Original Work

Impact of Heart Failure Improvement Clinic on Guideline-Directed Medical Therapy Optimization in Adult Patients with Heart Failure with Reduced Ejection Fraction: A Retrospective Study

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Abstract

Background: Nearly 1 in 4 heart failure patients are re-hospitalized within 30 days of discharge. Continuity of care, with early optimization of guideline-directed medical therapy (GDMT), including a preferred beta-blocker, renin-angiotensin system inhibitor (RASi), mineralocorticoid receptor antagonist (MRA), and sodium-glucose cotransporter-2 inhibitor (SGLT2i), is crucial. However, these therapies remain suboptimal in patients with heart failure with reduced ejection fraction (HFrEF), defined as ejection fraction less than or equal to 40%.

Methods: We aimed to evaluate the impact of our rural health system's Heart Failure Improvement Clinic (HFIC) on initiation and titration of GDMT in adult patients with newly diagnosed or chronic HFrEF who were hospitalized between April 1, 2022, and December 31, 2022. Primary outcomes were GDMT changes from index hospital discharge to 30 days and 90 days post discharge for HFIC patients and non-HFIC patients.

Results: Among 163 patients, a total of 92 patients (56.4%) were managed by the HFIC during the trial period, and 71 (43.6%) were not managed by the HFIC. No significant difference was found in number of GDMT medications prescribed between HFIC and non-HFIC patients (average diff. 30 days: 0.17 vs. 0.03, p=0.154; 90 days: 0.29 vs 0.14, p=0.266). Regarding GDMT medication titration, HFIC patients had significantly greater improvement in total number of GDMT medications titrated to target dosing at 90 days compared to non-HFIC patients (average diff. 0.25 vs. 0.02, p=0.014).

Conclusions: This study demonstrated that management of HFrEF patients by a specialized heart failure clinic has the potential to improve GDMT dose optimization post-hospitalization.

Keywords: Heart Failure, Heart Failure with Reduced Ejection Fraction, HFrEF; GDMT; rural health

Despite advances in evidence-based treatment and strong guideline recommendations for medical management, heart failure remains a leading cause of morbidity and mortality in the United States (U.S.) and globally. Approximately 26 million individuals across the world and 6.2 million individuals in the U.S. have heart failure, with about half of these cases in the U.S. categorized as heart failure with reduced ejection fraction (HFrEF).[1,2] The burden of disease not only contributes to reduced quality of life and significant direct and indirect costs for patients, but also places tremendous financial strain on the U.S. healthcare system. Annual direct costs of heart failure are estimated at over 30 billion dollars, which are largely associated with hospitalizations. Nearly 1 in 4 heart failure patients are re-hospitalized within 30 days of discharge and approximately half are readmitted within 6 months.[1] Furthermore, costs are projected to grow to $69.8 billion by 2030.[3] Growing economic and patient impact of heart failure necessitates further evaluation of current practices in heart failure medication prescribing to determine areas for optimization that improve patient outcomes and in turn reduce unnecessary financial burden for healthcare systems.

Pivotal clinical trials demonstrate significant reductions in morbidity and mortality in the HFrEF patient population, driven by timely initiation and titration

of guideline-directed medical therapies (GDMT) to target or maximally tolerated doses. The new model for GDMT, also referred to as quadruple therapy, involves four core pillars, including renin-angiotensin system inhibitors (RASi), guideline preferred β-blockers (BB) (metoprolol succinate, carvedilol, and bisoprolol), mineralocorticoid receptor antagonists (MRA), and the most recent addition of sodium-glucose cotransporter-2 inhibitors (SGLT2i). However, GDMT remains suboptimal in patients with HFrEF. In 2018, the Change the Management of Heart Failure Patients (CHAMP) registry, a compilation of data from 3,518 HFrEF patients from 150 primary care and cardiology practices in the U.S. receiving at least one oral heart failure medication, demonstrated a significant gap in use and dose titration of GDMT, reporting that among eligible patients, 26%, 33%, and 66% were not prescribed RASi, BB, and MRA therapy, respectively. Furthermore, only 1% of patients eligible for all 3 medications were receiving target doses.[4] At the time of this CHAMP registry publication, SGLT2i were not FDA approved for the treatment of heart failure.

In response to emerging clinical trials over the past decade, the American Heart Association (AHA) in collaboration with the American College of Cardiology (ACC) and Heart Failure Society of America (HFSA) published significant updates to their Guideline for the Management of Heart Failure in 2022.[5] Guidelines now recommend initiation of sacubitril/valsartan over other renin–angiotensin system inhibitor (RASi) medications in HFrEF patients when possible. Another clinically significant update was in response to the EMPEROR-Reduced and DAPA-HF trials that demonstrated reduced risk of cardiovascular death or hospitalization

TABLE 1. Baseline Patient Characteristics at Index Hospital Discharge

	All patients	*Patients not enrolled in HFIC*	*Patients enrolled in HFIC*	*p-value*
N	163	71	92	
Age (years)	71.6 ± 13.2	71.0 ± 12.7	72.0 ± 13.7	0.637
Sex				
Female	53 (32.5)	26 (36.6)	27 (29.3)	0.416
Male	110 (67.5)	45 (63.4)	65 (70.7)	
HF Diagnosis				
Chronic HFrEF	98 (60.1)	38 (53.5)	60 (65.2)	0.177
Newly diagnosed HFrEF	65 (39.9)	33 (46.5)	32 (34.8)	
EF, %	31.2 ± 6.9	31.3 ± 6.5	31.1 ± 7.2	0.818
Other Baseline Characteristics				
BMI, kg/m2	31.3 ± 13.9	31.3 ± 7.2	31.3 ± 17.3	0.973
Systolic BP, mmHg	120.1 ± 17.8	121.5 ± 16.0	119.1 ± 19.0	0.398
Diastolic BP, mmHg	68.6 ± 11.2	70.2 ± 11.7	67.3 ± 10.7	0.098
Heart rate, bpm	75.2 ± 14.8	76.1 ± 15.9	74.6 ± 13.9	0.531
Potassium, mmol/L	4.0 ± 0.4	4.0 ± 0.5	4.1 ± 0.4	0.202
Sodium, mmol/L	137.1 ± 3.3	137.2 ± 3.4	136.9 ± 3.3	0.619
HbA1c, %	6.7 ± 1.5	6.9 ± 1.8	6.5 ± 1.3	0.537
BNP, pg/mL	911.1 ± 882.2	1002.7 ± 862.5	829.2 ± 898.1	0.273
BUN, mg/dL	25.7 ± 12.8	25.7 ± 12.3	25.7 ± 13.2	0.974
eGFR, ml/min/1.73m2	62.8 ± 19.4	62.9 ± 18.8	62.7 ± 19.9	0.954
Diabetes	83 (50.9)	36 (50.7)	47 (51.1)	1.000
Atrial Fibrillation (AF)	95 (58.3)	41 (57.7)	54 (58.7)	1.000
Chronic Obstructive Pulmonary Disease (COPD)	52 (31.9)	22 (31.0)	30 (32.6)	0.959
Coronary Artery Disease (CAD)	137 (84.0)	55 (77.5)	82 (89.1)	0.072
Chronic Kidney Disease (CKD)	87 (53.4)	33 (46.5)	54 (58.7)	0.164

