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Sodium-Glucose Cotransporter 2 Inhibition in Heart Failure with Preserved Ejection Fraction: From Mechanism to Ward Round

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors entered cardiology as a secondary observation in trials designed to test glucose lowering, and have since become the first drug class to show a consistent benefit in heart failure with preserved ejection fraction (HFpEF), a population for which decades of neurohormonal-antagonist trials had produced little. This review assembles the trial programme from the original type 2 diabetes cardiovascular outcome trials through EMPEROR-Preserved and DELIVER to the pooled five-trial meta-analysis, and sets out what a clinician should actually expect at the ward round. Across the full ejection-fraction spectrum, SGLT2 inhibitors reduce the composite of cardiovascular death and heart failure hospitalization (pooled hazard ratio 0.77, 95% confidence interval 0.72-0.90); however, that benefit is overwhelmingly a hospitalization story rather than a mortality story, and it measurably narrows toward the highest ejection fractions, precisely the range in which true HFpEF is hardest to distinguish from its mimics. The mechanism remains unsettled. We argue that this qualification, not the headline hazard ratio, is what should be communicated to patients.

Keywords: *Heart failure with preserved ejection fraction; SGLT2 inhibitors; Empagliflozin; Dapagliflozin; Ejection fraction*

Introduction

Heart failure with preserved ejection fraction now accounts for roughly half of all heart failure presentations, and its share of new diagnoses has risen steadily as the population ages and cardiometabolic risk factors accumulate [1,2,4]. Heart failure overall affects an estimated tens of millions of people worldwide and remains a leading cause of hospital admission in adults over 65 [5]. Unlike heart failure with reduced ejection fraction, for which four drug classes now have an established mortality benefit, HFpEF has a long history of neutral or marginal trials: renin-angiotensin-system antagonists, beta-blockers and mineralocorticoid-receptor antagonists have each been tested in this population without producing the clear survival benefit seen in reduced ejection fraction [6,7]. Part of the difficulty is diagnostic. HFpEF is not one disease but a syndrome that overlaps substantially with obesity-related dyspnoea, atrial fibrillation, chronic pulmonary disease and simple deconditioning, and the phenotyping literature has increasingly emphasised that patients labelled HFpEF are heterogeneous both in pathophysiology and in how confidently the diagnosis can be made [6,7,8,9].

Figure 1 sets out the trial programme that produced this shift in as few as seven years. Sodium-glucose cotransporter 2 (SGLT2) inhibitors were developed as glucose-lowering agents for type 2 diabetes. Their cardiovascular story began

almost by accident: the mandatory cardiovascular outcome trials required by regulators after 2008 (EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58) were designed to demonstrate cardiovascular safety, not benefit, yet each showed an unexpected reduction in heart failure hospitalization that was disproportionate to any plausible glycaemic mechanism [10,11,12]. That observation prompted dedicated heart failure trials, first in reduced ejection fraction (DAPA-HF, EMPEROR-Reduced) [13,14], then in the acute, worsening-heart-failure setting (SOLOIST-WHF) [16], and finally in heart failure with preserved and mildly reduced ejection fraction (EMPEROR-Preserved, DELIVER) [17,20]. EMPEROR-Preserved was the first adequately powered trial of any drug to show an unambiguous benefit in HFpEF, and DELIVER confirmed it in a complementary population; a pooled analysis of five trials has since argued that the benefit spans the entire ejection-fraction spectrum [23].

That is now the headline taught to trainees: SGLT2 inhibitors work in heart failure regardless of ejection fraction, and every major society guideline has endorsed them accordingly [1,2,3]. This review assembles that evidence from its origin in diabetes trials through to the current guideline position, and then sets out the qualification that the headline tends to omit. The benefit in HFpEF is real, but it is overwhelmingly a hospitalization story rather than a mortality story, and it narrows measurably toward the highest ejection fractions — precisely the range in which the diagnosis is hardest to make with confidence [8,9,18]. We think that qualification, not the pooled hazard ratio alone, is what should reach the patient in front of a clinician.

