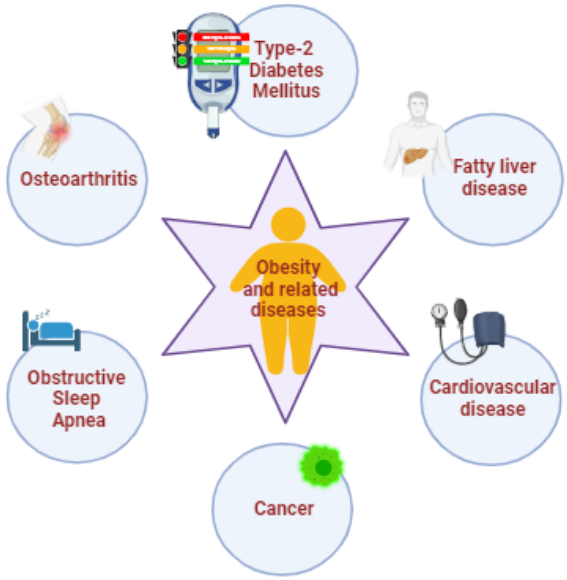
Therapeutic Concepts for Obesity and Related Diseases

According to the World Health Organisation, more than 2.5 billion adults, 18 years and older, were overweight in 2022. Of these, over 890 million were obese. At current, most of the world's population live in countries where overweight and obesity kills more people than underweight. In view of these alarming figures, health programmes and drug developments have been initiated worldwide to promote healthy lifestyles and prevent the development of obesity and related diseases in all ages. Obesity together with physical inactivity, insulin resistance, and genetic predisposition are the leading causes of the *Metabolic Syndrome* that puts people at higher risk of cardiovascular diseases (coronary heart disease, heart failure, or stroke), type-2 diabetes mellitus (T2DM), and diseases related to fat accumulation in organs such as non-alcoholic fat liver disease/non-alcoholic steatohepatitis (NAFLD/NASH). Various innovative treatment strategies based on incretin mimetics such as glucagon like agonists on the peptide 1 receptor (GLP1R) or agonists on the glucose dependent insulinotropic peptide receptor (GIPR) are now in development as therapeutic options to treat obesity and related diseases.



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The **Charité Research Organisation GmbH** has longstanding experience in the conduction of early phase projects for new medicines to improve metabolic diseases. We want to share our expertise and experience in this special Whitepaper that comes in three parts.

In **Part 1**, new treatment approaches for *obesity with or without T2DM* will be presented and discussed based on current research and applicable guidelines. The management of T2DM patients has much improved since the introduction of GLP1R agonists and sodium-glucose cotransporter 2 inhibitors (SGLT2i). Their use as treatment intensification for T2DM patients with cardiovascular and/or renal disease and/or corresponding risk factor obesity will be described according to national guidelines.

In **Part 2**, the key drivers in the pathophysiology of NAFLD/NASH and the recommended diagnostic tools to be used in clinical trials will be discussed. The recently approved THR-ß agonist Resmetirom and other pharmacological approaches for the treatment of *NAFLD/NASH with or without obesity* will be presented. Most of these are targeting metabolic dysregulations, intrahepatic lipotoxicity or inflammation. Other strategies include modification of genetic risk factors or activation of inflammatory immune cells.

In this **Part 3**, the diverse phenotypes of heart failure (HF) will be discussed with a special focus on the *cardiometabolic phenotype of HF with preserved ejection fraction (HFpEF)*, in which chronic cardiometabolic stress resulting from T2DM and/or obesity are key drivers of HF pathophysiology. The new treatment options for the cardiometabolic HFpEF population will be described based on the recent focused update of the ESC Guideline in 2023.

Introduction

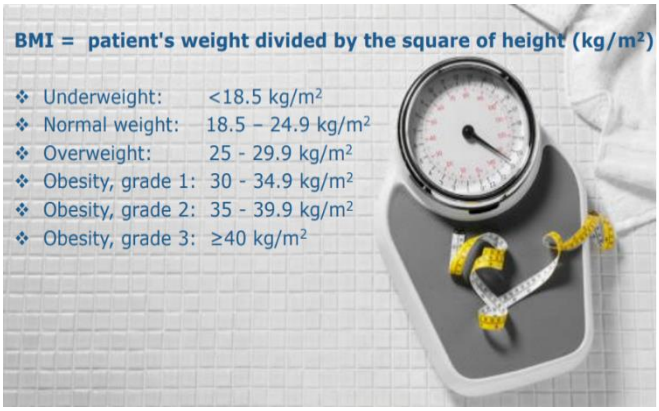
Human being is seemingly genius to circumvent its natural limits. Magnificent monuments like the Pyramids of Giza or the Colosseum in Rome bear witness to his genius.

Since then the big *Industrial Revolutions*, *Scientific-Technical Revolution* and now the *Digital Evolution* have made even the unbelievable possible. Reaching out to the moon and the stars - Whatever it takes! Any challenge is welcome, no hurdle too high. If not in real - the virtual is fine. Quantum computing, virtual and augmented reality, nanotechnology, driverless technology, artificial intelligence, incredible fast internet, workplace automation, robotics, reusable rockets will soon be part of our everyday lives. Everything around us is already moving faster than we ever could. Every tool we use gets smaller, but we get fatter and fatter just moving our brains but almost no muscle.

What are the numbers we are talking about?

According to the World Health Organisation (WHO), obesity has nearly tripled since 1975. In 2022, more than 2.5 billion adults, 18 years and older, were overweight. Of these, over 890 million were obese. Most of the world's population lives in countries where overweight and obesity kills more people than underweight [WHO 2024]. In view of these alarming figures, health programmes have been initiated worldwide to promote healthy lifestyles and prevent the development of obesity in all age groups. Education on healthy eating and avoiding a sedentary lifestyle is a top priority. For example, it is important to avoid soft drinks with high-fructose corn syrup as a sweetener as those increase the consumption of dietary fructose and contribute to the manifestation of overweight and/or obesity. In addition, the consumption of high-fat red meat should be reduced.

But how is overweight/obesity actually defined and what health risks can be derived from it?



Overweight and obesity mean abnormal or excessive fat accumulation in the body that may impair health. The Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). For adults, overweight is a BMI ≥ 25; and obesity is a BMI ≥ 30 (**Figure 1**).

Figure 1: BMI Categories [WHO 2000]

Obesity together with physical inactivity, insulin resistance, and genetic predisposition have been described as the leading causes of the *Metabolic Syndrome* in the 80's [Hanefeld & Leonhardt 1981] [**Figure 2**]. Metabolic syndrome including obesity puts people at higher risk of cardiovascular diseases (coronary heart disease and heart failure, or stroke), type-2 diabetes mellitus (T2DM), and diseases related to fat accumulation in organs such as non-alcoholic fat liver disease (NAFLD). In addition, obesity may provoke musculoskeletal disorders (especially osteoarthritis) and some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon). It is estimated that 4–9% of all cancer diagnoses are attributable to excess body fat, and that obesity correlates with

poorer prognosis for multiple malignant diseases (reviewed in Müller et al. 2022]. Obesity can consequently lead to serious diseases. Thus, it is of utmost importance to implement prevention programs stimulating life-style changes in the population and to develop drugs to treat obesity and related diseases.

