Use of Guideline-directed Medical Therapy in Patients ≥65 years after the Diagnosis of Heart Failure: A Canadian Population-based Study

by

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Abstract

Background: Guideline-directed medical therapy (GDMT) improves clinical outcomes in patients with heart failure (HF) with reduced ejection fraction (HFrEF). Despite proven efficacy, GDMT are under-utilized in clinical practice. The current study examines GDMT utilization after incident hospitalization for HF to promote medication initiation, and titration to target dosing within a reasonable time-period.

Methods: This observational study identified 66,372 patients with HFrEF with age ≥65 years and an incident HF hospitalization using administrative health data (2013-2018). GDMT (angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), β-blockers (BB), and mineralocorticoid receptor antagonists (MRA) received within the 6 months after hospitalization was evaluated by monitoring therapy combinations, optimal dosing (proportion receiving ≥50% of the target dose for ACEi/ARB/ARNI, and BB, and any dose of MRA), maximal and last dose assessed, and through a GDMT intensity score.

Results: Among patients with HFrEF, 4768 (7.2%) were on no therapy, 17,184 (25.9%), were on monotherapy, 30,912 (46.6%) were on dual therapy, 13,508 (20.4%) were on triple therapy. Only 8747 (13.2%) and 5484 (8.3%) achieved optimal GDMT based on the maximum dose and last dispensed dose, respectively, within 6 months post-discharge. Finally, 38,869 (58.6%) achieved <50% of the maximum intensity score, 23,006 (34.7%) achieved between 50-74% of the maximum intensity score, and 4497 (6.8%) achieved a score ≥75% of the maximum intensity score.

Conclusions: Current pharmacological management for patients with HFrEF does not align with the existing Canadian guidelines. Considering the gap in care, innovative strategies to optimize care in patients with HFrEF are needed.

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Table of Contexts

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List of Abbreviations

Guideline-directed medical therapy = GDMT

Heart failure = HF

Heart failure with reduced ejection fraction = HFrEF

Angiotensin converting enzyme inhibitors = ACEi

Angiotensin receptor blockers = ARB

Angiotensin receptor-neprilysin inhibitors = ARNI

β-blockers = BB

Mineralocorticoid receptor antagonists = MRA

Canadian Cardiovascular Society = CCS

Discharge Abstract Database = DAD

National Prescription Drug Utilization Information System = NPDUIS

International Classification of Diseases, version 10 = ICD-10

Charlson comorbidity index = CCI

The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure = GUIDE-IT

Change the Management of Patients with Heart Failure = CHAMP-HF

Left ventricular ejection fraction = LVEF

Introduction

With a yearly incidence of 50,000 and affecting approximately 600,000 Canadians, heart failure (HF) is a major health care problem.(1) Guideline-directed medical therapy (GDMT) with angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), β-blockers (BB), and mineralocorticoid receptor antagonists (MRA) have shown mortality and morbidity benefit in heart failure with reduced ejection fraction (HFrEF) in several landmark trials.(2–7) Unfortunately, observational studies of patients with HFrEF have shown sub-optimal initiation of HF-related pharmacotherapy post-diagnosis.(1, 8–10)

Several methods to evaluate GDMT have been proposed, including medication intensity scores,(11) opportunistic assessments and simple 'counting' of the number of medications in a class. Although there are advantages of summative methods (e.g. simple addition of a class as on/off), it fails to account for dosing which plays a major role in assessment in the quality of care. The current study utilizes dosing data and intensity scores to examine successful dose titration of GDMT throughout the study period.

The aim of current study was to examine the GDMT utilization in Canada in patients with HFrEF and a recent hospitalization, as defined by the Canadian Cardiovascular Society (CCS) guidelines in HF management.(11, 12) We explored trends of GDMT use over time, the different combinations of medical therapy and additionally, we explored GDMT dosing using a GDMT intensity score.

Methods

Study Design and Data Source

We conducted a population-based retrospective cohort study using the Discharge Abstract Database (DAD) and National Prescription Drug Utilization Information System (NPDUIS) datasets from the Canadian Institute for Health Information. The DAD contains data on admission dates, discharge dates, discharge disposition, primary and secondary diagnoses, procedures, and demographic information for all patients admitted to an acute care hospital in Canada except for the province of Quebec. Diagnoses are coded using International Classification of Diseases, version 10 (ICD-10) and procedures using the Canadian Classification of Health Interventions. NPDUIS database contains drug dispense data for adult Canadians covered by their provincial plan except for those from Quebec, Nova Scotia and the territories. Coverage varies across provinces, but all provinces cover ages 65 and older. The database contains drug dispense dates, drug description including drug dose, anatomic therapeutic chemical drug classification, drug supply and number of tablets/capsules dispensed. Data were linked longitudinally within and across datasets using a unique and anonymous patient identification number.

This study was approved by the University of Alberta Research Ethics Board (Pro00040008).

Patient Selection

Patients ≥65 years old with HF-related hospital admissions between October 1st 2013 and September 30th 2018 were identified using ICD-10 code I50.x as a primary or secondary diagnosis and followed-up for 6 months post-discharge. The study period and age criteria were

selected to allow data availability on drug prescriptions. Specifically, only patients ≥65 years old have universal drug coverage in Canada, thereby removing variables such as affordability of drugs which many be a factor for those under 65 years old. Patients hospitalized or residing in the provinces of Quebec, Nova Scotia and the territories were excluded as medication claims were not available for them. In patients with multiple HF admissions during the study period, the first admission was considered the index admission. To ensure that prevalent cases of HF were excluded, patients with a diagnosis of HF, any record of cardiac resynchronization therapy, implantable cardioverter defibrillator, or left ventricular assist device within five years prior to the index admission were excluded. Patients who died during the index admission were also excluded from the study. Figure 1 outlines the cohort selection process.

Study Variables

HFrEF

A simplified logistic model developed and validated by Uijl et al. (2020) was applied to differentiate between patients with HFrEF (ejection fraction < 40%) and non-HFrEF (ejection fraction ≥ 40%).(13) A prediction threshold of 0.44 was used to maximize the specificity and sensitivity of the model.(14) The variables incorporated in the Uijl model and their respective coefficients are provided in the Supplementary Table S1.

Other Medical History

Baseline patient characteristics were collected using demographic information at index hospitalization, and 6 months hospitalization and mediation history. Comorbidity was summarized using the Charlson comorbidity index (CCI).(14)

Pharmacotherapy

Pharmacotherapy achieved by the 6 months follow-up period was evaluated based on the drugs and doses recommended by the CCS HF guideline (Supplementary Table S2).(12) Pharmacotherapy treatment was classified as none, mono (1 drug class), dual (2 drug classes), and triple therapy (3 drug classes). The criteria for pharmacotherapy are defined in Supplementary Figure S1. In summary, any treatment with guideline recommended HF medications (ACEi/ARB/ARNI, MRA, BB) were included if dispensed with supplies lasting ≥14 days post index hospital discharge. If patients were on medication prior to index hospitalization, the medication was considered part of therapy if continued for ≥14 days post-discharge. Dual therapy was defined as two drug classes each dispensed with supplies lasting ≥14 days and overlapping for ≥7 days. Triple therapy was defined as three drug classes each dispensed with supplies lasting ≥14 days and overlapping for ≥7 days. A similar method was used by Deschaseaux et al. (2016) who also investigated treatment initiation patterns in HF. The overlap period used by Deschaseaux et al. was 14 days compared to the 7 days utilized in the current study.(15) We found no statistical difference between an overlap period of 14 days and 7 days when distinguishing dual therapy, and triple therapy (Supplementary Table S3). Any patients that did not meet the above conditions were considered to not be on pharmacotherapy.

