Circulation: Heart Failure

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Mechanisms of GLP-1 Receptor Agonists in HFpEF: Exploring Weight-Dependent and Independent Drivers of Therapeutic Benefit

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ABSTRACT: Heart failure with preserved ejection fraction is a complex and increasingly prevalent condition often associated with metabolic comorbidities such as obesity, diabetes, and hypertension. Although its burden is substantial, therapeutic progress has lagged compared with heart failure with reduced ejection fraction. GLP-1RAs (glucagon-like peptide-1 receptor agonists), initially developed for glycemic control in type 2 diabetes, have emerged as promising therapeutic agents for the obese/cardiometabolic heart failure with preserved ejection fraction phenotype. Recent trials, including STEP-HFpEF and SUMMIT, have demonstrated improvements in symptoms, quality of life, and reductions in heart failure events. Beyond inducing substantial weight loss, GLP-1RAs exert a range of metabolic, cardiovascular, and anti-inflammatory effects. In this review, we summarize weight-dependent and weight-independent actions of GLP-1RAs and outline how these mechanisms may influence cardiovascular physiology, myocardial remodeling, cardiac metabolism, renal sodium handling, and systemic inflammation in heart failure with preserved ejection fraction.

Key Words: atrial fibrillation ■ heart failure ■ interleukin ■ obesity ■ phenotype

Although the pace of advances in therapy for heart failure (HF) with preserved ejection fraction (HFpEF) or HF with mildly reduced ejection fraction (HFmrEF) has lagged substantially behind that for HF with reduced ejection fraction, recent major trials (STEP-HFpEF, SUMMIT, DELIVER, FINEARTS) have now provided much-needed therapeutic options for this patient cohort.[1–4] Progress in HFpEF/HF with mildly reduced ejection fraction has been challenged, in part, by its heterogeneous pathophysiology and by the limited sensitivity and specificity of diagnostic algorithms commonly applied in clinical practice and trials. In this context, invasive hemodynamic assessment, including during exercise, remains the gold standard for HFpEF diagnosis.

By incorporating multimodal approaches, several HFpEF phenotypes have been suggested, each with potentially differing treatment responses.[5] Proposed HFpEF phenotypes include the cardiometabolic/obese, hypertensive/ventriculo-vascular stiffness, atrial fibrillation (AF)/atrial myopathy, and right heart/pulmonary vascular clusters.[5] By designating these phenotypes, it is important to understand the cardiovascular physiology of each cluster and the impact on outcomes, including functional capacity, quality of life, HF hospitalization, and HF mortality. For example, in carefully phenotyped patients with HFpEF, prior studies have shown that left atrial (LA) pressure, particularly during exercise, is a key determinant of functional limitation and prognosis.[6,7] By extension, to progress advancements in HFpEF/HF with mildly reduced ejection fraction therapeutics, a detailed evaluation of the mechanisms by which therapies act in each phenotype is important.

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin converting enzyme inhibitor
AF	atrial fibrillation
Ang II	angiotensin II
BMI	body mass index
BP	blood pressure
CMR	cardiac magnetic resonance
CRP	C-reactive protein
eNOS	endothelial nitric oxide synthase
FFA	free fatty acid
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GLP-1RA	glucagon-like peptide-1 receptor agonist
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IL	interleukin
LA	left atrial
LV	left ventricular
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHE3	sodium-hydrogen exchanger 3
NOS	nitric oxide synthase
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RAAS	renin-angiotensin-aldosterone system
RV	right ventricle
SGLT2	sodium/glucose cotransporter 2
T2DM	type 2 diabetes
TGF-β1	transforming growth factor-β1
TNFα	tumor necrosis factor-α

Recently, landmark trials of the GLP-1RA (glucagon-like peptide-1 receptor agonist), semaglutide, and the dual GLP-1RA/GIP (gastric inhibitory polypeptide), tirzepatide, have demonstrated improved cardiovascular outcomes in patients with obese/cardiometabolic HFpEF phenotype.[3,4,8,9] Endogenous GLP-1 is a key incretin hormone, originally identified after studies demonstrated greater insulin secretion in response to oral versus intravenous glucose.[10] The primary actions of GLP-1RAs are to increase insulin secretion in a glucose-dependent manner, suppress glucagon secretion, slow gastric emptying, and promote satiety.[11] The GLP-1R has been detected in the heart, blood vessels, kidney, brain, adipose tissue, and lung (Figure 1).[11] GIP also inhibits insulin release via binding to its cognate receptor, GIPR (glucose-dependent insulinotropic polypeptide receptor), which is broadly expressed across multiple organ systems In the STEP-HFpEF and SUMMIT programs, semaglutide and tirzepatide, respectively, were shown to produce favorable improvements in Kansas City Cardiomyopathy Questionnaire scores, 6-minute walk distance, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, accompanied by significant weight loss and reductions in CRP (C-reactive protein) in patients with obesity and HFpEF, with or without type 2 diabetes (T2DM).[3,4,8] Both drugs were also found to significantly reduce the composite end point of worsening HF events or cardiovascular death, with results driven by a reduction in HF events rather than mortality, noting that these trials were not powered for a mortality end point.[3,4,8] It is also important to recognize that in the context of HFpEF, cardiovascular death is largely not HF related, but rather due to concomitant ischemic heart disease and stroke.[12] Prespecified subgroup analyses of STEP-HFpEF and SUMMIT found consistent results regardless of baseline T2DM, Kansas City Cardiomyopathy Questionnaire score, or underlying inflammation (plasma CRP level).[13–17]

The obese/cardiometabolic HFpEF phenotype in which these medications have shown benefit is increasingly common, although not uniform, with substantial geographic variation.[18] From the perspective of HFpEF, increasing body mass index (BMI) is associated with more impaired Kansas City Cardiomyopathy Questionnaire and 6-minute-walk-distance, lower natriuretic peptides, higher intracardiac filling pressures, and greater LA and left ventricular (LV) volumes.[19] Higher BMI in HFpEF, and obesity more broadly, is also accompanied by neurohormonal activation, systemic inflammation and complex alterations in adipokines, as recently reviewed.[20,21] The adipokine hypothesis links adipose-derived inflammatory signaling with myocardial, vascular, and metabolic dysfunction; however, its explanatory scope is limited.[21] Many individuals with obesity or elevated visceral adiposity do not develop HFpEF, and conversely, distinct nonobese HFpEF phenotypes exist, indicating that adipokine-driven mechanisms represent only 1 component of a heterogeneous disease process. The extent to which the cardiovascular benefits of GLP-1RAs in HFpEF are mediated by loss of fat mass is still unclear, with available trial data unable to disentangle weight-dependent from weight-independent therapeutic effects. Obesity class (defined by BMI) was found to have no differential effect on outcomes in either STEP-HFpEF or SUMMIT; however, an increasing percentage of weight loss was strongly associated with increased improvement in symptoms, functional status, and inflammation.[22,23] In the SELECT

