

Title: The use of the four-pillar regimen for heart failure management and the factors associated with it: results from the Jordanian Heart Failure Registry (JoHFR)

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The use of the four-pillar of heart failure

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Abstract

Background: Heart failure (HF) is a complex cardiovascular disease. Effective management typically involves four main medications: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers (BBs), angiotensin receptor-neprilysin inhibitors, and mineralocorticoid receptor antagonists, along with sodium-glucose co-transporter-2 inhibitors (SGLT2i). The primary objective of this article is to assess and identify the utilization of four-pillar regimen for HF management medications and and explore the characteristics of the patients being on the four-pillar regimen the potential variation in clinical practice and explore the factors influencing guideline adherence among healthcare professionals in Jordan.

Methods: Data from the Jordanian HF registry (JoHFR) was analyzed, encompassing records of HF patients treated in various cardiology centers from 2021 to 2023. The study included both chronic and acute HF cases, with a focus on the combined usage of the four-pillar medications and the factors influencing this usage.

Results: The medical records of 2,151 HF patients with HF who were admitted to cardiology centers throughout Jordan were collected. Males comprised 58.0% of the included patients. Moreover, 71.0% of patients had chronic HF, whereas the rest, 29.0%, had acute HF. Of these, only 0.6% received the complete four-pillar treatment for heart failure of HF. Beta-blockers were the most frequently used medication, prescribed to 74% of patients, while SGLT2 inhibitors were the least common, used by only 9%. Notably, patients with type 2 diabetes were more likely to be on the four-pillar regimen (P-value = 0.016). Additionally, patients with a glomerular filtration rate (GFR) below 60 and an HbA1c level above 6% were consistently more likely to be treated with this comprehensive approach using the four-pillar (P-values = 0.044 and 0.066, respectively). The analysis revealed no significant difference in mortality rates between the patient two groups (P-value = 0.475).

Conclusion: The low utilization of the four pillars of HF treatment in Jordan suggests a need for enhanced collaborative efforts to improve physician awareness and address issues such as medication costs and availability. Targeted governmental initiatives could also help address these challenges and improve adherence to these essential medications. Our study demonstrated an overall low utilization of the four-pillar regimen for HF treatment in Jordan with several patients' characteristics associated with it. This highlights the need for enhanced collaborative effort and governmental initiatives to address the challenges of the low utilization of these medications.

Concise conclusion from the conclusion below:

In conclusion, the use of the four-pillar regimen for HF was very low in Jordan. Patients with a of history of type 2 diabetes and impaired renal function were more likely to receive the four-pillar regimen for HF highlighting the underuse of the four-pillar regimen.

Keywords: Heart Failure · Guidelines · Pillars · Cardiovascular Disease in Jordan

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Introduction

Heart failure (HF) is a complicated and debilitating disease of the cardiovascular system characterized by the inability of the heart to function normally and to pump blood properly and adequately, leading to impairment of cardiac input [1, 2]. As one of the major causes of morbidity and mortality, HF places a significant burden on health systems worldwide, including ~~those in~~ Jordan. (3) ~~Where-As~~ the prevalence of HF is on the rise, the importance of in-depth ~~checking-investigation~~ and ~~inspection-assesing~~ of the current guideline-directed medical therapy (GDMT) is essential, ~~adding-to-it~~~~along with~~ how adherent the physicians and the system are ~~to-in following~~ it, ~~which is fateful~~~~This is fundamental~~ towards improving and identifying factors associated with compliance ~~to these guidelines~~ [3].

The main intervention for successfully treating HF is pharmacological [1]. The ~~main~~ drugs used worldwide in the management and treatment of HF are angiotensin-converting enzyme inhibitors (ACEi), beta-blockers (BBs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter-2 inhibitors (SGLT2i) [1]. ~~for Among patients with HF with reduced ejection fraction (HFrEF) the guidelines are more clear~~, ACEi, ARNI, BBs, and SGLT2i are ~~considered~~ the main disease-modifying treatments for improving symptoms, reducing hospital admissions, and increasing survival [4,5]. However, only SGLT2i improves ~~sd~~ mortality among patients with HF with preserved ejection fraction (HFpEF) [6].

