Role of Guideline Directed Medical Therapy Doses and Optimization in Patients Hospitalized With Decompensated Systolic Heart Failure

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Despite significant advances in evidence-based treatments for heart failure with reduced ejection fraction (HFrEF), the use of guideline directed medical therapy (GDMT) at recommended doses remains suboptimal. We examine the usage and modification of inpatient GDMT and its effect on outcomes in patients hospitalized with a diagnosis of acute on chronic HFrEF between 2013 and 2018. Overall use and modification of GDMT, which included heart failure appropriate beta-blockers (BB), renin-angiotensin system inhibitors (RASi) and aldosterone blockers (MRA) during the hospitalization were collected. Target dosages were based on guideline recommendations. Primary endpoints included 30-day hospitalization-free survival and 1-year survival. Among 1,655 patients, discharge use of BB, RASi, and MRA was 73.4%, 55.9% and 13.8%, respectively. Upon discharge, ≥50% target dose of BB, RASi, and MRA was used in 25.3%, 15.6%, and 13.7%, respectively. In multivariable analyses, there was a statistically significant improvement in 1-year survival and 30-day hospitalization-free survival in patients discharged on increasing number of medication classes optimized at ≥50% target dose (per extra medication, HR 0.74, 0.64-0.86, p <0.001, and HR 0.73, 0.62-0.86, p = 0.0002), respectively. Initiation and/or uptitration of BB and RASi was associated with improved 30-day hospitalization-free survival and 1-year survival, (HR 0.73 (0.57-0.92), p = 0.0087; HR 0.62 (0.46-0.82), p <0.001) for BB and (HR 0.77 (0.62-0.95), p <0.001; HR 0.62 (0.48-0.80), p <0.001) for RASi, respectively. In conclusion, inpatient optimization of GDMT in acute HFrEF is feasible and associated with improved 30-day hospitalization-free survival and 1-year survival. **(Am J Cardiol 2021;151:64−69)**

Heart failure (HF) affects an estimated 6.2 million people in the United States and approximately 50% have reduced ejection fraction (HFrEF).[1] They experience frequent hospitalizations, with 30-day readmission rates >20% and mortality rates reach 38% at 1-year.[2] Guideline directed medical therapy (GDMT) optimization is encouraged by guidelines, but many patients seldom achieve target dosing or initiation of multiple classes of medications.[3] Registry data suggests high proportion of patients on <50% target dose of GDMT and only 1% are treated with target doses of beta-blockers (BB), renin-angiotensin system inhibitors (RASi), and aldosterone blockers (MRA) therapy together.[4] Additionally, medication optimization in the outpatient setting over time is uncommon.[5,6] Hospitalization for decompensated HF presents an opportunity for GDMT optimization, although literature on the role of inpatient GDMT change is limited.[7] We sought to evaluate changes in GDMT during hospitalizations for decompensated HFrEF and the association between medication use and/or changes with clinically important outcomes including rehospitalization and mortality.

Methods

We conducted a retrospective analysis of adult patients with an admission for HFrEF from March 2013 to April 2018 at Loma Linda University Medical Center in Loma Linda, California. Medical record data was mined to identify patients discharged with an active hospital diagnosis of acute on chronic systolic (or acute on chronic systolic and diastolic) heart failure during the time frame studied. Heart failure did not need to be the primary discharge diagnosis. Diagnoses were based on International Classification of Diseases (ICD) and not diagnosis-related groups (DRG). If a patient had multiple hospitalizations over the study period, only the first was included for analysis. Patients discharged by internal medicine clinicians and specialists (including cardiology, internal medicine, and medical intensive care units) were included. Dosages of GDMT medications on admission and at discharge as well as relevant demographic data, comorbidities, and outcome data were collected. The primary outcomes of interest were 30-day all-cause hospitalization free survival and 1-year

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mortality. Patient mortality was obtained from the National Death Index, while only readmissions to our facility were available for inclusion in readmission data.