Vital Status

Mortality status was assessed in two ways: The discharge disposition code in any subsequent hospitalization during the follow-up period was used to identify patients who died in-hospital. For these patients, the discharge date of the last hospitalization was recorded as the date of death. For patients who did not die during a subsequent hospitalization, we used the medication claims data. If a patient had no medication claims after a certain date, the last medication prescription

date was recorded as the date of death. Patients with death dates preceding the 6 months follow-up date were considered dead at 6 months post-index discharge.

GDMT dosage and Intensity

Dosage of medication was calculated as the proportion of recommended target dose. Target dose for each HF medication is listed in Supplementary Table S2. Optimal GDMT was defined as receiving ≥50% of the target dose for ACEi, ARB, or ARNI, and a BB, and any dose of MRA.(16)

Intensity of pharmacotherapy was approximated using a GDMT scale adapted from Januzzi et al.(2019).(17) Medication dosages were converted into the equivalent dose and summarized into a scaled score for each drug class (Supplementary Table S4). ACEi, ARB, ARNI and BB were scored from 0 to 5, while MRA was scored from 0 to 4. The scores were added and summarized as a proportion of 14, the maximum achievable GDMT score (triple therapy: ACEi/ARB/ARNI + BB + MRA). The proportion of maximum achievable GDMT for all patients with HFrEF was calculated daily for the duration of 6 months using medication dispensary data. This was done by dividing the total daily intensity score for each patient by the maximum achievable intensity score of 14. Patients were then categorized into groups that achieved <50%, 50-74% and ≥75% of the maximum achievable intensity scores using either the last day's intensity score, or the maximum intensity score during the 6 months period. The proportion of the maximum intensity score for all patients with HFrEF was averaged daily for 6 months post-HF hospitalization and plotted to observe average trend of GDMT intensity for patients over 6 months.

Statistical Analysis

Categorical variables were summarized as counts and percentages, while continuous variables were summarized as mean and standard deviation (SD) or median with interquartile range (IQR), as appropriate.

The proportion of patients on GDMT and optimal GDMT each year were plotted from the 2013 and 2018 fiscal years, and the overall trend of change was analyzed using linear regression.

A logistic regression model was developed to identify factors associated with triple therapy prescription among patients with HFrEF. The multivariable model controlled for sex, age, CCI, academic/community hospital type, urban/rural residence, income quintile, HF rehospitalization within 6 months of index discharge, use of calcium channel blockers, hydrochlorothiazide, and other diuretics . We excluded 1023 (1.5%) patients with HFrEF with missing values for urban/rural residence, income quintile, and hospital type. Model results are presented as odds ratios with 95% confidence intervals.

Sensitivity analysis was conducted using a subset of the cohort alive at 6 months post-index discharge. Pharmacotherapy classification, GDMT dosage and intensity were calculated using the alive cohort. All analyses were conducted using SAS Studio 3.8.

Results

Patient Characteristics

The study cohort consisted of 202,396 patients with incident HF hospitalization between October 2013 and September 2018. The mean age for the cohort was 81.3 years old, and 47.9% were male (Table 1). Based on the Uijl model, 32.8% (n=66,372) of the cohort had HFrEF. The median (IQR) CCI was 3 (2-4).

Medication Use

Among 66,372 patients with HFrEF, 13,508 (20.4%) were on triple therapy at any dose, 30,912 (46.6%) on double therapy, 17,184 (25.9%) on monotherapy, and 4768 (7.2%) were on no therapy (Figure 2). Supplementary Table S5 provides details on specific drug classification dispensed to patients in each therapy. Only 207 (1.5%) patients with HFrEF were on sodium-glucose transport protein 2 inhibitors (SGLT2i) and/or ivabradine. When considering all 66,372 patients with HFrEF, only 8747 (13.2%) achieved optimal GDMT based on the maximum dose within 6 months. According to the last dispensed dose, only 5484 (8.3%) patients with HFrEF were on optimal GDMT 6 months post-discharge. Moreover, between 2013 and 2018, there was an average of 1.2% (95% CI:1.0 – 1.4%) increase in the proportion of patients on GDMT (triple therapy at any dose) each fiscal year ($p<0.001$). There was an average of 0.6% (95%CI: 0.4 – 0.7%) increase in the proportion of patients on optimal GDMT each fiscal year($p<0.001$).

In the multivariable analysis of patients with HFrEF, women, patients who were treated in academic hospitals, and those who were re-hospitalized within 6-months of their index discharge had higher odds of achieving triple therapy. Conversely, patients with age ≥80 years, with more comorbidity, those residing in an urban setting, and those on calcium channel blockers

or hydrochlorothiazide were less likely to reach triple therapy compared to their counterparts (Table 2).

Intensity of Heart Failure Therapy

Of the patients with HFrEF, 38,869 (58.6%) achieved a score <50% (<7 points) of the maximum intensity score (14 points), 23,006 (34.7%) achieved between 50-74% (7-10.4 points) of the maximum intensity score, and 4497 (6.8%) achieved a score ≥75% (≥10.5 points) of the maximum intensity score (Figure 3). Observing the intensity score on the last day of the 6-month period, 52, 572 (79.2%), 11,992 (18.1%), and 1808 (2.7%) patients had intensity scores <50%, between 50-74%, and ≥75% of the maximum intensity score, respectively (Figure 3).

Including all patients with HF, 155,573 (76.9%) achieved a score of <50% of the maximum intensity score, 40,910 (20.2%) achieved a score between 50-74%, and 5913 (2.9%) achieved a score ≥75% of the maximum intensity score, when considering the peak dosage filled during the study period (Figure 3). Similarly, observing the intensity score on the last day of the 6-month period, 179,321 (88.6%), 20,777 (10.3%), and 2298 (1.1%) had intensity scores <50%, between 50-74%, and ≥75% of the maximum intensity score, respectively (Figure 3).

The mean proportion of the maximum intensity score for patients with HFrEF calculated daily over 6-months post discharge is shown in Figure 4. For patients on triple therapy, the mean proportion of the maximum intensity score increased from 0.44 to 0.47 between day 1 and 31, respectively. For all patients with HFrEF, the mean proportion of the maximum intensity score began at 0.31 on day 1 and continued to decline to a low of 0.25 on day 180 (Figure 4).

Sensitivity Analysis

A sensitivity analysis was performed using the sub-cohort of patients with HF who were classified as HFrEF and were considered alive at 6 months post-discharge (Figure 2). Of the

alive patients with HFrEF, 11,983 (21.4%) were on triple therapy and 3204 (5.7%) did not receive any pharmacotherapy within 6 months of discharge from index hospitalization (Figure 2). Moreover, 7996 (14.3%) of alive patients with HFrEF achieved optimal GDMT based on the maximum dispensed dosage within 6 months, and 4989 (8.9%) were on optimal GDMT at 6 months post-discharge according to the last dispense dose. The mean proportion of the maximum intensity score for alive patients with HFrEF increased slightly from 0.43 to 0.48 between day 1 to 31, then declined to 0.44 on day 180 (Supplementary Figure S2).

