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Foundation Four Therapy in Heart Failure: A Real-World Experience from a Cardiac Clinic in India

Kanimozhicharulatha Pitchai, Prof.Dr.Harikrishnan Parthasarathy
MBBS, Guangzhou Medical University, Guangzhou, China
MD, FRCP. Consultant Cardiologist
Shri Krishnasai Clinic, Koyambedu, Chennai & Apollo Specialty Hospital – Vanagaram, Chennai, India

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ABSTRACT

Introduction

Foundation Four Therapy(FFT) is the emerging pharmacological intervention for Heart Failure(HF) patients with reduced (EF<40%) and mid-range (EF≥40% and <50%) EF. The purpose of this study is to identify if FFT is feasible for all HF patients, if not, what are the various reasons for not being able to start or continue these medicines in an Indian setting.

Methodology

A retrospective observational study was done with a clinic database, which included 100 patients with HF (NYHA class 1 to 4) above 18 years of age and EF less than 50%. Clinical reports consisting of patients' echo, co-morbidities, and prescribed medicines were studied.

Results

Only 7 out of 100 patients were on all 4 medicines of FFT. A total of 83 patients were on Beta Blocker, 74 patients on MRA, 35 on ARNI, and 34 on SGLT2i. Notable reasons for not starting include acute HF (7 patients) and intolerance (5 patients) for BB, CKD in 15 patients for MRA, stable symptoms on ACEi/ARB in 25 patients for ARNI, no opportunity to start and in the plan to be started in 22 patients for SGLT2i.

Conclusion

Patients with ongoing acute HF, or those who have an intolerance to BB, or have COPD/wheezing/asthma were not under BB. CKD patients or those with elevated Cr were not started on MRA with the motive of starting it when the condition improves. Patients stable under ARB/ACEi is the main reason for not starting ARNI. SGLT2i and ARNI are to be prescribed in the upcoming clinical visits of many patients since they are new interventions in HF. Unaffordability, and unwillingness to take medicines are other reasons for patients not being prescribed these new therapies, so these patients are under conventional therapy for HF.

KEYWORDS: Foundation Four Therapy, HFrEF, HFpEF,ARNI, SGLT2i

I. INTRODUCTION

Foundation Four Therapy (FFT) is the emerging pharmacological intervention in heart failure (HF) and reduced ejection fraction (HFrEF) and heart failure and mildly reduced ejection fraction (HFmrEF). It consists of Beta Blockers (BB), Angiotensin Receptor blocker and Neprilysin Inhibitor (ARNI), Mineralocorticoid Receptor Antagonist (MRA) and Sodium Glucose Co-transporter 2 inhibitor (SGLT2i)(1).The conventional therapy for HF includes the BB and MRA, which are included in the FFT along with ARNI and a novel agent, SGLT2i. The 2022 ACC/AHA/HFSA guidelines recommends FFT in patients of HFrEF and HFmrEF(2). Guideline-directed medical therapy (GDMT) for HFrEF patients include all four classes of medicines under FFT. The PARADIGM-HF trial showed that ARNI was superior to ACEi in preventing cardiovascular deaths or hospitalization for HF(3). The SGLT2i in patients of HFrEF has confirmed to show 25% risk reduction of the primary end point of cardiovascular death or hospitalization for HF from both EMPEROR- Reduced and DAPA-HF trials(4, 5). All the four classes of medicines are together called the four pillars of HF management. Despite these recommendations, the utilization of ARNI and SGLT2i in the real-world has been suboptimal in HF patients. Our study intends to find out if all HFrEF and HFmrEF patients are on all classes of medicines under FFT, if not, why is a patient not on any particular class of medicine under FFT. To study and find out the various reasons why any particular class of medicine cannot be prescribed to a patient, the study was conducted in a tertiary cardiac clinic in India with a motive to improve the implementation of FFT in HF patients. The study involves Indian population.

II. METHODOLOGY

With more HF patients visiting the clinic, to understand and monitor if FFT can be achieved

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in patients with HF, and if not, the reasons for not being able to initiate or continue any class of medicine under FFT, the study was conducted at a tertiary cardiac clinic in Chennai, India.

The study involved 100 HF patients, who were classified based on their EF into HFrEF (EF ≤ 40%) and HFmrEF (EF 41% to 49%).The study was done using clinic database which includes the patients' prescription reports and echo reports. Under the guidance of a cardiologist, the patients' co-morbidities were studied and recorded.

