



How Guideline Directed Medical Therapy Is Practiced for Patients with Heart Failure? A Cross-Sectional Study in Yazd, Iran

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ARTICLE INFO

Article Type:
 Research Article

Article History:
 Received: 29 Aug 2021
 Revised: 8 Dec 2021
 Accepted: 21 Dec 2021

Keywords:
 Heart Failure
 Drug Therapy
 Iran

ABSTRACT

Background: In Heart Failure reduced Ejection Fraction (HFrEF), there is a clear Guideline Directed Medical Therapy (GDMT) for drug treatment. However, there are usually differences between what is recommended and what is actually done in the community. Additionally, no clear data are available regarding the types and doses of drugs used for HFrEF in patients with chronic heart failure.

Objectives: The present study aimed to investigate the current drug treatment for HFrEF in the community.

Methods: This cross-sectional study aimed to investigate the types and doses of drugs used by cardiologists for HFrEF patients. The data were collected using a researcher-made questionnaire by attending cardiologists' offices and reviewing patients' drugs. Considering the probability of 20% of patients using optimal drug doses (according to a pilot study), the sample size was estimated as 250 patients. Thus, 300 patients with stable drug regimens for three months were enrolled into the study.

Results: The mean age of the patients was 62.3 ± 14 years and 65% were male. The mean Left Ventricular Ejection Fraction (LVEF) was $27.3 \pm 7\%$. Additionally, the rates of using Beta Blockers (BBs), Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers (ACEIs/ARBs), and Mineralocorticoid Receptor Antagonists (MRAs) were 91%, 89%, and 63%, respectively. Only 5% of the patients received the target dose of BBs and 11% took the target dose of ACEs/ARBs. A significant gap was discerned between the recommended target doses and the patients' current doses.

Conclusion: The frequency of consumption of BBs, ACEs/ARBs, and MRAs in HFrEF was reasonably acceptable in the study population. However, there was a marked difference between the recommended and actual drug doses for HFrEF. Hence, further studies are required to evaluate and resolve the barriers.

1. Introduction

Heart failure is a chronic disease that is associated with increased mortality and disability, imposing high costs on the health system (1, 2). For patients with Heart Failure reduced Ejection Fraction (HFrEF), there are specific guidelines that are accompanied by sufficient clinical evidences (3, 4). In recent years, novel treatments for HFrEF including Beta Blockers (BBs), Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers (ACEIs/ARBs), Mineralocorticoid Receptor Antagonists

(MRAs), and Angiotensin Receptor Neprilysin Inhibitors (ARNIs) have contributed to a significant improvement in survival and clinical symptoms (3). Instructions have underlined that in order to achieve the desired goal with drug therapies, these drugs must be taken at the appropriate dose recommended in the guideline (3).

In randomized clinical trials, patients are closely monitored and the drug type and dose are regularly controlled. However, the use of heart failure drugs outside research areas is less likely accomplished with such precision. Therefore, varying studies have been carried out on how these drugs are used in the population of patients with heart failure. Some studies have shown that these drugs have not been used as recommended by guidelines (5-11). ESC

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Heart Failure Long-Term Registry indicated that nearly 30% of patients with HFrEF received the target dosage of these drugs. More relevant reasons for non-implantation of a device, when clinically indicated, were related to physicians' uncertainties on the indication, patients' refusal, or logistical/cost issues (9). ASIAN-HF registry also demonstrated that guideline-directed medical therapies at recommended doses were underutilized in patients with HFrEF (11). In a US registry, most eligible HFrEF patients did not receive the target doses of medical therapies at any point during follow-up, and few patients received increased doses over time (12). However, no clear data are available regarding the types and doses of drug therapy for HFrEF in patients with heart failure

2. Objectives

The present study aims to evaluate this issue and to compare it with guideline recommendations.

3. Patients and Methods

This cross-sectional, observational, descriptive-analytical study was conducted on patients suffering from HFrEF. Due to the lack of a long-term registry in Yazd, identification of these patients and their way of taking medications was possible by visiting a cardiologist's office. The patients who had an ejection fraction of less than 40%, were being treated by a cardiologist with a diagnosis of HFrEF, and had a consistent medication schedule for the past three months were enrolled into the research. The researchers recorded the necessary information by attending the office and completing a questionnaire by questioning the patients and recording their medications as well as their types and doses. Considering the probability of 20% of patients using optimal drug doses (according to a pilot study), the sample size was estimated as 250 patients. Thus, 300 patients were selected via census. Patients with acute heart failure and those whose physicians intended to dose up the titration

Table 1. Patients' Characteristics

Characteristics	N/%
Age, mean ± SD (Y)	62.3 ± 14
Male gender, n (%)	195 (65)
LVEF, mean ± SD	%27.3 ± 7
Beta blockers user, n (%)	274 (91)
ACE inhibitors user, n (%)	117 (39)
ARB user, n (%)	152 (50)
MRA user, n (%)	197 (65)
ARNI user, n (%)	0 (0)

Abbreviations: LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ARNI, angiotensin receptor neprilysin inhibitor.

were excluded. Written informed consent forms were obtained from all the patients before beginning the study.

