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How optimal is the treatment for heart failure patients with low ejection fraction?

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ABSTRACT

Objectives: The aim of our study was to investigate the medical treatment and doses used in patients with a diagnosis of heart failure (HF) and whether these vital drugs were used by cardiologists at the required doses in patients with indications.

Patients and methods: This single-center, prospective study included a total of 419 chronic HF (CHF) patients (275 males, 144 females; mean age: 65.2±13.8 years; range, 22 to 94 years) between April 1st, 2020 and November 15th, 2020. Patients and their relatives were interviewed and sociodemographic data of the patients were recorded. Routine hematological and biochemical parameters, electrocardiographic findings, electrocardiographic and echocardiographic findings, and systolic and diastolic pressure data were recorded during follow-up. The New York Heart Association (NYHA) functional classes were also determined.

Results: The causes of CHF were as follows: 55.6% ischemic heart disease, 33.9% dilated cardiomyopathy (CMP), 3.8% valvular, 1.9% peripartum CMP, 1.9% post-chemotherapy (CT), 1% non-compaction CMP, and 1.9% other causes. The most common reason for not receiving medical treatment at the maximal doses recommended by the guidelines was "not recommended by the physician" (beta-blockers 49.6%, n=208, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEI/ARBs] 44.6%, n=187, mineralocorticoid receptor antagonists [MRAs] 38.7%, n=162). The second most common reason was the lack of desired follow-ups due to socioeconomic reasons.

Conclusion: The most common reason why HF patients do not receive optimal treatment, including beta-blocker, ACEI/ARB, and MRA groups is that clinicians do not recommend it. This study may be a reference to the fact that clinicians' maximal sensitivity in treatment optimization in fragile patient groups, such as HF, would significantly change patient outcomes.

Keywords: Angiotensin-converting enzyme inhibitors, beta-blockers, heart failure.

Heart failure (HF) is a cardiac structural or functional disorder which causes the heart to fail to provide enough oxygen to meet metabolic needs of the tissues.[1] It is increasing worldwide as a result of the gradual aging of the population, and according to the data of the Heart Failure Prevalence and Predictors in Turkey (HAPPY) study recently conducted in our country, there are over two million HF patients in Türkiye.[2]

Heart failure is a major health problem with a mortality rate ranging from 5 to 40%, corresponding to a fivefold increased risk of death compared with the general population.[3] It is estimated that HF patients have a worse life expectancy than most cancer patients, with a median survival of approximately two to three years.[4,5]

Several studies have shown that to obtain optimal benefit from drug groups that are used in the medical treatment of HF and have been proven to prolong life, it is not sufficient to reduce mortality by starting the

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patient on these drugs, and that the dose at which they are used is also of great importance. Current HF treatment guidelines also emphasize the importance of this situation and recommend that these drug groups should be started at low doses and titrated to the maximum tolerated doses in patients with stable chronic HF (CHF).[6]

In the present study, we aimed to investigate the medical treatment and doses used in patients with a diagnosis of HF and whether these vital drugs are used by cardiologists at the required doses in patients with indications.

PATIENTS AND METHODS

This single-center, prospective study was conducted at Dicle University, Faculty of Medicine, Department of Cardiology between April 1st, 2020 and November 15th, 2020. Patients who were older than 18 years, had an ejection fraction (EF) of <40%, and had a diagnosis of HF for at least three months were included in the study. Participants who did not become volunteer or had communication problems were excluded from the study. Finally, a total of 419 CHF patients (275 males, 144 females; mean age: 65.2±13.8 years; range, 22 to 94 years) were recruited. Written informed consent was obtained from each patient. The study protocol was approved by the Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 06.02.2020, No: 171). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients and their relatives were interviewed and sociodemographic data of the patients (age, sex, height, weight, occupation, income level, place of residence), smoking status, presence of comorbidities such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HPL), coronary artery disease (CAD), atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), history of chemotherapy (CT), thyroid dysfunction, history of hospitalization in the last year, cause and duration of HF, whether he/she is receiving HF treatment, if so, which medication and at what dose, if not, why not, presence of intracardiac device were questioned by a face-to-face questionnaire method. Routine hematological and biochemical parameters, electrocardiographic findings (rhythm, heart rate, bundle branch block), echocardiographic findings, and systolic and diastolic pressure data were recorded during follow-up. The New York Heart Association (NYHA) functional classes were also determined.

