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CHRONIC HEART FAILURE: NEW TREATMENT STRATEGIES

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Annotation: Heart failure is a condition where our heart can't pump enough heart blood to meet the body demand. It is also called congestive heart failure or cardiomyopathy which represents the weakness of heart muscle . When heart is unable to pump effectively it's called systolic heart failure or unable to fill properly called diastolic heart failure. In both of the cases blood output is reduced . Ejection fraction in systolic heart failure is reduced and in diastolic heart failure it is preserved . Heart failure is a complex clinical syndrome with signs and symptoms that result from any structural and functional impairment of ventricular filling or ejection of blood . It's a growing health and economic burden for the united state . In 2017 , there were 1.2 million heart failure hospitalization in the US among ~1 million patient with diagnosis of heart failure.This shows that a 26% increase in the heart failure hospitalizations from 2013 to 2017 . From 2000 - 2013 the rise was not this much high but lately it has been growing every year so thats why it's a topic of growing concern and manage it appropriately.Pathophysiology of heart failure involves a vicious cycle in which reduced cardiac output as a compensatory response activates RAAS (Renin Angiotensin Aldosterone system) pathway and Sympathetic system, these system's causes vasoconstriction,increases heart rate and blood pressure makes even harder for heart to pump , increased aldosterone level also promotes ventricular remodeling, myocardial scarring and vascular injury, hence worsening the disesase. Also on the other hand Natriuretic peptide system is also activated to protect heart which promotes vasodilation, Sodium/water excretion and inhibit cardiac remodelling. So most of the drugs used in heart failure therapy aim to inhibit RAAS Pathway and sympathetic system or /and promotes Natriuretic system. Other drugs increase ventricular contractility or reduce retention which is a major symptom of heart failure.

In the united state , a large proportion of people have hypertension, obesity, diabetes and atherosclerotic cardiovascular disease. Therefore, a large proportion are at risk of heart failure or stage A heart failure. The most common causes of HF include ischemic heart disease and myocardial infarction (MI) , hypertension and valvular heart disease (VHD) . other causes are familial or genetic cardiomyopathies, Amyloidosis, substance abuse such as alcohol, cocaine, or methamaphetamine, Tachycardia, right ventricular pacing or stress- induced cardiomyopathies, peripatum cardiomyopathy, chemotherapy- induced cardiotoxicity, Hemochromatosis , and thyroid disease.

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ACC/AHA (American college of cardiology or American heart association) both classified heart failure in 4 stages- Stage A - patients at risk for heart failure but without current or previous signs/symptoms of HF and without structural or functional heart disease or abnormal biomarkers . Stage B - pre heart failure , patients without current or previous symptoms/signs of heart failure but evidence of 1 of the following: structural heart disease, evidence of increased filling pressures , risk factors and increased natriuretic peptide levels or persistently elevated cardiac troponin in the absence of competing diagnosis. Stage C - symptomatic heart failure-patients with current or previous signs/symptoms of heart failure. Stage D - Advanced heart failure- marked HF symptoms that interfere with daily life and with recurrent hospitalization despite attempts to optimize GDMT. NYHA classification- it is independent predictor of mortality, and it is widely used in clinical practice to determine the eligibility of patients for treatment strategies. NYHA Class I - no symptoms with normal physical activity and normal function status. NYHA Class II- Mild symptoms with normal physical activity, comfortable at rest and slight limitation of functional status . NYHA Class III - Moderate symptoms with less than normal physical activity , comfortable only at rest and marked limitation of functional status. NYHA IV- severe symptoms with features of heart failure with minimal physical activity and even at rest and severe limitation of functional status .The new classification of heart failure primarily categorizes patients based on their left ventricular ejection fraction (LVEF), with three main groups: heart failure with reduced ejection fraction (HFrEF) for LVEF below 40%, heart failure with preserved ejection fraction (HFpEF) for LVEF above 50%, and heart failure with mildly reduced ejection fraction (HFmrEF) for LVEF between 41% and 49%. Recent research has introduced innovative pharmaceutical approach that hold promise for improving patients outcome. New drugs like Sodium -glucose co- transporter 2 (SGLT2) inhibitors , angiotensin receptor/neprilysin inhibitor (ARNI) - sacubitrl/valsartan , which is combination of angiotensin receptor blocker (ARB) and a neprilysin inhibitor which works to reduce strain on the failing heart by managing blood pressure and supporting natriuretic peptide. Beta blockers like bisoprolol, carvedilol, sustained - release metaprolol succinate . Mineralocorticoid receptor antagonists (MRAs) like spironolactone and eplerenone . In patients with HFrEF with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality and hospitalizations. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNI is recommended to reduce morbidity and mortality. In patients with HFrEF and NYHA class II to IV symptoms an MRA is recommended to reduce morbidity and mortality if eGFR is >30ml/min/1.73m^2 and serum potassium is <5.0mEq/L. Careful monitoring of potassium, renal function and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency . In patients with symptomatic chronic HFrEF SGLT2 inhibitors are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes. Initially SGLT2 inhibitors comes into market for use in diabetes because their main mechanism of action is inducing glucosuria by inhibiting Na/Glucose co-transporter 2 pump in proximal nephron. The FDA mandatory in 2008 that all new type 2 diabetes medication had to prove CVS Safety . Trials shows that Empagliflozin shows 35% risk reduction of heart failure in patients of diabetes also Canagliflozin shows 33% risk reduction. Based on recent strong clinical trials Now Empagliflozin and Dapagliflozin are heart failure specific FDA approved and uses in the individuals with HFrEF and HFpEF regardless of the underlying type 2 diabetes .

