or more unplanned hospitalizations between visits. Furthermore, only 2 (1.1 %) patients were hospitalized due to GDMT-associated adverse events, supporting the safety and tolerability of aggressive GDMT titration. HF hospitalization is associated with increased likelihood of GDMT de-escalation and discontinuation in those on prior therapy, as well as increased all-cause mortality [10]. Thus, low rates of hospitalization and readmission rates in our HFrEF cohort may have allowed for increased GDMT usage and decreased mortality.

Many patients demonstrated signs or symptoms of recovery or reverse remodeling. Nearly 4 in 10 patients demonstrated functional HF recovery as defined as an absolute increase in LVEF of $\geq$10 % with a mean LVEF increase of 5 % among all patients. Patients also had significant improvement in HF symptoms or clinical recovery as evidenced by decreased NYHA classification scores. HF recovery is an important clinical outcome as it has been associated with improved survival and quality of life [11,12].

It is important to note that blood pressure did not significantly change despite significant up-titration of GDMT in our study. While symptomatic hypotension with systolic blood pressure <90 mmHg has been observed as a rare adverse event during GDMT treatment [13], most HFrEF patients tolerate GDMT despite low blood pressure measurements. This is due to a few reasons. One, afterload reduction directly offloads work required from an already weakened cardiac muscle. Two, afterload reduction allows cardiac muscle to strengthen. As the heart muscle regains strength over time, cardiac output increases, and subsequently blood pressure increases, allowing for additional up-titration of GDMT (Fig. 5). Transient drops in blood pressure shortly after GDMT dosing can be avoided by spacing out medication administration. Patients in our study were counseled on staggering their medications to allow for asymptomatic drops in blood pressure. Rather than an effect of GDMT, low blood pressure may be a sign of advanced HF and is a bad prognostic marker [14]. Care was taken to ensure that low blood pressure was not caused by dehydration, gastrointestinal bleeding, or infection, to name a few etiologies, prior to up-titration of GDMT.

Heart rate did significantly decrease with GDMT up-titration. Although a 3 beats per minute reduction in heart rate may not seem clinically significant, heart rate reduction is associated with improved clinical outcomes in HF [15]. Conversely, higher resting heart rate is a risk factor for cardiovascular events in HF [16].

Our favorable outcomes were likely a reflection of aggressive up-titration of GDMT. GDMT scores have been proposed to compare the degree of background therapy across clinical trials in HF. We used a scoring system adapted from a consensus Heart Failure Academic Research Consortium meeting, which assigns point values based on class and dose of drug [5]. Mean GDMT score significantly increased from 4.7 to 5.9 between visits. More specifically, there were statistically significant increases in the prescription rates of BBs, ARNI/ACEI/ARBs, and SGLT2Is both at any dose and at target dose. Most patients in our study were not newly diagnosed with HF and had been managed by other physicians previously. Referral to our clinic allowed for medication optimization in patients otherwise not thought to be candidates for such.

Our protocol favors certain medications within GDMT. For example, our protocol directs the use of carvedilol and sacubitril-valsartan over other BBs and ACEI/ARBs, respectively, in keeping with evidence from clinical studies and guidelines [2,7,13,17–19]. As a result, prescription rates of carvedilol and sacubitril-valsartan significantly increased between visits partly at the expense of patients taking metoprolol succinate, lisinopril, and losartan. Prescription rates of SGLT2Is in our cohort were considerably lower than that of other GDMT classes likely because they weren't approved for the treatment of HFrEF until the middle of our