Discussion

In this national observational study of patients with incident HF-related hospitalization, we found that achieving optimal GDMT within 6 months of a hospitalization is an area requiring greater attention. First, we identified that approximately one-fifth of patients with HFrEF are achieving triple therapy at any or optimal dose by 6 months after a HF hospitalization. Early initiation of optimal GDMT after index-HF hospitalization has proven to increase adherence and improve mortality outcomes.(18) The exploration of the 6-month window allows for potential delays in care or further optimization of therapy, however, it does not appear that this is occurring. Second, although patients with HFrEF achieved a higher intensity of pharmacotherapy compared to patients with HF without reduced EF, more than half of patients with HFrEF fail to achieve ≥50% of the maximal possible intensity score. Higher intensity of GDMT has been shown to be associated with better outcomes.(17) This study demonstrated the gap in achieving optimal GDMT in patients with HFrEF remains wide, even in a publicly funded system with universal healthcare.

An externally validated model developed by Uijl et al. to identify patients with HFrEF using ICD-10 codes was used in the current study.(13) Unless prescribed for comorbid conditions, the aforementioned medications are only shown to provide morbidity and mortality benefit in patients with HFrEF.(11) In our cohort, 32.8% of patients were identified as HFrEF, which is similar to reports from other HF cohorts.(19) However, these results should be interpreted understanding the limitations of the model used for identifying potential patients with incident HFrEF. The simplified Uijl model had a specificity (accurate HFrEF prediction) of 83.1% for predicting EF ≥40% when sensitivity and specificity is maximized using prevalence

data.(13) Compared to incident HF cohorts, prevalence HF cohorts are shown to yield higher percentages of HFrEF.(20, 21)

Notably, 7.2% of patients with HFrEF in this study received no ACEi/ARB/ARNI, BB or MRA in the 6 months post-hospitalization, and 25.9% received only monotherapy. Our findings confirmed previous observations of suboptimal initiation of HF medications after HF diagnosis. For instance, 23.3% of patients with HFrEF did not receive any HF pharmacotherapy, and 22.1% received only monotherapy during the first year after diagnosis in the United States,(8) and this under-utilization was shown to be linked to poorer outcomes.(22) The current study observes data prior to the inclusion of SGLT2i and ivabradine into the CCS guidelines. Consequently, inconsequential number of patients were on either medication and were therefore not included in the study.

Overall, 20.4% of patients with HFrEF were on triple therapy at any dose at 6 months of index hospitalization. Optimal GDMT, defined as receiving ≥50% of the target dose for ACEi/ARB/ARNI, and BB, and any dose of MRA, was achieved only in 13.2% of patients with HFrEF based on the maximum dispensed dosage within 6 months. The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial demonstrated similar results, with 15.5% of patients with HFrEF achieving optimal GDMT at 6 months.(16) Even with biomarker-guided GDMT titration, many patients in GUIDE-IT trial did not achieve optimal GDMT, which was attributed to patients being either clinically stable, or already at maximally tolerated therapy.(23) Similarly, medication data from the CHAMP-HF (Change the Management of Patients with Heart Failure) registry, which included outpatients with HFrEF in the United States receiving ≥1 oral HF medication, also showed underutilization of HF medications individually or in combination.(9) In that study, only 1.0% of eligible patients were

treated with triple-therapy at target doses, while 22.1% of patients were treated with any dose of triple-therapy.(9)

Reasons for underutilization of GDMT is likely multifactorial. Concordant with our findings, older age, those with more comorbidities and advanced New York Heart Association (NYHA) functional class (III and IV) have been reported as factors associated with less intense medication titration (1, 24). These patients are also at the greatest absolute risk and have often similar outcomes on GDMT in clinical trials. Our study also demonstrates that patients on calcium channel blockers and hydrochlorothiazide are less likely to achieve GDMT. Although observational, this may coincide with precipitating side effects (i.e. hypotension) that prevent initiation or up-titration of GDMT; consequently, physicians should prioritize GDMT over non-GDMT anti-hypertensives. Rehospitalization, on the other hand, increases the rate of GDMT usage in patients with HFrEF, potentially indicating severity of condition as a justification for aggressive GDMT titration.

The GDMT intensity score data provides information on aggressiveness of dose titration within the 6 months after index-hospitalization. In the current study, only 41.4% of patients with HFrEF achieved a score ≥50% of the maximal intensity score; however, patients with HFrEF are appropriately achieving higher intensity of pharmacotherapy compared to all patients with HF. The mean proportion of the maximum intensity score for all patients with HFrEF was calculated daily over 6 months post discharge; in summary, it showed a gradual decline throughout the study period (Figure 4). Notable periods where a steeper decline in intensity scores appear are days 31 and 91, likely corresponding to timing of medication refill, or assessment for side effects, or intolerance by the physician. Nonetheless, higher intensity of GDMT is associated with lower mortality rates;(17) therefore, the intensity scores and trends noted in the current

study require significant improvement. However, the current study shows an overall yearly increase in the proportion of patients on GDMT, both at any and optimal dosing, between 2013 and 2018 (Figure 5). Translation of guidelines into clinical practice may take years, but the trend is reassuring.

The strengths of the current study include the use of a large sample size from a representative cohort in a universal health care system, thereby mitigating interprovincial variables and establishing generalizable results. The current study also provides insight into prescription and adherence patterns in single-payer, largely public healthcare systems; whereas previous studies have largely looked at data from the United States, a multi-payer, heavily private system. The focus on patients ≥65 years of age also removes variables such as drug affordability, which may affect filling prescriptions, due to universal drug coverage being available to this age cohort in Canada. We infer that prescribing patterns, however, should not change for those younger than 65 years old. The study also has potential limitations. As mentioned, the cohort is limited to patients ≥65 years of age, therefore the results may not be entirely generalizable to the younger HFrEF population. In an epidemiological study of patients in Australia with HFrEF ≥45 years of age, 42.3% of patients were between 45-64 years of age.(25). As an observational study, there is potential for unmeasured confounders. The lack of echocardiography-based left ventricular ejection fraction (LVEF) data, and utilization of an administrative data-based model to predict LVEF in patients with HF, may result in misclassification bias. Moreover, due to the lack of out-of-hospital mortality data, we assumed that those without any prescription dispense during the follow-up period were deceased. Finally, the analysis utilizes records of medications that were dispensed, but does not include prescriptions that were not filled, or indicate if they were taken as prescribed.

Conclusion

Achieving optimal GDMT in patients with HFrEF post-index HF-related hospitalization remains suboptimal. Current clinical practice, where optimal pharmacological management of HFrEF falls short, does not align with the existing evidence that supports aggressive titration of GDMT post-HF diagnosis. Considering the observed gap in care, further studies are required to investigate innovative strategies to optimize the HF care in this patient population.

Clinical Perspectives

The current study outlines the care gaps evident in the treatment of patients with HFrEF. GDMT has significant morbidity and mortality benefits; unfortunately, current practice fails to initiate and titrate medications effectively. Solutions to improve GDMT post-discharge include more frequently scheduled outpatient appointment at the time of discharge (i.e. every 4-6 weeks where possible); lack of follow-up appointments may explain some of the issues with slow titration. Clinician's should also prioritize GDMT over non-GDMT antihypertensives when initiating and titrating medications.