The primary objective of this article is to assess and identify the utilization of ~~four-pillar regimen for HF management medications and explore the characteristics of the patients being on the four-pillar regimen factors influencing guideline adherence among healthcare professionals in Jordan. Ultimately, the results will inform healthcare providers, policymakers, and other relevant stakeholders of the current state of HF management in the country, facilitating the implementation of strategies aimed at optimizing patient care, reducing morbidity and mortality rates, and improving overall health outcomes for individuals living with HF in Jordan.~~

Methods

Setting, Design, and Population

~~We analyzed data from the ongoing Jordanian HF Registry (JoHFR).~~ This is a national ~~heart failure~~HF registry in Jordan. Detailed methodology information is found in the ~~study~~-protocol registration-~~(NCT04829591)~~[7]. In brief, medical records ~~from of heart failure patients~~patients with HF who ~~reviewed-visited~~ cardiology medical centers across Jordan from 2021 to 2023 were ~~collected and studied~~reviewed. The study population included~~s~~ patients who were seen in ~~the inpatient wards or~~ outpatient clinics ~~for chronic HF and patients who were admitted through the ER for either new onset HF or an acute on top of chronic exacerbation attack~~with a diagnosis of HF. A total of 21 centers were involved in the study, including private centers, teaching and nonteaching hospitals, ~~and public secondary~~ and tertiary university hospitals. ~~Patients were divided in to two groups: patient on four-pillar regimen for HF and patient who are not on it.~~ ~~In T~~this is a prospective ~~multicenter study registry, in which patients were are being followed up to 1 year after the first medical record was collected.~~ Patients under the age of 18 were excluded from the study. According to Jordanian research data collection guidelines, each ~~site's~~ principal investigator was responsible for getting an institutional review board (IRB) approval from their institution. The IRB of the Specialty Hospital approved the conductance of this research (approval number: 5/1/t/104826). Patients were informed of the conduct of a heart failure registry and given the option to reject their data entry. A written informed consent was obtained from all the participants. All patients' data were dealt with anonymously.

Data Collection

An online Google form was distributed among the data collection team. This form was based on similar forms made by other heart failure registries. In summary, the form had several sections, including demographic characteristics of the patients, baseline co-morbidities, baseline laboratory investigations, ~~and what~~ drugs the

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patients were on, and clinical outcomes including 30-day mortality, need for mechanical ventilation, and length of hospital stay.

This form was filled out after hospital discharge or outpatient clinic visits. It was then shared into a database managed by this research's administrative and analytic team. Heart failure with reduced ejection fraction (HFrEF) is defined by an echocardiogram ejection fraction $<45\%$; meanwhile, heart failure with preserved ejection fraction (HFpEF) is diagnosed by an echocardiogram with an ejection fraction of $>50\%$ with (versus and?) a diastolic dysfunction. Lipid profiles were abnormal if one or more of the following were positive: total cholesterol was ≥ 200 mg/dL, LDL ≥ 130 mg/dL was high, triglycerides ≥ 150 mg/dL, or HDL levels were <40 . Elevated BNP and NT-ProBNP were ≥ 100 pg/L and ≥ 125 pg/L, respectively. The normal sodium (Na) range is 136 to 145 mmol/L. Meanwhile, the normal potassium (K) range was 3.5–5 mmol/L; any result that exceeded or fell outside this range is considered abnormal. Anemia was defined when hemoglobin levels (Hg) were less than 10 g/dL. Kidney function tests were abnormal when urea levels were >20 mmol/L, creatinine was >115 micromoles/L, and eGFR was <60 ml/min/1.73 m². Lastly, HbA1c levels above 6% were considered abnormally high. The 30-day mortality, need for mechanical ventilation, and length of hospital stay were collected for the patients admitted to the hospital.

In 2021, the ACC (American College of Cardiology (ACC)) and the AHA (American Heart Association (AHA)) gave SGLT2i inhibitors a class I indication for treating HFrEF and a class IIa indication for both mildly reduced EF (versus ejection fraction?) (41–49%) and HF with preserved EF (versus HFpEF?) ($\geq 50\%$). These recommendations made SGLT2i inhibitors one of the main four pillars of treating heart failure. Accordingly, the main four-pillar 4-pillars of treating HF in this study were ~~are~~ BB, ACEI/ARBs, ARNI, and SGLT2i. Therefore, the outcome of interest in this study was the prevalence of using the main 4 pillars in Jordan. In addition, we aimed to investigate the factors associated with the use of these 4 pillars.

Data Analysis

The data was entered using Microsoft Office Excel 2019 and then imported and analyzed using IBM SPSS v.25 software. The patients' demographics, comorbidities, laboratory investigations, and echocardiographic measures were compared using 4 pillars of HF using T test and Chi-square was used to compare patients variables according to the use of the four pillars of HF. Chi-square for continuous and categorical variables, respectively. The data is described using counts with percentages for categorical variables. We have conducted survival analyses using Kaplan-Meier curve to assess the difference between patients who were on the 4 pillars of HF and patients who were not. A p-value <0.050 was considered statistically significant.

