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Original article

Guideline-directed medical therapy in heart failure patients with reduced ejection fraction in Palestine: Retrospective clinical audit study

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ABSTRACT

Objectives: To assess the characteristics of patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with mid-range ejection fraction (HFmrEF), as well as the current application of guideline-directed medical therapy (GDMT) in Palestine.
Methods: This retrospective cohort study involved a population of heart failure (HF) patients who visited cardiology clinics at An-Najah National University Hospital and the National Hospital, Palestine. The primary outcome measures of interest were the proportions of patients prescribed guideline-based cardiovascular medications (GBCMs), such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists (MRAs), and the corresponding optimized doses at $\geq$ 50 % of targets and the reasons underlying the non-prescription of GDMT.
Results: A total of 70.5%, 56.6%, and 88.6% of patients were on ACEIs/ARBs, MRAs, and β-blockers, respectively. Of all patients, 38.7% were on the triple GDMT regimen.
Conclusion: Less than half the patients received the triple combination treatment. Age, diabetes mellitus, chronic renal disease, and admission to the hospital for HF all had significant independent relationships with the reduced utilization and inadequate dosage of GDMT.

1. Introduction

Heart failure (HF) is a prevalent condition affecting over 26 million people worldwide and can lead to high morbidity and mortality rates, thereby imposing significant economic strain on healthcare systems. In Europe and North America, HF accounts for 1–2 % of total healthcare spending (Ambrosy et al., 2014; Farré et al., 2016). The global prevalence of HF is increasing rapidly, with an estimated 64.3 million cases in 2017, corresponding to 8.52 cases per 1,000 people and resulting in 9.91 million years lost due to incapacity, as well as $346.17 billion in expenditures in the US alone (Lippi and Sanchis-Gomar, 2020). While registry-based estimates suggest that 1–2 % of the adult population has HF (Groenewegen et al., 2020), a recent *meta*-analysis of echocardiographic studies of the general population, including previously unreported patients, estimated the prevalence to be as high as 4.2 % (van Riet et al., 2016).

HF is classified into three subtypes based on ejection fraction (EF): HF with reduced EF (HFrEF), HF with mid-range EF (HFmrEF), and HF with preserved EF (HFpEF) (Ponikowski et al., 2016). Treatment objectives for HF patients include improving their clinical status, functional capacity, and quality of life while reducing their risks of hospital readmissions and death. Guideline-based cardiovascular medications (GBCMs), including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), angiotensin receptor–neprilysin

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inhibitors (ARNIs), β-blockers, and mineralocorticoid receptor antagonists (MRAs) (Ezekowitz et al., 2017; Ponikowski et al., 2016; Yancy et al., 2018), are among the recommended treatments for hypertension and HF (Koh et al., 2017; Pitt et al., 2014; Solomon et al., 2016; Tsuji et al., 2017; Yancy et al., 2018; Yusuf et al., 2003). These medications have been shown to benefit both HFrEF patients and some HFmrEF patients.

Despite the established efficacy of GBCMs, studies have highlighted substantial discrepancies between the recommended guidelines and clinical practice, with underuse of medications and a reluctance to increase drug dosages to the appropriate levels in various regions, including Europe, North America, the Far East, and the Arabian Gulf (Balakumaran et al., 2018; Brunner-La Rocca et al., 2019; Chang et al., 2017; Diamant et al., 2019; Gjesing et al., 2013; Greene et al., 2018; Komajda et al., 2016; Krantz et al., 2011; Maggioni et al., 2013; Teng et al., 2018; Zubaid et al., 2020). These findings indicate a pressing need for increased awareness and implementation of evidence-based practices for managing HF.

