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MANUSCRIPT TITLE: AN UPDATE ON CURRENT USAGE OF SGLT2-INHIBITORS IN HEART FAILURE WITH REDUCED EJECTION FRACTION: SPECIAL FOCUS ON DAPAGLIFLOZIN

[1]Dr. Jay Shah, MD, DNB (Cardiology) FACC, FESC, [2]Dr Johann Christopher MD DNB FACC , [3]Dr. Saketkant, MD, DM, [4]Dr. Soumik Goswami, MD, DM (Endocrinology), [5]Dr. Biswajit Aich, [6]Dr.Sameer K. Muchhala.

[1]Senior Interventional Cardiologist,HCG Hospital, Ahmedabad,jayshah08@yahoo.in

Consultant Cardiologist, Director Of Cardiac Imaging, Care Hospitals, Hyderabad,johann1403@gmail.com

[3]Senior consultant Endocrinology(Adult and Pediatric), Max Super-speciality Hospital Shalimar Bagh, Balaji Action Medical and Cancer Hospital, New Delhi,drsaketkant@gmail.com

[4]RMO cum Clinical Tutor,Dept. of Endocrinology, Nilratan Sircar Medical College, Kolkata.dr.soumikgoswami@gmail.com

[5]Senior Manager, Medical Services
Zydus Healthcare Ltd., Goregaon (E), Mumbai
Aich.Biswajit@Zyduscadila.com
[6]General Manager, Medical Services
Zydus Healthcare Ltd., Goregaon (E), Mumbai
Sameer.Muchhala@zyduscadila.com
Corresponding Author:
Dr. Biswajit Aich
Senior Manager, Medical Services
Zydus Healthcare Ltd., Goregaon (E), Mumbai
Aich.Biswajit@Zyduscadila.com
Phone Number - 9864159889
All authors have contributed to the below mentioned criteria:
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Importance of the Article: This review article is a conglomerate of the current therapies in heart failure management with special focus on Dapagliflozin and associated clinical guidelines. This will help the cardiologists and endocrinologists with a quick updated reference to the developments in the management of heart failure with low ejection fraction.

ABSTRACT: Heart failure (HF) is a complex clinical syndrome resulting from impairment of ventricular filling or ejection of blood.Management of patients with HF still remains a clinical challenge and many current therapies have uncertain impacts on long-term morbidity and mortality.Sodium-glucose co-transporter 2 inhibitors (SGLT2i) were initially developed for their glucose-lowering effect and subsequently have been shown to decrease the risk of Hospitalization for Heart Failure (HHF).After the initial Cardiovascular Outcome Trials (CVOTs)new datahaveprovided the evidence of benefits ofthese agents in reducing cardiovascular mortality and HHFin patients with Heart Failure with reduced ejection fraction (HFrEF) with or without co-existing Type 2 Diabetes (T2DM).In this narrative review, we have summarized the current therapies in the management of heart failure and clinical evidences with SGLT2i with special focus onDapagliflozin for clinical

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outcomes in HFrEF patients. We have also reviewed the latest guidelines that have proposed the use of SGLT2i in the management of HFrEF.

Keywords: Heart failure; Sodium-glucose Co-transporter Inhibitors; Dapagliflozin; Type 2 diabetes

Introduction: Heart failure is a complex clinical syndrome resulting from impairment of ventricular filling or ejection of blood associated with symptoms of dyspnoea, fatigue, and peripheral and/or pulmonary edema. Although there have been great advances in the modalities of management of heart failure in recent decades, the incidence of heart failure continues to increase. Heart failure syndrome affects more than 23 million people worldwide [1].The disease-specific estimates projected that a conservative estimate of the prevalence of heart failure in India is in the range of 1.3 to 4.6 million, with an annual incidence of 0.4–1.8 million[2].The heart failure epidemic has a staggering impact on quality of life, functioning, and longevity while imposing heavy costs on the health care system. The identification of the syndrome of advanced heart failure requires a focussed clinical assessment integrating routinely available clinical risk markers and investigations.

