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Original Research

Guideline-directed medical therapy in heart failure patients with reduced ejection fraction in Oman: utilization, reasons behind non-prescribing, and dose optimization

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Abstract

Background: Objective: To determine the reasons behind guideline-directed medical therapy (GDMT) non-prescribing, drug utilization before and after excluding those intolerable to GDMT, as well as dose optimization in heart failure (HF) patients with reduced ejection fraction (<40%) (HFrEF) in Oman. **Methods:** The study included HF patients seen at the medical outpatient clinics at Sultan Qaboos University Hospital, Muscat, Oman, between January 2016 and December 2019 and followed up until the end of June 2021. The use of renin-angiotensin-system (RAS) blockers (angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitors (ARNIs)), beta blockers and mineralocorticoid receptor antagonists (MRAs) were evaluated as per the European, American, and Canadian HF guidelines. Analyses were performed using univariate statistics. **Results:** A total of 171 HFrEF patients were enrolled for this study, the overall mean age of the cohort was 63 ± 15 years old and 59% were male. Over 65% of the patients had chronic kidney disease. Almost 55% of the patients were intolerable to GDMT. The proportion of patients on beta blockers, RAS blockers/ hydralazine-isosorbide dinitrate combination, and MRAs, before and after excluding those intolerable to GDMT, were 89%, 97%, and 77%, and, 94%, 47% and 85%, respectively, while the proportion of patients on the GDMT combination concomitantly was 41% and 83%, respectively. A total of 61%, 44% and 100% of the patients were prescribed ≥50% of the target dose for beta blockers, RAS blockers/ HYD-ISDN combination and MRAs respectively, while 19%, 8.2% and 94% of the patients attained 100% of the target dose for beta blockers, RAS blockers/ HYD-ISDN combination and MRAs respectively. **Conclusions:** Reasons behind GDMT non-prescribing were frequent and not clearly obvious in patients' medical notes. The majority of the patients were prescribed GDMT. However, dose optimization, specifically for beta blockers and RAS blockers/ HYD-ISDN combination, was still suboptimal. The findings should be interpreted in the context of low study power and that future studies, with larger sample sizes, are warranted to minimize this limitation.

Keywords: Heart failure; Treatment; Maximal tolerated doses; Guideline adherence; Oman; Middle East

INTRODUCTION

Heart failure (HF) is a growing global public health challenge associated with a significant clinical and economic burden. The worldwide prevalence of HF has been increasing steadily, with the 2017 data estimated at 64.3 million cases (8.52 per 1,000 individuals) accounting for 9.91 million years lost due to disability, consequently leading to 346.17 billion dollars expenditure in the US.[1] The prevalence of HF in the adult population, based on registries, is reported to be between 1-2%.[2] However, a recent meta-analysis based on echocardiographic studies in the general population, including those of previously unrecognized cases, estimated the prevalence to be as high as 4.2%.[3]

American (American College of Cardiology (ACC), American Heart Association (AHA), and the Heart Failure Society of America (HFSA)),[4] Canadian (Canadian Cardiovascular Society (CCS) and the Canadian Heart Failure Society (CHFS))[5] and European (European Society of Cardiology (ESC))[6] HF guidelines have recommended the use of evidence-based angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitors (ARNIs), beta blockers and mineralocorticoid receptor antagonists (MRAs), in HF patients with reduced ejection fraction (EF) (HFrEF). The guidelines also advocate the use of hydralazine/isosorbide dinitrate (HYD-ISDN) combination if an ARNI/ACEI/ARB cannot be used.[4-6] This guideline-directed medical therapy (GDMT) combination (ACEI/ARB/ARNI, beta blocker and MRA) is associated with lower all-cause mortality.[7]

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However, these medications are significantly underutilized, not only in North America[8-11] or Europe,[12-15] but also in the Middle East.[16,17] A number of studies[13,17] have hypothesized that the underutilization of GDMT could be due to intolerability and contraindications which are not routinely reported. The addition of evidence-based sodium-glucose cotransporter-2 (SGLT2) inhibitors to GDMT therapy, which is reported to reduce cardiovascular deaths and worsening of HF in patients with HFrEF,[18,19] is also recommended irrespective of whether patients have diabetes or not. The guidelines[4-6] have also recommended maximal appropriate dosing in HF patients to optimize clinical outcomes and this is defined as greater ≥50% of the target GDMT dosing.[20] However, a number of studies,[9-15] including some in the Middle East,[16,17] have reported suboptimal dosing of HF medications.