The data were analyzed through the Excel 2013 software and SPSS 24 software. Kolmogorov–Smirnov test was used for determining the normal distribution of the data, and mean and standard deviation were used for describing the quantitative variables. Additionally, one-sample t-test was applied for statistical comparisons. Chi-square test was also used to compare different age groups in terms of drug consumption.

4. Results

This study was done on 300 patients with heart failure. The general characteristics of the patients have been presented in Table 1. Totally, 91% of the patients were taking beta-receptor blocking drugs. The types and average doses of the drugs as well as the minimum, maximum, and median doses have been depicted in Table 2. Accordingly, no significant difference was observed between males and females regarding the frequency of using beta-blocking drugs (94% vs. 91%, P = 0.284). However, BBs consumption was significantly lower in the people older than 70 years (82% vs. 93%, P = 0.001). Additionally, only 5% of the

Table 2. Beta Blockers Use

Beta Blocker Type	User, N (%)	Mean Daily Dose (mg)	Minimum Daily Dose (mg)	Maximum Daily Dose (mg)	Median Daily Dose (mg)
Carvedilol	158 (52.6%)	16.3 ± 10	3.125	50	12.5
Metoprolol succinate	72 (24%)	46.8 ± 25	12	143	47.5
Bisoprolol	44 (14.6%)	4.9 ± 3.8	1.25	20	2.5

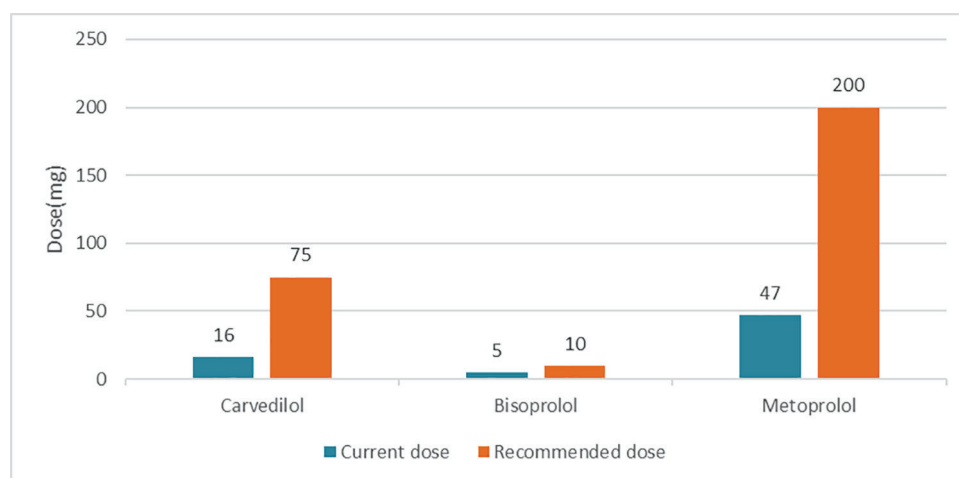


Figure 1. Comparison of the Current and Recommended Doses of Beta Blockers

patients received the target dose of BBs. Comparison of the current and recommended doses of BBs in the HF_rEF patients has been illustrated in Figure 1.

Totally, 89% of the patients took ACEIs or ARBs. The type and mean, minimum, maximum, and median doses of the drugs have been presented in Table 3. According to the results, only 11% of the patients took the target doses of these drugs. Besides, no significant difference was found between males and females in terms of using the drugs (93% vs. 96%, P = 0.212). Moreover, no significant difference was discerned between the patients aging below

and above 70 years concerning the consumption of these drugs (90% vs. 93%, P = 0.562). Comparison of the current and recommended doses of ACEIs/ARBs in the HF_rEF patients has been presented in Figure 2.