Translational Outlook

GDMT initiation and titration in patients with HFrEF remains sub-optimal. Further studies are required to determine strategies to optimize GDMT therapy in these patients. Research should focus on determining causal factors influencing poor GDMT prescribing patterns and establishing solutions to counteract these problems.

Tables

Table 1. Patient demographics and clinical characteristics at index HF diagnosis

	All patients with HF (n=202,396)	**Patients with HFrEF (n=66,372)**
Age, year; mean (SD)	81.3 (8.5)	79.3 (8.1)
Male sex, n(%)	97,028 (47.9)	51,180 (77.1)
Income Quintile, n(%)		
1 (lowest)	53,092 (26.2)	16,263 (24.5)
2	45,518 (22.5)	14,679 (22.1)
3	39,251 (19.4)	13,317 (20.1)
4	32,922 (16.3)	11,243 (16.9)
5 (highest)	29,928 (14.8)	10,351 (15.6)
Residence type, n(%)		
Rural	39,180 (19.4)	13,536 (20.4)
Urban	162,129 (80.1)	52,521 (79.1)
Hospital type, n(%)		
Academic	68,872 (34.0)	23,364 (35.2)
Community	133,517 (66.0)	43,007 (64.8)
HFrEF, n(%)	66,372 (32.8)	66,372 (100.0)
Alive 6 months post index, n(%)	166,169 (82.1)	55,882 (84.2)

HF rehospitalization within 6 months of index discharge	45,356 (22.4)	14864 (22.4)
Comorbidities, n(%)		
Hypertension	101,265 (50.0)	24,578 (37.0)
Diabetes	74,413 (36.8)	27,239 (41.0)
Chronic obstructive pulmonary disease	42,499 (21.0)	10,005 (15.1)
Ischemic heart disease	61,234 (30.3)	27,329 (41.2)
Atrial fibrillation	78,865 (39.0)	19,183 (28.9)
Renal disease	28,103 (13.9)	8,455 (12.7)
Charlson comorbidity index, Median (IQR)	3 (2-4)	3 (1-4)
Medication History, n(%)		
ACEi/ARB	89,082 (44.0)	45,807 (69.0)
Betablocker	128,265 (63.4)	59,461 (89.6)
MRA	31,243 (15.4)	19,955 (30.1)
Digoxin	23,322 (11.5)	9,673 (14.6)
Diuretics	151,468 (74.8)	59,086 (89.0)
Calcium channel blockers	81,885 (40.5)	26,412 (39.8)
Hydrochlorothiazide	24,954 (12.3)	8,648 (13.0)

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; IQR: interquartile range; MRA: mineralocorticoid receptor antagonist; N: number; SD: standard deviation.

Table 2. Adjusted odds ratios (OR) for being on triple therapy compared to not on triple therapy for patients with HFrEF.

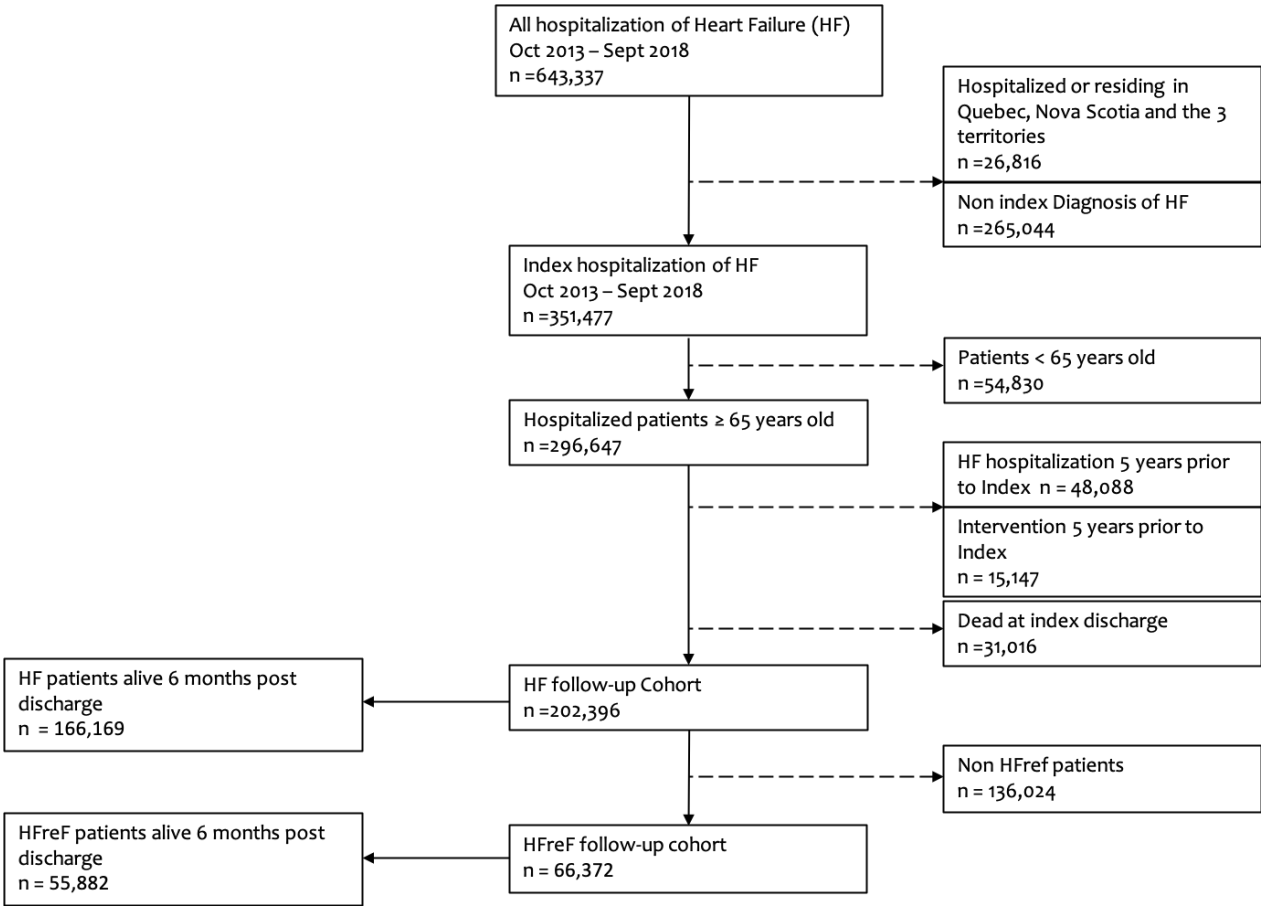
Factor	Adjusted OR (95%CI)	p-value
Sex		
Male (ref)		
Female	**1.52 (1.46 – 1.59)**	**<0.0001**
Age		
65-79 yrs (ref)		
≥ 80 yrs	**0.58 (0.56 – 0.60)**	**<0.0001**
Residence		
Rural (ref)		
Urban	**0.96 (0.91 – 1.01)**	**0.08**
Income quintile		
Lowest 1 (ref)		
2	**1.07 (1.01 – 1.13)**	**0.02**
3	**1.08 (1.02 – 1.14)**	**<0.01**
4	**1.04 (0.98 – 1.10)**	**0.24**
Highest 5	**1.08 (0.98 – 1.11)**	**0.16**
Hospital type		
Community (ref)		
Academic	**1.15 (1.10 – 1.20)**	**<0.0001**

Comorbidity **Higher CCI score**	**0.91 (0.90 – 0.92)**	**<0.0001**
Other diuretics **No (ref)** **Yes**	**1.69 (1.57 – 1.81)**	**<0.0001**
Calcium channel blockers **No (ref)** **Yes**	**0.66 (0.64 – 0.69)**	**<0.0001**
hydrochlorothiazide **No (ref)** **Yes**	**0.79 (0.75 – 0.84)**	**<0.0001**
re-hospitalized with 6 months of index discharge **No (ref)** **Yes**	**1.41 (1.35 – 1.47)**	**<0.0001**

Multivariable logistic regressions were used. CCI: Charlson Comorbidity Index; CI: confidence interval; HFrEF: heart failure with reduced ejection fraction; OR: odds ratio.

