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RESEARCH ARTICLE

EFFECTIVENESS AND OUTCOMES OF H-ISDN IN ADDITION TO CONVENTIONAL THERAPY IN ACUTE HEART FAILURE PATIENTS WITH RENAL IMPAIRMENT

Faizah Khan[1], Tayseen Sultana[1], Syeda Hafsa[1], Hafsa Anjum[1], Dr. Azmath Unnisa Begum[2], Dr. G. Rajashekar Reddy[3] and Dr. Abhishek Golla[4]

1. Graduate Student(Pharm D), Darussalam, Aghapura, Hyderabad-500001,Telangana.
2. Professor, Department of Pharmacology,Deccan School of Pharmacy,Darussalam,Aghapura,Hyderabad-500001,Telangana.
3. Professor,Department of Cardiology,Princess Esra Hospital,Deccan College of Medical Sciences, Shah AliBanda,Hyderabad-500002,Telangana.
4. Assistant Professor,Department of Cardiology,Princess Esra Hospital,Deccan College of Medical Sciences,Shah Ali Banda,Hyderabad-500002,Telangana.

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Abstract

Objective: The primary objective of the study is todetermine whether the addition of H-ISDN to conventional therapy improves the cardiovascular outcomes and also to assess both short term(1 and 3 months) and long term outcomes(1 year).

Materials and Methods: This is a prospective observational study.A total of 82 acute heart failure patients with renal impairment were divided into two groups based on exposure to H-ISDN;Group I-Patients on H-ISDN plus conventional therapy;Group II-Patients on conventional therapy. Followup of all the subjects to study the outcomes of improvement in NYHA class,rehospitalisation and mortality rate at 1 month,3 months and 1 year was done for both the groups.

Results: We observed that out of the 82 acute heart failure patients with renal impairment,43 patients were receiving H-ISDN in addition to conventional therapy(Group I) and 39 patients were receiving conventional therapy(Group II) .The length of stay(6.03± 2.906 vs 6.93± 3.845) was shorter in the treated group when compared to the non treated group.A greater difference in reduced hospitalisation was seen at 3 months(2.32% vs 12.82%).The treated group had higher improvement in NYHA class at 1 month(67.44% vs 46.15%), 3 months(51.16% vs 41.02%) and 1 year (44.18% vs 20.51%;*P*=0.023).

Conclusion: Acute heart failure patients with renal impairment have poor prognosis. Randomised controlled trials are required to validate if the use of H-ISDN is associated with better outcomes in AHF patients.

Corresponding Author:- Faizah Khan
Address:- Graduate Student(Pharm D), Deccan School of Pharmacy, Hyderabad-500001,Telangana.

Introduction:-

Comorbid heart failure (HF) and renal impairment (RI) is a highly prevailing condition which can result in a viscious cycle leading to significantly increased morbidity and mortality rate worldwide.[1,2,3]The rates of readmission after discharge remain high particularly in heart failure patients above 65 years of age.[4] More than 50% of patients are rehospitalised within 6 months after discharge further contributing to clinical and economic health burden.[5]Heart failure patients often have multiple comorbidities that complicate management and contribute to worse outcomes.[6]Renal impairment is present in 26-70% of heart failure patients and is associated with higher readmissions and mortality rate.[7,8]The management of heart failure with renal impairment is challenging for medical practitioners, as most of the guideline recommended therapeutic options may be contradictory and also because there is lack of evidence of beneficial heart failure therapies in them.[9,10]Caution is manifested with regard to the usage of certain drugs (ACEIs,MRAs) in heart failure patients with impaired renal function .H-ISDN therapy is a class IIa recommendation for patients of all races in case of intolerance to angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) as per the international guidelines .[11,12,13]The principle for effectiveness of H- ISDN combination lies in the presumption that CRS is a ramification of endothelial dysfunction subsequent to reduced nitric oxide(NO) bioavailability.[14,15,16]Isosorbide dinitrate(ISDN) enhances NO bioavailability, improves LV afterload, and subendocardial perfusion while the former hydralazine (H) prevents oxidative stress- induced degradation of nitric oxide ,intercepts nitrate tolerance and reduces preload.[17,18,19]Furthermore real-world overall effectiveness of H-ISDN when prescribed in addition to conventional therapy in population other than black patients remained to be demonstrated as it may differ from that observed in clinical trials.[20,21,22.23]The aim of this study are to study the outcomes of H-ISDN in heart failure patients with renal impairment.

