CODEN: WJAPAC Impact Factor: 5.48 ISSN: 3049-3013

World Journal of Advance Pharmaceutical Sciences

Volume 3, Issue 6, Page: 183-192 Review Article www.wjaps.com

SGLT2 INHIBITORS AND GLP-1 AGONISTS IN HEART FAILURE: SHARED AND DISTINCT MECHANISMS

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How to cite this Article: [1]Saad Suleman, [2]Mario Gergis Azez Awed Awadala, [3]Rashedul Hoq, [4]Bibi Iram Hadi, [5]Ufaq Hamid, [6]Alabi Damilola, [7]Muhammad Khaliq, [8]Arshad Ali Zia, [9]Mahmuda Kabir Humu, [10]Dr. Nitesh Mandal, [11]Nafiz Tareq Hasnain, [12]Husnain Ramzan. (2026). SGLT2 INHIBITORS AND GLP-1 AGONISTS IN HEART FAILURE: SHARED AND DISTINCT MECHANISMS. World Journal of Advance Pharmaceutical Sciences, 3(6), 183-192.

Article Info

Article Received: 29 April 2026,

Article Revised: 19 May 2026,

Article Accepted: 09 June 2026.

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DOI: https://doi.org/10.5281/zenodo.20691868

ABSTRACT

Background: Heart failure (HF) remains one of the leading causes of morbidity and mortality worldwide, with an estimated 64 million individuals affected globally. Despite established pharmacotherapy, residual cardiovascular risk and hospitalizations remain unacceptably high. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as transformative therapies with robust evidence from major cardiovascular outcomes trials. **Objective:** To critically appraise and synthesize published evidence regarding the shared and distinct mechanistic pathways through which SGLT2 inhibitors and GLP-1 receptor agonists exert cardiovascular benefit in heart failure, spanning both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). **Methods:** A systematic literature search was conducted across PubMed/MEDLINE, Embase, and the Cochrane Library (2015–2025). Landmark randomized controlled trials (RCTs), mechanistic studies, and major international cardiology guidelines were reviewed and synthesized using the SANRA framework for narrative reviews. **Key Findings:** SGLT2 inhibitors consistently reduce cardiovascular death and HF hospitalization across HFrEF and HFpEF phenotypes. GLP-1 RAs demonstrate significant benefit predominantly in obese HFpEF patients with metabolic comorbidities. While both drug classes share anti-inflammatory, antifibrotic, and metabolic modulatory properties, they differ fundamentally in direct cardiac receptor activity, neurohormonal effects, and influence on myocardial energetics. SGLT2 inhibitors exert unique benefits through osmotic diuresis, NHE1 inhibition, and mitochondrial protection, whereas GLP-1 RAs act via direct GLP-1 receptor agonism with cardioprotective, anorexigenic, and systemic metabolic effects. **Conclusion:** SGLT2 inhibitors and GLP-1 RAs represent complementary rather than competing therapeutic strategies in heart failure. Their distinct mechanistic profiles, coupled with emerging evidence supporting combination therapy, offer an unprecedented opportunity to target multiple HF pathophysiological pathways simultaneously.

KEYWORDS: SGLT2 inhibitors, GLP-1 receptor agonists, heart failure, HFrEF, HFpEF, cardiovascular outcomes, cardiac mechanisms, dapagliflozin, empagliflozin, semaglutide.

1. INTRODUCTION

Heart failure is a complex clinical syndrome representing the final common pathway of numerous cardiac and systemic conditions, characterized by structural or functional myocardial abnormalities that impair ventricular filling or ejection. Globally, heart failure affects approximately 64 million individuals, with a lifetime risk estimated at one in five among adults aged 40 years and older.[4,5] The condition is associated with substantial morbidity, recurrent hospitalization, and a 5-year mortality rate comparable to many malignancies, underscoring the urgent need for novel and effective therapeutic strategies.[6]

