**Evaluation of Prescribing Adherence to Guideline-Directed Medical Therapy in Patients with Chronic Heart Failure. A Retrospective Study at The National Heart Centre in Oman**

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**Abstract**

**Purpose:** Guidelines-directed medical therapy (GDMT) may benefit patients with heart failure (HF) reduced ejection fraction ((HFrEF, ≤40%), however, there are significant gaps between guidelines and real-world practices. The aim of this study was to evaluated prescribing adherence to the recommended GDMT in HFrEF patients using the global guideline adherence score. **Method:** A retrospective study among HFrEF patients at the National Heart Centre in Muscat, Oman, was conducted between 1st January and 30th June 2022. The optimum target doses were identified according to the 2021 European Society of Cardiology HF guidelines. Thus, for eligible patients, prescribing all indicated GDMT in doses ≥50% of the target dose is considered good adherence; the use of more than half of the medications in doses ≥50% of the target dose, moderate adherence; and the use of less than half the recommended medications and/or in doses <50% of target dose, poor adherence. Univariate statistics were used for the analysis. **Results:** The overall mean age of the cohort was 57 ±13.6 years with a predominance of male patients (70%; n=180). The overall prescribing adherence to guideline-recommended HF medications was 71% good, 22% moderate, and 7% poor. There was a significate association between the sub-optimal dose of GDMT and patients with hypertension (P=0.004), dilated cardiomyopathy (P=0.015), older age (P=0.004) and chronic kidney disease (P=0.001). **Conclusion:** Prescribing adherence to recommended GDMT in Oman is similar to that of international studies. Furthermore, sub-optimal GDMT titration was significantly associated with older age and comorbidity, suggesting that frailty perception may have an impact on GDMT titration.

**Keywords:**

Guideline-directed medical therapy. GDMT. Prescribing. Guideline adherence. Heart Failure. Oman.

**Key Points**

* The Global Guideline Adherence Score was used to evaluate GDMT and related dosages in Omani patients with HFrEF.
* The global guideline adherence score is a scoring system that integrated not only the prescription of recommended classes of GDMT in eligible patients, but also the use of at least 50% of recommended dosages.
* The overall prescribing adherence to guideline-recommended HF medications was 71% good, 22% moderate, and 7% poor. There was a significate association between the sub-optimal dose of GDMT and patients with hypertension (P=0.004), dilated cardiomyopathy (P=0.015), older age (P=0.004) and chronic kidney disease (P=0.001).
* Prescribing adherence to recommended GDMT in Oman is similar to that of international studies. In addition, sub-optimisation of GDMT was significantly associated with older age and comorbidities suggesting that perceived frailty may influence physician decision-making regarding GDMT titration.

**The Plain Language Summary**

Our study examined adherence to guideline-recommended heart failure medications in the Omani population using the Global Guideline Adherence Score. A second objective of the study was to determine whether sub-optimization of guidelines-directed medical therapy in Omani heart failure patients with a reduced ejection fraction (HFrEF, 40%) was associated with patient demographics, including age, gender, and chronic diseases. Using data from the Al-Shifa 3Plus health information system established by Oman's Ministry of Health, we found that the overall prescribing adherence to guideline-recommended heart failure medications was 71% good, 22% moderate, and 7% poor which was similar to that of international studies. Patients with hypertension, dilated cardiomyopathy, older age, and chronic kidney disease were significantly associated with sub-optimal Guidelines-directed medical therapy, suggesting that frailty perception may have an impact on Guidelines-directed medical therapy titration.

**Background:**

Globally, 64.3 million people are estimated to have suffered from heart failure (HF) in 2017 [1,2]. HF can be classified according to the left ventricular ejection fraction (LVEF) into three phenotypes, namely HF with reduced (HFrEF, ≤40%), mildly reduced (HFmrEF, 41–49%) and preserved ejection fraction (HFpEF, ≥50%) [3].