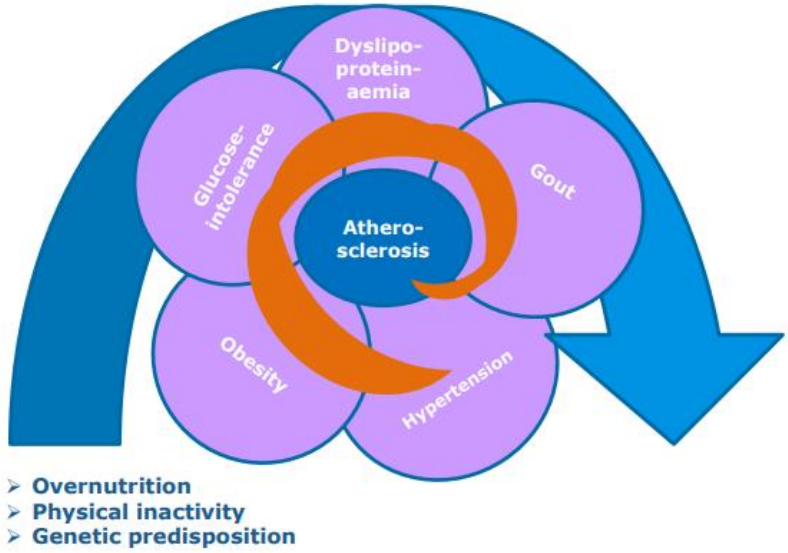


Figure 2: Metabolic Syndrome
Source: Adopted from Hanefeld & Leonhardt 1981

Various innovative treatment strategies based on incretin mimetics such as glucagon like agonists on the peptide 1 receptor (GLP1R) or agonists on the glucose dependent insulinotropic peptide receptor (GIPR) are now in development as anti-obesity drugs. The GLP1R agonists Liraglutide and Semaglutide have been already approved for weight reduction and/or improved control of hyperglycemia in T2DM patients. Dual incretin mimetics are in development and some of them such as Tirzepatide (GIPR/GLP1R agonist), which has been approved by the FDA in 2023, will probably soon be approved in Europe. And, triple incretin agonists are already on the horizon such as Retatrutide (GIPR/GLP1R + glucagon receptor (GCR) agonist). In the following, we will give an overview of the current management of *Obesity (Body Weight Reduction)* based on current practice and applicable guidelines.

Obesity Management

Overweight and obesity are recognized as disease states that in some circumstances can develop into complications. They are considered to be the result of interactions of genetic, metabolic, environmental and behavioral factors and are associated with increases in both morbidity and mortality [EMA Guideline Weight Management, 2017]. The recognition of obesity as a chronic disease serves to destigmatize the common belief that obesity is just a life-style condition resulting from lack of self-discipline [Bray et al. 2017; Burki et al., 2021]. This further provides the basis for healthcare providers and insurance companies to establish obesity management programs, promotes incentives for basic and clinical research, and encourages pharmaceutical companies to develop new medicines for body weight reduction. In Germany, these considerations have been taken up in the National Diabetes Strategy 2020 requesting complex measures for the prevention and treatment of obesity and diabetes. Four years later, the proposed national programs for an individualized, multimodal and interdisciplinary care for people with grade 1 to 3 obesity in Social

House Institution-accredited medical care (at the expense of the health insurance funds) needs still to be implemented. Fortunately, the healthcare market has already recognized the great medical need. For example, some small companies offer electronic aids (apps) for personalized weight management, some of which are also paid for by health insurance companies.

At present, the basic therapy for obesity continues to consist of reduced-calorie diet, exercise and behavioral therapy. The treating physician should skillfully motivate a comprehensive change in lifestyle risk factors including self-management education, nutritional counselling (5:2 diet, Mediterranean diet), increasing physical activity, and psychosocial counselling (if indicated). As smoking is associated with an increased risk of diabetes, possibly through increased insulin resistance [Maddatu et al., 2017]. Smokers should give up tobacco consumption. The goal is to achieve a decrease of at least 5 % of the body weight for BMI 25-35 kg/m^2 and of more than 10 % of the body weight for BMI >35 kg/m^2 [German Interdisciplinary S3 Guideline, 2014]. As lifestyle changes are often not sufficient to achieve a significant and long-lasting weight loss, adding pharmacological and/or surgical interventions is often indicated. Bariatric surgery represents the most effective approach to weight loss, leading to decreased mortality from cardiovascular diseases or cancer by 30% and 23%, respectively [Carlsson et al. 2020].

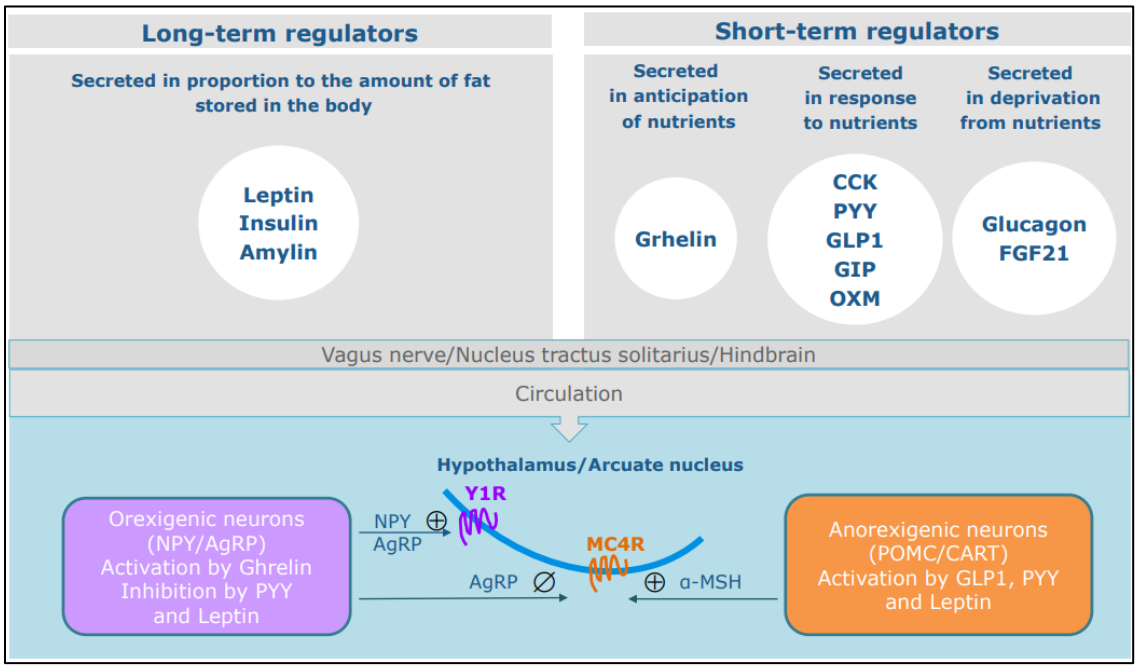


Figure 3: Regulators of food intake signaling to the brain
Figure based on review by Müller et al., 2022

In contrast, until recently it was a seemingly impossible task to achieve weight loss with sufficient tolerability and safety through long-term pharmacotherapy. Many drugs that were initially authorised had to be withdrawn due to cardiovascular adverse effects (Amfepramon), increased suicide risk (Rimonabant) or an increased likelihood of dependence and abuse (methamphetamine). In Germany, the lipase inhibitor Orlistat (generic) is still used to reduce triglyceride absorption; however, therapy is often discontinued due to gastrointestinal side effects (fatty stools, flatulence) and impaired absorption of hormone preparations. In 2021, EMA approved the melanocortin-4 receptor analogue Setmelanotide as therapy for genetic obesity (confirmed biallelic proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency). Over the last two decades, our

knowledge about the regulation of food intake has expanded enormously. We learned that various food intake-regulating hormones are involved in the central control of homeostatic and hedonistic eating behaviour [Müller et al., 2022] (**Figure 3**).

