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CLINICAL OUTCOMES OF DAPAGLIFLOZIN IN HEART FAILURE WITH REDUCED EJECTION FRACTION: A COMPREHENSIVE REVIEW

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ABSTRACT
Heart failure with reduced ejection fraction (HFrEF) remains an important health challenge worldwide, especially in Asia and India where there is a younger patient population, along with a high prevalence of type 2 diabetes, hypertension, and chronic kidney disease. Despite advances in the standard management of heart failure, considerable residual risk of hospitalization and death exists. This review highlights the clinical significance of dapagliflozin and includes data from the DECLARE-TIMI 58 trial and its subgroup analyses with more than 17,000 patients having type 2 diabetes. Dapagliflozin (10 mg per day) decreased the rate of cardiovascular mortality or hospitalization due to HF by 17% and the rate of heart failure hospitalization by 27%. These effects were independent of sub-group analysis, including in patients with HFrEF, with no impact on the eGFR decline and adverse effects primarily limited to genital infections. Also, real-life data and economic analysis provide additional evidence to consider this drug. Nowadays, international and Indian guidelines recommend dapagliflozin as one of the mainstays of the therapy in patients with HFrEF along with other GDMT. In conclusion, dapagliflozin offers a safe, effective strategy to improve outcomes in HFrEF, particularly in resource limited settings. Early and wider adoption could significantly decrease the burden of heart failure.

KEYWORDS: Dapagliflozin, SGLT2 inhibitors, HFrEF, DECLARE-TIMI 58, heart failure, cardiorenal protection.

1. INTRODUCTION

Epidemiology and Burden HFrEF, which involves LVEF of less than or equal to 40%, accounts for a substantial proportion of patients with heart failure worldwide. Heart failure is a prevalent condition in the world, affecting over 56-64 million people with a prevalence rate of 1-3% in adults.[1,2] Although there has been stability in the proportion of HFrEF in some developed countries due to better management of ischemic heart disease, HFrEF remains highly prevalent in other regions, especially low and middle-income countries.[3]

The prognosis remains poor for symptomatic HFrEF. The mortality rate within five years exceeds 50%, and the one-year mortality rate ranges between 5% and 34%. Rehospitalization after one year occurs in 30% of

patients, and rehospitalization is the major reason behind the rise in the healthcare costs.[1,4] The burden of HFrEF in India and Asia is quite high. People suffering from heart failure in India are relatively young with an average age ranging between 56 and 62 years, in comparison to their western counterparts.[5,6]

An estimation states that from 1.3 to 4.6 million people in India are suffering from heart failure (7). In addition to this, the co-morbid conditions of type 2 diabetes in 35-51%, hypertension, and ischemic heart diseases make it even more dangerous. Out of total people having acute heart failure registered in the Kerala Heart Failure Registry, the number of HFrEF patients was 67.5% with very high inpatient (7.7%) and 90 days (12.3%) mortality.[5] In many cases, the patient also suffers from CKD.

Constraints to standard treatment methods Despite the progress that has been realized through GDMT treatments, including ARNIs, beta-blockers, MRAs, and loop diuretics, optimal application of quadruple GDMT leads to approximately 75% reductions in the relative risk of cardiovascular mortality (25% reduction in absolute risk).[9]

However, there are numerous risks that remain despite the optimized therapy. In the present population of patients undergoing quadruple GDMT, the rates of mortality, heart failure admission, and mortality/heart failure are roughly 19%, 26%, and 37% respectively after one year.[10] The patients continue to exhibit symptoms, recurrent admissions, declining kidney function, and even acute myocardial incidents. The problem with implementation is widespread, with less than 50% of suitable patients attaining all four components of the regimen at optimal dosage levels, particularly in developing countries like India.[11]

EVOLUTION OF SGLT2 INHIBITORS IN HEART FAILURE

The SGLT2 inhibitors were initially introduced into the market as glucose-lowering agents against Type 2 Diabetes Mellitus. Unexpectedly, the CVOTs revealed that SGLT2 inhibitors provided the advantage of reduced hospitalizations due to heart failure (by approximately 30% reduction in risk of hospitalization due to heart failure) irrespective of glucose levels.[12,13] This prompted further clinical trials of SGLT2 inhibitors specifically in heart failure patients.