Patients with HF are treated to improve their clinical status, functional capacity, and quality of life while reducing their risk of hospital readmissions [4]. For patients with HFrEF, recommended treatments include guideline-directed medical therapy (GDMT), which includes β-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor–neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs) [5]. A new drug class, sodium-glucose cotransporter-2 inhibitors (SGLT2Is), has been added to the GDMT, creating four core GDMT classes for HFrEF [5]. Additionally, various therapeutic adjuncts, including ivabradine, vericiguat and omecamtiv-mecarbil, have been found to be effective in some cases [6]. When initiated and titrated to maximally tolerated doses, the GDMT for HFrEF decreases mortality and morbidity [5,7]. The combination of ACEI, BB, MRA, and SGLT2I, as compared with no treatment, extended life expectancy for 70-year-olds by 5 years in two independent cohort studies [8].

While there is robust scientific evidence that GDMT has benefits, studies demonstrate that despite the absence of contraindications or intolerances, many HFrEF patients are not receiving one or more of the recommended GDMT, and most patients receive inadequate GDMT doses, even when treated. A patient with HFrEF receiving sub-optimal doses may not achieve the survival outcomes shown in clinical trials. As shown by Ouwerkerk et al. (2017), patients treated with less than 50% of the guideline-recommended dose of ACEIs/ARBs and BBs have poorer prognoses than those treated at 100% dosage [9]. As per the analysis by Zubaid et al. (2020) of the Gulf DYSPNEA HF registry, which included Oman and the other four Arabian Gulf countries, although a high proportion of patients with HFrEF received treatment (87% ACEI/ARB/ARNI, 91% BB and 64% MRA), only a small percentage received GDMT target doses (13% ACEI/ARB/ARNI, 27% BB and 4.4% MRA) [10]. Furthermore, similar findings were seen in other HF registries from Europe and the United States, indicating that the problem persists across different healthcare systems [11-13].

Failure to prescribe or/and optimise GDMT in patients with HFrEF is frequently related to either (i) physician-related factors such as lack of awareness of therapy goals, focus on symptom relief rather than reduction of mortality, or fear of side effects; (ii) patient-related factors such as frailty, intolerance or contraindications; (iii) non-medical factors such as availability of GDMT or access to the healthcare system [14]. According to a meta-analysis by Denfeld et al. on the prevalence of frailty in HF, nearly one in two patients have frailty. [15]. Frailty was linked to an increased risk of death, an increase in hospital readmissions, and a reduction in functional ability over the course of a year among older patients with chronic HF. As part of their study of the quality of adherence to guideline recommendations for lifesaving treatment in HF, Komajda et al. (2016) developed a global guideline adherence score for measuring physicians' prescribing with the following classes of medication: ACEIs/ARBs/ARNIs, BBs, MRAs, and ivabradine [14]. This scoring system integrated not only the prescription of recommended classes in eligible patients, but also the use of at least 50% of recommended dosages. This adherence score has been used by several studies around the world, but no research articles have been published from Oman or other countries in the Middle East. Thus, the purpose of this study was to evaluate, using the Global Guideline Adherence Score, the usage of GDMT and related dosages in patients with HFrEF in the Omani population. Furthermore, the study sought to ascertain whether the sub-optimization of GDMT (<50%) among the Omani HFrEF population was associated with patient demographics, including age, gender, and comorbidities.

**Methods**

**Study design and population:** Patients with chronic heart failure (HF) (≥18 years of age) who visited the HF Clinic at the National Heart Centre (NHC) in Muscat, Oman, between January 1, 2022, and June 30, 2022, were assessed for eligibility. All patients with LVEF ≤40% measured on the most recent echocardiogram (≤2 years) were enrolled. If a patient had multiple ejection fraction (EF) measurements, the most recent one was used. Eligible patients had a documented diagnosis of HF from a hospital admission at least 3 months before enrolment and an echocardiogram confirming the diagnosis. The study uses a convenience sample, a non-probability sampling method, since no previous data exist on local HFrEF prevalence.

**Setting:** NHC provides comprehensive care for cardiovascular conditions and heart diseases in Muscat, Oman. It is considered a referral tertiary care health institution that receives patients from all regional primary and secondary health care institutions (hospitals, polyclinics and health centres) in Oman. At NHC, HF patients are treated and followed up by cardiologists with sub-speciality in HF management with work experience ranging from 5 to 10 years.

