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Dapagliflozin (Farxiga) - An SGLT2 Inhibitor For Diabetes And Heart Failure

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ABSTRACT –

Dapagliflozin (Farxiga), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, has emerged as a critical therapeutic option for managing type 2 diabetes mellitus and heart failure. This review evaluates the pharmacological mechanisms, clinical efficacy, and safety profile of dapagliflozin. By promoting urinary glucose excretion and lowering blood glucose levels, dapagliflozin effectively improves glycemic control in diabetic patients. Recent clinical trials have also demonstrated its significant benefits in reducing hospitalization rates for heart failure and improving overall cardiovascular outcomes, even in patients without diabetes. The drug's favorable renal protective effects further underscore its multifaceted role in managing comorbid conditions. However, potential adverse effects, such as urinary tract infections and dehydration, necessitate careful patient selection and monitoring. This review aims to provide a comprehensive overview of the current evidence surrounding dapagliflozin, highlighting its dual benefits in diabetes management and heart failure, as well as implications for clinical practice.

Category:-Pharmacology ,endocrinology, cardiology.

Keywords:-Dapagliflozin, SGLT2 inhibitors, Type 2diabetis, Heart failure, Renal protection Safety profile, adverse effect, Combination therapy.

Introduction:-

. Diabetes mellitus type 2(T2DM) is a fleetly growing metabolic disorder affecting over 400 million people worldwide[1]. The adding prevalence is identified with the direct global increase in fatness, which is a significant threat factor of T2DM. The pathophysiology of T2DM is primarily related to insulin resistance, which leads to hyperglycemia and a gradational drop in the β- cells ' capacity to produce insulin. likewise, pancreatic α- cell dysfunction, increased hepatic glucose output, bloodied incretin effect, increased renal glucose reabsorption, and neurotransmitter dysregulation in the central nervous system also contribute to T2DM development[2]. The disease is explosively associated with both micro- and macrovascular complications. thus, cardiovascular(CV) conditions, especially heart failure(HF), are the topmost burden on healthcare expenditure and have the loftiest impact on mortality within the diabetic population[3]. The Candesartan in Heart failure Assessment of mortality and Morbidity(CHARM) study demonstrated thata 1 increase in glycosylated hemoglobin A1c(HbA1c) is associated with a 25 increase in the danger for CV events or death in T2DM patients [4]. The close association between diabetes mellitus and HF is a result of the mischievous effect of vital pathogenic factors habitual glucotoxicity and lipotoxicity, as well as altered insulin signaling. Myocardial structural and functional derangement is a consequence of oxidative stress, increased formation of advanced glycation end products, altered intracellular calcium handling, endothelial dysfunction, and inflammation [5]. According to the most recent 2021 guidelines published by the European Society of Cardiology(ESC), HF is a clinical pattern comprising essential symptoms for illustration, dyspnea, fatigue, and ankle swelling — that may be associated with signs — elevated jugular venous pressure, pulmonary crackles, or supplemental edema — due to structural and/ or functional abnormality of the heart performing in elevated intracardiac pressures and/ or inadequate cardiac affair at rest and/ or during physical activity. utmost generally, HF is a result of myocardial systolic and/ or diastolic dysfunction; still, pathology of the faucets, endocardium, pericardium, or arrhythmias may also contribute to the disease[6]. HF is common in T2DM cases, and its current prevalence is estimated at> 64 million cases[7]. This highlights not only the significance of tight glycemic control for T2DM patients but also CV operation. While metformin(MET) seems to parade cardioprotective effects, other traditional antidiabetic drugs have neutral or indeed dangerous impacts on CV issues [8]. It's well established that saxagliptin and alogliptin should be avoided in the HF population, whereas pioglitazone is unequivocally contraindicated[9]. Although glucagon- suchlike peptide- 1(GLP1) receptor agonists reduce the risk of myocardial infarction(MI), stroke, and CV death in cases with T2DM, they aren't recommended for the prevention of HF events(6). Sodium- glucoseco-transporter 2 inhibitors(SGLT2i) are a new antidiabetic medicine class that mediates epithelial glucose transport at the renal proximal tubules, inhibiting glucose absorption — performing in glycosuria — and thus perfecting glycemic control [10]. SGLT2i have also demonstrated CV benefits, especially in the treatment of HF. Canagliflozin(CANA) displayed effective glycemic control while reducing HbA1c, getting the first Food and medicine Administration(FDA)- approved SGLT2i in 2013. also, the Canagliflozin Cardiovascular Assessment Study(Oil) demonstrated the eventuality of CANA to reduce the threat of CV complications in T2DM cases, includingnon-fatal stroke,non-fatal MI, and HF management, farther pressing the cardioprotective qualities of SGLT2i and their role in T2DM treatment, in confluence with first- line treatment with MET [11]. The FDA and the European Medicines Agency(EMA) have presently approved four oral SGLT2i agents for T2DM treatment CANA, dapagliflozin(DAPA), ertugliflozin(ERTU), and empagliflozin(EMPA). Ipragliflozin, luseogliflozin, and tofogliflozin have been approved in Japan. Remogliflozin etabonate was first commercially launched in India. exploration on sergliflozin etabonate was discontinued after phase II trials. specially, sotagliflozin(SOTA) is a binary SGLT1/ SGLT2 asset. The FDA refused to authorize its use in combination with insulin for diabetes mellitus type 1(T1DM), and phase III trials on SOTA in cases with T2DM and HF were regrettably and untimely terminated due to fiscal reasons and the COVID- 19 epidemic. The 2021 ESC guidelines recommended two SGLT2i, DAPA and EMPA,