DAPA-HF study that became known in 2019 was the pioneer randomized controlled trial investigating dapagliflozin among patients with HFrEF with or without diabetes.[14] It can be considered the principal medication. Additionally, other post hoc studies including the one of DECLARE-TIMI 58 have provided further confirmation about the advantages of SGLT2 inhibitors on mortality, hospitalization, renal status, and quality of life.[15-26]

2. CLINICAL EVIDENCE FROM RANDOMIZED TRIALS

This section consists of a detailed and complete discussion of the studies related to dapagliflozin based only on the clinical trial, DECLARE-TIMI 58, and its 25 post hoc analysis (References 1–26). DECLARE-TIMI 58 forms the foundation for large clinical trials which prove the cardiorenal and heart failure advantages of dapagliflozin in diabetic patients.

DECLARE-TIMI 58 – THE CORE TRIAL STUDY DESIGN

DECLARE-TIMI 58 was a Phase III randomized, double-blind, placebo-controlled, event-driven trial that consisted of 17,160 patients with Type 2 Diabetes Mellitus at higher risk for cardiovascular diseases. Such patients could either suffer from atherosclerotic cardiovascular disease (ASCVD; 40.6%) or have many risk factors for the disease (multiple-risk factors, MRF; 59.4%). The patients were allocated randomly to receive 10 mg/day of oral Dapagliflozin or placebo along with their existing therapies. The mean follow-up period of the trial was 4.2 years. The co-primary endpoints involved: (1) Major Adverse Cardiovascular Events (MACE: Cardiovascular mortality, myocardial infarction or ischemic stroke); and (2) CV Death/HHF.[22,23]

BASELINE CHARACTERISTICS

The sample consisted of a high-risk population with regards to T2DM, since the mean age was 64 years, the percentage of female subjects was 37%, the mean hemoglobin A1C level was 8.3%, as well as the presence of co-morbidities like hypertension, dyslipidemia, and impaired kidney function. The incidence rate of HF with LVEF ≤ 40% was estimated at 3.9% (n=671).[22]

PRIMARY AND KEY SECONDARY OUTCOMES

Although dapagliflozin could not make an impact on 3MACE, it still had a 17% relative risk reduction on cardiovascular mortality and/or hospitalization for heart failure, and the finding is statistically significant (HR 0.83; 95% CI 0.73-0.95; p = 0.005).[22] Dapagliflozin made its impact by showing a 27% relative risk reduction on hospitalization for heart failure (HR 0.73; 95% CI 0.61-0.88).[22] The drug also exhibited a positive effect.

HOSPITALIZATION OUTCOMES

A complete post hoc analysis involving all hospitalizations (Schechter et al., 2023) revealed a 11% decrease in the risk of non-elective hospitalization and a similar percentage reduction in overall hospitalizations.[3] The beneficial effects of dapagliflozin extended beyond those suffering from heart failure.

SUBGROUP CONSISTENCY ACROSS KEY VARIABLES

- Background CV medications: Consistent efficacy and safety regardless of ACEi/ARB, betablockers, diuretics, or MRAs (Oyama et al., 2022).[6]

- Baseline blood pressure: Benefits preserved across normotensive to hypertensive ranges (Furtado et al., 2022).[7]
- HbA1c levels: Efficacy independent of glycaemic control.[8]
- Obesity: Greater absolute risk reductions in obese patients.[9]
- Age: Consistent benefits and safety in elderly.[17]
- Sex: Similar efficacy in women and men.[14]
- Peripheral artery disease: Cardiorenal and limb benefits.[15]
- Atrial fibrillation: Reduction in AF events.[16]
- Prior MI: Strong benefits in secondary prevention.[20]
- Primary prevention (MRF cohort): Significant HHF and renal reductions.[13]
- Long-term Maintenance Earlier data supported sustained efficacy.[26]

3. SAFETY AND TOLERABILITY

In the DECLARE-TIMI 58 trial, dapagliflozin was shown to have an overall positive safety and tolerance profile. In general, there was no difference between dapagliflozin and placebo regarding serious adverse events. There was no additional risk for any type of serious adverse events such as fracture, amputation, or cancer. These results were found in various subgroups such as older patients and patients taking various cardiovascular drugs.

ADVERSE EVENTS PROFILE

Overall, there was no significant difference in the incidence of severe adverse effects between the dapagliflozin group and the placebo group in the primary DECLARE-TIMI 58 study, which included 17,160 patients and lasted a median of 4.2 years. Non-inferiority criteria were established for the combined endpoint of 3-point MACE in patients taking dapagliflozin, with an upper confidence interval limit of less than 1.3 ($P<0.001$).[22]

Adverse event-related withdrawals were relatively common among those taking dapagliflozin, as compared to the placebo group (8.1% against 6.9%). However, the most withdrawals observed among those who had taken dapagliflozin were mainly because of class effects like genital infection rather than serious systemic reactions. Hypoglycemia was relatively uncommon among the dapagliflozin patients.

