Curr Heart Fail Rep (2015) 12:24–32
DOI 10.1007/s11897-014-0232-6

PHARMACOLOGIC THERAPY (WHW TANG, SECTION EDITOR)

Incretin-Related Drug Therapy in Heart Failure

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Published online: 17 October 2014

Abstract The new pharmacological classes of GLP-1 agonists and DPP-4 inhibitors are now widely used in diabetes and have been postulated as beneficial in heart failure. These proposed benefits arise from the inter-related pathophysiologies of diabetes and heart failure (diabetes increases the risk of heart failure, and heart failure can induce insulin resistance) and also in light of the dysfunctional myocardial energetics seen in heart failure. The normal heart utilizes predominantly fatty acids for energy production, but there is some evidence to suggest that increased myocardial glucose uptake may be beneficial for the failing heart. Thus, GLP-1 agonists, which stimulate glucose-dependent insulin release and enhance myocardial glucose uptake, have become a focus of investigation in both animal models and humans with heart failure. Limited pilot data for GLP-1 agonists shows potential improvements in systolic function, hemodynamics, and quality of life, forming the basis for current phase II trials.

Keywords Incretins · GLP-1 · DPP-4 · Heart failure · Left ventricular dysfunction · Diabetes · Obesity · Reperfusion injury · Myocardial metabolism

Introduction

Recent decades have seen several advances in heart failure (HF) therapy, but there remains a huge unmet need in pharmacological treatment of this chronic condition. HF is the leading cause of adult hospitalization in the developed world and half of the five million Americans living with HF will die within 5 years of diagnosis [1]. Pharmacological developments have largely targeted the sympathetic and renin-angiotensin-aldosterone systems aiming to optimize the neurohumoral state. However the hormonal dysregulation in HF is not restricted to the renin-angiotensin-aldosterone system. There are alterations in whole-body metabolism and myocardial energetics that contribute towards the downward clinical spiral characteristic of end-stage HF [2]. Central to this pathophysiology is the decreased energy efficiency in the heart itself.

The heart has been recognized as a metabolically active organ since the 1950s [3]. It generates and immediately consumes up to 30 kg of ATP daily [4], with around a 25 % reduction in ATP generation observed in cardiomyopathic hearts [5]. HF patients also demonstrate a shift in myocardial energy source; the normal heart principally utilizes fatty acid as an ATP source, but in decompensated HF, there is greater reliance on glucose metabolism [6]. Downregulation of fatty acid oxidation and upregulation of glucose utilization improves myocardial efficiency. Animal models have demonstrated superior contractile performance at a given myocardial oxygen consumption (MVO_2) when the heart is oxidizing more glucose and lactate and less fatty acids [7]. It has also been suggested that chronically compensated HF patients have an upregulation in lipid oxidation and decreased carbohydrate oxidation compared to healthy age-matched individuals [8–10]. Thus, therapies that acutely switch the cardiac energy substrate away from fatty acids and towards glucose may improve ventricular performance in the failing heart. As detailed below, use of the incretin-related therapies has emerged as a novel attempt to improve both myocardial energetics and whole-body metabolic status for HF patients, as a means to potentially improving clinical outcomes. Interest in this treatment strategy arose from the observation that HF and diabetes are closely related disease processes; not only does diabetes markedly increase the risk of incident HF [11],

This article is part of the Topical Collection on *Pharmacologic Therapy*

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but HF is also associated with subsequent onset of impaired glucose tolerance and insulin resistance [12,13].