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In patients with HFmrEF (symptomatic HF with LVEF 41%- 49%) after treatment GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic.

HFpEF is highly prevalent and is associated with significant morbidity and mortality, it's a heterogeneous disorder, contributed to by comorbidities that include hypertension, diabetes, obesity, CAD, CKD and cardiac amyloidosis. So key points for treatment of HFpEF are blood pressure control, diuretics as needed,SGLT2 inhibitors, treat underlying Atrial fibrillation, CAD , and evaluation for amyloidosis.

Key words - Ejection fraction , GDMT (guideline- directed medical therapy) , RAAS Pathway , Amylodosis , Natriuretic Peptide , Hemachromatosis.

Purpose of study- Main aim to revolutionize heart failure management , leading to longer , healthier lives for patients and informing new clinical guidelines as it's a life threatening condition

Material and methods - A study was performed in 4 patients groups to compare the outcomes in patients receiving different types of drugs based on the condition of the patients and all the drugs are continued indefinitely unless there are contraindications or significant side effects developed . Group 1 had 23 patients (12 men and 11 women) , group 2 had 19 patients (8 men and 11women) , group 3 had 11 patients (5 men and 6 women) , group 4 had 18 patients (11 men and 7 women) . Average age of the patients of group 1 was 58 ± 5 , for second group 80 ± 6.6 , for third group 73 ±4.3 years , for fourth group 77 ± 4 . Group 1 patients had diagnosis of heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) confirmed by echocardiography, estimated glomerular filtration rate (eGFR) = 48±5 ml /min/1.73m2 and was prescribed by SGLT2 inhibitors . In group 2 patients diagnosed with HFrEF or HFpEF with baseline eGFR is 058 ml /min/1.73m2 , serum potassium level less than equal to 5.0 mEq/L were prescribed by MRA's . In group 3 patients all are diagnosed with HFrEF and they were on stable doses of ACE inhibitors or ARBs for 6 months , had an baseline eGFR is 60 ml/ min/1.73m2 , systolic BP 118 mmHg were prescribed ARNI(Sacubitril/Valsartan) . In group 4 patients diagnosed with HFrEF and HFmrEF were on GDMT , had systolic BP = 118 mmHg , Heart rate = 85 bpm were prescribed beta blockers. Laboratory values like NT-proBNP levels (heart failure biomarker) , renal function test , potassium levels for each group was noted . Patients who were on SGLT2 inhibitors there lipid profile and HbA1c was also noted . Baseline echocardiographic parameters (LVEF, LV dimensions) and hospitalization events and mortality was noted for each of the groups . Regular follow up at the interval of 3 - and 6 - months. A detailed statistical analysis was performed using softwares which transforms raw data into clinically meaningful insights, helps in making evidence based decisions for chronic heart failure treatment.