GDMT included BB, (metoprolol succinate, carvedilol or bisoprolol), any RASi, and use of MRA (spironolactone or eplerenone). Medications were converted to equivalent dosages for carvedilol, lisinopril or spironolactone to facilitate statistical analysis. Given lack of direct comparison and equivalence studies, dose equivalents were based on approximate starting dose within each medication class. For equivalent analyses, metoprolol succinate 25mg/day ≈ 6.25mg/day carvedilol ≈ 2.5mg bisoprolol daily. For RASi, the equivalent doses were as follows: Captopril 18.75 mg/day ≈ enalapril 2.5 mg/day ≈ ramipril 2.5 mg/day ≈ lisinopril 5 mg/day ≈ candesartan 4 mg/day ≈ valsartan 40 mg/day ≈ losartan 25 mg daily. Doses of spironolactone and eplerenone were considered equivalent. Target doses of carvedilol equivalents were 50 mg/day day, lisinopril equivalents were 40 mg/day and spironolactone equivalents were 25 mg/day, based on American College of Cardiology Foundation/American Heart Association guidelines.[3] SGLT2-inhibitors were not included in this study as they were not yet shown to be beneficial in heart failure. In addition, hydralazine, isosorbide dinitrate, and ivabradine were not included due to low number of prescribing rates and more specialized indications for these medications. Institutional Review Board of Loma Linda University approved this study and informed consent was not required.

Student's *t* tests and ANOVA analyses were used for group comparisons as appropriate. Multivariable Cox proportional hazards models looking at the 1-year primary endpoint were adjusted for gender, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, chronic ischemic heart disease, chronic atrial fibrillation, and continuous variables of age at admission, discharge potassium levels, discharge creatine levels, and mean blood pressure. Multivariable-adjusted survival curves were also generated. The proportional hazard assumptions were tested for all Cox regressions using Schoenfeld residuals.[8] The only violation was for the 30-day endpoint, testing the effect of the number of medications ≥50% target dose when they were modeled with 3 indicator variables. Therefore, logistic regression was used to estimate the odds of an event before 31 days. R version 1.1.383 was used for analyses.

Results

A total of 1,655 patients between 2013 to 2018 matching inclusion criteria were identified. The average age was 64.4 years and about 39% were women. The mean and median length of stay were 7.0 and 4.3 days, respectively. Patient characteristics and labs values on admission and discharge are listed in Table 1.

Data regarding medication use on admission and discharge, including the percent of patients at ≥50% target and target doses, are shown in Supplementary Table 1. On admission, 50.2% of patients were on a RASi (mean lisinopril dose equivalent of 16.8 mg) and at discharge 55.9% were on a RASi (mean dose of 14 mg). Similarly, 54.6% of patients were on a HF appropriate BB (mean daily carvedilol dose equivalent of 24 mg) on admission and 73.4% on discharge (mean dose 19.4 mg). Regarding MRA, 15.5% of patents were on therapy on admission (mean spironolactone dose equivalent of 29.9 mg) and 13.8% on discharge (mean dose 28.6 mg). RASi, BB and MRA were initiated or uptitrated in 25.5%, 39.6%, and 5.2% of patients respectively, while they were down titrated in 39.2%, 34.6%, and 42.6% respectively. Further information on dosing can be seen in Supplementary Table 1.

Table 1
Patient baseline characteristics and mean laboratory values

Laboratory Values	Admission	Discharge	p-value
Sodium (mMol/l)	137.8 ± 5	137.3 ± 4.1	<0.05
Potassium (mMol/l)	4.3 ± 0.7	4.1 ± 0.4	<0.05
Blood Urea Nitrogen (mg/dl)	29.4 ± 19.3	29.2 ± 16.8	0.89
Creatinine (mg/dl)	1.7 ± 1.6	1.6 ± 1.3	0.06
Alanine Transaminase (U/l)	45.6 ± 128.7	36.8 ± 74.8	<0.05
Aspartate Transaminase (U/l)	43.7 ± 102.2	31.7 ± 44.3	<0.05
Alkaline Phosphatase (U/l)	106.0 ± 83	101.3 ± 79.4	0.11
Total Bilirubin (mg/dl)	0.90 ± 1.3	1.0 ± 1.9	0.11
Glucose (mg/dl)	145.6 ± 93	135.4 ± 59.6	<0.05
Systolic Blood pressure (mm Hg)	129.8 ± 25.9	116.5 ± 18.8	<0.05
Diastolic Blood Pressure (mm Hg)	78.1 ± 18.6	67.0 ± 12.3	<0.05
Pulse (beats/min)	89.8 ± 21.3	79.5 ± 14.4	<0.05
Weight (kilograms)	86.6 ± 29	84.6 ± 28.1	<0.05
Average Age (years)	64.4 ± 16.2		
Men	1017 (61.4%)		
Diabetes Mellitus	439 (26.5%)		
Chronic Obstructive Pulmonary Disease	159 (9.4%)		
Chronic Kidney Disease	359 (21.7%)		
Chronic Ischemic Heart Disease	510 (30.8%)		