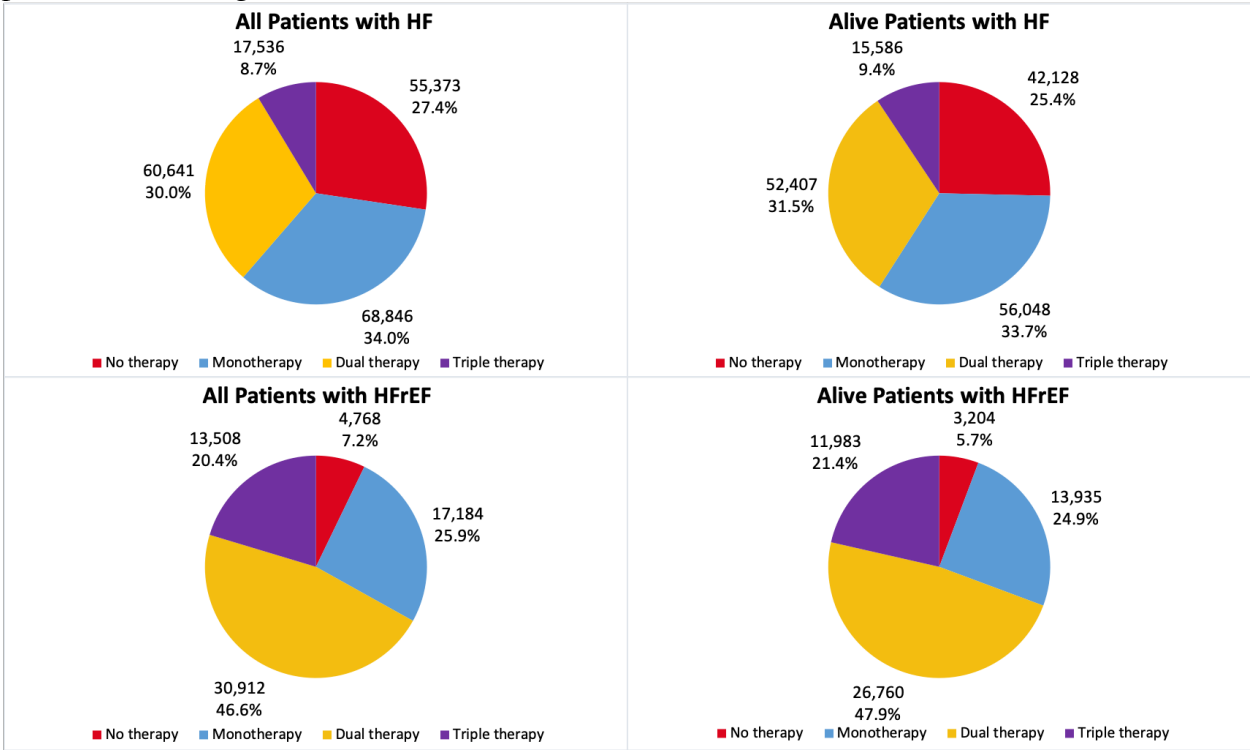
Figures

Figure 1. Study flow diagram.



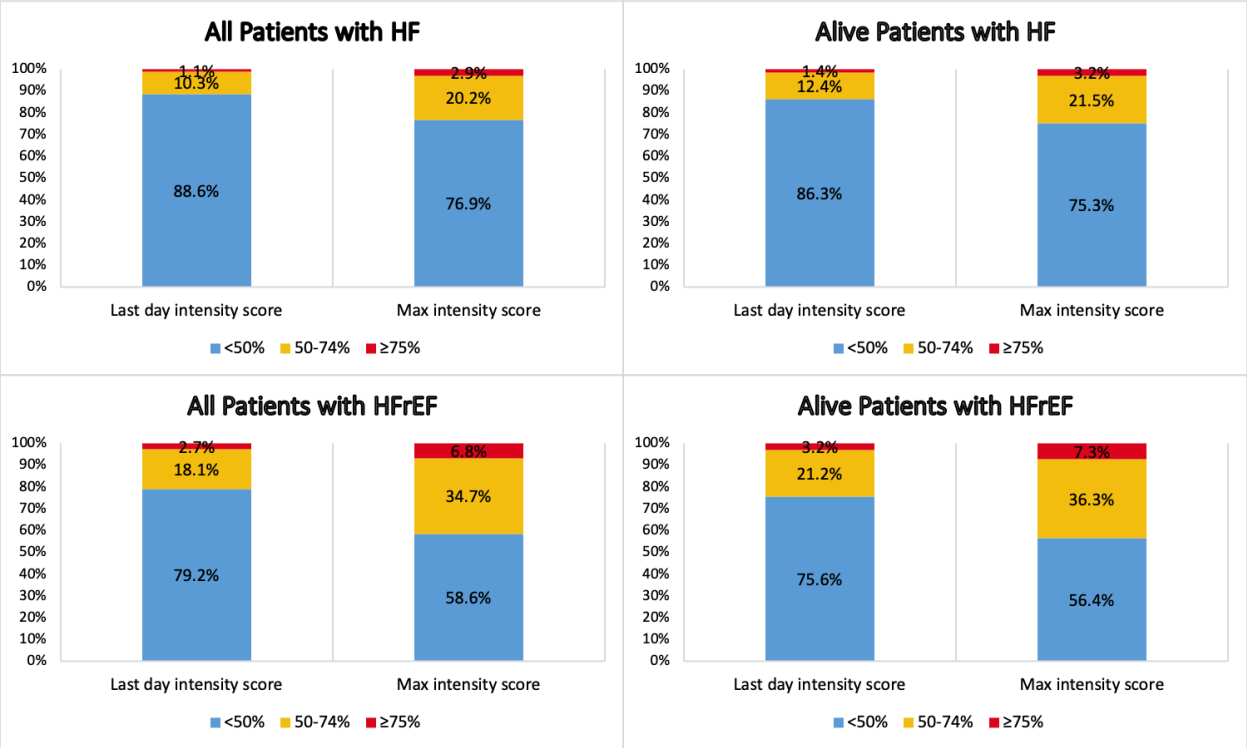
HF: heart failure; HFrEF: Heart failure with reduced ejection fraction; n: number.

Figure 2. Pharmacotherapy achieved by patients with HF and those with HFrEF by 6 months post index discharge.



