THE ROLE OF GLP 1 RECEPTOR AGONISTS IN TREATING HEART FAILURE: USEFUL OR NOT?

Laura Lungeanu-Juravle[1], Andra Nica[2], Emilia Rusu[2], Gabriela Radulian[2]
[1]Department of Cardiology - Clinical Hospital "Nicolae Malaxa", Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
Corresponding author: Dr. Laura Lungeanu-Juravle, Department of Cardiology - Clinical Hospital "Nicolae Malaxa", street Vergului, nr 12, Bucharest, Romania
Email: lungeanulaura86@yahoo.com

Abstract

Heart failure is not a single disease but a clinical syndrome with symptoms and/or signs caused by a structural/functional cardiac abnormality and represents a public health problem, leading to significant functional impairment, morbidity, and poor quality of life. In 2023, 64 million people had been diagnosed with heart failure and needed specific treatment. An important percentage is associated with diabetes mellitus type 2 (T2DM) as well. Because of the large etiology of this syndrome treatment should be leaded by the cause who underwent to heart failure. A few glucose-lowering therapies showed their efficacy in treating heart failure for patient with or without T2DM such as sodium glucose cotransporter inhibitors (SGLT-2 inhibitors) but the role of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is still investigated. At this point, evidence show no improvement in heart failure with reduced ejection fraction (HFrEF) treated with GLP-1 RAs but in heart failure with preserved ejection fraction (HFpEF) proves otherwise.

Rezumat

Insuficiența cardiacă nu este o singură boală ci un sindrom însoțit de semne și simptome determinate de modificări cardiace structurale sau funcționale și reprezintă o problemă de sănătate publică, determinând scăderea calității vieții și morbi-mortalitate crescută. In 2023, 64 de milioane de persoane au fost diagnosticate cu insuficiență cardiacă și au necesitat tratament specific. Un procent important din acești pacienți asociau și diabet zaharat tip 2. Tratamentul insuficienței cardiace este ghidat de către etiologia acesteia. Anumite terapii hipoglicemiante și-au demonstrat eficiența în tratamentul insuficienței cardiace cu sau fără diabet zaharat precum inhibitorii SGLT-2 dar rolul agoniștilor de receptor GLP1 este încă incert. Datele colectate în studii nu au demonstrat ameliorarea pacienților cu insuficienta cardiaca cu fracție de ejecție redusă tratați cu agonist de receptor GLP. In managementul insuficienței cardiace cu fracție de ejecție păstrate, agonistul de receptor GLP1 a demonstrat contrariul și poate reprezenta o terapie de viitor pentru aceasta categorie.

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Keywords: *heart failure (HF), diabetes mellitus type 2 (T2DM), Glucagon-like peptide-1 receptor agonists (GLP-1 Ras).*

Abbreviations: *heart failure (HF), diabetes mellitus type 2 (T2DM), Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), heart failure with preserved and reduced ejection fraction (HFpEF, HFrEF), diabetes mellitus type 2 (T2DM), left ventricle ejection fraction(LVEF), N-terminal pro–B-type natriuretic peptide(NTproBNP), Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-minute walk distance(6MWD), glucose-dependent insulinotropic polypeptide (GIP), glucagon (GCG), major adverse cardiovascular events (MACE), renin-angiotensin-aldosterone system (RAAS).*

Introduction and background

Heart failure is a challenging issue and a world-wide health problem with important consequences being the most frequent cause for hospitalization for patients over 65 years old. Almost half of them associate diabetes mellitus type 2 (T2DM) as well, this patient being even more vulnerable in developing more complications and deceasing early in their evolution.

Definition and classification

Heart failure is not a single disease but a clinical syndrome with symptoms and/or signs caused by a structural/ functional cardiac abnormality that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise[1].
It is mandatory to find out the etiology of the underlying cardiac dysfunction that led to HF to decide on subsequent treatment. The etiology varies: coronary artery disease[2], hypertension, valve disease, arrhythmias, cardiomyopathies (Takotsubo, peripartum, dilated, restrictive and others), congenital heart diseases, infective (HIV, LYME, myocarditis), drug-induced, infiltrative (amyloid, sarcoidosis), storage disorders (Fabry, haemochromatosis, glycogen abnormal storage), endomyocardial disease (postradiotherapy, carcinoid), pericardial, metabolic (endocrine and nutritional disease), neuromuscular disease (muscular dystrophy)[1,2].
The most common terminology used to determine the severity of HF is the New York

Heart Association (NYHA) functional classification but is not the best because there are many other better indicators in HF which are superior in prognostic value such as LVEF, NTproBNP, Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-minute walk distance (6MWD) and cardiopulmonary exercise testing[3].