For decades, the pharmacological cornerstone of heart failure management with reduced ejection fraction (HFrEF) has rested on neurohormonal blockade—angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs).[2,3] The landmark PARADIGM-HF trial further advanced the field with sacubitril/valsartan, demonstrating superiority over enalapril in reducing cardiovascular death and HF hospitalization.[36] Despite these advances, residual cardiovascular risk remains high, and effective pharmacotherapy for HFpEF—which now accounts for more than 50% of all HF cases—has historically been elusive.[25]

The emergence of SGLT2 inhibitors as a therapeutic class for heart failure represents a paradigm shift. Originally developed as glucose-lowering agents for type 2 diabetes mellitus (T2DM), SGLT2 inhibitors were serendipitously found to reduce cardiovascular mortality and HF hospitalization in the EMPA-REG OUTCOME trial.[18] Subsequent dedicated heart failure trials—DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER—confirmed robust, consistent benefits across the entire ejection fraction spectrum, leading to guideline-level class I recommendations from both AHA/ACC and ESC.[8,9,10,11]

GLP-1 receptor agonists (GLP-1 RAs) represent another transformative drug class, initially deployed for glycemic control and weight management in T2DM.[13] Cardiovascular outcomes trials including LEADER (liraglutide), SUSTAIN-6 (semaglutide), and PIONEER 6 (oral semaglutide) demonstrated significant reductions in major adverse cardiovascular events (MACE), establishing a cardiovascular mortality benefit particularly through atherosclerotic mechanisms.[13,14,50] The landmark STEP-HFpEF trial with subcutaneous semaglutide subsequently demonstrated that GLP-1 RAs may substantially improve symptoms, exercise capacity, and quality of life specifically in obese patients with HFpEF, positioning this class as a potential adjunctive therapy in this challenging phenotype.[12]

Despite the extensive body of clinical evidence supporting both drug classes, a comprehensive understanding of their mechanistic underpinnings in the context of heart failure—particularly their shared and divergent pathways—remains incompletely delineated.[17] Such mechanistic clarity is critically important for several reasons: it facilitates rational drug selection based on HF phenotype and comorbidity profile; it informs the biological rationale for combination therapy; and it guides the design of future clinical trials targeting specific mechanistic nodes.[45]

Both SGLT2 inhibitors and GLP-1 RAs modulate inflammation, metabolic substrate utilization, and neurohumoral activation, yet they do so through fundamentally different receptor systems and signaling cascades.[16,19] SGLT2 inhibitors exert their primary cardiac effects through glucose-independent mechanisms including osmotic diuresis, NHE1 inhibition, mitochondrial protection, and erythropoiesis stimulation.[28,44] In contrast, GLP-1 RAs signal through GLP-1 receptors expressed in the heart, pancreas, kidney, and gut, with pleiotropic anti-inflammatory, vasoprotective, and anorexigenic effects.[20,21]

This narrative review aims to systematically synthesize the mechanistic evidence underlying the cardiovascular benefits of SGLT2 inhibitors and GLP-1 RAs in heart failure, explicitly delineating mechanisms that are shared between the two classes from those that are class-specific.[7] In doing so, we address an important knowledge gap and provide a mechanistic framework to guide clinicians, researchers, and policymakers in optimizing the use of these agents across HF phenotypes.[34] We further discuss clinical trial evidence supporting differential efficacy across HFrEF and HFpEF, safety considerations, and emerging evidence for combination therapy.[48]

2. METHODOLOGY

2.1 Study Design

This study was conducted as a narrative review following the Scale for the Assessment of Narrative Review Articles (SANRA) framework, which provides methodological guidance for evaluating the scientific rigor of narrative reviews. No prospective registration was required given the narrative design; however, predefined search strategies, inclusion/exclusion criteria, and synthesis methodology were established prior to data extraction.

2.2 Literature Search Strategy

A comprehensive literature search was conducted from January 2015 to March 2025 across the following electronic databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). Additional searches were conducted on ClinicalTrials.gov for ongoing and completed phase III trials, and supplementary manual reference searching was performed on major cardiology guidelines from the American Heart Association (AHA), American College

of Cardiology (ACC), and European Society of Cardiology (ESC).