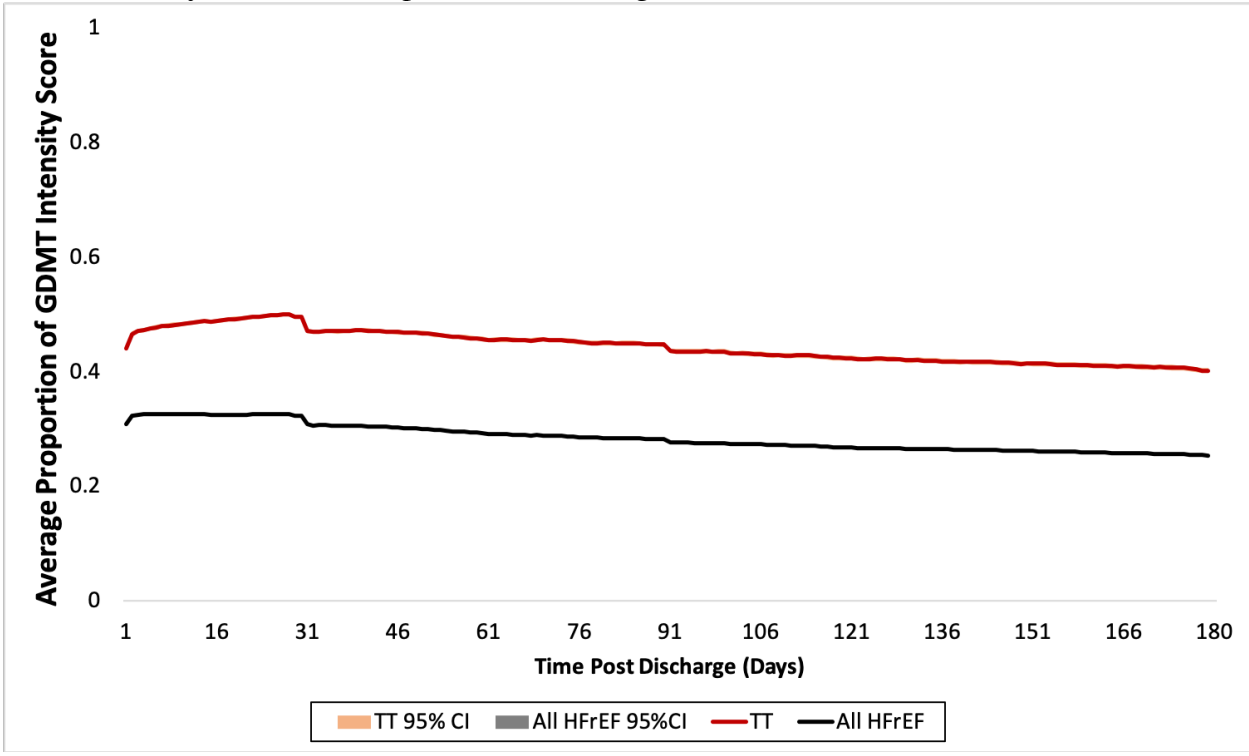
HF: heart failure; HFrEF: Heart failure with reduced ejection fraction.

Figure 3. Categorization of patients with HF by proportion of maximum GDMT intensity score achieved.



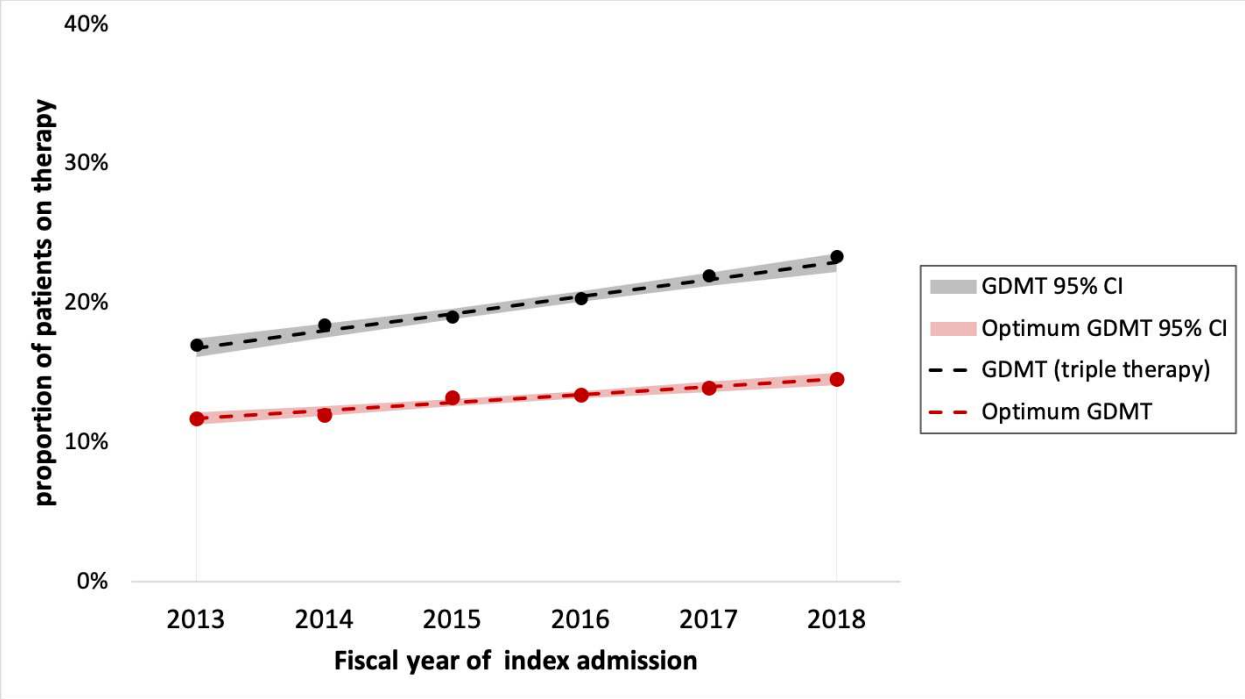
Intensity scores were calculated for each patient using either the last day therapy or the maximum therapy dose within 6 months post index, then divided by the maximum achievable Intensity score. HF: heart failure; HFrEF: heart failure with reduced ejection fraction

Figure 4. Average proportion of maximum GDMT Intensity score for patients with HFrEF calculated daily over 6 months post index discharge.



Each data points are the average intensity scores with 95% CI for all patients with HFrEF (black, n=66,372) or patients with HFrEF on triple therapy (red, n=13,508) divided by the maximum achievable Intensity score. GDMT: guideline-directed medical therapy; HFrEF: heart failure with reduced ejection fraction; TT: triple therapy.

Figure 5. Trend of GDMT between 2013 and 2018.



Black; proportion of patients on triple therapy at any dose each fiscal year (%). Red; proportion of patients on optimum GDMT each fiscal year. Optimum GDMT defined as receiving ≥50% of the target dose for ACEi/ARB/ARNI, ≥50% of the target dose for BB, and any dose of MRA.

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Appendix/Supplementary Material

Supplementary Table S1. Uijl Model coefficients and codes.