Results and discussion - Group 1 patients recieved SGLT2 inhibitors - Dapagliflozin (10 mg once a day) or Empagliflozin (10 mg once daily) , out of 23 patients 4 patients (17 %) were showing serious adverse effects like diabetes ketoacidosis , Urinary tract infections , genital

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fungal infections, and potentially lower limb amputations rest 19 patients respond very well to the therapy with very mild or no adverse effects . Before treatment NT-proBNP- 1800pg/ml and after 12 weeks use of SGLT2 inhibitors baseline NT- proBNP [mean 1400 pg/ml (reduced by 22%)] , reduces HbA1c levels for diabetic patients, slight increase in LDL and HDL cholesterol were noted with no significant changes in triglycerides . A slight reduction in eGFR (45±2 ml/min/1.73 ㎡) is noted which is associated with long term kidney protection rather than true kidney damage. Prior to treatment 30% hospitalization rate over 3months but post treatment 13% hospitalization rate over 3months (reduced by 57%) . Hence overall SGLT2 inhibitors significantly reduces heart failure symptoms and hospitalization confirming their clinical benefits . Group 2 patients recived MRA's - Spironolactone (12.5mg to 50mg OD) or Eplerenone (25 mg to 50mg OD) . Out of 19 patients 4 patients (21%) developed mild hyperkalemia (k > 5.5 meq/L) requiring dose adjustments , no severe hyperkalemia developed. Spironolactone related gynecomastia was noted in 2 male patients , leading to a switch to Eplerenone . Overall MRA's is effective therapy in CHF , in rest of the patients after 12 weeks we noted reduced NT- proBNP levels upto 20 % , mild improvement in LEVF upto 5% increase, eGFR = 55 ml/ min/ 1.73 ㎡ (reduced 5% , mild expected decline) serum creatinine increased slightly in some patients. 10 patients moved from NYHA III to NYHA II (improved functional capacity) . Prior to treatment 26% hospitalization rate over 3 months but it reduced to 12% over 3 months (reduced 54%) . Group 3 patients were given ARNI (Sacubitril / Valsartan) - starting dose : 24/26 mg or 49/51 mg twice daily based on renal function and blood pressure and target dose : 97/103 mg twice daily if tolerated. Prior to treatment there NT-proBNP levels are 2200 pg/ mL , LEVF = mean 30% . After 12 weeks of follow up there mean NT - pro BNP levels reduces to 1350 pg/ ml (39% reduced) and there LEVF = 38% - 8 % significant improvement in left ventricular function suggesting reverse remodeling. eGFR = 58mL/min/ 1.73 ㎡ , systolic bp= 110 mmHg . 8 patients (73%) improved from NYHA III to NYHA II . Hospitalization rate reduces from 27% to 9% over 3 months 67% reduction is noticed No cases of severe hyperkalemia or renal dysfunction were noticed confirming good tolerability in this small cohort . No cases of angioedema or severe hypotension were reported. The most common side efffect was mild dizziness reported by 2 patients only . These results confirm that ARNI is highly effective in CHF treatment, reinforcing it's role as a first line therapy in HFrEF . Group 4 patients were given B blockers - Bisoprolol: 1.25 mg to 10 mg once daily , Carvedilol: 3.125 mg to 25 mg twice daily , Metoprolol succinate (extended-release): 12.5 mg to 200 mg once daily . Out of 18 patients 3 patients shows adverse effects like fatigue and dizziness , only 1 patient discontinued beta - blockers due to worsening fatigue, which improved after dose adjustment. Prior to treatment NT-proBNP levels are 1900 pg/ ml , baseline LEVF - mean 31% after 12 weeks there mean NT - proBNP levels reduces to 1450 pg/ ml (24% reduced) , LEVF = 36% (5% improvement in LV function) . Heart rate = 70 bpm (18% reduced) , systolic bp = 114 mmHg (reduces by 4 mmHg) . The heart rate reduction confirms beta- blockers negative chronotropic effect , which reduces myocardial oxygen demand and improves efficiency. The small drop in SBP was expected but well tolerated. 10 patients (56%) improved from NYHA III to NYHA II . Hospitalization rate reduces from 22% to 11 % (50% reduced) which makes beta blockers remain a cornerstone therapy for CHF, particularly in HFrEF , improving both survival and quality of life .

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Conclusion - This study highlights the effectiveness and safety of four key drug classes used in chronic heart failure (CHF) management: SGLT2 inhibitors, MRA's , ARNIs , and beta-blockers. The duration of these all drugs are typically long term and indefinite , as long as pati tolerates the medication and continues to benefit from it .All four drug classes significantly reduced NT-proBNP, improved LVEF, and lowered hospitalizations. ARNI had the most pronounced effect on NT-proBNP reduction and reverse remodeling. SGLT2 inhibitors showed strong benefits in symptom relief and renal protection. MRAs were effective but required close monitoring for hyperkalemia. Beta-blockers remained a cornerstone therapy, reducing heart rate and improving survival. These results confirm that guideline- directed medical therapy (GDMT) is crucial for improving outcomes in CHF patients. Regular monitoring and individualised treatment adjustments help optimize therapy and minimize side effects .

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