The information was collected and recorded in Google forms and Excel. Information collected comprise of categories like the patients' EF, NYHA class, Co-morbidities, cause for HF, patients' compliance to therapy, medicines taken by the patients, and if a patient was not on any class of medicine in the FFT, the reasons were also recorded. The categories of information required about the patients for the study, were self-formulated and inspected, and revised by the senior consultant cardiologist in the clinic.

The echo report was studied to know the EF and patients' structural and functional condition of the heart. In the majority of patients, the echo and screening were done at the clinic by the cardiologist. Clinical examinations and lab investigations of the patients were considered when prescribing medicines and tailoring doses according to the patient's needs. The information regarding the medicines taken by the patients was taken from the prescription reports. It was a pilot study done as part of a bigger study, which we intend to do in the future.

Inclusion Criteria

- Patients aged ≥ 18 years
- Either sex
- HF with an EF < 50%
- NYHA class 1 to 4

Exclusion Criteria

- Patients < 18 years
- HF with an EF ≥ 50%
- Patients visiting clinic very inconsistently
- Patients whose EF improved to adequate/normal with conventional medicines
- HF patients who visited the clinic post the study time period

EJECTIONFRACTION(%)	NO. OFPATIENTS
LESS THAN 30	30
30 TO 39	41
40 TO 49	29

Figure 1: Ejection fraction of patients

NYHA CLASS	NO. OF PATIENTS
NYHA CLASS 1	4
NYHA CLASS 2	53
NYHA CLASS 3	30
NYHA CLASS 4	13

Figure 2: NYHA class of patients

III. RESULTS

A total of 100 HF patients were studied, in which 79 were male and 21 were female. Patients were grouped into HFrEF and HFmrEF based on their EF. Under the class HFrEF, there were 71 patients, and under the class HFmrEF there were 29 patients. The EF of patients was recorded (figure 1) and was found that 41 patients had an EF ranging from 30% to 39%, 30 patients had an EF less than 30% and 29 patients had an EF ranging from 40% to 49%. The patients' comorbidities were recorded and studied (figure 4), and was found that all 100 patients had dyslipidemia, 63 patients had diabetes, 56 patients had hypertension, 19 patients had CKD, 13 patients

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had other comorbidities like asthma, wheezing disorder, TB and other infectious diseases, 9 patients had hypothyroidism, 4 patients had an elevated Cr, 2 patients had PAD and 2 patients had atrial fibrillation.

Grade of LV diastolic dysfunction	NO. OF PATIENTS
GRADE 1	23
GRADE 2	18
GRADE 3	25
NO LVDD	2

Figure 3: LVDD of patients

The grade of Left Ventricular Diastolic Dysfunction (LVDD) was recorded for only 68 patients (figure 3), as 32 patients did not have a record of the same at the time of the study. Of the 68 patients, 25 patients had grade 3 LVDD, 23 patients had grade 1 LVDD, 18 patients had grade 2 LVDD and 2 patients had no LVDD. Ischemic heart disease was the cause of HF in 71 patients (figure 5), followed by idiopathic causes in 18 patients, Type 2 DM in 7 patients, Valvular heart disease in 2 patients, and other causes like viral myocarditis in 2 patients.