The gut-brain communication is driven by complex molecular communication between peripheral organs (gut, liver, and pancreas) and brain to avoid extreme situations such as starvation or overfeeding. The positive effects of the glucagon like peptide 1 (GLP1) on postprandial metabolism (improved glucose-dependent insulin secretion and insulin sensitivity of liver cells) led to the development of GLP1R agonists that are now integrate part of modern antidiabetic therapy. Weight loss however leads to a reactive influence on this complex gut-brain control system. Appetite and its hormonal mediators increase permanently. This is the biological reason for recurrent weight gain after dieting (*yo-yo effect*). If treatment is discontinued or reduced, a relapse inevitably occurs and long-term therapy seems unavoidable. The discovery that GLP1 receptor agonism in the arcuate nucleus (hypothalamus) causes an increased release of α-melanocyte stimulating hormone/activation of the melanocortin 4 receptor (MC4R) and a greater feeling of satiety, leading to weight loss has stimulated the development of new anti-obesity drugs such as Semaglutide (Wegovy®, NovoNordisk) that achieves clinical relevant and sustained weight loss without severe side effects [Müller et al., 2022; Rubino et al., 2021]. Similarly, the glucose dependent insulinotropic peptide (GIP) functions by improving insulin sensitivity in peripheral organs as well as in white adipose tissue and skeletal muscle [Samms et al., 2020]. The functional GIP-receptor (GIPR) is also expressed in human brain regions regulating food intake (such as hypothalamic nuclei and brainstem). As central or peripheral administration of GIPR agonists lowered weight by reducing caloric intake in animals, it is supposed that GIPR positive cells in the brain may enhance GLP1R signaling to anorexigenic neurons [Adriaenssens et al., 2019]. For these reasons, dual GLP1R/GIPR agonists have been developed such as Tirzepatide that has been already FDA approved as Mounjaro™ for the treatment of T2DM (2022) and as anti-obesity drug (2023). In April 2024, the EMA approved tirzepatide (Mounjaro®) solution for injection in a multi-dose KwikPen® presentation, for the treatment of T2DM (to be used alone for patients who cannot take metformin or in addition to other medicinal products for the treatment of T2DM as an adjunct to diet and exercise) and for weight management in adults with BMI ≥30 kg/m^2, or overweight (BMI ≥27 kg/m2 to <30 kg/m^2) with at least one weight-related comorbidity, alongside a reduced calorie diet and increased physical activity.

Finally, triple incretin mimetics are already on the horizon such as Retatrutide (GIPR/GLP1R and glucagon receptor (GCR) agonist). GCR agonism is known to delay gastric emptying, and reduces body weight by increasing energy expenditure with additional positive effects on lipid metabolism (reduced serum triglycerides and cholesterol). Retatrutide has already shown positive phase 2 results in overweight or obese people [Jastreboff et al., 2023].

The new drug candidates for the treatment of obesity (body weight reduction) are described in detail in Part 1 of this Whitepaper, which can be accessed via this LINK: https://www.charite-research.org/de/white-paper-therapeutic-concepts-obesity-and-related-diseases-inc-type-2-diabetes-mellitus-part-1.

In the following we focus on the pathophysiology and potential treatment approaches for obese patients with the *cardiometabolic phenotype of heart failure (HF), namely HF with preserved ejection fraction (HFpEF)*.

Obesity and Heart Failure

The HEART has played an important role since time immemorial. When people were excited, this organ beats faster. People were worried when it beats irregularly. In a moment of exuberance, people even want to give their hearts away. Its central role as a pump, which supplies all organs via the blood vessels and blood, was recognized at the latest since William Harvey (1628). William Withering discovered cardiac glycosides, which increased the strength of the heart (1785). In the 20th century, coronary artery disease, hypertension, valve diseases and arrhythmias were identified as the main causes of *congestive heart failure,* and which were targeted by several new drug developments. However, the CAST study (1986-98) with the increased mortality in the class 1 antiarrhythmic drug group demotivated the developers of new active substances with a direct effect on the heart muscle and its conduction system. Significant pharmacological progress was achieved through more indirect vascular relief (ACE inhibitors, AT1 receptor antagonists, endothelin receptor antagonists, etc.). Coronary artery disease has been treated by balloon dilatation since Andreas Grüntzig in 1977. Nutritionists must have been desperate, as the treatment of lipid metabolism disorders by diet or pharmacological intervention did not lead to a reduction in mortality until the early 1990s. It was not until the WOSCOP study that the considerably stronger statin effect proved the link between coronary sclerosis and hyperlipidemia.

The definition of Heart Failure (HF) refers to an inability of the heart to pump blood adequately to the body. HF is a highly prevalent condition, particularly in older age groups. In 2021, HF affected about 56 million people worldwide [Roth et al., 2023]. In 2022, heart failure was the third most common cause of death from cardiovascular disease in Germany with a percentage of 10.5 % [Statistisches Bundesamt (Destatis), 2022]. Measurement of the left-ventricular ejection fraction (LVEF) is used to distinguish HF with reduced EF (HFrEF; LVEF ≤ 40%) from HF with mildly reduced EF (HFmrEF; LVEF 41-49%) or HF with preserved EF (HFpEF; LVEF ≥ 50%). Over half of all HF patients are diagnosed with HFpEF [Pfeffer et al., 2019] that is associated with cardiac structural and/or functional abnormalities resulting in LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides [ESC Guidelines 2023, **Table 1**].

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.
[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy, or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.
[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

Table 1. Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction, and preserved ejection fraction
Source: ESC Guidelines 2023

As with other forms of heart failure, HFpEF is associated with cardiac energy deficiency resulting from impaired mitochondrial energy generation. This leads to impaired cardiac functional reserve on exertion and is associated with exercise-induced pulmonary congestion, resulting in heart failure symptoms such as exertional breathlessness, fatigue, and markedly reduced exercise capacity leading to severe impairment in quality of life.

Divergent trends of decreasing HFrEF and increasing HFpEF incidence, with stable overall HF incidence and high risk for mortality were observed in several U.S. community-based samples from 1990 to 2009 combining the Framingham Heart Study and Cardiovascular Health Study cohorts [Tsao et al., 2018]. Based on both study cohorts, an overall 67% mortality rate was documented within 5

years following HF diagnosis, but with only a small difference between HFrEF (33%) and HFpEF (29%). However, the risk of HF hospitalization is in general higher in patients with higher glycated haemoglobin, (diabetes), AF, a higher body mass index, and a low estimated glomerular filtration rate [Mosterd and Hoes, 2007]. Since the finding that more than 80% of patients with HFpEF are either overweight or obese with median/mean BMI of 31 kg/m^2 (TOPCAT study) or over 35 kg/m^2 (RELAX trial) [Redfield et al., 2013, Aggarwal et al., 2016] metabolic mechanisms are attracting greater interest as potential targets by drug developers.

Despite being associated with severe morbidity and mortality, HFpEF has very few evidence-based therapies. Disease-modifying HFrEF therapies could not be adopted for HFpEF as clinical trials with angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), and angiotensin receptor–neprilysin inhibitors (ARNI) failed to meet their primary endpoint in large HFpEF outcome trials [Martin et al., 2021; Solomon et al., 2019]. This dilemma led to the assumption of different systemic and myocardial signaling in HFpEF and HFrEF. Potential diverse phenotypes are since then discussed within the HFpEF population. Among the diverse HFpEF phenotypes, the ***cardiometabolic HFpEF phenotype***, in which chronic cardiometabolic stress resulting from type-2 diabetes mellitus (T2DM) and/or obesity are key drivers of HF pathophysiology, is rapidly emerging as the most prevalent form in HFpEF [Obokata et al., 2017; Savji et al., 2018]. In several clinical trials an increased epicardial adipose tissue was observed especially in obese HFpEF patients, which is supposed to exert deleterious effects on the myocardium such as myocardial steatosis and fibrosis [Packer 2018].

Obese HFpEF is associated with greater systemic inflammation indicated by significant higher plasma C-reactive protein concentrations, worse functional capacity, and more severely impaired quality of life as compared with non-obese HFpEF [Reddy et al., 2019; Reddy et al., 2020]. Thus, there is growing evidence for a central role of visceral adipose tissue (VAT) and associated insulin resistance as the key drivers for inflammatory processes in obese HFpEF resulting in an altered myocardial metabolism, microvascular endothelial dysfunction, myocardial steatosis/fibrosis and diastolic dysfunction [Verma et al., 2024] (**Figure 4**).