To optimize the treatment of HFrEF patients, the current guidelines recommend using ARNIs/ACEIs/ARBs, β-blockers, and MRAs. If ARNIs/ACEIs/ARBs cannot be utilized, the guidelines suggest using a combination of hydralazine (HYD) and isosorbide dinitrate (ISDN) (Maddox et al., 2021; McDonagh et al., 2021; McDonald et al., 2021). This implementation of guideline-directed medical therapy (GDMT) is associated with decreased all-cause mortality (Burnett et al., 2017). However, studies have revealed significant underutilization of these drugs, not only in North America (Balakumaran et al., 2018; Diamant et al., 2019; Greene et al., 2018; Tsuji et al., 2017) and Europe (Gjesing et al., 2013; Greene et al., 2018; Komajda et al., 2016; Maggioni et al., 2013) but also in the Middle East (Hanbali et al., 2020; Zubaid et al., 2020). Intolerance and contraindications that are not frequently mentioned may be responsible for the underutilization of GDMT (Gjesing et al., 2013; Hanbali et al., 2020).

The addition of SGLT2 inhibitors to GDMT is recommended to reduce cardiovascular mortality and the worsening of HF in individuals with HFrEF, regardless of whether they have diabetes (McMurray et al., 2019; Packer et al., 2020). To improve clinical outcomes, guidelines (Maddox et al., 2021; McDonagh et al., 2021; McDonald et al., 2021) have suggested using the maximal suitable dose, which is > 50 % of the target GDMT dose (Fiuzat et al., 2020). However, several studies (Balakumaran et al., 2018; Brunner-La Rocca et al., 2019; Diamant et al., 2019; Gjesing et al., 2013; Greene et al., 2018; Komajda et al., 2016; Maggioni et al., 2013) have found that HF medications are not being prescribed at the recommended doses; some of these studies were conducted in the Middle East (Balakumaran et al., 2018; Brunner-La Rocca et al., 2019; Diamant et al., 2019; Gjesing et al., 2013; Greene et al., 2018; Hanbali et al., 2020; Komajda et al., 2016; Maggioni et al., 2013; Zubaid et al., 2020). Despite the availability of overwhelmingly good data (CIBIS-II Writers, 1999; Cohn and Tognoni, 2001; Granger et al., 2003; MERIT-HF Study Group, 1999; Packer et al., 1996, 2002; Pitt et al., 1999; Zannad et al., 2011), fewer than 25 % of HFrEF patients receive the recommended target levels of therapy (Komajda et al., 2016).

Research has demonstrated that patients who receive doses of ACEIs/ARBs and β-blockers that are < 50 % of the guideline-recommended doses have a poorer prognosis than those who receive the full target doses (Ouwerkerk et al., 2017). However, limited research has been conducted on the use and dosages of these medications in the Palestinian population.

Therefore, this study aimed to assess the use and corresponding dosages of GDMT in patients with HFrEF and HFmrEF in Palestine in accordance with the guidelines of the European Society of Cardiology (ESC), American College of Cardiology Foundation/American Heart Association (ACCF/AHA), and Canadian Cardiovascular Society (CCS) for HF. Additionally, the study aimed to identify the reasons behind the non-prescription of GDMT in Palestine.

2. Material and methods

2.1. Study design and setting

This retrospective study was based on a population of HF patients (>18 years of age) who visited cardiology clinics at An-Najah National University Hospital and the National Hospital, Nablus, Palestine, between January 2020 and December 2022.

2.2. Study population

2.2.1. Inclusion criteria

Patients with an EF of < 50 % as per an echocardiogram were included in the study. If a patient had multiple EF measurements, the most recent one was used. Patients were then classified into the HFmrEF or HFrEF categories. Eligible patients had a documented diagnosis of HF from a hospital admission at least 3 months before enrollment and an echocardiogram confirming the diagnosis. The echocardiogram was recorded as being performed 3–6 months, 6–12 months, or > 12 months prior to enrollment.

2.3. Sampling method

This retrospective study involved a cohort analysis based on the medical records of patients with HF who were registered at cardiology clinics at An-Najah National University Hospital and the National Hospital in Palestine. Data collection for this study occurred from January 2020 to December 2022. The study sample was selected using a convenience sampling method that met predefined inclusion and exclusion criteria.

