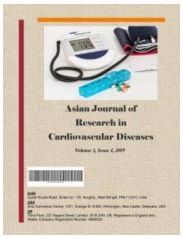

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Effect of Sodium Glucose Co-transporter-2 Inhibitors in Heart Failure Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Author GRR helped in the research design, approval of final manuscript supervision of conduct and findings of the study and was also the treating physician of all the heart failure patients. Authors ZH, ZF, AS and SSM managed the literature searches, writing of protocol, data collection, data compilation, data analysis, statistical analysis and drafting of manuscript. Authors MH and MMAB helped in conceptualization and representation of work for approval from IRB. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To study the management outcomes of heart failure therapy with SGLT2-inhibitors added to conventional therapy and to compare its effect in diabetic and non- diabetic heart f ailure patients.
Methods: This is a prospective observational study done at the Department of Cardiology of a tertiary care hospital from November 2020 to January 2022. The study included 100 heart failure patients who were divided into two groups based on administration of SGLT2 inhibitors. Group I consists of HF patients without SGLT2i and Group II: HF patients with SGLT2i. Subjective and objective parameters were recorded as well as the management patterns of the patients were recorded during the hospital stay and the outcomes (improvement in NYHA class, rehospitalisation and mortality) were assessed at follow up.
Results: Most of the patients included in the study belonged to NYHA class-III. In this study HFrEF was found to be more prevalent in both group I (71.4%) and group II (83.6%). There was a

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significant difference observed for ejection fraction both in Group-I (36.45 ± 0.6 vs 38.85 ± 0.75) and Group- II (34.3 ± 0..6 vs 39.2 ± 1.01) at admission and after follow up (P=0.001). In our study when the outcomes were compared between group-I and group-II, there was statistical significance observed for the improvement in NYHA class (54.2% vs 61.2%) and decrease in mortality (11.4% vs 4%) was also observed (P=0.01) at the end of 1 year follow up. The effect of SGLT2i on the primary outcome was consistent in patients regardless of the presence or absence of diabetes.

Conclusion: Our study highlights that when SGLT2 inhibitors are used for treating HF patients with or without diabetes, they can have a positive impact as they achieve outcomes like improvement in NYHA class, decreased rehospitalisation and reduction in mortality risk. The study also indicates improvement in Left ventricular ejection fraction in case of HFrEF patients. Furthermore, randomization trials are required to determine the efficacy of SGLT2 inhibitors in Indian population to ascertain its association with better outcomes and to further promote its use.

Keywords: Heart failure; left ventricular ejection fraction; SGLT2 inhibitors; diabetes; HFrEF.

1. INTRODUCTION

Heart failure (HF) occurs when the heart is unable to supply adequate blood and oxygen to the peripheral tissues to meet their metabolic demands [1]. India lacks reliable heart failure estimates due to a lack of a surveillance programme to evaluate incidence, prevalence, outcomes, and key causes of HF [2,3]. Diabetes mellitus (DM) is a well-established risk factor for cardiovascular diseases, including HF [4,5]. Although there is still an unmet need for additional HF therapies in diabetic patients, SGLT2 inhibitors [SGLT2i] have begun to shift this paradigm [4,6,7]. SGLT2 are major transport proteins responsible for reabsorption of glucose (90%) in the kidneys proximal convoluted tubule [8]. Land-mark cardiovascular outcome trials have shown a benefit of SGLT2i over placebo in the composite end point of cardiovascular mortality or HF hospitalizations [4,7,9,10]. At this point, a number of SGLT2i that have been approved for treatment of type-2 diabetes [T2D], are: empagliflozin [11], canagliflozin [10], and dapagliflozin [12], which have each shown improvement in cardiovascular outcomes in clinical trials.

This study aims for the management outcomes of HF therapy with SGLT2i added to conventional therapy and compare its effect in diabetic and non- diabetic HF patients.

We sought to perform a prospective observational study examining the efficacy of SGLT2i, Empagliflozin (Jardiance 10 mg) and Dapagliflozin (Udapa 10 mg) in patients with HF, with or without diabetes, specifically interested in mortality and hospitalization endpoints, as well as the outcomes in subpopulations of HF patient.