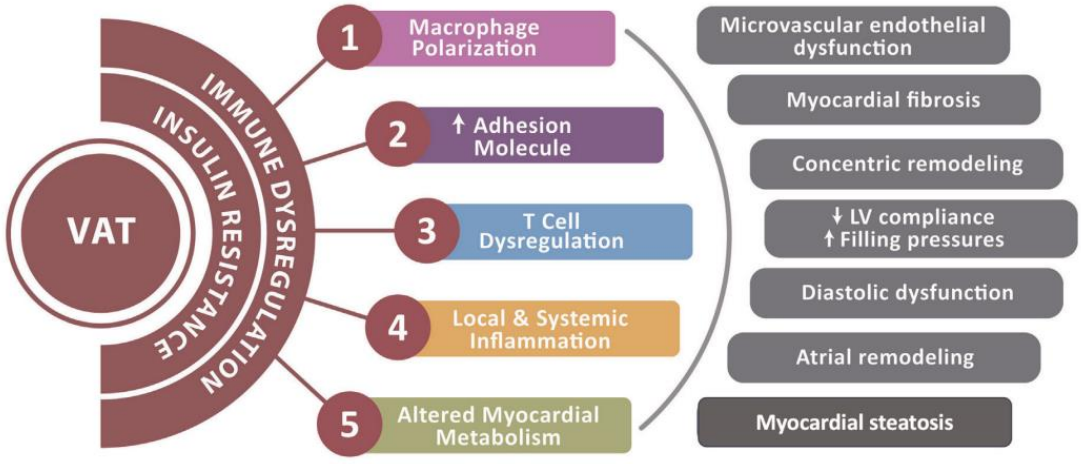


Figure 4. Central role of visceral adipose tissue in the genesis of HFpEF.
Source: [Verma et al., 2024]

Treatment approaches targeting T2DM and/or obesity are therefore thought to reduce mortality and hospitalization rate in HFpEF patients. As sodium-glucose cotransporter-2 (SGLT2) inhibitors have been already approved for their efficacy in HFrEF, it seemed obvious to test this drug class also in HFpEF. Two trials, the EMPEROR-Preserved trial and the DELIVER trial [Anker et al., 2021; Solomon et al., 2022], have recently shown positive results for SGLT2 inhibitors empagliflozin and dapagliflozin in patients with HF and LVEF >40%, that justify a class I recommendation for these drugs also in HFpEF [2023 Focused Update of the 2021 ESC Guidelines, **Figure 5**].

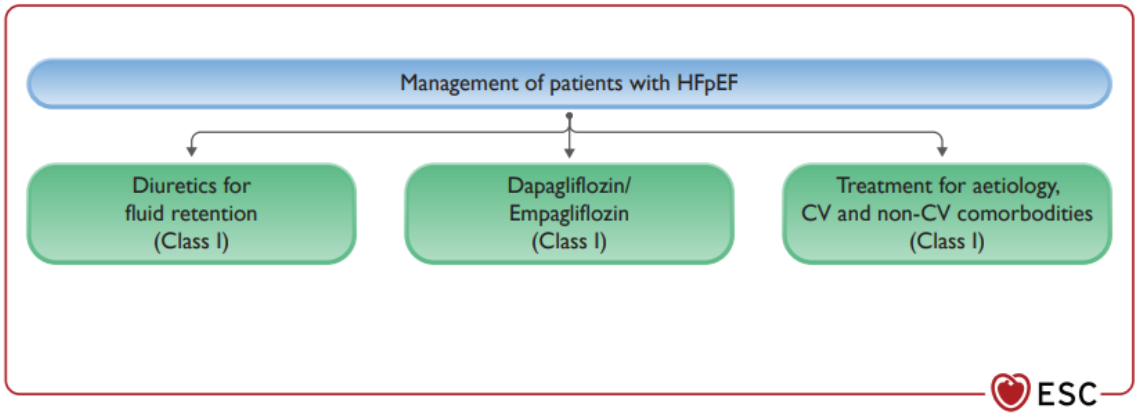
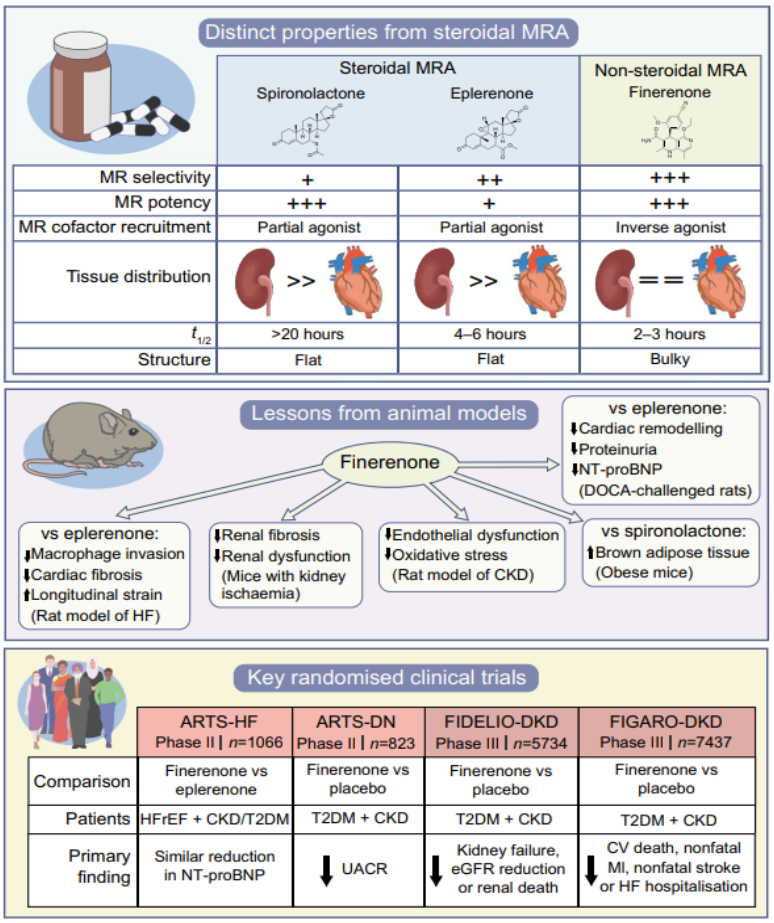


Figure 5: Management of patients with heart failure with preserved ejection fraction.
CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction
Source: 2023 Focused Update of the 2021 ESC Guidelines

Of note, the main benefit in both trials was a significant reduction in heart failure hospitalization rate, but not in cardiovascular mortality. In addition, in the EMPEROR-Preserved trial, about 48 % of screened HF patients were excluded mainly due to fact that the rather restrictive criteria for NT-proBNP elevation [i.e., >300 pg/ml for patients without atrial fibrillation, and >900 pg/ml for patients with atrial fibrillation were not met [Anker et al., 2021] - Supplement Table S1. In this study population with rather high NT-proBNP elevations, the *number need to treat (NNT)* to save one patient from HF hospitalization was calculated to be 32 over a period of 2 years. In the clinics and according to national health care guideline, the cutoff value for significant elevations of natriuretic peptides in this patient population is however lower (NT-proBNP > 125 pg/ml) [National Health Care Guideline Chronic Heart Failure, 2023]. Thus, it is questionable whether the study population really corresponded to the overall target group HFmrEF and HFpEF. The number needed to treat for those with NT-proBNP > 125 pg/ml and <300pg/ml remains elusive and should be elucidated in further trials.

The protective mechanisms responsible for the improvements observed in HFpEF patients treated with SGLT2 inhibitors are still under investigation. A recent meta-analysis demonstrated that patients treated with SGLT2 inhibitors as well as combined SGLT1/SGLT2 inhibitors, regardless of diabetic status, had a reduction in weight [−1.79 kg (95% CI: −1.93 to −1.66, $p < 0.001$)] and BMI [−0.71 kg/m2 (95% CI: −0.94 to −0.47, $p < 0.001$)] compared with placebo [Cheong et al., 2022]. This effect was also observed across different durations of follow-up and in patients with chronic kidney disease, cardiovascular disease, heart failure, or hypertension alike. Furthermore, combined SGLT1/SGLT2 inhibitors demonstrated a larger treatment effect than SGLT2 inhibitors compared with placebo. The magnitude of weight loss caused by SGLT2 inhibitors or SGLT1/SGLT2 inhibitors is however modest and can only partly explain the clinical improvements observed in obese or non-obese HFpEF in the EMPEROR-Preserved trial. SGLT2 inhibitors were originally developed as treatment for T2DM as they lower plasma glucose concentration by increasing renal glucose excretion. The increased glucose excretion via the kidneys results in an increased diuresis. This additional diuretic effect of SGLT2 inhibitors may enhance the effect of the diuretics that most HFpEF patients receive to treat pulmonary edema and volume overload and associated symptoms. It is therefore assumed that

obese or non-obese HFpEF patients mainly benefit from the additional diuretic effects of SGLT2 inhibitors.