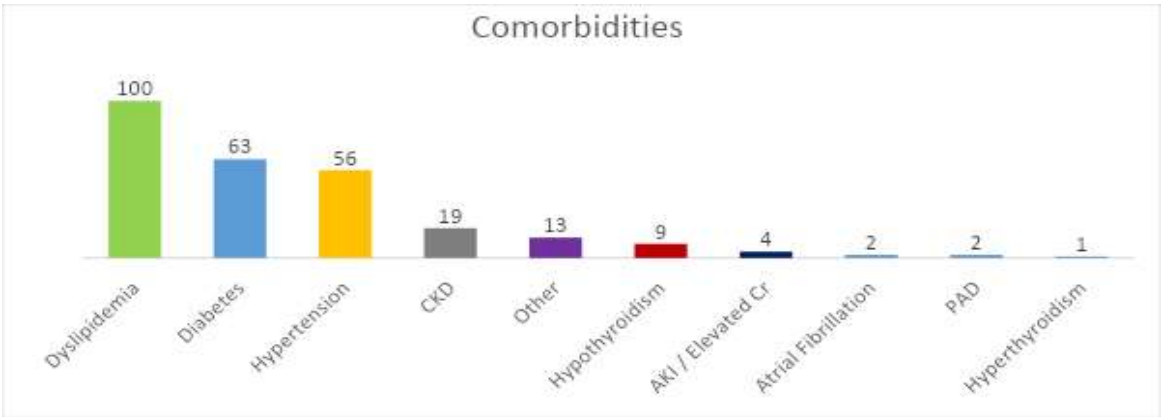

Figure 4: Comorbidities of patients

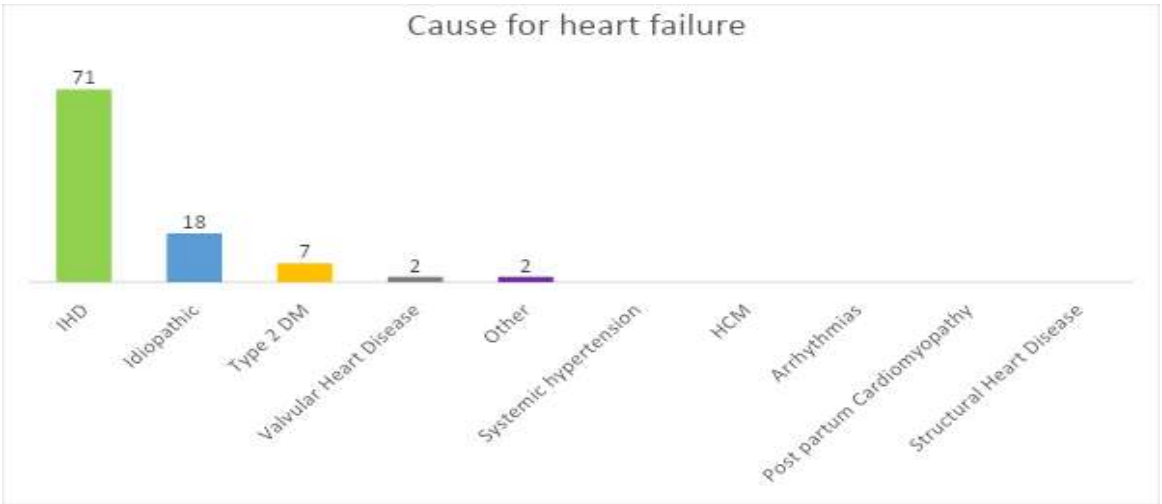

Figure 5: Cause for HF

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Medications or therapy taken by patients were recorded and studied (figure 6). We found that 92 patients were taking statins/fibrates, 83 patients were on BB, 77 patients were on loop or thiazide diuretics, 74 patients were on MRA, 35 patients were on ARNI, and 34 patients on SGLT2i, 2 patients were implanted with ICD and 1 patient was implanted with CRT. To better understand why FFT was not implemented in all HF patients, we studied the compliance of patients with their therapy and we found that 82 patients were compliant with their therapy and 18 were not. The symptoms of patients were recorded with respect to their NYHA class (figure 2) and was found that 53 patients were NYHA class 2, 30 patients were NYHA class 3, 13 patients were NYHA class 4 and 4 patients were NYHA class 1.