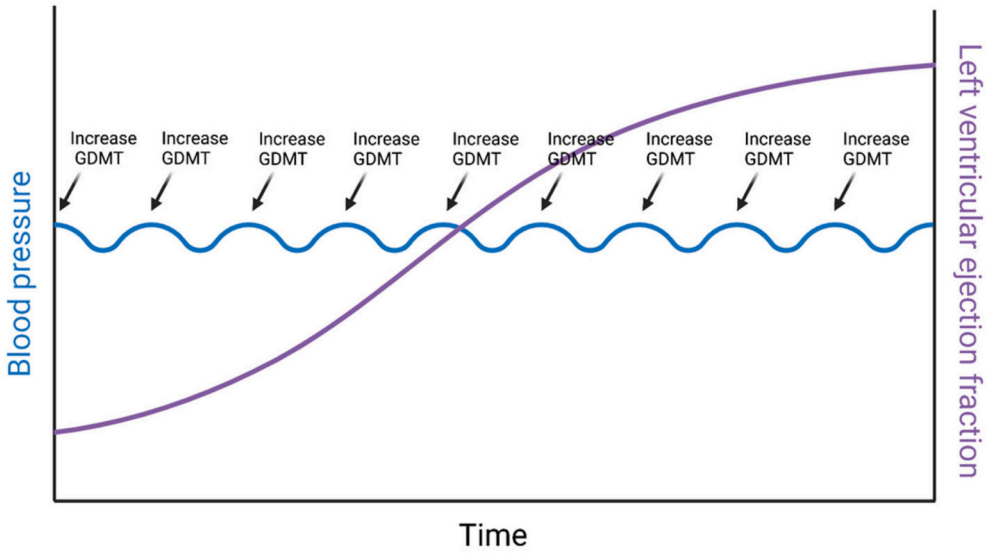

Fig. 5. GDMT effect on blood pressure and LVEF over time.
Line graph showing a conceptual depiction of the effect of GDMT on blood pressure and LVEF over time. Up-titration of GDMT may transiently lower blood pressure but should also gradually improve LVEF. As LVEF improves, cardiac output increases, and blood pressure increases, allowing for cyclical up-titration of GDMT. Abbreviations as in Figs. 1 and 3.

study. We suspect MRA prescription rates did not significantly increase possibly because our protocol directs the addition of spironolactone after optimization of sacubitril-valsartan as large randomized controlled trials demonstrating the mortality-sparing effects of MRAs were performed on a background of ACEI/ARB therapy [19,20]. Our protocol utilizes H-ISDN after optimization of first-line agents, regardless of race given lack of evidence against its use in other races [2]. However, its practical use is limited by its thrice a day dosing, as well as limitations in mean arterial pressure.

Our improvements in GDMT prescription rates are considerable when compared to that of analyses from large registries of HFrEF patients. The CHAMP-HF study found that with usual care there was no significant change in GDMT prescription rates over a 12-month period [21]. The IMPROVE HF study sought to improve the use of GDMT in cardiology clinics by implementing a multi-pronged intervention incorporating clinical decision support tools, educational materials, and practice-specific data reports. After 12 months, BB, ACEI/ARB, and MRA prescription rates only increased by 4.8 %, 3.4 %, and 13.6 %, respectively [22].

Our protocol has a few key differences from other published GDMT titration protocols. First and foremost, our protocol does not allow lower blood pressures or chronic kidney disease to hinder up-titration of GDMT. In patients with chronic kidney disease stage 3a and above, labs were monitored 2 weeks post initiation or up-titration of an ARNI/ACEI/ARB or MRA. Additionally, previously described protocols do not include use of SGLT2Is and/or H-ISDN [23–27] and thus provide incomplete guidance for GDMT optimization. Our protocol clearly delineates each step in GDMT titration, whereas other real-world protocols give a general overview on how to achieve an end goal [23,25,26]. Considering a major reason for suboptimal GDMT titration is ambiguity surrounding how to achieve known targets, our protocol minimizes ambiguity and this likely contributed to our significant improvement in GDMT prescription. Most GDMT optimization studies examine nurse- or pharmacist-led interventions [27], whereas our protocol was physician-led. The STRONG-HF trial is one of the most recent clinical trials evaluating GDMT use, and its protocol directed achievement of half target doses of GDMT prior to discharge in patients hospitalized for acute HF and full target doses at 2 weeks post-discharge [24]. In contrast, our protocol guides GDMT titration in a real-world, outpatient setting.

Finally, our cohort had a large proportion of underrepresented minorities in cardiology research. Almost half of our cohort identified as Hispanic or Latino with most of these patients identifying as White race. Almost 4 in 10 patients were women, while >4 in 10 patients were Black race. Our study demonstrated important clinical findings that can be applied to traditionally underrepresented groups in contrast to many clinical trials.