2. MATERIALS AND METHODS

2.1 Objectives

The primary objective of the study was to assess the variation in the management outcomes of heart failure (HF) therapy with SGLT2-inhibitors added to conventional therapy and compare its effect in diabetic and non- diabetic heart failure patients. The secondary objectives were to assess and compare the clinical characteristics, laboratory parameters, medication adherence and mortality risk in acute heart failure patients. The study also aims for optimizing the use of sodium-glucose co-transporter 2 inhibitor (SGLT2i) in patients with HFrEF and HFmEF.

2.2 Study Design and Participants

This is a prospective observational study with a sample size of 100 patients who were admitted in the cardiology department of a tertiary care hospital. Patient enrolment was done from November 2020 to January 2022. The subjects were divided into two groups depending on the administration of SGLT2i Group I: conventional HF therapy without SGLT2i (n=35) and Group-II: conventional HF therapy with SGLT2i (n=49).

2.3 Inclusion and Exclusion Criteria

Patients who were above 18 years of age, NYHA(New York Heart Association) classification II-IV, diagnosed with de-novo or pre-existing heart failure(HFREF-heart failure with reduced ejection fraction and HFMEF- heart failure with mid-range ejection fraction) were included in this study and also subjects with or without diabetes. Exclusion Criteria included patients below 18 years of age, patients with

incomplete lab data, patients who do not comply to participate in the study, pregnant and lactating women, patients with type-1 diabetes and hypotension.

2.4 Assessment of Medication Adherence

The assessment of medication adherence was done using Morisky Medication Adherence Scale is a validated assessment tool which has an eight item questionnaire that can be used to measure non-adherence in a variety of patient populations. The tool uses a series of short behavioral questions geared in such a way to avoid "yes-saying" bias commonly seen with chronic care patients. This allows the patient to respond to questions about non-adherence in a spirit of full disclosure. If a patient scores higher on the scale, they are evaluated as more adherent. If they score lower on the scale, they are presumed to be struggling with nonadherence. By understanding how the patient scored on the scale, it helps to identify underlying issues that prevent patients from taking their medications correctly [13].

2.5 Assessment of Mortality Risk

The assessment of 1 year and 3 year mortality risk of HF patients was done using Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) Risk Calculator [14,15]. The variables included in the risk score are as follows: age, gender, body mass index (BMI), New York Heart Association (NYHA) class, systolic BP, smoking, DM, left ventricular ejection fraction (LVEF), serum creatinine, use of RAAS blockers, beta blocker use, chronic obstructive pulmonary disorder (COPD) and HF diagnosed >18 months ago [16].

2.6 Follow up

The follow up of all the patients was done at 3 months (hospital follow up), 6 months (hospital follow up) and 1 year (telephonic follow up) respectively and the outcomes of the study were recorded at each follow up.

2.7 Outcomes

The primary end point of this study was mortality and the secondary end points were recurrent hospitalizations (for acute heart failure) and improvement in symptoms according to NYHA classification which was compared between both the groups.

2.8 Statistical Analysis

Means and standard deviations are provided for continuous variables whereas numbers and percentages for qualitative variables. Comparative analysis were performed using chi-square test and fisher's exact test for categorical variables and student t-test was used for continuous variables. The 5% level was used to identify differences in between groups that were of statistical significance (P value <0.05), since the CI is 95%. Statistical evaluations were performed using Sigma Plot Version 12.0

3. RESULTS

In this study a total of 100 patients admitted in the cardiology department of the hospital during the duration of 6 months i.e. from August 2020 to January 2021 were assessed. Out of which 11 subjects were excluded from the study due to incomplete data and 5 were excluded as they did not meet the inclusion criteria. Hence 84 patients met the inclusion criteria and were included in the study, these HF patients were then categorised into two groups.

3.1 Groupwise Distribution

Group-I included HF patients that were on conventional drug therapy without SGLT2i (n=35) while Group-II had HF patients with SGLT2i added to the conventional drug therapy (n=49). In Group-II (51.3%) there were mainly two SGLT2i drugs used based on availability of drug in the hospital pharmacy, these included dapagliflozin (81.08%) and empagliflozin (18.92%). Dapagliflozin is less expensive than empagliflozin.