Myocardial and Whole-Body Metabolic Changes in Heart Failure

There is a small existing literature supporting the concept of enhancing myocardial glucose and insulin availability to improve HF. Glucose-insulin-potassium infusions were shown to significantly reduce noncontractile basal MVO_2 in pigs, compared to those who received high-plasma fatty acids [14]. Similarly, in 12 male patients with ischemic cardiomyopathy, a glucose-insulin-potassium infusion was associated with acute improvements in wall motion score and ejection fraction [15]. A study of severe acute HF after brain death demonstrated that glucose-insulin-potassium was as efficient as dobutamine in improving ventricular systolic function [16]. However, it should be emphasized that the practice of using the combination of intravenous glucose, high-dose insulin, and potassium ("GIK" therapy) was concluded to offer no benefit in the setting of ST elevation myocardial infarction and may have caused harm in some settings [17]. Hence, there is no role for GIK in the routine management of myocardial infarction. If increased myocardial glucose delivery is beneficial in HF, this would also need to be achieved without the large intravenous volume load associated with GIK therapy.

The whole-body metabolic status is significantly disturbed in advanced HF. HF patients tend towards an insulin-resistant state [12], with impaired insulin sensitivity in the skeletal muscle and the potential for cardiac cachexia development [18]. Thus, it becomes challenging to differentiate the changes in cardiac energy substrate utilization that are inherent to the failing myocardium versus those that arise from changes in the peripheral metabolic milieu. Regardless, the incompletely understood dysregulation of myocardial energetics and whole-body metabolic status appear to be a reasonable focus for developing new treatment strategies. Specifically, incretin-related therapies that increase myocardial glucose delivery and counteract the insulin resistance of HF may hold promise for HF patients.

Incretin-Related Therapies in Diabetes

The incretins are a family of gut hormones that augment insulin secretion in a glucose-dependent manner. Incretin stimulation accounts for 50–70 % of postprandial insulin release [19]. Other effects include glucagon inhibition, decreased rate of gastric empting, promotion of weight loss, and protective effects on the pancreatic beta-cell, as illustrated in Fig. 1 [20]. The two main human incretins are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP, previously known as gastric inhibitory peptide). In patients with type 2 diabetes (T2DM), the response to GIP is impaired, but GLP-1 continues to be effective and has therefore been the focus of pharmacological development.

Over the past decade, incretin-related therapies have become increasingly popular in the management of T2DM. The subcutaneously injected GLP-1 receptor agonists offer improved glycemic control without the weight gain and higher incidence of hypoglycemic that complicate the use of sulphonylureas and insulin. They require subcutaneous administration because of their peptide structure that is susceptible to degradation by gastrointestinal enzymes. The current FDA-approved GLP-1 receptor agonists are listed in Table 1. Exenatide shows 50 % sequence homology with native GLP-1, whereas liraglutide retains 97 % homology. Exenatide is administered twice daily or once weekly as a microsphere preparation. Liraglutide is a once-daily formulation, whereas dulaglutide and albiglutide are once weekly. Lixisenatide, a once daily GLP-1 agonist, is licensed in Europe but not the United States. Conversely, the oral DPP-4 inhibitors prevent breakdown of native GLP-1 by blocking its enzyme degradation by DPP-4, so causing a physiological increase in GLP-1 levels. However, DPP-4 inhibitors offer slightly inferior glycemic control and are generally weight neutral [21]. There are currently four FDA-approved DPP-4 inhibitors, which are all administered once daily, as listed in Table 1. A fifth, vildagliptin, is available only in Europe and is administered twice daily. DPP-4 inhibitors and the GLP-1 agonist exenatide (twice-daily formulation) are only contraindicated in individuals with hypersensitivity to any of the compound ingredients. Exenatide (weekly formulation), liraglutide, albiglutide and dulaglutide are additionally contraindicated in individuals with a personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia syndrome type 2. Any of these drugs should be discontinued promptly if pancreatitis is suspected; a recent case control study demonstrated double the odds of admission for pancreatitis in patients with recent GLP-1 agonists or DPP-4 inhibitor use, relative to the odds in nonusers of these medications [22]. Hypoglycemia is an infrequent complication of the incretin-related medications in T2DM.

