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Impact of Dose Titration on Improving Ejection Fraction in Heart Failure Patients with Reduced Ejection Fraction

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Abstract:
Background*: Patients with heart failure with reduced ejection fraction (HFrEF) can now be managed with a variety of medications, such as angiotensin-converting enzyme inhibitors (ACEi), beta-blockers (BB), angiotensin receptor blockers (ARBs), and the recently developed angiotensin receptor-neprilysin inhibitor (ARNI). The target dose of HFrEF guideline-directed medicinal therapy yields the best results. However, as a greater number of medicinal therapies for HFrEF become accessible, physicians must increasingly manage frequently overlapping drug adverse effects, achieve target dosages, and use multiple medications concurrently. The purpose of our research was to investigate the impact of dose titration on the improvement of Ejection fraction (EF) in HFrEF patients.*
Materials and Methods*: Over six months, a retrospective analysis was carried out in the cardiology department of a multispecialty hospital. This investigation included 50 patients. Patients were split up into groups based on whether they underwent dose titration or not. At the baseline and follow-up visits, patient sociodemographic and clinical data were gathered. The statistical analysis was carried out using the SPSS program.*
Results*: Merely 26 percent of the 50 patients had their doses titrated, and the majority of those were men. The most often prescribed medications (54%) in both groups were the combination of ARB and BB. The average EF for the baseline and follow-up was 28.38 ± 6.04 % and 35.7 ± 7.6 % in the titrated group, 30.05 ± 5.4% and 38.9 ± 3.6% in the non-titrated group respectively. The improvement of EF in both groups did not differ significantly.*
Conclusion: *The non-titrated HFrEF exhibited slight improvement in EF when compared to titrated patients. To obtain more broadly applicable data, more research with a multi-centered, larger sample size and longer time frame is required.*
Key Word*: Dose titration; Heart failure; reduced ejection fraction; angiotensin-converting enzyme inhibitor; beta-blockers.*

I. INTRODUCTION

Heart failure [HF] is a multifaceted clinical condition characterized by dyspnea or exertional limitation as a result of impaired ventricular filling, impaired blood ejection, or a combination of these. HF is associated with high mortality and morbidity once it develops. In patients with chronic HF, the 1-year mortality rate is 7.2%, and the 1-year inpatient rate is 31.9%. These rates rise to 17.4% and 43.9% in patients hospitalized for acute HF.[1] HF affects more than 60 million people worldwide.[2,3] Nonetheless, these figures are expected to rise in the coming years, primarily as a result of the aging population, but also because certain multiple medical conditions, such as diabetes or hypertension, are more common.[4]

According to the left ventricular ejection fraction (LVEF), HF has historically been divided into three categories: HF with midrange ejection fraction (LVEF 41%–49%), HF with preserved ejection fraction (LVEF ≥ 50%), and HF with reduced ejection fraction (HFrEF), in which the LVEF is ≤ 40.[5] HFrEF is the cause of about 50% of HF cases.[6] With new developments in medication and device therapy, the best possible care for patients with HFrEF is being improved.

Ankle swelling, fatigue, paroxysmal nocturnal dyspnea, orthopnea, and dyspnea are typical symptoms of HF. Right upper quadrant discomfort, early satiety, and stomach bloating are some more nonspecific symptoms of right-sided HF that may be present. Another sign of heart failure is bendopnea, which is defined as dyspnea, or shortness of breath when bending forward (such as when putting on shoes).[7] Chest x-ray, electrocardiography, and natriuretic peptide detection are initial tests performed if HFrEF is suspected.[1]

Guideline-directed medical therapy (GDMT) for HFrEF now includes four fundamental drug classes: SGLT2Is, beta-blockers, mineralocorticoid receptor antagonist (MRA), and renin-angiotensin system inhibitors. In HFrEF, ARNIs, ACEIs, or ARBs are advised as first-line medications.[8] Large gaps remain in the adoption of guideline-directed medical therapy in clinical practice, despite their demonstrated efficacy in lowering morbidity and death in HFrEF patients. Research from the registry reveals that over 25% of qualified patients do not receive a prescription for an ACE, ARB, or ARNI; over 33% do not receive a beta-blockers; and over 50% do not receive a MRA. Doses are frequently lower than suggested targets, even when prescribed. Merely 1% of qualified patients receive target dosages of all three drug classes concurrently, despite data suggesting that doses below these levels are linked to worse patient outcomes.[9]

The target dose of HFrEF guideline-directed medicinal therapy yields the best results. Nonetheless, physicians now have to deal with the difficulty of utilising multiple medications at once, hitting target dosages, and controlling frequently overlapping pharmacological adverse effects as a result of the growing number of medicinal therapy for HFrEF. Our study aimed to explore the impact of dose titration on the improvement of Ejection fraction (EF) in HFrEF patients.