Subgroup analyses have additionally shown that According to Oyama et al. (2022), the safety of enarodustat appeared to be independent of the presence of cardiovascular drugs, such as ACEi/ARBs, beta-blockers, MRAs, or diuretics.[6] In the study by Furtado et al. (2022), investigating the different baseline categories of BP, the authors revealed equal event rates in terms of adverse events among the treated individuals.[7] Furthermore, the study by Cahn et al. (2020), concentrating on older patients (≥75 years old), demonstrated similar event rates of adverse events, fractures.

VOLUME DEPLETION, RENAL FUNCTION, AND ELECTROLYTES

Renal safety of dapagliflozin was another highly important clinical finding from the DECLARE-TIMI 58 study. Apart from the anticipated initial decrease in eGFR, which occurred during the first weeks after treatment initiation (approximately 3-5 mL/min/1.73 m2), stabilization and a subsequent gradual decrease in eGFR were seen at a later time than in the placebo group.

Renal event composite defined as sustained ≥40% eGFR reduction, ESKD, or renal death had a statistically significant risk reduction with dapagliflozin (HR 0.76, 95% CI 0.67-0.87).[22] Kidney-specific analyses revealed that dapagliflozin offered beneficial effects independent of baseline eGFR or albuminuria status without increasing the risk of AKI.[5, 10, 12, 19] In truth, there were plenty of analyses that showed numerically fewer incidents of renal adverse events in the dapagliflozin.

There were similar findings for events indicative of volume depletion (hypotension, dizziness, and signs of dehydration) in both groups on average and even after stratification by different patient subgroups, such as use of diuretics or presence of low blood pressure before treatment initiation.[7] Dapagliflozin did not also increase the risk of electrolyte disorders; the frequency of hyperkalemia among individuals using mineralocorticoid receptor antagonists or patients with CKD was either similar or somewhat reduced. Further research carried out by Haller et al. (2025) explored the impact of galectin-3 (a biomarker of fibrosis) on kidney safety parameters.[1]

GENITAL INFECTIONS, KETOACIDOSIS, AND OTHER RISKS

Unsurprisingly, the reason for the cessation of treatment was a genital fungal infection. It is reported in primary analysis that significant differences existed between the groups of dapagliflozin and placebo in terms of genital infections, which led to termination of treatment, occurring in 0.9% and 0.1% cases, respectively (HR 8.36, 95% CI 4.19-16.68; $P<0.001$).[22] Genital infections occurred somewhat more frequently in females but were manageable under normal conditions. Neither of the groups experienced a statistically significant difference in UTIs (1.5% vs. 1.6%).

The prevalence of DKA was low and more prevalent in the dapagliflozin arm (0.3% vs. 0.1%; $P=0.02$). All DKA patients used insulin. Fournier's gangrene was also reported equally in both arms (one patient under dapagliflozin vs. five placebo-treated patients). No differences in the rate of amputations were found (1.4% vs. 1.3%). There were no signs of an increased risk of amputations among patients with PAD.[15]

SAFETY IN SPECIAL POPULATIONS

Safety remained consistent across key vulnerable populations examined in DECLARE-TIMI 58:

- Elderly (≥65 or ≥75 years): Cahn et al. (2020) confirmed no excess in volume depletion, fractures, amputations, or serious adverse events.[17]
- Chronic Kidney Disease: Benefits and safety were maintained down to lower eGFR levels, with slower long-term eGFR decline and no increase in AKI.[1,5,10,12]
- Sex differences: O'Donoghue et al. (2021) reported similar safety in women and men, with the expected higher genital infection rate in females but overall tolerability.[14]
- Obesity, different HbA1c, and blood pressure levels: No treatment-by-subgroup interactions for safety outcomes.[7,8,9]
- Background polypharmacy: Oyama et al. (2022) showed no safety concerns when added to multiple cardiovascular drugs.[6]

CLINICAL IMPLICATIONS FOR PRACTICE

With regard to safety data from the DECLARE-TIMI 58 study, it can be recommended to use dapagliflozin safely among type 2 diabetes mellitus subjects who are at risk of HFrEF development or have established HFrEF. It is necessary to ensure proper genital hygiene among patients in order to prevent any infections, and to test them for DKA among patients using insulin. In general, there is no need for any special monitoring.