Echocardiographic images of the patients were obtained at the end of expiration in the left lateral decubitus position using a Vivid 6 (General Electric, Horten, Norway) 1.7/3.4 MHz transducer, and analyses were performed based on the American Society of Echocardiography (ASE) guidelines for left ventricular evaluation.[7] All echocardiographic procedures were performed by a single investigator. After transthoracic echocardiographic images were obtained with parasternal long axis (PSLAX), parasternal short axis (PSSAX), apical two, three, and four space images, two-mode (2D), M-Mode, and color Doppler techniques were used for cardiac evaluation. In the light of ASE recommendations, LV systolic and diastolic diameters, left atrium (LA), interventricular septum (IVS), posterior wall diameter, and left ventricular EF (LVEF) were measured in M-mode measurements with appropriate parasternal long-axis images obtained.

Hemoglobin and other whole blood values were evaluated with XN-1000 (SYSMEX, Japan), biochemical values with AU5800 (Beckman Coulter, CA, USA), and hormone evaluation with ADVIA CENTAUR XP (Siemens Diagnostics, NY, USA).

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Kolmogorov-Smirnov test (if the number of participants in each group was 30 or more) and graphs were used to determine whether continuous data were normally distributed. A p value of <0.05 was considered statistically significant.

RESULTS

The causes of CHF in patients were as follows: 55.6% ischemic heart disease, 33.9% dilated cardiomyopathy (CMP), 3.8% valvular, 1.9% peripartum CMP, 1.9% post-CT, 1% non-compaction CMP, and 1.9% other causes (Figure 1). The comorbidities included HT in 56.7%, CAD in 55%, DM in 36.4%, HPL in 23.2%, CKD in 19.6%,

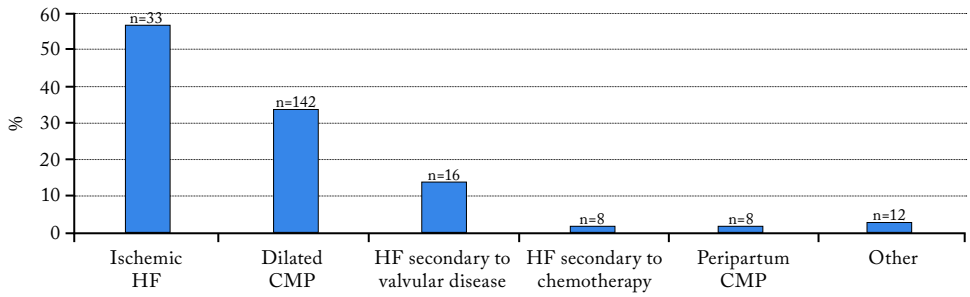

Figure 1. Causes of heart failure.
HF: Heart failure; CMP: Cardiomyopathy.

COPD in 8.3%, history of CT in 2.4%, and thyroid dysfunction in 9.1%. In addition, 48% of the patients had a history of smoking. The duration of HF was six to 10 years in 27%, four to five years in 19%, three years in 19%, two years in 18%, one year in 14%, and >10 years in 2%. Also, AF rhythm was present in 26% of patients at the time of presentation.

Table 1
Treatments used by patients

	n	%
Beta blocker	416	99.3
ACE inhibitor/ARB	382	91.1
ACE inhibitor	311	74.2
ARB	71	16.9
MRA	283	67.7
Non-MRA diuretics	388	93.0
Digoxin	54	12.9
Valsartan + sacubitril	7	1.9
Ivabradin	17	4.1
ASA	191	45.6
Klopidogrel	13	3.1
Nitrat	21	5
OAK	122	29.1
Amiodaron (%)	8	1.9
Statin	72	17.3
Device treatment		
ICD	70	16.7
ICD-CRT	34	8.1
LVAD	1	0.2

ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; MRA: Mineralocorticoid receptor antagonists; ASA: Acetylsalicylic acid; OAK: Oral anti-coagulant; ICD: Implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; LVAD: Left ventricular assist device.