Our findings highlight the need to aggressively increase GDMT prescription rates to realize significant clinical outcomes. Our findings are particularly relevant and timely considering the systematically poor GDMT prescription rates among HFrEF patients in the United States [3]. Future research should investigate and target common barriers to real-world application of GDMT.

5. Limitations

Our study has a number of limitations. First, its retrospective design limits conclusions regarding causation. Second, our sample size was small. Third, the effect of usual care on GDMT up-titration and clinical outcomes in our population is unknown. Fourth, the protocol was implemented by a single physician which inherently introduces bias.

6. Conclusions

An aggressive, personalized physician-led protocol for GDMT titration in patients with HFrEF resulted in significant improvements in clinical outcomes, specifically heart rate, LVEF, NYHA classification, hospitalization, and mortality in a real-world setting. This protocol may help serve as a road map to lessen the gap between clinical knowledge and practice surrounding optimization of GDMT and move HFrEF patients toward a path to recovery.

Ethics approval

Institutional Review Board approval was obtained for this study.

Funding

This work received no funding.

CRediT authorship contribution statement

Crystal Lihong Yan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **David Snipelisky:** Supervision, Validation, Writing – review & editing. **Mauricio Velez:** Supervision, Validation, Writing – review & editing. **David Baran:** Supervision, Validation, Writing – review & editing. **Jerry D. Estep:** Supervision, Validation, Writing – review & editing. **E. Joseph Bauerlein:** Supervision, Validation, Writing – review & editing. **Nina Thakkar Rivera:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest.

Availability of data and materials

Not applicable.

Acknowledgements

The authors would like to acknowledge Ryan A. Gallo, PhD for his help creating the figures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100438.

References

[1] Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 392 (10159) (2018) 1789–1858.
[2] P.A. Heidenreich, B. Bozkurt, D. Aguilar, L.A. Allen, J.J. Byun, M.M. Colvin, et al., 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Circulation 145 (18) (2022) e895–e1032.
[3] S.J. Greene, J. Butler, N.M. Albert, A.D. DeVore, P.P. Sharma, C.I. Duffy, et al., Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry, J. Am. Coll. Cardiol. 72 (4) (2018) 351–366.
[4] S.J. Pocock, C.A. Ariti, J.J.V. McMurray, A. Maggioni, L. Køber, I.B. Squire, et al., Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies, Eur. Heart J. 34 (19) (2012) 1404–1413.
[5] M. Fiuzat, C.E. Hamo, J. Butler, W.T. Abraham, E.M. DeFilippis, G.C. Fonarow, et al., Optimal background pharmacological therapy for heart failure patients in clinical trials: JACC review topic of the week, J. Am. Coll. Cardiol. 79 (5) (2022) 504–510.
[6] G. Vergaro, N. Ghionzoli, L. Innocenti, C. Taddei, A. Giannoni, A. Valleggi, et al., Noncardiac versus cardiac mortality in heart failure with preserved, midrange, and reduced ejection fraction, J. Am. Heart Assoc. 8 (20) (2019) e013441.
[7] J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F. A. Martinez, et al., Dapagliflozin in patients with heart failure and reduced ejection fraction, N. Engl. J. Med. 381 (21) (2019) 1995–2008.
[8] A.H. Lin, J.C. Chin, N.M. Sicignano, A.M. Evans, Repeat hospitalizations predict mortality in patients with heart failure, Mil. Med. 182 (9) (2017) e1932–e1937.