As proinflammatory-profibrotic processes have been elucidated as important in the pathophysiology of HFpEF, these are also considered as attractive therapeutic targets [Paulus et al., 2021].
Regarding this, steroidal and non-steroidal mineralocorticoid receptor antagonists and specifically finerenone have shown potent anti-inflammatory and anti-fibrotic activity and improved multiple pathophysiological parameters of HFpEF in preclinical models. [Agarwal et al., 2021; Savarese et al., 2024] (**Figure 6**).

Figure 6. Characteristics and mechanisms of finerenone and classical steroidal MRAs
Abbreviation: CV = cardiovascular, DOCA = deoxycorticosterone acetate, HF = heart failure, MI = myocardial infarction; NTproBNP = N-terminal pro-B-type natriuretic peptide; T2DM = type 2 diabetes mellitus
Source: Savarese et al., 2024

Treatment with the steroidal MRA spironolactone in the TOPCAT trial (NCT00094302) resulted in a reduced HF hospitalization rate but no effect on mortality in HFpEF was seen [Pitt et al., 2014]. In 2022, the American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines have given a class 2b recommendation for MRA use, with the aim of reducing HF hospitalization, especially in the lower LVEF range [Heidenreich et al., 2022]. The ongoing SPIRRIT-HFpEF trial (NCT02901184) is now investigating in more detail whether the generic spironolactone may have indeed beneficial effects in HFPEF.
Interestingly, the non-steroidal MRA finerenone seems to exert also favorable effects in HF patients. In the FIGARO-DKD study, finerenone reduced the incidence of new-onset HF in patients with chronic kidney disease (CKD) and T2DM [Filippatos et al., 2022a]. In addition, subgroup analysis of the FIGARO-DKD and the FIDELIO-DKD trials have demonstrated favorable actions of finerenone in a larger population of patients with baseline characteristics of HFpEF (more female patients, higher BMI, and higher C-reactive protein) with CKD and T2DM [Filippatos et al., 2022a and 2022b]. The therapeutic potential of finerenone in HFpEF is currently investigated in a phase 3 study (NCT04435626, FINEARTS-HF) that evaluates the efficacy and safety of finerenone on morbidity and mortality in patients with HFmrEF and HFpEF. And, further nonsteroidal-MRAs such as KBP-5074 (Ocedurenone, NovoNordisk) are on the horizon of the HFpEF drug pipeline.

Furthermore, a significant proportion of HF patients presents some form of thyroid dysfunction including hypothyroidism, hyperthyroidism, or low T3 syndrome [Vale et al., 2019] (**Figure 7**). At the same time, patients with thyroid diseases are at potential risk of cardiovascular disease and associated pathophysiological conditions including a compromised myocardial contractility, ejection fraction, and heart failure [Razvi et al., 2018].

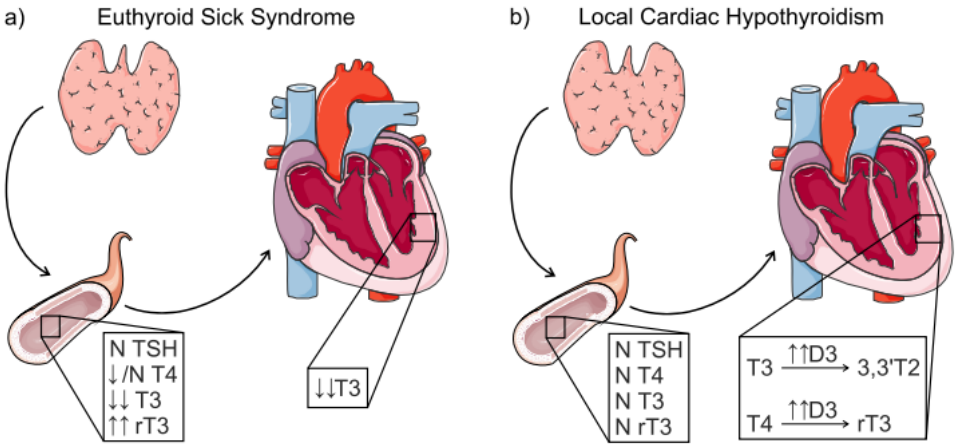


Figure 7. Systemic and local cardiac thyroid function in Euthyroid Sick Syndrome and Local Cardiac Hypothyroidism

a) Euthyroid sick syndrome presenting with its key features: low T3 and high rT3 serum levels as well as normal TSH and low to normal T4 serum levels. Local cardiac T3 levels are decreased.

b) Local cardiac hypothyroidism presenting with a normal systemic thyroid function and increased D3 (deiodinase 3) activity in the cardiac tissue leading to decreased local T3 and T4 levels. D3 inactivates T4 and T3, converting them into inactive reverse T3 (rT3) and 3,3-diiodothyronine (T2), respectively.

Source: Vale et al., 2019

Modulation of thyroid hormone receptors (THR) has emerged as potential therapeutic approach for several metabolic diseases including obesity, fat liver diseases, and cardiometabolic HFpEF. While the selective THR-β agonists, such as Resmetirom can selectively restore intrahepatic thyroid hormone function by increasing fatty acid β-oxidation, mitochondrial biogenesis, de novo lipogenesis, cholesterol and bile acid synthesis, and decreasing LDL cholesterol levels. [Karim & Bansai, 2023], other THR-β1 agonists such as Eprotirome have been withdrawn from clinical trials due to their undesirable effects [Jakobsson et al., 2017; Zucchi, 2020]. In March 2024, Resmetirom (Madrigal Pharmaceuticals) became the first drug which has been received the FDA approval for the treatment of NASH (non-alcoholic steatohepatitis) with liver scars due to fibrosis under the trade name Rezdiffra™. As the THR-α isoform is predominant in the human heart, the development of a tissue isoform-specific modulator for the treatment of cardiovascular disease including heart failure would be a promising approach to achieve therapeutic efficacy without deleterious side effects [Zucchi, 2020]. No such approaches are however currently in the drug pipeline.

New therapies *directly* targeting obesity in obesity-related HFpEF such as the incretin mimetics semaglutide (GLP1-RA) or tirzepatide (dual GIP/GLP1-RA) are considered promising drugs, and are currently in phase 3 of clinical development for HFpEF. In the STEP-HFpEF trial (NCT04788511), treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo in patients with HFpEF and obesity [Kosiborod et al., 2023]. Both, semaglutide and tirzepatide have been already approved for the treatment of patients with T2DM and as anti-obesity drugs. Therefore, one may assume that patients with cardiometabolic HFpEF will benefit from these treatments.