The following Medical Subject Headings (MeSH) terms and free-text keywords were utilized: 'SGLT2 inhibitors', 'sodium-glucose cotransporter-2 inhibitors', 'dapagliflozin', 'empagliflozin', 'canagliflozin', 'GLP-1 receptor agonists', 'glucagon-like peptide-1', 'semaglutide', 'liraglutide', 'heart failure', 'HFrEF', 'HFpEF', 'heart failure with preserved ejection fraction', 'cardiovascular outcomes', 'cardiac remodeling', 'natriuretic peptides', 'left ventricular function', 'myocardial fibrosis', and 'cardiometabolic'.

Table 1: Literature Search Strategy by Database.

Database	Keywords Used	Date Range	Articles Screened
PubMed/MEDLINE	SGLT2 inhibitors, GLP-1 agonists, heart failure, HFrEF, HFpEF, cardiovascular outcomes	2015–2025	412
Embase	Dapagliflozin, empagliflozin, canagliflozin, semaglutide, liraglutide, cardiac remodeling	2015–2025	287
Cochrane Library	Heart failure mortality, hospitalization, LVEF, natriuretic peptides, RCT	2018–2025	94
ClinicalTrials.gov	Phase III trials SGLT2, GLP-1, HFpEF, HFrEF	2018–2025	61
Manual reference search	Review articles, AHA/ESC guidelines 2021–2024	2020–2025	38

2.3 Inclusion and Exclusion Criteria

Articles were screened by title and abstract, followed by full-text review of eligible studies. Studies were included or excluded based on predefined criteria detailed in Table 2.

Table 2: Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
RCTs and prospective cohort studies	Case reports and case series
Adult patients (≥18 years) with heart failure	Pediatric studies
SGLT2 inhibitor or GLP-1 agonist as intervention	Studies without heart failure endpoint
Studies published 2015–2025 in English	Non-English publications without translation
HFrEF, HFmrEF, or HFpEF populations	Animal/in vitro only studies
Studies reporting cardiovascular outcomes or mechanistic data	Conference abstracts without full-text data

2.4 Data Synthesis

Data were synthesized narratively, with emphasis on mechanistic, clinical trial, and guideline-based evidence. Findings were organized thematically under seven discussion subheadings. Quantitative synthesis (meta-analysis) was not performed given the heterogeneity of study designs and endpoints included. A total of 492 articles were screened after deduplication; 89 full-text articles met final inclusion criteria and informed this review.

3. DISCUSSION

Table 3: Landmark Clinical Trials of SGLT2 Inhibitors and GLP-1 Agonists in Heart Failure.

Trial	Drug / Class	Population	Primary Endpoint	Key Result	Reference
EMPEROR-Reduced	Empagliflozin	HFrEF	CV death / HF hospitalization	25% RRR (HR 0.75)	Packer et al., NEJM 2020
DAPA-HF	Dapagliflozin	HFrEF	CV death / worsening HF	26% RRR (HR 0.74)	McMurray et al., NEJM 2019
EMPEROR-Preserved	Empagliflozin	HFpEF	CV death / HF hospitalization	21% RRR (HR 0.79)	Anker et al., NEJM 2021
DELIVER	Dapagliflozin	HFpEF	CV death / worsening HF	18% RRR (HR 0.82)	Solomon et al., NEJM 2022
STEP-HFpEF	Semaglutide	HFpEF + obesity	KCCQ + body weight	Significant improvement	Kosiborod et al., NEJM 2023
LEADER	Liraglutide	T2DM + high CV risk	MACE	13% RRR (HR 0.87)	Marso et al., NEJM 2016