Patient characteristics were measured at discharge. Mean ± SD reported for continuous variables with p-values generated from t-tests. Count and percentages reported for categorical variables with p-values generated from chi-squared tests.
Patients with missing values were excluded from univariate tests for the following variables: BMI (n=4), heart rate (n=1), potassium (n=3), sodium (n=3), BNP (n=38), BUN (n=3), eGFR (n=1)

for HFrEF patients with initiation of SGLT2i medications dapagliflozin and empagliflozin, regardless of diabetes status. Guidelines now recommend the initiation of SGLT2i medications as the fourth pillar of medication management in HFrEF patients.

With the recent guideline changes in the medical management of HFrEF, researchers are beginning to explore the potential benefits of a transition from traditional GDMT to quadruple heart failure therapy with an ARNi, BB, MRA, and SGLT2i. A cross-analysis of the EMPHASIS-HF, PARADIGM-HF, and DAPA-HF trials aimed to evaluate the potential benefits of quadruple therapy compared to an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and BB alone.[6] The study estimated an expected 62% reduction in risk of cardiovascular death or hospital admission for heart failure (HR 0.38; 95% CI [0.30-0.47]) with quadruple therapy compared to traditional therapy. The study projected a nearly 50% reduction in the risk of all-cause mortality (HR 0.53; 95% CI [0.40-0.70]) with implementation of quadruple therapy over traditional therapy. Furthermore, mortality and/or hospitalization benefits were seen as early as 14 to 30 days after initiation of quadruple therapy. Thus, early initiation and titration of GDMT is crucial for patient-centered clinical outcomes.

Although there is a clear potential benefit of initiation and up-titration of quadruple heart failure therapy, barriers to medication optimization exist. Unmodifiable factors, including medication contraindications, intolerances, and side effects can limit the initiation and titration of heart failure medications. However, modifiable factors such as medication cost, access to healthcare, and adequate continuity of care can be addressed to promote early initiation and titration of quadruple therapy and to improve outcomes for heart failure patients. Limited studies addressing the current prescribing practices and potential barriers to the adoption of new heart failure guideline recommendations for initiation and up-titration of quadruple heart failure therapy exist, especially in the space of a rural healthcare setting, where these challenges may be amplified. Specialized heart failure clinics in a rural health setting are uniquely positioned to increase continuity of care for patients post-discharge. The goal of this study was to evaluate the impact of a rural health system's Heart Failure Improvement Clinic (HFIC) on initiation and titration of GDMT in patients with HFrEF and associated survival and re-hospitalization outcomes. More than 2,000 patients are enrolled in the Marshfield Clinic Health System (MCHS) HFIC at any given time. MCHS HFIC is an interdisciplinary team consisting of a medical director, nurse practitioners (NPs), pharmacists, registered nurses (RNs), and other healthcare providers. Referrals to HFIC come from hospitalists, cardiologists, and primary care providers. Pharmacy is consulted to perform comprehensive medication reviews prior to each patient's first HFIC appointment. Better understanding of the barriers to initiation and titration of quadruple therapy, as well as current adoption of recent heart failure guideline updates, is critical for evaluating and addressing gaps in practice to improve real-world optimization of quadruple therapy. Addressing these barriers can lead to improved clinical outcomes and reduce the financial burden of re-hospitalizations due to suboptimal medical management of HFrEF. We sought to evaluate differences in survival and re-hospitalization outcomes between HFrEF patients managed by the HFIC compared to those not managed by the HFIC in relation to whether patients were initiated on and met target dosing of GDMT within a specified time period.

Methods

We conducted a multi-center, retrospective observational study of adult patients with HFrEF with an index hospital admission from April 1 to December 31, 2022, at an MCHS inpatient facility. The trial start date was selected to capture implementation of the most recent update in April 2022 of the AHA/ACC/HFSA Guideline for the Management of Heart Failure.[5] Patients were included if they were 18 years of age or older, had an index hospital admission to a pre-specified MCHS acute care site within the study time period with at least one of the pre-specified diagnosis ICD10 codes (Supplemental Table 1), and had an echocardiogram left ventricular ejection fraction ≤ 40% during their index hospitalization or within 90 days preceding their index hospitalization. Both patients with newly diagnosed HFrEF upon index hospitalization and chronic HFrEF were included. Heart failure did not need to be the primary discharge diagnosis. Chronic HFrEF was defined as having a diagnosis of heart failure, or HFrEF, specifically, with at least one prior documented echocardiogram ejection fraction of ≤ 40% prior to the index hospitalization. Newly diagnosed HFrEF patients were those with the first documentation of HFrEF diagnosis and echocardiogram ejection fraction ≤ 40% falling within their index hospitalization.

Exclusion criteria included patients participating in a clinical trial; patients receiving hospice or comfort care during the study period; patients with a history of or plan for heart transplantation during the trial period; patients with a primary care provider outside of MCHS; a baseline estimated Glomerular Filtration Rate

TABLE 2. Counts of Guideline Directed Medical Therapy (GDMT) and Other heart Failure (HF) Medications at Discharge, 30 and 90 Days Post Discharge

	Baseline	*30 days*	*90 days*
GDMT Medications			
Mean	1.9	2.0	2.1
Range	0-4	0-4	0-4
Other HF Medications			
Mean	1.2	1.1	1.0
Range	0-3	0-3	0-4
All HF Medications			
Mean	3.0	3.1	3.1
Range	0-6	0-5	0-7

(eGFR) of < 20 mL/min/1.73 m^2; and those with a history of left ventricular assist device (LVAD) implantation before the beginning of the study period. Additionally, if documentation within the electronic health record did not allow for determination of heart failure medication changes at 30- and 90-day time points, patients were excluded.