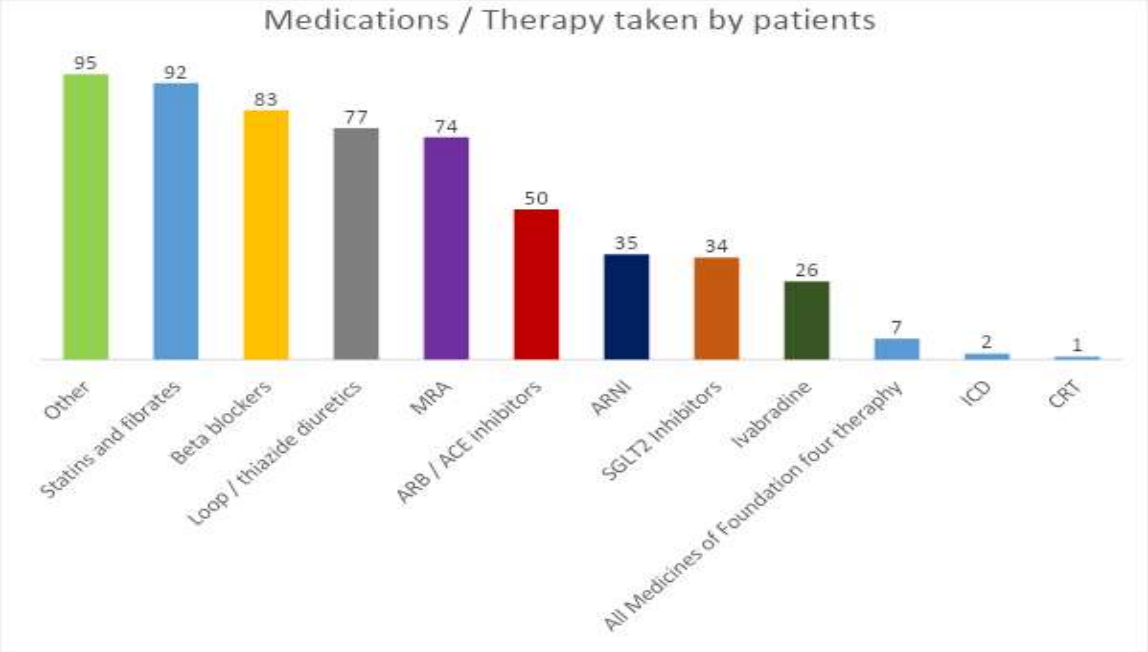

Figure 6: Medications/therapy taken by patients

Under the reasons why patients were not under BB, 7 patients showed signs and symptoms of acute HF, 5 patients showed intolerance to BB, 3 patients had COPD/Asthma, 2 patients were grouped in the category other, which included pulmonary TB and pulmonary edema caused by BB. In 1 patient bradycardia was a reason and in 1 patient hypotension.

Under the reasons why patients were not under MRA, 15 had CKD/elevated Cr, 5 did not come for clinic follow-ups timely, in 5 patients it was to be added in the consecutive visits, 1 patient could not afford, 1 patient had hypotension and 1 patient was stable with other medicines.

Under the reasons why patients were not under ARNI, 25 patients were stable with ACEi/ARB, In 12 patients it was to be initiated in the consecutive visits, 10 patients did not come for clinic follow-ups timely, 9 had hypotension, 8 had CKD/elevated Cr, In 5 patients, their EF improved with conventional therapy, 4 patients were unwilling to take the medicine, 3 patients were showing signs and symptoms of acute HF, In 2 patients unaffordability was the reason, 1 patient showed intolerance and 1 patient had hyperkalemia.

Under the reasons why patients were not under SGLT2i, In 22 patients, it was planned to be added in consecutive visits, 14 patients were grouped under the category "other", which included reasons like patients not coming for follow-ups timely, low body weight and malnourishment. In 8 patients the reason was CKD/elevated Cr, 6 patients were unwilling to take the medicine, In 5 patients, their EF improved with conventional therapy, 4 patients could not afford the medicine, 4 patients showed signs and symptoms of acute HF, 3 patients had hypotension, 2 patients were stable under conventional therapy.

V. DISCUSSION

This was a retrospective observational study based on clinic database of HF patients visiting the clinic. In reference to the question, if all patients with HFrEF are under FFT, it is clear from our results that out of 100 HF patients, only 7 were taking all classes of medicines under FFT. And majority of patients were taking BB (83%, n= 83),

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followed by MRA (74%, n=74). Being conventional molecules and in use for long time now, BB and MRA have been prescribed to more number of patients.