Drug Pipeline: Cardiometabolic HFpEF

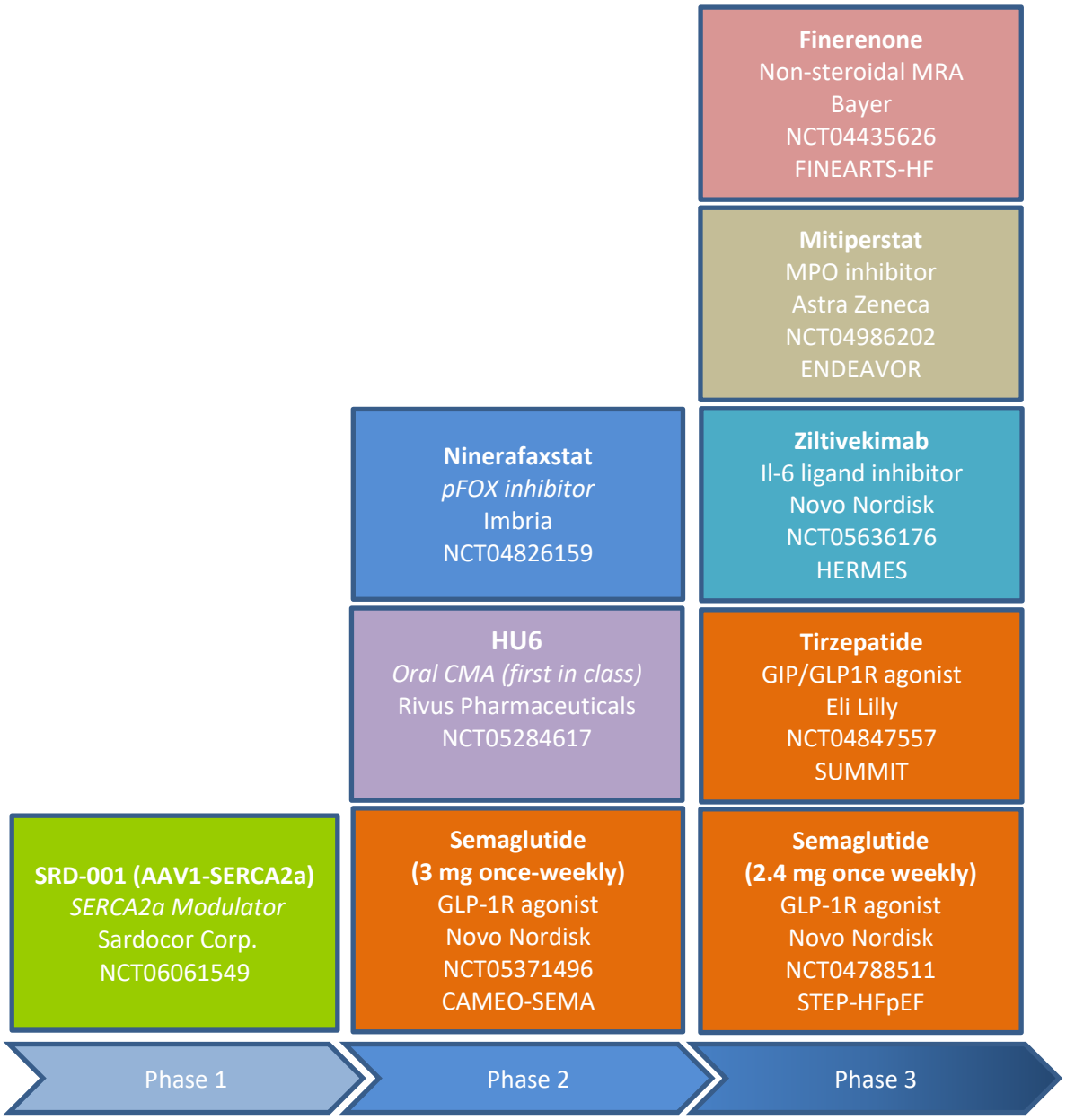


Figure 8. Drug pipeline for cardiometabolic HFpEF
Abbreviations: MPO = Myeloperoxidase; pFOX inhibitor = partial Fatty acid Oxidation Inhibitor; SERCA2a = Ca ATPase that regulates intracellular Ca levels by pumping Ca into sarcoplasmic and endoplasmic reticulum (SER)

Phase 1

SRD-001 (AAV1-SERCA2a) (Sardocor Corp.) is an investigational adeno-associated virus (AAV) vector-based gene therapy being evaluated for the treatment of HFpEF in the phase 1/2a MUSIC-HFpEF clinical trial (NCT06061549). SRD-001 has been designed to increase the protein expression and functional activity of SERCA2a, which is a subtype of sarcoplasmic/endoplasmic reticulum Ca2+ ATPase (SERCA) expressed in the heart. SERCA2a drives Ca2+ in the cytoplasm to re-enter into the SR and thus determines the contraction-relaxation cycle of cardiomyocytes. The rate of uptake of Ca2+ by the SR determines the rate of myocardial relaxation. The expression and activity of SERCA2a are reduced in failing hearts and are associated with calcium-handling defects leading to deteriorated ventricular relaxation [Zhihao et al., 2020] (**Figure 9**).

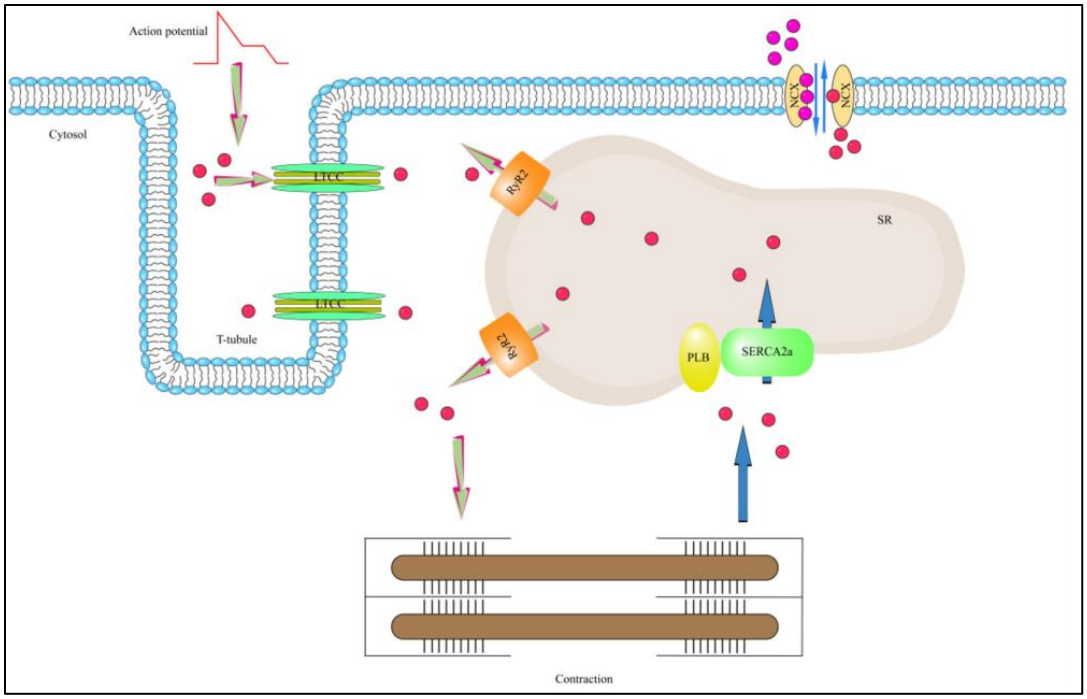


Figure 9. Calcium cycle in cardiomyocytes

During systole, in the presence of membrane depolarization, calcium ions enter the cytosol through LTCCs, which triggers a large amount of Ca2+ in the SR to enter the cytoplasm through RyR2. After reaching the critical concentration, Ca2+ bind to troponin C and the myofilament slides. During diastole, a large amount of Ca2+ re-uptake into the SR through SERCA2a, and the remaining Ca2+ are excreted from the cells through NCX.

Ca2+ are represented by red balls; Na+ are represented by purple balls. Two-color arrows indicate the contraction process and blue arrows indicate the diastolic process. LTCC, voltage-dependent L-type Ca2+ channel; RyR2, ryanodine receptor 2; SR, sarcoplasmic reticulum; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; PLB, phospholamban; NCX, Na+/Ca2+ exchanger

Source: [Zhihao et al., 2020]

SRD-001 is expected to improve relaxation defects in HFpEF via overexpression of SERCA2a protein. Sardocor's intracoronary infusion system allows for lessened dependence on tropism and for viral titers less than 1/100-fold per patient than seen in other conventional methods of administering gene therapy. The MUSIC-HFpEF trial will enroll up to 10 participants, who will be treated at a fixed dose of $3x10^{13}$ viral genomes. The primary end point is the change in pulmonary capillary wedge pressure measured at Week 24 and 52 posttreatment. In February 2024, SRD-001 has been granted *fast track designation* by the FDA and the first 3 patients have been dosed with the AAV vector-based gene therapy [HTTPS://WWW.CGTLIVE.COM/VIEW/SARDOCOR-HEART-FAILURE-GENE-THERAPY-SRD-001-GARNERS-FAST-TRACK-DESIGNATION-FIRST-PATIENTS-DOSED].

Phase 2

Ninerafaxstat -formerly IMB-1018972- (Imbria) is a novel, investigational cardiac mitotrope in development for a range of cardiac diseases characterized by a fundamental imbalance between energy consumption and energy supply in the heart resulting in cardiac energy deficiency. As a partial fatty acid oxidation (pFOX) inhibitor, ninerafaxstat is designed to shift cardiac substrate selection towards glucose oxidation which generates more energy in the form of ATP per unit of oxygen consumed than any other carbon substrate, thus increasing cardiac metabolic efficiency and support better cardiac mechanical efficiency and function.