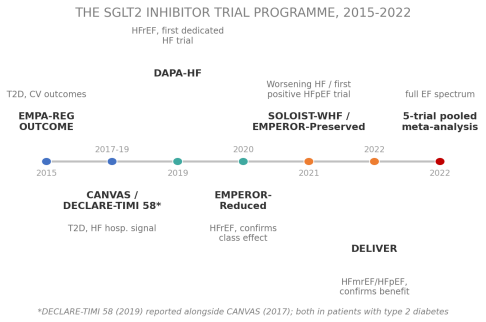

Figure 1: The SGLT2 inhibitor trial programme in heart failure, 2015-2022. What began as a secondary observation in type 2 diabetes trials [10-12] became a dedicated heart-failure-across-the-spectrum programme within seven years.

Material and Methods

This is a narrative review, not a systematic review or a new meta-analysis. The literature was assembled by searching PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials for randomised trials and their pre-specified subgroup or secondary analyses, combining an SGLT2 inhibitor search term with heart failure and ejection fraction terms, supplemented by the reference lists of current major-society guidelines [1,2,3] and each trial's registry entry. Priority went to pivotal phase 3 reports, their pre-specified analyses, published individual-participant or trial-level meta-analyses, and current guideline documents; conference abstracts and preprints were excluded unless no peer-reviewed report existed.

Every hazard ratio, confidence interval and event rate reproduced here is taken directly from the cited primary report or meta-analysis; none was recalculated or estimated by the present authors, and a subgroup comparison lacking a formal interaction test is identified as such rather than implied to be definitive. No new statistical pooling was performed for this article: where trial results sit alongside one another (Table 1, Figure 2), the juxtaposition is descriptive, not an independent indirect comparison.

Results

The trial programme, from an incidental signal to a dedicated indication

Table 1 and Figure 2 summarise the five randomised trials that established SGLT2 inhibitors as heart failure therapy. In DAPA-HF, 4,744 patients with heart failure and an ejection fraction of 40% or below were randomised to dapagliflozin or placebo; the primary composite of cardiovascular death, heart failure hospitalization or an urgent heart failure visit occurred in 16.3% of the dapagliflozin group versus 21.2% of the placebo group (hazard ratio 0.75, 95% CI 0.65-0.86) [13]. EMPEROR-Reduced, in 3,730 patients with a similarly reduced ejection fraction, found an almost identical effect size for death from cardiovascular causes or first heart failure hospitalization (hazard ratio 0.75, 95% CI 0.65-0.86; event rates 19.4% versus 24.7%) [14]. A pooled analysis of these two trials found a consistent benefit across pre-specified subgroups [15]. SOLOIST-WHF then extended the observation to patients recently hospitalised for worsening heart failure and diabetes, regardless of ejection fraction, using the dual SGLT1/2 inhibitor sotagliflozin (hazard ratio 0.67, 95% CI 0.52-0.85); the trial was stopped before its planned sample size was reached after its sponsor withdrew funding, so this estimate is less precise than the others in Figure 2 despite the narrow-looking confidence interval [16].

Two further trials then answered the question this review is really about. EMPEROR-Preserved randomised 5,988 patients

with heart failure and an ejection fraction above 40% to empagliflozin or placebo. The primary composite of cardiovascular death or hospitalization for heart failure was reduced (hazard ratio 0.79, 95% CI 0.69-0.90, p<0.001), driven by a clear reduction in heart failure hospitalization (hazard ratio 0.73, 95% CI 0.61-0.88) alongside a 9% reduction in cardiovascular death that did not reach statistical significance on its own [17]. That composite result partitions in a specific way: roughly three-quarters of the primary-endpoint events prevented in EMPEROR-Preserved were hospitalizations or urgent visits rather than deaths. DELIVER, in 6,263 patients with an ejection fraction above 40% — a broader population than EMPEROR-Preserved that included patients recently hospitalised for heart failure and a substantial minority whose ejection fraction had previously been reduced and had since recovered — found a closely concordant result (hazard ratio 0.82, 95% CI 0.73-0.92; event rates 16.4% versus 19.5%) [20], with the benefit preserved across age groups including the very elderly [21] and unaffected by a common comorbidity that itself mimics the HFpEF syndrome, chronic obstructive pulmonary disease [22]. Health status, measured by the Kansas City Cardiomyopathy Questionnaire, improved early and to a clinically meaningful degree in EMPEROR-Preserved [19,30].