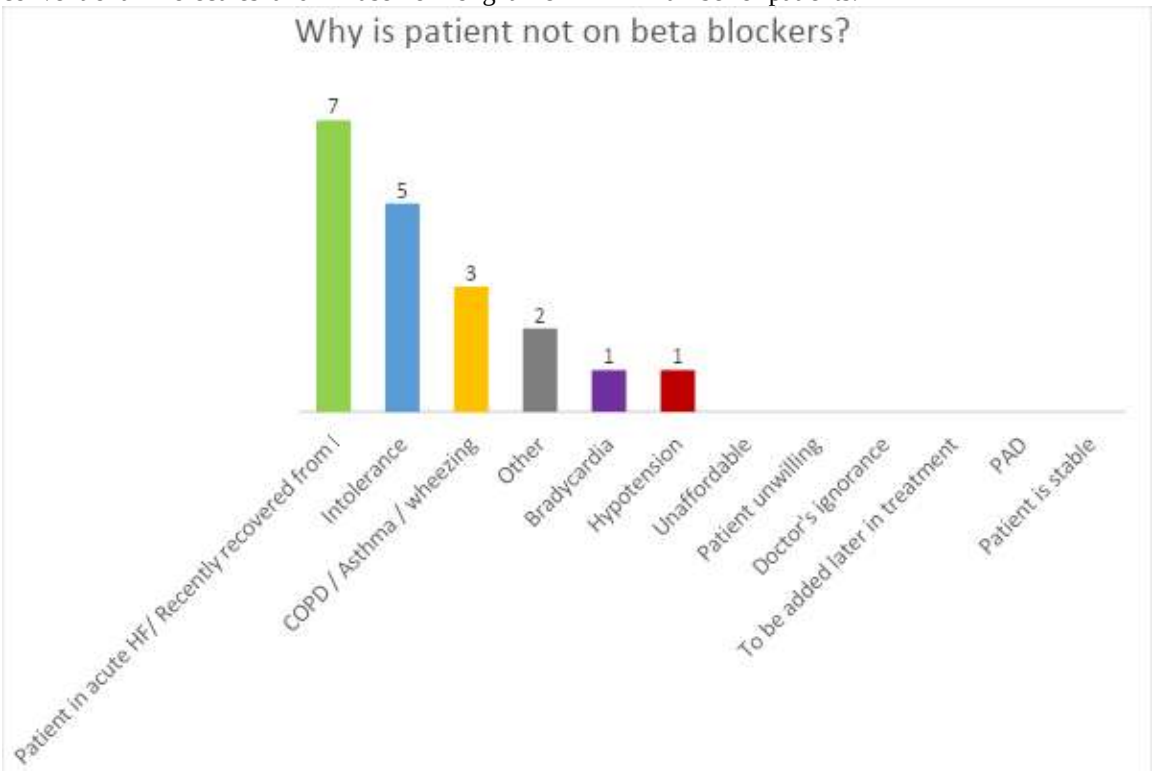

Figure 7: Patients not on BB

In the CIBIS 2 trial, the study conducted on 2647 patients, there was 34% risk reduction of all-cause mortality in the bisoprolol group(6). Also, from the MERIT HF study conducted in 1999 on 3991 patients, it was observed that there was 34% risk reduction in all-cause mortality in metoprolol group(7).**In COPERNICUS study in HFrEF, Carvedilol reduced the combined risk of death or hospitalization for a cardiovascular reason by 27% and the combined risk of death or hospitalization for heart failure by 31% (8**). BB has been a key molecule in the HF management and is included in the FFT. BB help in the reversing of left ventricular remodeling and neurohormonal effects on the heart and improve the contraction of viable non-contractile myocardium (stunning and hibernating).These effects translate into reducing mortality and decrease in hospitalization and the improvement of symptoms in patients.. Under the reasons why patients were not on BB (figure 7), 7 patients were showing signs and symptoms of acute HF like fluid retention and symptoms related to it. This was the common reason why patients were not under BB. In 5 patients, we could see intolerance to the drug. In 3 patients, COPD/ Asthma / wheezing disorders prevented us from continuing or initiating BB. Pulmonary TB, existing pulmonary edema were reasons in 2 patients. 2 patients were not on BB because of bradycardia and hypotension. According to the study by Daniele Masarone(12), on the use of BB in Heart Failure with Reduced Ejection Fraction, the absolute contraindications for starting BB in HF patients are 2nd or 3rd degree heart block, critical limb ischemia, recent exacerbation of heart failure and severe asthma/COPD. This evidence is supporting the results we got, except, that the study recommends to continue BB as long as the patient is asymptomatic with bradycardia. Indeed, we could implement BB in patients with bradycardia as long as they don't show any symptoms.

Next to BB, more number of patients were on MRA. 74 patients were on MRA, the main reason being, its effect on reducing the volume overload and attenuating the effect of RAAS system which leads to cardiac remodeling.