3.2 Age and Gender Distribution

Heart failure has become the main cause of hospitalization in people older than 65 years of age but in the present study the mean age among HF patients was found to be 56.42 ±2.2 whereas among Group II patients it was found to be 54.81±1.9. There was no significant difference obtained in age when both the groups were compared (p value = 0.586). (Table-1). The data collected on gender distribution revealed that there were more number of male subjects in both Group-I [65.71%] and Group-II [59.46%] (Table-1).

3.3 Comparison of NYHA Class

The NYHA class was assessed and recorded upon admission for all patients. The results from

the data obtained showed that HF patients with and without SGLT2i were found to be more in NYHA class III. We found no significant statistical difference in the NYHA class between the two groups [p-value=0.657].

3.4 Comparison of Risk Factors and Comorbidities

Smoking is a more common risk factor in both Group-I [28.3%] and Group-II [24.4%], it was observed that there is no statistical significance [p=0.681]. On comparing both the groups for the presence of comorbidities, a significant difference was observed in case CKD [28.5% vs. 8.1%; p=0.014].

3.5 Prevalence of Different Types of Heart Failure based on Ejection Fraction

In this study HF patients with and without SGLT2i were found to be more with HFrEF. There was a significant difference observed for ejection fraction both in Group-I (36.45 ± 0.6 vs 38.85 ± 0.75; p < 0.001) and Group- II (33.86 ± 1.06 vs 37.15 ±0.99; p<0.001) at admission and after follow up of 1month. [Table-2] Improvement in LVEF was also observed both in diabetics (33.7 ± 0.9 vs. 37.4±1.05; p < 0.001) as well as non-diabetics (34.3 ±3.8 vs. 37.7± 2.7; p<0.03). [Table-3]

Table 1. Comparison of general parameters between both the groups

General parameters	Group-I	Group-II	P-Value
Age			
20-80	56.42±2.2	54.81±1.9	0.668
Gender			
Male	23 [65.71%]	33 [67.31%]	0.938
Female	12 (34.2%)	16 [32.6%]	
NYHA class			
II	5 [14.28%]	4 [8.1%]	0.657
III	20 [57.14%]	29 [59.1%]	
IV	10 [28.57%]	16 [32.6%]	
Variables at admission			
SOB	27 [77.1%]	33 [67.3%]	0.333
Systolic BP	120.87 ±2.26	129 ± 2.4	0.020
Diastolic BP	78.28 ± 1.66	80.7 ± 1.5	0.261
Pedal Edema	16 [45.7%]	23 [46.9%]	0.916
Risk Factors			
Smoking	10 [28.5%]	12 [24.4%]	0.681
Alcoholic	4 [11.4%]	3 [6.1%]	0.394
Tobacco chewer	4 [11.4%]	4 [8.1%]	0.624
Comorbidities			
HTN	24 (68.5%)	41 (83.6%)	0.070
DM	22 (62.8%)	39 (79.5%)	0.093
IHD	13 (37.1%)	19 (38.7%)	0.884
CKD	10 (28.5%)	4 (8.1%)	0.014*
COPD	3 (8.57%)	3 (6.1%)	0.667
Prevalence of HF			
HFrEF [<40% EF]	25 [71.4%]	41 [83.6%]	0.097
HFmEF [40-49% EF]	10 [28.5%]	8 [16.3%]	
Cardiac biomarkers			
Hs-troponin-1	1.64±0.66	3.26 ± 1.21	0.528
Nt-pro BNP	4881.0286±1668.59	5929.65 ± 1050.89	0.389
Length of stay	6.61 ± 0.39	6.78 ± 0.38	0.771
Follow up	35 (100%)	49 (100%)	0.974

Data are number (%) of patients, mean, standard deviation P value is calculated by independent t-test, chi square test Group I: patients on conventional therapy; Group II: patients on conventional therapy with SGLT2i; HTN-hypertension; DM-diabetes mellitus; IHD-Ischemic heart disease; AF-Atrial fibrillation; COPD-Chronic obstructive pulmonary disease; OSA-obstructive sleep apnea; BP-blood pressure; NT-proBNP-N-terminal pro b-type natriuretic peptide

3.6 Comparison of Random Blood Sugar

For our study, we took Random blood sugar [RBS] as a parameter that indicated a significant difference both in Group-I (224.3±16.63 vs 161.65±6.49; p<0.001) and Group- II (253.91 ±14.38 vs 187.08± 9.3; p=<0.001) at admission and discharge.