Results

Characteristics of the included patients

The medical records of 2,115 heart failure patients with HF who were admitted to cardiovascular cardiology centers throughout Jordan were collected. Males comprised 58.0% (4235/2115) of the included patients.

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Moreover, 71.0% of patients had chronic HF, whereas the rest, 29.0%, had acute HF. A percentage of 70.3% of patients had heart failure with reduced ejection fraction (HFrEF). whereas, 29.7% had heart failure with preserved ejection fraction (HFpEF). Patients who were on the 4-pillars four-pillar of HF (the pillars are SGLT2 inhibitors, ARNI, B-blockers, and MRA) were 0.6% of all study samples participants. Figure 1 describes the use of each of the 4 pillars in HF management. The most commonly used medication was beta-blockers BBs (74%), while the least commonly used were ARNI (10%) and SGLT2i inhibitors (9%). Figure 2 shows the percentage of usage of the 4-four-pillars among the included patients. Furthermore, 69.2% of pts-the patients had type 2 diabetes, whereas 80.7% had hypertension. The percentage of smoking and alcohol among the included patients was 31.3% and 0.6%, respectively.

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Commented [RK6]: Unclear! Suggestion: Descriptive statistics of mean and standard deviation for continuous variable and frequency with percentages for categorical variables were presented. To detect significant mean differences between the study groups for continuous variables, student t-tests were applied. Chi-squared tests were applied for categorical variables.

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Comparison of the Characteristics of the Patients According to the Use of the HF-4 Pillars

Table 1 summarizes the factors variable studied between two study distinct-patient groups: those on the four-pillar regimen for heart failure (HF) management and those not on the regimen. A pronounced discrepancy was observed in the prevalence of type 2 diabetes between these groups. Remarkably, all patients with type 2 diabetes were treated with the four-pillar regimen (P-value = 0.016), underscoring a targeted approach for this subset of the population. This association is further visualized in Figure 3, which delineates the proportional use of each of the four pillars across patients with and without type 2 diabetes, demonstrating a higher utilization rate among diabetic individuals with type 2 diabetes. Furthermore, every patient prescribed SGLT2i-inhibitors had a concurrent diagnosis of type 2 diabetes.

The employment of the four-pillar treatment strategy was also evaluated across different types of heart failure HF. Figure 4 highlights a greater percentage of patients with heart failure with reduced ejection fraction (HFrEF) receiving all four medications in contrast to those with heart failure with preserved ejection fraction (HFpEF), suggesting a trend towards more aggressive treatment protocols in HFrEF. However, the analysis indicated no significant distinction in the use of the four-pillar four pillars when comparing patients with acute HF to those with chronic HF. Also, there was no, nor was there a significant difference in the use of the four-pillar in the adoption of this regimen between genders sex, or across the variables of hypertension (HTN), smoking, alcohol use, dyslipidemia, obesity, or family history of atherosclerotic cardiovascular disease (ASCVD) or premature death.

Furthermore, renal function and glycemic control were pivotal in determining the use of the four pillars, as all patients who had GFR<60 or HbA1c>6 were found to be on the complete four-pillar treatment (P-value = 0.044, and 0.066, respectively). In contrast, no significant correlations-associations were observed between the use of the four-pillar therapy and other laboratory findings, such as lipid profiles, B-type natriuretic peptide (BNP), N-terminal pro b-type natriuretic peptide (NT-proBNP), sodium, potassium, hemoglobin, urea, and creatinine levels. Furthermore, the 30-day mortality rate did not significantly differ between the patient groups (P-value = 0.475).

Survival Analysis

Survival analysis demonstrated that patients who were not on the 4 pillars had worse survival compared to their counterparts. However, the difference was not statistically significant (HR=1.954; 95%CI: 0.272-14.010) (Figure 5).

Discussion

This is the first large-scale national prospective multi-center registry to study heart failure-patients with HF in Jordan, that has continued enrolling patients for two years. Data regarding patient demographics, medical history, clinical characteristics, prescribed medications, and follow-up visits is collected and analyzed. The results of this study shed light on several important aspects related to the utilization of medications for the treatment of heart failure (HF) in Jordan and the degree of adherence to current guidelines. A notable observation is the low percentage of patients receiving the recommended combination therapy consisting of beta-blockers, angiotensin receptor neprilysin inhibitors (ARNIs), sodium glucose cotransporter 2 inhibitors (SGLT2 inhibitors), and mineralocorticoid receptor antagonists (MRAs).