2.4. Sample size calculation

Prior research has found that 33–41 % of patients are on triple GBCM classes (Al-Aghbari et al., 2022; Hanbali et al., 2020). The alpha level for the current study was set at 5 % to allow for a 95 % CI. The precision (d) of the 95 % CI was fixed at 5 % so that the width of the 95 % CI was a maximum of 10 %. Given these metrics and a further assumption that there would be a 40 % reduction in sample size at baseline, a sample size of 620 patients was determined to be required.

2.5. Data collection

For the purposes of the current study, various patient measurements were collected. These are presented in Table 1.

The baseline demographic and clinical data were collected during the patient admission process.

The optimal target doses for carvedilol, bisoprolol, lisinopril, irbesartan, valsartan, the sacubitril/valsartan combination, HYD/ISDN, spironolactone, and eplerenone were based on the 2021 guidelines for

Table 1
Patient data.

Demographics	Clinical and disease characteristics	Medications
AgeGender	Diabetes mellitus Chronic kidney disease Hypertension Myocardial infarction Atrial fibrillation Dyslipidemia Stroke Admission heart rate Systolic blood pressureDiastolic blood pressureGlycated hemoglobin (HbA1c)	GDMT: ACEIs (lisinopril) GDMT: ARBs (irbesartan and valsartan) GDMT: ARNIs (sacubitril/valsartan) GDMT: HYD/ISDNGDMT: β-blockers (carvedilol and bisoprolol) GDMT: MRAs (spironolactone and eplerenone) Other medications for comorbid conditions

HF published by the American (ACC/AHA/HFSA), Canadian (CCS/CHFS), and European (ESC) societies. These guidelines recommend a dose of 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 the 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 (Maddox et al., 2021; McDonagh et al., 2021; McDonald et al., 2021).

2.6. Outcome measures

The primary outcome measures of interest were the proportions of patients in Palestine who were prescribed GBCMs (ACEIs/ARBs, β-blockers, and MRAs) and the corresponding optimized doses at ≥ 50 % and 100 % of targets. Furthermore, we assessed the reasons underlying the non-prescription of GDMT.

2.7. Statistical analysis

Chi-square (χ^2) tests (or Fisher's exact tests for expected cells < 5) and unpaired sample *t*-tests were employed to analyze categorical variables (summarized using frequencies and percentages) and continuous normally distributed variables (presented as means and standard deviations, SDs), respectively. The clinical indicators linked to the prescription of the triple GDMT regimen were identified using multivariate logistic regression. Statistical significance was defined as a *p*-value < 0.05. The Statistical Package for the Social Sciences (SPSS, version 26; IBM Corporation) was used to perform the statistical analyses.

2.8. Ethical considerations

An-Najah National University's Institutional Review Board approved this retrospective cohort study (ref: Med. May 2022/4).

3. Results

3.1. Demographics and baseline characteristics

Demographic and clinical parameters are displayed in Table 2. A total of 650 patients enrolled in the study. The mean ± SD age was 66 ± 8 years. Men constituted 44 % of the study cohort and women 56 %. Of the total, 30 % patients ($n = 195$) had HFmrEF, and 70 % ($n = 455$) had HFrEF. The comorbid conditions among the study cohort were as follows: 365 (56.2 %) had diabetes mellitus, 423 (65.1 %) had chronic kidney disease, 412 (63.4 %) had hypertension, 155 (23.8 %) had myocardial infarction, 167 (26 %) had atrial fibrillation, 188 (29 %) had dyslipidemia, and 120 (18.5 %) had stroke. The mean ± SD heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated hemoglobin (HbA1c), and EF were 78 ± 12, 135 ± 12, 73 ± 11, 7.98 ± 2.6, and 29 ± 7, respectively. Patients who had HFrEF more likely to have chronic kidney disease (69.7 % vs. 30.3 %; $p = 0.001$) and atrial fibrillation (57.5 % vs. 43.5 %; $p = 0.014$) than patients with HFmrEF. However, there were no statistically significant differences between the groups in other demographic or clinical parameters.