as first- line treatment for HF patients with reduced left ventricular ejection bit(LVEF), videlicet HF with reduced ejection bit(HFrEF), along with other recommended first- line agents anyhow of the presence of diabetes, unless contraindicated or not permitted(class I). likewise, CANA, DAPA, EMPA, ERTU, and SOTA are recommended in T2DM cases at threat of CV events in order to reduce hospitalizations due to HF, major CV events, endstage renal complaint(ESRD), as well as CV death(also class I)[6]. This review aims to assess the efficacity and safety of these newanti-glycemic oral agents in the operation of diabetic and HF cases.

Pharmacology:-

Dapagliflozin competitively, reversibly, and largely widely inhibits SGLT2. Type 2 SGLT2s are expressed in the kidney and on the epithelial lining of the S1 segment of the proximal sophisticated tubule. Physiologically, these transporters are responsible for roughly 90 of renal glucose immersion(Wright, 2001 Wright and Turk, 2004). By blocking SGLT2 with dapagliflozin, reabsorption of glucose into the bloodstream is lowered. Dapagliflozin promotes glucose filtration through the kidneys and into the urine to be excluded from the body. To quantify the degree of glucose excretion that occurs with dapagliflozin, studies have examined 24 h glucose excretion amounts in healthy subjects as well as patients with T2DM given a range of dapagliflozin doses. Dapagliflozin doses of 20 – 100 mg have redounded in urinary glucose excretion of roughly 60 g over 24 h in healthy volunteers(Komoroski etal. 2009). In subjects with T2DM who entered dapagliflozin doses between2.5 and 20 mg, the 24 h glucose excretion after 1 day ranged between 38 and 77 g and after 14 days ranged between 42 and 73 g(Kasichayanula etal. 2011a). In comparison, patients who have a mutation of the SGLT2 gene SLC5A2 can excrete up to 125 g per day of glucose with no clinically applicable adverse outcomes(van den Heuvel etal. 2002). Studies have demonstrated that the 24 h urine glucose excretion with dapagliflozin represents only about 40 – 50 of the mortal- filtered glucose load. One implicit reason for this ceiling effect is that when SGLT2 is inhibited, SGLT1 may compensate by adding reabsorption of glucose(Defronzo etal. 2013). Dapagliflozin is cured starting at 5 mg orally in the morning and can be titrated up to 10 mg orally in the morning if clinically indicated. Dapagliflozin is 78 bioavailable and fleetly absorbed. Its partial life is12.9 h, qualifying for formerly- diurnal dosing(Bristol- Myers Squibb Company, 2014). Dapagliflozin isn't known to have any meaningful drug – drug interactions. It's generally metabolized by UGT1A9 and has minor cytochrome 450-intermediated metabolism. Dapagliflozin has been estimated in combination with glimepiride, metformin, pioglitazone, and sitagliptin; it neither affects the metabolism of these antihyperglycemic agents nor is its metabolism affected by them and there are no given pharmacokinetic(PK) alterations(Bristol- Myers Squibb Company, 2014; Kasichayanula etal. 2011b). Because dapagliflozin can beget decreases in systolic BP via its bibulous diuretic effect, patients entering antihypertensive agents(especially loop diuretics) or those known to witness hypotension should be nearly covered when initiating or titrating dapagliflozin(BristolMyers Squibb Company, 2014).[13]