Given that the benefits gained based on high-risk subjects (elderly individuals, those with CKD or HFrEF) exceed possible risks, which can easily be managed, dapagliflozin should be recommended because it was confirmed by 26 conducted studies.

That is why this excellent tolerability and efficacy allow recommending dapagliflozin to be used for treating heart diseases and diabetes.

4. REAL-WORLD EVIDENCE AND IMPLEMENTATION

It is essential for the transferability of RCT evidence to clinical settings when establishing the efficiency of effectiveness of the new drug therapy. Even though the DECLARE-TIMI 58 trial together with the 26 other studies concerning the same issue provide level one evidence regarding the application of dapagliflozin among diabetic individuals who have cardiovascular risks (or even at risk of HFpEF), real-world evidence (RWE) is significant for supporting the above findings. The following part will present the translation of evidence gained from the DECLARE-TIMI 58 trial to the real world setting with particular emphasis on the issue of prescribing, cost-effectiveness and experience in places like India and Asia.

OBSERVATIONAL STUDIES CONFIRMING TRIAL BENEFITS

There is ample evidence from observations and registries confirming the favorable cardio-renal outcomes and heart failure effects found in DECLARE-TIMI 58. Cohorts of patients with HFrEF and diabetes in real-world settings have shown significantly lower rates of heart failure admissions and MACEs similar to the risk reduction of 27% for HHF and 17% for CV death/HHF found in the trial.[22]

In particular, propensity score-matched cohorts from real-life data sets, both in Europe and the United States, showed almost identical decreases in the composite of cardiovascular death or heart failure hospitalization, with hazard ratios falling within 0.70-0.85, quite comparable to the advantages of using dapagliflozin for the HFrEF subgroup in the DECLARE-TIMI 58 study (HR 0.62 for CV death/HHF). Notably, patients included in the observational data sets usually have a greater age, are in more severe stages of CKD and on polypharmacy compared to those in randomized trials; nevertheless, the magnitude of benefits remains comparable. Similarly, the advantages for renal endpoints in real-world are comparable to those obtained in DECLARE kidney studies.[5,10,12,19] – lower eGFR decline rate and lower incidence of sustained ≥40% reduction in eGFR.

Nevertheless, in Asian patients, where early development of diabetes, greater ischemia, and early development of heart failure are frequent events, there is clinical efficacy of dapagliflozin in terms of hospitalization for HF and the effects on kidneys. Specifically, it was determined that the results of post hoc analysis of the DECLARE trial conducted among certain subpopulations including those who had increased BP, obesity, high levels of HbA1c, and those using background medications, provided significant insights into its application in practice.[6-9,17] The long-term effectiveness of the drug, first seen in previous trials[26], was validated again in subsequent observational studies extending for over 4 years.[3]

PRESCRIPTION PATTERNS

Although it is well proven that such drugs should be used for their therapeutic benefits, their prescription in clinical settings leaves a lot to be desired. According to analysis conducted using big datasets in the USA and Europe, less than 10 to 25% of patients eligible for SGLT2 inhibitors, suffering from type 2 diabetes and HFrEF or CKD, are prescribed such drugs even after updating guidelines. It was observed that cardiologists and endocrinologists were relatively regular in prescribing these drugs, whereas primary care physicians and nephrologists varied widely.

BARRIERS TO USE

Several recurring barriers limit broader implementation:

1. cost-effectiveness - Dapagliflozin has become available in generic form in India, although despite

improved access, costs remain a major determinant. The following section details the cost-effectiveness analysis of dapagliflozin.

2. Physician Inertia and Knowledge Gaps - The concerns about genital infection, fluid loss problems, and ketoacidosis persist regarding DECLARE in light of the safety data available.[6,14,17,22] The decrease in eGFR observed at baseline represents a positive effect rather than harm, but this fact has been misinterpreted.
3. Patient-Related Factors - Polypharmacy, low health literacy, genital hygiene awareness, and adherence challenges are common. In Asian populations, cultural factors and dietary patterns may influence tolerability.
4. Healthcare System Issues — Fragmented care between cardiologists, diabetologists, and nephrologists leads to missed opportunities. Formulary restrictions and insurance coverage gaps further hinder use.
5. Special Population Concerns — Elderly patients (well-studied in Cahn et al., 2020)[17], those with low blood pressure[7], or advanced CKD are sometimes undertreated despite consistent safety and efficacy in DECLARE subgroups.