GDMT included guideline preferred beta-blockers (i.e., metoprolol succinate, carvedilol, bisoprolol), any RASi (ACEi, ARB, ARNi), SGLT2 inhibitors, and MRA as defined in Supplemental Table 2. Dosing of GDMT was defined in accordance with the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure (Supplemental Table 2) and study dosing was categorized according to guideline target dosing as meeting or not meeting minimum target dosing.[5] Other heart failure medications included diuretics, ivabradine, hydralazine/isosorbide dinitrate combination, hydralazine, isosorbide dinitrate, isosorbide mononitrate, digoxin, and vericiguat (Supplemental Table 2). Dosages of the four pillars of GDMT at index hospital discharge, 30 days, and 90 days post-discharge were abstracted from health records through manual chart review, along with chronic versus newly diagnosed HFrEF status. Other previously specified guideline heart failure medications at index hospital discharge, 30 days, and 90 days post-discharge were manually abstracted, along with dosing data collected for diuretic therapy, specifically. All other relevant baseline characteristics, demographics, laboratory values, and health history data were abstracted electronically, along with readmission and survival outcome data. Electronic data was validated through screening of a 10% subset of the study population. Primary outcomes of interest were GDMT changes within the period from index hospital discharge to 30 days and 90 days post-discharge for HFIC patients and non-HFIC patients within our health system. In addition, secondary goals included evaluation of 30- and 90-day survival following index hospitalization, with variables of interest including HFIC status and whether patients met or did not meet guideline target GDMT dosing within the 30- and 90-day timeframe. A descriptive look at reasons for suboptimal titration of GDMT medications was also explored. This study was deemed exempt from Institutional Review Board (IRB) review.

Number of GDMT medications, other heart failure medications, and all HF medications were described using mean and range at baseline, 30 days, and 90 days. GDMT medications were described in greater detail. For each medication class, the number and proportion of patients prescribed and optimally titrated were reported at baseline, 30, and 90 days. Average dose was also reported. Total number of GDMT medications prescribed and optimally titrated were also reported as proportions. Differences in medications prescribed and optimally titrated, and differences in average dose, were compared

TABLE 3. Survival and Hospital Free Survival Outcomes

	Hazard Ratio	*95% Confidence Interval*	*p-value*
90-Day Hospitalization-Free Survival			
Total GDMT medications initiated at baseline			
0 medications (Ref)	1.00	-	-
1 medication	1.57	0.41-5.99	0.510
2+ medications	2.23	0.58-8.59	0.250
Total GDMT medications at target dose at baseline			
0 medications (Ref)	1.00	-	-
1 medication	0.92	0.46-1.84	0.810
2+ medications	0.82	0.23-2.86	0.750
HFIC enrollment	1.20	0.67-2.15	0.540
Age, per 10 years	1.11	0.89-1.40	0.360
Female	1.64	0.94-2.86	0.083
Potassium, mmol/L	0.89	0.41-1.94	0.770
BUN, mg/dL	1.03	0.99-1.06	0.110
Sodium, mmol/L	1.04	0.93-1.15	0.510
eGFR, ml/min/1.73m^2	1.01	0.98-1.03	0.630
Survival			
Total GDMT medications initiated at baseline			
0 medications (Ref)	1.00	-	-
1 medication	0.14	0.03-0.75	0.022
2+ medications	0.21	0.04-1.07	0.061
Total GDMT medications at target dose at baseline			
0 medications (Ref)	1.00	-	-
1 medication	1.12	0.38-3.26	0.839
2+ medications	0.85	0.15-4.88	0.854
HFIC enrollment	0.93	0.39-2.23	0.872
Age, per 10 years	1.65	1.10-2.49	0.016
Female	0.60	0.18-2.01	0.404
Potassium, mmol/L	1.93	0.73-5.12	0.188
BUN, mg/dL	1.02	0.98-1.07	0.348
Sodium, mmol/L	0.88	0.78-1.00	0.043
eGFR, ml/min/1.73m2	1.00	0.96-1.04	0.863

Hazard ratios for 90-day hospitalization-free survival were estimated from a multivariate Fine-Gray subdistribution hazard model with death as a competing risk. Three patients were omitted for missing lab values. Hazard ratios for survival were estimated from a multivariate Cox proportional hazard model.
GDMT, guideline directed medical therapy; HFIC, heart failure improvement clinic; BUN, blood urea nitrogen; eGFR, estimated Glomerular Filtration Rate;

between patients enrolled in HFIC and patients not enrolled. Other heart failure medications were also described using counts, proportions, and average dose at baseline, 30, and 90 days.

Patient characteristics were measured at discharge. Continuous variables were described using means and SD, and categorical variables were described with counts and percentages. Comparisons of patient characteristics were made for the following comparison groups: (1) number of GDMT medications prescribed, (2) number of GDMT medications optimally titrated, (3) specific GDMT medication prescribed, and (4) specific GDMT medication optimally titrated compared to those sub-optimally titrated. Each of these comparisons were made at baseline, 30 days, and 90 days. No adjustment was made for multiple testing.

Hazard ratios for 90-day hospitalization-free survival were estimated from a Fine-Gray sub-distribution hazard model with death as a competing risk. Hazard ratios for survival were estimated from a Cox proportional hazard model. Covariates with $p<0.10$ in univariate Cox proportional hazard models for survival or hospitalization-free survival were included in the final model. Proportional hazards assumption was assessed using Schoenfeld residuals.

The distribution of dose adjustments (discontinued, no change, dose decreased, dose increased) for patients with suboptimal titration was reported for each GDMT medication at 30 and 90 days. Relative frequency of clinical presentations among sub-optimally titrated patients was also reported for each GDMT medication at 30 and 90 days. Reasons and clinical presentation for non-initiation of GDMT medications were also reported. Proportions were out of patients not prescribed a specific GDMT medication at 30 or 90 days. All analyses were completed in R 4.1.1 with the following packages: lubridate, tidyverse, survival, survminer, cmprsk, and aod.

Results

A total of 163 patients between April 1, 2022, and December 31, 2022, met study inclusion criteria. The average age was 71.6 years, with the majority identified as male (67.5%). A total of 92 patients (56.4%) were managed by the HFIC during the trial period, with the remaining 71 (43.6%) not managed by the HFIC. Approximately 60% of patients had chronic heart failure, while about 40% had newly diagnosed heart failure, with an average ejection fraction (EF) of 31.2% at baseline. There were no significant differences in baseline characteristics and labs between patients managed by the HFIC and those not managed by the HFIC. Patient characteristics and lab values at index hospital discharge are listed in Table 1.