Supplementary Table 2 shows the patient characteristics associated with initiation and/or uptitration, no change, and down titration of each class of medications. Notably, RASi, and MRA down titration occurred more commonly in patients with higher discharge creatinine and potassium values. For all classes, down titration was more common in patients with lower discharge blood pressure.

At discharge, 58% of patients were not optimized at ≥50% target dose of the three GDMT medication classes, while 32%, 9% and 2% of patients were at least half-optimized on 1, 2, and all 3 classes of medications, respectively. Patient characteristics associated with each group are listed in Supplementary Table 3. Patients optimized on larger number of medication classes at ≥50% target dose were more likely to be younger, weigh more, and have higher systolic and diastolic blood pressures.

Thirty-day survival for our cohort was 92% and total 30-day all cause readmission to our facility was 20%. For the primary endpoints, 76% of patients experienced the endpoint of 30-day hospitalization-free survival and total 1-year survival was 70%.

Multivariable analyses were used to evaluate the role of medication dosing as independent predictors of 30-day combined endpoint of mortality and/or readmission and 1-year mortality as shown in Table 2. The results suggest that for RASi and BB, the use of any dose was generally associated with improved outcomes compared to no medication use, and goal doses were associated with greater

Table 2
30-day multivariable-adjusted hospital-free survival and 1-year mortality according to medication dose and class*

30-Day Hospitalization-Free Survival			
RASi	HR	95% CI	p-value
< 50% dose	0.48	0.38-0.60	<0.001
50% dose	0.75	0.51-1.08	0.12
Full dose	0.61	0.38-0.97	0.04
Beta Blocker			
< 50% dose	0.57	0.46-0.72	<0.001
50% dose	0.45	0.32-0.64	<0.001
Full dose	0.48	0.32-0.72	<0.001
MRA			
50% dose	0.38	0.16-0.92	0.033
Full dose	0.57	0.38-0.84	0.005
1-Year Survival			
RASi	HR	95% CI	p-value
< 50% dose	0.72	0.59-0.87	<0.001
50% dose	0.53	0.36-0.79	0.002
Full dose	0.56	0.35-0.88	0.01
Beta Blocker			
< 50% dose	0.82	0.67-1.0	0.048
50% dose	0.72	0.53-0.96	0.028
Full dose	0.49	0.32-0.73	<0.001
MRA			
50% dose	0.37	0.16-0.82	0.01
Full dose	0.95	0.70-1.30	0.77

* No medication use for each medication class was used as reference.