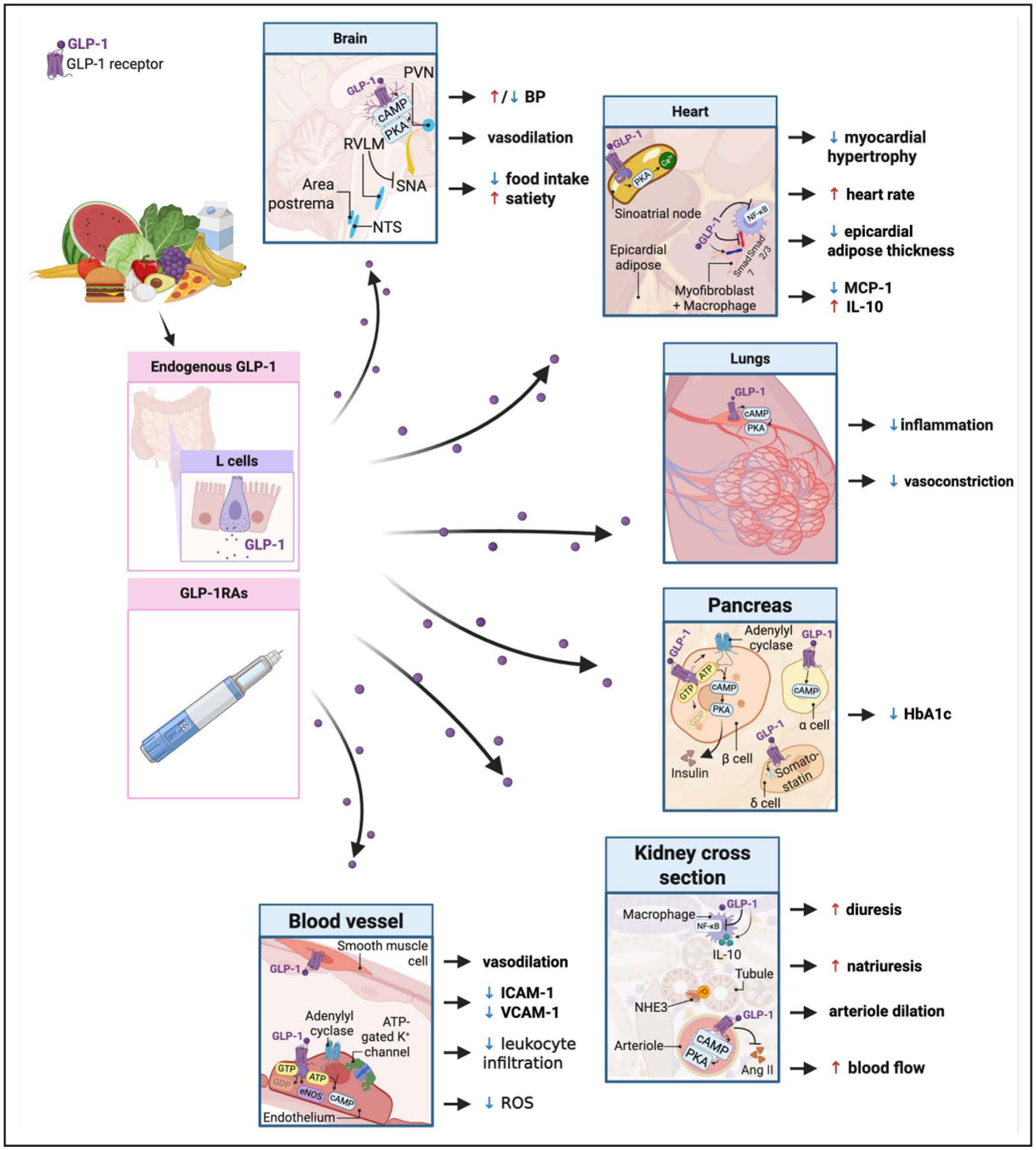

Figure 1. Organ-specific effects of GLP-1 (glucagon-like peptide-1) signaling.
Endogenous GLP-1 or exogenous GLP-1RAs (GLP-1 receptor agonists) act via widely distributed GLP-1 receptors to modulate key physiological processes. In the brain, GLP-1 reduces food intake and regulates blood pressure (BP) via sympathetic nerve activity. In the heart, it influences heart rate and inflammation, reducing hypertrophy and promoting anti-inflammatory signaling. In the lung, it reduces inflammation and contributes to vasodilatation. In the pancreas, it enhances insulin secretion and glucose control. In the kidney, GLP-1 improves renal blood flow and promotes natriuresis by modulating Ang II (angiotensin II) and NHE3 (sodium-hydrogen exchanger 3). In the vasculature, it supports vasodilation and reduces endothelial inflammation and leukocyte infiltration. IL indicates interleukin; and PKA, protein kinase A. Created with BioRender.com.

trial of >17 000 participants with BMI >27 kg/m^2, semaglutide reduced cardiovascular events independent of the magnitude of weight loss.[24] Although there was a relationship between reduction in waist circumference and cardiovascular outcomes, waist circumference reduction accounted for only one-third of the

cardiovascular benefit of GLP-1RA/incretin treatment, suggesting weight-independent mechanisms at play.[24]

Given the favorable effects of these cardiometabolic therapies in HFpEF, the fundamental pathophysiological and therapeutic question is how these agents confer benefits on defined HF outcomes, including HF stability, quality of life/functional capacity, and cardiovascular survival? In this review, we explore the pathophysiological components of HFpEF and consider their potential intersection with the effects of GLP-1 receptor activation, weight loss, modulation of inflammation, and neurohormonal modulation (Figure 2). By delineating the mechanisms through which GLP-1RAs confer benefit in HFpEF, we aim to provide directions for ongoing research into improving HFpEF outcomes.

HOW DO GLP1RAS REDUCE HF EVENT RATES IN HFPEF?

As outlined above, from the cardiovascular perspective, the key pathophysiologic abnormality in HFpEF is an elevation in LA pressure, often most notable during exertion.[25] The importance of intracardiac filling pressures as a key determinant of decompensation in HFpEF is underscored by observations made in patients with a pulmonary pressure sensor device, in which a progressive increase in pulmonary artery pressure typically precedes HF hospitalization.[26] From the perspective of cardiovascular mechanics, LA pressure is determined by several factors, including LV diastolic and systolic performance, LV afterload, heart rate (HR), and blood volume.[27] Below, we review the evidence for GLP1-RA modifications in these contributory parameters and their relative weight loss-dependent and -independent contribution.