Aim:

Several recent articles have thrown light on the benefits of SGLT2i and their role in the changing paradigm of heart failure management. This review article is an attempt to conglomerate briefly the current therapies in heart failure management with special focus on Dapagliflozin and clinical guidelines with regard to the management of heart failure with SGLT2i.

Methodology: This being a narrative review, we did not conduct a systematic literature search. A search of the PubMed database was conducted in April 2021, with no date limits, using the search terms “Heart Failure”, “Sodium Glucose Transporters 2 Inhibitors”, “Dapagliflozin” and “Treatment”, and the results were screened for relevance to the review the topic. Articles were also added based on the authors’ knowledge of the area.

History of Advent of Pharmacological Therapy in Heart Failure:

Before 1980, treatmentwasmainly focused on lifestyle changes or limitations on physical activities such as bed rest, inactivity, and fluid restrictions. Vasopressors agents, digitalis, and diuretics were the mainstay of treatment during this time. In 1986 the first landmark trial Vasodilator Heart Failure Trial (V-Heft) marked the beginning of the era of other pharmacological modalities of treatment.The trial shows good mortality benefits with use of combination of isosorbidedinitrate (ISDN)/hydralazine, prazosin, compared to placebo in symptomatic chronic compensated systolic heart failure. Till this time, digitalis and diuretics continued to be mainstays, but vasodilators - particularly the combination of nitrates and hydralazine -- played a prominent role, with some or limited benefit. So, in the era before beta-blockers and Angiotensin Converting Enzyme (ACE) inhibitors, ISDN/hydralazine showed a path towards improved survival benefits amongst patients with systolic heart failure[3].

In the 1990s, neuro-hormonal interventions in the management of Heart failure came to the forefront. ACE inhibitors, beta-blockers, and spironolactone for the treatment of advanced heart failure were shown to alter the natural history of heart failure progression[4]. The goals of treatment for heart failurewere reduction of symptoms, reducing hospitalizations, and prevention ofuntimely death. The mainstay of treatment was pharmacologic therapy and lifestyle modifications. ACE inhibitors or angiotensin receptor blockers (ARBs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRA) were shown to improve clinical conditionsurvival as also quality of life(QOL) of patients with Congestive Heart Failure (CHF) with HFrEF. Concomitant diuretic therapy caused reduction in cardiac load therebyleading to improvement in left ventricular function[5].

Classes of Drugs in the Management of Heart Failure:

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Conventional Drug Therapy	Comprehensive Disease Modifying Drug
Renin Angiotensin Aldosterone System (RAAS) Inhibitors:ACEIs, ARBs	*Oral Anti Diabetes Agents: SGLT2 inhibitors*
Cardiac Glycosides	*Angiotensin Receptor-Neprilysin Inhibitors (ARNI)*
Beta Blockers	*Mineralocorticoid Receptor Antagonist (MRA)*
Diuretics	
Calcium Channel Blockers	
I(f) Inhibitor Ivabradine	

A New Domainin Heart Failure Management:
An important development in the management of Heart Failure is the development of SGLT2i, a class of medications primarily developed as an oral anti-diabetic drug. The recent Food and Drug Administration's approval of SGLT2iin patients with HFrEF and its addition to the armamentarium of medications available for the treatment of patients with HFrEF has further expanded the horizon of their usage.

Sodium Glucose Co-Transporter 2 inhibitors In Heart Failure:
Thelatest category of drugs that proved to be promising in patients with HFrEF are the SGLT2i.Evidence of the CV benefits with SGLT2i have been demonstrated in the initial CVOTs with various SGLT2i. Considerable developments with SGLT2i have occurred over the last few years across various sub-set of patients.Various mechanisms have been postulated as to how SGLT2i are beneficial in Heart Failure. Apart from the anti-hyperglycaemic action, SGLT2i possess multidimensional properties that may beneficially influence the CV prognosis. Along with the hormonal and metabolic effects, it is also hypothesised that increase in glucagon and slight increase in ketone bodies can result in shift substrate utilization for CV benefits[6].