3.7 Comparison of Mortality Risk using MAGGIC Risk Score

The MAGGIC risk score was calculated for both group at the time of admission. When both of these groups were compared a very highly significant difference (p value<0.001) was observed in mortality risk at 1year and 3 year.

3.8 Comparison of Medication Adherence using MMAS-8

The adherence to SGLT2-inhibitors [77.5%] was observed by comparing the conventional therapy [74.2%] adherence which indicated no statistical significance (p value = 0.661).

Table 2. Laboratory parameters comparison between heart failure patients with conventional therapy and SGLT2 inhibitor therapy

Parameter	HF patients with conventional therapy		P-Value	HF patients with conventional therapy and SGLT2 inhibitor		P-Value
	Before	After		Before	After	
Sodium	139.54 ±1.9	139.14 ± 0.97	0.446	139.5± 1.46	138 ± 1.11	0.150
Potassium	4.58 ± 0.22	4.05 ± 0.12	0.020*	4.2 ± 0.09	3.8 ± 0.09	0.001*
Chloride	100 ± 0.55	99.94 ± 0.66	0.934	99.75 ± 0.6	97.5 ± 0.62	0.007*
Blood urea	50.74 ± 5.4	56.17 ± 5.01	0.285	55.28 ± 4.74	47.1 ±2.4	0.443
Serum creatinine	1.65 ± 0.14	2.22 ± 0.54	0.217	1.5 ± 0.17	1.54 ± 0.07	0.359
RBS	224.3 ± 16.63	161.65± 6.49	<0.001*	249 ± 11.7	181.1 ± 7.2	<0.001*
EF	36.45 ± 0.6	38.85± 0.75	<0.001*	34.3 ± 0.9	39.2 ± 1.01	<0.001*

Data are mean ± standard error, P value is calculated by paired t-test, Group I: patients on conventional therapy; Group II: patients on conventional therapy with SGLT2i; RBS-Random Blood Sugar; EF-Ejection Fraction; Before are lab results at the time of hospital admission; After are lab results at discharge

Table 3. Comparison based on laboratory parameters for diabetic and non-diabetic patients

Parameter	Diabetic patients [n=39]		P-value	Non-diabetic patients [n=10]		P-value
	Before	After		Before	After	
Sodium	139±1.7	138 ± 1.3	0.317	140.8± 2.8	137 ± 1.8	0.397
Potassium	4.1 ± 0.1	3.8 ± 0.1	0.003*	4.3 ± 0.25	4.1 ± 0.23	0.251
Chloride	99.9 ± 0.6	97 ± 0.7	0.005*	99 ± 1.2	97 ± 1.4	0.478
Blood urea	57 ± 5.7	46 ± 2.9	0.291	45 ± 5.8	47 ± 3.1	0.743
Serum creatinine	1.67 ± 0.2	1.57 ± 0.07	0.68	1.16 ± 0.14	1.56 ± 0.2	0.158
RBS	249 ± 13.03	180 ± 8.5	<0.001*	137 ± 10.1	107 ± 7.2	<0.001*
EF	34 ± 0.9	39 ± 1.14	<0.001*	33.5 ± 3.07	38.6 ± 2.25	<0.03*

Data are mean ± standard error, P value is calculated by paired t-test, Group I: patients on conventional therapy; Group II: patients on conventional therapy with SGLT2i; RBS-Random Blood Sugar; EF-Ejection Fraction; Before are lab results at the time of hospital admission; After are lab results at discharge

Table 4. Comparison of final outcomes in diabetic and non-diabetic patients after 1 year

OUTCOMES	GROUP-II		P-value
	Diabetics (n=39)	Non-Diabetics (n=10)	
Improvement in NYHA class	18 (46.1%)	6 (60%)	0.448
Rehospitalisation	6 (15.3%)	0 (0%)	0.222
Mortality	1 (2.5%)	0 (0%)	0.649

Data are number (%) of patients, P value is calculated by chi square test, fisher's exact test Group I: patients on conventional therapy; Group II: patients on conventional therapy with SGLT2i; NYHA-New York heart association