Protective Effects in Ischemia/Reperfusion

Incretin-related therapies quickly attracted attention regarding potentially favorable cardiovascular effects, both due to large-scale clinical data and smaller basic science studies. GLP-1 receptors are found on mouse cardiomyocytes and microvascular endothelium. GLP-1 delivery has been demonstrated to increase myocardial glucose uptake in rats, beyond the glucose uptake expected from GLP-1-dependent increases in coronary blood flow. It has been proposed that in normal rat hearts, GLP-1-stimulated myocardial glucose uptake occurs through increased myocardial nitric oxide production, p38

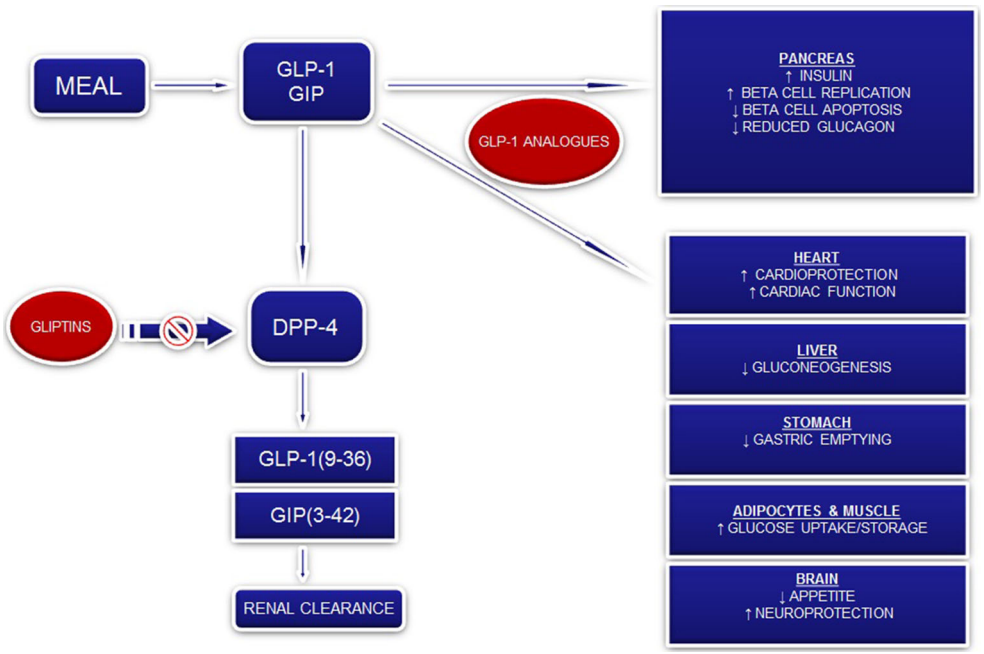

Fig. 1 Physiology of Incretins. Reproduced from *Khan MA, Deaton C, Rutter MK, Neyses L, Mamas MA. Incretins as a novel therapeutic strategy in patients with diabetes and heart failure. Heart Fail Rev. 2013 Mar;18(2):141–8* [59], with permission from Springer

MAP kinase activity, and GLUT-1 translocation, rather than via the classic insulin-signaling cascade involving Akt-1 activation and GLUT-4 translocation [23]. The p38 MAP kinase-mediated, nitric oxide-dependent mechanism of GLP-1-stimulated glucose uptake has since been endorsed in a conscious dog model too [24].

GLP-1 in Animal Models

Several animal studies have shown positive responses to GLP-1 in the setting of ischemia/reperfusion. In both isolated rat hearts and whole animal models, GLP-1 infusion (with an additive to prevent degradation by DPP-4) was seen to protect the myocardium from ischemia/reperfusion injury [25]. In the in vitro model, rat hearts treated with GLP-1 demonstrated markedly reduced infarct sizes compared to the control and additive-only groups. Furthermore this rat study suggested that phosphoinositide 3-kinase and p42/44 MAP kinase were on the pathway to GLP-1-mediated ischemia/perfusion injury protection. In an open-chest porcine heart model, GLP-1 treatment was associated with decreased interstitial levels of pyruvate and lactate during ischemia and reperfusion both in ischemic and nonischemic tissue, although the infarct size was unchanged [26]. A mouse model demonstrated higher post-infarct survival with liraglutide. After 7 days of twice daily treatment (liraglutide vs saline), liraglutide reduced post-infarct cardiac rupture (12 of 60 vs 46 of 60; $p=0.0001$) and infarct size (21±2 vs 29±3 %, $p=0.02$) and improved cardiac output (12.4±0.6 vs 9.7±0.6 mL/min; $p=0.002$). Liraglutide also altered the expression and activity of cardioprotective genes in the mouse heart [27]. Similar reductions in infarct size and prevention of ventricular function deterioration were demonstrated in a porcine model—this study used exenatide, which was administered by intravenous bolus and then twice-daily subcutaneous injection, rather than an intravenous GLP-1 infusion [28]. GLP-1 was also shown to limit myocardial stunning following brief occlusion of the left circumflex coronary artery in six conscious canines, versus eight controls [29].