On average, patients were prescribed two GDMT medications and 1 other HF medication at index hospital discharge, which remained consistent at 30 and 90 days post-discharge (Table 2). In the overall population, there was a significant increase in the total number of GDMT medications prescribed at 30 days and 90 days (average diff. 30 days: 0.11, p=0.026, 90 days: 0.22, p=0.001). At 90 days, 6.1% of patients were taking all 4 GDMT pillars, compared to 0.6% of patients at baseline. No significant difference was found in number of GDMT medications prescribed between HFIC and non-HFIC patients in the follow-up period (average diff. 30 days: 0.17 vs. 0.03, p=0.154; 90 days: 0.29 vs 0.14, p=0.266) (Figure 1, Supplemental Table 3).

In regard to GDMT medication titration in the overall population, there was a statistically significant improvement in total number of GDMT medications optimally titrated at 90 days (average diff. 0.15, p=0.003), but not at 30 days post-discharge (average diff. -0.01, p=0.639). Notably, HFIC patients had significantly greater improvement in total number of GDMT medications titrated to target at 90 days compared to non-HFIC patients (average diff. 0.25 vs. 0.02, p=0.014) (Figure 2, Supplemental Table 3).

Data regarding GDMT medication initiation and target dosing by medication class is displayed in Figures 3 & 4. In the overall population, roughly two-thirds of patients are prescribed any RASi at baseline. Similar rates were found for guideline recommended BB medications at baseline. Within the RASi pillar, patients tend to

FIGURE 1. Average Number of Guideline Directed Medical Therapy (GDMT) Medications Prescribed

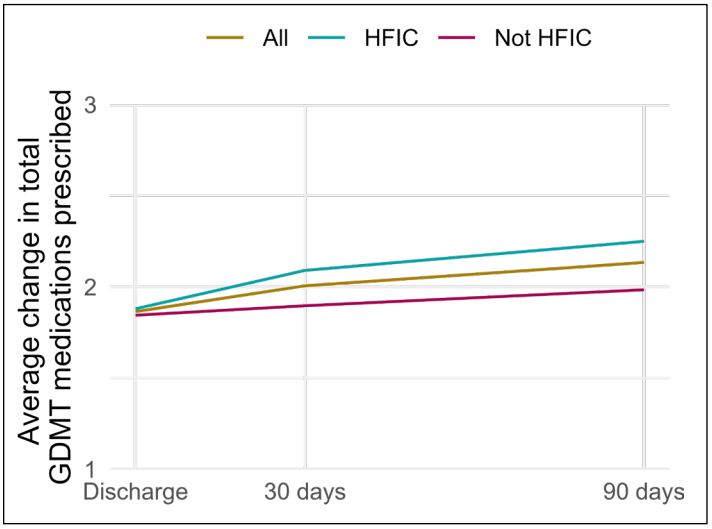
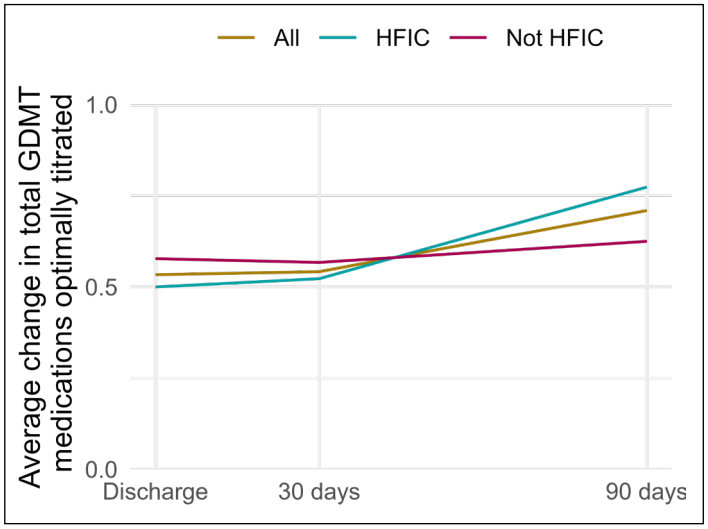


FIGURE 2. Average Number of Guideline Directed Medical Therapy (GDMT) Medications Optimally Titrated



discontinue ACEi medications or switch to an ARB or ARNi during the follow-up periods. Additionally, patients are less often prescribed an MRA and SGLT2i at baseline, but these medications are prescribed later during the follow-up period. In regard to dosing, there are small increases in average dose for all medication classes, with the exception of ARNis, which showed a larger increase in average dose from 54.3/58.2 mg to 91.8/96.7 mg during the follow-up period (Supplemental Table 4). The number of patients meeting target doses increased from 30 days to 90 days, usually by about 5-10% with SGLT2i, MRA, and ARB medications having the highest rate of patients meeting target dosing (88.5%, 52.1%, and 39.5% respectively).

When comparing GDMT medication initiation by class and whether or not target dosing was met, patients not managed by the HFIC were more often prescribed ACEi medications and at higher doses throughout the follow-up period, whereas patients managed by the HFIC were more often prescribed ARNis and at higher doses (Figures 5 & 6). Regardless of management, patients had similar prescription rates of guideline preferred and non-preferred BB medications at baseline. However, patients managed by the HFIC were more likely to be switched to a preferred BB. Furthermore, patients managed by the HFIC were more likely to be prescribed an MRA at baseline and throughout the follow-up period.

Patient characteristics associated with number of GDMT medications prescribed were assessed at baseline, 30 days, and 90 days post hospital discharge. Generally, patients with higher estimated glomerular filtration rate (eGFR) and a younger baseline age had a significantly higher number of GDMT prescribed at discharge, 30, and 90 days.

In regard to number of GDMT medications at target dose, patients with diabetes had more medications at target dose at baseline and 30 days. Younger age and lower baseline EF were associated with more medications at target dose at 90 days. Patients with no medications at target dose was associated with lower baseline heart rate.