**Data collection and generation:** Demographic and clinical characteristics for this study were collected from the NHC's data registry, Al-Shifa 3Plus (the healthcare information system established by the Ministry of Health, Oman). Additionally, GDMT (ACEI/ARB/ARNI, BB, MRA, ivabradine) medications and their corresponding doses were also collected from patients' electronic records. The optimum target doses for carvedilol, bisoprolol, lisinopril, valsartan, the sacubitril/valsartan combination, ivabradine, spironolactone, and eplerenone were identified according to the 2021 European Society of Cardiology (ESC) HF guidelines which was the most update guidelines for HF at the time study conducted and utilized by HF cardiologists at NHC. Additionally, other medications for co-morbid conditions were also collected. The adherence score was calculated for each patient as follows: 1 point for each prescription of an ACEI/ARB/ARNI, BB, MRA, ivabradine (if indicated), and 0 points for no prescriptions. In the case of contraindications or intolerance, 1 point was given. Thus, for eligible patients,

1. use of all indicated medications in doses ≥50% of the target dose is considered good adherence,
2. use of more than half of the medications in doses ≥50% of the target dose, moderate adherence, and
3. use of less than half the recommended medications and/or in doses <50% of target dose, poor adherence.

**Statistical analysis:** Continuous variables normally distributed were reported as mean ± standard deviation while categorical variables were reported as numbers and percentages. Chi-square test or Fisher’s exact were used to assess the association between categorical variables as appropriate. Statistical significance was defined as a p-value < 0.05. The Statistical Package for the Social Sciences (SPSS, version 28; IBM Corporation) was used to perform the statistical analyses.

**Outcome measures:** The primary outcome measures of interest were the assessment of the use and corresponding dosages of GDMT in patients with HFrEF in Oman population using the Global guideline adherence score. Secondary outcome measures included determining the association between patients' demographic characteristics, such as age, comorbidities, and gender, and the sub-optimisation of GDMT (<50%) among the Omani HFrEF population.

**Results**

This study included 259 HFrEF patients, which met the inclusion criteria for enrolment, with a mean EF of 28 ± 6.9%. The overall mean age of the cohort was 57 ± 13.6 years old, of which 4.2% (n=11) were smokers. There was a marked predominance of male patients (70%; n=180). Furthermore, comorbid conditions were common, particularly hypertension (HT) (42.1%; n=109), diabetes mellitus (DM) (35.1%; n=91), dilated cardiomyopathy (DCM) (32.8%; n=85) coronary artery disease (CAD) (18.1%; n=47) and chronic kidney disease (CKD) (12%; n=31). As presented in Table 1, most patients were receiving diuretic agents (78.4%; n=203) and majority was treated with statins (56.8%, n=147) or antiplatelet agents (43.6%; n=113). The use of digoxin (2.7%, n=7) was reported in only a minority.