Diastolic Function

Diastolic dysfunction and LA volumes are linked to increased rates of HF events[28]; therefore, improving these parameters may contribute to the cardiovascular benefits observed in GLP-1RA trials. In preclinical studies of HFpEF models, GLP-1RAs have been shown to improve diastolic performance. In a rodent HFpEF model, treatment with a constant infusion of GLP-1 for 4 weeks resulted in significantly improved diastolic parameters, including mitral valve deceleration time, improved LV pressure/volume curves, and reduced LV stiffness compared with control treatment.[29] These findings were corroborated in another rodent HFpEF model in which 14 weeks of liraglutide treatment resulted in improvement in LA size, early and late septal annular velocities, index of LA filling pressure (E/e'), and the slope of end diastolic pressure-volume relationship.[29,30]

Following these preclinical findings, several studies have examined the impact of GLP-1RAs on diastolic function in humans. In patients with T2DM with and without HFpEF, no significant change in the E/A ratio was seen after 3 to 6 months of GLP-1RA therapy; however, other diastolic measures, including E/e' ratio, significantly improved.[31–34] In the randomized STEP-HFpEF echocardiography substudy, which included both patients with and without T2DM, treatment with semaglutide for 52 weeks was associated with a significant improvement in E-wave velocity (P=0.037), E/A ratio (P=0.0075), E/e' (P=0.05), and a reduction in LA volume (P=0.0013) without a change in LA strain.[35] As expected, patients with AF had larger LA volumes and lower LA strain at baseline; however, the observed reduction in LA volume occurred independently of the presence of AF.[35] In contrast, other echocardiographic and cardiac magnetic resonance imaging (CMR) studies have not demonstrated a change in LA volume.[36,37] In a retrospective observational study, Yagi et al[34] evaluated changes in E/e' over the course of liraglutide therapy in those with and without diastolic dysfunction at baseline (E/e' above and below 13). They found that the significant reduction in E/e' was isolated to those who had diastolic dysfunction at baseline, and there was no change in those who had an E/e' <13 to begin with. This observation is directly relevant to HFpEF, where elevated filling pressures are central to symptoms and prognosis.

Relation to weight loss: Obesity is linked to diastolic dysfunction and LA dilatation independent of comorbidities, including hypertension.[38] It is, therefore, plausible that GLP-1RA-associated weight loss contributes to improvements in diastolic function. In patients with HFpEF and obesity, the degree of weight loss with semaglutide correlated with reductions in LA volume.[35] This relationship likely reflects the expected decrease in total blood volume, preload, and afterload that accompanies substantial weight loss. By contrast, improvements in E wave velocity and E/e′ did not parallel weight loss,[35] a pattern also observed following surgical weight reduction.[39] Together, these findings point to both indirect-weight loss mediated and direct effects of GLP-1RA on intrinsic myocardial and atrial mechanical properties, potentially related to enhanced energetic handling.

Cardiac Remodeling

GLP-1R mRNA has been detected in human cardiomyocytes at levels comparable to those in the pancreas, with additional expression noted in microvascular endothelial and smooth muscle cells.[40] Although further studies are needed to confirm the precise localization and functional relevance of GLP-1R on cardiomyocytes, the presence of GLP-1R transcripts supports the potential for a direct cardioprotective effect of GLP-1RA therapy. Consistent with this distinction, preclinical studies of purified

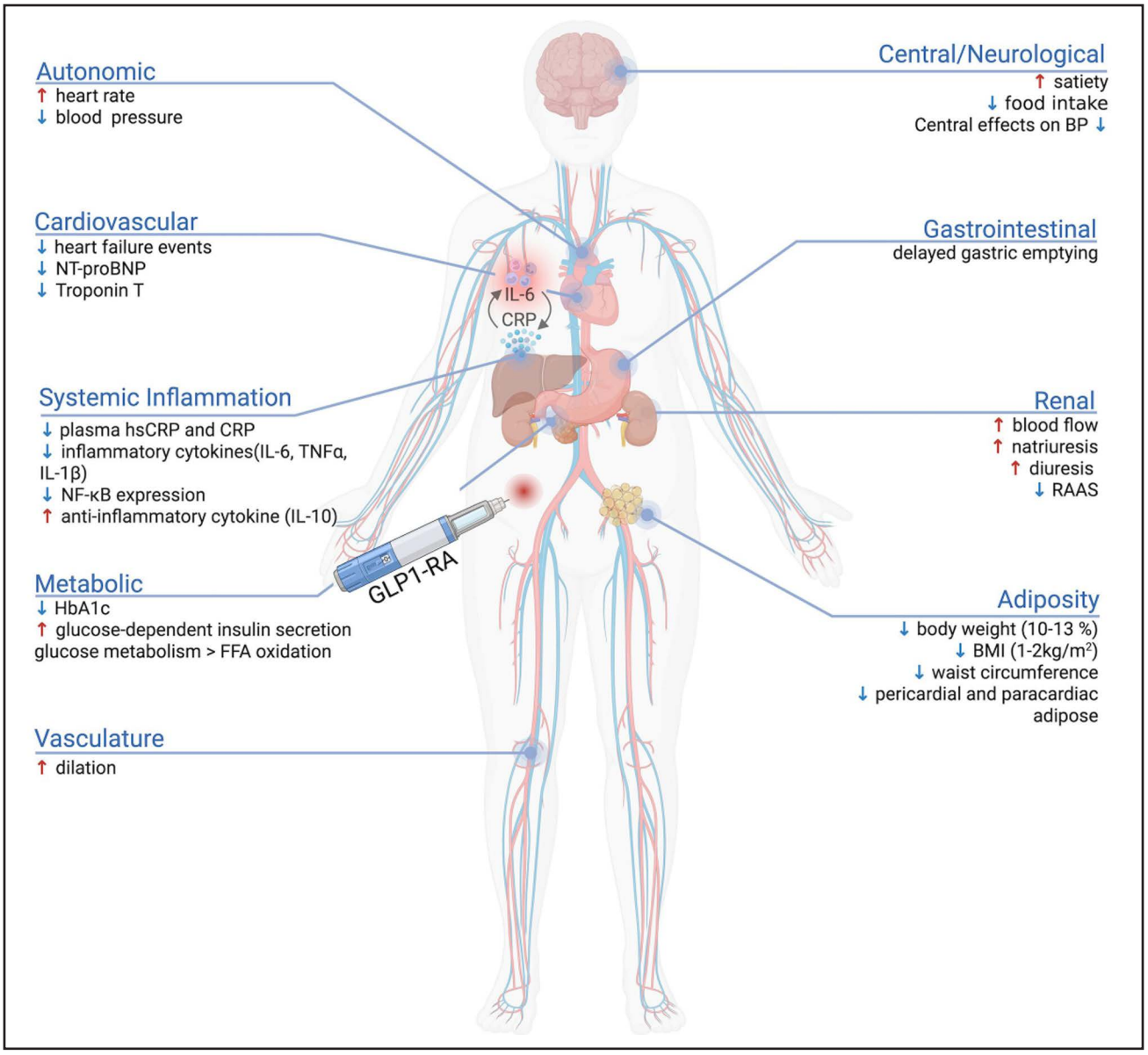

Figure 2. Summary of GLP-1RA (glucagon-like peptide-1 receptor agonist) effects in heart failure with preserved ejection fraction (HFpEF).