Table 3
Multivariable-adjusted outcomes for GDMT at ≥50% target dosing*

30-Day Hospitalization-Free Survival			
	OR	95% CI	p-value
1 medication ≥ 50% dose	0.54	0.41-0.70	<0.001
2 medications ≥ 50% dose	0.55	0.35-0.85	0.007
3 medications ≥ 50% dose	0.19	0.05-0.82	0.025
Age at Admission	1.00	0.99-1.00	0.44
Gender	1.26	1.00-1.58	0.054
Diabetes Mellitus	1.26	0.97-1.63	0.079
Chronic Obstructive Pulmonary Disease	0.77	0.51-1.15	0.20
Chronic Kidney Disease	0.99	0.71-1.38	0.96
Chronic Ischemic Heart Disease	1.00	0.81-1.34	0.74
Atrial Fibrillation	1.41	1.09-1.83	0.009
Discharge Potassium	0.97	0.75-1.25	0.81
Discharge Creatinine	1.09	0.99-1.21	0.085
Mean Blood Pressure	0.99	0.98-1.00	0.003
1-Year Survival			
	HR	95% CI	p-value
1 medication ≥ 50% dose	0.68	0.55-0.84	<0.001
2 medications ≥ 50% dose	0.61	0.41-0.90	0.014
3 medications ≥ 50% dose	0.56	0.21-1.52	0.26
Age at Admission	1.03	1.02-1.04	<0.001
Gender	0.95	0.79-1.14	0.59
Diabetes Mellitus	1.03	0.84-1.26	0.80
Chronic Obstructive Pulmonary Disease	0.99	0.73-1.34	0.95
Chronic Kidney Disease	1.24	0.97-1.59	0.081
Chronic Ischemic Heart Disease	0.89	0.73-1.08	0.23
Atrial Fibrillation	0.98	0.80-1.20	0.86
Discharge Potassium	1.05	0.86-1.29	0.62
Discharge Creatinine	1.10	1.03-1.19	0.008
Mean Blood Pressure	0.98	0.97-0.99	<0.001

* No medication classes at ≥ 50% target dose was used for reference; OR is odds ratio.

improvement in 1-year survival. The use of any MRA was associated with improved 30-day outcomes but only less than goal dose (but not goal dose) was associated with 1-year survival. Other factors associated with increased mortality in a multivariable model included older age, higher discharge creatinine, and lower discharge blood pressure (Supplementary Table 4).

Data on the effect of medication use at ≥50% target dose on outcomes are shown in Table 3 and the 1-year multivariable survival data is shown in Figure 1, coding each dose with a separate indicator variable. The unadjusted 30-day readmission free survival among patients receiving 0, 1, 2, and 3 medication classes at ≥50% target doses was 69%, 80.9%, 81%, and 93% respectively, while 1-year survival was 65%, 77%, 82%, and 85% respectively. When the number of medications optimized at ≥50% target dose was coded as a single continuous variable, there was a statistically significant improvement in 1-year survival among patients discharged on increasing number of medication classes (HR 0.74, 0.64-0.86, p <0.001). This was confirmed in Figure 1 coding the three exposure levels separately. Similarly, for 30-day hospitalization-free survival, there was a statistically significant improvement in patients discharged on increasing number of medication classes (HR 0.73, 0.62-0.86, p = 0.0002).

Multivariable analyses on the effect of medication changes on endpoints are shown in Table 4. While down titration of medication classes was not associated with worsened outcomes, initiation or uptitration of medications, particularly RASi and BB, was associated with improved outcomes. Separating the category of initiation and/or uptitration into the two individual components (initiation and uptitration) did not demonstrate a difference between the 2 versus the combined category (data not shown).

Discussion

The present study describes the use of GDMT among patients admitted for acute on chronic HFrEF and demonstrates several important findings. Consistent with other cohorts, the use of GDMT, especially at optimal doses, remains low. Increased number of GDMT classes administered at ≥50% target dose are associated with improved outcomes including 1-year survival and 30-day all cause hospitalization-free survival. In addition, GDMT initiation and/or uptitration during a decompensated HF hospitalization is feasible and associated with improved outcomes of 1-year survival and 30-day hospitalization-free survival. These results may have important implications in optimizing care of patients with HFrEF by further focusing efforts on GDMT optimization during inpatient hospitalizations for decompensated heart failure.

The utilization of individual HF therapies was similar in this cohort compared to other studies. The present cohort was prescribed BB, RASi, MRA at rates of 73.4%, 55.9%, 13.8%