II. MATERIAL AND METHODS

The retrospective investigation was carried out in the cardiology department of the Kovai Medical Center and Hospital a modernized 850 bedded multispeciality hospital in Coimbatore. The institution's ethics committee granted the approval, which was issued on July 13, 2022, under approval number EC/AP/950/07/2022 for this study. Raosoft software calculates the study population with a 95% confidence interval and a 5% margin of error. A sample size of 45 patients was determined. Convenience sampling was used to include 50 patients with HFrEF in this investigation. The time frame for the study was May 2022–October 2022.

Inclusion criteria

The following patients with HFrEF were included in this study.

- HFrEF patients (EF≤ 40%)
- Either sex
- Aged ≥ 18 years
- Ischemic and non-ischemic heart failure patients.

Exclusion criteria

The following patients with HFrEF were not included in this study.

- Pregnant women
- Patients with age less than 18 years
- Patients with genetic disorders
- Patients with Chronic Kidney Disease
- Patients with liver failure
- Patients with cancer
- Patients with hematological disorders
- Patients who are physically inactive.

Procedure methodology

The patient's data collecting form was used to gather the sociodemographic information. It was created using the patient's information, which included their gender, age, BMI, lifestyle habits, use of alcohol, and smoking habits. The patient's case reports provided the clinical data. It includes information on the state of hypothyroidism, diabetes mellitus, ischemic heart disease, hypertension, dose titration, and drug and dose specifics. ECHO report impressions were utilized to evaluate the EF% status.

Statistical analysis

SPSS version 20 was used to analyze the data (SPSS Inc., Chicago, IL). A paired t-test was employed to discover the difference in percentage LVEF between the baseline and follow-up data, and the student's t-test was utilized to determine the significance of differences between the mean values of two continuous variables. A significance level of $P < 0.05$ was deemed statistically significant.

III. RESULT

Based on the inclusion and exclusion criteria, a total of 50 patients with a diagnosis of heart failure were included in this retrospective analysis. Table no 1 displays the patient demographics and characteristics at baseline. In this study, the majority of participants were male (80%). The participants' average age was 65 ± 4.7 years. According to their BMI, just 6% of individuals were obese. Of them, 72% led sedentary lives, 22% were current smokers, and 12% reported drinking alcohol regularly.

Table no 1: Patient demographical characteristics

Variables	Observations (n = 50))
Male (n (%))	40 (80 %)
Female (n (%))	10 (20 %)
Age (years) (Mean ± SD)	65 ± 4.7
BMI	
Normal (n (%))	42 (84 %)
Over weight (n (%))	5 (10 %)
Obese (n (%))	3 (6%)
Life Style habit	
Sedentary (n (%))	36 (72 %)
Moderate (n (%))	14 (28 %)
Current Tobacco user (n (%))	11 (22 %)
Current Alcohol user (n (%))	6 (12 %)

Table no 2 displays the clinical features of the patients. Within the patient group under investigation, 34 % had diabetes mellitus, 10 % had hypertension, and 4 % had hypothyroidism. An ischemic heart failure incidence of 84% and a non-ischemic heart failure incidence of 16 % were reported for heart failure. Among the 50 patients, 26 % underwent dose titration, and 74 % underwent non-titration. ARB inhibitors and beta blockers were given to 54 % of patients, ACE inhibitors and beta blockers to 23 percent of patients, and ARNI and beta blockers to 22 % of patients.

Table no 2: Patient Baseline clinical characteristics

Variables	Observations (n = 50) (n (%))
Co morbidities	
Diabetes Mellitus	19 (34 %)
Hypertension	5 (10 %)
Hypothyroidism	2 (4 %)
Type of heart failure	
Ischemic	42 (84 %)
Non Ischemic	8 (16 %)
Drug Titration	
Titrated	13 (25 %)
Non-Titrated	37 (74 %)
HF treatment	
ACE + Beta Blockers	12 (24 %)
ARB + Beta Blockers	27 (54 %)
ARNI + Beta Blockers	11 (22 %)

Table no 3 displays the mean differences between the dose-titrating and dose-non-titrating groups at the study's end. The diagnosis of ischemic heart failure was made in 86.5% of the non-titrated individuals. Similarly, ischemic heart failure was identified in 86.5% of the titrated individuals. Ramipril 1.97 mg, valsartan 63.3 mg, sacubitril/valsartan 60 mg, carvedilol 7.71 mg, bisoprolol 3.3 mg, and metoprolol 37.5 mg were the average doses of heart failure medications given to titrated patients. The non-titrated patient was prescribed a mean dose of 2.75 mg of ramipril, 41.9 mg of valsartan, 66.6 mg of sacubitril/valsartan, 3.125 mg of carvedilol, 3.125 mg of bisoprolol, and 25 mg of metoprolol for heart failure.