Trial	Drug	Population (LVEF)	N	Primary endpoint HR (95% CI)
DAPA-HF	Dapagliflozin	≤40%	4,744	0.75 (0.65-0.86)
EMPEROR-Reduced	Empagliflozin	≤40%	3,730	0.75 (0.65-0.86)
SOLOIST-WHF	Sotagliflozin	any, worsening HF	1,222	0.67 (0.52-0.85)
EMPEROR-Preserved	Empagliflozin	>40%	5,988	0.79 (0.69-0.90)
DELIVER	Dapagliflozin	>40%	6,263	0.82 (0.73-0.92)

Table 1: The five pivotal SGLT2 inhibitor heart failure trials. Primary endpoint in every trial was a composite of cardiovascular death and a heart failure event (hospitalization, or in DAPA-HF and EMPEROR-Preserved also an urgent visit) [13,14,16,17,20].

Benefit across the ejection-fraction spectrum, and where it narrows

A pre-specified analysis of EMPEROR-Preserved compared patients with heart failure with mildly reduced ejection fraction (41-49%) against those with an ejection fraction of 50% or above. The hazard ratio for the primary endpoint was 0.71 (95% CI 0.57-0.88) in the mildly-reduced group and 0.83 (95% CI 0.71-0.98) in the 50%-or-above group; the formal interaction test across these categories was not statistically significant (p=0.27), but the point estimate was numerically smaller at higher ejection fraction, and the same analysis reported an attenuated response at an ejection fraction of 60% or above for recurrent hospitalizations, citing a pooled treatment-by-ejection-fraction interaction across EMPEROR-Preserved and DELIVER (p=0.008) that favoured lower ejection fractions within the preserved range [18]. DELIVER's own age-independent efficacy analysis reported the same pattern from the other direction: the hazard ratio was 0.77 (numerically better) among patients with an ejection fraction of 60% or above and 0.83 among those below it [20]. Figure 3 sets these estimates side by side. None of these differences reaches formal statistical significance within its own trial, and the pooled interaction term is derived from combining two trials' subgroup data rather than from a single adequately powered test — so this pattern should be read as a consistent signal across independent analyses rather than as a settled effect-modification finding. It nonetheless argues against the flattest possible reading of the class's HFpEF story, which is that benefit is uniform across the entire preserved range.

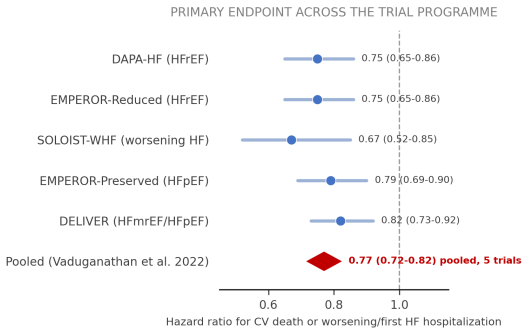

Figure 2: Primary composite endpoint hazard ratio in each of the five pivotal trials, with the pooled five-trial estimate [13,14,16,17,20,23].

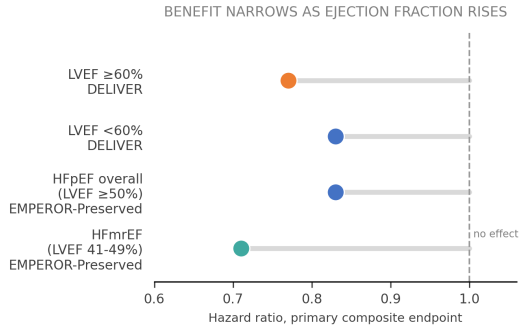

Figure 3: The primary-endpoint hazard ratio by ejection-fraction category, drawn from the EMPEROR-Preserved mildly-reduced-versus-preserved comparison and the DELIVER ≥60% versus <60% comparison. Benefit narrows, though not significantly within either trial on its own, as ejection fraction rises [18,20].