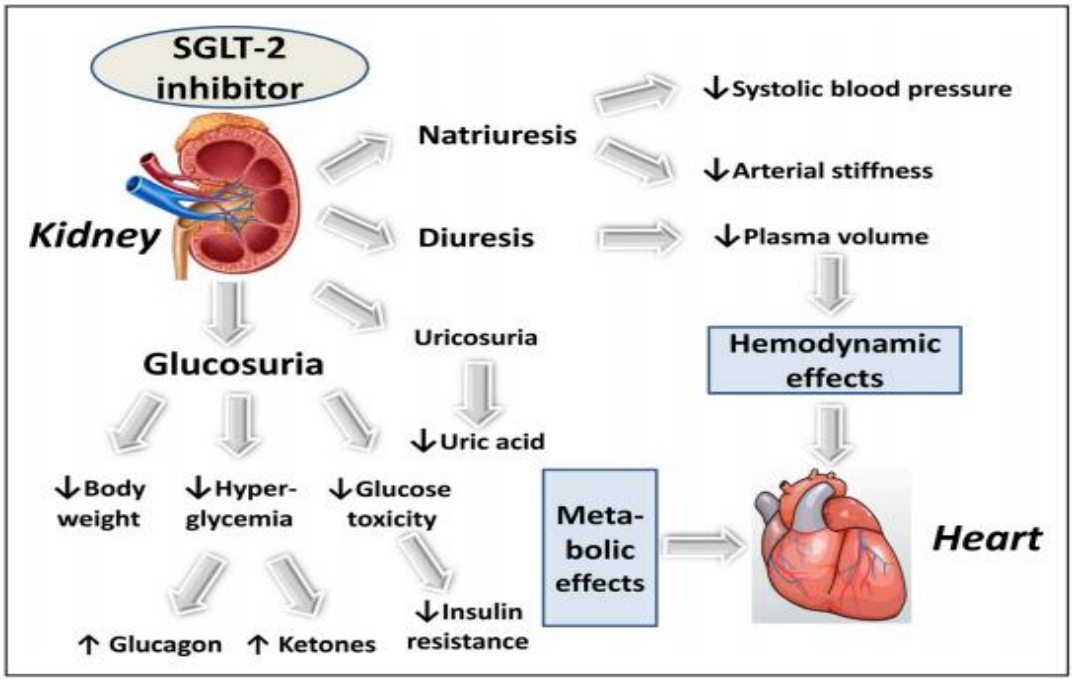

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Figure: Primary mechanisms of action of Sodium Glucose Co-transporter Type 2 inhibitors and their hemodynamic and metabolic effects.

Dapagliflozin:

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is C21H25ClO6•C3H8O2•H2O and the molecular weight is 502.98.

Indications:

Dapagliflozin is indicated in adults aged 18 years and older with T2DM to improve glycemic control:

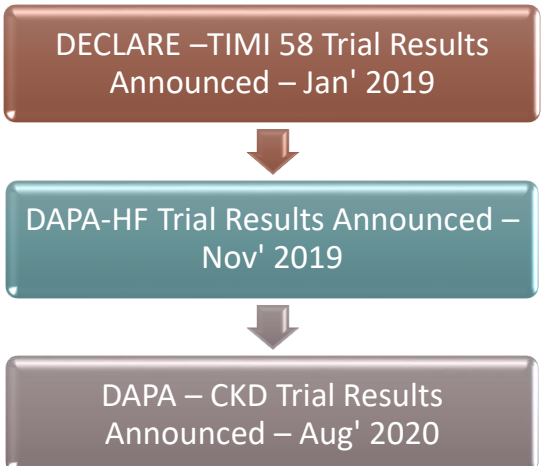
- As an adjunct to diet and exercise to improve glycemic control in adults with T2DM.
- To reduce the risk of hospitalization for heart failure in adults with T2DM and either established cardiovascular disease or multiple cardiovascular risk factors.
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression [7].