The medical treatments used by the patients are summarized in Table 1. Of 419 patients, 99.3% (n=416) used beta-blockers, 91.1% (n=382) used angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs), 67.7% (n=283) used mineralocorticoid receptor antagonists (MRAs), and 93% (n=388) used non-MRA diuretics. Acetylsalicylic acid (ASA) use was 45.6% (n=191), digoxin 12.9% (n=54), ivabradine 4.1% (n=17), valsartan sacubitril 1.9% (n=7), OAC 29.1% (n=122), statin 17.3% (n=72). Implantable cardioverter-defibrillator (ICD) was present in 16.7% (n=70), ICD-cardiac resynchronization therapy (CRT) in 8.1% (n=34), and left ventricular assist device (LVAD) in 0.2% (n=1).

Electrocardiography findings of the patients are summarized in Table 2. Of the patients, 74% (n=310) were in sinus rhythm and 26% (n=109) were in AF rhythm. The mean heart rate was 75.4±8.8 bpm. There was no bundle branch block in 72.3% of patients (n=303). 24.8% (n=104) had left

Table 2
Electrocardiography findings (n=419)

	n	%	Mean±SD
Rhythm			
Sinus	310	74	
Atrial fibrillation	109	26	
Heart rate			75.4±8.8
Branch block			
None	303	72.3	
LBBB	104	24.8	
RBBB	12	2.9	

SD: Standard deviation; LBBB: Left bundle branch block; RBBB: Right bundle branch block.

Table 3
Echocardiogram findings (n=419)

	n	%	Mean±SD
Ejection fraction (%)			31.9±6.7
LVDD (mm)			57.6±8.7
LVSD (mm)			46.0±10.8
Left atrial diameter			45.2±6.8
Systolic pulmonary artery pressure			38.5±16.1
Mitral regurgitation			
None	71	17	
Light	173	41.4	
Moderate	150	35.9	
Excessive	24	5.7	
Aortic regurgitation			
None	298	71.1	
Light	109	26	
Moderate	12	2.9	
Excessive	0	0	
Tricuspid regurgitation			
None	121	28.9	
Light	178	42.5	
Moderate	84	20	
Excessive	36	8.6	

SD: Standard deviation; LVDD: Left ventricular end-diastolic diameter; LVSD: Left ventricular end-systolic diameter.

bundle branch block (LBBB), and 2.9% (n=12) had right bundle branch block (RBBB).

The echocardiographic findings are summarized in Table 3. The mean EF of the patients was 31.9±6.7%. The mean left ventricular end-diastolic diameter was 57.6±8.7, left ventricular end-systolic diameter 46.0±10.8 mm, LA diameter 45.2±6.8 mm, and systolic pulmonary artery pressure 38.5±16.1. On admission echocardiography, Grade 2 or higher mitral regurgitation was found in 41.6%, Grade 2 or higher aortic regurgitation in 2.9%, and Grade 2 or higher tricuspid valve regurgitation in 28.6%.

It was assessed why the patients were not receiving the optimal dose of beta-blocker agents in Figure 2. Those not recommended by the physician were 49.6% (n=208). Dose increase could not be

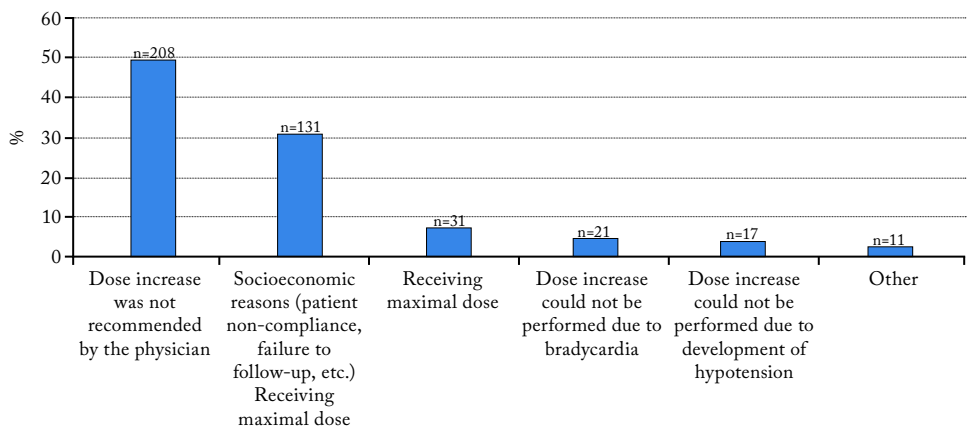

Figure 2. Why the beta-blocker dose was/could not increased.