GLP-1RAs impact autonomic signaling, cardiovascular function, inflammation, metabolism, vasculature, central control, gastric emptying, renal function, and adiposity—factors linked to reduced morbidity and hospitalizations, as shown in the SUMMIT and STEP-HFpEF trials. BP indicates blood pressure; BMI, body mass index; CRP, C-reactive protein; FFA, free fatty acid; HbA1c, hemoglobin A1c; hs, high sensitivity; IL, interleukin; NF-κB, nuclear factor-κB; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAAS, renin angiotensin aldosterone system; and TNFα, tumor necrosis factor α. Created with BioRender.com.

GLP-1 infusion have not demonstrated changes in LV mass, whereas treatment with GLP-1RAs has been associated with favorable cardiovascular effects, suggesting that sustained pharmacological receptor activation may confer benefits not observed with native GLP-1 alone.[29,41] In a multihit HFpEF mouse model induced by high fat diet, Ang II (angiotensin II) and old age (18–22 months), treated with liraglutide for 12 weeks, there were significant reductions in LV mass, LA mass, myocardial fibrosis, and cardiac hypertrophy.[42] Another HFpEF mouse model examining liraglutide treatment also demonstrated significant reductions in myocardial collagen deposition.[43] These histological changes are consistent with preclinical data postmyocardial infarction, which also showed a reduction in myocardial hypertrophy, collagen deposition, and fibrosis with GLP-1RA administration.[44]

In the absence of histological studies of the effects of GLP-1RA on the human heart, CMR provides the best available indirect evidence regarding the impact on myocardial structure. In a randomized study over an 18-week period, GLP-1RA treatment was not

found to alter LV mass, and there was no detectable effect on fibrosis. However, the cohort was small, with only 20 participants receiving therapy.[37] In another CMR study investigating liraglutide in patients with T2DM who were overweight, there was a significant reduction in LV end diastolic volume, while LV mass index was unchanged.[45] The much larger SUMMIT CMR substudy, with longer follow-up, found a significant reduction in LV mass as well as LV end diastolic volume.[46] This is in line with several other preclinical and clinical studies that have also demonstrated beneficial effects of GLP-1RAs on cardiac remodeling in HFpEF (Figure 3).

Role of weight loss: In the SUMMIT CMR substudy, reduction in LV mass was only weakly correlated with weight loss at 52 weeks, but coincided with a meaningful fall in systolic blood pressure (BP).[46] Similar patterns have been observed with bariatric surgery, where substantial reductions in LV mass index at 12 months were disproportionate to the degree of weight loss but closely paralleled a marked reduction in antihypertensive requirements.[39] The temporal relationship between weight loss, BP reduction, and cardiac reverse remodeling remains incompletely defined. However, these data would suggest that afterload reduction, potentially mediated by altered aldosterone signaling and attenuation of neurohormonal activation, may be the dominant driver of LV mass regression.

LV Systolic Function

The available preclinical and clinical evidence collectively suggests that GLP-1RA therapy does not impact LV contractility. In vitro studies of human cardiomyocytes found that exenatide had no impact on ventricular contractility.[47] Across all clinical studies, echocardiographic parameters of LV systolic function, including LV ejection fraction, stroke volume, cardiac index, and LV global longitudinal strain, were unchanged by GLP-1RA use.[31,32,35] Similarly, CMR parameters of LV systolic function were also unchanged.[37,46] These findings suggest that GLP-1RAs do not directly augment LV systolic function, reinforcing the concept that their benefits in HFpEF arise through mechanisms other than enhanced contractility.

Right Ventricular Structure and Function

Despite the known importance of right ventricular (RV) involvement in HFpEF pathophysiology and its association with mortality,[48] the RV has been largely overlooked in GLP-1RA studies. Notably, the SUMMIT CMR substudy specifically did not assess RV structure and function.[46] Nor did the other CMR studies available in this area.[37,45] In STEP-HFpEF, however, significant reductions in RV end-diastolic and end-systolic areas were observed, without concurrent changes in RV systolic function.[35]Althoughthese structural changes may reflect

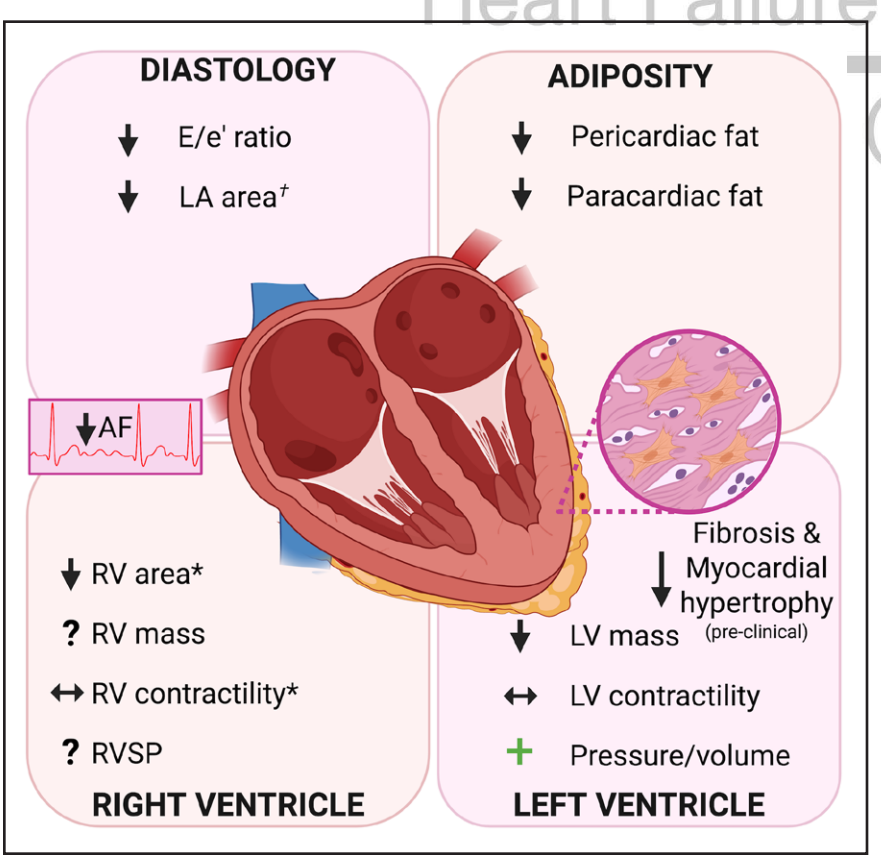

Figure 3. Cardiac effects of GLP-1RAs (glucagon-like peptide-1 receptor agonists) in heart failure with preserved ejection fraction (HFpEF). GLP-1RAs improve diastolic function (lower E/e' and left atrial [LA] area), reduce atrial fibrillation, peri- and paracardiac fat, right ventricular (RV) area, left ventricular (LV) pressure/volume curves, and ventricular mass. Preclinical data show reduced fibrosis and myocardial hypertrophy. Effects on contractility are variable, and impacts on RV mass and systolic pressure are unclear. *Data from 1 study only. †Observed with GLP-1RA, but not with dual GIP (glucose-dependent insulinotropic polypeptide)/GLP-1RA therapy. RVSP indicates right ventricular systolic pressure. Created with BioRender.com.

a reduction in volume status mediated by the natriuretic and diuretic effects of GLP-1RAs, the consistent reduction in background diuretic use across trials suggests additional mechanisms may be involved.[14,49] These may include improved RV-PA coupling or reduced ventricular interdependence. Further mechanistic investigation into the RV effects of GLP-1RAs is warranted, particularly given the prognostic importance of RV remodeling in HFpEF.