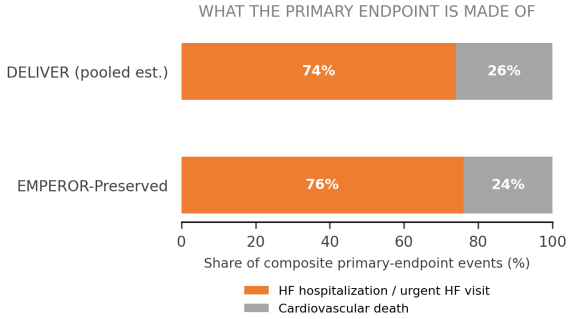

Figure 4: What the primary composite endpoint is made of in EMPEROR-Preserved and DELIVER: most of the events prevented are heart failure hospitalizations or urgent visits, not cardiovascular deaths [17,20].

The pooled picture, and the honest limits of the mortality claim

A trial-level meta-analysis pooling DELIVER, EMPEROR-Preserved, DAPA-HF, EMPEROR-Reduced and SOLOIST-WHF reported a pooled hazard ratio of 0.77 (95% CI 0.72-0.82) for cardiovascular death or first heart failure hospitalization across the full ejection-fraction spectrum, with no significant heterogeneity across thirteen pre-specified subgroups including one defined by ejection fraction [23]. That headline is accurate, and it is the basis for the class-wide guideline recommendation discussed below. It is worth being precise, though, about the pooled effect on cardiovascular death considered on its own: the same meta-analysis reported a pooled hazard ratio of 0.87 (95% CI 0.79-0.95) for cardiovascular death alone [23], a materially smaller and less certain effect than the composite headline, and one that reached statistical significance only once the trials were pooled — not, for the preserved and mildly-reduced ejection-fraction trials individually, on cardiovascular death by itself. Observational and mechanistic work in DAPA-HF is consistent with a genuine decongestive effect rather than a chance finding: patients assigned dapagliflozin were more likely to have loop-diuretic doses reduced, and less likely to need them increased, than patients assigned placebo [24].

Mechanism: several credible candidates, none yet settled

Why SGLT2 inhibition should reduce heart failure events, in a population whose median patient does not have diabetes, remains open. Osmotic diuresis and natriuresis contract plasma volume and lower filling pressures, the most direct route to fewer hospitalizations and the one best supported by early haemodynamic and diuretic-sparing data [24,25]. A more speculative hypothesis holds that SGLT2 inhibition shifts cardiac substrate use toward ketone bodies, a state its proponents call pharmacological fasting mimicry [26]. Reduced epicardial fat and inflammation, and direct myocardial ion-exchange effects, have also been proposed, with less direct human evidence than for the natriuretic and metabolic hypotheses [25]. Figure 5 sets these out deliberately as candidates: no trial here was designed to adjudicate between them, and the benefit is better established than its explanation.

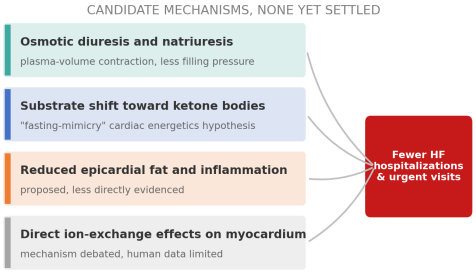

Figure 5: Candidate mechanisms proposed to explain the clinical benefit of SGLT2 inhibition in heart failure. None has been established as causal in human HFpEF specifically [25,26].