Material And Methods:-

Objectives:-

The primary objective of the study is to determine whether the addition of H-ISDN to conventional anti-heart failure therapy improves the cardiovascular outcomes and also to assess both short term(1 and 3 months) and long term outcomes(1 year).

Study design:

A prospective observational study was carried out in the cardiology department of a tertiary hospital from August 2019 to January 2021.Enrollment of patients was done from August 2019 to January 2020.The enrolled patients were then followed upto 1 year.A total of 130 acute heart failure patients were assessed for eligibility based on renal function.The renal function was determined by calculating GFR using the MDRD(Modification of Diet in Renal Disease) equation.Patients who had GFR <60 ml/min were considered to be having renal impairment and were included in the study. Exposure was defined as a filled prescription of H-ISDN. The lack of H-ISDN filled prescription was defined as nonexposure.In this study Isolazine tablet a fixed dose combination Isosorbide Dinitrate (20mg) + Hydralazine (37.5mg)was being used at a frequency of three times a day.

A total of 82 patients were enrolled in the study and were allocated into two groups i.e Group I receiving H-ISDN plus conventional therapy and Group II receiving conventional therapy.The study was approved by the Institutional Review Board of our hospital and a written informed consent was obtained from all the subjects of the study.

Inclusion and exclusion criteria:

Inclusion criteria included:age greater than 18 years,acute heart failure patients with renal impairment,patients on conventional acute heart failure therapy. Patients were excluded from the study if the patient's age was below 18 years,diagnosed with chronic heart failure,rheumatic heart disease, congenital heart disease, STEMI, patients on dialysis and patients who were not willing to participate in the study.

Data sources and Covariates

The medical charts of the patients were assessed. Acute heart failure patients were identified if such a diagnosis was made by the treating physician as per the case sheet.Clinical data recorded included age,gender comorbidities, LVEF,variables at admission(heartrate, bloodpressure), physicalstatus (pedal oedema) inhospital drug use,laboratory values both at admission and discharge(sodium,potassium,chlorine) and length of stay.

Renal function data:

Renal function tests(serum creatine and blood urea)both at admission and discharge were recorded.Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation: $eGFR=186 \times (Sr.\ creatinine)^{-1.154} \times (age)^{-0.203}$(for females the value obtained was multiplied by 0.742.[23]

Outcomes:
The expected outcomes was also an evidence that showed whether addition of H+ISDN brought about beneficial outcomes in acute heart failure patients with renal impairment.The primary end point of the study was mortality while the secondary end points were improvement in NYHA class, rehospitalisations and length of stay.

Statistical analysis:
Mean and standard deviation were determined for quantitative variables,frequency and percentages for categorical variables. The results on continuous variables were calculated by using independent t-test. Comparative analysis were performed using chi-square test and fisher's exact test wherever suitable for categorical variables.Two sided p-values were calculated with a value of <0.05 which was considered statistically significant.Statistical evaluations were performed using SPSS version 20.0