Role of weight loss: Any observations regarding RV remodeling and function with GLP-1RA therapy should also be interpreted within the broader context of weight loss, which can independently influence RV structure and function. Prior hemodynamic studies have demonstrated the presence of poorer RV function and RV-PA coupling with greater degrees of overweight and obesity, although the strength of the association is only modest.[19,50] The mechanisms linking obesity to RV dysfunction and pulmonary hypertension are multifactorial, involving contributions from ventricular interdependence, volume expansion, obstructive sleep apnea, and metabolic and inflammatory signaling.[51] Accordingly, part of the RV remodeling observed in STEP-HFpEF may reflect weight-loss mediated improvements in these upstream processes, acting alongside any direct effects of GLP-1RA therapy.

Epicardial Adipose Tissue

Accumulation of epicardial adipose tissue is a postulated contributor to the pathogenesis of HFpEF, mediated via several mechanisms, including direct mechanical compression and paracrine secretion of proinflammatory and profibrotic cytokines, adipokines, and catecholamines. In healthy individuals, epicardial adipose tissue thickness is strongly associated with LV mass, independent of BMI, age, and LV wall thickness,[52] and CMR studies in HFpEF have demonstrated a relationship with diastolic dysfunction.[53]

Given the central role of adipose-derived signaling in HFpEF and the therapeutic emphasis on weight loss with GLP-1RA therapy, interest has grown in the reduction of epicardial adipose tissue as a mediator of treatment response in HFpEF. In patients with T2DM, GLP-1 analogues produce a significant reduction in epicardial adipose tissue area, an effect that appears independent of glucose-lowering.[54] Further, a meta-analysis of 18 echocardiographic studies demonstrated that GLP-1RAs reduce epicardial adipose thickness to a greater extent than statins or SGLT2 (sodium/glucose cotransporter 2) inhibitors.[55] In HFpEF specifically, the SUMMIT CMR sub-study demonstrated a reduction in pericardial and para-cardiac adipose tissue without measurable change in epicardial fat.[46] This finding may reflect the relative insensitivity of echocardiography for quantifying epicardial fat compared with CMR. Taken together, these data suggest that GLP-1RA therapy preferentially reduces extra-cardiac adipose tissue, a process that may contribute to favorable cardiometabolic effects and improved clinical status in HFpEF.

Role of weight loss: Given that epicardial adipose tissue expands with obesity, reductions in epicardial adipose tissue area should be viewed in light of accompanying body-weight reduction.[56] Although correlations between weight loss and epicardial adipose tissue reduction have not been specifically characterized in HFpEF, the pattern observed with GLP-1RAs is consistent with nonpharmacological weight loss data. In patients undergoing bariatric surgery, a 22% reduction in BMI was associated with a 14% reduction in epicardial adipose tissue, findings which are corroborated in a systematic review and meta-analysis.[51,57] Taken together, the reduction in extra-cardiac adiposity observed with GLP-1RAs is likely driven by weight-loss per se.

Cardiac Metabolism

The healthy heart is a metabolically demanding organ that relies predominantly on free fatty acid (FFA) oxidation for ATP generation but retains the flexibility to shift toward glucose and ketone body metabolism as needed. In HFpEF, this metabolic flexibility becomes impaired, particularly in the setting of common comorbidities, such as T2DM and obesity. These conditions promote hyperglycemia, insulin resistance, and hyperlipidemia, leading to glucotoxicity and lipotoxicity, and ultimately contributing to ATP deficiency. Magnetic resonance spectroscopy has revealed a decreased phosphocreatine: ATP ratio in patients with HFpEF compared with healthy controls, indicating reduced energy reserves and correlating with impaired diastolic relaxation, contractile function, and cardiac output during exercise.[58] Despite these insights, the relative contributions of impaired FFA oxidation, glucose oxidation, and ketone utilization to metabolic insufficiency in HFpEF remain unclear. In HFpEF, transmyocardial flux studies demonstrated less utilization of FFAs,[59] and tissue analysis shows myocardial levels of FFA, glucose, and ketone body metabolism intermediates are reduced, suggesting a myocardial-specific pattern of metabolic inflexibility.[60] This characteristic metabolic phenotype raises the possibility that therapies which improve systemic metabolic health, such as GLP-1RAs, may confer cardiac benefit.

To date, no clinical studies have directly investigated GLP-1RA effects on cardiac metabolism in HFpEF; however, preclinical data offer some insight. In a diabetic mouse model, liraglutide increased cardiac glucose oxidation, an effect also observed in lean mice, mediated through enhanced phosphorylation of Akt and pyruvate dehydrogenase.[61] Notably, this effect was absent in isolated hearts, implying involvement of extracardiac or systemic factors in mediating GLP-1RA induced metabolic

changes.[61] Consistent with this, in adults with T2DM, GLP-1RA therapy significantly reduced circulating FFAs,[32] reinforcing preclinical findings.

Role of weight loss: Although the effect of GLP-1RA on cardiac metabolism has yet to be studied in detail, weight loss itself has been shown to improve myocardial substrate utilization, even in the absence of changes in myocardial triglyceride content.[56] These observations raise the possibility that weight-loss mediated restoration of metabolic flexibility may complement any direct effects of GLP-1RAs on cardiac metabolism.