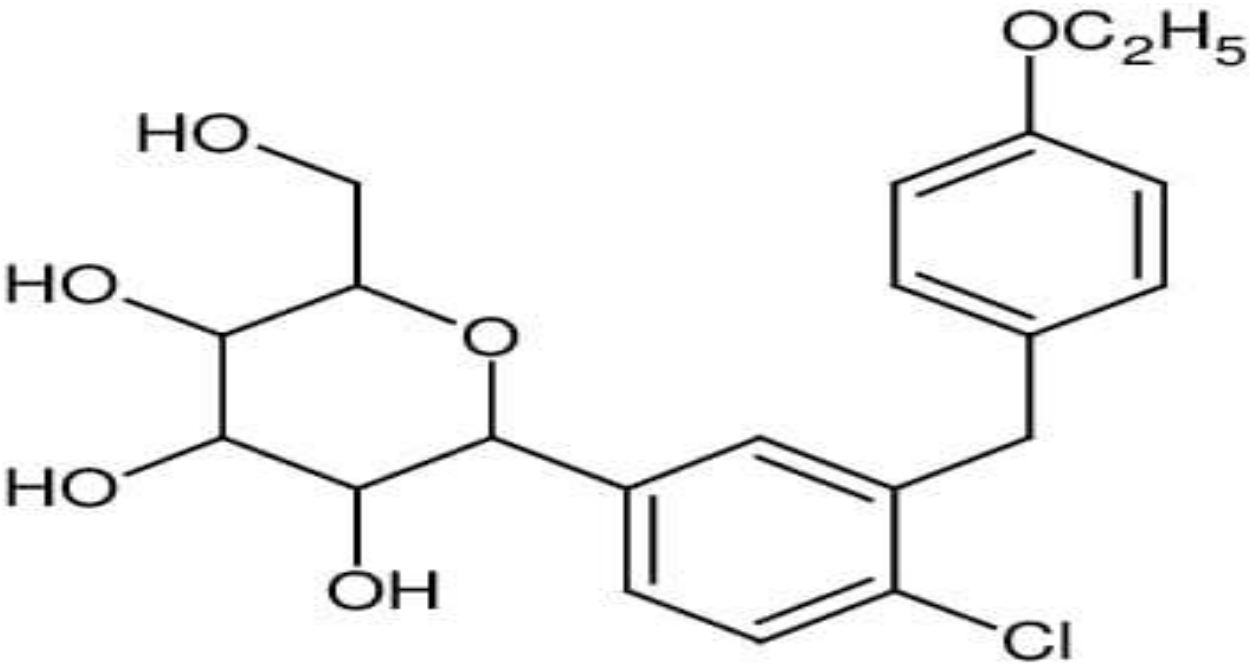

Fig.1.Structure of Dapagliflozin

Clinical efficacy of Dapagliflozin:-

1 Glycaemic and Other Outcomes

As reviewed previously in Drugs , numerous randomized, double-blind, multicentre, phase 3 trials with dapaglifozin as monotherapy and combination therapy have demonstrated its efcacy in improving glycaemic control and reducing bodyweight and BP in a broad spectrum of patients with T2D, including those with high baseline HbA1c (≥ 9%) and the elderly (aged ≥ 65 years) . Results from more recent trials, including special populations such as patients with chronic kidney disease (CKD) stage 3A , hypertension or CVD , are summarized . In a randomized, double-blind, multinational, phase 3 study in patients inadequately controlled with metformin (n = 182), add-on dapaglifozin reduced bodyweight largely by reducing fat mass relative to placebo, with fat mass accounting for approximately two-thirds of the total weight loss . At week 24, patients receiving add-on dapaglifozin 10 mg once daily had signifcantly lower total bodyweight (primary endpoint; diference from placebo − 2.1 kg; baseline≈ 92 kg; $p < 0.0001$) smaller waist circumference (− 1.5 cm; baseline≈ 105 cm $p = 0.0143$) and less fat mass as assessed by dual X-ray absorptiometry (DXA) (− 1.5 kg; baseline≈ 33 kg; $p = 0.0001$) than those receiving add-on placebo. A rapid decline in bodyweight was seen in the frst few weeks of dapaglifozin treatment, with a gradual decline thereafter that had not plateaued at week 24. This change in bodyweight was refected in the daily spot urinary glucose level, which showed an initial rapid increase and stable levels thereafter, supporting the DXA fndings that the loss in bodyweight and fat mass with dapaglifozin was largely because of caloric loss from glucosuria. However, the initial rapid decline in bodyweight in dapaglifozin recipients may partly be because of fuid loss . Additionally, the proportion of patients with a decrease in bodyweight of ≥ 5% was signifcantly higher in patients receiving dapaglifozin than those receiving placebo (31 vs. 4%; $p <0.0001$). Moreover, magnetic resonance imaging in a substudy in 80 patients showed that both visceral and subcutaneous adipose tissues were reduced in dapaglifozin relative to placebo recipients (diference from placebo − 258 and − 185 cm3 , respectively; both nominal $p <0.05$) The reductions in bodyweight, fat mass and waist circumference with add-on dapaglifozin versus add-on placebo at week 24 were maintained over 102 weeks' therapy .