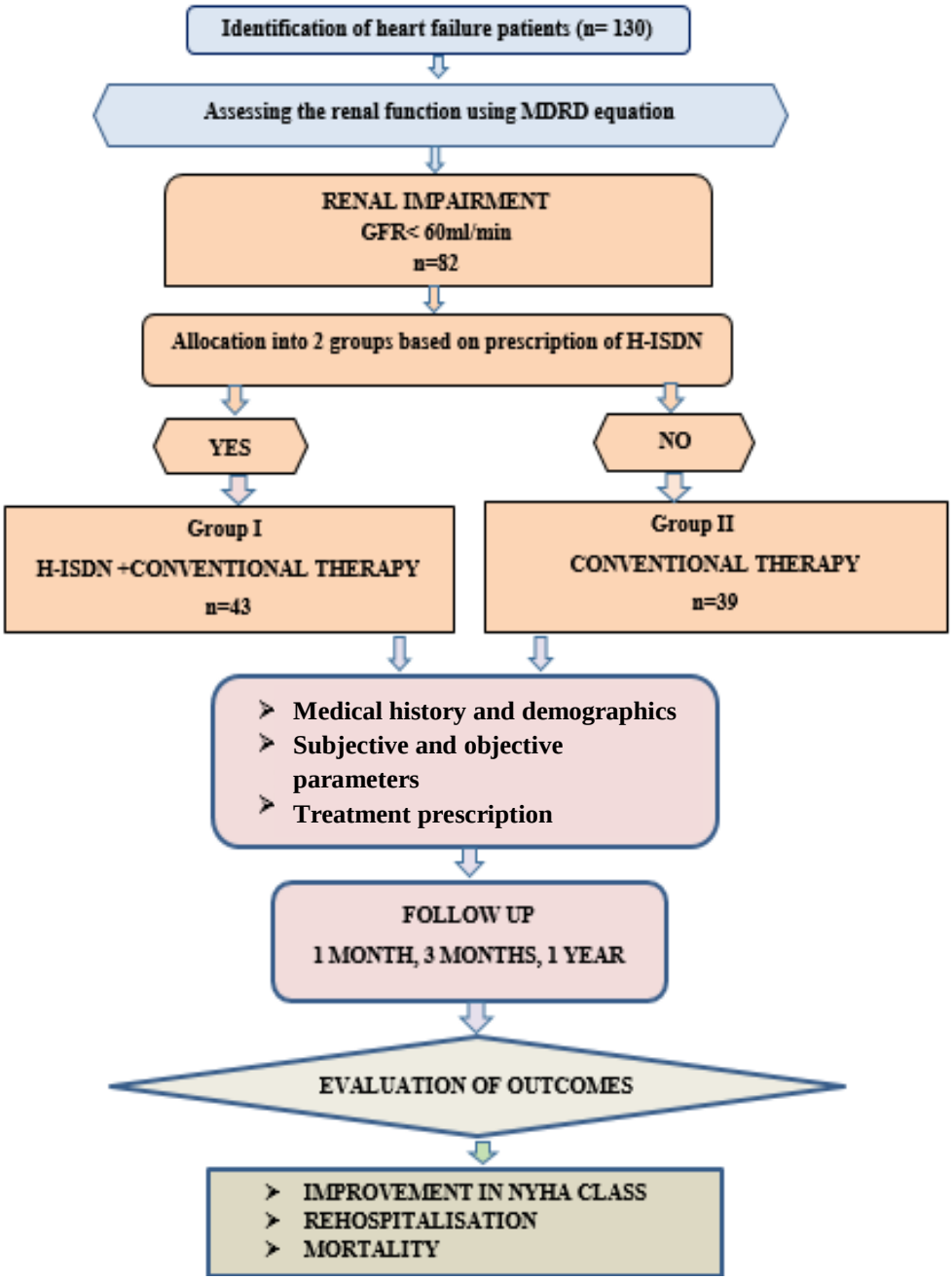

Figure 1:Allocation of patients and plan of conduct of study.

Results:-

Group distribution:

We observed that out of the 82 heart failure patients with renal impairment,43 patients were receiving H-ISDN in addition to conventional therapy(Group I) and 39 patients were receiving conventional therapy(Group II) as shown in Figure 2.

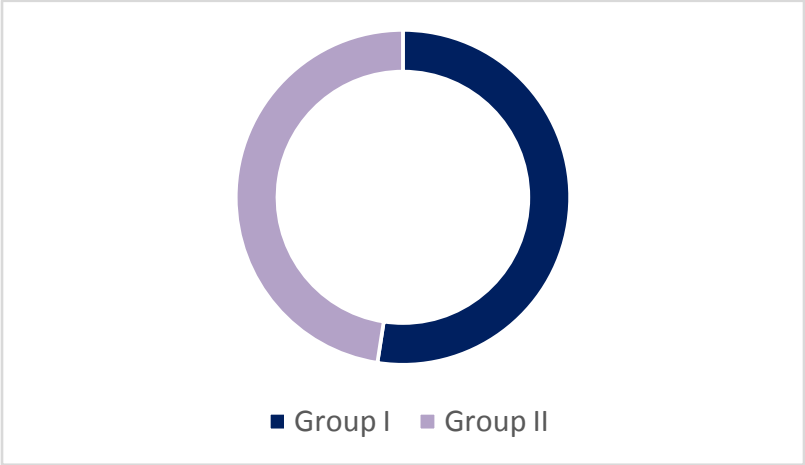

Figure. 2:- Group Distribution.