Dose and Method of Administration:

The recommended starting dose of Dapagliflozin to improve glycemic control is 5 mg orally once daily, taken in the morning, with or without food. In patients tolerating Dapagliflozin5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.

Renal function should be assessed prior to initiation of Dapagliflozin therapy and then as clinically indicated. In patients with volume depletion, correction of this condition prior to initiation of Dapagliflozin is advised.

Timelines in Developments Related To Dapagliflozin:



Major Approvals and Decisions in The Course Of Approval In Heart Failure:

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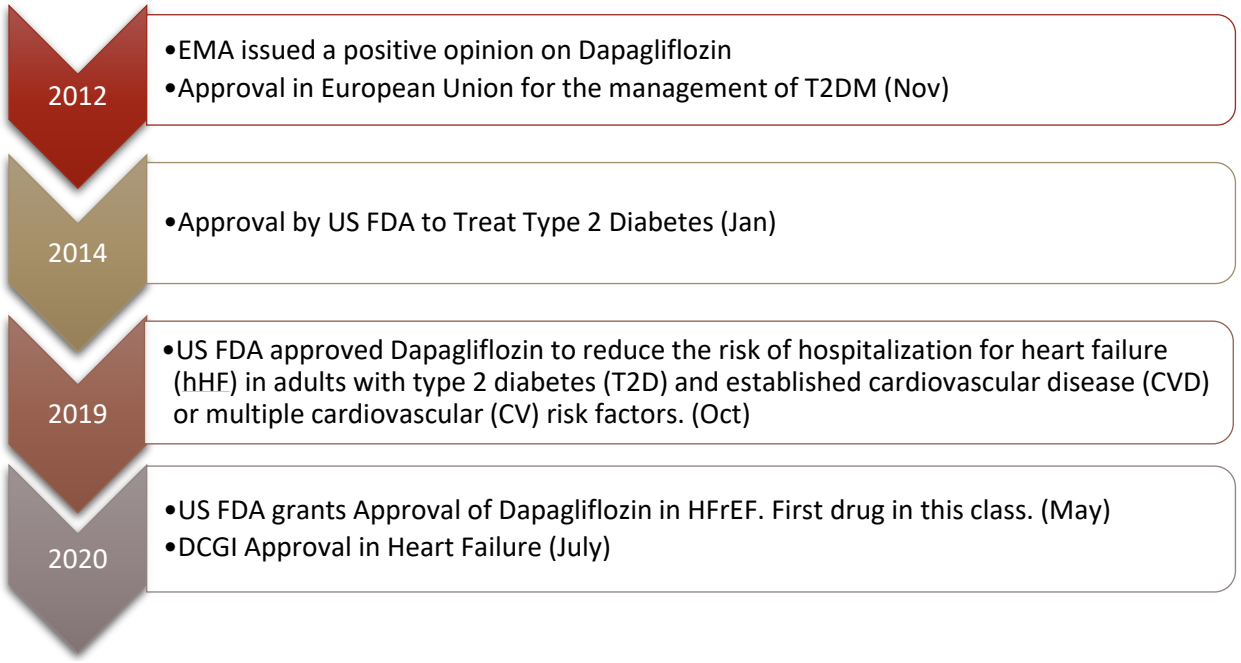
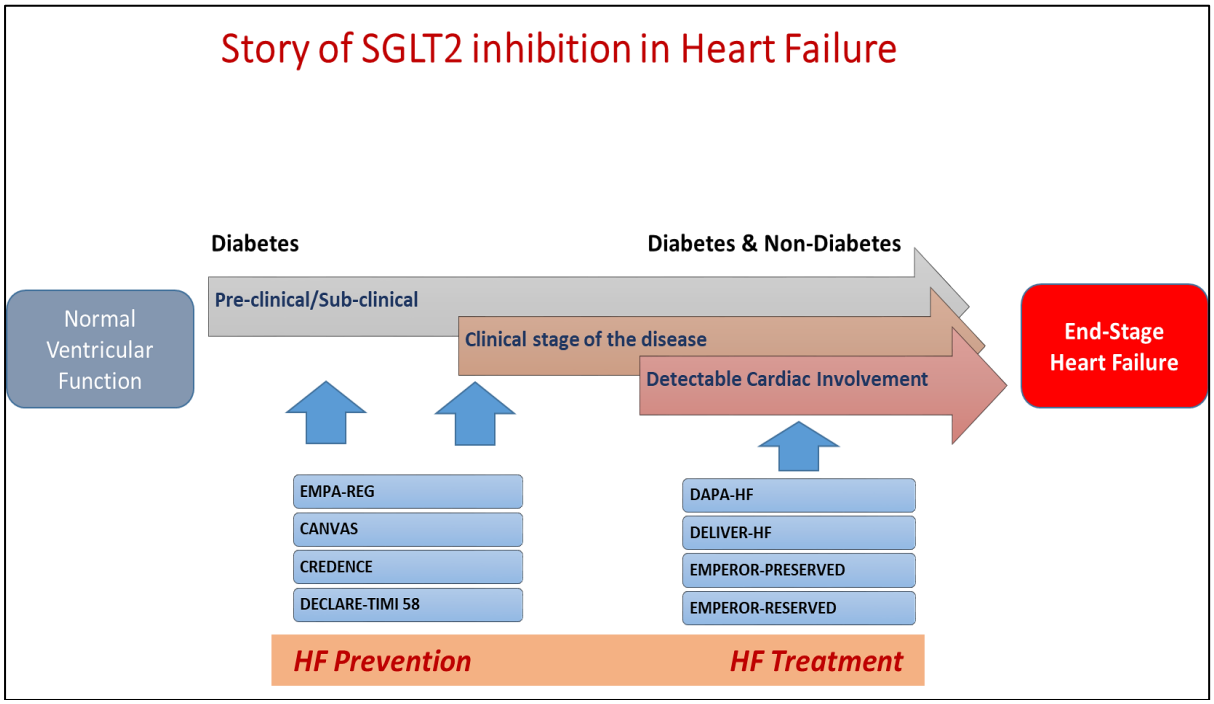