Data from four HF clinical trials were used to examine the association of NYHA functional class with survival: TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist)[4], DIG (The Effect of Digoxin on Mortality and Morbidity in Patients With Heart Failure)[5], HF-ACTION (Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure)[6], and GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure)[7].

The results are implying that the prognostic value of NYHA classification is largely dependent on the baseline risk of the patient in which it is assessed[3]. So, the general assumption that the NYHA classification is an accurate measure of mortality risk and is consistent across studies for patients of a similar class is controversial[3].

Another classification of HF according to left ventricular ejection fraction (LVEF) includes HF with reduced ejection fraction (HFrEF): HF with LVEF ≤40%; HF with mildly reduced ejection fraction (HFmrEF): HF with LVEF 41–49%; HF with preserved ejection fraction (HFpEF): HF with LVEF ≥50%; and HF with improved ejection fraction (HFimpEF): HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF, and a second measurement of LVEF > 40%[8].

The burden of HF is increasing due to ageing, and this is paradoxally due to a better management of cardiovascular diseases in developed countries. Generally, is considered that the incidence is about 5/1000 person-year in Europe, but this assumption is based on the cases that are revealed by hospitalization[9, 10]. Worldwide there are 64 million of people diagnosed with HF and under specific treatment.

The prevalence is different and depends on the age of the patients: it is> 10% at over 70 years and less than 1% at <55 years[11,12,13,14].

HF is also underestimated being a diagnosis many times challenging, especially in primary care. From a base of patients of 36 748, diagnosed with HF at the time a hospitalization, during January 2010 to March 2013, more than 41% had a primary care consultation with one of three key HF symptoms recorded within 5 years prior to the hospitalization but no more investigation was required by a primary physician[15].

Review- Glucagon-like peptide-1 receptor agonists and cardiovascular diseases including heart failure

GLP-1 RAs was designed to function like the endogenous glucagon-like peptide 1 (GLP1), an incretin hormone produced by L cells in the intestine. Postprandially, the levels of GLP1 increase dramatically to stimulate insulin biosynthesis and release, suppress glucagon release, delay gastric emptying, improve glucose metabolism, and increase satiety[16, 17]. Drugs such as GLP-1 RAs enable control of blood glucose and weight loss with minimal side effects, proving beneficial in several other pathologies, including cardiovascular diseases, neurodegeneration, kidney disease, and cancer[17]. Several studies proven cardiovascular benefits by reduction of MACE for dulaglutide (REWIND), albiglutide (Harmony), Semaglutide (SUSTAIN-6), liraglutide (LEADER)[18]. However, the role of GLP-1 RAs in HF is still under research.

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Coronary artery disease is the most frequent etiology which leads to heart failure. Physiological acute inflammation is essential for cardiac repair and defense mechanisms after an injury such as myocardial infarction[19].

Sometimes inflammation becomes chronic under some cardiometabolic defects such as obesity, hypertension, and diabetes which are underlying causes for the genesis of sustained and suboptimal resolution of this process[19].

Some antidiabetic cardiovascular drugs (e.g., SGLT2 inhibitors, GLP-1 analogs) seem to have immunomodulatory properties and display potent antioxidant effects, with results on lowering cardiovascular risk[20]. In a double-blind, randomized and placebo-controlled trial, a group of 195 patients was included in four arms and examined during one year period: placebo, moderate-to-vigorous exercise (minimum of 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic physical activity or an equivalent combination of both), the GLP-1 RA liraglutide 3.0 mg/day, or a combination (exercise + liraglutide)[21]. The results showed that the patients who were on the combination of exercise and GLP-1 RA improved metabolic syndrome severity, abdominal obesity and inflammation measured by hsPCR[21].

So, it is reasonable to think that using GLP-1 RA in heart failure could be a critical breakthrough in treatment options available for these patients. A systematic review and meta-analysis published in 2023 used the information obtained by pooling the data from 9 randomized controlled trials (RCTs) comprising 871 subjects with HFrEF[22]. Patients from small study populations available with different modes of administration and in varying settings with established HFrEF on GLP-1 RAs with or without diabetes were evaluated on mortality, hospitalization due to acute exacerbation, left ventricular function, and aerobic endurance through 6-minute walk test (6MWT)[22].

The results suggested that GLP-1 RAs could not improve mortality or hospitalizations in HFrEF patients on this treatment and could not improve cardiac remodeling which is an important indicator of morbidity and long-term outcomes, with no improvement in LVEF or 6MWT[22].