3.1 Overview of Clinical Efficacy: SGLT2 Inhibitors in Heart Failure

The clinical evidence supporting SGLT2 inhibitors in heart failure is among the most compelling and consistent in cardiovascular medicine. The DAPA-HF trial demonstrated that dapagliflozin reduced the composite of cardiovascular death, worsening heart failure, or urgent HF visit by 26% (HR 0.74; 95% CI 0.65–0.85; $p<0.001$) in patients with HFrEF (LVEF ≤40%), independently of diabetes status.[8] This landmark finding was replicated and extended in the EMPEROR-Reduced trial, where empagliflozin reduced the primary composite endpoint of CV death or HF hospitalization by 25% (HR 0.75; 95% CI 0.65–0.86; $p<0.001$), with particularly notable reductions in HF hospitalization.[9]

The benefit of SGLT2 inhibitors was subsequently extended to the HFpEF population. The EMPEROR-Preserved trial demonstrated that empagliflozin reduced the primary composite of CV death and HF hospitalization by 21% (HR 0.79; 95% CI 0.69–0.90; $p<0.001$) in patients with LVEF >40%, irrespective of diabetes status.[10] The DELIVER trial, which enrolled patients with LVEF >40%, confirmed dapagliflozin's efficacy in HFpEF and heart failure with mildly reduced ejection fraction (HFmrEF), with an 18% relative risk reduction (HR 0.82; 95% CI 0.73–0.92; $p<0.001$).[11]

A comprehensive meta-analysis pooling data from five major SGLT2 inhibitor trials in HF confirmed that these agents significantly reduce HF hospitalization, CV death, and all-cause death across the ejection fraction spectrum.[48] The consistency of this benefit regardless of diabetes status is particularly notable, suggesting that the mechanisms of benefit extend beyond glucose lowering.[23] These findings have been incorporated into the 2022 AHA/ACC/HFSA Heart Failure guidelines with Class I recommendations for SGLT2 inhibitors in both HFrEF and HFpEF.[3]

3.2 GLP-1 Receptor Agonists in Heart Failure: Clinical Evidence

The cardiovascular benefits of GLP-1 RAs in patients with diabetes and established cardiovascular disease are well established through cardiovascular outcomes trials. The LEADER trial demonstrated that liraglutide reduced the composite of MACE by 13% (HR 0.87; 95% CI 0.78–0.97; $p<0.001$ for non-inferiority) in patients with T2DM and high cardiovascular risk.[13] The SUSTAIN-6 trial similarly demonstrated a 26% relative reduction in MACE with once-weekly semaglutide.[14] However, these benefits were primarily attributed to reduction in atherothrombotic events rather than direct HF effects.

A pivotal meta-analysis of cardiovascular outcomes trials evaluating GLP-1 RAs demonstrated a significant 11% reduction in HF hospitalization, though this was less pronounced than the effects observed with SGLT2 inhibitors.[21] Importantly, earlier mechanistic studies demonstrated paradoxically neutral or even potentially harmful effects of liraglutide in established HFrEF; the FIGHT trial found no benefit and numerically higher events in advanced HFrEF patients treated with liraglutide, raising important caution regarding this phenotype.[31] The LIVE trial similarly found no significant effect on LVEF improvement with liraglutide.[30]

The STEP-HFpEF trial marked a watershed moment for GLP-1 RAs in heart failure, enrolling obese HFpEF patients (BMI ≥30 kg/m²) who received subcutaneous semaglutide 2.4 mg weekly.[12] The trial demonstrated clinically meaningful and statistically significant improvements in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS)

and body weight compared to placebo, alongside improvements in six-minute walk distance.[12] These findings established a specific phenotype—obese HFpEF—as an important target population for GLP-1 RA therapy, reflecting the cardiometabolic nature of this HF phenotype.[32]

The clinical evidence therefore suggests an important distinction: whereas SGLT2 inhibitors demonstrate universal benefits across HFrEF and HFpEF regardless of obesity or diabetes, GLP-1 RAs appear to confer their greatest benefit in the cardiometabolic HFpEF phenotype, particularly in the context of obesity.[45] Ongoing trials such as SOUL and FLOW may further clarify the role of GLP-1 RAs in diverse HF populations.[29]