3.2. The use of guideline-directed pharmacological medications in patients with HFrEF

Table 3 presents the usage of guideline-recommended treatments for patients with HF. A total of 70.5 % ($n = 458$), 56.6 % ($n = 368$), and 88.6 % ($n = 576$) of patients were on ACEIs/ARBs, MRAs, and β-blockers, respectively. The most commonly prescribed ACEI and ARB were lisinopril (84.9 %, $n = 259$) and irbesartan (73.8 %, $n = 113$), respectively. Carvedilol (53.5 %, $n = 308$) and bisoprolol (46.5 %, $n = 268$) were the most common β-blockers prescribed. Of all patients, 38.7 % ($n = 252$) were on the triple GDMT regimen.

Table 2
Demographic and clinical characteristics stratified by heart failure ejection fraction.

Demographic and clinical characteristics	All ($N = 650$)	Heart failure		*p*-value
		HFmrEF (EF 40–49 %) ($n = 195$)	HFrEF (EF < 40 %) ($n = 455$)	
Age	66 ± 8	65 ± 11	64 ± 14	0.561
Gender				
Male	286 (44 %)	134 (46.8 %)	152 (53.1 %)	0.112
Female	364 (56 %)	143 (39.3 %)	221 (60.7 %)	0.091
Diabetes mellitus	365 (56.2 %)	179 (49 %)	186 (51 %)	0.663
Chronic kidney disease	423 (65.1 %)	128 (30.3 %)	295 (69.7 %)	0.001*
Hypertension	412 (63.4 %)	190 (46.1 %)	222 (53.8 %)	0.114
Myocardial infarction	155 (23.8 %)	76 (49 %)	79 (50.9 %)	0.721
Atrial fibrillation	167 (26 %)	71 (42.5 %)	96 (57.5 %)	0.041*
Dyslipidemia	188 (29 %)	99 (52.6 %)	89 (47.3 %)	0.057
Stroke	120 (18.5 %)	48 (40 %)	72 (60 %)	0.069
HR, bpm, mean ± SD	78 ± 12	80 ± 15	79 ± 13	0.262
SBP, mmHg, mean ± SD	135 ± 12	131 ± 16	128 ± 11	0.131
DBP, mmHg, mean ± SD	73 ± 11	71 ± 18	784 ± 15	0.338
HbA1c, %, mean ± SD	7.98 ± 2.6	8.7 ± 2.8	7.9 ± 2.5	0.291
Ejection fraction, mean ± SD	29 ± 7	27 ± 2	28 ± 6	0.609

Abbreviations: HFmrEF, heart failure (HF) with mid-range ejection fraction (EF); HFrEF, HF with reduced EF; SD, standard deviation; HR, heart rate; bpm, beats/min; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Patients with HFrEF were more likely to be prescribed spironolactone (62.8 % vs. 36.4 %; $p = 0.014$), diuretics (88.6 % vs. 65.1 %; $p = 0.012$), and the triple GDMT regimen (44.4 % vs. 25.6 %; $p = 0.026$) than those with HFmrEF. However, patients with HFmrEF were more likely to be prescribed clopidogrel (45.1 % vs. 28 %; $p = 0.013$) and CCBs (30.8 % vs. 13.6 %; $p = 0.007$).

The percentages of patients on sacubitril/valsartan, HYD/ISDN, statins, clopidogrel, diuretics, aspirin, and CCBs were 8.5 %, 24.3 %, 68.2 %, 33.1 %, 81.5 %, 57.7 %, and 18.8 %, respectively.