Table 5. Comparison of final outcomes

Outcomes	GROUP-I	GROUP-II	P-value
3 months			
Improvement in NYHA class	5 (14.2%)	18 (36.7%)	0.045
Rehospitalisation	7 (20%)	4 (8.1%)	0.001
Mortality	2 (5.7%)	1 (2%)	0.057
6 months			
Improvement in NYHA class	11 (31.4%)	24 (48.9%)	0.111
Rehospitalisation	9 (25.7%)	7 (14.2%)	0.193
Mortality	3 (8.57%)	1 (2%)	0.172
1 year			
Improvement in NYHA class	19 (54.2%)	30 (61.2%)	0.013
Rehospitalisation	11 (31.4%)	12 (24.4%)	0.001
Mortality	4 (11.4%)	2 (4%)	0.01

Data are number (%) of patients, P value is calculated by chi square test, fisher's exact test Group I: patients on conventional therapy; Group II: patients on conventional therapy with SGLT2i; NYHA-New York heart association

3.9 Comparison of Final Outcomes after 3 Months, 6 Months and 1 Year

The final outcomes (improvement in NYHA class, rehospitalisation and mortality) were compared and assessed for both group-I and group-II after a period of 3 months, 6 months and 1 year. Re-hospitalization was defined as a patient's re-admission to the hospital for acute heart failure. In group I, there was an improvement in NYHA class (14.2% vs 36.7%) and a lower death rate (5.7% vs 2%), and the outcomes were similar in terms of re-hospitalization (20% vs 8.1%) when patients were followed up for 3 months.

At the 6-month follow-up, there was a significant difference in terms of improvement in NYHA class, rehospitalization and mortality. In group I patients, a 1 year follow-up demonstrated significant improvements in NYHA class, decreased re-hospitalization, but group I patients had a higher mortality rate (P=0.01). (See Table 4) There was one death linked to COVID-19. Only 2 patients (2.3%) died in the hospital, whereas the majority of the deaths (4.7%) occurred outside of the hospital.

The effect of SGLT2i on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. In group II, when diabetic and non-diabetic patients with HF receiving SGLT2i were compared both of them indicated improvements in NYHA class (41.3% vs 50%) and decrease in mortality (3.4% vs 0%). Comparatively rehospitalisation within 1 year was also reduced in HF patients receiving SGLT2i, but there was no statistical significance.

4. DISCUSSION

Heart disease associated with diabetes mellitus (DM) continues to be the leading cause of death worldwide [17]. Until recently, there were no HF therapies directed at glucose metabolism [18,19]. However, with the development of renal sodium glucose transport inhibitors (SGLT2i) there appears to be new hope. SGLT2 inhibition can reverse the cardiac remodeling seen in heart failure, thereby reducing left ventricular [LV] wall stress and improving cardiac function [20]. The study aims for the management outcomes of HF therapy with SGLT2-inhibitors added to conventional therapy and compare its effect in diabetic and non- diabetic heart failure patients.

Most of the patients included in the study had both class III and IV symptoms [21]. On

comparing for the presence of comorbidities, a significantly more number of heart failure patients suffered with hypertension, diabetes, ischaemic heart disease and CKD. At admission and discharge, blood samples from all patients underwent biological analysis. The serum electrolytes showed a significant difference for potassium both in Group-I and Group- II at admission and discharge which indicates that SGLT2i are not associated with an increased risk of hyperkalemia or severe hypokalemia in patients with T2DM [22]. In case of chloride, only Group-II showed significant difference, indicating that SGLT2i do not affect serum chloride levels which was not comparable to other studies. Diabetic patients with HF taking SGLT2i showed a significant difference both in potassium and chloride at admission and discharge.

There was no statistical significance found in blood urea and serum creatinine investigated in Group-II (serum creatinine for non-diabetics, was also not significant) at admission and discharge but adding SGLT2i to conventional therapy can reduce blood urea [23].

For glycemic efficacy, the mean changes from baseline in HbA1c and FPG and the change from baseline in 2-hour PPG are more dynamic parameters (23; 24) but the proper data for this was not recorded, instead Random blood sugar [RBS] was taken as a parameter that indicated a significant difference both in Group-I and Group-II at admission and discharge this was also observed for both diabetics and non-diabetics.