Demographics, baseline characteristics and other general observations:

The age distribution was similar in both the groups.More number of patients were found to be in the age group of above 60 years .The prevalence of male subjects(60.5%) was higher in the treated group while there were more females(55.8%) in the non treated group.There was evidence of slightly declined renal function with a higher serum creatinine(2.01 ±0.65 vs 1.58 ±0.57) and blood urea(63.55± 31.29 vs 57.17 ±27.36)in the treated group.Functional status as per the NYHA class and other laboratory values were generally similar in both the groups.With respect to comorbidities , the prevalence of Ischemic heart disease(88.4% vs 74.4%) and hypertension(86% vs 74.4%)was slightly higher in the treated group.The non treated group had slightly more prevalence of atrial fibrillation(9.3% vs 4.7%) than the treated group. The prevalence of all other comorbidities was quite similar in both the groups.More number of patients with pedal oedema(51.2% vs 34.9%) were prescribed H-ISDN.The treated group patients were those who presented with higher blood pressure (134.3 ±30.87 vs 130± 23.73) at admission when compared to the non treated group.The length of stay(6.03± 2.906 vs 6.93± 3.845) was shorter in the treated group when compared to the non treated group .(Table 1)

Different types of heart failure

The LVEF of the patients was recorded and the prevalence of different types of heart failure in the treated group was observed to be as follows:HFrEF(n=19)>HFpEF(n=13)>HFmEF(n=11) while in the non treated group was as follows :HFrEF(n=20)>HFmEF(n=10)>HFpEF(n=9) .It was also observed at followup that mortality rate was higher in the HFpEF patients of the treated group.(Figure 3)

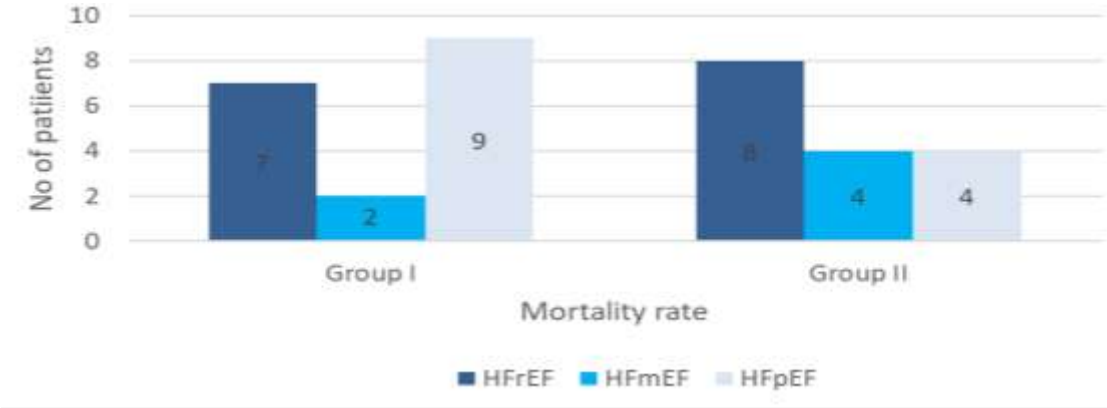

Figure. 3:- Mortality rate in different types of heart failure in both the groups.