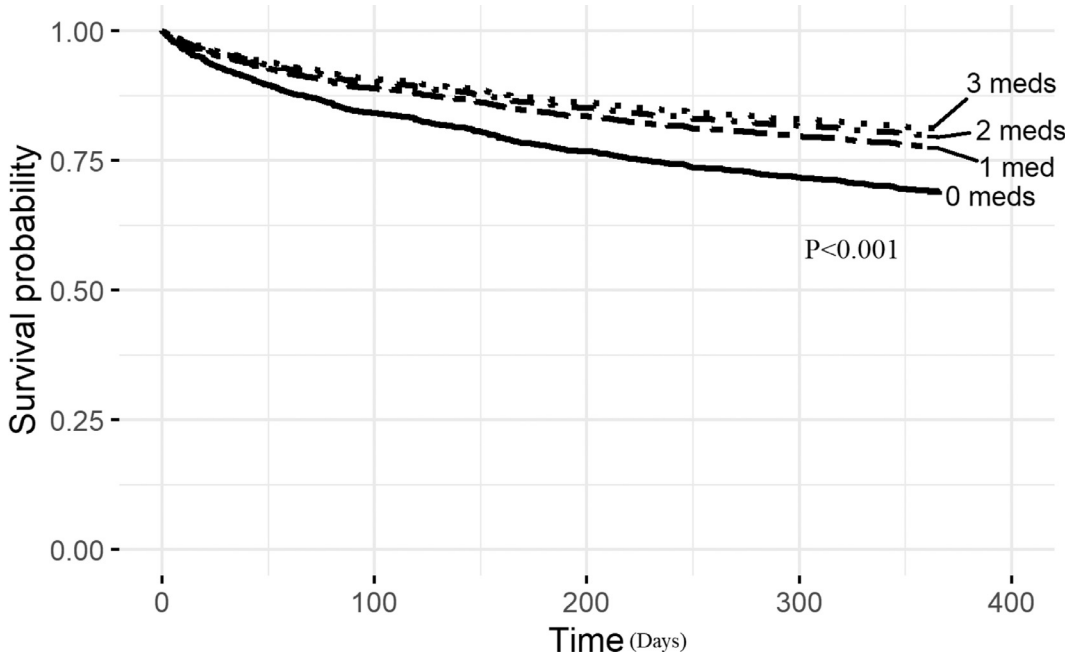

Figure 1. One-year multivariable-adjusted survival probability based on number of GDMT medication classes at ≥ 50% target dose.

while a US registry called Get With The Guidelines (GWTG) had discharge usage rates of 73.4%, 88%, and 24.9%, respectively.[2] In Change the Management of Patients with Heart Failure (CHAMP-HF) registry, BB, RASi, and MRA was prescribed at 81.7%, 61.7%, 35.7%, and another US cohort showed prescription rates of 69.1%, 46%, and 24.7%, respectively.[5,9] Even when prescribed, GDMT is often underdosed. In CHAMP-HF, target dosing for BB, RASi, and MRA was about 22%, 10%, and 27% while an ASIAN-HF registry showed patients achieving target dosing at rates of 13%, 17%, and 29%, respectively,[5,10] which are comparable to the present cohort, where target dosing of BB, RASi, and MRA was achieved in 10.6%, 6.6%, and 10.9%, respectively. Target dosing of all 3 medication classes was achieved in >1% of patients in CHAMP-HF as well as our cohort.[5]

Table 4
Multivariable-adjusted outcomes for changes in dosing of GDMT*

30-Day Hospitalization-Free Survival			
	HR	95% CI	P-value
RASi			
Down titration	1.2	0.95-1.5	0.12
Initiation or uptitration	0.6	0.46-0.82	**<0.001**
Beta Blocker			
Down titration	1.18	0.92-1.5	0.18
Initiation or uptitration	0.73	0.57-0.92	**0.009**
MRA			
Down titration	1.13	0.78-1.6	0.52
Initiation or uptitration	0.76	0.44-1.3	0.34
1-Year Survival			
	HR	95% CI	P-value
RASi			
Down titration	0.94	0.75-1.2	0.58
Initiation or uptitration	0.62	0.48-0.80	**<0.001**
Beta Blocker			
Down titration	1.05	0.83-1.3	0.67
Initiation or uptitration	0.77	0.62-0.95	**0.01**
MRA			
Down titration	0.97	0.67-1.40	0.86
Initiation or uptitration	0.61	0.34-1.09	0.09

* No change in medication dose was used for each medication class as reference.