Table 1 Summary of incretin-related pharmacological therapies

Incretin-related class	Glucagon-like peptide 1 (GLP-1) agonists	Glucose-dependent insulinotropic peptide (GIP)	Dipeptidyl peptidase-4 (DPP-4) inhibitors
Physiological role	Stimulates glucose dependent insulin release, inhibits glucagon release	Simulates glucose-dependent insulin release, stimulates lipogenesis in adipose tissue and reduces glucagon-stimulated lipolysis	Inhibits the enzyme that inactivates GLP-1 (conversion of 7–36 amide to 9–36) and GIP
Current FDA-approved pharmacological agents	Exenatide (twice-daily and once-weekly formulations), liraglutide, dulaglutide, albiglutide	(No pharmacological mimetics)	Sitagliptin, saxagliptin, linagliptin, alogliptin

DPP-4 Inhibitors in Animal Models

The DPP-4 inhibitor vildagliptin was similarly shown to reduce infarct size in a porcine model [30]. Use of early or late vildagliptin in a rat infarct model was reported as showing no significant effect on cardiac remodeling at 12 weeks, but there was evidence of systolic protection in both vildagliptin treatment groups (left ventricular ejection fraction, LVEF, in infarct control group decreased from 49±3 % at 3 weeks to 36±5 % at 12 weeks, as compared with 48±4 to 45±5 % in the early vildagliptin group and 49±3 to 48±4 % in the late vildagliptin group) and a nonsignificant reduction in infarct size [31].

GLP-1 in Human Trials

Parallel ischemia/reperfusion findings have been published for humans. Ten patients who received a 72-h GLP-1 infusion after successful primary angioplasty for myocardial infarction (MI) achieved improvements in left ventricular (LV) systolic function compared to 11 controls, although this study was nonrandomized [32]. In a randomized pilot trial of patients with normal systolic function and single-vessel coronary disease, the 10 individuals who received an infusion of GLP-1 showed improved recovery of LV stunning after left anterior descending balloon occlusion, as compared to 10 saline-infusion controls [33]. In another small study, 14 patients underwent two dobutamine stress echos, with an intravenous infusion of GLP-1 during only one of the studies. Global LV function at peak stress was superior during the GLP-1 infusion as compared to the control study (LVEF 77.0±4.4 vs 70.8±5.0 %, $p<0.0001$). GLP-1 also improved the regional wall LV function in 12 non-apical segments as evaluated by velocity, strain, and strain rate imaging, with the benefits predominantly seen in the ischemic regions. During recovery, infusion of GLP-1 was associated with reduced post-ischemic stunning compared to the control scan [34•].

DPP-4 in Human Trials

Similar findings were reported from a crossover study of 12 patients awaiting revascularization who underwent two dobutamine stress echos, one with a single dose of 100 mg sitagliptin and one with placebo [35]. Global LV function at peak stress was superior after sitagliptin compared to controls (LVEF 72.6±7.2 vs 63.9±7.9 %, $p<0.0001$), although it is unknown if the effect was GLP-1-mediated or due to off-target activity of the DPP-4 inhibitor. These preliminary studies raise the possibility that incretin-related therapies could acutely reduce infarct size and enhance functional recovery in patients with diabetes and coronary artery disease.