Table 4 shows the target dose achievement of the different cardiovascular therapies. A total of 45.8 % ($n = 210$), 96.5 % ($n = 355$), 50 % ($n = 325$), 43.6 % ($n = 24$), and 48.7 % ($n = 77$) of patients were prescribed ≥ 50 % of the target doses for ACEIs/ARBs, MRAs, β-blockers, sacubitril/valsartan, and HYD/ISDN, respectively.

3.3. Factors associated with the prescription of guideline-directed pharmacological medications for patients with HFrEF and the reasons for non-prescription

Table 5 displays the results of multivariate logistic regression to assess the factors influencing the prescription of guideline-directed pharmacological medications for patients with HFrEF. Accordingly, increased age (OR 0.681; 95 % CI 0.603–0.768), diabetes mellitus (OR 0.872; 95 % CI 0.813–0.961), chronic kidney disease (OR 0.919; 95 % CI 0.889–0.951), and hospital admission for HF (OR 0.913; 95 % CI 0.882–0.937) were strong predictors of not being prescribed the triple GDMT regimen.

Table 6 shows reasons for not prescribing GBCMs. The main two reasons for not prescribing renin–angiotensin system (RAS) blockers were severe renal impairment (40.1 %) and hypotension (23.4 %). The

Table 3
Use of guideline-directed medical therapy in heart failure patients stratified by ejection fraction.

Medications	All (*N* = 650)	Heart failure		*p*-value
		HFmrEF (EF 40–49 %) (*n* = 195)	HFrEF (EF < 40 %) (*n* = 455)	
ACEIs	305 (46.9 %)	82 (42 %)	223 (49 %)	0.114
Lisinopril	259 (84.9 %)	70 (35.9 %)	189 (41.5 %)	0.712
Captopril	46 (15.1 %)	7 (3.6 %)	39 (8.6 %)	0.067
ARBs	153 (23.5 %)	46 (23.6 %)	107 (23.5 %)	1.00
Valsartan	40 (26.1 %)	12 (6.2 %)	28 (6.1 %)	0.981
Irbesartan	113 (73.8 %)	34 (17.4 %)	79 (17.3 %)	0.879
ACEI/ARB	458 (70.5 %)	133 (68.2 %)	325 (71.4 %)	0.455
ARNIs	55 (8.5 %)	19 (9.7 %)	36 (7.8 %)	0.418
Sacubitril/valsartan	55 (8.5 %)	19 (9.7 %)	36 (7.8 %)	0.216
HYD/ISDN	158 (24.3 %)	76 (39 %)	82 (18 %)	0.056
MRAs	368 (56.6 %)	70 (35.9 %)	298 (65.5 %)	0.057
Spironolactone	357 (97 %)	71 (36.4 %)	286 (62.8 %)	0.041*
Eplerenone	11 (3 %)	4 (2.1 %)	7 (1.5 %)	0.884
β-blockers	576 (88.6 %)	155 (79.5 %)	421 (92.5 %)	0.062
Carvedilol	308 (53.5 %)	68 (34.8 %)	240 (52.7 %)	0.071
Bisoprolol	268 (46.5 %)	86 (44.1 %)	182 (40 %)	0.213
Triple GDMT regimen	252 (38.7 %)	50 (25.6 %)	202 (44.4 %)	0.026*
Other medications				
Statins	443 (68.2 %)	120 (61.5 %)	323 (70.9 %)	0.151
Clopidogrel	215 (33.1 %)	88 (45.1 %)	127 (28 %)	0.031*
Diuretics	530 (81.5 %)	127 (65.1 %)	403 (88.6 %)	0.012*
Aspirin	375 (57.7 %)	116 (59.5 %)	259 (57 %)	0.162
CCBs	122 (18.8 %)	60 (30.8 %)	62 (13.6 %)	0.007*

Abbreviations: HFmrEF, heart failure (HF) with mid-range ejection fraction (EF); HFrEF, HF with reduced EF.

most common reasons for not prescribing β-blockers were hypotension (55.4 %) and asthma (17.6 %). The most common reasons for not prescribing MRAs were EF ≥ 35 % (55 %) and low estimated glomerular filtration rate (eGFR) (19.1 %).