But this meta-analyze contradicts some of the previous research published: in 2015 several 90 patients with non-ST-segment elevation myocardial infarction (NSTEMI) were randomized 1:1 to receive either liraglutide (0.6 mg for 2 days, 1.2 mg for 2 days, followed by 1.8 mg for 3 days) or placebo for 7 days and the results showed improved LVEF AND 6 MWT[23]. Another systematic review and meta-analysis for injectable or oral GLP-1 receptor agonists in patients with type 2 diabetes estimate the overall hazard ratio (HR) for MACE; its components; all-cause mortality; hospital admission for heart failure; a

composite kidney outcome consisting of the development of macroalbuminuria, doubling of serum creatinine, or at least 40% decline in estimated glomerular filtration rate (eGFR), kidney replacement therapy, or death due to kidney disease; worsening of kidney function, based on eGFR change; and odds ratios for key safety outcomes had encouraging results[24]. GLP-1 RA reduced the risk of individual MACE components, all-cause mortality, hospital admission for heart failure, and worsening kidney function in patients with type 2 diabetes[24].

So is plausible to assume that GLP-1 RAs is effective before the loss of LVEF after myocardial infarction and modulate inflammation and endothelial dysfunction in patients with cardiometabolic risk such as obesity and diabetes.

In August 2023 a randomized, double-controlled study using GLP-1 RAs in HFpEF for obese patients without diabetes randomly assigned 529 to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks[25]. The primary endpoints were the change from baseline in the clinical summary score KCCQ and the change in body weight, the secondary endpoints included the change in the 6-minute walk distance[25]. It is also known that patients with HFpEF and obesity have more adverse hemodynamic and clinical features and a greater symptom burden, worse functional capacity, and more severely impaired quality of life than those with heart failure with preserved ejection fraction but no obesity[25, 26, 27]. The results proved that 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[25]. In a prespecified analysis was assessed the effects of semaglutide across the baseline LVEF in patients with the obesity phenotype of HF with preserved ejection fraction (HFpEF) in the STEP-HFpEF where patients were categorized into 3 groups based on LVEF: 45% to 49% (n = 85), 50% to 59% (n = 215), and ≥60% (n = 229)[28]. The results on symptoms, physical limitations, and exercise function, and reduced inflammation and body weight to a similar extent across LVEF categories mentioned above[28].

HFpEF is frequent in patients with obesity because of the underlying common mechanism that include modulation of cardiac load (modified at obese persons), plasma volume, filling pressures, energy expenditure, sympathetic nervous activity, cardio-renal interactions, accumulation of fat and lipids. Essential is inflammatory cascade that triggers endothelial dysfunction, microvascular dysfunction, atrial fibrosis, insulin resistance, all of these known to contribute to coronary artery disease, atrial fibrillation, hypertension, diabetes, chronic kidney disease, and last but the most important to HFpEF[29].

Human epicardial adipose tissue (EAT) is a unique and multifunctional fat compartment of the heart, which is composed of adipocytes, nerve tissues, inflammatory, stromovascular, and immune cells[30]. Due to its distinctive composition and functional proximity to the heart, EAT can play an important role in the development and progression of coronary artery disease, atrial fibrillation, and heart failure, and given its rapid metabolism and simple measurability, can be considered a novel therapeutic target, owing to its responsiveness to drugs with pleiotropic and clear beneficial cardiovascular effects such as the glucagon-like peptide-1 receptor (GLP-1R) agonists[30]. Using microarray and immunohistochemistry analyses for samples of epicardial adipose tissue collected from 33 patients affected by cardiovascular diseases undergoing open

heart surgery the presence of glucose-dependent insulinotropic polypeptide (GIP), glucagon (GCG), and glucagon-like peptide-1 (GLP-1) was demonstrated. So, it may be a future development for associate treatments using two or three combinations of those molecules to target pleiotropic therapies for these patients who developed heart failure with coronary artery disease[30].

It is considered that GLP-1 RA has a key role in inflammation. That role can be partially explained by the interactions between renin-angiotensin-aldosterone system (RAAS) and GLP-1 RA. GLP1-RA counteract the action of angiotensin II inhibiting its synthesis, increasing the inactivation of its circulating form, and contrasting its action on target tissue like glomerular endothelial cells and cardiomyocytes, in this way being explained better the cardio-renal protective effects[31].

Conclusions

The role of GLP-1 RAs in HF needs more research to establish when it is beneficial (for example in HFpEF where needs to be compared with the effect of SGLT-2 inhibitors) and when is controversial to administrate. More studies in this area are needed because HF is a disease with growing incidence and prevalence and a public health problem leading to severely impaired quality of life and high mortality for patients.

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