MRAs were used in 65% of the patients, and the types and mean doses have been shown in Table 3. Based on the results, there was no significant difference between males and females regarding the use of these drugs (61% vs. 68%, P = 0.25). Nonetheless, the frequency of the consumption of these drugs reduced with increasing age. According to the findings, this measure was 78%, 65%, and 45% in the people

Table 3. Use of ACEIs, ARBs, and MRAs

ACEIs, ARBs, MRAs	User, N (%)	Mean Daily Dose (mg) ± SD	Minimum Daily Dose (mg)	Maximum Daily Dose (mg)	Median Daily Dose (mg)
Lisinopril	73 (24.3%)	10 ± 5.7	2.5	20	10
Captopril	37 (12.3%)	46 ± 27	12.5	100	37.5
Enalapril	7 (2.3%)	12.8 ± 7	5	20	10
Losartan	91 (30%)	52.8 ± 30	12.5	150	50
Valsartan	61 (20%)	154 ± 83	40	320	160
Spiroolactone	184 (61%)	22.7 ± 8	6.25	50	25
Eplerenone	13 (4.3%)	27 ± 47	25	50	25

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

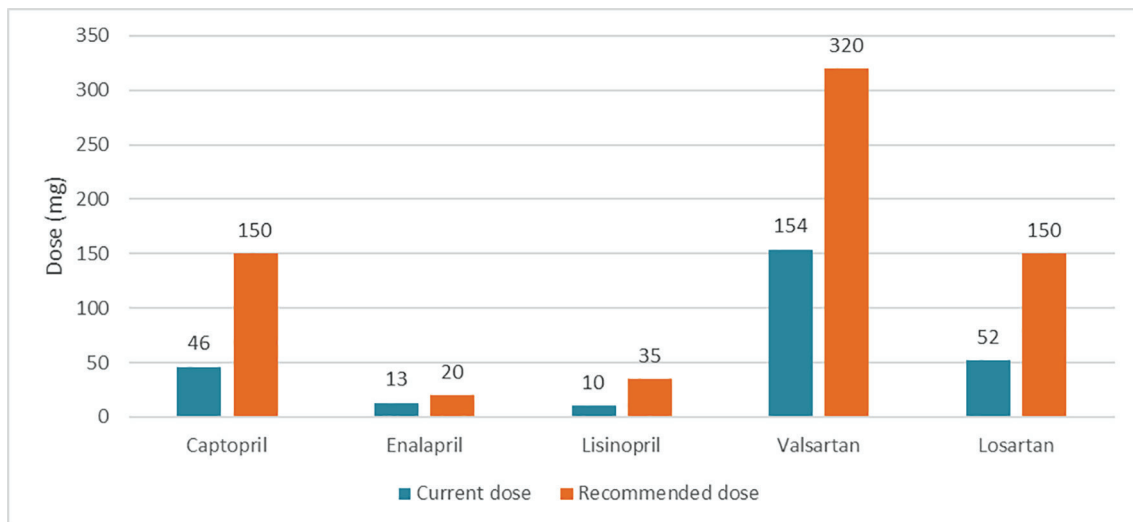


Figure 2. Comparison of the Current and Recommended Doses of Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers

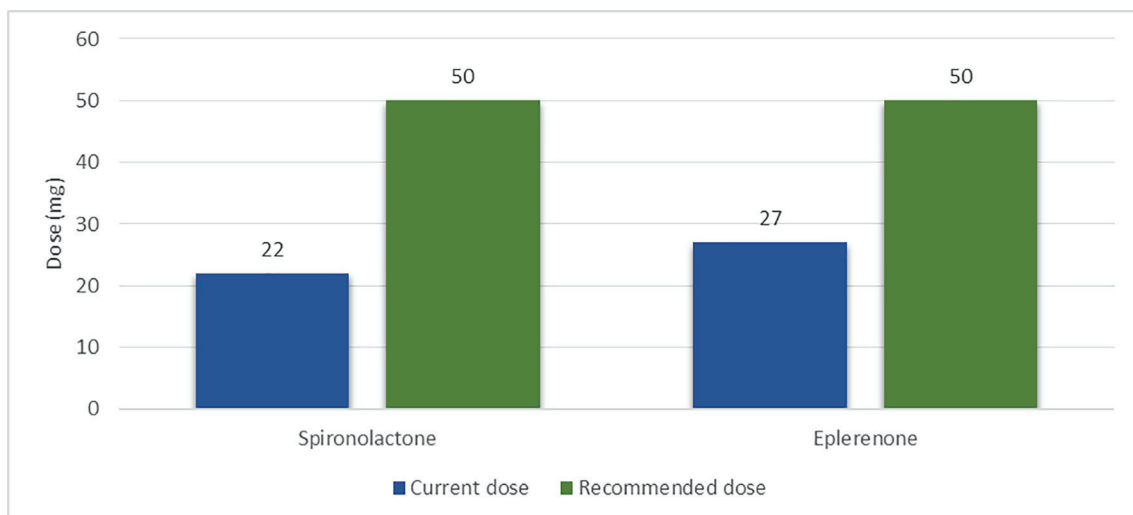


Figure 3. Comparison of the Current and Recommended Doses of Mineralocorticoid Receptor Antagonists

aged below 50, 50 - 69, and above 70 years, respectively ($P < 0.05$). Comparison of the current and recommended doses of MRAs in the HFREF patients has been depicted in Figure 3.