Variable	Coefficient ln(OR)	ICD / CCI / ATC codes	When measured
Intercept	0.3646		
Age (> 75yrs)	0.2776		At index
Sex (female)	0.6881		at index
Ischemic heart disease	-0.2485	I21 – I25	1 year prior to index + 30 days post index
Anemia	0.2070	D50-D53, D55-D64	1 year prior to index + 30 days post index
Atrial fibrillation	0.4187	I48.x	1 year prior to index + 30 days post index
COPD	0.2070	J41.x, J42.x, J44.x, J43.x	1 year prior to index + 30 days post index
Diabetes	0.0583	ICD10: E10, E11, E12, E13, E14	1 year prior to index + 30 days post index
Hypertension	0.5306	I10, I11 I15, I12, I13	1 year prior to index + 30 days post index
Valvular disease	0.1222	I05.0, I05.1, I05.2, I05.8, I05.9, I06.0, I06.1, I06.2, I06.8, I06.9, I08.0, I08.8, I08.9, I07.1, I07.2, I07.8, I09.89, I09.1, I09.9, I09.81, I09.89, Z95.3, Z95.2, 1.HU, 1.HS, 1.HT, 1.HV, 1.HW	1 year prior to index + 30 days post index
Malignant cancer	0.0862	C00.x–C26.x, C30.x–C34.x, C37.x– C41.x, C43.x, C45.x–C58.x, C60.x– C76.x, C77.x–C80.x, C81.x–C85.x, C88.x, C90.x–C97.x	3 year prior to and including index
Device therapy (implantable	-1.0788	CRT (CCI codes: 1.HZ.53.GR-NM, 1.HZ.53.LA-NM,	1 year prior to index + 30 days post index

cardioverter defibrillator or cardiac resynchronization therapy)		1.HZ.53.QA-NM, 1.HZ.53.GR-NK, 1.HZ.53.LA-NK, 1.HZ.53.QA-NK, 1.HZ.53.GR-NL, 1.HZ.53.LA-NL, 1.HZ.53.QA-NL, 1.HZ.53.GR-FR, 1.HZ.53.LA-FR, 1.HZ.53.SY-FR), ICD (CCI codes: 1.HZ.53.GR-FS, 1.HZ.53.HA-FS, 1.HZ.53.LA-FS, 1.HZ.53.SY-FS)	
RAAS inhibitor use	-0.7765	C09A C09B, C09C C09D	6 months prior to index + 30 days post index
Beta blocker use	-0.5978	C07	6 months prior to index + 30 days post index
MRA	-0.3711	C03DA01, C03DA04	6 months prior to index + 30 days post index
Digoxin	-0.1985	C01AA05	6 months prior to index + 30 days post index
Diuretics	-0.3011	C03CA01, C03CA02, C03CA04, C03CC01, C03AA01, C03AA03, C03AA08, C03BA04, C03BA08, C03BA11, C03DB01 C03DB02 C03EA01	6 months prior to index + 30 days post index

Supplementary Table S2. Evidence based heart failure medication and doses recommended by the Canadian Cardiovascular Society

Medication Class	**Drug Name**	**Target Dose**	**ATC code**
ACEi	Enalapril	10 mg BID	C09AA02, C09BA02, C09BB02, C09BB06
	Lisinopril	20 mg	C09AA03, C09BA03, C09BB03
	Perindopril	4 mg	C09AA04, C09BA04, C09BB04, C09BX02
	Ramipril	5 mg BID	C09AA05, C09BA05, C09BB05
	Trandolapril	4 mg	C09AA10, C09BB10
ARB	Candesartan	32 mg	C09CA06, C09DA06, C09DB07
	Valsartan	160 mg BID	C09CA03, C09DA03, C09DB01, C09DB08, C09DX01, C09DX02, C09DX04, C09DX05
MRA	Spironolactone	50 mg	C03DA01
	Eplerenone	50 mg	C03DA04
BB	Carvedilol	25 mg BID	C07AG02, C07FX06
	Bisoprolol	10 mg	C07AB07, C07FX04, C07FB07, C07BB07
	Metoprolol	200 mg	C07AB02, C07FX03, C07FB13, C07FB02, C07FX05, C07BB02, C07CB02
Ivabradine	Ivabradine	7.5 mg BID	C01EB17, C07FX06, C07FX05
ARNI	Sacubitril/Valsartan	200 mg BID	C09DX04
SGLT2 inhibitors	Empagliflozin	-	A10BK03
	Dapagliflozin		A10BK01
	Canagliflozin		A10BK02

*BID: twice a day

Supplementary Table S3. Patients achieving each category of therapy (no-, mono-, dual-, triple-) with prescription overlap of 7 days and 14 days.

Therapy	7 days overlap	14 days overlap
No therapy	54,163 (27.2%)	54,163 (27.2%)
Monotherapy	68,216 (34.2%)	68,646 (34.4%)
Dual therapy	59,894 (30.0%)	59,736 (30.0%)
Triple therapy	16,928 (8.5%)	16,662 (8.4%)

Supplementary Table S4. Conversion of guideline directed medication dosage to an intensity score

Conversion and standardization of medication class	Score assigned to converted dose levels
Beta blockers converted to carvedilol equivalent (CarvEquiv) CarvEquiv = Carvedilol TDD CarvEquiv = Metoprolol TDD / 2 CarvEquiv = Bisoprolol TDD * 5	0 mg = 0 < 6.25 mg = 0.5 6.25 – 12.49 mg = 1 12.5 – 24.99 mg = 2 25.0 – 37.49 mg = 3 37.5 – 49.9 mg = 4 ≥ 50 mg = 5
ACEi converted to lisinopril equivalent (LisEquiv) LisEquiv = Lisinopril TDD LisEquiv = Perindopril TDD * 5 LisEquiv = Trandolapril * 5 LisEquiv = Ramipril *2	0 mg = 0 < 5.0 mg = 0.5 5.0 – 9.9 mg = 1 10 – 14.9 mg = 2 15 – 19.9 mg = 3 20 – 39.9 mg = 4 ≥ 40 mg = 5
ARB converted to losartan equivalent (LosEquiv) LosEquiv = Candesartan TDD * 6 LosEquiv = Valsartan TDD * 0.6	0 mg = 0 < 25 mg = 1 25 – 49.9 mg = 2 50 – 74.9 mg = 3 75 – 99.9 mg = 4 ≥ 100 mg = 5
MRA converted to spironolactone equivalents (SpiroEquiv) SpiroEquiv = spironolactone TDD SpiroEquiv = Eplerenone TDD	0 mg = 0 < 25 mg = 1 25 – 37.49 mg = 2 37.5 – 49.9 mg = 3 ≥ 50 mg = 4
ARNI Sacubitril/Valsartan	0mg = 0 ≤ 50mg = 3 >50mg = 5