Effects of Incretin-Related Therapies in Heart Failure

GLP-1 in Animal Models

In addition to the cardioprotective effects seen after MI, GLP-1 may also benefit subjects with cardiomyopathies. Sixteen conscious dogs with a dilated cardiomyopathy treated with a continuous GLP-1 infusion showed improved LV systolic function after a 48-h infusion of recombinant GLP-1, as compared to eight cardiomyopathic control dogs who received 48 h of saline. GLP-1 was associated with significant increases in LV stroke volume and cardiac output and significant decreases in LV end-diastolic pressure, heart rate, and systemic vascular resistance. GLP-1 also increased myocardial insulin sensitivity and glucose uptake [36]. A spontaneously hypertensive HF-prone rat was used to evaluate a longer-term GLP-1 infusion [37]. At 9 months of age, 50 rats were randomized to either a 3-month continuous GLP-1 infusion or a saline infusion. Rats receiving GLP-1 had better survival after 3 months of treatment (72 vs 44 %, $p=0.008$), decreased myocyte apoptosis, and increased myocardial glucose uptake. Other small animal models have shown that exenatide administration from 8 to 10 weeks of age in cardiomyopathic mice improves ventricular function and survival [38] and that chronic treatment with GLP-1 in rats with post-infarct HF is associated with improved ejection fraction, ventricular filling pressures, cardiac output, and ventricular remodeling [39].

GLP-1 in Human Trials

A human pilot study of a 3-day GLP-1 infusion in 6 patients with T2DM and New York Heart Association (NYHA) class II–III HF reported a trend towards improved myocardial tissue Doppler imaging with GLP-1, although the small sample size and absence of controls limit interpretability [40]. A larger pilot study by Sokos et al. investigated the safety and efficacy of a 5-week infusion of GLP-1 (2.5 pmol/kg/min) in addition to standard therapy in 12 NYHA class III/IV patients, as compared to 9 HF patients on standard therapy alone in a non-randomized, non-blinded study design [41]. Left ventricular ejection fraction showed significant improvement in the GLP-1 group (21±3 to 27±3 %; $p<0.01$) but not controls (21±4 to 22±4 %); peak oxygen consumption (peak VO_2) improved in the GLP-1 group (10.8±0.9 to 13.9±0.6 mL/kg/min; $p<0.001$) but not controls (13.3±0.9 to 13±1.0 mL/kg/min); 6-min walk distance improved significantly in the GLP-1 group (232±15 to 286±12 m; $p<0.001$) and trended towards improvement in controls (233±21 to 258±21 m); and quality of life score also significantly improved in the GLP-1 group (64±4 to 44±5; $p<0.01$) with a nonsignificant improvement in controls (52±12 to 46±12). The improvement in LVEF in the GLP-1 group could not be accounted for by changes in blood pressure and was observed both in patients

with and without diabetes. Of note, the mean body mass index was in the mildly obese range, and so it is unclear if the apparent benefits of GLP-1 in HF would extend into normal- or under-weight patients.

Another small human HF study randomized 20 NYHA II–III patients without diabetes and with ischemic HF in a double-blind crossover design. Participants received both a 48-h GLP-1 intravenous infusion (0.7 pmol/kg/min) and a 48-h placebo infusion, in a random order, on two separate occasions at least 14 days apart. Fifteen patients completed the crossover protocol. GLP-1 increased insulin (90±17 vs 69±12 pmol/L, $p=0.025$) and reduced glucose levels (5.2±0.1 vs 5.6±0.1 mmol/L, $p<0.01$). However, there was no significant impact on cardiac function: cardiac index remained unchanged (1.5±0.1 vs 1.7±0.2 L/min/m^2, $p=0.54$), as did LVEF (30±2 vs 30±2 %, $p=0.93$), tissue Doppler indexes, body weight, and BNP [42•]. This negative result may have been related to the lower HF acuity of this study population (NYHA II–III symptoms), an underpowered sample size, use of a lower GLP-1 infusion dose than Sokos et al., or the limitations of a short GLP-1 infusion as opposed to a more chronic administration period. However, it is also notable that Halbirk et al. established the most rigorous protocol of the small GLP-1 HF trials (randomized doubled-blinded crossover design), which highlights the need for caution in interpreting less strictly designed pilot studies.