Overcoming these barriers requires targeted education, simplified protocols, and policy support areas where the broad DECLARE dataset (especially safety across subgroups) can build clinician confidence.

COST-EFFECTIVENESS ANALYSES

Consistently, cost-effectiveness analyses clearly show that the use of dapagliflozin becomes highly cost-effective as add-on treatment in HFrEF as well as cardiorenal protection. Cost-effectiveness analyses with the use of event rate from DECLARE-TIMI 58 show that the ICER is favorable and significantly under the threshold level for most countries.

However, in case of countries with high prevalence of diabetes and especially lower-middle-income countries like India, low generic prices make dapagliflozin highly attractive. The cost savings in modeling are due to reduced hospital admissions due to heart failure and initiation of dialysis treatment, thus producing savings along with increased QALYs. Even at its branded price, dapagliflozin is shown to be intermediate-high value in models from European countries and USA, but more in case risk factors such as obesity, CKD, or prior Hf are involved, just like seen in the DECLARE trial.[9,12,18]

Brazil and other middle-income countries have ICERs between $4,000-$8,000 per QALY, far below local threshold levels. Sensitivity analysis remains robust with different adherence rates and discount rateS.

EXPERIENCE IN INDIAN AND ASIAN POPULATIONS

Type 2 diabetes and its related cardiac and renal consequences affect India disproportionately in terms of burden among all nations. Early onset of diabetes, occurrence of premature ischemic heart disease, and commonality of CKD in patients render dapagliflozin to be more pertinent. In real-world studies from India, there have been significant benefits noted in relation to glycemic improvement, weight loss, blood pressure, and HF symptoms. Adverse effects have been few.

Data for Asians from global trials and local Asian patients have demonstrated consistent efficacy and safety of the drug. Relative risk reductions were found to be the same for Asians from South Asia in DECLARE sub-study groups. Rehospitalization was reduced for SGLT2 inhibitors in Asian HF registries.

Practical Indian experience highlights:

- Early initiation in newly diagnosed HFrEF or diabetes + CKD
- Combination with ARNI, beta-blockers, and MRAs (supported by background therapy analysis)[6]
- Use in elderly and low-BP patients.[7,17]
- Generic formulations improving affordability

Challenges remain in rural areas, but urban tertiary centers increasingly adopt dapagliflozin as part of foundational GDMT.

STRATEGIES TO IMPROVE IMPLEMENTATION

- Education Programs - Leverage DECLARE safety data to address concerns.
- Integrated Care Pathways - Multidisciplinary clinics (cardio-diabetes-nephrology).
- Patient Support - Apps, counselling on genital hygiene, and adherence tools.
- Policy Advocacy - Inclusion in national essential medicines lists and insurance coverage.
- Risk Stratification Tools - Use DECLARE-derived predictors (e.g., biomarkers, HF risk scores)[4,18] for prioritized initiation.

FUTURE DIRECTIONS FOR REAL-WORLD RESEARCH IN INDIA/ASIA

More research with registries of greater length, comparative effectiveness studies against other SGLT2 inhibitors, adherence studies, and the costs involved with Indian healthcare economics would be essential.

In conclusion, the findings from the DECLARE-TIMI 58 study are very well supported with real-world evidence with regards to implementation. Without much resistance and with cost-effectiveness, especially because of generics, the future of using dapagliflozin in the management of the cardiorenal manifestations of type 2 diabetes and heart failure with reduced ejection fraction is bright, not only in India but also in other places.

5. PRACTICAL ASPECTS IN CLINICAL PRACTICE

The translation of this very strong evidence from DECLARE-TIMI 58 trial along with its 26 sub-analyses into practice is vital for ensuring the best outcomes while mitigating any potential risks associated with this drug. In this section, an evidence-based approach to using this medication will be discussed in terms of its application in patients with HFrEF and/or type 2 diabetes.

PATIENT SELECTION AND ELIGIBILITY CRITERIA

Dapagliflozin is suitable for a broad range of patients with HFrEF (LVEF ≤40%, NYHA class II–IV) and type 2 diabetes at high cardiovascular risk, as demonstrated across DECLARE-TIMI 58.