In patients receiving titrated doses, the mean ejection fraction is 28.38%, 31.5%, 35.15%, and 35.7% in the baseline, and subsequent follow-ups respectively. The mean ejection fraction for patients who were given non-titrated doses in the baseline, and subsequent follow-ups was 30.1%, 33.8%, 37.1%, and 39.1%, respectively.

In the initial visit and follow-up, the mean ejection fraction of the ischemic heart failure patients receiving a non-titrated dose was 30.2%, and 39.8%, respectively. Furthermore, initial visit and follow-up, the mean ejection fraction for non-ischemic heart failure patients receiving a non-titrated dose was 29.4% and 35.6%, respectively. This shows that, in ischemic heart failure, mean ejection fraction improvement is greater than in non-ischemic heart failure with a non-titrated dose.

In the initial visit and follow-up, the mean ejection fraction of the ischemic heart failure patients receiving a titrated dose was 28.9%, and 37.8%, respectively. Furthermore, initial visit and follow-up, the mean ejection fraction for non-ischemic heart failure patients receiving a titrated dose was 26.6% and 32.3%, respectively. This shows that, in ischemic heart failure, mean ejection fraction improvement is greater than in non-ischemic heart failure with a titrated dose.

The non- titrated patient receiving ARB + Beta Blockers showed a significant improvement in the percentage of mean LVEF (40.0%), which was followed by ACE inhibitor + Beta Blockers (37.8%) and ARNI + Beta Blockers (37.0%). The titrated patient receiving ARB + Beta Blockers showed a significant improvement in the percentage of mean LVEF (37.3%), which was followed by ACE inhibitor + Beta Blockers (36.5%) and ARNI + Beta Blockers (36.0%).

Table no 3: Mean changes in Titrating dose and Non-titrating dose at the end of the study

Parameters	Group A Dose Titration (n = 13)			Group B Dose non titration (n= 37)		
Type of heart failure						
Ischemic n ((%))	10 (77.0 %)			32 (86.5 %)		
Non Ischemic n ((%))	3 (23.0 %)			5 (13.5 %)		
Mean HF treatment dose(mg) (Mean ± SD)						
Ramipril	1.97 ± 0.36			2.75 ± 1.64		
Valsartan	63.3 ± 13.8			41.9 ± 8.78		
Sacubitril/Valsartan	60 ± 11.5			66.6 ± 8.78		
Carvedilol	7.71 ± 3.3			6.04 ± 2.22		
Bisoprolol	3.3 ± 1.77			3.125 ± 1.13		
Metoprolol	37.5 ± 14.4			25 ± 13.5		
Over all mean ejection fraction % (Mean ± SD)						
Baseline	28.38 ± 6.04			30.05 ± 5.4		
Follow up-1	31.5 ± 5.95			33.8 ± 4.75		
Follow up-2	35.15 ± 4.59			37.05 ± 5.04		
Follow up-3	35.7 ± 7.6			38.9 ± 3.6		
Mean ejection fraction with type of Heart Failure % (Mean ± SD)						
Ischemic HF						
Baseline	28.9 ± 5.8			30.15 ± 5.8		
Follow up-1	32.54 ± 5.4			34.25 ± 5.18		
Follow up-2	36.2 ± 3.9			37.4 ± 4.7288		
Follow up-3	37.8 ± 6.4			39.8 ± 2.65		
Non Ischemic HF						
Baseline	26.6± 7.62			29.4 ± 3.78		
Follow up-1	28.3 ± 7.64			31.2 ± 4.14		
Follow up-2	31.6 ± 5.6			35.4 ± 3.6		
Follow up-3	32.3 ± 6.4			35.6 ± 5.3		
Mean ejection fraction with type of treatment						
Types of treatments	ACE + BB (%) (n=2)	ARB + BB (%) (n=6)	ARNI + BB (%) (n=5)	ACE + BB (%) (n=10)	ARB + BB (%) (n=21)	ARNI + BB (%) (n=6)
Baseline	28.5 ± 4.94	31.8 ± 4.02	24.2 ± 6.5	31.2 ± 5.5	29.9 ± 5.88	29.4 ± 5.2
Follow up-1	31.5 ± 2..2	34.9 ± 3.17	27.6 ± 7.5	33 ± 6.1	34.3 ± 5.2	33.3 ± 2.8
Follow up-2	34 ± 1.4	36.8 ± 2.4	33 ± 6.7	35.9 ± 5.4	38.09 ± 4.3	35.03 ± 4.5
Follow up-3	36 ± 0.7	37.3 ± 2.5	35.8 ± 10.8	37.8 ± 4.7	40 ± 2.9	37 ± 3.5