Patient characteristics associated with initiation and titration to target dosing by medication class were explored. Notably, baseline characteristics of younger age, male sex, higher diastolic blood pressure, higher eGFR, and lower blood urea nitrogen were significantly associated with the presence of a RASi at discharge, 30 days, and 90 days. Additionally, chronic kidney disease was negatively associated with the presence of a RASi at discharge and throughout the follow-up period. Target dosing of RASi medications at discharge and throughout the follow-up period was significantly associated with higher baseline blood pressure readings, specifically systolic blood pressure at discharge and 30 days and diastolic blood pressure at 30 and 90 days.

For the overall population, mortality rate was 15% (n=25) between index hospitalization and March 2023. For patients that died, the median number of days to death was 64 days. Thirty-day and 90-day all-cause re-hospitalization rates were 23% (38/163) and 35% (57/163), respectively. For patients who were readmitted, the median number of days to readmission was 14 days. Multivariate analysis was used to evaluate the role of baseline characteristics and GDMT medication initiation and titration to target dosing on 90-day survival and hospitalization-free survival in the overall study cohort. Patients with one GDMT medication at discharge had 86% lower mortality hazard than patients without any GDMT medications (HR: 0.14, 95% CI: 0.03-0.75). Similarly, patients with two or more GDMT medications at discharge had 79% lower hazard of 90-day mortality, though this result did not meet the threshold for statistical significance (HR: 0.21, 95% CI: 0.04-1.07). Furthermore, an increase in age per 10 years was associated with 1.65 times the hazard of death (HR: 1.65, 95% CI: 1.10-2.49), while the baseline characteristic of higher serum sodium was associated with lower hazard

FIGURE 3. Prescription Rates by Drug Class

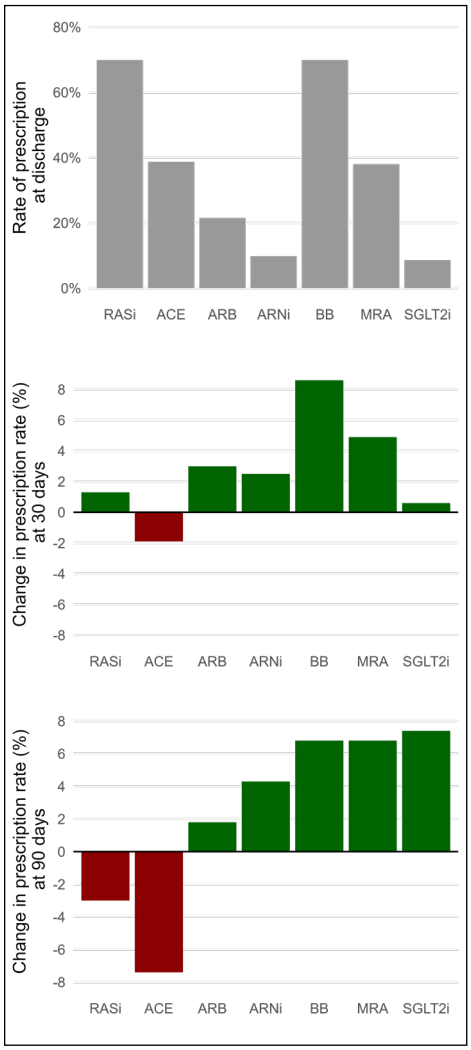
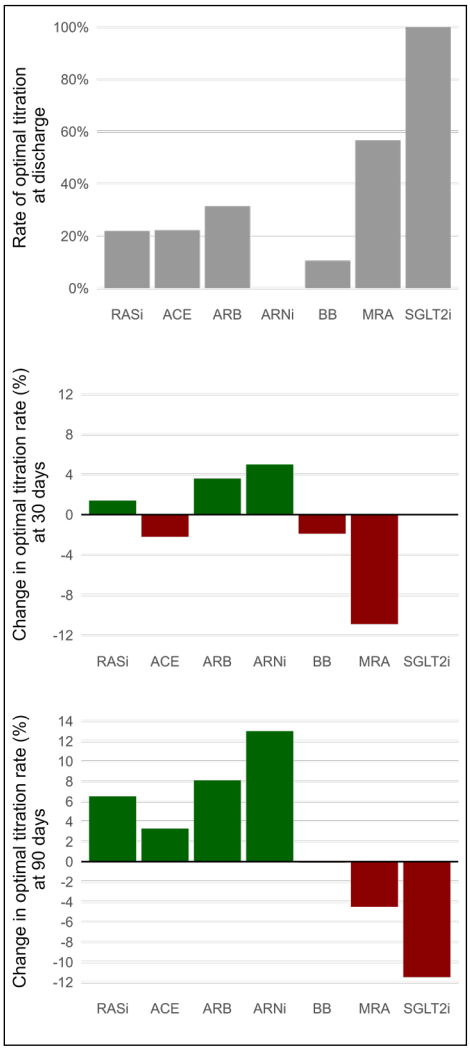