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| --- | --- |
| **Characteristics, n (%) unless specified otherwise** | **Patients n=259** |
| Male | 180 (69.5%) |
| Female | 79 (30.5%) |
| Age, mean ±standard deviation (SD), years | 57 ±13.6 |
| Smoking status | |
| None-smoker | 13 (5%) |
| Smoker | 11(4.2%) |
| Ex-smoker | 26(10%) |
| New York Heart Association Class | |
| I | 58 (22.4%) |
| II | 81(31.3%) |
| III | 21 (8.1%) |
| IV | 2 (0.8%) |
| Heart Rate, mean ±SD, beats per minute | 75.32 ±14.29 |
| Blood Pressure (millimetres of mercury, mmHg) | |
| Systolic blood pressure, mean ±SD, mmHg | 132.34 ±22.49 |
| Diastolic blood pressure, mean ±SD, mmHg | 76.92 ±15.6 |
| Ejection Fraction | |
| Less than 35% | 194 (75%) |
| 35% and more | 65 (25%) |
| Serum Creatinine, mean ±SD, micromoles/litre | 95.44 ±28.49 |
| Haemoglobin, mean ±SD, grams/decilitre | 13.48 ±4.09 |
| Time since first Heart Failure diagnosis, mean ±SD, years | 4.45 ±3.33 |
| Co-morbidities | |
| Asthma/Chronic obstruction pulmonary disease | 12 (4.6%) |
| Chronic kidney disease | 31(12%) |
| Hypertension | 109(42.1%) |
| Diabetes Mellitus | 91 (35.1%) |
| Anaemia | 3 (1.2%) |
| Atrial Fibrillation | 27 (10.4%) |
| Coronary artery disease | 47 (18.1%) |
| Stroke/ Transient ischemic attack | 3 (1.2%) |
| Left bundle branch block | 26 (10%) |
| Ischemic Cardiomyopathy | 27 (10.4%) |
| Dilated Cardiomyopathy | 85 (32.8%) |
| Others | 218 (84.2%) |
| Pharmacological treatment and devices | |
| Amiodarone | 14 (5.4%) |
| Antidiabetics | 83 (32%) |
| Anticoagulants | 53 (20.5%) |
| Antiplatelets | 113 (43.6%) |
| Calcium channel blockers | 17 (6.6%) |
| Diuretics | 203 (78.4%) |
| Digoxin | 7 (2.7%) |
| Nitrate | 37 (14.3%) |
| Statins | 147 (56.8%) |
| Cardiac resynchronisation therapy | 21 (8.1%) |
| Implantable cardioverter defibrillator | 23 (8.9%) |

**Table 1. Demographic and clinical characteristics of study population.**

As shown in Figure 1, 71% of the overall population had good class adherence (i.e., received all the recommended medications for their individual profile in doses ≥50% of the target dose), 22% moderate (more than half of the recommended medications in doses ≥50% of target dose) and 7% poor (less than half the recommended medications and/or in doses <50% of target dose). With regards to target dose attainment, a total of 46% (119/259), 41% (106/259), 96% (246/259), and 100% (67/67) of the patients were prescribed ≥50% of the target dose for BBs, ACEI/ARB/ARNI, MRAs and ivabradine respectively. At the same time, 33% (84/259), 24% (59/259), and 1% (2/259) of patients were prescribed 100% of the target dose for BBs, ACEI/ARB/ARNI, and MRAs, respectively Figure 2.

**Figure 1. Global guideline adherence score at NHC, Oman.**

NHC, National Heart Centre; Good adherence, defined as use of all indicated medications in doses ≥50% of the target dose; moderate adherence defined as use of more than half of the medications in doses ≥50% of the target dose; poor adherence defined as and use of less than half the recommended medications and/or in doses <50% of target dose.

**Figure 2. The proportion of GDMT dose attainment**

GDMT, guideline-directed medical therapy; BBs, β-blockers; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor–neprilysin inhibitors, and MRAs, mineralocorticoid receptor antagonists.

Univariant analyses of the variables associated with the sub-optimisation (<50%) of BBs, ACEI/ARB/ARNI, and MRAs are displayed in Table 2. According to univariant analysis, there was a significate association between the sub-optimal dose of BB and HT (odd ratio [OR]: 2.64; 95% confidence interval [CI]: 1.36 to 5.13; P=0.004). Also, patients with ACEI/ARB/ARNI and with DCM (OR: 2.1; 95% CI 1.18 to 3.75; P=0.012), and CAD (OR: 0.45; 95% CI 0.24 to 0.86; P=0.015) had a greater likelihood of being sub-optimised. Finally, sub-optimisation of MRAs was associated with older age (OR: 7.51; 95% CI 1.93 to 29.16; P=0.004), patients with a history of CKD (OR: 10.70; 95% CI 3.05 to 37.6; P=0.001), and with history of HT (OR: 3.88; 95% CI 1.01 to 14.98; P=0.04).