Blood Pressure

Hypertension is prevalent in 55% to 90% of patients with HFpEF and follows a J-shaped association with HF and overall cardiovascular risk, while controlled BP is associated with improved outcomes.[62,63] Notably, clinically meaningful BP reductions have been demonstrated with GLP-1RA therapy in HFpEF, with systolic BP falling by up to 5 mm Hg as early as 4 weeks posttreatment initiation.[64]

Preclinical studies have revealed that GLP-1RAs modulate BP through effects on the vasculature, central nervous system, heart, and kidney, via GLP-1R on endothelial cells, vascular smooth muscle cells, area postrema of the brain, heart, and renal blood vessels.[65] In Ang II induced hypertensive rodent models, GLP-1RAs produce significant BP-lowering effects, an effect abolished in GLP-1R knockout mice or with pretreatment with the GLP-1R antagonist exendin$_{9\text{-}39}$.[66] Liraglutide also stimulates atrial natriuretic peptide secretion, a pathway that promotes natriuresis, diuresis, and vasodilation.[66] Additionally, GLP-1RAs inhibit Ang II signaling,[67] and reduce renal Ang II production, which is discussed in more detail below.[68]

Vascular reactivity studies add further mechanistic insight into the BP-modulating effects of GLP-1RAs. Myography experiments showed that GLP-1RAs induce concentration-dependent relaxation of isolated rat aorta, likely via ATP-sensitive potassium channels and cAMP pathways.[69] In mesenteric arteries from *Glp1r*$^{-/-}$ mice, GLP-1RAs promote vasorelaxation through NOS (nitric oxide synthase) dependent mechanisms, independent of GLP-1R.[70] GLP-1RAs also protect against endothelial dysfunction in Ang II–treated mice by reducing endothelial activation, leukocyte infiltration, and oxidative stress while enhancing eNOS (endothelial nitric oxide synthase) expression.[71]

Human studies corroborate these vascular findings: GLP-1RAs increase microvascular perfusion in healthy adults,[72] and enhance postischemic radial artery blood flow via ATP-sensitive potassium channels.[73] These results were replicated in subjects with obesity, where GLP-1RA administration was superior to insulin at increasing flow to microvascular vessels, although this effect was not due to any changes in vessel diameter.[72,74]

GLP-1Rs are also expressed in brain regions integral to sympathetic and cardiovascular regulation, including the area postrema, nucleus tractus solitarius, rostral ventrolateral medulla, paraventricular nucleus, and the carotid body.[75,76] In spontaneously hypertensive rats, daily liraglutide administration into the area postrema and nucleus tractus solitarius activated neurons in these regions, as evidenced by increased c-Fos expression, and reduced BP by 40 mm Hg, accompanied by lower urinary norepinephrine excretion.[76] Conversely, direct injection of GLP-1RAs into the paraventricular nucleus increased BP and renal sympathetic nerve activity in spontaneously hypertensive rats, while antagonism of GLP-1R had the opposite effect.[75] Exendin-4, given intravenously or intracerebroventricularly, also induced dose-dependent increases in mean arterial pressure over 10 to 14 days. Reduced GLP-1R expression in rodent models of cardiometabolic disease is associated with heightened sympathetic activity.[76] When GLP-1RAs were targeted to the carotid body, they attenuated BP elevations in response to acute carotid body stimulation with sodium cyanide. Collectively, these preclinical findings and localization of GLP-1Rs to central and peripheral sites involved in BP regulation suggest that GLP-1RAs may modulate BP through actions on sympathetic neurons.

Role of Weight Loss: Further to the direct central and peripheral mechanisms, reduction in BP with GLP-1RA use has also been strongly correlated with weight loss in randomized trials.[77] This is biologically intuitive, given the close link between obesity and hypertension and evidence that weight loss improves BP in individuals with obesity.[19,78] Nevertheless, the early BP response to GLP-1RAs exceeds what would be expected from weight loss alone. In SUMMIT, systolic BP fell by ≈5 mm Hg within 4 weeks despite only ≈2 kg of weight loss,[64] a magnitude not explained by weight reduction itself. This early fall in BP, together with early modulation of the renin-angiotensin-aldosterone system (RAAS; discussed below), supports the presence of weight-independent GLP-1RA effects on BP regulation.[79]

HR and Rhythm

Cardiomyocytes in the sinoatrial node are a major site of GLP-1R expression in the heart[80], and GLP-1RA therapy consistently increases HR in clinical trials.[3,4] In SUMMIT, tirzepatide increased HR by ≈3 bpm compared with ≈0.3 bpm with placebo,[3] consistent with findings from the SURMOUNT and STEP-HFpEF trials.[4,81] Ambulatory monitoring suggests that these increases reflect reduced HR variability and shorter beat-to-beat intervals,[82] while preclinical work in pigs shows this effect arises from

shortened sinoatrial action potentials and earlier pacemaker activation.[83]

The clinical relevance of these chronotropic effects to HFpEF remains uncertain. Although some individuals with HFpEF exhibit chronotropic incompetence, and atrial pacing has been proposed as a therapeutic strategy to lower LV end-diastolic pressure and volume,[84,85] the degree of HR elevation produced by GLP-1RAs is far smaller than that used in pacing studies, and the relationship between modest HR changes and HF outcomes has not been established. Importantly, however, GLP-1R expression is higher in human atria than in ventricles,[47] and experimental work suggests GLP-1RAs may enhance atrial contractility even in the absence of effects on ventricular systolic function.[47]

Atrial GLP-1R expression provides a conceptual link to the observed associations between GLP-1RA therapy and AF. HFpEF and AF share a close, bidirectional relationship driven by elevated LA pressure, atrial fibrosis, and impaired atrial mechanical performance. In a large propensity-matched cohort, GLP-1RA use was associated with a 20% relative risk reduction of new-onset AF or atrial flutter.[86] Randomized data from STEP-HFpEF also demonstrated lower incident AF with semaglutide (1.1% versus 3.4%; $P<0.001$), and a meta-analysis of randomized controlled trials similarly reported reduced new-onset AF with GLP-1RAs.[87] However, the absolute event numbers were low (1.1% across nearly 49 000 participants), limiting certainty.[87] In contrast to GLP-1RA only studies, the SUMMIT trial observed numerically higher rates of new onset AF with active treatment compared with placebo (6.3% versus 3.3%),[3] suggesting potential heterogeneity in atrial arrhythmic outcomes across incretin-based therapies. Given the important interaction between AF and HFpEF, both in pathophysiology and symptom burden, dedicated trials powered to investigate the impact of GLP-1RAs on incident AF in this population are needed. The role of other indirect mediators of atrial arrhythmias, such as sleep apnea, also requires further consideration in the GLP-1RA context.

Role of weight loss: Weight reduction itself influences atrial electrophysiology and autonomic tone. Modest diet-mediated reduction in body weight is accompanied by a small but significant fall in HR, while marked weight loss elicited by bariatric surgery is accompanied by a further reduction in HR,[88] resulting from a reduction in sympathetic tone and an increase in cardiac parasympathetic drive. In the ANBP2 trial (in both the diuretic and ACE [angiotensin-converting enzyme] inhibitor arms), substantial BP lowering was not accompanied by HR changes,[89] suggesting that HR modulation with weight loss is not simply secondary to reduced BP or plasma volume. These observations raise the possibility that both weight-loss mediated autonomic effects and direct GLP-1RA actions may contribute to the complex interplay between HR, atrial function, and AF risk.