Hence, the aim of this current study was to elicit the reasons behind GDMT non-prescribing, its utilization before and after excluding those with valid clinical reasons, as well as dose optimization in patients with HFrEF in Oman.

METHODS

Study population and design

All HF patients that had an echocardiogram performed while attending internal medicine and cardiology clinics at Sultan Qaboos University Hospital (SQUH), Muscat, Oman, between January 2016 and December 2019, were evaluated for inclusion into the study. This was a retrospective cohort study where patients were then followed up until the end of June 2021.

Inclusion criteria

Only patients (≥13 years of age) that had an EF of <40% (HFrEF) were enrolled. The latest EF was selected if a patient had multiple EFs.

Data collection

The study collected demographic (age, gender, smoking, and alcohol status) and clinical (coronary artery disease (CAD), deep vein thrombosis (DVT), pulmonary embolism, atrial fibrillation, stroke, transient ischemic attack (TIA), myocardial infarction (MI), angina pectoris, diabetes mellitus, hypertension, dyslipidemia, ST-elevation MI (STEMI), admission heart rate (HR), systolic blood pressure (BP), diastolic BP, glycated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), serum creatinine and potassium) as well as GDMT medications (ACEIs (lisinopril), ARBs (irbesartan and valsartan), ARNIs (sacubitril/valsartan), HYD-ISDN, beta blockers (carvedilol and bisoprolol) and MRAs (spironolactone and eplerenone)) and their corresponding doses. Other medications for comorbid conditions were also collected. The baseline demographic and clinical characteristics were collected during the index admission.

Based on the 2021 American (ACC/AHA/HFSA), 2021 Canadian (CCS/CHFS) and 2021 European (ESC) HF guidelines, the optimum target doses were 25-50 mg twice daily for carvedilol, 10 mg once daily for bisoprolol, 20-40 mg once daily for lisinopril, 300 mg once daily for irbesartan, 160 mg twice daily for valsartan, 97/103 mg twice daily for sacubitril/valsartan combination, 300/120 mg once daily for HYD/ISDN, 25-50 mg once daily for spironolactone and 50 mg once daily for eplerenone.[4-6]

Outcome measures

The main outcome measures collected were the reasons behind GDMT non-prescribing, proportion of patients prescribed GDMT concomitantly (before and after excluding those with valid clinical reasons) as well as their corresponding optimized doses at ≥50% and 100% targets. The main outcomes measures were collected during the index admission. Secondary outcome measures included emergency room (ER) visits, hospital readmission rates, length of hospital stay (LOS), all-cause mortality, and major adverse event (which was either an ER visit, hospital admission or death). The secondary outcome measures were collected during follow-up after the index admission. Data was collected by the first author (SA) and data verification check was done by co-authors (JM, MZ, and IZ). The internal medicine consultant (co-author - AA) conducted data validation.

Ethical approval

This retrospective cohort study was approved by the Medical and Research Ethics Committee at the College of Medicine and Health Sciences (CoM&HS), Sultan Qaboos University (SQU), Muscat, Oman (MREC#2488; SQU-EC/485/2021; dated: 4th July 2021).

Power analysis

The Gulf DYSPNEA study[16] of ambulatory HF patients with reduced EF in the Arabian Gulf region reported a prevalence of around 87% and 91% for RAS and beta blockers, respectively. We hypothesized that, based on a prevalence of around 90% for both RAS and beta blockers, a sample size of 138 HFrEF patients with a margin of error of 5% and 95% confidence interval was needed. However, to allow for missing information, loss to follow-up, and exclusion due to valid reasons behind GDMT non-prescribing, the sample size for this study was further increased to 171 patients.

Statistical analysis

Categorical (summarized using frequencies and percentages) and continuous normally distributed (presented using mean and standard deviation) variables were analyzed using Pearson's χ^2 test (or Fisher's exact test for expected cells <5) and Student's t-test, respectively. Continuous abnormally distributed variables (e.g. LOS) were summarized using the median and interquartile range, and data analysis was done using Wilcoxon-Mann-Whitney test. An a priori two-tailed level of significance was set at $p < 0.05$ level. Statistical analyses were conducted using STATA version 16.1 (STATA Corporation, College Station, TX, USA).