Interestingly, eight patients in this trial experienced hypoglycemia related to GLP-1, which typically has a low incidence in diabetic populations using GLP-1 and underscores the potential for different side effect profiles in the HF/non-diabetic subpopulation. In addition, the use of intravenous infusions in these studies, rather than the subcutaneous preparations approved for T2DM, may limit the clinical utility in a chronic HF setting. The half-life of bioactive GLP-1—the GLP-1 (7–36) amide—is less than 2 min due to rapid degradation by DPP-4, and so it will be critical to determine whether these cardiac benefits can be reproduced using delivery methods other than a continuous intravenous infusion. The cleavage product of GLP-1 (7–36) is GLP-1 (9–36), the predominant plasma metabolite. Encouragingly, this metabolite did seem to produce the same effects as GLP-1 (7–36) in canine models of both HF and ischemia/reperfusion injury. This implies existence of an additional signaling pathway, as GLP-1 (9–36) is not thought to interact with the known GLP-1 receptor [43,44].

Nathanson et al. demonstrated a rapid hemodynamic impact during intravenous exenatide infusion among patients with diabetes and HF [45•]. Of 237 patients screened, 20 males with class II–IV HF participated in the randomized, double-blinded crossover protocol. After an overnight fast, all participants received an infusion of glucose and insulin to maintain normoglycemia, followed by 6-h infusions during two consecutive days of exenatide (0.12 pmol/kg/min) and placebo, and finally an 18-h washout period. The pulmonary capillary wedge pressure decreased at 1, 3, and 6 h after infusion initiation by −1.3±0.8 (−8 %), −1.2±1 (−8 %), and −2.2±0.9 (−15 %) mmHg during exenatide infusion versus 0.3±0.5 (2 %), 1±0.6 (6 %) and 1.4±0.7 (8 %) mmHg during placebo infusion ($p=0.001$). The thermodilution cardiac index also increased at 3 and 6 h by 0.4±0.1 (23 %) and 0.33±0.1 (17 %) L/min/m^2 during exenatide infusion, versus −0.02±0.1 (−1 %) and −0.08±0.1 (−5 %) L/min/m^2 during placebo infusion ($p=0.003$). The portion of participants attaining the primary outcome of a 20 % decrease in wedge pressure was 10/20 in the exenatide group and 2/20 in placebo ($p=0.008$); a 20 % increase in cardiac index was achieved by 15/20 in the exenatide group and 4/20 in placebo ($p=0.001$). However, the increased cardiac output was due to higher heart rates with exenatide: heart rate increased at 1, 3, and 6 h by 8±3 (11 %), 15±4 (21 %) and 21±5 (29 %) beats per min (bpm), during exenatide infusion versus −1±2 (−2 %), 1±1 (2 %) and 6±2 (8 %) bpm during placebo ($p=0.006$), with no significant increase in stroke volume during exenatide treatment. Two patients required digoxin to terminate rapid atrial fibrillation. It is unclear why such marked chronotropy was seen and whether this represents improved myocardial energetic performance or a potentially detrimental upregulation in sympathetic activity in the heart, which is known to be a poor prognostic factor in HF.