KEY ELIGIBILITY CRITERIA SUPPORTED BY EVIDENCE

- Adults with type 2 diabetes and established ASCVD or multiple risk factors (primary trial population).[22]
- Patients with HFrEF (stronger benefit observed in the HFrEF subgroup) (22, Kato et al. referenced analyses).
- eGFR ≥25–30 mL/min/1.73 m² (benefits maintained in lower eGFR strata).[5,10,12]
- Regardless of baseline HbA1c, blood pressure, obesity status, age, sex, or background cardiovascular medications.[6–9,14,17]

PRIORITIZE PATIENTS WHO DERIVE GREATER ABSOLUTE BENEFIT

- Those with prior heart failure or high HF risk (Berg et al., 2019).[18]
- Patients with albuminuria or CKD.[1,5,10,12,19]
- Obese individuals (greater absolute risk reduction).[9]
- Patients with elevated cardiac biomarkers.[4]

CONTRAINDICATIONS / CAUTIONS

- eGFR <25 mL/min/1.73 m² (limited data).
- History of recurrent genital infections or severe DKA.
- Type 1 diabetes or history of diabetic ketoacidosis.

Patient selection should be individualized using DECLARE-derived risk stratification tools (e.g., HF risk score from Berg et al.).[18]

DOSING AND INITIATION STRATEGY

Recommended dose: 10 mg orally once daily, with or without food (consistent across all DECLARE analyses).

Initiation strategy:

- Can be started at any time- no need for titration.
- No loading dose required.
- Can be initiated in both outpatient and inpatient settings (post-stabilization).
- In patients with eGFR 25–45 mL/min/1.73 m², start at 10 mg with close monitoring (supported by kidney subgroup data).[12]

TIMING CONSIDERATIONS

- Morning dosing preferred to align with daily routines.
- Can be added to existing GDMT without interrupting other therapies (strong evidence from background medication analysis).[6]

Monitoring and Follow-up

BASELINE ASSESSMENT (BEFORE INITIATION)

- eGFR, serum creatinine, electrolytes (especially potassium), HbA1c, blood pressure, weight, and symptoms.
- Screen for genital infections or volume depletion risk.

FOLLOW-UP SCHEDULE (EVIDENCE-BASED)

- Week 1–2: Phone/telemedicine check for symptoms of volume depletion, genital infection, or DKA.
- Week 2–4: Repeat eGFR and electrolytes (expect 3–5 mL/min/1.73 m² dip — this is hemodynamic and predictive of long-term benefit).[1,5,10]
- Month 3: Full review — symptoms, weight, BP, HF status, renal function.
- Every 3–6 months thereafter: Routine monitoring aligned with standard HFrEF/CKD care.

RED FLAGS FOR DISCONTINUATION

- Sustained symptomatic hypotension.
- Recurrent severe genital infections.
- Confirmed DKA.

Most patients require no additional laboratory monitoring beyond usual care.

Combination with Other GDMT

Dapagliflozin is an excellent fourth pillar of foundational GDMT and can be safely combined with:

- ARNI/ACEi/ARB (no interaction noted in background therapy analysis).[6]
- Evidence-based beta-blockers.
- Mineralocorticoid receptor antagonists (MRAs).
- Loop diuretics (monitor volume status).
- Vericiguat, ivabradine, or digoxin (limited direct data but no signals of harm).

DECLARE data showed consistent efficacy and safety irrespective of background CV medications.[6] Early combination (“quadruple therapy”) is now preferred in HFrEF guidelines, supported by the additive benefits seen in the trial.

MANAGEMENT OF SIDE EFFECTS

Genital mycotic infections (most common):

- Counsel on daily genital hygiene (front-to-back wiping in women, foreskin hygiene in men).
- Over-the-counter antifungal treatment (fluconazole or topical).
- Rarely requires discontinuation.

Volume depletion / Hypotension

- Review diuretic dose — temporary reduction may be needed.

- Ensure adequate fluid intake.
- Monitor BP at home.

Diabetic ketoacidosis (rare)
- Educate on "sick day rules" — never stop insulin abruptly.
- Check ketones if unwell, nauseated, or dehydrated.
- Hold dapagliflozin temporarily during acute illness.

Initial eGFR dip
- Reassure patient and continue therapy unless eGFR falls >30% or patient is symptomatic.

Other rare events:
- Amputations, fractures, and bladder cancer rates were balanced in DECLARE (no increased risk).

USE IN SPECIAL POPULATIONS

Chronic Kidney Disease (eGFR ≥25–30 mL/min/1.73 m²)

Strong evidence from multiple kidney analyses.[1,5,10,12,19] Initiate with monitoring; expect slower long-term eGFR decline and reduced albuminuria. Elderly (≥65 or ≥75 years): Excellent safety and efficacy data (Cahn et al., 2020).[17] Start at 10 mg; monitor volume status and renal function more closely in frail patients.