RESULTS

During the study period (2016-2019), a total of 240 patients attended the cardiology clinics and had their EF measured.

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However, only 171 HFrEF patients, who satisfied inclusion criteria, were enrolled for this study and their mean EF was 28 ± 8%. The overall mean age of the cohort was 63 ± 15 years old and 59% (101/171) were male. Over 65% (112/171) of the patients had chronic kidney disease (CKD). Besides CKD, the three other most common comorbidities were hypertension (58%; 100/171), diabetes mellitus (51%; 87/171), and CAD (46%; 78/171). Furthermore, a total of 27% (47/171) of the cohort had atrial fibrillation. As presented in Table 1, there were largely no significant differences between the groups except that CKD patients, when compared to those that did not have CKD, were older (65 vs 58 years; p = 0.002), more likely to have CAD (53% vs 32%; p = 0.011), diabetes mellitus (63% vs 29%; p < 0.001) and hypertension (68% vs 41%; p = 0.001).

Table 2 outlines the reasons behind GDMT non-prescribing. The most three prevalent reasons behind beta blockers non-prescribing were hypotension (<90/60 mmHg) (26%; 5/19), asthma/ chronic obstructive pulmonary disease (16%; 3/19), bradycardia (<60 bpm) (16%; 3/19) and follow-up at local health center (16%; 3/19). The most three prevalent reasons behind RAS blockers non-prescribing were those associated with kidney impairment/failure (49%; 19/39), hypotension (18%; 7/39), and hyperkalemia (>5 mmol/l) (13%; 5/39) while the three most documented reasons behind MRAs non-prescribing were EF ≥35% (27%; 24/88), low eGFR (<30ml/min/1.73 m2) (25%; 22/88) and hyperkalemia (9.1%; 8/88).

The valid reasons for not prescribing an evidence-based HF medication excluded those with 'no clear reason'.

As shown in Table 3, before the exclusion of patients intolerable to GDMT, 89% (149/168), 77% (128/167), and 47% (78/166) of

Table 1. Demographic and clinical characteristics stratified by chronic kidney disease (CKD)

Characteristic, n (%) unless specified otherwise	All (N = 171)	CKD		p-value
		No (n = 59)	Yes (n = 112)	
Demographic				
Age, mean±SD, years	63±15	58±17	65±13	0.002
Male gender	101 (59%)	33 (56%)	68 (61%)	0.545
Smoker	6 (3.5%)	3 (5.1%)	3 (2.7%)	0.417
Alcohol consumer	2 (1.2%)	1 (1.7%)	1 (0.9%)	1.000
Clinical				
CAD	78 (46%)	19 (32%)	59 (53%)	0.011
DVT	4 (2.3%)	1 (1.7%)	3 (2.7%)	1.000
Pulmonary embolism	4 (2.3%)	2 (3.4%)	2 (1.8%)	0.609
Atrial fibrillation	47 (27%)	17 (29%)	30 (27%)	0.778
Stroke	17 (9.9%)	4 (6.8%)	13 (12%)	0.316
Transient ischemic attack	7 (4.1%)	1 (1.7%)	6 (5.4%)	0.424
Myocardial infarction	46 (27%)	14 (24%)	32 (29%)	0.497
Angina pectoris	4 (2.3%)	1 (1.7%)	3 (2.7%)	1.000
Diabetes mellitus	87 (51%)	17 (29%)	70 (63%)	<0.001
Hypertension	100 (58%)	24 (41%)	76 (68%)	0.001
Dyslipidemia	56 (33%)	19 (32%)	37 (33%)	0.912
STEMI	17 (9.9%)	2 (3.4%)	15 (13%)	0.057
Admission				
HR, mean±SD, b/m	78±15	80±14	77±15	0.29
SBP, mean±SD, mmHg	126±23	127±23	126±23	0.726
DBP, mean±SD, mmHg	72±13	73±13	71±13	0.297
Investigations				
HbA1c, mean±SD, %	7.9±2.4	8.5±2.6	7.8±2.4	0.338
eGFR, mean±SD, ml/min/1.73m2	60±24	79±16	51±22	<0.001
Serum creatinine, mean±SD, µmol/l	135±135	85±77	161±132	<0.001
Serum potassium, mean±SD, mmol/l	4.5±0.6	4.5±0.5	4.5±0.6	0.471
Ejection fraction, mean±SD, %	28±8	27±9	28±7	0.452

SD, standard deviation; CAD, coronary artery disease; DVT, deep vein thrombosis; STEMI, ST-elevation myocardial infarction; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin among diabetics (78/87); eGFR, estimated glomerular filtration rate (159/171); Serum creatinine (162/171); Serum potassium (159/171).