FIGURE 4. Titration Rates by Drug Class

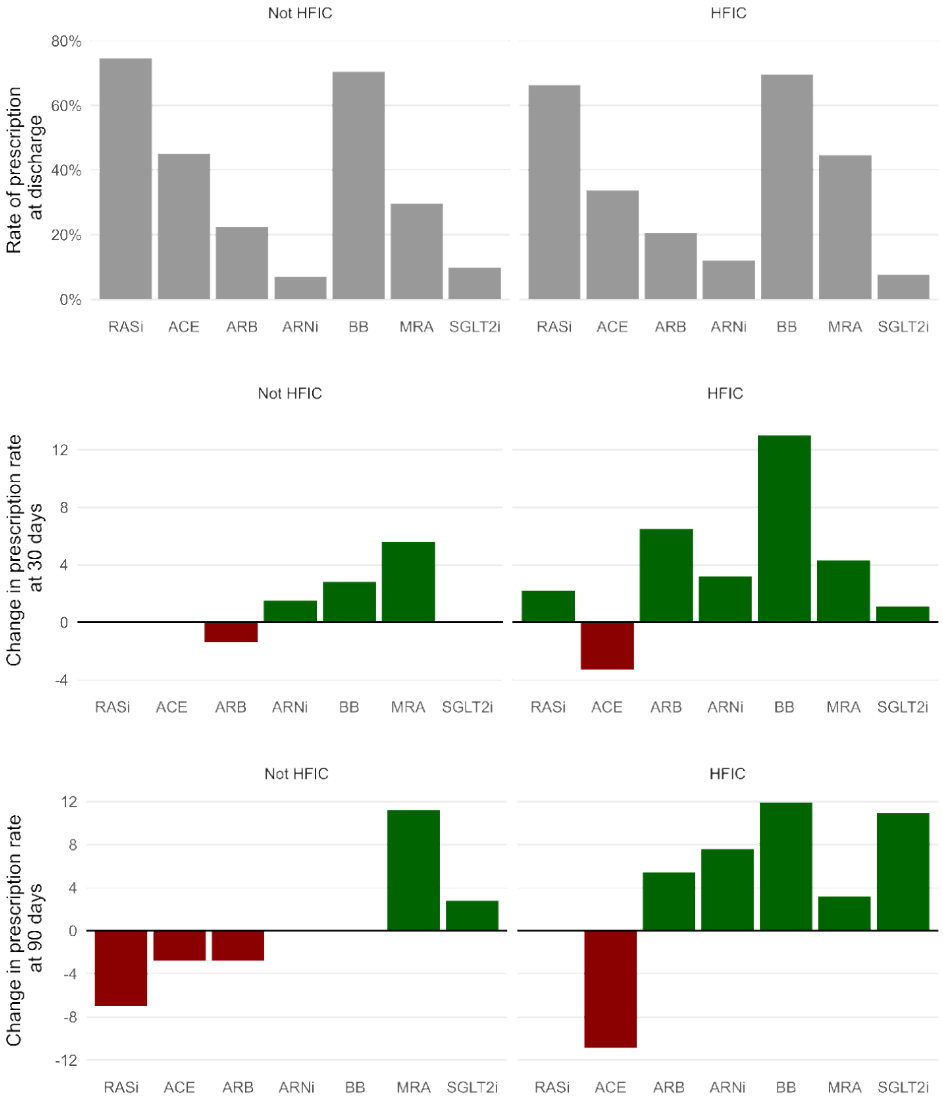


of death (HR: 0.88, 95% CI: 0.78-1.00). Additionally, the baseline characteristic of female sex was negatively associated with hospitalization-free survival. Female patients had a 64% greater hazard of readmission than male patients (HR: 1.64. 95% CI: 0.94-2.86), though this did not meet the threshold for statistical significance. There were no other significant risk factors for hospital-free survival in this cohort. Lastly, HFIC-enrolled patients did not show a statistically significant difference in 90-day survival or hospital-free survival compared to those not enrolled in the HFIC.

Reasons for suboptimal titration of GDMT medications were summarized. At 30 days, acute kidney injury and hypotension were the most common clinical presentations. Guideline medications with the highest proportion of discontinuations at 30 days were ACEi and MRA (14.6% and 15.8%, respectively), while ARNis had the highest proportion of patients with a dose increase (26.3%). At 90 days post-discharge, ACEi, MRA, and SGLT2i medications were most commonly discontinued, and bradycardia, dizziness/lightheadedness, and hypotension were among the most common clinical presentations.

Reasons for non-initiation were summarized. At 30 days post-discharge, contraindications were the most common reason for non-initiation, with cough and hypotension as the most common clinical presentations. Cost and insurance were prohibitive for ARNi and SGLT2i medications. These trends persisted at 90 days post-discharge.

FIGURE 5. Prescription Rates by Heart Failure Improvement Clinic (HFIC)



Discussion

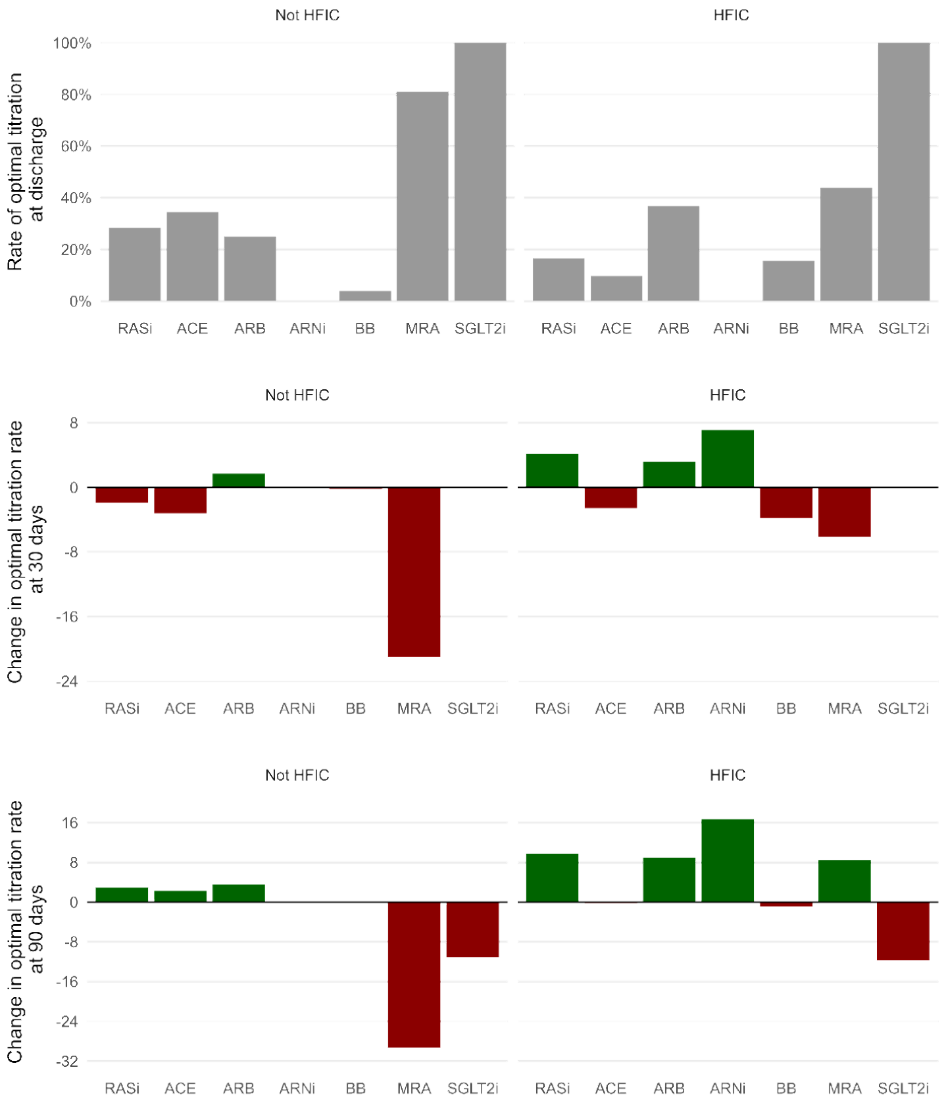
This study demonstrates several important findings regarding the initiation and titration of GDMT among the HFrEF study population as a whole and, in comparison, of HFIC patients and non-HFIC patients within a rural health system. Consistent with the current body of literature, initiation and titration of all 4 pillars of GDMT remain low within our HFrEF patient population. At 90 days, 6.1% of patients were taking all 4 GDMT pillars, compared to 0.6% of patients at baseline. An average of 2 GDMT medications were initiated at index hospital discharge and throughout the follow-up periods. Although data showed no significant difference in average GDMT medication counts between patients managed by the HFIC and those not managed by the HFIC, we did see a significant impact of the clinic on GDMT dose optimization within the follow-up period. Of note, the most significant dose titrations occurred between 30 and 90 days post-discharge for the overall population and for HFIC patients specifically. Emerging literature suggests a potential benefit of rapid GDMT initiation and titration in an inpatient setting, based on the idea that mortality and/or hospitalization benefit in pivotal trials was seen as early as 14 to 30 days for individual heart failure therapies.[7] However, more real-world data is needed to validate this new paradigm, and several clinical, health system, and logistical barriers may limit its implementation. The present study bridges the gap between this new paradigm and a more conservative practice, specifically looking for potential modifiable and non-modifiable factors limiting initiation and titration of all 4 pillars of GDMT, as well as presenting a specialized heart failure clinic as an alternative to inpatient GDMT initiation and titration. This clinic model has shown potential in encouraging close follow-up and prompt optimization of GDMT when clinically appropriate. Furthermore, the present study provides real-world data on the use of newer guideline additions, namely SGLT2i and ARNi medications, with the goal of building upon real-world evidence of quadruple therapy benefits on clinical outcomes for HFrEF patients.