The Journey of SGLT2 inhibitors:



Indications for Use of an SGLT2 Inhibitor in Heart Failure[8]:

- HFrEF (EF ≤40%) with or without diabetes
- NYHA class II-IV HF
- Administered in conjunction with a background of GDMT* for HF

* GDMT- guideline-directed medical therapy

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DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) study is the first to demonstrate the benefit of SGLT2 inhibitor - Dapagliflozin in patients with HFrEF. The study demonstrated that amongst 4,744 patients with HFrEF, the risk of worsening HF or death from CV causes was lower inpatients who received Dapagliflozincompared to those who received placebo, regardless of the presence or absence of T2D (16.3% in the Dapagliflozin group versus 21.2% in the placebo group; hazard ratio: 0.74; 95% CI: 0.65 to 0.85). Besides, Dapagliflozin demonstrated a significant reduction in each of the individual components of the composite endpoint, with a 30% decrease in the risk of a first episode of worsening HF (hospitalization for HF/urgent HF visit) and an 18% decrease in the risk of CV death[9].

In the EMPEROR-Reduced (EMPagliflozinoutcomEtRial in Patients With chrOnicheaRt Failure with Reduced Ejection Fraction) trial, 3,730 patients with chronic HFrEF were studied divided equally between empagliflozin and placebo. The primary end point was the composite outcome of CV death and HFH.This trial demonstrated that patients on empagliflozin hadsignificantly reduced composite endpoint of CV death or HF hospitalization with and without diabetes (Hazard ratio: 0.75; 95% CI: 0.65 to 0.86). This clinical benefit of empagliflozin was primarily driven by a 30% reduction of HHF and urgent visits for HF (HR, 0.69; 95% CI, 0.59–0.81) but the CV mortality reduction by empagliflozin was neutral (HR, 0.92; 95% CI, 0.75–1.12).The trial also showed that treatment with empagliflozin slowed the decline in the eGFR over time[10].