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Table 2. Reasons (as reported by the treating physicians) behind not prescribing guideline-directed medical therapy

Beta blockers	**19/168**	**RAS blockers**	**39/167**	**MRAs**	**88/166**
1. Hypotension	5 (26%)	1. Severe renal impairment	11 (28%)	1. Ejection fraction ≥35%	24 (27%)
2. Asthma/ COPD	3 (16%)	2. Hypotension	7 (18%)	2. Low eGFR	22 (25%)
3. Bradycardia (<60 bpm)	3 (16%)	3. AKI	6 (15%)	3. Hyperkalemia	8 (9.1%)
4. Follow-up at the LHC	3 (16%)	4. Hyperkalemia	5 (13%)	4. Other stated reasons	5 (5.7%)
5. Could not tolerate	1 (5.3%)	5. Worsening renal failure	2 (5.1%)	5. AKI	5 (5.7%)
6. No clear reason	4 (21%)	6. Follow-up at the LHC	2 (5.1%)	6. Worsening renal failure	4 (4.6%)
		7. No clear reason	6 (15%)	7. Follow-up at the LHC	2 (2.3%)
				8. No clear reason	18 (20%)

COPD, chronic obstructive pulmonary disease; bpm, beats per minute; LHC, local health center; RAS, renin-angiotensin-system; AKI, acute kidney injury; MRAs, mineralocorticoid receptor antagonists; eGFR, estimated glomerular filtration rate;
Column percentages might not add up to 100% due to rounding off.
Severe renal impairment (defined as creatinine clearance of <10 ml/min).
Hyperkalemia (defined as >5 mmol/l).
Hypotension (defined as <90/60 mmHg).
Low eGFR (define as <30ml/min/1.73 m2).
Hypokalemia (defined as <2.5 mmol/l).

Table 3. Prescribed medications stratified by chronic kidney disease (CKD) before the exclusion of those intolerable to GDMT

Characteristic, n (%) unless specified otherwise	**All (N = 171)**	**CKD**		**p-value**
		No (n = 59)	**Yes (n = 112)**	
Beta blockers (168/171)	149 (89%)	51 (86%)	98 (90%)	0.498
Bisoprolol	68 (40%)	25 (42%)	43 (39%)	
Carvedilol	81 (48%)	26 (44%)	55 (50%)	
ACEIs (168/171)	69 (41%)	28 (48%)	41 (38%)	0.183
Lisinopril	69 (41%)	28 (48%)	41 (38%)	
ARBs (166/171)	28 (17%)	13 (22%)	15 (14%)	0.162
Irbesartan	18 (%)	9 (16%)	9 (8.3%)	
Valsartan	10 (%)	4 (6.9%)	6 (5.6%)	
Sacubitril/valsartan (166/171)	6 (3.6%)	2 (3.5%)	4 (3.7%)	1.000
RAS blockers (166/171)	102 (61%)	43 (74%)	59 (55%)	0.014
Hydralazine (166/171)	31 (17%)	2 (3.5%)	29 (27%)	<0.001
Oral nitrate (166/171)	31 (17%)	4 (6.9%)	27 (25%)	0.004
HYD/ISDN (166/171)	26 (16%)	2 (3.5%)	24 (22%)	0.001
RAS / HYD/ISDN (167/171)	128 (77%)	45 (78%)	83 (76%)	0.834
MRAs (166/171)	78 (47%)	35 (60%)	43 (40%)	0.012
Spironolactone	77 (47%)	35 (60%)	42 (39%)	
Eplerenone	1 (<0.1%)	0	1 (0.1%)	
Triple GDMT regimen (165/171)	67 (41%)	31 (54%)	36 (33%)	0.009
Frusemide	142 (83%)	47 (80%)	95 (85%)	0.393
Calcium channel blocker	17 (9.9%)	3 (5.1%)	14 (13%)	0.179
Clopidogrel	43 (25%)	16 (27%)	27 (24%)	0.666
Aspirin (166/171)	79 (48%)	19 (33%)	60 (56%)	0.004
Statins	113 (66%)	33 (56%)	80 (71%)	0.042