Cardiovascular Effects of Incretin-Related Therapies in Diabetes

The cardiovascular safety studies for incretin-related therapies for glycemic control in patients with diabetes have also been suggested to support potential cardioprotective benefits. Many therapies for diabetes, including the sulphonyulureas, thiazolidinediones, and insulin have shown either a neutral or a negative effect on cardiovascular events [46–49]. Hence, there has been great interest in the possibility that the incretins could represent the only diabetes therapy, other than perhaps metformin [50], to have a potential beneficial effect on cardiovascular outcomes in the high-risk diabetic population. There have been reports that the GLP-1 agonists may improve lipid panels, even independent of weight loss, and reduce high-sensitivity C-reactive protein levels [51–53]. A meta-analysis of 32 GLP-1-agonist trials reported a very minor reduction in systolic blood pressure by −1.79 mmHg (95 % confidence interval, CI, −2.94 to −0.64) and −2.39 mmHg (−3.35 to −1.42) compared to placebo and active control, respectively [54]. There was also a small overall increase in heart rate by 1.86 beats/min (95 % CI 0.85 to 2.87) versus placebo and 1.90 beats/min (1.30 to 2.50) versus active

control, which is comparatively mild compared to the rate increases seen in HF subjects by Nathanson et al. above.

Best et al. retrospectively analyzed a medical and pharmaceutical insurance claim database and identified 39,275 patients with T2DM treated with exenatide twice daily and 381,218 patients treated with other glucose-lowering therapies, all with no ischemic events in the preceding 9 months [55]. Patients initiated on exenatide had greater baseline cardiovascular risk, with higher prevalences of coronary artery disease, obesity, hyperlipidemia, and hypertension. However, the exenatide-treated patients had a lower rate of cardiovascular events during the retrospective study period than non-exenatide-treated patients (hazard ratio 0.81, 95 % CI 0.68–0.95, $p=0.01$) and lower rates of CVD-related hospitalization (0.88, 95 % CI 0.79–0.98, $p=0.02$) and all-cause hospitalization (0.94, 95 % CI 0.91–0.97, $p<0.001$). Prospective randomized trials are reportedly in progress investigating the impact of the GLP-1-agonists liraglutide, exenatide, lixisenatide, and dulaglutide (not yet FDA-approved) on cardiovascular events [56]. These studies may prove useful in further clarifying whether the postulated cardiovascular benefits of GLP-1 agonists translate to improved cardiac outcomes for high-risk patients with diabetes.

A meta-analysis of 18 studies evaluated the cardiovascular risk of DPP-4 inhibitors for patients with diabetes. In pooled analysis, the risk ratio for any adverse cardiovascular event with a DPP-4 inhibitor was 0.48 (95 % CI 0.31–0.75, $p=0.001$) and for nonfatal MI or acute coronary syndrome was 0.40 (0.18–0.88, $p=0.02$) [57]. However, in a recent randomized controlled trial of 16,492 high-risk patients with diabetes assigned to saxagliptin versus placebo showed no impact on ischemic events at median 2.1 years and actually increased the rate of HF hospitalization (3.5 vs 2.8 %; hazard ratio 1.27, 95 % CI 1.07–1.51, $p=0.007$) [58]. The reason for this discrepancy remains unclear.

Current Trials of Incretin-Related Therapies in Heart Failure

A phase II trial is currently underway to specifically evaluate the role of GLP-1 therapy in the setting of advanced HF. The FIGHT trial ("Functional Impact of GLP-1 for Heart Failure Treatment") began in April 2013, with estimated completion in April 2016 (ClinicalTrials.gov NCT01800968). Acute HF patients, with or without diabetes, who have been recently hospitalized, are randomized to 6 months of subcutaneous liraglutide versus placebo. Participants are discharged on a dose of 0.6 mg liraglutide/placebo daily for 7 days. The dose is incremented to 1.2 mg daily from days 7 to 30 and then further escalated to 1.8 mg daily from days 30 to 180. The study will compare primary endpoints of time to death, time to hospitalization, and time-averaged proportion change in NT-proBNP, over 180 days. Secondary endpoints include echocardiographic change in LV structure and function, change in symptom score (Kansas City Cardiomyopathy Questionnaire) from baseline to 180 days, and change in 6-min walk distance at 30, 90, and 180 days. It is hoped that the results will determine whether subcutaneous GLP-1 is associated with improved clinical stability in the 6 months after a decompensation admission. The broad objective is to provide a basis for a larger randomized phase III clinical trial. The results of FIGHT are eagerly anticipated because they represent a departure from reliance on surrogate parameters of HF treatment efficacy measured at short intervals after therapy initiation, as described in the pilot studies above.