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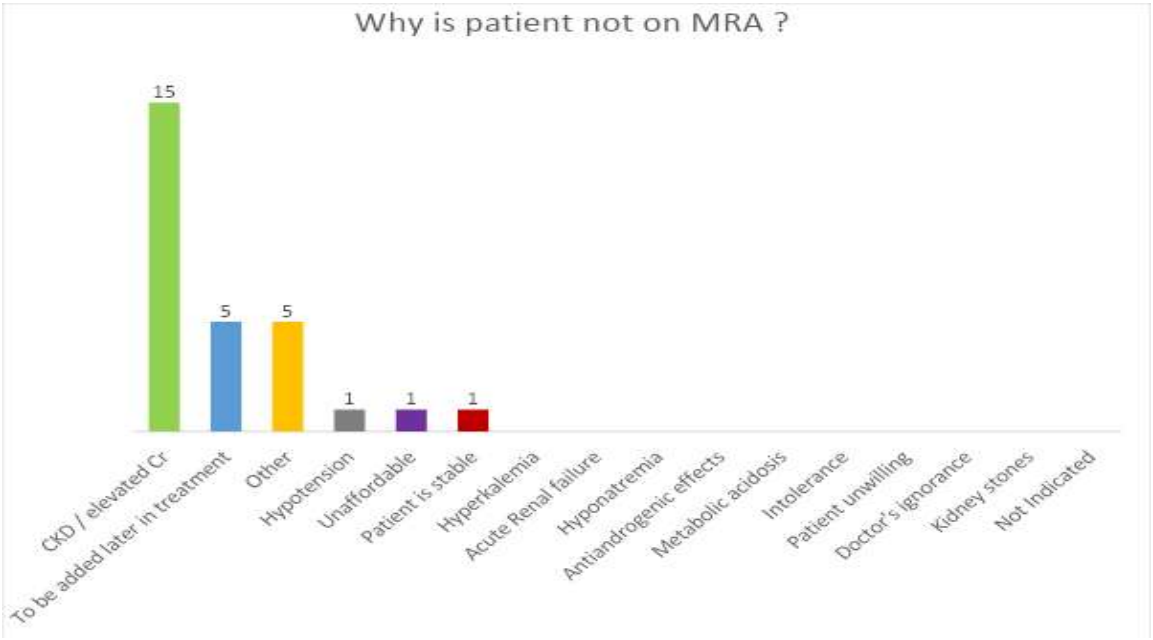

Figure 8: Patients not on MRA

Aldosterone causes sodium and fluid retention. Increased aldosterone release leads to sodium and water retention causing hypervolemia. It also causes cardiac remodeling and fibrosis. Additionally, It can lead to endothelial dysfunction by causing oxidative stress. MRAs work by blocking the mineralocorticoid receptors and hence preventing fluid and salt retention and cardiac remodeling. Studies show that spironolactone prevents aldosterone-mediated collagen synthesis(11).

RALES study conducted on 1663 patients with HF, showed that primary end point of cardiovascular (CV) deaths and HF hospitalizations were seen in 38.1% of patients taking spironolactone as compared to 50.5% in placebo(9). The EPHEUS study conducted on 6642 HF patients(post-MI 2 weeks) showed that primary end-point of CV deaths and hospitalizations were seen in 26.6% of patients taking eplerenone as compared to placebo(10). With there being significant role played by MRA, it's vital to add this molecule in HF management and is hence one of the class of medicine under FFT. Even among patients with HF and diabetes mellitus or CKD, MRA use was associated with lower risk of all-cause readmission in hospitals despite risks of acute renal insufficiency and hyperkalemia. Under the reasons why patients were not on MRA (figure 8), the most common reason was CKD/elevated Cr. In patients who had CKD or acutely elevated Cr, MRA was either stopped or was not initiated. The other reasons were that it was to be added later/ patients not coming for follow ups regularly. At the time, when the study was done, in 5 patients, MRA was planned to be added in their consecutive visits. Other 5 patients were not coming for follow ups regularly so we were not able to start MRA timely. In 1 patient we didn't add MRA because of hypotension. In 1 patient, MRA was not added because the patient was stable with other conventional medicines like BB, ACEi/ARB. And in 1 patient because of unaffordability, MRA was not prescribed and the patient was on basic medicines like ACEi/ARB and BB.

A comparatively lesser number of patients are on ARNI and SGLT2i.