3.3 Shared Mechanisms: Anti-inflammatory and Antifibrotic Pathways

Both SGLT2 inhibitors and GLP-1 RAs share significant anti-inflammatory properties that may contribute to their cardiovascular benefit in heart failure. Chronic low-grade systemic inflammation is a well-recognized pathophysiological driver of HF progression, particularly in HFpEF, where inflammatory biomarkers including IL-6, TNF-α, C-reactive protein, and soluble ST2 are consistently elevated.[25]

SGLT2 inhibitors suppress the NLRP3 inflammasome, a critical mediator of cardiac sterile inflammation, and reduce the production of pro-inflammatory cytokines through NF-κB pathway inhibition.[17] Studies evaluating dapagliflozin demonstrated significant reductions in high-sensitivity CRP, NT-proBNP, and soluble ST2 in HFrEF patients, correlating with improvements in functional status.[27] Empagliflozin has similarly been shown to attenuate myocardial inflammation through reduction of ICAM-1, monocyte chemoattractant protein-1, and oxidative stress markers.[33]

GLP-1 RAs exert anti-inflammatory effects through direct GLP-1 receptor-mediated signaling, suppressing NF-κB activation and reducing circulating levels of TNF-α, IL-6, and CRP.[21] Mechanistic studies in animal models of HF have demonstrated that GLP-1 receptor agonism attenuates macrophage-mediated myocardial inflammation and reduces oxidative stress.[20]

With respect to myocardial fibrosis—a cardinal feature of both HFrEF and HFpEF—both drug classes suppress TGF-β signaling, a central mediator of cardiac fibroblast activation and collagen deposition.[17,19] SGLT2 inhibitors additionally reduce galectin-3, a fibrosis biomarker associated with poor prognosis in HF, and attenuate interstitial fibrosis in preclinical models.[44] GLP-1 RAs reduce cardiac fibrosis markers in both diabetic and non-diabetic cardiomyopathy models, with semaglutide demonstrating significant reductions in myocardial collagen content in the STEP-HFpEF mechanistic substudies.[12,32]

Table 4: Mechanistic Comparison of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Heart Failure.

Mechanism	SGLT2 Inhibitors	GLP-1 Agonists	Shared?
Diuresis / Natriuresis	Osmotic glucosuria, Na excretion	Modest natriuretic effect	Partial
Cardiac energy metabolism	Shifts to ketone/FA oxidation	Reduces FFA oxidation, promotes glucose use	Distinct (opposite)
Anti-inflammatory	NLRP3 inflammasome, NF-κB suppression	Suppresses IL-6, TNF-α, CRP	Yes (shared)
Cardiac fibrosis	↓ TGF-β, galectin-3	↓ TGF-β, myocardial fibrosis markers	Yes (shared)
Mitochondrial function	↑ Mitophagy, biogenesis, ↓ ROS	Limited direct evidence	Partial
Body weight reduction	Modest (~2–3 kg)	Significant (~5–15 kg)	Yes (shared, degree differs)
RAAS modulation	↓ Aldosterone, angiotensin II	Indirect via weight loss	Partial
GLP-1 receptor activation	No direct GLP-1R activity	Direct GLP-1R agonism	No (distinct)
NHE1 inhibition (cardiac)	Yes – reduces Ca2+ overload	Not demonstrated	No (distinct)

3.4 Distinct Mechanisms of SGLT2 Inhibitors: Hemodynamic, Mitochondrial, and Renal Pathways

The mechanistic profile of SGLT2 inhibitors in heart failure is multifaceted, encompassing hemodynamic, metabolic, mitochondrial, and renal components that collectively explain their robust clinical benefits. Perhaps the most immediately recognized effect is osmotic diuresis and natriuresis resulting from inhibition of glucose reabsorption in the proximal tubule.[28] This effect reduces ventricular preload and, through activation of tubuloglomerular feedback, modestly reduces intraglomerular pressure, thereby conferring simultaneous cardiac and nephroprotective benefits.[35]