Our study revealed that only 0.6% of HF-patients with HF were prescribed this optimal combination therapy. This low percentage of utilizing these medications can be attributed to several factors, including cost and availability. SGLT2i inhibitors are relatively newer agents demonstrating substantial cardiovascular benefits in HF-patients with HF. However, their higher acquisition costs compared to traditional HF medications, coupled with their limited availability within healthcare facilities, may contribute to the lower prescription rates. Cost-related factors and medication availability also play a crucial role in the utilization of other HF medications. Patients with limited financial resources or inadequate health insurance coverage may face barriers to accessing prescribed medications, leading to non-compliance or suboptimal treatment.

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Also, refile the figures captions!

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Similarly, the availability of certain medications within healthcare facilities, particularly in resource-limited settings, can influence prescription patterns. Addressing these barriers through policy interventions, such as improved reimbursement systems or the inclusion of essential medications in formularies, may help increase the utilization of guideline-recommended HF therapies. The suboptimal usage of combined medications raises concerns about the potential impact on patient outcomes. Several studies have demonstrated the significant benefits of these medications in improving survival, reducing hospitalizations, and enhancing quality of life in HF patients [8, 9]. Cardiovascular risk factors and co-morbidities, as well as cost and availability, are several patient-related factors that impact the selection and usage of HF medications.

Our study highlights that there was an association between the use of the four-pillar of HF and significance of comorbid conditions such as type 2 diabetes mellitus (DM), Haemoglobin A1C, and kidney function, measured by estimated glomerular filtration rate (GFR). These factors are found to be significant in influencing medication choices and dosing strategies. In a long-term HF registry done by the European Society of Cardiology, the and included patients with chronic HF, the prevalence of type 2 diabetes, atrial fibrillation, and renal dysfunction were 31.9%, 37.7%, and 18.4 for DM, Atrial Fibrillation, and Renal dysfunction, respectively [8]. HF itself is considered an insulin-resistant state and is associated with a significant risk for the future development of type 2 diabetes [8]. Higher HbA1C levels are associated with increased mortality, which is mainly multifactorial and may involve both direct and indirect effects of hyperglycemia. Adverse effects of hyperglycemia are potentially represented by endothelial dysfunction, high oxidative stress, increased protein kinase C activation, and potentially accelerated atherosclerosis [8]. In addition, the magnification of glycation end products (AGEs), resulting from chronic hyperglycemia, may lead to many detrimental processes such as increased myocardial stiffness and activation of the receptor for AGEs leads to upregulation of cellular signals and that results in cellular dysfunction [8] Also, elevated levels of HbA1C may be an indicator for a greater level of insulin resistance with the associated that is associated with derangements of myocardial energy and cardiac metabolism utilization in the insulin-resistant myocardium and increased activation of the sympathetic nervous system [8]. Finally, high HbA1C levels also may be reflective of poor compliance with medications, which in turn may be associated with poor outcomes, and that could clarify the considerable association between high HbA1C and the significant percentage of HF patients with HF who were described on in the four-pillar regimen 4-pillars [1]. In addition, 100% of the patients were on SGLT2i inhibitors had type 2 diabetes. This highlights that SGLT2i is still being considered as a medication to control HbA1c and type 2 diabetes and not a main pillar of heart failure treatment as recommended by the international guidelines [4]. Similarly, impaired renal function, as indicated by decreased GFR, was also associated with the physicians' adherence to with prescribing the four-pillar 4-pillars of HF, indicating that physicians are still cautious about the safety of these medications among patients with reduced GFR. Thus, we recommend conducting clinical trials investigating the safety of the 4 pillars of HF among HF patients with reduced GFR.

Moreover, our study included patients with HFpEF and HFrEF and demonstrated that the prevalence of the use of the four-pillar was double among patients with HFrEF compared to patients with HFpEF. This result highlight that patients with HFrEF were more likely to be on the four-pillar which is consistent with the most recent European and American guidelines in the management of HF. [10,11] Our findings also highlight that a percentage of patients with HFpEF also are on the four-pillar. This reflect the uncertainty in the management of patients with HFpEF. However, the most recent guidelines recommend the use of hypertension medications such as ACEi and ARBs along with BBs as appropriate. [11] The guidelines also recommend the use of [ARNI] to decrease hospitalizations, yet with lower level of evidence. This evidence along with the results of Empagliflozin in Heart Failure with a Preserved Ejection Fraction trial (EMPEROR-Preserved trial) that showed positive results on the use of SGLT2i highlight that the use of the four-pillar might also be beneficial among patients with HFpEF. [12]. MRAS