**Table 2. Simple logistic regression model results of association between patient-level factors and sub-optimisation (<50%) of BBs, ACEI/ARB/ARNI and MRAs.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variables | BBs | | ACEI/ARB/ARNI | | MRAs | |
| OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Age per 5 years increase | 0.98(0.51-1.88) | 0.942 | 0.56(0.32-0.98) | 0.042 | 7.51(1.93-29.16) | 0.004 |
| Female vs male | 1.26(0.65-2.44) | 0.496 | 1.09(0.63-1.90) | 0.765 | 1.96(0.58-6.62) | 0.279 |
| EF per 5% increase | 0.89(0.49-1.62) | 0.707 | 1.16(0.70-1.94) | 0.560 | 0.53(0.15-1.85) | 0.317 |
| NYHA III-IV vs I-II | 1.27(0.40-4.05) | 0.685 | 1.86(0.64-5.36) | 0.254 | 0.72(0.09-6.01) | 0.763 |
| ICM | 0.96(0.37-2.51) | 0.936 | 0.56(0.25-1.24) | 0.152 | 3.50(0.87-14.08) | 0.078 |
| DCM | 0.94(0.50-1.76) | 0.842 | 2.10(1.18-3.75) | 0.012 | 0.20(0.03-1.55) | 0.122 |
| CKD | 1.50(0.55-4.10) | 0.431 | 0.73(0.34-1.58) | 0.428 | 10.70(3.05-37.6) | 0.001 |
| HT | 2.64(1.36-5.13) | 0.004 | 1.05(0.63-1.76) | 0.850 | 3.88(1.01-14.98) | 0.049 |
| DM | 1.19(0.63-2.23) | 0.596 | 0.61(0.36-1.04) | 0.070 | 3.42(0.97-12.00) | 0.055 |
| AF | 1.24(0.45-3.44) | 0.679 | 1.35(0.57-3.21) | 0.500 | 0.86(0.11-6.94) | 0.883 |
| CAD | 0.88(0.42-1.87) | 0.743 | 0.45(0.24-0.86) | 0.015 | 1.74(0.44-6.82) | 0.428 |
| Abbreviations: β-blockers (BBs), Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin receptor blockers (ARBs), Angiotensin receptor–neprilysin inhibitors (ARNIs), Mineralocorticoid receptor antagonists (MRAs), Odd Ratio (OR), Confidence Interval (CI), Probability value (P-value), Ejection Fraction (EF), New York Heart Association (NYHA), Ischemic Cardiomyopathy (ICM), Dilated Cardiomyopathy (DCM), Chronic Kidney Disease (CKD), Hypertension (HT), Diabetes Mellitus (DM), Atrial Fibrillation (AF), Coronary Artery Disease (CAD). | | | | | | |

**Discussion**

In this study, adherence to guideline-recommended HF medications was similar to the one conducted in Poland by Opolski et al. (2017), which had a similar care setting as the NHC, and used the same method [16]. However, a study by Komajda et al. (2016), revealed slightly lower adherence rates, including 67% good, 25% moderate, and 8% poor [14]. One potential explanation for this trend is timing of the studies (2016 versus 2022). According to the Institute of Medicine report, new evidence is delayed for a long time in integrating into clinical practice, and guideline-directed care is not delivered uniformly [17]. Globally, the average time between the publication of trial results and widespread uptake is 17 years [18]. Additionally, the current study demonstrated greater enhancement of GDMT optimisation (≥50% of target dose) within each drug class than that found in other studies published from Oman. A study carried out by Hanbali et al. (2020) at a tertiary educational healthcare institution in Oman, found that only 56% and 42% of patients received ≥50% of the BB and ACE/ARB target doses, respectively [19]. The measure was repeated by Al-Aghbari et al. (2022) even though patients with intolerances and contraindications to GDMT were excluded from the dose optimisation analysis; only 61% and 44% of patients treated with the BB and ACEs/ARBs reached ≥50% of target doses [20]. A major difference between the two healthcare settings can be seen in the types of providers (non-specialists, general practitioners versus cardiologists). The general practitioners are found to be less likely to adhere to guideline recommendations when prescribing medication or titrating dosage for HF patients, probably due to a lack of awareness regarding the guidelines, focusing more on symptoms relief rather than mortality reduction or fear of intolerance and side effects [21]. This study result suggests that when HFrEF patients are being treated by cardiologists, there is a high rate of adherence to guidelines and drug class optimisation.