2 Patients with Hypertension

Dapaglifozin 10 mg once daily reduced SBP and improved glycaemic control in two phase 3 studies in patients with inadequately controlled T2D and hypertension despite receiving antihypertensive therapy (angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy alone or in combination with one other antihypertensive). At week 12, mean SBP and HbA1c were signifcantly lower with dapaglifozin than placebo in both studies (frst and second coprimary endpoints, respectively) . A post hoc analysis of one study suggested that SBP was lowered with dapaglifozin to a greater degree in patients receiving a β blocker or a calcium-channel blocker as their additional antihypertensive drug than in those receiving a thiazide diuretic[14] .

Current Status of Dapaglifozin in the Management of T1D:-

Insulin therapy is vital for the survival of T1D patients, in whom insulin defciency may be idiopathic or occur due to autoimmune β-cell destruction [. The 2016 National Institute for Health and Care Excellence (NICE) and 2019 ADA guidelines recommend treating adult T1D patients with MDIs of prandial and basal insulin; while CSII is recommended in both guidelines, NICE guidelines only recommend CSII if patients have experienced debilitating hypoglycaemia, or if HbA1c levels remain high, with MDI therapy. Insulin therapy should be tailored to the individual (with respect to e.g. dose, dose timing, injection methods) . However, insulin therapy alone is often not enough for T1D patients to achieve glycaemic control, with adverse efects such as hypoglycaemia becoming more likely with intensive insulin therapy, and obesity and insulin resistance becoming more prevalent in T1D (Sect. 1). To overcome these limitations, research into the adjunctive use of various agents with diferent mechanisms of action is currently underway in T1D . SGLT2 inhibitors act independently of insulin to facilitate the improvement of glycaemic control without exacerbating insulin-related risks, such as hypoglycaemia and weight gain (Sect. 1). Recent research suggests that SGLT2 inhibitors may also have renal and CV protective efects , which would be of particular beneft in the context of suboptimal insulin control and in obesity. DKA is a known risk with SGLT2 inhibitor therapy, potentially more so with higher doses and with certain patient lifestyles (e.g. excessive drinking and ketogenic diets) . Certain strategies, including starting SGLT2 inhibitor treatment at the lowest possible dose and adjusting insulin dose reduction to the patient's blood glucose and ketone levels and the SGLT2 inhibitor used, may reduce the risk of DKA in patients with T1DM. Dapaglifosin, originally approved for use in type 2 diabetes, is the first SGLT2 inhibitor approved in the EU as an adjunct to insulin in patients with type 1 diabetes with a BMI of 27 kg/m2 or more (section 4). Recently, sotagliposin, a dual SGLT1/2 inhibitor, was also approved in the EU for the same indication. However, the US FDA has issued full response letters for both dapaglifosin and sotaglifosine for T1DM. In the placebo-controlled DEPICT-1 and DEPICT-2 studies, dapaglifosine 5 mg/day was effective as an adjunct to insulin therapy in adults with type 1 diabetes (Section 2). After 24 weeks of treatment, patients with a BMI ≥ 27 kg/m2 experienced improvements in glycemic control similar to the overall study population, as measured by HbA1c. Improvements in CGM-assessed glycemic control parameters (although nominally statistically significant) were also observed with dapaglifosine (Section 2.1.1). These parameters include glycemic stability, an important unmet need in type 1 diabetes, and time to target glycemic range, which have been reported to be useful in assessing treatment effectiveness and risk of complications, and may therefore be useful indicators for optimizing treatment. Dapaglifosine has also been associated with total daily insulin dose and weight loss, which may be particularly beneficial in patients with a high BMI (Section 2.1.2). Extension data were exploratory, but efficacy results at week 52 were consistent with those obtained at week 24 (Section 2.2). At week 52, improvements in blood pressure were also observed in patients with hypertension (i.e., blood pressure ≥ 140/90 mmHg), and UACR data suggested that dapaglifosine 5 mg/day may have a renal protective effect in patients with albuminuria (Section 2.2.2). Dapaglifosine 5 mg/day was generally well tolerated in these trials with a manageable safety profile over 52 weeks of treatment (Section 3). The hypoglycemic profile of dapaglifosine was similar to placebo at week 52. 3.1) Although not common overall, specific cases of DKA were observed more than 3 times more