	DAPA-HF[9] (2019)	EMPEROR-Reduced[10] (2020)
Comparison	Dapagliflozin 10 mg daily vs. placebo	Empagliflozin 10 mg daily vs. placebo
HFrEF definition	EF ≤ 40%	EF ≤ 40%
Median LVEF (%)	31.1	27.4
Median follow-up	18.2 months	16 months
Number of participants	4744	3730
Median age (years)	66.3	64.6
NYHA class, no. (%) **I** **II** **III** **IV**	 0 3203 (67.5) 1498 (31.6) 43 (0.9)	 0 2800 (75.1) 910(24.4) 20(0.5)
Median NT-proBNP (pg/Ml)	1437	1907
History of Diabetes	1983 (41.8)	1856 (49.8)
Primary outcomes	Composite ofworsening heartfailure or death fromcardiovascular causes;HHF;CV Death;composite ofHHF or CV Death;Death from any cause.	Composite ofCV deathor HHF;HHF;CV Death;Death from any cause.
Results Related to HF Outcomes	26% reduction in the risk of worsening HF or death from CV causes.	25 % reduction in the risk of the composite endpoint of CV death or HF hospitalization.

The DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients with HF) study demonstrated that patients on Dapagliflozin experienced clinically meaningful improvements in HF-related health status or natriuretic peptides concentrations in those with HFrEF. Larger number of patients i.e., 61.5% in Dapagliflozin groupcompared to 50.4% in placebo achieve the end point (p=0.039). The beneficial effects of Dapagliflozin in heart failure with reduced ejection fraction was found to be uniform across patients with or without T2DM[11].

In a secondary analysis of the DAPA-HF Trial it was found that Dapagliflozin rapidly reduced the risk of cardiovascular death or worsening heart failure, with a sustained statistically significant benefit seen as early as 28 days. Patients with a more recent heart failure andhospitalization were at particularly high risk and had higher relative and absolute risk reductions[12].Dapagliflozin reduced worsening HF events and death across all age categories, with larger absolute benefits in older patients. Dapagliflozin also improved symptoms in each age group, with no heterogeneity of treatment effect[13].

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In the Get with Guidelines–Heart Failure (GWTG-HF) registry which included a cohort of 1,54,714 patients with HFrEF (left ventricular ejection fraction ≤40%), the generalizability of use of Dapagliflozin in patients hospitalized with HFrEF was evaluated under FDA label. The robust data from this registry of patients hospitalized with heart failure suggest that 4 out of 5 patients with HFrEF would be an ideal candidate for initiation of Dapagliflozin, supporting its broad usage, irrespective of their T2DM[14].

In a meta-analysis of DAPA-HF and EMPEROR-Reduced on cardiovascular outcomes in patients with HFrEF with or without diabetes; ofthe 8474 patients evaluated, the effects of Empagliflozin and Dapagliflozin on hospitalizations for heart failure were consistent across these trials. There was a 26% relative reduction in the combined risk of cardiovascular death or first hospitalisation for heart failure (0·74, 0·68-0·82; p<0·0001), and a 25% decrease in the composite of recurrent hospitalisations for heart failure or cardiovascular death (0·75, 0·68-0·84; p<0·0001)[15].

Accumulating evidence from randomized clinical trials support the use of SGLT2i in patients who have stable heart failure (with or without diabetes) and a reduced ejection Fraction. The impact of DAPA-HF trial was such that the SGLT2 inhibition with Dapagliflozin now representsa new foundational therapy pillar in the management of HFrEF to reduce mortality[16]. On a similar front the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial also favoured the use of SGLT2i therapy which when initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure[17].