A particularly novel and important mechanism is the inhibition of the sodium-hydrogen exchanger 1 (NHE1) in cardiomyocytes.[44] NHE1 overactivation in the failing heart leads to cytoplasmic sodium and calcium overload, mitochondrial dysfunction, and cardiomyocyte death. By inhibiting NHE1, SGLT2 inhibitors reduce intracellular Na+/Ca2+ levels, preserving mitochondrial function and reducing reactive oxygen species (ROS) production.[17,44] This direct cardiomyocyte mechanism—independent of glycemic effects—provides a mechanistic explanation for the consistent benefit observed in non-diabetic HF patients.[23,33]

SGLT2 inhibitors shift myocardial substrate utilization away from inefficient glucose oxidation toward ketone body metabolism.[16] The failing heart is metabolically inflexible and exhibits impaired fatty acid oxidation; ketone bodies (beta-hydroxybutyrate) serve as a 'super fuel' with superior energetic efficiency, generating more ATP per oxygen molecule consumed.[19] This 'thrifty substrate hypothesis' proposed by Lopaschuk and Verma provides a compelling explanation for improved cardiac energy metabolism and function with SGLT2 inhibition.[17]

SGLT2 inhibitors also stimulate erythropoiesis, increasing hemoglobin and hematocrit levels, which improves oxygen-carrying capacity and potentially augments myocardial oxygen delivery.[44] Additionally, these agents attenuate maladaptive activation of the renin-angiotensin-aldosterone system (RAAS), reducing sympathetic nervous system activity and improving cardiac remodeling.[28] Taken together, these distinct hemodynamic, metabolic, and cytoprotective mechanisms form a unique mechanistic signature that differentiates SGLT2 inhibitors from all other HF pharmacotherapy.[46]

3.5 Distinct Mechanisms of GLP-1 Receptor Agonists: Central, Vascular, and Weight-Mediated Effects

GLP-1 receptor agonists exert their cardiovascular effects through a fundamentally different set of mechanisms centered on direct GLP-1 receptor activation. GLP-1 receptors are expressed not only in pancreatic beta cells but also in cardiomyocytes, vascular smooth muscle, endothelial cells, and the central nervous system, providing multiple targets for pleiotropic cardiovascular modulation.[20,21]

At the vascular level, GLP-1 RAs improve endothelial function, reduce arterial stiffness, and decrease platelet aggregation, mechanisms that predominantly underlie their anti-atherosclerotic benefits demonstrated in MACE reduction trials.[29] These atheroprotective effects are largely independent of glycemic control and are mediated through cAMP-dependent signaling downstream of GLP-1 receptor activation in endothelial and vascular smooth muscle cells.[50]

One of the most clinically significant and quantitatively important benefits of GLP-1 RAs is profound body weight reduction, averaging 5–15 kg in dedicated obesity trials and 4–6 kg in cardiovascular outcomes trials.[12,41] In the context of HFpEF—where obesity is both a major risk factor and a pathophysiological driver—weight loss reduces epicardial fat burden, decreases hemodynamic loading conditions, and attenuates the adipokine-mediated inflammatory milieu that characterizes cardiometabolic HFpEF.[32] This adipose tissue-targeted mechanism fundamentally distinguishes GLP-1 RAs from SGLT2 inhibitors in the pathophysiological treatment of obese HFpEF.[45]

In the central nervous system, GLP-1 RAs reduce sympathetic nervous system activity through hypothalamic GLP-1 receptor activation, a mechanism that may complement the direct cardiac effects of beta-blockers.[21] Furthermore, GLP-1 RAs demonstrate important anti-apoptotic effects in cardiomyocytes, activating PI3K/Akt and MAPK/ERK survival signaling pathways.[20] These direct cytoprotective effects have been demonstrated in models of ischemia-reperfusion injury, suggesting a potential role in acute myocardial infarction settings.[41]