GDMT, guideline-directed medical therapy that include a beta blocker, a RAS blocker (or a hydralazine-nitrate combination), and an MRA; ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin receptor blockers; RAS, renin-angiotensin-system blockers; HYD/ISDN, hydralazine-nitrate combination; MRAs, mineralocorticoid receptor antagonist.
Column percentages might not add up to 100% due to rounding off.

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the patients were on beta blockers, RAS blockers/ HYD-ISDN combination, or MRAs, respectively. The three other prevalent medications that the patients were on were statins (66%; 113/171), aspirin (48%; 79/166) and clopidogrel (25%; 43/171). Those with CKD were less likely to be on MRAs (40% vs 60%; p = 0.012) and the triple GDMT combination (33% vs 54%; p = 0.009) but more likely to be on statins (71% vs 56%; p = 0.042) and aspirin (56% vs 33%; p = 0.004). Only 41% (67/165) of the patients were on GDMT combination concomitantly.

When the analyses were repeated excluding those with clear reasons for not being on GDMT (except for 'no clear reason'), the proportions of patients on beta blockers, RAS blockers/ HYD-ISDN combination, and MRAs, were 97% (149/154), 94% (100/106) and 85% (66/78), respectively, while the proportion of patients on the GDMT combination concomitantly was 83% (64/77) (Figure 1). A total of 61% (47/77), 44% (32/73) and 100% (73/73) of the patients were prescribed ≥50% of target dose for beta blockers, RAS blockers/ HYD-ISDN combination, and MRAs, respectively, while 19% (15/77), 8.2% (6/73) and 94% (62/66) of the patients attained 100% of target dose for beta blockers, RAS blockers/ HYD-ISDN combination and MRAs, respectively.

As outlined in Table 4, those on the triple GDMT combination were associated with significantly lower ER visits (75% vs 88%; p = 0.03), hospital admissions (70% vs 88%; p = 0.005), LOS (6 vs 12.5 days; p = 0.012), and overall major adverse events (81% vs 95%; p = 0.005). When the analysis was repeated after excluding those with valid reasons behind GDMT non-prescribing, the apparent differences were no longer significant.

DISCUSSION

This study has demonstrated that more than half of the patients with HFrEF had valid clinical reasons behind GDMT non-prescribing that included renal impairment, hypotension, and hyperkalemia. After taking into account the valid clinical reasons behind GDMT non-prescribing, the majority of the patients were on beta blockers (97%), RAS blockers/ HYD-ISDN combination (94%) and MRAs (85%). Additionally, most of the patients (83%) were also on the triple GDMT combination. With regard to dose optimization, 61%, 44% and 100% of the patients on beta blockers, RAS blockers/ HYD-ISDN combination and MRAs respectively, were prescribed ≥50% of the target doses as per the international HF guidelines. Those on the triple GDMT combination were associated with significantly lower ER visits, hospital admissions, LOS and overall major adverse events, when compared to those that were not on the triple GDMT combination. However, the findings became non-statistically significant after the exclusion of those with valid clinical reasons.

Despite the apparent GDMT non-prescribing in the initial cohort, when the reasons for non-prescribing were taken into account, most of the patients (83%) were prescribed the recommended HF medications concomitantly. These figures