Table 1:- Patient demographics,baseline characteristics and other observations in both groups

Variable	Group I (n=43)	Group II (n=39)	P value
Age distribution	62.72± 11.009	62.38 ± 15.006	0.908
Gender			
Male	26(60.5%)	15(38.5%)	0.225
Female	17(39.5%)	24(61.5%)	
NYHA class			
II	3(7%)	3(7.69%)	0.283
III	23(53.5%)	19(48.7%)	
IV	17(39.5%)	17(43.6%)	
Comorbidities			
HTN	37(86%)	32(82%)	0.563
DM	29(67.4%)	30(76.9%)	0.669
IHD	38(88.4%)	32(82%)	0.563
AF	2(4.7%)	4(10.2%)	0.624
COPD	5(11.6%)	3(7.7%)	0.542
Anemia	6(14%)	6(15.4%)	0.574
OSA	4(9.3%)	3(7.7%)	1.000
At admission			
Heart rate	99.67± 20.87	101.82± 23.92	0.666
Systolic BP	134.3 ±30.87	130± 23.73	0.485
Diastolic BP	80.23± 13.88	82.31± 15.12	0.519
Pedal edema	22(51.2%)	15(38.5%)	0.744
Laboratory parameters at admission			
Sodium	138±4.92	137.12± 5.98	0.472
Potassium	4.1± 0.55	3.87± 0.66	0.095
Chloride	98.55± 4.00	97.58± 5.64	0.378
Creatinine	2.01 ±0.65	1.58 ±0.57	0.002
Blood Urea	63.55± 31.29	57.17 ±27.36	0.331
Laboratory parameters at discharge			
Sodium	137.18±6.43	138.28±3.71	0.343
Potassium	4.04±0.56	3.93±0.46	0.308
Chloride	98.13±5.10	98.12±4.46	0.992
Creatinine	2.20±0.98	1.80±1.04	0.075
Blood Urea	70.81±33.56	60.20±35.27	0.167

Data are number (%) of patients, mean, standard deviation
P value is calculated by independent t-test, chi square test
Group I: Exposure to H-ISDN; Group II: Conventional therapy
HTN-hypertension; DM-diabetes mellitus; IHD-Ischemic heart disease; AF-Atrial fibrillation; COPD-Chronic obstructive pulmonary disease; OSA-obstructive sleep apnea; BP-blood pressure.

Management:

The use of diuretics (97.7% vs 76.7%), statins (100% vs 81.4%),anticoagulants (83.7% vs 23.3%) and Ivabradine (83.7% vs 18.6%) was higher in the treated H-ISDN group in comparison to non-treated group. Rates of beta blockers was less than 50 % in both while the prescription of MRAs was more than 80% in both the groups.CCBs (97.4% vs 44.2%), digoxin (38.1% vs 11.6%), and antiarrhythmics (23.3% vs 9.3%) were prescribed more in the non treated group.

Table 2:Management patterns in both groups

Therapeutic drugs	Group I n=43	Group II n=39	P value
ACEIs/ARBs	8(18.6%)	17(43.6%)	0.672
Beta blockers	11(25.6%)	9(23%)	0.085
CCBs	19(44.2%)	38(97.4%)	0.373
Diuretics	42(97.7%)	33(84.6%)	1.000
MRAs	35(81.4%)	37(94.9%)	0.373
Statins	42(97.6%)	31(79.5%)	0.340
Anti-platelets	40(93%)	29(74.3%)	1.000
Anti-coagulants	36(83.7%)	10(25.6%)	0.757
Anti-anginals	12(27.9%)	2(5.1%)	1.000
Anti-arrhythmics	4(9.3%)	10(25.6%)	0.860
Digoxin	5(11.6%)	25(64%)	0.609
Ivabradine	36(83.7%)	8(20.5%)	0.652
Calcium Sensitisers	8(18.6%)	2(5.1%)	0.497

Data are number (%) of patients, mean, standard deviation
P value is calculated by chi square test, fisher exact test
Group I: Exposure to H-ISDN; Group II: Conventional therapy
ACEIs/ARBs-Ace inhibitors/Angiotensin receptor blockers. CCBs-Calcium channel blockers, MRAs-Mineralocorticoid receptor antagonists.