4. Discussion

Based on previous evidence-based research, the management guidelines for HFrEF have consistently emphasized the importance of combination treatment with ACEIs/ARBs/ARNIs, β-blockers, and MRAs. However, clinical practice often lags behind guideline recommendations, resulting in patients either not receiving these evidence-based medications or not receiving them at the recommended target doses. This discrepancy between recommendations and practice can negatively impact patients' quality of life, symptoms, and survival (Fonarow et al., 2012; Komajda et al., 2017; Poelzl et al., 2014). Therefore, our study aimed to assess the characteristics of HFrEF and HFmrEF patients, the current application of guideline recommendations for pharmacological therapies, and the factors influencing the non-prescription of GDMT in Palestine.

Table 4
Target dose achievement of various cardiovascular medications stratified by heart failure ejection fraction.

Medications	All (*N* = 650)	Target dose achievement (≥50 %)		*p*-value
		HFmrEF (EF 40–49 %)	HFrEF (EF < 40 %)	
ACEIs				
Lisinopril (*n* = 259)	66 (25.5 %)	16 (22.8 %)	50 (26.5 %)	0.241
Captopril (*n* = 46)	15 (33.3 %)	4 (57.1 %)	11 (28.2 %)	0.064
ARBs				
Valsartan (*n* = 40)	25 (62.5 %)	8 (66.7 %)	17 (60.7 %)	0.822
Irbesartan (*n* = 113)	104 (92 %)	34 (100 %)	70 (88.6 %)	0.181
ARNIs				
Sacubitril/valsartan (*n* = 55)	24 (43.6 %)	13 (68.4 %)	11 (30.6 %)	0.212
HYD/ISDN (*n* = 158)	77 (48.7 %)	36 (47.4 %)	41 (50 %)	0.922
MRAs				
Spironolactone (*n* = 357)	350 (98 %)	67 (94.4 %)	283 (99 %)	0.611
Eplerenone (*n* = 11)	5 (45.5 %)	3 (75 %)	2 (28.6 %)	0.121
β-blockers				
Carvedilol (*n* = 308)	151 (49 %)	27 (39.7 %)	124 (51.7 %)	0.071
Bisoprolol (*n* = 268)	174 (65 %)	62 (72.1 %)	112 (61.5 %)	0.081

Abbreviations: HFmrEF, heart failure (HF) with mid-range ejection fraction (EF); HFrEF, HF with reduced EF.

Table 5
Multivariate logistic regression associating clinical parameters with use of the triple GDMT regimen.

Demographic and clinical characteristics	Triple GDMT regimen			
	OR	95 % CI		*p*-value
		Lower	Upper	
Age	0.681	0.603	0.768	**0.012***
Diabetes mellitus	0.872	0.813	0.961	**0.004***
Chronic kidney disease	0.919	0.889	0.951	**0.001***
Hypertension	1.031	0.901	1.172	0.631
Myocardial infarction	1.021	0.903	1.156	0.753
Atrial fibrillation	0.929	0.823	1.050	0.236
Dyslipidemia	0.933	0.820	1.062	0.295
Stroke	0.905	0.798	1.026	0.120
Hospital admission for heart failure	0.913	0.882	0.937	**0.01***
SBP, mmHg	1.021	0.885	1.192	0.750
DBP, mmHg	1.022	0.881	1.197	0.721
HbA1c, %	1.611	1.689	1.843	0.621
Ejection fraction	1.163	1.751	1.821	0.991

Our findings indicated that only 70.5 %, 88.6 %, and 56.6 % of HF patients with reduced and mid-range EF received ACEIs/ARBs, β-blockers, and MRAs, respectively. Furthermore, most patients were prescribed suboptimal dosing with 100 %, and only 45.8 %, 96.5 %, 50 %, 43.6 %, and 48.7 % of patients were prescribed ≥ 50 % of the target dose of ACEIs/ARBs, MRAs, β-blockers, sacubitril/valsartan, and HYD/ISDN, respectively. Additionally, less than half the patients were on the triple HF regimen. These findings highlight the need to improve adherence to guideline recommendations for GDMT for managing HFrEF and HFmrEF to improve patient outcomes.