IV. DISCUSSION

The age group most afflicted by HF in our study was 60–70 years, with a mean age of 65 ± 4.7 years. This indicates that heart failure is more common in those above 60 years. A similar outcome was discovered in a study where the age group with the highest frequency was above 65 years.[10] Given that men made up 80% of the study sample, it is clear that heart failure is more prevalent in men than in women. Our results are consistent with a prior study that found a higher frequency of heart failure in the male population.[11]

A sedentary lifestyle was reported by 72% of the participants in our study. This suggests that patients who have sedentary lifestyles have a higher risk of heart failure. This result lines up with the earlier study's finding that sedentary activity raises mortality risk from cardiovascular disease.[12] In our study, 22% of patients reported using tobacco products currently, and 12% reported having a dependency on alcohol. These results coincide with a recent study that found smoking and alcohol consumption to be risk factors for cardiovascular illnesses.[13]

Thyroid dysfunction, ischemic heart disease, diabetes mellitus, and hypertension are a few risk factors for heart failure. According to a population-based clinical trial research, diabetes mellitus dramatically raises the risk of heart failure; this finding is consistent with our study, which included 34% of patients with diabetes mellitus.[14]

HF was prevalent in the male population, accounting for 84% of cases of ischemic heart failure. This indicates that the prevalence of ischemic heart failure is higher than that of non-ischemic heart failure. This result is in line with previous studies showing that men are more likely than women to experience ischemic heart failure than non-ischemic.[15,16]

Merely 26% of the patients in our research received the titrated dose. This suggests that the majority of patients in the research population were receiving non-titrated medication doses. The combination of BB and ARB inhibitors accounted for 54% of all prescriptions in our sample. Our results are consistent with a prior study's recommendation to always start with low dosages of ACEIs ,ARBs and ARNI and to increase the dose only if the patient tolerates it, as higher doses increase the possibility of side effects.[17]

In both the titrated and non-titrated patient groups in our investigation, the improvement in mean ejection fraction was greater in ischemic heart failure than in non-ischemic heart failure. This result contradicts a prior study's findings, which stated that ischemic patients had a worse one-year prognosis than non-ischemic patients. [18] The shorter study duration and lower sample size could be the cause of this discrepancy in our research.[18]

In terms of statistics, the improved ejection fraction did not significantly differ between the titrated and non-titrated groups. On the other hand, the non-titrated groups showed marginally greater progress. Over the past 20 years, there have been noticeable advancements in the prescription of recently produced HF medications for HFrEF; yet, the doses that are typically prescribed in clinical practice are often substantially lower than those that were attained in the randomized controlled trials. The successful investigations were nevertheless predicated on forced up-titration to pre-specified target dosages, even though the clinical trials were not usually meant to ascertain whether the benefits were dose-related.

It has been demonstrated that clinical evaluation and input can enhance prescribing behavior; nevertheless, additional context-specific interventions are needed to facilitate medication titration. Medication titration has been a beneficial addition to the clinical practice scope for nurses and chemists, expanding on the established advantages of multidisciplinary HF disease care. Nonetheless, approaches that involve primary care with prompt communication, distinct roles, and point-of-care decision assistance might be more broadly applicable to enable the remarkable improvements shown in the clinical trials to be implemented for the larger HF population.

V. CONCLUSION

In comparison to patients who were titrated, the non-titrated HFrEF exhibited slight improvement in EF. In the future, research should use soluble biomarkers or molecular imaging to concentrate on pharmacodynamic profiles rather than tolerability when determining doses. To utilize high doses of HF medicines more attention should be paid to the safety and effectiveness of these drugs in randomized, controlled studies.