Other current trials of GLP-1 agonists in HF populations include a trial of liraglutide (1.8 mg daily) and metformin versus glimepiride (4 mg daily) and metformin in patients with non-insulin-dependent diabetes and HF (ClinicalTrials.gov NCT01425580). The primary endpoint will be LV longitudinal function and/or functional reserve during rest and/or after exercise using tissue Doppler echocardiography at 18 weeks. Glaxo-Smith-Kline has recently completed a multi-center, placebo-controlled study to evaluate the safety of a new GLP-1 agonist GSK716155 and determine its effects on myocardial metabolism, myocardial function, and functional capacity in NYHA Class II/III HF (ClinicalTrials.gov NCT01357850). This study utilized three metabolic primary outcomes at 3 months: myocardial glucose utilization as assessed by fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, resting myocardial efficiency (work performed/myocardial oxygen uptake) using echocardiography and 11C-acetate PET imaging, and peak oxygen uptake (VO_2 max) as assessed by bicycle cardiopulmonary exercise testing. No data has been reported thus far. The "LIVE-study" using liraglutide in chronic HF patients with and without diabetes also recently began recruiting patients (ClinicalTrials.gov NCT01472640). This multi-center, randomized, double-blind study aims to recruit 240 systolic HF patients (half with T2DM) to study the effect of liraglutide 1.8 mg daily versus placebo, with a primary outcome of change in LVEF from baseline to week 24. DPP-4 inhibition is also being further evaluated in HF patients. Novartis have completed, but not yet reported, a study to evaluate the effect of vildagliptin on LV function in patients with T2DM and NYHA class I–III HF over 52 weeks (ClinicalTrials.gov NCT00894868). The primary outcome measure was non-inferiority to placebo with respect to change in LVEF; a secondary measure evaluated the efficacy of hemoglobin A1c change in patients with diabetes and HF at 16 weeks.

The data obtained from these ongoing studies will be crucial in deciding the viability of incretin-related therapies as a novel strategy in HF management.

Conclusion

This review has presented a range of small, but generally consistent, animal and human studies suggesting beneficial effects of incretin-related therapies in the setting of ischemia/reperfusion and HF. Thus, there is cautious optimism in the HF field that GLP-1 agonists may offer a novel treatment strategy. It should be acknowledged that the proposed role for incretin-related therapy remains largely theoretical and the clinical benefits may be restricted to GLP-1 agonists administered by continuous infusion. Additionally, HF trials of incretin-related therapies will need to discriminate between overweight/obese subjects and those who are developing cardiac cachexia, as it is conceivable that there may be differential responses to augmented insulin secretion in differing body habitus subgroups. HF patients without T2DM may also be more vulnerable to hypoglycemia.

It remains important to underscore the limitations to current knowledge regarding the changes in metabolic function during HF. Myocardial substrate utilization is particularly poorly understood, with contradictory basic science reports, an absence of human studies comparing the in vivo heart in health and disease, and the inability to specifically manipulate substrate uptake as HF progresses. Fundamentally, it is still unclear whether shifts in substrate utilization are adaptive or maladaptive, and hence, it remains possible that augmenting myocardial glucose uptake may not be the correct route to improving energetics in the failing heart. Furthermore, if GLP-1 does improve clinical HF outcomes, it will be difficult to determine whether the benefit lies in modulating myocardial energetics or in ameliorating the whole-body metabolic dysfunction and insulin resistance that accompanies HF. However, given the current shortfall of available medical therapies in advanced HF, the use of GLP-1 agonists appears to be a worthy strategy to pursue in seeking novel treatment pathways to improve HF outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Amanda R. Vest declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Funding and Disclosures The author did not receive funding for this work, and has no financial relationships or other industry disclosures to make. This article does not contain any studies with human or animal subjects performed by the author.

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