We found that only 38.7 % of eligible patients were receiving the triple GDMT regimen, a figure lower than the prescription rate reported in a study by Al-Aghbari et al. (2022) (83 %) but higher than the rate reported by Hanbali et al. (2020) (33 %). Our study's prescription rates

Table 6
Reasons for not prescribing guideline-based cardiovascular medications.

RAS blockers ($n = 192$)	n (%)	β-blockers ($n = 74$)	n (%)	MRAs ($n = 282$)	n (%)
Acute kidney injury	22 (11.5 %)	Asthma	13 (17.6 %)	Acute kidney injury	22 (7.8 %)
Hyperkalemia	30 (15.6 %)	Bradycardia (<60 bpm)	11 (14.9 %)	Ejection fraction ≥ 35 %	155 (55 %)
Hypotension	45 (23.4 %)	Hypotension	41 (55.4 %)	Hyperkalemia	26 (9.2 %)
Severe renal impairment	77 (40.1 %)	Patient's inability to tolerate the medication	9 (12.2 %)	Low eGFR	54 (19.1 %)
Worsening renal failure	18 (9.4 %)			Worsening renal failure	25 (8.9 %)

Abbreviations: RAS, renin–angiotensin system; MRAs, mineralocorticoid receptor antagonists; eGFR, estimated glomerular filtration rate.
Severe renal impairment: creatinine clearance of < 10 ml/min
Hyperkalemia: > 5 mmol/l.
Hypotension: < 90/60 mmHg.
Low eGFR: < 30 ml/min/1.73 m^2.
Hypokalemia: < 2.5 mmol/l.

of ACEIs/ARBs (70.5 % vs. 62 %), β-blockers (88.6 % vs. 87 %), and MRAs (56.6 % vs. 39 %) were all higher than those reported by Hanbali et al. (2020). However, compared to the Gulf DYSPNEA registry study, which was conducted in the Arabian Gulf (Zubaid et al., 2020), the utilization rates of ACEIs/ARBs (70.5 % vs. 87 %), β-blockers (88.6 % vs. 91 %), and MRAs (56.6 % vs. 64 %) in our analysis were much lower. Furthermore, these prescription rates were much lower than those observed by Al-Aghbari et al. (2022), who reported that 94 %, 97 %, and 85 % of eligible patients received prescriptions for ACEIs/ARBs, β-blockers, and MRAs, respectively.

The study also found that HF patients were mainly treated by cardiologists and internists, who may have less knowledge of HF treatment recommendations and may prioritize symptom relief over lowering mortality and avoiding negative outcomes. This may have contributed to the lower use of GBCMs. Unfortunately, with the exception of MRAs, the majority of patients did not receive these drugs at the target doses indicated by the guidelines, with only around half our patients receiving ACEIs/ARBs, β-blockers, sacubitril/valsartan, and HYD/ISDN at > 50 % of the target dose.

We found that a substantial proportion of patients were prescribed suboptimal doses of ACEIs/ARBs, β-blockers, sacubitril/valsartan, and HYD/ISDN. Specifically, only 45.8 %, 50 %, 43.6 %, and 48.7 % of patients receiving ACEIs/ARBs, β-blockers, sacubitril/valsartan, and HYD/ISDN, respectively, received doses that were ≥ 50 % of the target dose recommended by the guidelines. Unfortunately, this is not an uncommon finding (Brunner-La Rocca et al., 2019; Chang et al., 2017; Chioncel et al., 2017; Diamant et al., 2019; Greene et al., 2018; Komajda et al., 2016; Teng et al., 2018; Zubaid et al., 2020), as other studies have reported similar or even higher rates of inadequate dosing for these medications. One potential explanation for this trend is that HF specialists and cardiologists handle pharmacological and device therapy differently. Specifically, cardiologists are more likely to prescribe target dosages of medications and to employ device therapy for patients with HFrEF, which may explain the lower prescription rates of these medications by non-specialists.