Table 4
Beta-blockers used by patients and doses (n=416)

	n	%
Metoprolol	197	47.4
25 mg/day	13	6.6
50 mg/day	113	57.4
100 mg/day	51	25.4
200 mg/day	20	10.2
Karvedilol	170	40.9
6.25 mg/day	11	6.5
12.5 mg/day	74	43.5
25 mg/day	76	44.7
50 mg/day	9	5.3
Bisoprolol	15	3.6
5 mg/day	13	86.6
10 mg/day	2	13.4
Nebivolol	34	8.2
5 mg/day	34	100
Receivers of maximum dose of beta blockers	31	7.5

performed in 31.3% (n=131) due to socioeconomic reasons, 5% (n=21) due to bradycardia, and 4.1% (n=17) due to hypotension. The rate of those who were recommended a dose increase, but did not accept it and the rate of those who discontinued the drug without a physician's recommendation were the same at 0.7%.[3] One patient had a condition that prevented him from taking beta-blockers, and in another patient, beta-blocker treatment was discontinued due to the development of erectile dysfunction. Additionally, beta-blocker drugs and their doses used by our patient population are given in Table 4. The number of those receiving beta-blocker treatment at the optimal dose was only 31 (7.5%).

We questioned why patients were not receiving ACEI/ARB treatment at the optimal dose in Figure 3. The rate of those for whom a dose increase was not recommended by the physician was 44.6% (n=187). Of the patients, 27% (n=113) could not receive the optimal dose due to socioeconomic reasons, 5.5% (n=23) due to the development of acute kidney injury, and 1.7% (n=7) due to the development of hypotension. The number of patients with a condition that prevented them from taking ACEI/ARB was 18, and the number of those who developed a cough due to a dose increase (ACEI) was 1. The distribution of ACEI/ARB drugs used by our patient population with HF and the doses used are given in Table 5. The number of those receiving the maximum dose of ACEI/ARB drugs was only 53 (13.9%).

Patients who did not receive high-dose MRA were asked why they did not receive high-dose MRA in Figure 4. The proportion of patients who were never started on MRA treatment was 29.4% (n=123), and the proportion of patients in whom a dose increase was not recommended by the physician was 38.7% (n=162). Among the other reasons, the rate of socioeconomic reasons was 17.7% (n=74), the rate of patients with a condition that prevented them from receiving MRA was 4.3%, the rate of patients who could not receive dose increase due to ABF was 3.6% (n=15), and the rate of patients who could not receive dose increase due to hypotension was 1.4% (n=6). The number of patients who were recommended a dose increase by the physician but did not accept it was 1,

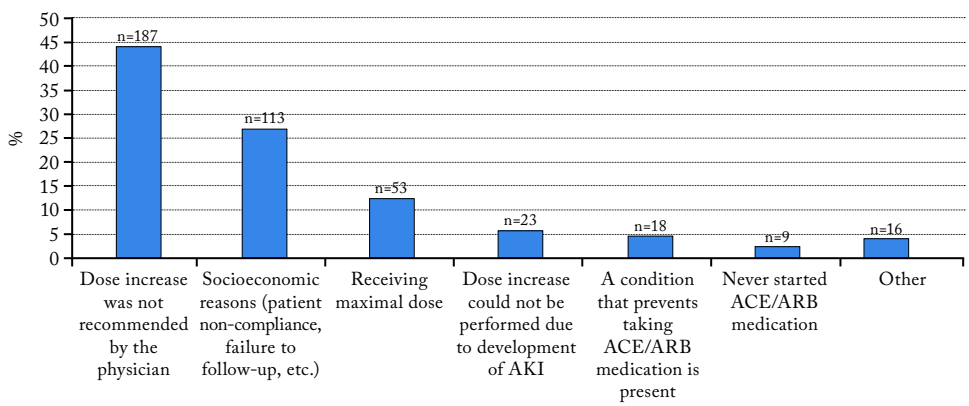

Figure 3. Why the dose of ACE/ARB was/could not increased.
AKI: Acute kidney injury; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker.