Reduction in NT-proBNP levels as the primary endpoint of this study would have provided robust evidence with respect to therapeutic effects of SGLT2i in heart failure [22] but in this study only at admission values for troponin and NT-proBNP were obtained for HF patients due to COVID-19 pandemic restrictions.

Randomized trials for SGLT-2 inhibitors have indicated reductions in LV mass, LV sphericity and also improvement in LV ejection fraction in patients with HFrEF both in diabetics and non-diabetics [25]. In this study although a greater number of patients suffered with HFrEF. There was a significant difference observed for ejection fraction both in Group-I and Group- II at admission and after follow up of 1 year. Improvement in LVEF was also observed both in diabetics as well as non-diabetics which supports various trials conducted for SGLT2i [mainly, empagliflozin and dapagliflozin] [25].

Of all the different risk scores the use of Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) Risk Calculator is recommended which calculates 1 year and 3-year mortality risk [14,15,26] In this study, despite the fact that the MAGGIC risk calculator predicted a three-year difference in mortality between the groups, there was a substantial difference in mortality at one year in our investigation. This is likely attributable to poor outcomes among the Indian population, particularly those in lower socioeconomic strata, such as those in our study cohort. No new evidence was found in literature review that used MAGGIC risk score for predicting mortality risk with the use of SGLT2i in HF patients.

There was no new reports regarding adherence to SGLT2i in Heart Failure patients, we are reporting this for the first time.

Empagliflozin trials have demonstrated a striking reduction for hospitalization for heart failure in subjects with established cardiovascular disease, an effect later also seen with other compounds of the SGLT2i class [27] . In our study when the outcomes were compared between the HF patient without and with SGLT2i, improvements in NYHA class, reduced rehospitalisation and decrease in mortality was observed in case of patients taking SGLT2-inhibitors, although there was no statistical significance observed. The effect of SGLT2i on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. In group II, when diabetic and non-diabetic patients with HF receiving SGLT2 inhibitor were compared both of them also indicated improvements in NYHA class, reduced rehospitalisation and decrease in mortality but this indicated no statistical significance.

Our study highlights that when SGLT2 inhibitors are used for treating HF patients with or without diabetes, they can have a positive impact as they achieve outcomes like improvement in NYHA class, decreased rehospitalisation and reduction in mortality risk. The study also indicates improvement in Left ventricular ejection fraction in case of HFrEF patients. Furthermore, randomization trials are required to determine the efficacy of SGLT2 inhibitors in Indian population to ascertain its association with better outcomes and to further promote its use.

5. CONCLUSION

This study provides an insight into the effect of SGLT2 inhibitors when treating heart failure

patients in a tertiary care hospital setting. We also compared the HF patients receiving SGLT2i based on the presence of diabetes. We can conclude that the study has a positive impact on patients with HFrEF as it helps in improvement of LVEF. We can also conclude the study aids in achieving outcomes like improvement in the NYHA class, reduced rehospitalisation and mortality which is similar in case of diabetic and non-diabetic HF patients in this study. Since this study was conducted during the COVID-19 pandemic it's possible that the results and some of the study's shortcomings were influenced by it. In addition, randomization trials are needed to assess the efficacy of SGLT2 inhibitors in the Indian population in order to determine their link to better outcomes and to encourage their use. This analysis needs repeating on a larger scale to ensure these findings are representative of wider practice. SGLT2i are also likely to be useful in HFpEF. Future studies should explore this possibility.

6. LIMITATIONS

The design of our study is a prospective observational study. It is a single centre study, considering our institution's management of HF with SGLT2i differs from that of other institutions, the findings are less generalizable across all populations. Because of the pandemic condition and the limited number of hospital admissions, the sample size was reduced, and the study length was similarly limited. Self-reported adherence and adverse events evaluation interview have short comings such as social desirability bias and a tendency to overestimate adherence. Although measures such as pill count method was used, it can sometimes misinterpret adherence, since it fails to measure whether the medication was taken on schedule. For reasons of feasibility, we limited the sub grouping of patients according to ejection fraction. We restricted the study population to only reduced and mid-range EF. The COVID-19 pandemic may have also had an impact on the outcome.

CONSENT AND ETHICAL APPROVAL

This study has been approved by institutional review board (IRB) of the hospital. A written informed consent form was obtained from all the subjects enrolled in the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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