In our study, data about the reasons of not using the four-pillar of HF is not available. However, a finding that should be noted from our study is that the medication that limits the rate of the use of the four-pillar regimen is SGLT2 inhibitors. SGLT2 inhibitors is a medication used to manage type 2 diabetes yet, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial demonstrated that among patient with type 2 diabetes, SGLT2i was associated with significant reduction in HF hospitalizations. [13] These benefits were persistent even among patients with no history of HF. In addition, these benefits were independent from improvement in renal function, [13,14] glucose levels [15] and baseline glycated hemoglobin [15,16]. Moreover, it is known that 20% to 60 % of patients with HF have CKD [17] with patients who have both comorbidities had 25% increase in risk of mortality compared to patients with HF alone. [18] SGLT2i also offer benefit to patients with HF through renoprotection with this effect mediate a portion of the reduction in HF hospitalization observed with SGLT2i. [19] Although the medication also showed great benefits in reducing mortality and hospitalization rates among patients with HFpEF [12] and HFrEF. [17,20] we demonstrate that its

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In contrary, there is evidence that SGLT2i are beneficial in patients with CKD based on the DAPA-CKD and EMPA-Kidney trials.

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utilization is very low in our study. We hypothesize that several reasons are behind this low utilization including low insurance rate in Jordan, high cost of the medication, and the low adoption rate by the physicians. Future studies are needed to study the reasons and factors associated with this low utilization rate.

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Additionally, we did not find differences in survival rates between patients on the four-pillar and patients who were not which contradicts previous findings.[21] However, we consider our analysis limited due to the low number of patients who were on the 4 pillars of heart failure.

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Several limitations should be acknowledged. Due to the observational design of this study, it is not possible to establish cause-and-effect relationships for many of the associations mentioned. Additionally, we cannot dismiss the potential impact of unmeasured confounding factors on the non-use of the four-pillar 4-pillars of HF. The study included patients enrolled in the Jordanian Heart Failure Registry (JoHFR), so we cannot disregard the possibility of changes in the prescription practices following the termination of the enrolment in the JoHFR trial in 2023. Data about the specific types of BB, ARNI, ACEI, and SGLT2i used in the registry was unavailable in our dataset. The applicability of our findings to other countries relies on similarities in population characteristics, healthcare systems, and heart failure management. An additional limitation is the short follow up time in our study which limits our findings on mortality and hospitalization rates. However, an ongoing work in our group to collect data on one-year follow up. Finally, a significant limitation of this and other registry studies is the absence of longitudinal data and the ability to establish the timing of clinical variables, particularly prior measurements of serum potassium levels, which could have influenced decisions regarding the initiation of therapy and medication usage.

In conclusion, we used the data from the JoHFR study, which is considered the largest HF registry in the Middle East, to assess the prevalence of the four HF management pillars and investigate the factors associated with it. Our analysis revealed that the use of the four-pillar regimen for HF 4-pillars was very low in Jordan. In addition, Patients with a history of type 2 diabetes, as well as high HbA1c levels and impaired renal function reduced GFR were more likely to receive significantly associated with decreased increased prescription of the four-pillar regimen for HF 4 medications. This highlighting the that there is still a large underuse of the four-pillar regimen. 4-pillars of HF. National efforts are needed to collaborate with international HF associations to improve the knowledge of physicians about the use of the 4 pillars of HF. Also, Governmental initiatives should focus on reducing the underuse of these medications by addressing high costs, low availability, and poor insurance coverage.

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Declarations

Conflict of Interest

The authors declare that there are no conflict of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

The Institutional Review Board (IRB) at each participating center has reviewed and approved the conductance of this study. Moreover, the IRB at the specialty hospital approved the conductance of this study (Approval #5/1/t/104826).

Informed Consent Statement

An informed consent was obtained from all the participants.

Acknowledgments

None.

Data Availability

The data associated with this manuscript is available as supplementary material.

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Field Code Changed

Tables and Figures:

Figure 1. The Usage of each class of the 4 main pillars of HF Management.

Figure 2. The usage of the 4 main pillars of HF Management.

Figure 3. Distribution of the Use of the 4 Pillars of Management of HF across Diabetes Status.

Figure 4. Distribution of the Use of the 4 Pillars of Management of HF across HF Types.

[Figure 5. Survival analysis.](#)