5. Discussion

Heart failure is the most common cause of hospitalization in people over 65 years old (2). Despite advances in the treatment of cardiovascular diseases, the rate of hospitalization due to heart failure has not changed in the last 20 years. Hence, it is one of the most serious challenges for healthcare systems worldwide (1).

Starting heart failure medications based on guidelines, increasing the dose of medications gradually, and most importantly, high medication compliance in heart failure patients appear to be the key to success in this chronic disease (4). Adherence to treatment recommendations in these patients has been reported to be associated with reduced complications and death. Nonetheless, patients with heart failure are less committed to treatment recommendations (10).

To date, the number of beneficial drugs for HFREF is increasing. However, due to their varying adverse effects, consumption of large amounts of these drugs during the day and overlap of drugs may limit their use. On the other hand, drug dose may be affected by blood pressure, kidney function, hyperkalemia, and several other factors. Additionally, physicians' knowledge of the order of starting the drug and increasing the dose, adverse effects, and follow-up as well as allocation of adequate time for explaining the importance of drugs to patients can be effective in their consumption by patients (10).

Guidelines have suggested that the closer the dose of the drug to the target dose, the greater the survival benefit will be (4). In clinical practice, however, applied doses are frequently lower than those recommended by the guideline (6).

The present study evaluated the drug regimens and drug doses prescribed by cardiologists for HFREF patients. The prescription of BBs, ACEIs/ARBs, and MRAs was approximately acceptable and comparable with other studies (7-9). However, a small number of the patients reached the recommended dose specified by the guideline. Yet, the reason for failure to achieve the target dose could not be specified. Underutilization and suboptimal doses of drugs have several causes and may reflect true non-tolerability. In addition, they may be related to patients and/or physicians. Achieving the target dose is of particular importance, because optimization of doses is accompanied by improved symptoms and survival (4). In the current study, only 5% and 11% of the patients reached the target dose of BBs and ACEIs/ARBs, respectively. This result was somewhat similar to that of the Asian-HF registry (11), but significantly different from those of other investigations (6).

Evidence has shown variations in patients' adherence to medications and behaviors to treat diseases. Loneliness and aging are the most crucial predictors that affect patient compliance. Due to comorbidity and polypharmacy, drug compliance tends to reduce in the elderly population (13). Low patient compliance also depends on such factors as the underlying conditions leading to heart failure, the course of heart failure, patients' characteristics subsuming education

level, awareness, involvement in the treatment process, social support, availability of medications, and potential adverse effects (10, 11).

Defining the target dose is somewhat arbitrary in clinical trials. Even in principal trials, reaching the target dose was not possible for all patients and the lower dose was accompanied by improved symptoms and survival (14-17). Therefore, it is better to compare the dose taken by patients to the mean dose used in clinical trials. Furthermore, the reason why a small percentage of patients use the target dose should be determined and attempts should be made to stave off the cause. On the basis of the studies performed on the issue, some of the reasons that can be addressed are physician-based such as self-efficacy, attitude, and knowledge, while some others are related to patients including age, Body Mass Index (BMI), comorbidities, polypharmacy, hypotension, heart rate, and renal dysfunction (9, 13, 18). Absence of heart failure symptoms or mild symptoms in HFREF patients may also be an important factor in optimal drug doses (19). Interventions for improving medication adherence amongst patients with heart failure have shown significant effects on reducing the number of readmissions and the rate of mortality (20). Thus, medication adherence should be addressed in regular follow-up visits, and interventions to improve adherence should be a key part of heart failure self-care programs (20). Improving post-discharge follow-up with providers is also an opportunity to improve dose titration (21).

5.1. Conclusions

In conclusion, BBs, ACEs/ARBs, and MRAs were used as frequently as deployed in other populations, but it was still far from the target dose.

5.2. Limitations

One of the limitations of the study was that the patients were not followed for a long period of time. In addition, the barriers against reaching the target dose could not be investigated.

5.3. Ethical Approval

IR.IAU.YAZD.REC.1398.046.

5.4. Informed Consent

Informed consent forms were obtained from the patients after providing them with explanation about the study objectives and procedures.

Acknowledgements

There is no acknowledgement.

Authors' Contribution

Study concept and design: M.S.; acquisition of data: F.D. and F.B.; analysis and interpretation of data: M.S.; drafting of the manuscript: A.S.; statistical analysis: A.S.; study supervision: E.Z.; critical revision of the manuscript for important intellectual content: M.S.

Funding/Support

The authors received no financial support for the research

(registration No. 76124).

Financial Disclosure

The authors have no financial interests related to the material in the manuscript.

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