LOW BLOOD PRESSURE

Benefits preserved across BP spectrum (Furtado et al., 2022).[7] Safe in patients with systolic BP ≥95 mmHg if asymptomatic.

Obese patients: Particularly high absolute benefit (Oyama et al., 2022).[9]

Women vs Men: Similar efficacy; higher genital infection risk in women but manageable.[14]

Peripheral Artery Disease: Cardiorenal and limb benefits observed.[15]

Atrial Fibrillation: Reduction in AF burden.[16]

Primary Prevention Cohort: Significant benefit in patients without established ASCVD.[13]

Table 1: Practical Guide-Dosing, Monitoring, and Contraindications.

Aspect	Recommendation
Standard Dose	10 mg once daily
Initiation	Outpatient or inpatient (stable)
eGFR Threshold	≥25–30 mL/min/1.73 m²
Monitoring (eGFR)	Baseline, 2–4 weeks, then 3–6 monthly
Genital Infection	Hygiene + antifungal as needed
DKA Risk	Sick day rules, ketone education
Combination Therapy Full GDMT (ARNI + BB + MRA + SGLT2i)	Background meds analysis
Contraindications	eGFR <25, active DKA, recurrent severe infections Trial exclusion & safety

6. CURRENT GUIDELINE RECOMMENDATIONS

The announcement of the results of DECLARE-TIMI 58 trial in 2019 and its 25 post-hoc and subgroup analyses (references 1–26) and DAPA-HF trial heralded a paradigm shift in the treatment of heart failure. These have now been included in all major international and national guidelines and dapagliflozin is considered an essential drug for the management of HFrEF. This chapter provides a thorough overview of current guidelines along with the background, rationale, comparisons, regional modifications (with emphasis on India and Asia), implementation, clinical cases, cost, challenges, and future prospects.

HISTORICAL EVOLUTION LEADING TO CURRENT RECOMMENDATIONS

Prior to 2019, the guidelines for heart failure centered on neurohormonal blocking through the use of ACEi/ARB, beta-blockers, and MRAs. The surprising discovery in the DECLARE-TIMI 58 study showing a 27% decrease in heart failure hospitalization[22], even more so in the HFrEF group, led to very quick changes in guidelines. By 2021-2022, SGLT2 inhibitors gained Class 1 recommendation status worldwide.

ACC/AHA/HFSA 2022 Guideline

The 2022 AHA/ACC/HFSA guideline on the management of heart failure is among the most influential guidelines in contemporary cardiology. It recommends SGLT2 inhibitors (dapagliflozin and empagliflozin) as a Class 1, level of evidence A intervention for patients with symptomatic chronic HFrEF (NYHA class II-IV) for the reduction of heart failure hospitalizations and cardiovascular mortality irrespective of diabetes.

DETAILED KEY POINTS FROM THE GUIDELINE

- SGLT2i are listed as one of the four foundational pillars of GDMT, alongside ARNi/ACEi/ARB, beta-blockers, and MRAs.
- Recommendation applies to Stage C HFrEF.
- Early initiation is encouraged, including during hospitalization once the patient is euvolemic and hemodynamically stable.
- No titration is required (dapagliflozin 10 mg once daily).
- Benefits are consistent across prespecified subgroups, including age, sex, race, baseline eGFR, and diabetes status — directly supported by

DECLARE-TIMI 58 subgroup analyses (6–9,12–17).
- A formal Value Statement classifies SGLT2i as providing intermediate economic value, citing reductions in costly HF hospitalizations.

The guideline explicitly references data from diabetes CVOTs (including DECLARE-TIMI 58) as complementary to dedicated HF trials, noting the particularly strong effect on heart failure endpoints in diabetic populations.

EUROPEAN SOCIETY OF CARDIOLOGY (ESC) GUIDELINES

2021 ESC Guidelines SGLT2 inhibitors received a Class I, Level A recommendation for HFrEF to reduce the risk of HF hospitalization and cardiovascular death.

2023 Focused Update This update significantly broadened the scope:
- Class I, Level A recommendation for dapagliflozin or empagliflozin in HFrEF.
- Class I, Level A in HFmrEF and HFpEF for reducing HF hospitalizations and cardiovascular death.
- Strong recommendation in patients with type 2 diabetes and CKD.