Table 5
ACEIs and ARB doses used by patients

	n	%
ACEIs (n=311)		
Ramipril (n=211)		
2.5 mg/day	116	55
5 mg/day	79	37.4
10 mg/day	16	7.6
Perindopril (n=78)		
2.5 mg/day	5	6.4
5 mg/day	52	66.7
10 mg/day	21	26.9
Zofenopril (n=17)		
15 mg/day	3	17.6
30 mg/day	14	82.4
Enalapril (n=2)		
10 mg/day	1	50
20 mg/day	1	50
Fosinopril (n=2)		
10 mg/day	2	100
Lisinopril (n=2)		
5 mg/day	2	100
Maximum dose ACE inhibitor recipients total	52	16.7
ARB (n=71)		
Valsartan (n=41)		
80 mg/day	20	50
160 mg/day	19	47.5
320 mg/day	1	2.5
Kandesartan (n=22)		
8 mg/day	5	22.7
16 mg/day	17	77.3
Olmesartan (n=4)		
20 mg/day	3	75
40 mg/day	1	25
Irbesartan (n=3)		
150 mg/day	2	66.7
300 mg/day	1	33.3
Telmisartan (n=1)		
80 mg/day	1	100
Maximum dose ARB recipients total	1	1.4

ACEIs: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blocker.

and the number of patients who discontinued their treatment without the physician's recommendation was 2. One patient developed hyperkalemia, and two patients developed gynecomastia, and MRA treatment could not be increased. The distribution of MRA drugs used by our HF patient population and the doses used are given in Table 6. The number of people receiving MRA drug therapy at the maximum dose was only 15 (5.3%).

Table 6
MRA doses used by patients (n=283)

	n	%
Spiranolactone (n=256)		
25 mg/day	241	94.1
50 mg/day	3	1.2
100 mg/day	12	4.7
Eplerenone		
25 mg/day	27	9.5
Max dose MRA recipients total	15	5.3

MRA: Mineralocorticoid receptor antagonists.

DISCUSSION

In our study, 416 (99.3%) patients used beta-blockers, 382 (91.1%) used ACEI/ARBs, and 283 (67.7%) used an MRA as standard treatment for HF. Although the proportion of patients receiving these drug therapies seemed high, the number of patients using beta-blockers at the optimal dose according to current guidelines was 31 (7.5%), the number of patients using ACEI/ARBs was 53 (13.9%), and the number of patients using MRAs was extremely low at 15 (5.3%). In our study, it was striking that the most common reason for not receiving medical treatment at the maximal doses recommended by the guidelines was "not recommended by the physician" (beta-blockers 49.6% [n=208], ACEI/ARBs 44.6% [n=187], MRAs 38.7% [n=162]). The second most common reason was the lack of desired follow-ups due to socioeconomic reasons.

Similar to previous guideline recommendations, beta-blockers (i.e., bisoprolol, carvedilol, nebivolol, and metoprolol succinate) are recommended in patients with stable HF to reduce the risk of hospitalization and death from HF with reduced ejection fraction (HFrEF). Similarly, ACEIs and MRAs are recommended at Class I level to reduce the risk of hospitalization and death in patients with HFrEF. Current HF treatment guidelines also emphasize the importance of this situation and recommend starting these drug groups at low doses and titrating to the maximum tolerated doses in patients with stable CHF. However, despite the accumulation of a large amount of study data and clinical experience, problems persist in reaching