In regard to patient-centered outcomes, patients managed by the HFIC did not show improved survival or hospital-free

survival outcomes compared to non-HFIC patients, though study duration was relatively short, and sample size was small, which may impact the ability to detect a statistically significant difference in survival outcomes. However, in the overall cohort, GDMT count appeared to impact survival. Initiation of at least one GDMT medication at discharge showed a protective effect on 90-day survival and initiation of two or more GDMT medications at discharge trended towards significance for improved survival. Other factors impacting survival included age and baseline serum sodium levels. Increased age per 10 years had a significant harmful effect on survival, whereas baseline higher serum sodium levels had a protective effect. Generally, younger patients appeared to be target candidates for initiation of more GDMT medications and titration of these medications to goal dosing. There were no significant risk factors found for hospital-free-survival, and though the baseline characteristic of female sex showed a negative association, this outcome did not reach the threshold of statistical significance.

Additionally, the present study demonstrates several key findings regarding GDMT medication initiation and dose optimization by medication class. In line with the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, data shows an overall shift from ACEi medications at discharge to ARB or ARNi medications during the follow-up period, indicating adoption within our health system, of guideline recommendations to use an ARNi when possible for RASi therapy.[5] Furthermore, data suggests an association between HFIC patients and higher rates of ARNi use at higher doses, compared to non-HFIC patients throughout the follow-up period. Additionally, low rates of MRA and SGLT2i medications at baseline, but increases later during the follow-up period, may indicate barriers to initiation of GDMT medications in an inpatient setting and the need for strong continuity of care to promote GDMT optimization in an outpatient setting. In particular, the non-formulary status of SGLT2i medications and reservation for continuation, rather than new start, within the inpatient setting of our health system, among other reasons, limits initiation of these medications to discharge and the outpatient setting.

FIGURE 6. Titration Rates by Heart Failure Improvement Clinic (HFIC)



Furthermore, data demonstrates the role of the HFIC in ensuring patients are initiated on or transitioned to appropriate guideline recommended BB therapy post-discharge. The HFIC allows for prompt follow-up within a week of hospital discharge to promote transition from non-preferred to preferred BB therapy.

This study specifically assessed barriers to GDMT initiation and titration, and reasons for discontinuation or de-escalation of GDMT were manually abstracted (e.g., medication contraindications, side effects, cost/insurance, patient preference, and specific patient characteristics). As anticipated, cost/insurance barriers were common reasons why ARNi and SGLT2i medications were not initiated, which may be a potential non-modifiable barrier to initiation of these newer guideline medications. Other common reasons for discontinuing, not initiating, or not titrating GDMT were medication side effects and contraindications. Although these barriers may limit GDMT optimization initially, close follow-up and continued assessment for changes in clinical status by a specialized heart failure clinic may allow for identification of opportunities for GDMT optimization. Addition of a similarly structured specialized interdisciplinary heart failure clinic consisting of NPs, pharmacists, and RNs could be incorporated into other rural health care practices.

This study has several limitations. The retrospective nature of the study design poses the potential for confounding variables. For example, baseline

characteristics were not matched between the HFIC group and the non-HFIC group, representing potential confounding variables. Additionally, reasons that GDMT medications were discontinued, not initiated, or not titrated were not always explicitly, consistently, or clearly documented in the electronic health record, making this endpoint difficult to manually abstract. Furthermore, patient adherence to GDMT medications could not be confirmed. As the time frame for the study was designed around the most recent heart failure guideline updates, the sample size is small, which may reduce statistical power. As there may be a lag between guideline updates and implementation of these updates in clinical practice, guideline updates may not have been fully employed for patients hospitalized earlier in the study period. An extension of this study is needed to fully assess implementation of the most current heart failure guidelines and long-term, patient-centered outcomes.

Conclusion

Heart failure remains a leading cause of morbidity and mortality. Despite the availability of evidenced-based guidelines, GDMT remains suboptimal in patients with HFrEF. This study demonstrated that management of HFrEF patients by a rural, specialized heart failure clinic has the potential to increase continuity of care, GDMT initiation and dose optimization of all 4 pillars. The study expands upon previous literature, specifically looking at real-world SGLT2i and ARNi utilization data, as well as identifying potential modifiable and non-modifiable barriers to GDMT initiation and titration. Pharmacist involvement in an interdisciplinary HFIC team can help identify candidates for GDMT and target dose titration opportunities.