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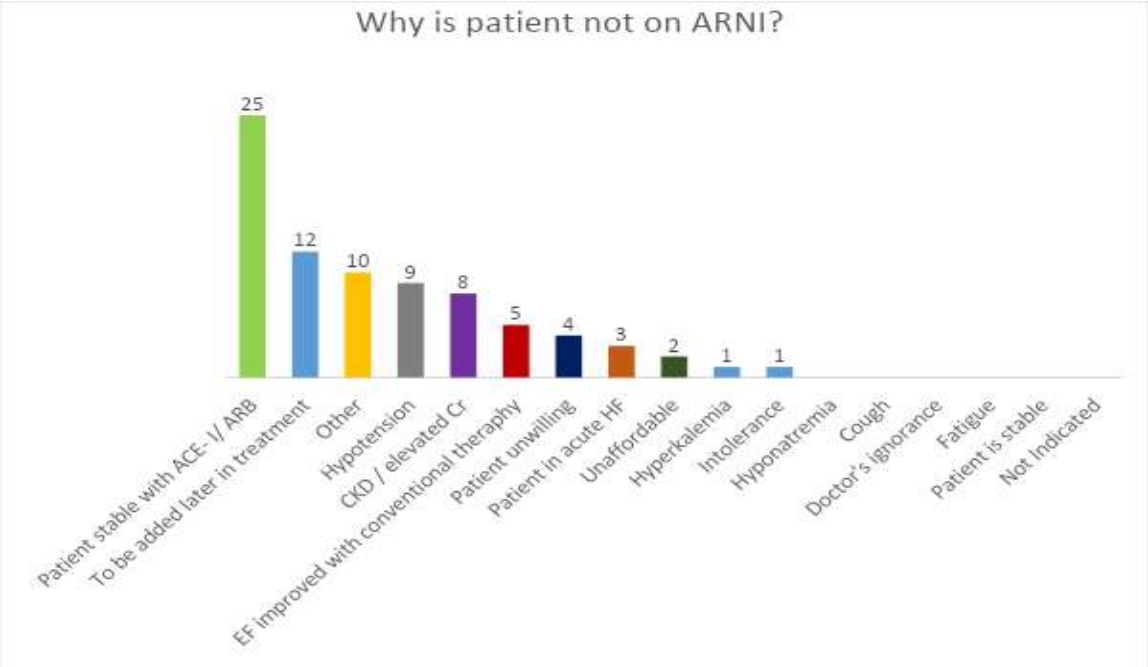

Figure 9: Patients not on ARNI

35 patients were on ARNI. It is known that ACEi / ARB have beneficial roles in the treatment of HF and have been in use for a long time now. With increasing knowledge of the pathophysiology of HF, we can identify and bring about different classes of medicines and their combinations to treat HF. One such combination is ARNI. From the PARADIGM study, we know that the effect of ARNI in reducing death from CV causes and hospitalization was superior to ACEi(3). In the PARADIGM trial, it was found that death from CV causes or hospitalizations for HF occurred in 21.8% of the ARNI group and in 26.5% in the enalapril group.In spite of this, it is still observed that many patients are not on ARNI.

The most common reason was that patients were stable on ACEi/ARB. 25 patients who were stable on ACEi/ARB were just left to continue the same as they were doing just fine with conventional medicines(figure 9).There is ongoing debate whether there is enough evidence to switch all these patients to ARNI. In 12 patients, it was to be added in consecutive visits since it's a new class of medicine in the market. In 10 patients, ARNI was not initiated or continued mainly because the patient did not come for their follow ups regularly or was malnourished . These patients were just left on ACEi/ARB. And in patients who didn't come for follow ups regularly, it was not possible for the physician to add ARNI. 9 patients were not on ARNI because of hypotension, these patients were just on ACEi/ARB. 8 patients had CKD/elevated Cr. In 5 patients, the EF improved with conventional medicines. 4 patients were unwilling to take more medicines, so these patients were maintained on just conventional, basic medicines according to their condition. 3 patients were showing signs and symptoms of acute HF, so they were not started on ARNI. In 2 patients, unaffordability was the cause and 1 patient had hyperkalemia and 1 had intolerance to ARNI. From this we understand that causes like unwillingness and unaffordability play a role in Indian population. But it is a limitation that the study was conducted in a clinic so we were not able to start all four classes of medicines under FFT in a month time as suggested by the ACC/AHA/HFSA guidelines(2). In the clinic we had to tailor and manage the doses when the patients come for follow-ups.