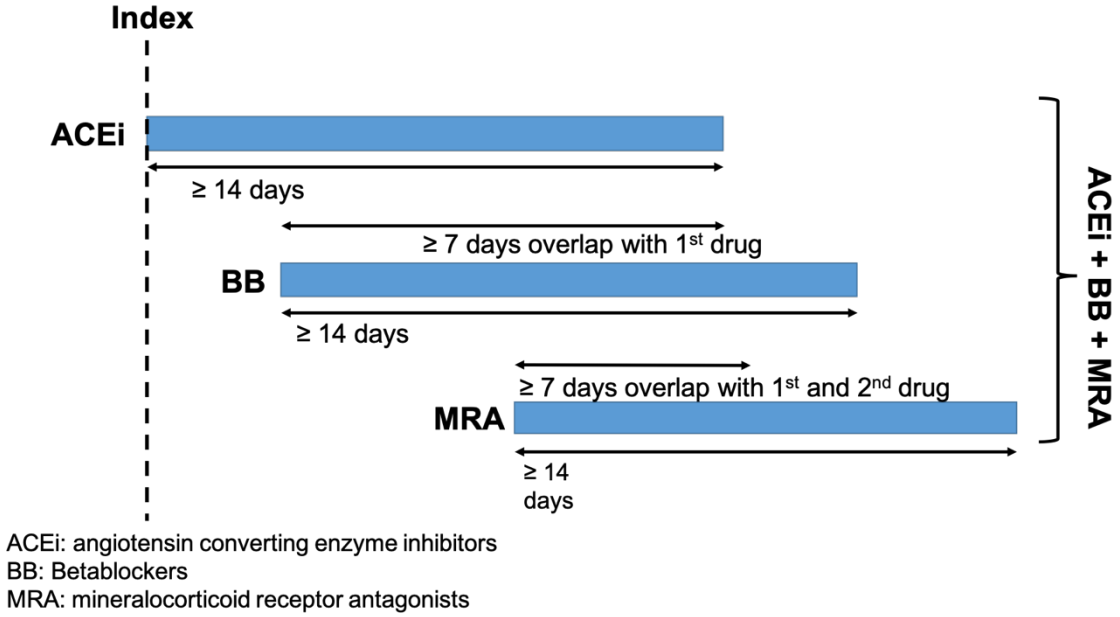
*TDD = total daily dose

Supplementary Table S5. Specific drug classification for all patients with HF on mono, double or triple therapy

	All HF patients		Alive patients	
Monotherapy	All HF patients n = 68,846	HFrEF Patients n = 17,184	All HF patients n = 56,048	HFrEF Patients n = 13,935
Monotherapy with ACEi	18,552 (26.9)	4,765 (27.7)	15,495 (27.6)	3,951 (28.4)
Monotherapy with ARB	4,967 (7.2)	1,066 (6.2)	4,186 (7.5)	889 (6.4)
Monotherapy with BB	40,438 (58.7)	10,204 (59.4)	32,531 (58.0)	8,224 (59.0)
Monotherapy with MRA	4,528 (6.6)	1,058 (6.2)	3,515 (6.3)	793 (5.7)
Switch between ACEi, ARB and or ARNi	361 (0.5)	91 (0.5)	321 (0.6)	78 (0.6)
Double Therapy	n = 60,641	n = 30,912	n = 52,407	n = 26,760
Double therapy with ACEi and BB	38,647 (63.7)	20,455 (66.2)	33,571 (64.1)	17,792 (66.5)
Double therapy with ARB and BB	8,020 (13.2)	3,570 (11.6)	7,025 (13.4)	3137 (11.7)
Double therapy with ACEi and MRA	3,158 (5.2)	1,623 (5.3)	2,656 (5.1)	1355 (5.1)
Double therapy with ARB and MRA	763 (1.3)	352 (1.1)	662 (1.3)	305 (1.1)
Double therapy with BB and MRA	8,252 (13.6)	3,937 (12.7)	6,843 (13.1)	3275 (12.2)
Switch between (ACEi, ARB and or ARNi) + (BB or MRA)	1,801 (3.0)	975 (3.2)	1,650 (3.1)	896 (3.4)
Triple Therapy	n = 17,536	n = 13,508	n = 15,586	n = 11,983
Triple therapy with ACEi, BB and MRA	13,688 (78.1)	10,644 (78.8)	12,102 (77.6)	9,390 (78.4)
Triple therapy with ARB, BB, and MRA	2,473 (14.1)	1,779 (13.2)	2,224 (14.3)	1,597 (13.3)
(Switch between ACEi, ARB and or ARNi) + BB + MRA	1,375 (7.8)	1,085 (8.0)	1,260 (8.1)	996 (8.3)

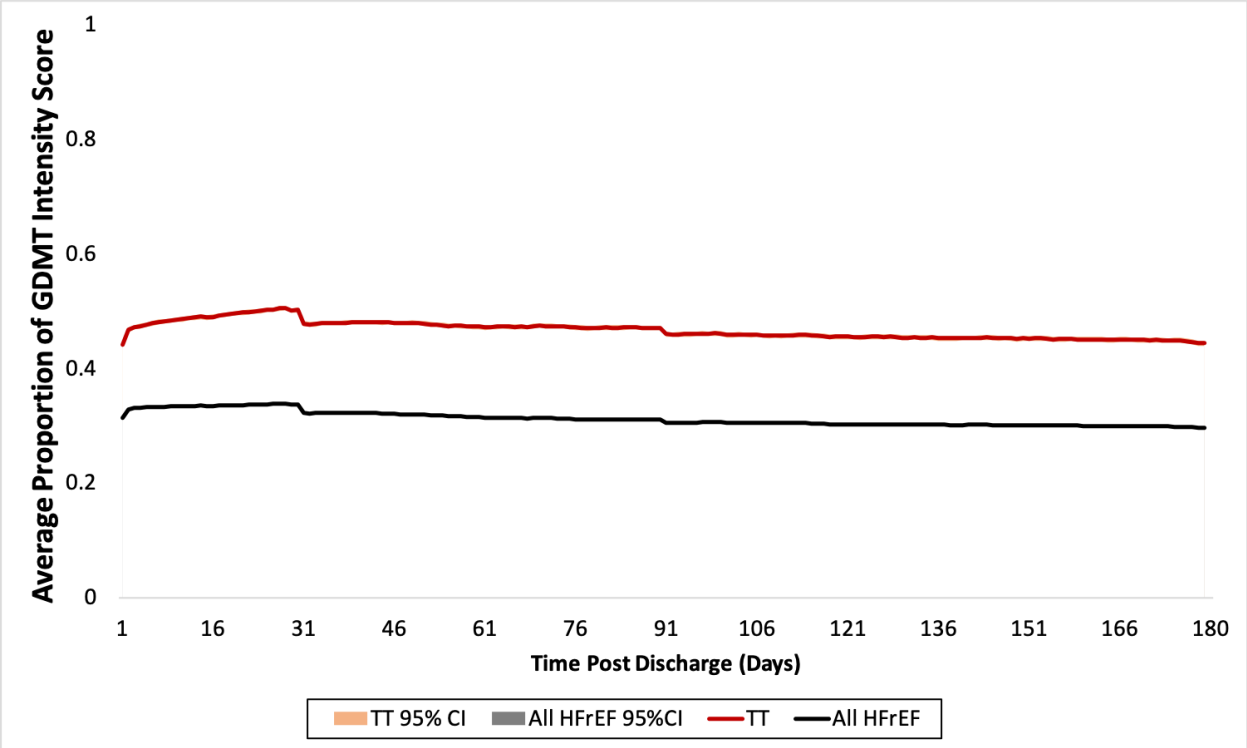
Triple therapy + SGLT2i (aka quadruple therapy)	244 (1.4)	207 (1.5)	222 (1.4)	188 (1.6)

Supplementary Figure S1. Schematic presentation of HF pharmacotherapy algorithm



ACEi: angiotensin converting enzyme inhibitors
BB: Betablockers
MRA: mineralocorticoid receptor antagonists

Supplementary Figure S2. Average proportion of maximum GDMT Intensity score calculated daily over 6 months post index discharge for patients with HFrEF alive at 6 months.



Only patients with HFrEF that were alive 6 months post discharge were included. Each data points are the average intensity scores with 95%CI for all patients with HFrEF (black, n=55,882) or patients with HFrEF on triple therapy (red, n=11,983) divided by the maximum achievable Intensity score (14). GDMT: guideline-directed medical therapy; HFrEF: heart failure with reduced ejection fraction.