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Supplement Tables

SUPPLEMENT TABLE 1. International Classification of Disease, Tenth Revision (ICD-10) Codes

ICD-10 Code	Classification	ICD-10 Code	Classification
I09.81	Rheumatic Heart Failure	I50.41	Acute Combined Systolic And Diastolic (Congestive)
I11.0	Hypertensive Heart Disease With Heart Failure	I50.42	Chronic Combined Systolic And Diastolic Heart Failure
I13.0	Hyp Hrt & Chr Kdny Dis W Hrt Fail And Stg 1-4/Unsp	I50.43	Acute On Chronic Combined Systolic And Diastolic Heart Failure
I13.2	Hyp Hrt & Chr Kdny Dis W Hrt Fail And W Stg 5 Chr	I50.814	Right Heart Failure Due To Left Heart Failure
I50.1	Left Ventricular Failure, Unspecified	I50.82	Biventricular Heart Failure
I50.2	Systolic (Congestive) Heart Failure	I50.83	High Output Heart Failure
I50.20	Unspecified Systolic (Congestive) Heart Failure	I50.84	End Stage Heart Failure
I50.21	Acute Systolic (Congestive) Heart Failure	I50.89	Other Heart Failure
I50.22	Chronic Systolic (Congestive) Heart Failure	I50.9	Heart Failure, Unspecified
I50.23	Acute On Chronic Systolic (Congestive) Heart Failure	I97.130	Post-procedural Heart Failure Following Cardiac Sur
I50.4	Combined Systolic And Diastolic (Congestive) Heart Failure	I97.131	Post-procedural Heart Failure Following Other Surge
I50.40	Unsp Combined Systolic And Diastolic (Congestive)		

SUPPLEMENT TABLE 2. Initial and Target Dosing Thresholds Per 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Drug	*Initial Daily Dose(s)*	*Initial Daily Dose(s)*
	ACEi	
Captopril	6.25 mg 3 times daily	50 mg 3 times daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Fosinopril	5-10 mg once daily	40 mg once daily
Lisinopril	2.5-5 mg once daily	20-40 mg once daily
Perinodopril	2 mg once daily	8-16 mg once daily
Quinopril	5 mg twice daily	20 mg twice daily
Ramipril	1.25-2.5 mg once daily	10 mg once daily
Trandolapril	1 mg once daily	4 mg once daily
	ARB	
Candesartan	4-8 mg once daily	32 mg once daily
Losartan	25-50 mg once daily	50-150 mg once daily
Valsartan	20-40 mg once daily	160 mg twice daily
	ARNi	
sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily
	Beta Blocker	
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25-50 mg twice daily
Carvedilol CR	10 mg once daily	80 mg once daily
Metoprolol succinate extended release (metoprolol CR/XL)	12.5-25 mg once daily	200 mg once daily
	MRA	
Spironolactone	12.5-25 mg once daily	25-50 mg once daily
Eplerenone	25 mg once daily	50 mg once daily
	SGLT2i	
Dapagliflozin	10 mg once daily	10 mg once daily
Empagliflozin	10 mg once daily	10 mg once daily
	Other Heart Failure Medications	
Loop diuretics: furosemide, bumetanide torsemide	ibravadine	hydralazine/isosorbide dinitrate combination
hydralazine	isosorbide dinitrate,	isosorbide mononitrate,
vericiguat	digoxin	hydrochlorothiazide
metolazone		

SUPPLEMENT TABLE 3. Counts and dosing status of Guideline Directed Medical Therapy (GDMT) medications for entire study population and by HFIC status

Follow	Mean Number of GDMT Medications			Mean Improvement at 30 days	p-value	Mean Improvement at 90 days	p-value
	Dis-charge	30 days	90 days				
Prescribed							
All patients	1.87	2.00	2.13	0.11	**0.026**	0.22	**0.001**
Non-HFIC	1.85	1.90	1.98	0.03	0.154	0.14	Oral
HFIC	1.88	2.09	2.25	0.17		0.29	Oral
Optimally Titrated							
All patients	0.53	0.54	0.71	-0.01	0.639	0.15	**0.003**
Non-HFIC	0.58	0.57	0.63	-0.04	0.306	0.02	**0.014**
HFIC	0.50	0.52	0.77	0.01	0.306	0.25	

SUPPLEMENT TABLE 4. Guideline Directed Medical Therapy (GDMT) counts and dosing by medication class

	Baseline			30 Days			90 Days		
	Initiated	Target	Dose (mg)	Initiated	Target	Dose (mg)	Initiated	Target	Dose (mg)
Prescribed									
Any RASi	114 (69.9%)	25 (21.9%)	--	116 (71.2%)	27 (23.3%)	--	109 (66.9%)	31 (28.4%)	--
ACE	63 (38.7%)	14 (22.2%)	8.9	60 (36.8%)	12 (20%)	8.8	51 (31.3%)	13 (25.5%)	11.1
ARB	35 (21.5%)	11 (31.4%)	46.8	40 (24.5%)	14 (35%)	44.7	38 (23.3%)	15 (39.5%)	48.2
ARNi	16 (9.8%)	0 (0%)	54.3-58.2	20 (12.3%)	1 (5%)	79.2-84	23 (14.1%)	3 (13%)	
BB	114 (69.9%)	12 (10.5%)	51.6	128 (78.5%)	11 (8.6%)	54.4	125 (76.7%)	13 (10.4%)	57.8
BB non-preferred	29 (17.8%)	--	65	13 (8%)	--	79.2	11 (6.7%)	--	77.3
MRA	62 (38%)	35 (56.5%)	20.8	70 (42.9%)	32 (45.7%)	19.7	73 (44.8%)	38 (52.1%)	20.2
SGLT2i	14 (8.6%)	14 (100%)	11.1	15 (9.2%)	15 (100%)	11.7	26 (16%)	23 (88.5%)	12
Total GDMT medications									
0	10 (6.1%)	92 (56.4%)	--	7 (4.3%)	87 (53.4%)	--	**7 (4.3%)**	**70 (42.9%)**	--
1	48 (29.4%)	56 (34.4%)	--	31 (19%)	54 (33.1%)	--	**32 (19.6%)**	**55 (33.7%)**	--
2	60 (36.8%)	14 (8.6%)	--	74 (45.4%)	13 (8%)	--	**54 (33.1%)**	**19 (11.7%)**	--
3	44 (27%)	1 (0.6%)	--	42 (25.8%)	0 (0%)	--	**46 (28.2%)**	**4 (2.5%)**	--
4	1 (0.6%)	0 (0%)	--	2 (1.2%)	1 (0.6%)	--	**10 (6.1%)**	**0 (0%)**	--

Non-preferred beta-blockers are not counted towards total GDMT medications