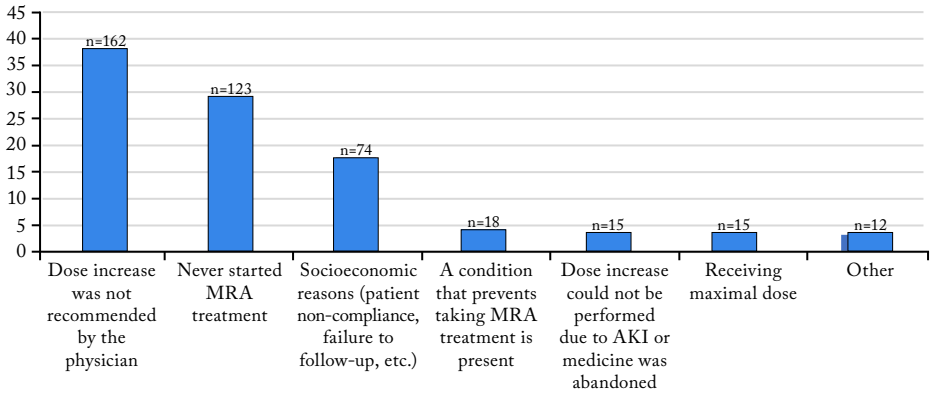

Figure 4. Why the MRA dose was/could not be increased.
MRA: Mineralocorticoid receptor antagonist; AKI: Acute kidney injury.

optimum or maximum tolerated doses in clinical practice.[6]

Studies have shown that to obtain optimal benefit from drug groups that are used in the medical treatment of HF and have been proven to prolong survival, it is not sufficient to reduce mortality just by starting these drugs, and the dose at which they are used is also of great importance.[8-13] In an analysis conducted in the Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) population, patients who failed to reach >50% of the target dose with RAS inhibitors or beta-blockers had an increased risk of hospitalization and death due to HF compared to those who reached the target dose.[8] The Medical Management of Chronic Heart Failure in Europe and Its Related Costs (MAHLER) Study revealed that excellent adherence to HF guidelines, as determined by the global adherence indicator, was a strong and independent predictor of delayed hospitalization in patients with CHF.[8] This report also showed that monotherapies were less effective than combination therapies.[14] A meta-analysis of 57 randomized-controlled trials showed that combination therapy of renin-angiotensin system (RAS) inhibitors with beta-blockers or MRAs was associated with a 43% relative risk reduction in all-cause mortality.[15] Furthermore, combined treatment with RAS inhibitors, beta-blockers, and MRAs resulted in a 56% reduction in mortality.[15] The real-world study of 14,359 patients with HF with low ejection fraction reported a two-year mortality rate of 27.9%. Compared to patients receiving monotherapy, patients receiving triple therapy had a 29.3% lower two-year mortality risk, and all-cause mortality was highest in patients not receiving any HF medication.[16] In another study, there is a suggestion that titration of neurohormonal blocking agents guided by healthcare professionals in patients with HFrEF results in fewer hospitalizations and improved mortality.[17] Current observations in HF patients suggest that a large proportion of the affected population fails to take the recommended medications, and less than half take 'target doses'.[18] Data from the European registry show that although prescription rates improved from admission, only about 77 and 72% of inpatients were discharged with ACEI/ARB or beta-blockers, respectively.[19] The 2021 European Society of Cardiology HF guidelines recommend that patients hospitalized for HF should be carefully assessed and evidence-based oral medical therapy initiated before discharge to exclude signs of persistent congestion and optimize oral therapy. An early follow-up visit, one to two weeks after discharge, was also recommended to assess symptoms of congestion, drug tolerance, and to initiate and/or escalate evidence-based treatment. A report from Türkiye enhances awareness, updates national HF insights, and fosters collaboration between specialized and general care centers.[20]

Nonetheless, there are many limitations to our study. First, the number of patients included in our study is relatively small for the HF patient group. Second, our study was conducted in a single center. Therefore, the results of the study are not generalizable. Testing the results in larger populations would increase the reliability of the results of our study. Third, patients who were diagnosed with HF

at least three months ago were included in our study. However, our patient population is not homogeneous, since there are also patients with a HF diagnosis for much longer periods in our population. While investigating the outcome of our study, records were created based on the verbal statements of the patients and their relatives. A possible bias could not be completely excluded from the study.

In conclusion, the most common reason why HF patients do not receive optimal treatment, including beta-blocker, ACEI/ARB, and MRA group is that clinicians do not recommend it. Taken together, this study may be a reference to the fact that clinicians' maximal sensitivity in treatment optimization in fragile patient groups, such as HF, would significantly change patient outcomes.

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

Author Contributions: Idea/concept, data collection and/or processing, literature review, writing the article, materials, other: M.S.C., M.Ö., M.O.; Design, analysis and/or interpretation, critical review, references and fundings: F.E., T.G., A.A., S.S.; Control/supervision: O.Ş., M.O., R.K.

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