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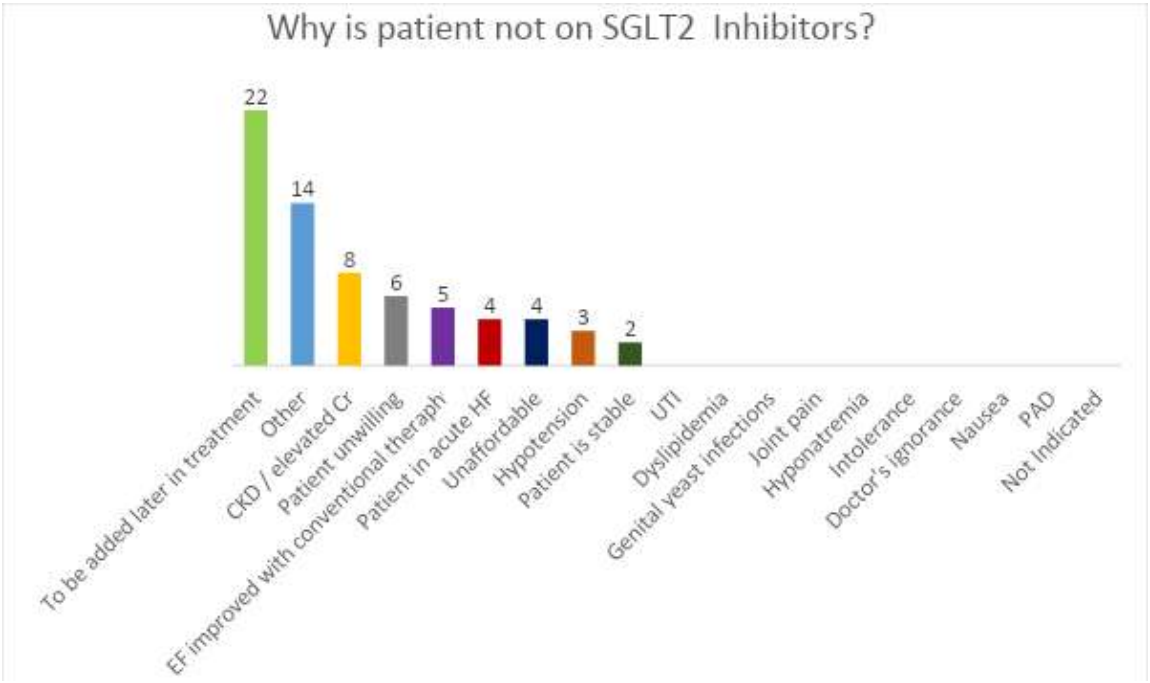

Figure 10: Patients not on SGLT2i

The number of patients on SGLT2i are 34. The use of SGLT2i was initially to control blood sugars in diabetic patients. But from study trials like DAPA-HF and EMPEROR-reduced(4, 5), we know that the use of SGLT2i is associated with reduction in the risk of hospitalization for heart failure, CV death and all-cause mortality in patients with HFrEF primarily. From the EMPEROR – Reduced, we know that the primary composite outcome of death from CV causes or hospitalizations occurred in 19.4% in Empagliflozin group as compared to 24.7% in the placebo group(25% reduction in primary composite end point) . In DAPA-HF trial ,the primary composite of death from CV causes or hospitalization for HF occurred in 16.3% in dapagliflozin group as compared to 21.2% in the placebo group(26% reduction of the primary composite end point).

It is a class 1a indication to start SGLT2i in patients with HFrEF. Under the reasons why patients were not started on SGLT2i, the most common reason was that it was planned to be added in the consecutive visits of patients. At the time of the study (figure 10), in 22 patients, it was to be added in consecutive visits since it's a new molecule. 14 patients were not initiated or continued on SGLT2i, mainly because they didn't come for follow-ups or was poorly built and malnourished or was not compliant with medicines. Those patients who were not compliant, were made to follow conventional medicines. In 8 patients, CKD or end stage kidney disease was a reason to not initiate or continue SGLT2i. 6 patients were unwilling to take more medicines, so such patients were also on conventional medicines. 5 patients, whose EF improved with conventional medicines were not on SGLT2i. 2 patients who were stable on other medicines under FFT were not initiated on SGLT2i, but, in these patients it could certainly be added in the future depending on the condition of the patient. 4 patients showed signs and symptoms of acute HF. Unaffordability was a reason in 4 patients. 3 patients had hypotension. SGLT2i being a new molecule, its use in management of HF is growing. And since the study was done in a clinic setting, to implement this molecule in the treatment of HF demands the patients to come for follow-ups regularly. In the clinics, we should try to incorporate SGLT2i in the early management of HF as suggested by the guidelines.

VI. CONCLUSION

It is in similarity to the other studies that we got results with respect to the reasons why any particular medicine under FFT was not initiated or continued. Not all HF patients were on all classes of medicines under FFT. As expected, majority of patients were on conventional drugs like BB and MRA. We got acceptable results with expected contraindications for BB and MRA. In patients with acutely elevated Cr, MRA will eventually be added as their Cr normalizes . Newer molecules in HF management like ARNI and SGLT2i are

comparatively less prescribed and continued in HF patients because of various contraindications and also for reasons like patients not regularly visiting clinics for follow-ups, not being compliant with medicines, unwillingness to take more medicines and unaffordability. With these reasons, we can understand that in an Indian population, reasons like compliance, discipline to visit clinics regularly, along with unaffordability plays a vital role. Newer medications availability at affordable cost will also help in initiating these new molecules. Even physicians' awareness in FFT needs improvement and patients education on the importance of FFT in reducing mortality and decreasing hospitalizations and improvement of symptoms are vital.

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