Renal Function and Blood Volume

Blood volume expansion is a central physiological feature of HF and an important therapeutic target. Using gold standard radiotracer methods, a modest correlation has been shown between BMI and plasma volume in patients with HF; however, no clear correlation between right atrial pressure or pulmonary capillary wedge pressure and plasma volume is evident.[90] From a mechanistic point of view, mathematical modeling studies suggest that increased stressed blood volume plays a key role in HFpEF pathophysiology.[27] On this basis, it has been proposed that GLP-1RA-associated weight loss may be accompanied by modest reductions in blood volume; however, this assumption derives from weight-based estimations, and no studies to date have directly evaluated the effect of GLP-1RAs on invasive hemodynamic parameters using right heart catheterization.[64]

Beyond potential effects on blood volume, GLP-1RAs exert important renal actions. Semaglutide has demonstrated substantial renal protective effects, including marked reductions in albuminuria. In SUMMIT, semaglutide reduced urinary albumin-to-creatinine ratio by 52% over 24 weeks in patients with chronic kidney disease and obesity, an effect strongly associated with the degree of weight loss.[91] A broader systematic review further showed that GLP-1RAs reduce microalbuminuria by 24% and slow chronic kidney disease progression.[92]

GLP-1R is expressed in the renal vasculature, and experimental evidence shows that GLP-1RA administration acutely increases renal blood flow, urine output, and natriuresis in rodents, responses attenuated by GLP-1R antagonism.[70,93] GLP-1RAs also mildly dilate afferent arterioles in a receptor-dependent fashion,[70] supporting enhanced renal perfusion as a mechanism for their natriuretic effects. In both healthy individuals and patients with T2DM, GLP-1RAs influence Na^+ homeostasis via the NHE3 (sodium-hydrogen exchanger 3) in the proximal convoluted tubule.[93,94] Reduced NHE3 activity decreases Na^+ absorption and increases natriuresis.[95] These renal effects may have direct implications for blood volume regulation and thus HF hospitalizations.

A substantial body of evidence indicates that GLP-1RAs modulate RAAS activity. GLP-1RAs significantly reduce serum aldosterone concentrations in patients with chronic kidney disease,[93] and reduce plasma Ang II in patients with T2DM as well as healthy controls.[96] These hormonal changes likely contribute to the renoprotective profile of GLP-1RAs and may help explain the lower rates of HF hospitalization seen in randomized trials.[97] Consistent with improved renal sodium handling, clinical trials in HFpEF have demonstrated consistent down-titration of background loop diuretics in participants treated with GLP-1RAs[14,49]

Role of weight loss: Weight loss itself is strongly associated with suppression of RAAS activity.[21] Mechanistically,

weight reduction decreases sympathetic drive to renin release, lowers adipose-derived angiotensinogen production, reduces insulin levels, and diminishes renal sodium reabsorption. Bariatric surgery studies demonstrate that substantial reductions in adiposity are accompanied by improvements in neurohormonal and hemodynamic status, along with marked reductions in HFpEF-related hospitalizations.[98] However, GLP-1RAs appear to exert additional weight-independent RAAS effects. Notably, liraglutide leads to a significant reduction in serum aldosterone concentration within just 48 hours of administration, well before any meaningful change in body weight, suggesting direct modulation of blood volume and renal sodium handling via the RAAS pathway, independent of weight loss.[93]

Inflammation

HFpEF is increasingly recognized as a proinflammatory condition, and the degree of inflammatory upregulation appears to be associated with the severity of diastolic dysfunction in HFpEF.[99] One contributor to this inflammatory milieu is hepatic dysfunction related to metabolic dysfunction-associated steatotic liver disease, which commonly co-exists with HFpEF. Metabolic dysfunction-associated steatotic liver disease promotes secretion of inflammatory cytokines (CRP, IL-1β, IL-6, TNF [tumor necrosis factor]-α), neurohormonal modulation (RAAS and sympathetic nervous system activation), insulin resistance, and altered metabolic signaling, including the generation of β-hydroxybutyrate, thereby amplifying systemic inflammation and potentially worsening HFpEF pathophysiology.[100]

In this context, the anti-inflammatory actions of GLP-1RAs are biologically plausible and potentially clinically meaningful. In nondiabetic nonobese mice, infusion of a GLP-1 mimetic for 4 weeks postmyocardial infarction resulted in significantly reduced inflammatory gene expression independent of glycemic control.[44] In this study, mRNA expression of the inflammatory cytokines, IL (interleukin)-10, IL-1β, and IL-6, was normalized, and myocardial infiltration of leukocytes and macrophages was completely prevented with GLP-1 administration.[44] Similarly, HFpEF mouse models (Ang II/obese/aged) also showed a significant reduction in myocardial macrophage and myofibroblast infiltration with liraglutide.[101,102] Notably, liraglutide has demonstrated interaction with the proinflammatory TGF (transforming growth factor)-β1/Smad signaling pathways, whereby treatment induced inhibition of Smad2/3 phosphorylation and upregulation of Smad 7.[102] Additionally, NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) , an important proinflammatory transcription factor, has also been implicated.[101] Not only was NF-κB activation attenuated by liraglutide treatment, but in vitro macrophage NF-κB mRNA expression was significantly reduced within only 48 hours of liraglutide administration.[101] Upstream from NF-κB, restoration of the Raf kinase inhibitor protein by GLP-1RA also resulted in attenuation of cardiac inflammation.[103] By reducing IL-6 production, NF-κB inhibition directly influences hepatic CRP synthesis, linking cardiac, hepatic, and systemic inflammatory pathways.

Clinical data mirrors these mechanistic observations. The SUMMIT trial demonstrated that tirzepatide treatment significantly reduced systemic hs-CRP (high-sensitivity C-reactive protein) levels by nearly 40%.[3] This was accompanied by a reduction in troponin T, raising the possibility that an anti-inflammatory effect resulted in an important reduction in cardiac injury.[64] In the STEP-HFpEF and STEP-HFpEF DM trials, a similarly impressive reduction in CRP levels of 42% to 44% was seen with semaglutide.[4,8] Given the strong hepatic contribution to circulating CRP levels, improvements in liver-driven inflammation may partly underpin these clinical observations. Moreover, treating metabolic dysfunction-associated steatotic liver disease, including via weight loss and GLP-1RAs, also results in improved HF outcomes,[104] further reinforcing the interconnectedness of hepatic dysfunction, systemic inflammation, and HFpEF pathophysiology.