In a cross-trial analysis, EMPHASIS-HF[18] (eplerenone), PARADIGM-HF[19] (sacubitril-valsartan, ARNI) and DAPA-HF[9] (dapagliflozin) were analysed to evaluate the treatment effects of comprehensive disease modifying pharmacological therapy (ARNI, β blocker, MRA, and SGLT2 inhibitor) versus the conventional therapy (ACE inhibitor or ARB and β blocker) in patients with HFrEF. The primary endpoint of CV death or HHF was 0·38 (95% CI 0·30–0·47). Treatment with comprehensive disease modifying therapy was alsofound to add additional years in patients' lives and also decrease the MACE compared with conventional therapy. The anticipated aggregate treatment effects of early comprehensive disease modifying pharmacological therapy are substantial and support the combination use of this quadruple therapy as a new standard for HFrEF management[20].

Guidelines on Recommendations of SGLT2 inhibitors use In HFrEF:

1. **2021CCS/CHFS Heart Failure Guidelines Update**[21]: The recommendations in the table are those of the latest CCS/CHFS Heart Failure Guidelines.

Recommendations	Comments
An SGLT2 inhibitor, such as dapagliflozin or empagliflozin, be used in patients with HFrEF, with or without concomitant T2DM, to improve symptoms and quality of life and to reduce the risk of HF hospitalization and/or CV mortality.	Strong Recommendation, High-Quality Evidence
An SGLT2 inhibitor can be used for treatment of patients with T2DM and atherosclerotic CV disease to reduce the risk of HF hospitalization and death.	Strong Recommendation, High-Quality Evidence
SGLT2 inhibitors, such as Dapagliflozin be used in patients with T2DM aged > 50 years with additional risk factors for atherosclerotic cardiovascular disease to reduce the risk of HHF.	Strong Recommendation, High-QualityEvidence
SGLT2 inhibitors such as Canagliflozin or Dapagliflozin be used in patients with albuminuric renal disease, with or without T2DM, to reduce the risk of HF hospitalization and progression of renal disease.	Strong Recommendation, High-Quality Evidence

2. **2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment**[9]:

Since the 2017 Expert consensus decision pathway (ECDP) recommendations, new therapies have been added in the list of HFrEF treatment. The addition of SGLT2i as part of the therapy for patients with chronic HFrEF

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who are already receiving beta-blockers, an ARNI/ACEI/ARB or an aldosterone antagonist has broadened the scope of treatment options in Guideline Directed Medical Therapy. In both DAPA-HF and EMPEROR Reduced, the benefit of SGLT2 inhibition was significant despite underlying background ARNI therapy. Scope for the usage has also widenedas the committee has suggested thatSGLT2i can be addedto any other therapy for the management of HFrEFeven before the target or maximum tolerated doses of thesedrugsare achieved.

Recommendations	Additional Suggestions
Ensure eGFR ≥ 30 mL/min/1.73 m2 for Dapagliflozin before initiation	SGLT2i can be added to any therapy for the management of HFrEF even before the target or maximum tolerated doses of other drugs have been achieved.
Ensure eGFR ≥ 20 mL/min/1.73 m2 for Empagliflozin before initiation	

3. 2021 NICE Guidelines; Dapagliflozin for treating Chronic Heart Failure With Reduced Ejection Fraction[22]:

Dapagliflozin is now recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimized standard care with ARNI or ACEI/ARB with Beta Blockers and if tolerated MRAs. It should be startedin patients with symptomatic heart failure with reduced ejection fraction on the advice of a heart failure specialist. Monitoring should be done by the most appropriate healthcare professional.

4. 2020 Position paper of the Heart Failure Association of the European Society of Cardiology[23]:

A position paper by the European Society of Cardiology has suggested that SGLT2 inhibitors (Empagliflozin, Canagliflozin, and Dapagliflozin) can be recommended to reduce the risk of HF hospitalisation in T2DM patients with either established cardiovascular disease or at high cardiovascular risk. In the management of HFrEF, Dapagliflozin has particularly shown important clinical benefits within weeks of its initiation. The DAPA-HF trial also shows a significant improvement in Quality of Life of patients in the trial which is of high clinical value given that HFrEF is associated with much morbidities. Observations from the DAPA-HF trial indicate a supportive value of dapagliflozin in addition to the established GDMT for HF.Trial indicate that dapagliflozin has earned its place as the fifth pillar in the medical management of HF.