[9] M.S. Khan, J. Sreenivasan, N. Lateef, M.S. Abougergi, S.J. Greene, T. Ahmad, et al., Trends in 30- and 90-day readmission rates for heart failure, Circ. Heart Fail. 14 (4) (2021) e008335.
[10] P.K. Srivastava, A.D. DeVore, A.S. Hellkamp, L. Thomas, N.M. Albert, J. Butler, et al., Heart failure hospitalization and guideline-directed prescribing patterns among heart failure with reduced ejection fraction patients, JACC Heart Fail. 9 (1) (2021) 28–38.
[11] K. Wang, E. Youngson, J.A. Bakal, J. Thomas, F.A. McAlister, G.Y. Oudit, Cardiac reverse remodelling and health status in patients with chronic heart failure, ESC Heart Fail. 8 (4) (2021) 3106–3118.
[12] D.G. Kramer, T.A. Trikalinos, D.M. Kent, G.V. Antonopoulos, M.A. Konstam, J. E. Udelson, Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach, J. Am. Coll. Cardiol. 56 (5) (2010) 392–406.
[13] J.J.V. McMurray, M. Packer, A.S. Desai, J. Gong, M.P. Lefkowitz, A.R. Rizkala, et al., Angiotensin–neprilysin inhibition versus enalapril in heart failure, N. Engl. J. Med. 371 (11) (2014) 993–1004.
[14] S. Ather, W. Chan, A. Chillar, D. Aguilar, A.M. Pritchett, K. Ramasubbu, et al., Association of systolic blood pressure with mortality in patients with heart failure with reduced ejection fraction: a complex relationship, Am. Heart J. 161 (3) (2011) 567–573.
[15] D. Kotecha, M.D. Flather, D.G. Altman, J. Holmes, G. Rosano, J. Wikstrand, et al., Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure, J. Am. Coll. Cardiol. 69 (24) (2017) 2885–2896.
[16] M. Böhm, K. Swedberg, M. Komajda, J.S. Borer, I. Ford, A. Dubost-Brama, et al., Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial, Lancet 376 (9744) (2010) 886–894.
[17] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey, M.M. Colvin, et al., 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, Circulation 134 (13) (2016) e282–e293.
[18] M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, et al., Cardiovascular and renal outcomes with empagliflozin in heart failure, N. Engl. J. Med. 383 (15) (2020) 1413–1424.
[19] B. Pitt, F. Zannad, W.J. Remme, R. Cody, A. Castaigne, A. Perez, et al., The effect of spironolactone on morbidity and mortality in patients with severe heart failure, N. Engl. J. Med. 341 (10) (1999) 709–717.
[20] F. Zannad, J.J.V. McMurray, H. Krum, D.J. van Veldhuisen, K. Swedberg, H. Shi, et al., Eplerenone in patients with systolic heart failure and mild symptoms, N. Engl. J. Med. 364 (1) (2010) 11–21.
[21] S.J. Greene, G.C. Fonarow, A.D. DeVore, P.P. Sharma, M. Vaduganathan, N. M. Albert, et al., Titration of medical therapy for heart failure with reduced ejection fraction, J. Am. Coll. Cardiol. 73 (19) (2019) 2365–2383.
[22] G.C. Fonarow, N.M. Albert, A.B. Curtis, W.G. Stough, M. Gheorghiade, J. T. Heywood, et al., Improving evidence-based care for heart failure in outpatient cardiology practices, Circulation 122 (6) (2010) 585–596.
[23] K. Balakumaran, A. Patil, S. Marsh, J. Ingrassia, C.L. Kuo, D.L. Jacoby, et al., Evaluation of a guideline directed medical therapy titration program in patients with heart failure with reduced ejection fraction, Int. J. Cardiol. Heart Vasc. 22 (2019) 1–5.
[24] A. Mebazaa, B. Davison, O. Chioncel, A. Cohen-Solal, R. Diaz, G. Filippatos, et al., Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial, Lancet 400 (10367) (2022) 1938–1952.
[25] J. Slade, M. Lee, J. Park, A. Liu, P. Heidenreich, N. Allaudeen, Harnessing the potential of primary care pharmacists to improve heart failure management, Jt. Comm. J. Qual. Patient Saf. 48 (1) (2022) 25–32.
[26] G.C. Fonarow, C.W. Yancy, N.M. Albert, A.B. Curtis, W.G. Stough, M. Gheorghiade, et al., Improving the use of evidence-based heart failure therapies in the outpatient setting: the IMPROVE HF performance improvement registry, Am. Heart J. 154 (1) (2007) 12–38.
[27] J. Zheng, T. Mednick, P.A. Heidenreich, A.T. Sandhu, Pharmacist- and nurse-led medical optimization in heart failure: a systematic review and Meta-analysis, J. Card. Fail. 29 (7) (2023) 1000–1013.