The ESC places heavy emphasis on rapid initiation and optimization of the four pillars of GDMT within weeks of diagnosis. It highlights the glucose-independent mechanisms of action, making dapagliflozin suitable for both diabetic and non-diabetic patients with heart failure — a concept reinforced by DECLARE-TIMI 58 analyses showing benefits independent of HbA1c.[8]

INDIAN GUIDELINES AND REGIONAL ADAPTATIONS

Heart Failure Association of India (HFAI) 2025 Guidelines This guidance classifies dapagliflozin as Class I evidence in HFrEF, HFmrEF, and HFpEF. In particular, it emphasizes its importance within the Indian environment due to the younger age of patients, increased incidence of cardiomyopathy, ischemic heart disease, and CKD, which are caused by diabetes. The guideline promotes early administration of the drug, especially in resource-poor areas, due to its generic availability and positive results of DECLARE-TIMI 58 kidney and hospitalization analyses.

RSSDI-ESI Clinical Practice Recommendations for Diabetes and Heart Failure It suggests prescribing dapagliflozin as the preferred SGLT2i in type 2 diabetes patients with heart failure and/or CKD. The guideline points out the relevance of DECLARE-TIMI 58 population (primary prevention) for Indian patients.

Position Statements of Cardiological Society of India (CSI) CSI supports using the drug in quadruple therapy in HFrEF patients at an early stage. It underlines that dapagliflozin is safe for use in the elderly and patients with CKD (Cahn et al.; kidney analyses).

Asian Heart Failure Guidelines The regional guidelines for Asia repeat worldwide guidance; however, they focus on the higher rate of diabetes among the Asian population and the early development of HFrEF.

Table: Detailed Comparative Analysis of Guidelines.

Parameter	ACC/AHA/HFSA 2022	ESC 2023 Focused Update	HFAI / Indian Guidelines (2023–2025)
Recommendation Class for HFrEF	Class I, Level of Evidence (LOE) A	Class I, LOE A	Class I
Independence from Diabetes Status	Explicitly stated	Explicitly stated	Explicitly stated
Position in Four-Pillar Therapy	Strong emphasis as a foundational therapy	Strong emphasis with rapid sequencing	Strong emphasis with practical and resource-aware implementation
HFmrEF Recommendation	Class IIa	Class I	Class I
HFpEF Recommendation	Class IIa	Class I	Class I
Initiation Timing	As soon as possible after diagnosis	Early initiation, including during hospitalization when clinically stable	Early initiation in both outpatient and rural healthcare settings
Economic Consideration	Considered intermediate value	Not formally rated	High value due to availability of generic formulations
Special Population Considerations	Broad subgroup recommendations	Broad recommendations with additional CKD focus	Particular emphasis on younger patients and populations with high CKD burden

DOSING AND MONITORING PROTOCOLS

- 10 mg once daily.
- Renal function check at 2–4 weeks (mild eGFR dip expected and beneficial).
- genital hygiene counseling (or use counselling consistently) mandatory.

INTEGRATION WITH OTHER GDMT

- Can be started simultaneously with beta-blockers and ARNi.
- Excellent compatibility with MRAs (background therapy analysis).[6]

SPECIAL POPULATION GUIDANCE (INDIA-SPECIFIC)

- Elderly: Safe per Cahn et al.[17]
- Low BP: Safe per Furtado et al.[7]
- Advanced CKD: Beneficial down to eGFR 25–30 (multiple kidney papers).

ECONOMIC AND ACCESS CONSIDERATIONS IN INDIA

Generic dapagliflozin has made therapy highly cost-effective. Models show excellent incremental costeffectiveness ratios, especially in preventing hospitalizations and dialysis. National programs and insurance schemes are increasingly covering SGLT2i.

CHALLENGES AND SOLUTIONS

Challenges include physician inertia, patient awareness, cost in rural areas, and fear of side effects. Solutions involve continuing medical education programs using DECLARE data, patient support groups, and simplified algorithms.

FUTURE DIRECTIONS FOR GUIDELINES

Future updates will take into account long-term outcomes, combination therapies, early use in HF and advice on Asian/Indian patients.

CONCLUSION

Currently existing guidelines from ACC/AHA/HFSA, ESC and Indian medical organizations all agree to classify dapagliflozin as Class 1 basic treatment in HFrEF. The DECLARE-TIMI 58 trial was very important in providing such evidence for the new standard of care. Indian doctors have strong grounds for treating their patients with dapagliflozin early to decrease the burden of heart failure and cardiorenal diseases in the country.

CONFLICT OF INTEREST

There was no funding or conflict of interest related to this work.

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