Improvement of NYHA class, readmissions and mortality rate:
A greater difference in reduced hospitalisation was seen at 3 months(2.32% vs 12.82%).The treated group had higher improvement in NYHA class at 1 month(67,44% vs 46.15%) 3 months(51.16% vs 41.02%) and 1 year (44.18% vs 20.51%). Not muchdifference was observed in mortality rate at 1 year in both groups while there was decreased mortality rate in the exposed group at both 1 month(11.62% vs15.38%) and 3 months (20.93% vs 28.20%)

Table 3: Final Outcomes in both groups

FINAL OUTCOMES	Group I	Group II	P VALUE
1 month			
Improvement in NYHA Class	29(67.4%)	18(46.1%)	0.0516
Re-hospitalisation	3(7%)	3(7.7%)	0.9011
Mortality	5(11.6%)	6(15.4%)	0.6181
3 months			
Improvement in NYHA Class	22(51.1%)	16(41%)	0.358
Re-hospitalisation	1(2.3%)	5(12.8%)	0.068
Mortality	9(20.9%	11(28.2%)	0.444
1 year			
Improvement in NYHA Class	19(44.1%)	8(20.5%)	0.023
Re-hospitalisation	5(11.6%)	11(28.2%)	0.059
Mortality	18(41.9%)	16(41%)	0.939

Data are number (%) of patients, mean, standard deviation;
P value is calculated by chi square test, fisher exact test
Group I: Exposure to H-ISDN; Group II: Conventional therapy;
NYHA-New York Heart Assosciation
Rehospitalisation only for acute heart failure was considered here.

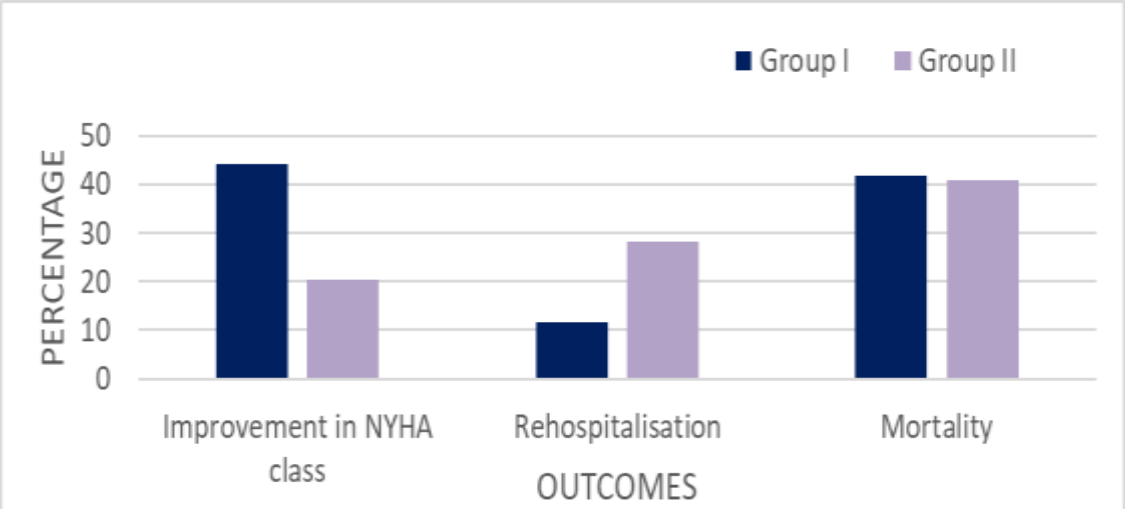

Figure. 4:- Final Outcomes at one year in both the groups.

Discussion:-

Renal dysfunction is associated with increased risk of mortality and readmissions in heart failure patients.[24]The risks and benefits associated with disease-modifying therapies in patients with renal impairment has not been studied probably as a result of their exclusion from trials.[25]Data regarding heart failure outcomes mostly comes from western populations, with limited data from Asia.[26,27] This is a prospective observational study conducted to ascertain the outcomes of H-ISDN in acute heart failure patients with renal impairment**.**From the 130 patients that were assessed for eligibility we observed that more than 50% of the patients admitted with acute heart failure were having renal impairment which is comparable to Damman et al (2014).[29]

It was also observed that H-ISDN was prescribed to 33% of acute heart failure patients which follows the study reporting low prescription rates of H-ISDN despite its recommendation for use as per the guidelines.[20]This maybe because of lack of evidence based studies proving their efficacy in heart failure patients. The patients with renal impairment were distributed into two groups based on exposure to H-ISDN.In majority of the patients renal impairment had been identified after hospital admission (not a known case of CKD) highlighting the fact that heart failure and renal insufficiency are interdependent in nature.Early identification of renal impairment may help in better interventions directed towards patient care in these subset of patients.