3.6 Differential Efficacy Across Heart Failure Phenotypes

The clinical evidence clearly establishes that SGLT2 inhibitors and GLP-1 RAs demonstrate differential efficacy across the spectrum of HF phenotypes, a distinction rooted in their mechanistic profiles.[7] SGLT2 inhibitors exhibit consistent efficacy across the full ejection fraction spectrum—HFrEF, HFmrEF, and HFpEF—with benefits observed independently of diabetes, obesity, or renal function.[15,48] The phenotype-agnostic nature of SGLT2 inhibitor efficacy reflects their engagement of hemodynamic and cellular mechanisms universally relevant to HF pathophysiology.[46]

In contrast, GLP-1 RA efficacy in HF appears to be phenotype- and comorbidity-dependent. The neutral findings in HFrEF (FIGHT trial, LIVE trial) stand in contrast to the significant symptomatic and functional benefits observed in obese HFpEF (STEP-HFpEF).[30,31] The mechanistic basis for this divergence relates to the relative pathophysiological roles of inflammation-

fibrosis (dominant in HFrEF) versus cardiometabolic-adipose mechanisms (dominant in obese HFpEF).[25,32] GLP-1 RAs powerfully address the latter, while SGLT2 inhibitors engage both.[45]

Among patients with HFpEF, obesity, and diabetes—a common cluster—both drug classes demonstrate meaningful benefit, suggesting that combination therapy in this phenotype may be particularly rational.[45] The EMPEROR-Preserved and DELIVER trials demonstrated that SGLT2 inhibitor benefit was consistent across obesity categories and BMI strata, though qualitative interaction analyses in high-BMI subgroups are of ongoing interest.[10,24] Similarly, the STEP-HFpEF trial demonstrated that semaglutide benefits were maintained regardless of diabetes status in the obese HFpEF population.[12]

Importantly, in HFrEF, the safety of GLP-1 RAs remains an area of ongoing investigation. Current ESC guidelines do not recommend GLP-1 RAs specifically for HF management in HFrEF, and caution is advised based on the neutral-to-harmful signals observed in dedicated trials.[2,31] Conversely, SGLT2 inhibitors hold Class IA recommendations for HFrEF in both ESC and AHA/ACC guidelines as of 2022–2024 updates.[2,3]

3.7 Safety Profiles, Drug Interactions, and Special Populations

The safety profiles of SGLT2 inhibitors and GLP-1 RAs are well characterized and generally favorable in HF populations, though important differences exist. SGLT2 inhibitors are associated with a small but meaningful increase in risk of urogenital infections, including mycotic infections and, rarely, Fournier's gangrene.[38] Volume depletion and symptomatic hypotension may occur, particularly in combination with diuretics, necessitating careful monitoring in HF patients who are often already on aggressive diuretic regimens.[3]

SGLT2 inhibitors also carry a risk of euglycemic diabetic ketoacidosis (DKA), primarily in type 1 diabetes and type 2 diabetes under insulin therapy, and recommendations advise temporary discontinuation perioperatively.[38] Importantly, SGLT2 inhibitors have consistent renal protective effects, slowing the progression of chronic kidney disease, and are safe and effective in patients with eGFR ≥20 mL/min/1.73 m², extending their applicability to the substantial HF population with comorbid CKD.[26,35]

GLP-1 RAs are associated with gastrointestinal side effects—nausea, vomiting, and diarrhea—which are dose-dependent and typically transient with gradual dose escalation.[50] A historical concern regarding pancreatitis and pancreatic malignancy has not been substantiated in large RCTs or meta-analyses, though vigilance remains warranted.[41] Importantly, GLP-1 RAs are associated with slowing of gastric emptying, which may affect the absorption of co-administered oral medications—a relevant interaction in HF patients on multiple pharmacological regimens.[29]

In special populations—including elderly patients, those with advanced CKD, and patients with low BMI—both drug classes require individualized assessment.[46] The combination of SGLT2 inhibitors with GLP-1 RAs represents a pharmacologically rational and clinically tested approach in cardiometabolic HFpEF, with early mechanistic evidence supporting additive or synergistic effects on weight, inflammation, and hemodynamics.[45] Ongoing trials are prospectively evaluating combination therapy outcomes.[42]

4. Future Directions and Recommendations

Based on the mechanistic and clinical evidence synthesized in this review, several important directions for future research and clinical practice are identified:

- Combination Therapy Trials: Prospective RCTs specifically designed to evaluate SGLT2 inhibitor plus GLP-1 RA combination therapy in obese HFpEF are urgently needed. Mechanistic complementarity—SGLT2 inhibitors addressing hemodynamic and mitochondrial pathways and GLP-1 RAs targeting adipose-mediated inflammation and appetite regulation—provides a strong biological rationale for superiority over monotherapy.
- Phenotype-Specific Trials in HFpEF: Future trials should enroll HFpEF patients stratified by obesity, diabetes, and inflammatory phenotype, enabling precision medicine approaches. Given the heterogeneity of HFpEF, mechanistic substudies embedded within outcome trials are essential for elucidating which mechanistic nodes are most therapeutically relevant in specific subpopulations.
- Biomarker-Guided Therapy: Identification and validation of biomarkers—including NT-proBNP, soluble ST2, galectin-3, high-sensitivity CRP, and ketone body levels—as predictors of SGLT2 inhibitor or GLP-1 RA response would enable personalized therapy selection. Integrating multi-omic profiling may identify molecular endotypes that predict differential responsiveness.
- Mechanistic Studies in Non-Diabetic HFrEF: While clinical trials demonstrate benefit of SGLT2 inhibitors in non-diabetic HFrEF, the precise contribution of NHE1 inhibition versus erythropoiesis versus hemodynamic effects in this population remains uncertain. Well-designed mechanistic trials using cardiac MRI, invasive hemodynamics, and myocardial energetics are warranted.
- Safety of GLP-1 RAs in Advanced HFrEF: The safety and efficacy of newer, more potent GLP-1 RAs (including tirzepatide and retatrutide—dual and triple agonists) in HFrEF require dedicated evaluation. Dual GIP/GLP-1 agonism may offer mechanistic advantages but also novel risks in the structurally remodeled failing heart.

- Real-World Evidence and Implementation Science: Observational studies and registry data are critical to understand the real-world effectiveness and safety of these agents in diverse HF populations not represented in RCTs—including patients with advanced CKD, cardiac device therapy, cardiac cachexia, and frailty.
- Integration into Global HF Guidelines: Current AHA/ACC and ESC guidelines recommend SGLT2 inhibitors in both HFrEF and HFpEF. As evidence for GLP-1 RAs matures—particularly in obese HFpEF—updating guidelines to incorporate phenotype-specific GLP-1 RA recommendations is anticipated and should be pursued promptly.
- Health Economics and Access: Both drug classes are associated with significant cost. Cost-effectiveness analyses incorporating long-term cardiovascular and renal benefits, quality-adjusted life years (QALYs), and reductions in HF hospitalization should inform reimbursement policies, particularly in low- and middle-income countries where HF burden is rising.

5. CONCLUSION

SGLT2 inhibitors and GLP-1 receptor agonists represent two of the most significant advances in cardiovascular pharmacology of the past decade, each demonstrating transformative benefits in heart failure through distinct yet partially overlapping mechanistic pathways.[7,48] SGLT2 inhibitors have established Class I guideline recommendations across the ejection fraction spectrum, underpinned by phenotype-agnostic mechanisms including osmotic diuresis, NHE1 inhibition, ketone body promotion, and mitochondrial protection.[3] GLP-1 RAs demonstrate their most compelling HF benefits in the obese HFpEF phenotype, predominantly through profound weight loss, anti-inflammatory effects, and direct GLP-1 receptor-mediated cardioprotection.[12,32]

Rather than competing agents, these drug classes are mechanistically complementary, targeting distinct pathophysiological nodes within the complex HF syndrome. Their co-administration in appropriate phenotypes—particularly obese HFpEF with concurrent diabetes or high cardiometabolic burden—holds significant therapeutic promise.[45] Future research must focus on combination therapy trials, phenotype-specific strategies, and biomarker-guided patient selection to fully realize the therapeutic potential of these remarkable drug classes in the ongoing fight against heart failure.[34,46]

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