frequently in dapaglifosine 5 mg/day than in placebo recipients in the overall study population (Section 3.1). However, among those receiving dapaglifosine 5 mg/day, the incidence of DKA was 2.4 times lower in individuals with a BMI ≥27 kg/m2 compared to the general population (Section 3.1). Nevertheless, careful monitoring and management of any risks of DKA are crucial with dapaglifozin treatment . Further long-term clinical experience with dapaglifozin in T1D is needed to more defnitively establish the efcacy and safety profle of the drug for this chronic disease, especially in those with a high BMI (given the increasing prevalence of obesity in the T1D population [7]) and its relative position to that of other adjunctive therapies. According to the draft fnal guidance from NICE, analyses using 52-week DEPICT data predicted dapaglifozin, as an adjunct to insulin, to be a cost-efective use of National Health Service resources for the treatment of T1D in patients with a BMI of≥27 kg/m2 when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy [40]. Another UK-based cost-utility analysis using 24-week DEPICT-1 data predicted dapaglifozin as an adjunct to insulin to be cost efective relative to placebo, with a corresponding incremental cost-efectiveness ratio of £13,449 per quality-adjusted life years . Further robust pharmacoeconomic data concerning the cost efectiveness of dapaglifozin 5 mg/day in T1D would be of interest. In conclusion, dapaglifosine 5 mg/day as an adjuvant to insulin improves glycemic control and reduces total daily insulin dose and body weight without increasing the risk of hypoglycemia in adults with T1DM. Although further clinical experience is needed, dapaglifosine 5 mg/day as an adjuvant to insulin is a promising treatment option for adults with type 1 diabetes and a BMI ≥27 kg/m2 who do not achieve adequate glycemic control with insulin alone despite optimal insulin therapy.[15]

Place of Dapaglifozin in the Management of T2D :-

The aim of treatment in T2D is to prevent complications and optimize patient quality of life . The 2018 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus guidelines and the 2019 ADA guidelines recommend a patient-centred approach for the management of glycaemia and CV risk factors in T2D. Glycaemic targets should be individualized based on the risk of adverse events (e.g. hypoglycaemia and bodyweight gain), patient characteristics (e.g. comorbidity and patient frailty) and patient preference and goals . Several classes of AHAs with diferent mechanisms of action are available for use in T2D. Metformin (unless contraindicated or not tolerated) and comprehensive lifestyle changes (including bodyweight management and physical activity) are frst-line therapy. The choice of other AHAs should be individualized based on patient factors (including history of CVD, bodyweight, hypoglycaemic risk and CKD), the cost of treatment and patient preference . CVD is the major cause of mortality in T2D, with MI and stroke accounting for ≈ 80% of all deaths . Therefore, it is important that the AHA selected to improve glycaemic control in patients with T2D does not aggravate, and preferably improves, CV risk factors and reduces CV morbidity and mortality . SGLT2 inhibitors are a relatively new class of oral AHAs that reduce plasma glucose levels by increasing urinary glucose excretion . Because of their insulin-independent mechanism of action, SGLT2 inhibitors can be combined with other AHAs (including insulin) with minimal risk of hypoglycaemia . The SGLT2 inhibitors currently approved in the EU are dapaglifosine, canaglifosine, empaglifosine and ertuglifosine, which are taken orally once daily. Dapaglifosine is a potent and highly selective SGLT2 inhibitor (Section 2) with established efficacy and safety in patients with type 2 diabetes (Section 3). In well-designed phase 3–4 clinical trials, dapaglifosine, once daily as monotherapy and in combination with other AHAs, provided effective glycemic control and reduced body weight and blood pressure in a broad range of patients with type 2 diabetes, including those with hypertension and/or cardiovascular disease (Section 3). Real-world study data support the effectiveness of dapaglifosine in patients with type 2 diabetes (Section 3.3). In addition, dapaglifosine was non-inferior to placebo in MACE and significantly reduced the incidence of cardiovascular death and HHF in a large cardiovascular outcome trial, DECLARE-TIMI 58, in patients at high risk for cardiovascular events, with the between-group differences being mainly explained by: Dapaglifosine lowers the incidence of HHF (Section 3.2). Dapaglifozin also reduced the likelihood of progression of renal disease, although statistical signifcance of these fndings was not demonstrated because of hierarchical testing (Sect. 3.2). The CV and renal benefts with dapaglifozin were consistent across subgroups, suggesting treatment benefts across a broad patient population, regardless of history of ASCVD, HF or CKD at baseline (Sect. 3.2.1). Other subgroup analyses suggested that dapaglifozin reduced both MACE