Discussion:

There is a large unmet need for new therapies in the treatment of HFrEF in the current scenario and especially in certain sub group of population who are at high risk. Both DAPA-HFand EMPEROR-Reduced studies have showed that in addition to conventional HFrEF therapy, dapagliflozinand empagliflozin were effective in reducing HHF. Moreover, dapagliflozin also demonstrated a significantreduction in CV death.In both the studies the results were consistent irrespective of their diabetes status. The mechanisms explaining these results are not entirely clear and have been proposed to go beyond blood glucose control.In the early drug development phase, the therapeutic potential of a drug is not fully understood and trial endpoints other than mortality are needed to guide drug development decisions[24]. SGLT2i are a group of drugs whose potential is slowly being unleashed in each successive trial in varied patient populations.Various mechanisms have been postulated for the extensive benefits of SGLT2i in clinical practice which may include an increase in erythropoietin, inhibition of the sympathetic nervous system, improved kidney function, changes in substrate utilization and direct myocardial effects such as left ventricular remodelling. The early benefits of SGLT2ion HHFseen during the trialshas been evident from the early separation of the curveswhich may point toward changes in haemodynamic parameters in patients with heart failure[10]. In heart failure these agents promotes fractional sodium excretion after treatment initiation like that of loop diuretics and decrease the whole body water content. Hospitalization for heart failure is an area wherein patients should be initiated on Guideline Derived Medical Therapy to decrease morbidity and mortality as far as possible. The recent registry data also suggest that large proportion of patients with HFrEF are candidates for SGLT2i therapyalthough the real world usage is very meagre[13]. There is also good evidence of clinical benefits in patients with worsening heart failure with the early initiation of SGLT2i that has translated into significantly lower CV deaths and hospitalizations and urgent visits for heart that had resulted in a significantly lower CV deaths and hospitalizations and urgent visits for heart failure[25]. The latest addition of SGLT2i in the heart failure therapy space has created a paradigm shift in the management of HFrEF.

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Conclusion:

Managing patients with Heart Failure remains a clinical challenge and inspite of current therapies thereexists substantial long-term morbidity and mortality. The use of therapies that prevent or reverse organ injury may represent a comprehensive strategy to reduce morbidity which will be more successful in combination with the traditional approaches.The robust data for SGLT2i from clinical trials and real-world clinical practice has clearly established their role as the fifth pillar of GDMT in the treatment of heart failure in the days to come.

Abbreviations:

Sodium Glucose Transporter Inhibitor, SGLTi; Heart Failure with Reduced Ejection Fraction, HFrEF; Canadian Cardiovascular Society/Canadian Heart Failure Society, CCS/CHFS; American College of Cardiology, ACC; National Institute for Health and Care Excellence, NICE; American Heart Association, AHA; European Society of Cardiology, ESC; Heart Failure, HF; Hospitalization for Heart Failure, HHF; Type 2 Diabetes Mellitus, T2DM; Cardiovascular, CV; Cardiovascular Outcome Trials, CVOTs; 3 Point Major Averse Cardiovascular Events, 3P MACE; Angiotensin Converting Enzyme, ACE; Angiotensin Receptor Blockers, ARB; Mineralocorticoid Receptor Antagonists, MRA; Congestive Heart Failure, CHF; Renin Angiotensin Aldosterone System, RAAS; funny channel pacemaker current, If; Beta Blocker, b-blocker; Calcium Channel Blockers, CCBs; Angiotensin Receptor-Neprilysin Inhibitors, ARNI; New York Heart Association, NYHA; Guideline Directed Medical Therapy, GDMT; European Medicine Agency, EMA; United States Food and Drug Administration, US FDA; Drug Controller General Of India, DCGI

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