Safety, and guideline uptake

An individual-participant-level meta-analysis pooling four large empagliflozin trials found that serious genital infection was not increased with empagliflozin relative to placebo (0.04 versus 0.07 events per 100 patient-years; rate ratio 0.62, 95% CI 0.28-1.37), while ketoacidosis was slightly more frequent (0.07 versus 0.03 events per 100 patient-years; rate ratio 2.13, 95% CI 0.87-5.24), with 14 of the 15 empagliflozin-arm cases occurring in patients with known type 2 diabetes. Serious volume depletion was slightly more frequent with empagliflozin (0.94 versus 0.88 events per 100 patient-years; rate ratio 1.08, 95% CI 0.88-1.31), particularly among patients aged 85 years or above, and lower-limb amputation was not increased (rate ratio 1.01, 95% CI 0.76-1.35) [29]. Figure 6 sets these four events side by side. The efficacy and safety base has also extended into chronic kidney disease, a comorbidity common in HFpEF, where empagliflozin reduced the composite of kidney disease progression or cardiovascular death independent of diabetes status [27].

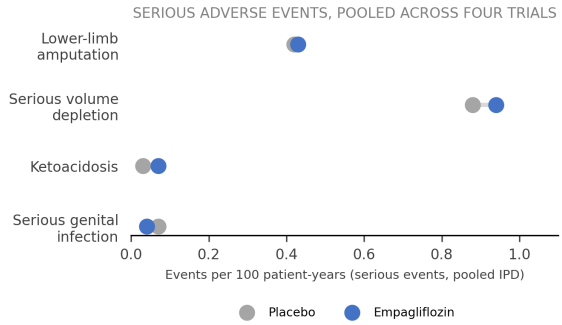

Figure 6: Serious adverse events with empagliflozin versus placebo, pooled across four large trials by individual-participant-level meta-analysis [29].

Every major society guideline now reflects this evidence. The 2021 European Society of Cardiology heart failure guideline recommended SGLT2 inhibitors for reduced ejection fraction and flagged the HFpEF trials as pending [1]; the 2023 focused update, published after EMPEROR-Preserved and DELIVER had reported, extended a recommendation for dapagliflozin or empagliflozin across the full ejection-fraction range [2], a position matched by the American guideline for the management of heart failure [3]. Because the cardiorenal benefit of this drug class appears independent of glycaemic status, current diabetes consensus guidance also recommends an SGLT2 inhibitor for patients with type 2 diabetes and heart failure regardless of the specific glucose-lowering rationale [28]. Table 2 lines up these four documents by ejection-fraction category and shows how quickly the guideline position moved once EMPEROR-Preserved and DELIVER had reported.

Guideline	Year	Reduced / mildly reduced EF	HFpEF
ESC heart failure guideline	2021	Recommended	Trials pending
ESC focused update	2023	Recommended	Recommended
ACC/AHA/HFSA guideline	2022	Recommended	Recommended
ADA/EASD diabetes consensus	2022	Recommended for HF, any EF	Recommended for HF, any EF

Table 2: Guideline recommendations for SGLT2 inhibitors in heart failure, by ejection-fraction category, at the time each document was published [1,2,3,28].

Discussion

The trajectory summarised above is genuinely unusual in heart failure pharmacology. Every other drug class with a mortality benefit in reduced ejection fraction — renin-angiotensin-system antagonists, beta-blockers, mineralocorticoid-receptor antagonists — has failed to show the same benefit above an ejection fraction of roughly 40-50% [6,7]. SGLT2 inhibitors are the first class for which the same drug, at the same dose, appears to help across that traditional divide [17,20,23]. That is a real advance for a population that has had very little to offer beyond diuretics and management of comorbidity, and it is the reason every guideline now recommends the class regardless of ejection fraction [1,2,3].

But the version of that story usually told at the ward round — "SGLT2 inhibitors work in heart failure, full stop" — elides two qualifications that matter for how a clinician should set expectations. First, the benefit is overwhelmingly one of fewer hospitalizations and urgent visits, not fewer deaths: the pooled hazard ratio for cardiovascular death alone, 0.87, is smaller and reached significance only once five trials were combined, and within EMPEROR-Preserved cardiovascular death was not significantly reduced at all [17,23]. A patient who asks whether this drug will help them live longer deserves an honest answer that the strongest evidence is for staying out of hospital and feeling better day to day [19,30], not for survival specifically. Second, the benefit measurably narrows toward the highest ejection fractions [18,20] — precisely the range in which HFpEF is hardest to diagnose with confidence and most easily confused with obesity-related dyspnoea, atrial fibrillation, or non-cardiac causes of breathlessness [6,7,8,9]. That pattern raises, without settling, the possibility that some of the apparent class benefit in the broadest HFpEF trials reflects enrichment with patients closer to HFmrEF physiology rather than a perfectly uniform drug effect across the whole preserved range.