and CV death/HHF in high-risk patients with T2D and prior MI , and reduced CV death/ HHF to a greater extent in patients with HFrEF than in those without HFrEF (mainly because of a larger reduction in CV death in patients with HFrEF) [30] (Sect. 3.2.1). The ongoing phase 3 DAPA-HF (NCT03036124) trial in patients with confrmed HFrEF and the phase 3 DELIVER (NCT03619213) and phase 4 PRESERVED-HF (NCT03030235) trials in patients with preserved ejection fraction HF are further evaluating the efects of dapaglifozin in these patient subgroups, while the phase 3 DAPA-CKD (NCT03036150) trial in patients with CKD is assessing whether dapaglifozin delays the progression of kidney disease. Dapaglifozin was generally well tolerated, with a low risk of hypoglycaemia and drug class-related AEs, including AEs of volume depletion, lower limb amputations, acute kidney injury and bladder cancer (Sect. 4). DKA (rare) and genital infections (common), also drug-class related, were reported more frequently with dapaglifozin than placebo; Fournier's gangrene was reported in one dapaglifozin and fve placebo recipients in DECLARE-TIMI 58 (Sect. 4.1). In addition to DECLARE-TIMI 58, the cardiovascular and renal benefits of SGLT2 inhibitors were also seen in the EMPA-REG OUTCOME study of empagliflozin and the CANVAS program of canagliflozin. EMPA-REG OUTCOME included only patients with ASCVD, whereas the DECLARE-TIMI 58 and CANVAS programs included only 41% and 65% of patients with established ASCVD, respectively. In all three cardiovascular outcome studies, the effects of SGLT2 inhibitors were more consistent and robust for heart failure prevention and renal outcomes than for atherosclerotic cardiovascular disease. These differences may be related to the mechanism of action of SGLT2 inhibitors on the kidney and other effects such as natriuresis, blood pressure reduction, and improvement in endothelial function. Across the trials, SGLT2 inhibitors also appeared to moderately reduce the risk of MACE in patients with ASCVD, but not in patients with multiple risk factors . However, in contrast to results from EMPA-REG OUTCOME, the rate of CV death and allcause death was not signifcantly reduced in DECLARE-TIMI 58, which may be because of diferences between the drugs or between the study designs . Results from a recent meta-analysis of the three CV outcome trials SGLT2 inhibitors have demonstrated significant cardiovascular (CV) benefits, particularly in reducing hospitalization for heart failure (HHF) and slowing renal disease progression, with moderate benefits in major adverse cardiovascular events (MACE), especially in patients with atherosclerotic cardiovascular disease (ASCVD). Proposed mechanisms for these benefits include improved ventricular loading conditions, enhanced cardiac metabolism and bioenergetics, inhibition of myocardial sodium/hydrogen exchange, and reduced cardiac necrosis and fibrosis. Among other antidiabetic agents (AHAs) evaluated in CV outcome trials, glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as liraglutide (LEADER) and semaglutide (SUSTAIN-6) significantly reduced MACE in type 2 diabetes (T2D) patients, whereas exenatide (EXSCEL) and lixisenatide (ELIXA) showed no CV benefit or harm. GLP-1RAs did not significantly impact HHF rates. A recent meta-analysis confirmed that SGLT2 inhibitors robustly reduce HHF and renal disease progression and moderately reduce MACE in ASCVD patients. However, the effect on CV death and all-cause mortality varied between trials, likely due to differences in the drugs or study designs. In comparative analyses, SGLT2 inhibitors were more effective than GLP-1RAs at reducing HHF risk (HR 0.71), but both had similar effects on MACE reduction (HR 1.02). Dipeptidyl peptidase-4 inhibitors (DPP-4is), such as sitagliptin (TECOS), saxagliptin (SAVOR-TIMI 53), and alogliptin (EXAMINE), demonstrated CV safety without clear benefits, though saxagliptin increased HHF risk by 27% ($p = 0.007$). Regarding renal outcomes, SGLT2 inhibitors significantly reduced albuminuria and slowed the decline in estimated glomerular filtration rate (eGFR). GLP-1RAs also reduced albuminuria but had no significant effect on eGFR, while the impact of DPP-4is on renal outcomes remains uncertain and warrants further investigation. Large real-world studies, such as the CVDREAL study involving over 300,000 matched T2D patients from six countries, have supported the CV benefits of SGLT2 inhibitors.[16]

Place of Dapaglifozin in the Management of Symptomatic HFrEF:-

Traditionally, treatment of heart failure has focused on targeting the renin–angiotensin–aldosterone system (via ACE inhibitors, ARBs, and MRAs) and the sympathetic nervous system (via beta-blockers) . The American Heart Association's recent update of its Expert Recommendations for the Treatment of HF (based on preliminary guidelines) demonstrates significant advances in the treatment of HFrEF and provides interim guidance. Evidence-based therapy (GDMT) for HFrEF currently includes the SGLT2 inhibitors dapagliflozin and empagliflozin, as well as established therapies. The Heart Failure Association's most recent consensus document recommends ACE inhibitors, ARBs, ARNIs, beta-blockers, MRAs, and SGLT2 inhibitors as "clinically important" (based on treatment data) for all patients with heart failure. The new European Society of Cardiology guidelines now include dapagliflozin and empagliflozin (Class I, Level of Evidence A) as recommended treatments for patients with HFrEF with the aim of reducing the risk of HHF and death, in addition to