Role of weight loss: While preclinical studies demonstrate that GLP-1RAs exert early, weight-independent anti-inflammatory effects, clinical data also support a complementary weight-loss–mediated reduction in inflammation, consistent with the adipokine hypothesis of HFpEF.[21] This pattern is evident in both STEP-HFpEF and SUMMIT, where higher BMI predicted higher baseline CRP, yet the magnitude of CRP reduction was similar across BMI strata and tracked closely with weight loss rather than BMI.[22] Non-pharmacological weight-loss interventions show a similar signal: in patients with HFpEF and obesity, the degree of weight loss correlates modestly but significantly with declines in CRP (r=−0.29, P=0.005).[105] This is aligned with extensive evidence from bariatric surgery, where weight loss leads to reductions in upstream inflammatory cytokines, including TNF-α, IL-1β, and IL-6, further supporting a weight-dependent anti-inflammatory pathway.[21]

ARE THE EFFECTS OF GLP-1RA IN HFPEF DUE TO WEIGHT LOSS?

The central question emerging from recent GLP-1RA trials in HFpEF is the extent to which their clinical benefits are mediated by weight loss versus weight-independent mechanisms. This distinction has been difficult to disentangle because GLP-1RAs exert multiple cardiometabolic, renal, hemodynamic, neurohormonal, and anti-inflammatory actions that overlap with

the physiological consequences of weight reduction (Figure 4). The accumulated data from STEP-HFpEF, SUMMIT, and related trials indicate that weight loss is an important mediator of benefit with GLP-1RAs in HFpEF, but not a sufficient explanation on its own. Across these programs, obesity class per se did not modify the primary outcome, whereas the magnitude of weight loss closely tracked improvements in symptoms, functional capacity, and inflammatory markers. At the same time, SELECT demonstrated event reduction with semaglutide that was only partly accounted for by changes in waist circumference, implying that loss of fat mass explains only a portion of the cardiovascular benefit. [24]

The mechanistic work summarized in this review suggests a useful conceptual framework. In the early phase of therapy, GLP-1RAs appear to exert predominantly weight-independent effects: rapid reductions in BP, aldosterone, and Ang II, natriuresis, and modest falls in NT-proBNP occur before substantial changes in body weight. These observations, together with preclinical data, are consistent with direct modulation of sympathetic outflow, RAAS activity, renal sodium handling, and vascular tone rather than simple unloading via reduced adiposity or plasma volume.

With longer-term treatment, weight loss and GLP-1R activation become increasingly difficult to disentangle. Reductions in LV mass and volumes, LA size, extracardiac fat depots, and systemic inflammation align with what is observed after nonpharmacological weight loss, yet the weak correlation between weight change and structural remodeling in some studies, and the scale of CRP reduction relative to BMI strata, point to superimposed drug-specific effects. In this sense, GLP-1RAs may be better viewed as amplifiers and accelerators of the beneficial hemodynamic, metabolic, and inflammatory consequences of weight reduction, rather than as mere pharmacological substitutes for dieting.

Crucially, the pathways influenced by GLP-1RAs, afterload and volume status, diastolic properties, atrial and pulmonary vascular load, renal sodium handling, metabolic flexibility, and systemic inflammation, all converge on the central HFpEF abnormality of elevated LA pressure, particularly during exertion. The improvement in HF events, quality of life, and functional capacity seen in obese/cardiometabolic HFpEF likely reflects the net effect of parallel weight-dependent and weight-independent actions acting on this shared final common pathway.

Important uncertainties remain. Invasive hemodynamic studies are needed to quantify changes in stressed blood volume, filling pressures, and ventricular-vascular coupling over time, and to distinguish GLP-1RA effects from those of weight loss alone. It is also unknown whether similar benefits will extend to nonobese HFpEF phenotypes such as hypertensive/ventriculo-vascular stiffness, atrial myopathy, or right heart/pulmonary vascular subtypes, where adiposity-related mechanisms may be less dominant. Until such data are available, GLP-1RA-mediated protection in HFpEF should not be ascribed solely to weight loss, but rather to an integrated, multimodal profile that happens to be particularly well suited to the obese/cardiometabolic HFpEF phenotype.

CONCLUSIONS

GLP-1RAs have revolutionized the management of patients living with obesity, including those with HFpEF. The noncardiovascular benefits of GLP-1RA treatment

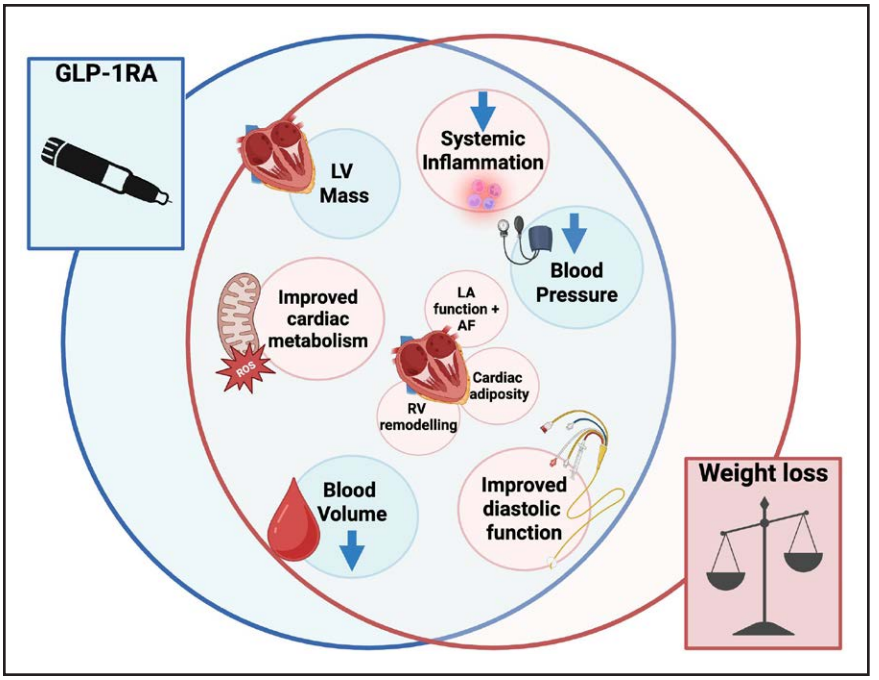

Figure 4. Overlapping effects of weight loss and GLP-1RA (glucagon-like peptide-1 receptor agonist) therapy.
GLP-1RAs contribute to improvements in left atrial (LA) function, atrial fibrillation (AF), blood pressure, blood volume, diastolic function, and cardiac metabolism, while also reducing systemic inflammation, left ventricular (LV) mass, right ventricular (RV) remodeling, and cardiac adiposity. The reductions in LV mass, blood pressure, and blood volume are likely directly related to GLP-1RA therapy, while other effects may also stem from the concomitant impact of weight loss.

are substantial, encompassing improvements in quality of life, endocrine/metabolic, sleep, and psychological well-being. In HFpEF, their therapeutic effects clearly extend beyond weight loss, reflecting additional hemodynamic, renal, neurohormonal, and anti-inflammatory actions. However, further research is needed to clarify how obesity, weight loss, and the various mechanisms of GLP-1RAs each contribute to the HF benefits observed in recent trials.

ARTICLE INFORMATION

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