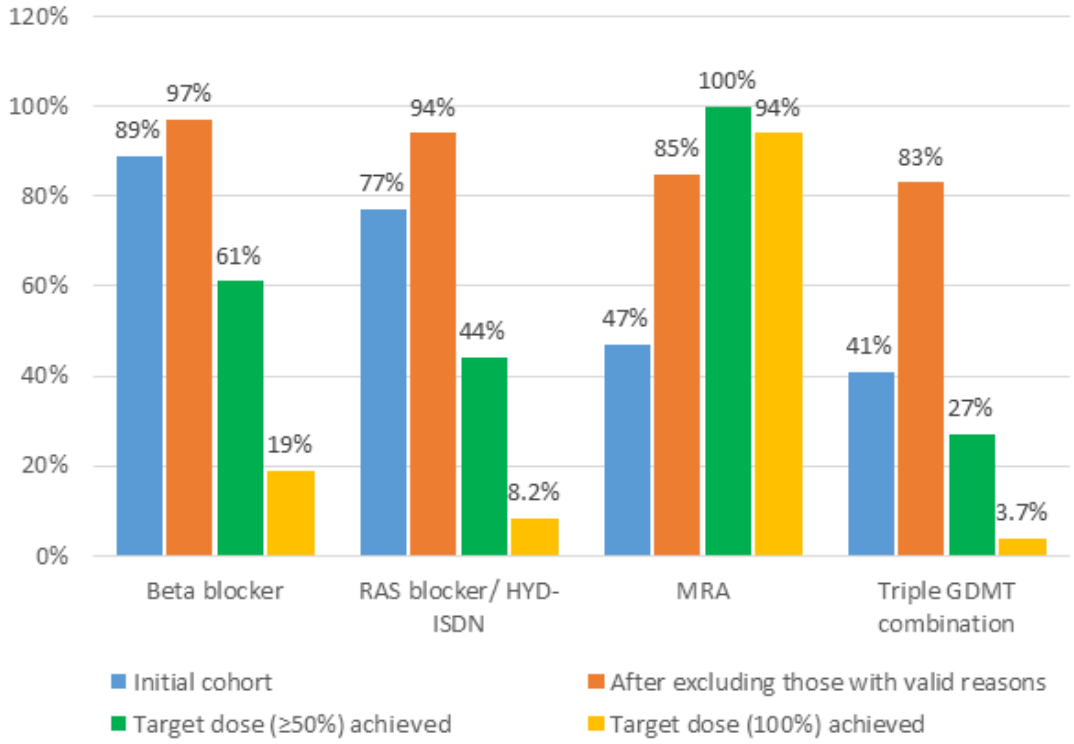

Figure 1. The proportion of evidence-based heart failure medication utilization before and after excluding those with valid reasons as reported by the treating physicians as well as the proportion of patients on optimum target dose (≥50% and 100%) after exclusion.
MRA, mineralocorticoid receptor antagonist; RAS blocker, renin-angiotensin-system blocker; HYD-ISDN, hydralazine nitrate combination; GDMT, a triple guideline-directed combination consisting of a beta blocker (carvedilol, bisoprolol), a RAS blocker (irbesartan, valsartan, sacubitril/valsartan) (or a HYD-ISDN combination), and an MRA (spironolactone, eplerenone), concomitantly.

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Table 4. Outcomes stratified by GDMT use as well as before and after excluding those with valid reasons as reported by the treating physicians

Outcome, n (%) unless specified otherwise	Initial cohort before exclusion (N = 165)			Final cohort after exclusion (N = 77)		
	Triple GDMT combination concomitantly			Triple GDMT combination concomitantly		
	No (n = 98)	Yes (n = 67)	p-value	No (n = 13)	Yes (n = 64)	p-value
Emergency room (ER) visit	86 (88%)	50 (75%)	0.03	10 (77%)	48 (75%)	0.883
Hospital admission	86 (88%)	47 (70%)	0.005	10 (77%)	45 (70%)	0.631
Length of stay, median (IQR), days	12.5 (4-30)	6 (0-19)	0.012	8 (4-10)	6 (0-18.5)	0.967
Mortality	3 (3.1%)	4 (6.0%)	0.443	0	2 (3.1%)	1.000
Major adverse event	93 (95%)	54 (81%)	0.005	11 (85%)	52 (81%)	1.000

GDMT, a triple guideline-directed combination therapy consisting of a beta blocker, a RAS blocker (or a hydralazine-nitrate combination), and an MRA, concomitantly; IQR, interquartile range.
Major adverse event was either an ER visit, a hospital admission or death.