previously approved ones (ACE inhibitors/ARNI, beta-1 blockers) and MRAs). The United Kingdom National Institute for Health and Care Excellence (NICE) recommends dapagliflozin as an option for the treatment of symptomatic HFrEF in adults when used as an adjunct to SOC therapy. The first evidence for the benefits of dapagliflozin in heart failure was provided by DECLARE-TIMI 58, in which dapagliflozin reduced the risk of cardiovascular death or heart failure in patients with T2DM (section 2.2.1). DECLARETIMI 58 paved the way for other phase III trials including DAPA-HF. In this study, dapagliflozin significantly reduced the risk of HF or CV death compared to placebo in patients with HFrEF, regardless of the presence of T2DM (Section 1). 2.1.1). It is noteworthy that DAPA-HF patients had a higher risk of HHF or CV death than patients in DECLARE-TIMI 58 and other previous SGLT2 inhibitor studies [13, 51]. The effects of dapagliflozin on the primary endpoints were similar across various patient subpopulations, including patients already receiving heart failure therapy such as sacubitril/valsartan (Section 2.1.1). NT-proBNP is a marker of cardiovascular disease. The DEFINE-HF study was designed in part to evaluate the effects of dapagliflozin on biomarkers, and dapagliflozin did not reduce NT-proBNP levels compared with placebo at 6 or 12 weeks (Section 2.2 .2). However, most patients receiving dapagliflozin had clinically meaningful improvements in NT-proBNP levels compared with those receiving placebo (Section 2.2.2). Longer term, in the DAPA-HF study, dapagliflozin reduced NT-proBNP levels at 8 months (section 2.1.2). The cardiovascular benefits of dapagliflozin in patients with heart failure have been confirmed in reviews and meta-analyses, where dapagliflozin reduced the risk of heart failure and cardiovascular death compared with placebo. In the DAPA-CKD study, dapagliflozin also significantly reduced the risk of HHF or CV death compared with placebo in CKD patients regardless of baseline HF history (Section 2.2.4). To date, there are no clinical trials directly comparing dapagliflozin with other drugs for the treatment of HFrEF. Indirect comparisons were found between dapagliflozin and other SGLT2 inhibitors, between dapagliflozin and sacubitril/valsartan, or between SGLT2 inhibitors and sacubitril/valsartan or vesiguat. There was no difference in efficacy (with respect to HHF and/or CV death) [60] . However, given the limitations of indirect comparisons, these results should be treated with caution. Clinical studies comparing dapagliflozin with other agents, particularly SGLT2 inhibitors, in patients with HFrEF would be of interest. A randomized, multicenter study is currently ongoing to evaluate the effect of initiating dapagliflozin in hospital in patients with HFrEF on cardiovascular death or heart failure (DAPA ACT HF-TIMI 68) and the effect of dapagliflozin in affected patients. Short-term functional capacity of patients: HFrEF (DAPA-VO2), efficacy and safety of dapagliflozin in hospitalized patients with heart failure (DICTATE-HF) and dapagliflozin in patients with acute myocardial infarction (DAPA-MI). Based on its known safety profile in other indications, dapagliflozin is generally beneficial in patients with heart failure (Section 3). he incidence of AESI (e.g. DKA, severe hypoglycemia and severe urinary tract infection) in patients treated with placebo dapagliflozin was generally low (>1%). It is noteworthy that all cases of DKA and severe hypoglycemia occurred in patients with T2DM (section 3). Heart failure is a leading cause of hospitalization and is associated with significant medical costs. NICE guidelines report that dapagliflozin plus SOC (as an ACE inhibitor or ARB) is better than improved sacubitril/valsartan plus beta-blockers and MRA (if tolerated), but less expensive and less effective [50] . In the opinion of the Panel, dapagliflozin is cost-effective as an adjunct to optimal SOC and represents a use of healthcare resources. Clinical studies in the United Kingdom, Germany, Spain, Australia, Thailand, the Philippines and the United States have shown that adding dapagliflozin to SOC/GDMT is cost-effective for the treatment of chronic HFrEF. Results from another Markov model from the United Kingdom National Health Service suggest that dapagliflozin plus an ACE inhibitor is more cost-effective than sacubitril/valsartan plus SOC in patients with HFrEF. The economic analysis showed that the cost savings of using dapagliflozin as an alternative to sacubitril/valsartan are greater than many alternatives (30–50%). In conclusion, dapagliflozin 10 mg/day plus SOC reduces the risk of heart failure or cardiovascular death in patients with HFrEF, independent of T2DM. Dapagliflozin is an effective and generally well-tolerated treatment and is an effective new adjunctive therapy for symptomatic HFrE . [17].