In this study, most of the sub-optimisation (<50%) of GDMT was attributed to limited physiological and clinical factors in the patients. Similarly, Ouwerkerk et al. (2017) conducted logistic regression analysis of factors associated with sub-optimal GDMT dosing and found that factors associated with lower ACEI/ARB dosing included female gender, lower body mass index, worse renal function, and higher alkaline phosphatase levels, while older age, a lower heart rate, lower diastolic blood pressure, and signs of pulmonary congestion were associated with lower BB dosing [9]. Moreover, Greene et al. (2018) found a lower likelihood of up-titration or initiation of GDMT in patients who were older (BB and ARNI), had a history of ventricular tachycardia/fibrillation (BB), had higher EF (ARNI and MRAs), and had hyperlipidaemia (MRAs) [11]. Furthermore, older age has been previously reported to impact adherence, with the perception of frailty contributing to this phenomenon, the “risk-treatment paradox,” where the most severely affected patients with HF are less likely to receive optimal treatment due to perceived frailty [22]. In fragile patients, disproportionate worries about clinical destabilisation can be caused by medication changes, along with lowered expectations of benefits from an appropriate dose of GDMT in a population that is underrepresented in clinical trials, which may explain this phenomenon [23]. Despite that, elderly patients who do not show signs of fragility or drug intolerance may benefit from target doses of GDMT. According to current guidelines, GDMT should be used and up-titrated regardless of age while considering each patient's unique circumstances and goals of care [5,7,24]. Studies such as this one and others suggest that co-morbidities and concerns about age-related intolerances are two major factors that influence sub-target dosing HF GDMT, which is consistent with the findings from a recent study on HF guidelines adherence gaps [25]. In most HFrEF trials, patients with more advanced comorbidities are excluded, and such patients may have a higher failure rate at the target dose. A lack of optimal use of GDMT due to intolerance or comorbidities may place patients at greater risk, so novel approaches that are effective and well-tolerated are needed.

This study is one of the few to provide insights into prescribing adherence to HF guidelines in specialised ambulatory HF settings in the Gulf region. However, there are several limitations to this study. Since this is a non-randomised retrospective study, its findings are limited. As this study population has a relatively young age group and a preponderance of males, it may not accurately reflect the profile of HF among older patients. In addition, patients on evidence-based SGLT2I were not included in this study, as this medication became available on the NHC formulary after the study concluded. Furthermore, the study did not evaluate other factors that could affect prescribing adherence (such as physician-related factors and non-medical factors). In view of this, future studies are needed to evaluate the prescribing adherence of GDMT in HFrEF patients' that also examine physician-related factors and non-medical factors.

**Conclusions**

Prescribing adherence to recommended GDMT in Oman is similar to that of international studies. In addition, sub-optimisation of GDMT was significantly associated with older age and comorbidities such as hypertension, chronic kidney disease, coronary artery disease, and dilated cardiomyopathy, suggesting that perceived frailty may influence physician decision-making regarding GDMT titration. Consequently, prescribing adherence to guidelines should be assessed according to patients' characteristics as part of patient-centred care since one size does not appear to fit all.

**Statements & Author Declarations**

**Availability of data and material:** The data that support the findings of this study are available from the corresponding author upon request.

**Code availability:** Not applicable.

**Consent for Publication:** Not applicable.

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**Conflict of Interest:** The authors declare no competing interests.

**Author Contributions:** MA and LN conceived the research idea and designed the study. MA and GhA conducted preliminary data analyses. MA 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.  
**Ethics approval:** Research approval for this study was granted by the Health Studies and Research Approval Committee at the Ministry of Health in Muscat, Oman (MOH/CSR/22/25991, dated 30 June 2022). As this was a thesis project for a master's student, Manal Al Balushi, the first author, Research Ethics Committee approval was also obtained on 18th May 2022 from Robert Gordon University, Aberdeen, United Kingdom.

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