Ninerafaxstat is currently investigated in part 2 of the phase 2 trial "IMPROVE-DiCE" (NCT04826159) that enrolls symptomatic patients with HFpEF to assess the impact of ninerafaxstat on cardiac energetics, diastolic function, functional capacity and heart failure symptoms. The trial uses multi-nuclear and state-of-the-art hyperpolarized MR spectroscopy to quantify the metabolic and energetic responses to ninerafaxstat in HFpEF. Part 1 enrolled pre-HFpEF patients with T2DM and obesity and demonstrated normalization of cardiac energetics, significant reduction in cardiac steatosis and improvements to the rate of diastolic filling, an important component of heart failure (results presented at the European Society of Cardiology Congress in August 2022 (HTTPS://WWW.IMBRIA.COM/MEDIA-CENTER/IMBRIA-ENROLLS-FIRST-PATIENT-IN-THE-PHASE-2-IMPROVE-DICE-CLINICAL-TRIAL-EVALUATING-NINERAFAXSTAT-IN-PATIENTS-WITH-HEART-FAILURE-WITH-PRESERVED-EJECTION-FRACTION/).

HU6 (Rivus Pharmaceuticals, Inc) is a *first in class* oral controlled metabolic accelerator (CMA) that provides a novel, measured approach activating proton leak and mitochondrial uncoupling, a natural process in the body that regulates and dissipates energy. HU6 is metabolized to 2,4-dinitrophenol (DNP) and increases proton leakage via adenine nucleotide translocase, thereby increasing fat oxidation and reducing the production of reactive oxygen species [Brand, 2000]. DNP was used as a weight loss drug in the early 1930s, but was never approved as drug due to its high peak concentrations which induce potentially dangerous side-effects, such as hyperpyrexia and increased basal metabolic rate. HU6 was therefore designed as a controlled-release formulation that minimizes the rapid absorption and high peak blood concentrations of DNP to provide a wider therapeutic index and improve safety.

HU6 has shown positive results in a phase 2a trial (NCT04874233) in subjects with NASH and high BMI between 28.0 and 45.0 kg/m^2 (inclusive), where it met the primary endpoint of reducing liver fat as well as secondary endpoints such as body weight loss, while conserving skeletal muscle mass. In addition, improvements in markers of insulin resistance and inflammation were observed [Noureddin et al., 2023].

HU6 is currently investigated in an exploratory phase 2 study (NCT05284617) to determine the safety, tolerability, PD, and PK of HU6 for the treatment of subjects with obese HFpEF. The primary outcome measure is the rate and amount of body weight loss over the course of 5 months treatment with HU6. Study completion is expected in June 2024. At current, the study status is however assigned as "Active, Not Recruiting" (accessed on 10-JUN-2024).

Phase 3

Semaglutide (Novo Nordisk) is a GLP1R agonist approved and established treatment for T2DM as well as for body weight reduction (obesity). Due to its positive pleiotropic effects including (but not limited to) improvements in the regulation of food intake, glucose metabolism and insulin sensitivity [Müller et al., 2022, Rubino et al., 2021; Samms et al., 2020], semaglutide is supposed to exert also positive effects on obese HFpEF. The results of the recently completed STEP-HFpEF trial (NCT04788511) support this hypothesis [Kosiborod et al., 2023; Verma et al., 2023; Borlaug et al., 2023]: The trial recruited 529 individuals with a well characterized phenotype of HFpEF and a BMI at least 30 kg/m^2 and randomized them to receive placebo or semaglutide 2.4 mg once-weekly for 52 weeks. Patients with T2DM were excluded from the trial. Therefore, only a few patients had been treated with an SGLT-2 inhibitor (3.6%) before the start of the study as those were not yet recommended for HFpEF patients at that time. Treatment resulted in marked improvements in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) with an estimated treatment difference of 7.8 points [95% confidence interval (95% CI) 4.8–10.9; P<0.001], in addition to an approximately 11% additional loss in body weight compared with placebo [Kosiborod et al., 2023] (**Figure 10**).

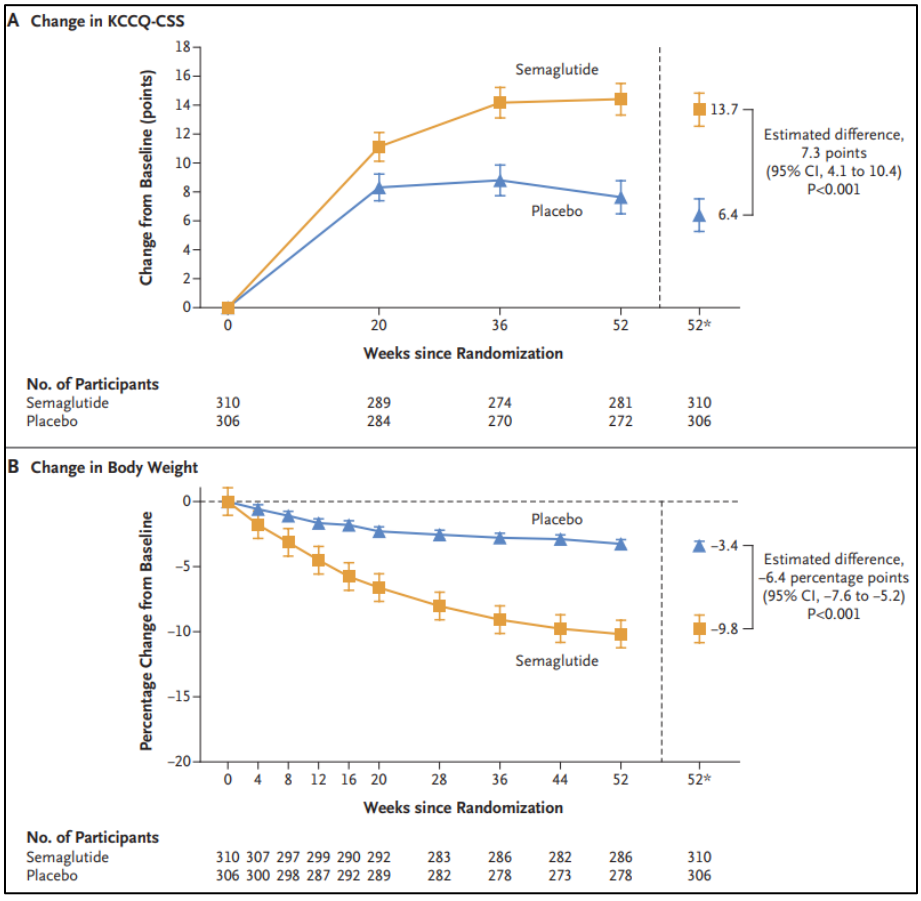


Figure 10. Change from Baseline to Week 52 in the Dual Primary End Points

Analyses are based on the treatment policy estimand, reflect the full analysis population, and are from the in-trial period. Shown are the observed (i.e., as-measured) mean changes from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and percentage changes in body weight. I bars indicate the standard error, and the numbers below the graphs are the numbers of participants contributing to the mean (with variations in participants attending certain trial visits). The data at week 52* are the estimated mean changes from baseline to week 52 based on analysis of covariance (ANCOVA) and an imputation approach for missing data.

Source: Kosiborod et al., 2023

Semaglutide treatment was also associated with statistically significant improvements in the 6 Meter Walking Test (6MWT)(estimated treatment difference of 20.3 meters (95% CI 8.6–32.1); P<0.001), a stratified win ratio of 1.72 (95% CI 1.37–2.15, P<0.001) in favor of semaglutide vs. placebo for the hierarchical composite outcome. The mean percentage change in the plasma concentration of C-reactive protein (CRP) was –43.5% with semaglutide and –7.3% with placebo (estimated treatment ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). Importantly, the benefits were observed consistently across the spectrum of ejection fraction, and across all domains of the KCCQ-CSS evaluated. Furthermore, sub-analysis suggested that greater weight loss on semaglutide was associated with higher improvements in KCCQ-CSS, and more reduction in CRP. The study was not powered for clinical events but showed numerical reductions in favor of semaglutide versus placebo for heart failure hospitalizations. These data are encouraging, and suggest that targeting weight reduction with GLP1R agonists is a promising approach in the treatment of obesity-related HFpEF.