Therefore, strategies should be implemented to make it easier for patients to adhere to prescribed doses. HF management programs, performance monitoring, record audits, physician and patient training, and the implementation of nurse- or pharmacist-driven dosage regimens, among other actions (Fonarow et al., 2010; Marti et al., 2019), can all help to increase the achievement of appropriate doses.

Another important discovery was that failure to prescribe ACEIs/ARBs/ARNIs, β-blockers, and MRAs was independently predicted by old age, diabetes mellitus, chronic renal disease, and hospital admission for HF. This agrees with past findings that showed a higher left ventricular EF and a decreased utilization of treatments for chronic renal disease indicated by guidelines (Zubaid et al., 2020). Doctors' hesitation to raise the dose of β-blockers due to concerns about hypotension may underlie these outcomes.

Our study also found that around half the HF patients had clinically sound justifications for not receiving GDMT, including renal impairment, hypotension, and an EF < 35 %. This is in line with research conducted by Al-Aghbari et al. (2022).

The results of this retrospective cohort study on the utilization of GDMT in HF patients in Palestine have important clinical and practical implications. The study highlights the critical issues of underutilization and underdosing of GDMT, specifically the triple regimen involving ACEIs/ARBs, MRAs, and β-blockers. These findings underscore the urgency of targeted interventions aimed at improving adherence to evidence-based guidelines.

Healthcare providers must exercise caution when identifying patient-specific factors that contribute to reduced GDMT utilization, including age, diabetes mellitus, chronic renal disease, and prior hospitalizations for HF. The identification of these variables offers a valuable risk-stratification tool, enabling medical professionals to tailor treatment plans to individual patient needs.

In addition, this study underscores the practical importance of establishing systematic protocols and providing education to healthcare practitioners to support optimal GDMT implementation. Addressing the gaps in GDMT usage can lead to a reduction in HF-related hospitalizations, improved patient outcomes, and enhanced overall quality of life for HF patients in Palestine.

These findings should serve as a call to action, urging physicians, legislators, and healthcare organizations to collaborate to implement measures aligned with best practices, thereby raising the standard of care for HF patients in this region.

This study had several important limitations. Its retrospective design limits its conclusions because it was not randomized. However, this is one of the few studies in the Arab region that offers a perspective on the causes of GDMT non-prescription. Furthermore, because we evaluated only the most recent prescriptions and their associated doses, it is possible that some patients were still in the up-titration period and that the actual final doses were lower than those we observed in this study. More investigation is required to identify the factors that influence doctors' prescriptions of GDMT, including adverse effects, contraindications, and other patient- and doctor-related factors.

5. Conclusions

There are still significant practice gaps in the use of GBCMs. With fewer than half the patients receiving the triple treatment, the usage of GDMT for HF patients with a reduced or mid-range EF is notably low in Palestine. In the current study, age, diabetes mellitus, chronic renal disease, and admission to the hospital for HF all had significant independent relationships with the reduced utilization and inadequate dosage of pharmacological therapy. Additionally, all patients taking MRAs reached at least 50 % of their target doses, whereas only around half the patients taking ACEIs/ARBs, β-blockers, sacubitril/valsartan, and HYD/ISDN did the same. Additional research is required to confirm these results.

Ethics approval and consent to participate

An-Najah National University's Institutional Review Board approved this retrospective cohort study (ref: Med. May 2022/4).

Declaration of competing interest

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

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