Neither qualification is a reason to withhold the drug. The risk-benefit balance remains favourable even at the highest ejection fractions, the safety profile pooled across four large trials is reassuring for routine use with modest, largely predictable and manageable signals for ketoacidosis in patients with diabetes and for volume depletion in the very elderly [29], and the practical recommendation — offer an SGLT2 inhibitor to essentially all patients with symptomatic heart failure regardless of ejection fraction — is unchanged by either point [1,2,3]. What changes is what the patient in front of the clinician should be told to expect, and how much weight should be placed on ejection fraction and diagnostic confidence, rather than on the drug's mechanism of action, when counselling at the highest end of the preserved range. The mechanism question is not academic in this respect: if the dominant effect really is haemodynamic decongestion [24,25] rather than a ketone-driven change in cardiac energetics [26],

that would itself help explain why benefit tracks more closely with hospitalization than with mortality, and why it narrows as filling pressures and volume status become less abnormal toward the upper end of the ejection-fraction range. Resolving which mechanism actually operates, and in which patients, is the most useful open question this trial programme has left behind.

The pooled trial programme also allows a check of whether the moderate, hospitalization-weighted benefit described above holds across the patient groups clinicians see most often at the ward round. In DELIVER, the primary composite outcome favoured dapagliflozin similarly across four pre-specified age bands spanning under 55 years to 75 years and older, with no significant age interaction (P for interaction=0.95 by category, 0.76 modelled continuously), and safety was likewise consistent by age despite adverse events occurring more often, as expected, in the oldest patients [21]. Chronic obstructive pulmonary disease, present in 694 of the 6,261 participants with baseline data recorded (11.1%), similarly failed to modify the treatment effect: the hazard ratio for the primary outcome was 0.82 in patients without COPD and 0.82 in patients with COPD, with an interaction p-value of 0.98 [22]. Findings of this kind do not enlarge the headline effect size, but they matter clinically: they suggest the qualifications above — a benefit weighted toward hospitalization rather than death, and one that narrows at the very highest ejection fractions — are not further concentrated within some more fragile subgroup that a clinician might otherwise be tempted to exclude from treatment on grounds of age or respiratory comorbidity.

Study limitations

This is a narrative synthesis, not a systematic review, and although the search was broad it followed no pre-registered protocol, so some selection judgement was unavoidable. The trials differ in population, drug (sotagliflozin also inhibits SGLT1, unlike the selective agents), background-therapy era and follow-up, so Table 1 and Figure 2 should be read qualitatively rather than as a formal indirect comparison. The ejection-fraction gradient we have emphasised comes from subgroup and pooled analyses that were not the primary, powered hypothesis of any single trial, and its pooled interaction term combines two trials' subgroup data rather than one adequately powered test; it is hypothesis-generating, not definitive. SOLOIST-WHF stopped early, widening uncertainty around its estimate. The pooled safety data are specific to empagliflozin across four trials [29]; dapagliflozin was not separately re-analysed here, though the two agents' individual trial safety profiles have been broadly concordant. Every statistic is reproduced from its cited source, with no independent patient-level reanalysis.

Conclusion

SGLT2 inhibitors are now guideline-endorsed, evidence-based therapy for heart failure across the full ejection-fraction spectrum, including heart failure with preserved ejection fraction, a genuine and hard-won addition for a population that had little effective pharmacotherapy before it [1,2,3,17,20,23]. The honest version of that achievement is that the benefit is real but modest, driven chiefly by fewer hospitalizations rather than fewer deaths, and measurably smaller at the very highest ejection fractions where the diagnosis itself is least certain. Clinicians should keep offering the drug broadly, while calibrating what patients are told to expect by ejection fraction and diagnostic confidence rather than by the class's mechanism of action, which remains, at the time of writing, unsettled.

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