Tolerability of Dapaglifozin:-

Dapagliflozin is generally well tolerated, and the overall safety profile in cardiac patients is not as good as its safety profile in other indications. Adverse events of special interest (AESI) in DAPAHF included volume depletion (7.5% in the dapagliflozin group vs. 6.8% in the placebo group), renal AEs (6.5% vs. 7.2%), fracture (2.1% vs. 2.1%), and amputation (0.5%) and 0.5%). A small number of patients (4.7% in the dapagliflozin group vs. 4.9% in the placebo group) discontinued further treatment due to AEs [13]. volume depletion (9.2% in the

dapagliflozin group vs. 5.3% in the placebo group), and renal injury (0.8% vs. 0.8%). AEs resulted in no treatment in 8.4% of those treated with dapagliflozin and 9.1% of those receiving placebo. Due to its mechanism of action (induction of diuresis), dapagliflozin may cause blood volume depletion, which may present as hypotension. The risk may be higher in the elderly, in patients taking antihypertensive medications (such as loop diuretics), and in patients with renal impairment. In DAPA-HF, serious AEs due to volume depletion occurred in 1.2% of patients in the dapagliflozin group and 1.7% of patients in the placebo group. Among patients not taking a diuretic at baseline, the incidence of volume depletion ($p = 0.004$) and renal AEs ($p = 0.024$) was lower in the dapagliflozin group than in the placebo group; the incidence of volume depletion was also lower when patients were taking a diuretic. Depletion in the dapagliflozin group was slightly higher in the elderly, in patients with renal impairment studies, and in patients taking loop diuretics than in the placebo group. Before initiating dapagliflozin treatment Volume and renal function should be monitored during treatment. If the patient becomes volume depleted, dapagliflozin should be temporarily discontinued until volume depletion is corrected. Dapagliflozin may increase the risk of hypoglycemia when used with insulin or insulin secretagogues. In DAPA-HF, serious hypoglycemic events occurred in 0.2% of patients in the dapagliflozin group and 0.2% of patients in the placebo group. In DEFINE-HF, the incidence of serious adverse events was 0.8% in the dapagliflozin group and 0.8% in the placebo group. All hypoglycemic events occurred in patients with T2DM. SGLT2 inhibitors, including dapagliflozin, have been associated with diabetic ketoacidosis (DKA), including complications and death. However, the incidence of DKA in DAPA-HF was 0.1% in the dapagliflozin group and 0% in the placebo group; DKA was not reported in DEFINE-HF. Patients with T2DM should be assessed for the risk of DKA before initiating dapagliflozin. DKA should be considered if a patient has nonspecific symptoms of DKA regardless of blood glucose levels. If DKA is suspected or confirmed, dapagliflozin should be discontinued immediately. Dapagliflozin may increase the risk of urinary tract infections (UTIs, including urosepsis and pyelonephritis) and genital tract infections [8, 9]. Fournier's gangrene (a rare but serious and potentially life-threatening condition called perineal necrotizing fasciitis) has also been reported in patients receiving SGLT2 inhibitors, including dapagliflozin. In DAPA-HF, serious urinary tract infections occurred in 0.6% of patients in the dapagliflozin group and 0.7% of patients in the placebo group, and complications due to UTI were 0.2% in both groups. Genitourinary tract infections occurred in 0.3% of dapagliflozin-treated patients and 0% of placebo-treated patients without treatment.[17]

Dosage and Administration:-

Dapagliflozin is approved in the EU as an adjunct to insulin for the treatment of adults with T1D and BMI ≥ 27 kg/m2 who, despite effective insulin therapy, do not provide adequate glycaemic control with insulin alone. In T1D, dapagliflozin should only be used as an adjunct to insulin. The recommended dose of dapagliflozin is 5 mg orally once daily, with or without food. In patients known to be at risk of frequent and/or severe hypoglycaemia, a lower starting insulin dose will reduce the risk of hypoglycaemia. The insulin dose should be reduced if necessary to prevent DKA and ketosis. Dapagliflozin should not be initiated in patients with GFR $<$ 60 mL/min and dapagliflozin should be discontinued in patients with GFR $<$ 45 mL/min. No dose adjustment is required in patients with compromised renal function or mild or moderate liver disease. In patients with severe liver disease, the starting dose of dapagliflozin should be 5 mg/day and the dose should be increased to 10 mg/day if effective. Local prescribing information should be consulted for additional information, including dosage and administration instructions, contraindications, warnings, and precautions.[17]

Conclusion:-

Dapagliflozin (Farxiga) stands out as a pivotal SGLT2 inhibitor, offering multifaceted benefits for patients with type 2 diabetes and heart failure. Its mechanism of action not only enhances glycemic control but also provides significant cardiovascular and renal protection, making it a cornerstone in the management of these conditions. Clinical trials have consistently demonstrated its efficacy in reducing the risk of hospitalization for heart failure and improving overall cardiovascular outcomes. As healthcare continues to evolve towards more integrated treatment approaches, dapagliflozin's role in managing comorbidities will likely expand, underscoring the importance of personalized medicine. Given its favorable safety profile and robust clinical evidence, dapagliflozin is an essential therapeutic option that healthcare providers should consider when treating patients with diabetes and concurrent heart failure, ultimately aiming to improve patient outcomes and quality of life.

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