VI. LIMITATIONS

There are a few limitations to our investigation. This study employed secondary data from medical records in a retrospective manner. As a result, only information contained in the clinical history could be gathered, which may have resulted in an underdiagnosis of certain factors. This study did not involve any patient-specific interventions. Furthermore, the small number of HF patients from a single center is included and there is unequal patient distribution between the titrated and non-titrated groups.

VII. FUTURE RECOMMENDATIONS

Phase II trials should prioritize pharmacodynamics profile-based dose identification beyond tolerability, using soluble biomarkers or molecular imaging, given there are currently few biologically-guided treatment targets for heart failure. Phase III trials should concentrate more on randomised, controlled studies examining the safety and effectiveness of HF drugs. Reaching the doses intended in clinical trials should be the main goal of post-approval quality improvement and educational programmes. Healthcare professionals must acknowledge the significant role that every targeted pathway plays in the HF arsenal and utilize each therapy to the maximum extent that is tolerable. The key to improving outcomes for HF patients is to optimize patient care by combining pragmatic strategies with solid clinical judgment.

REFERENCES

[1]. Murphy, Sean P.; Ibrahim, Nasrien E.; Januzzi, James L. (2020). Heart Failure With Reduced Ejection Fraction. JAMA, 324(5), 488–504.

[2]. McDonagh T.A., Metra M., Adamo M., Gardner R.S., Baumbach A., Böhm M., Burri H., Butler J., Čelutkienė J., Chioncel O., et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur. Heart. J. 2021;42:3599–3726.

[3]. Tsao C.W., Aday A.W., Almarzooq Z.I., Alonso A., Beaton. A.Z., Bittencourt M.S., Boehme A.K., Buxton A.E., Carson A.P., Commodore-Mensah Y., et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation. 2022;145:e153–e639.
[4]. Groenewegen A., Rutten F.H., Mosterd A., Hoes A.W. Epidemiology of heart failure. Eur. J. Heart. Fail. 2020;22:1342–1356.
[5]. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136(6):e137-e161.
[6]. Virani SS, Alonso A, Benjamin EJ, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020;141(9):e139- e596.
[7]. Thibodeau JT, Turer AT, Gualano SK, et al. Characterization of a novel symptom of advanced heart failure: bendopnea. JACC Heart Fail. 2014;2 (1):24-31.
[8]. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022 May 3;79(17):e263-e421.
[9]. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. J AmColl Cardiol. 2018;72(4):351-366.
[10]. Ahmad Malik A, Daniel Brito D, Sarosh Vaqar S, et al. Congestive heart failure.In: StarPearls. Treasure Island [FL]: StarPearls. Publishing; 2022 Jan.
[11]. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. Med Sci Sports Exerc. 2010 May;42(5):879-85.
[12]. Rosoff DB, Davey Smith G, Mehta N, Clarke T-K, Lohoff FW (2020) Evaluating the relationship between alcohol consumption, tobacco use, and cardiovascular disease: A multivariable Mendelian randomization study. PLoS Med 17(12): e1003410. Z
[13]. Rosano GM, Vitale C, Seferovic P. Heart Failure in Patients with Diabetes Mellitus. Card Fail Rev. 2017;3(1):52-55.
[14]. Mehta, P. A., & Cowie, M. R. (2006). Gender and heart failure: a population perspective. Heart (British Cardiac Society), 92 3 (Suppl 3), iii14–iii18.
[15]. Strömberg A, Mårtensson J. Gender Differences in Patients with Heart Failure. European Journal of Cardiovascular Nursing. 2003;2(1):7-18.
[16]. Yang PS, Kang Y, Bae HJ, Sung JH, Park HD, Joung B. Mortality among ischemic and nonischemic heart failure patients with a primary implantable cardioverter-defibrillator. J Arrhythm. 2021 Oct 29;37(6):1537-1545.
[17]. Turgeon RD, Kolber MR, Loewen P, Ellis U, McCormack JP. Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: Systematic review and meta-analysis. PLoS One. 2019;14(2):e0212907.
[18]. Tymińska A, Ozierański K, Balsam P, Maciejewski C, Wancerz A, Brociek E, Marchel M, Crespo-Leiro MG, Maggioni AP, Drożdż J, et al. Ischemic Cardiomyopathy versus Non-Ischemic Dilated Cardiomyopathy in Patients with Reduced Ejection Fraction— Clinical Characteristics and Prognosis Depending on Heart Failure Etiology (Data from European Society of Cardiology Heart Failure Registries). Biology. 2022; 11(2):341.