are remarkable when considering our hospital setting in which these patients are not cared for by HF specialists, but rather by internal medicine and cardiology physicians. Furthermore, SQUH lacks a multidisciplinary HF team (that includes internal medicine physicians/cardiologists, clinical pharmacists, clinical nurse specialists and dieticians) that follows up patients regularly, either at the hospital clinic or in the community, to adjust treatment and optimize dosages appropriately.[21] Almost 66% (112/171) of the patients in the initial cohort had CKD, who are more likely to have higher rates of contraindications or intolerability to GDMT than other comorbidities as shown in Table 2. The underutilization of GDMT in previous studies could have resulted from not performing detailed patients' chart reviews and excluding those not tolerating HF medications during analysis.[13,17]

Ouwerkerk et al. have demonstrated that those treated with <50% of the target dose, as per the HF guidelines, were more likely to die or have HF hospitalization when compared to those that attained ≥50% of the target optimum doses.[22] Despite the fact that all patients ineligible, intolerable or contraindicated to GDMT were excluded from the dose optimization analysis, only 61% and 44% of those treated with beta blockers and RAS blockers/ HYD-ISDN combination, respectively, attained ≥50% of the target dose. These disappointing results are not unique and that similar suboptimal findings have also been reported elsewhere.[9,10,12-17] In those on beta blockers to at least ≥50% of the target dose (30/47), their mean blood pressure was within the normal range (124/67 mmHg); however, 87% (26/30) of the patients had HRs ≥70 bpm. Unfortunately, only 10% (3/30) of the patients were on ivabradine, which is known to reduce HR without significant effects on blood pressure.[23] It is possible that the physicians didn't want to increase the dose of beta blockers as they might be concerned with hypotension. Age has also been mentioned as a factor as to why patients are not dose optimized.[17] However, there were no significant differences in age between those that attained and those that did not attain ≥50% of the target doses with regard to RAS blockers/ HYD-ISDN combination (59 vs 60 years; p = 0.705) or beta blockers (59 vs 61 years; p = 0.592). This is of great concern as physicians were not up-titrating GDMT doses to even at least 50% of the optimum dosage in eligible HF patients.

In the initial cohort of the current study, the use of GDMT concomitantly was associated with significant reductions in healthcare resource utilization (ER visits, admissions and LOS) and all-cause mortality compared to those not on the triple GDMT combination. This is in line with similar published studies that have demonstrated the advantages of the GDMT combination in reducing healthcare resource utilization and all-cause mortality.[11,22-26] However, the advantages became insignificant after the removal of those intolerable to GDMT. These discrepancies in the utilization of healthcare resources after the exclusion of those intolerable to GDMT, could have been due to the reduction in study power and that future studies with larger sample sizes are warranted to corroborate our findings.

This study has some limitations. As the study was not randomized, its retrospective design limits its findings. However, this is among the first few studies in the Gulf region to provide an insight into the reasons behind GDMT non-prescribing. The bias of up-titration of GDMT doses was minimized by the fact that patients were followed up for at least 18 months (sufficiently long enough of a period to up-titrate to optimum target doses) after diagnosis and initiation of GDMT. The exclusion of those ineligible or intolerable to GDMT had dropped the sample size by almost 55%, from 171 to 77 and this affected the study power. Additionally, patients were not on evidence-based SGLT2 inhibitors as these medications only became formulary items and available after the conclusion of this study. Future studies need to take into account the exclusion of those intolerable to GDMT when performing power calculations.

CONCLUSIONS

The reasons behind GDMT non-prescribing in HFrEF patients are frequent and not clearly obvious in patients' medical notes. After the exclusion of those intolerable to GDMT, the majority of the patients were prescribed beta blockers, RAS blockers/ HYD-ISDN combination and MRAs. All patients on MRAs received at least ≥50% of the optimum target dose, while in those on beta blockers and RAS blockers/ HYD-ISDN combination, the target doses were still suboptimal. Patients on the triple

GDMT combination were associated with significantly lower ER visits, hospital admissions, LOS and overall major adverse events. However, the apparent differences were no longer significant after the exclusion of those intolerable to GDMT. An establishment of a dedicated multidisciplinary HF team is highly warranted to optimize care in these patients. The findings should be interpreted in the context of low study power and that future studies, with larger sample sizes, are warranted to minimize this limitation.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR'S CONTRIBUTIONS

SA, JM, AA, MZ, and IA conceived the research idea and designed the study. IA conducted preliminary data analyses. SA and IA wrote the initial draft manuscript, but later ALL authors revised and made significant changes to the draft manuscript. All authors discussed the results and approved the final manuscript prior to submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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