Similar results were obtained in the phase 3 trial STEP-HFpEF DM (NCT04916470) demonstrating broad clinical benefits of semaglutide and safety findings to persons with HFpEF and T2DM [Kosiborod et al., 2024]. The weight loss observed with semaglutide in patients with T2DM was (as expected) about 40% less than the weight loss in patients without T2DM in the STEP-HFpEF trial. Thus, benefits with semaglutide may extend beyond weight loss and may include direct effects on vascular endothelial dysfunction, epicardial adipose tissue, inflammation, and insulin resistance. Consistent effects of semaglutide on heart failure–related outcomes were seen in the 32.8 % of patients who received SGLT2 inhibitors (which have emerged as a standard of care in heart failure with preserved ejection fraction) and in those who did not receive them.

In the recent phase 3 trial (NCT03819153, FLOW), semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease in the FLOW-trial [Perkovic et al., 2024]: The risk of a major kidney disease events (primary-outcome) was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P=0.0003). The risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P=0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).

In summary, the favorable effects of semaglutide on metabolism has the potential to reduce morbidity and mortality in patients with cardiometabolic HFpEF.

Therefore, Semaglutide high dose is now tested in the phase 2 trial CAMEO-SEMA (NCT05371496) to assess its cardiac and metabolic effects in 81 patients with HFpEF. The purpose of this research is to find out if an aggressive intervention for weight reduction, will improve symptoms in patients with obesity-related HFpEF. Subjects will receive semaglutide (3.0 mg titrated to 2.4 mg) subcutaneous once-weekly for 12 months in addition to counselling on healthy lifestyle intervention. The primary outcome measure is the change in Pulmonary Capillary Wedge Pressure (PCWP) during exercise. Study completion is expected by August 2026.

Tirzepatide (Eli Lilly) is a dual GIP/GLP1 receptor agonist that has already been approved by the FDA and EMA as Mounjaro® for the treatment of patients with T2DM and as an anti-obesity drug. Tirzepatide is currently in phase 3 stage of clinical trial evaluation to treat obesity-related HFpEF. The

main purpose of this trial (NCT04847557, SUMMIT) is to assess the efficacy and safety of tirzepatide in participants with HFpEF and obesity. At current, the trial status is assigned as active, not recruiting.

Finerenone (Bayer) is a novel highly selective, non-steroidal mineralocorticoid receptor antagonist (MRA) with high binding affinity. Based on preclinical and the currently available clinical data, finerenone has therapeutic potential in patients with HFpEF [Filippatos et al., 2022a; Filippatos et al., 2022 b]. Finerenone is currently investigated in a phase 3 trial (NCT04435626, FINEARTS-HF) to evaluate its efficacy and safety on morbidity and mortality in HFmrEF and HFpEF. Participants will be randomized to 20 mg finerenone (eGFR≤60mL/min/1.73m^2), 40 mg finerenone (eGFR>60mL/min/1.73m^2) or placebo. The primary outcome is a composite of cardiovascular death and heart failure events after 42 months of study treatments. The study has already enrolled about 6.016 participants. The estimated study completion date is June 2024. The current study status is Active, not recruiting.

Mitiperstat (AZD4831, Astra Zeneca) is a novel oral myeloperoxidase inhibitor in clinical development for treatment of patients with HFpEF or HFmrEF, non-alcoholic steatohepatitis (NASH) and chronic obstructive pulmonary disease [Parkinson et al., 2024]. In the previous phase 2a SATELLITE trial (NCT03756285), AZD4831 5 mg once-daily was given to 41 patients with HF and a LVEF of 40% or higher over a period of 90 days. Mitiperstat reduced normalized *ex vivo* myeloperoxidase specific activity by more than 50% from baseline and by 75% vs placebo, with few treatment-related adverse events and no safety signals of concern. Due to the Coronavirus pandemic, the trial was prematurely terminated and efficacy findings were exploratory and inconclusive, but the data support continued clinical development of mitiperstat as treatment for HFpEF [Lam et al., 2024]. Mitiperstat is currently tested in the phase 2b/3 trial (NCT04986202, ENDEAVOR) to evaluate its efficacy and safety in patients with HFmrEF or HFpEF with primary end points of change in KCCQ-OSS and 6MWD. The trial was completed in March 2024. No results are posted so far.

Ziltivekimab (Novo Nordisk) is a humanized monoclonal antibody directed against the IL-6 ligand. It was developed to inhibit pro-inflammatory IL-6 signaling in systemic inflammation, including atherosclerosis, chronic kidney disease, and rheumatoid arthritis [Kim et al., 2015]. The Fc domain of ziltivekimab has been engineered to extend its half-life (by increasing affinity for FcRn), to support once-monthly administration [Finch et al., 2011].

Ziltivekimab is currently investigated in the phase 3 trial (NCT05636176, HERMES) to evaluate the treatment effect for patients with HFpEF or HFmrEF and inflammation (CRP ≥ 2 mg/L). Participants will get study medication (ziltivekimab or placebo) for once-monthly injections. Study completion is expected in July 2027.

Concluding remarks

For many years we tried to treat obesity and related diseases by correcting single findings or metabolic deficiencies. Obese people were stigmatized due to the common belief that obese people have insufficient self-discipline:

- If you have overweight – „Lose weight! Eat half!“
- If you have type-2 diabetes - “Avoid carbohydrates, eat less! Substitute insulin!”
- If you have heart failure - „Reduce salt intake! Take medication!“

With increasing knowledge, a modern concept of obesity and its adequate treatment has been elaborated that includes the following:

- Obesity is not an isolated symptom but part of a complex *metabolic syndrome* that puts people at higher risk for cardiovascular diseases (coronary heart disease and heart failure, or stroke), T2DM, and diseases related to fat accumulation in organs such as non-alcoholic fat liver disease. Obesity is now recognized as an independent chronic disease with a high tendency to re-occur. This change in status is inextricably linked to the right to treatment.
- Obesity treatment consists of a comprehensive change in lifestyle risk factors including self-management education, nutritional counselling, increasing physical activity, and psychosocial counselling (if indicated). As lifestyle changes are often not sufficient to achieve a significant and long-lasting weight loss, adding pharmacological and/or surgical interventions is often indicated. The incretin mimetics semaglutide (Wegovy®, NovoNordisk) and tirzepatide (Mounjaro®, EliLilly) were recently approved by the FDA and EMA as new anti-obesity drugs, in addition to their approval as anti-diabetic drugs.
- As obesity is considered a risk factor for cardiovascular and/or renal diseases, therapy intensification with SGLT2 inhibitors or GLP1R agonists in addition to metformin should be considered.
- The most prevalent form in HFpEF is the cardiometabolic HFpEF phenotype (also called obese HFpEF), in which chronic cardiometabolic stress resulting from T2DM and/or obesity are key drivers of HF pathophysiology.
- Due to the positive results in the EMPEROR-Preserved and DELIVER trials, the SGLT2 inhibitors empagliflozin and dapagliflozin have recently received a class I recommendation as treatment for HFpEF [2023 Focused Update of the 2021 ESC Guidelines].
- New therapies *directly* targeting obesity in obese HFpEF could be the GLP1R agonist semaglutide and the dual GIP/GLP1R agonist tirzepatide which are currently in phase 3 of clinical development for this indication. Mineralocorticoid receptor antagonists (MRAs) such as spironolactone and finerenone have shown potent anti-inflammatory and anti-fibrotic activity, and improved multiple pathophysiological parameters of HFpEF in preclinical models. The phase 3 trials SPIRRIT-HFpEF with the generic spironolactone and the FINEARTS-HF trial with finerenone, are currently evaluating their clinical efficacy on morbidity and mortality in patients with HFmrEF and HFpEF.

The Charité Research Organisation GmbH is excited to watch, participate and contribute in a new era of medical science and clinical development. Stay tuned!

“It’s thrilling to chase after information which could potentially help hundreds of thousands of people. “

(Dr. Eugene Braunwald)

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