The impetus for achieving target doses of GDMT has been established in previous prospective trials and is the standard for HF therapy. The HEAAL and ATLAS studies demonstrated improved outcomes, driven largely by reduction in hospitalizations, in patients on higher doses of RASi.[11,12] When carvedilol was examined in a randomized, placebo controlled trial with none, low, medium, and high dose groups (0, 6.25, 12.5, and 25 mg BID respectively), patients demonstrated dose-related improvements in left ventricular function as well as survival.[13] Consequently, the higher doses of GDMT, particularly doses of ≥50% target, have been advocated for clinical use as well as for quality performance metrics.[5] While observational, the current data extends these findings to a cohort of patients hospitalized for decompensated systolic heart failure by demonstrating the beneficial effect of ≥50% target dose of combined GDMT medication classes on clinically important outcomes.

Patients discharged after an episode of decompensated HFrEF are at increased risk for short term adverse events and optimizing HF therapies can potentially mitigate the morbidity and mortality in these patients. The role of discharge medication on outcomes has been studied previously. The GREAT registry demonstrated the use of BB or RASi at hospital discharge for acute heart failure was associated with a lower 90-day mortality compared to untreated.[14] Benefits of

singular therapies lasted beyond the first 90 days after discharge and combination therapy of BB and RASi at discharge decreased mortality significantly compared to either therapy alone at the 90 day as well as 1-year mark.[14] These results mirror the findings by Yamaguchi et al which evaluated the effects of BB and RASi at discharge on 1-year all-cause mortality and HF readmission.[15] They found 1-year mortality was significantly different in the 3 groups (Both BB and RASi: 7.8% vs Either BB or RASi: 19.6% vs None 34.4%). However, their analyses showed no statistically significant difference in HF readmission in the groups at 1-year.[15] Other studies of inpatient GDMT adjustment, particularly focusing on RASi, demonstrated that inpatient downtitration was associated with worsened outcomes, but did not describe the effects of uptitration on outcomes.[16] In addition, recent trials have also shown positive results with inpatient initiation of GDMT, particularly with sacubitril-valsartan and sodium-glucose cotransporter 2 inhibitors in patients hospitalized with heart failure.[17,18] The present study expands on the previous literature and fills important gaps by addressing the effect of ≥50% target or greater dose of GDMT at discharge on outcomes and highlighting the important role of GDMT dose optimization on outcomes.

Our study has several limitations. We conducted an observational study which can make it difficult to establish causality between use of HF medications and outcomes. The results are for a single center, and the findings reflect the practice within one institute. Key demographic information including race and socioeconomic status, which may influence decision making and outcomes, were not available. Specific patient characteristics like ejection fraction, New York Heart Association class and types of cardiomyopathy are not available and inclusion criteria only included diagnosis based on coding. We were unable to collect data on readmissions to other facilities which could have impacted our results, although our 30-day readmission data mirrors national averages, suggesting that our facility which is the largest tertiary care facility in the area may capture the majority of re-admissions. There was no data available on prescriber practices in regard to medication changes during the hospitalization and medication use was at the discretion of the inpatient care team. Equivalent dosing within medication classes were approximated based on guideline dosing, and there is limited data regarding other measures to determine dose equivalence. The use of sacubitril-valsartan was very low in this cohort during the study period. Nevertheless, this study represents real-world practice patterns at a tertiary hospital system, which may have important clinical implications for other similar hospital systems.

In conclusion, this study demonstrates the use of GDMT in contemporary cohorts with HFrEF remains low. Higher number of medication classes at ≥50% target dose in discharged patients is associated with improved outcomes. Initiation and uptitration of GDMT in patients hospitalized with acute HFrEF is feasible and associated with improved 30-day hospitalization-free survival and 1-year survival. All patients admitted for acute HFrEF should be evaluated for medication optimization and further studies are needed to optimize the utilization of GDMT in hospitalized HF patients.

Credit Author Statement

Dennis Grewal: Visualization, Writing − Original Draft, Formal analysis, Data Curation *Rod Partow-Navid:* Data Curation, Investigation *Dante Garcia:* Data Curation *Joshua Coney:* Data Curation, Investigation *Gary Fraser:* Software, Formal Analysis, Resources, Writing − Review and Editing, Visualization *Liset Stoletniy:* Writing − Review and Editing *Antoine Sakr:* Writing − Review and Editing *Purvi Parwani:* Writing − Review and Editing *Dmitry Abramov:* Conceptualization, Methodology, Formal Analysis, Investigation, Writing − Review and Editing, Supervision

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

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