Asian patients present with HF on average at least a decade earlier than their white counterparts, with two thirds presenting with multimorbidity.[30]In the present study, most of the patients were affected by acute heart failure at a younger age and more than 60% of the presented patients were with hypertension,ischemic heart disease and diabetes mellitus.A few patient factors and laboratory findings were associated with increasing odds of receiving H-ISDN at baseline .Patients that were intolerant to ACE/ARBs and higher creatinine levels at admission were more likely to receive H-ISDN which is comparable to a previous study.[31]The reasons maybe pertaining to anxiety about rises in creatinine and the associated falls in estimated glomerular filtration rate [eGFR] that can lead to underprescription of ACEIs and ARBs.[32]

In this study,there was a development of AKI in patients (12 %)which was not associated with poorer outcomeswhich is contradictory to another study wherein it was reported that even a 0.2 mg/ dL increase in serum creatinine is associated with poor outcomes.[33]In acute HF, some increase in serum creatinine may be acceptable, as long as the overall clinical status does not deteriorate.[20]

The outcomes related to mortality rate were higher(69%) in heart failure with preserved ejection fraction as supported by previous studies wherein the efficacy of H-ISDN is shown only in heart failure patients with reduced ejection fraction.[20]Inhospital mortality was seen in<5% of patients.The length of stay was also shorter in the patients receiving H-ISDN which would further reduce the economic burden and inconvenience caused to the patients.

There was low medication adherence of H-ISDN seen in patients on follow up which maybe due to the frequency of the drug to be administered in a day which is similar to that reported elsewhere.[34]A single dose drug will benefit such patients who are already exposed to polypharmacy due to the prescence of several comorbidities in them .As clinical pharmacists we were able to increase the adherence in more than 40% of patients and were also able to develop a better understanding of the disease in patients. There were no serious adverse drug reactions identified due to the use of H-ISDN.

There was no significant difference observed in hospitalisation during 12 month observation which differed from that reported previously.[35]This could be due to the reluctance to hospital admission during the COVID-19 pandemic. Short term outcomes of rehospitalisation and improvement in NYHA class at 3 months were found to be better in the treated group which is comparable to Narasimha et al.[36]

A 15% mortality decrease was seen in African Americans[20] but in our study there was no major reduction in mortality rate in the treated group which may be because of a smaller study sample. We observed a modest association at 1 and 3 months while a significant association at 1 year between improvement in NYHA class and usage of H-ISDN.

The findings are suggestive of possible benefits of usage of H-ISDN in heart failure patients with renal impairment but this couldn't reach significant difference.More studies with newer drugs need to be carried out in this area to benefit these patients especially those with a preserved ejection fraction.

Limitations:
The major limitation of our study is it's a single centre study with a low sample size .We couldn't apply randomisation with regard to the receival of H-ISDN in the subjects of this study .COVID-19 pandemic could have also affected the overall outcomes.

Conclusions:-
Heart failure patients with renal impairment have very poor prognosis.In our study, when we administered H-ISDN to some AHF patients with renal impairment and compared it to those receiving conventional therapy, better outcomes were observed in those receiving the former treatment but this did not reach statistical difference due to various confounding factors as mentioned in the limitations. Randomization trials are required to determine the efficacy of H-ISDN in this population to ascertain its association with better outcomes and to further promote its use in all the populations rather than restricting its use to a particular population. Furthermore, studies are also required to study beneficial therapeutic options in heart failure patients with preserved ejection fraction and renal impairment. In future, we need evidence-based treatments and strategies specially curated for heart failure patients with renal impairment i.e low GFR in order to decrease the mortality rate in these patients.

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Competing Interests
Authors have declared that no competing interests exist.

Authors' Contributions
This work was carried out in collaboration among all authors. Author GRR helped in the research design and was also the treating physician of all the heart failure patients. Authors FK,TY,SH and HA managed the literature searches ,writing of protocol, data collection ,data compilation ,data analysis ,statistical analysis and drafting of manuscript. Authors AG and AUB helped in conceptualization and representation of work for approval from IRB. All authors read and approved the final manuscript.

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