

Review Article

Metabolic Modulation with Incretins: Is the Bloom off the Rose?

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Abstract

For the better part of a half century, cardiovascular physiologists have recognized that the failing heart is characterized by perturbations in myocardial metabolism whether or not heart failure is accompanied by myocardial ischemia. These metabolic derangements have long been a target of therapeutic intervention but with little or no evidence of therapeutic benefit. Attempts to drive substrate uptake, oxidation, or utilization have all proven ineffective in altering the natural history and clinical symptoms in heart failure. The shift in substrate preference from fatty acid to glucose oxidation as a means to achieve oxidative efficiency has led to a focus on driving glucose metabolism. Early efforts to employ supplemental insulin, glucose and potassium (GIK) inadvertently exacerbated heart failure due to the volume requirements. These early failure led to a consideration of agents which further impair fatty acid oxidation as an intrinsic means of driving glucose utilization but to no avail. Thus, the emergence of incretin based therapies as an intrinsic insulin dependent means to increase glucose uptake and disposal were heralded as a next generation of metabolic adjuvants. Their emergence on the scene corresponded to a period in which modifying cardiovascular outcomes in diabetes has become an equally compelling clinical objective particularly given the occurrence of diabetes and heart failure in the world's population. Here we review what has been learned regarding the cardiovascular effects of incretin based therapies and their impact on the progression of heart failure. At this point, effective metabolic modulation with incretins in heart failure remains elusive.

Keywords: Heart Failure; Myocardial Metabolism; Incretins; Glucagon-Like-Peptide-1; Metabolites

Metabolic Modulation in Heart Failure: The Rationale

In a normal functioning heart, fatty acids are the predominant energetic substrate. Under circumstances of stress, the relative balance of energetic substrate shifts toward the use of glucose as a more efficient source of ATP, reducing oxidative stress both in the cytosol and the mitochondria. Such a transition in substrate is characteristic of the failing human heart and serves to protect basic cellular function by preserving ambient ATP levels at the expense of contractile reserve. However, over time, intracellular accumulation of un-oxidized lipids interrupts intracellular signaling mechanisms that mediate insulin action and impair glucose uptake and oxidation. Myocardial insulin resistance leads to further metabolic stress and compromises not only myocyte contractility but cellular integrity. Deprived of available substrate, stores of high energy phosphates decline as heart failure progresses. These observations have spurred a search for metabolic modulators as innovative therapies to improve myocardial energetic and halt the progression of heart failure. Despite the well-established pathophysiological concepts of alterations in myocardial metabolism that occur with advancing heart failure, the pursuit of therapeutic interventions has proven elusive. Agents that reduce fatty acid oxidation in order to reduce oxidative stress have met with mixed results [1-3]. Similarly, administration of exogenous insulin to drive glucose metabolism as the preferred substrate in

advanced heart failure have been plagued by the requirements of simultaneous infusion of dextrose to avoid hypoglycemia, further exacerbating underlying volume overload [4,5]. Thus, the promissory note remains unfulfilled with respect to metabolic modulation in heart failure as a new therapeutic approach.

The Allure of Incretin Based Therapy

For these reasons, there was a great deal of enthusiasm when incretin therapies emerged as an effective treatment for Type 2 diabetes. Glucagon-Like Peptide-1 (GLP-1 7-36 amide) is a naturally occurring incretin peptide released from intestinal L cells that enhances cellular glucose uptake by stimulating insulin secretion. The insulin stimulating actions of GLP-1 cease at glucose levels below 4 mmol/L, mitigating the risk of hypoglycemia and the need for dextrose infusion. GLP-1 also promotes increased glucose uptake in target tissues via mechanisms independent of insulin action. GLP-1 receptors have been identified in myocardium and in vascular and endocardial endothelium making GLP-1 administration a putative pharmacologic intervention in heart failure and ischemic heart disease as a means to favorably influence myocardial metabolism.

Native GLP-1 (7-36) amide requires continuous infusion due to rapid hydrolysis *in vivo* by the ubiquitous peptidase, Dipeptidyl Peptidase-4 (DPP-4). GLP-1 analogs that are resistant to DPP-4 permit intermittent subcutaneous administration with dosing

intervals from 12 hours to one week. These properties have stimulated both GLP-1 analog development as well as inhibitors of DPP-4 as new treatments for type 2 diabetes. However, despite being effective in lowering the glucose and glycated hemoglobin levels as well as weight reduction, several historical classes of anti-diabetic medications (thiazolidinediones) have increased rather than decreased the risk of cardiovascular events. Therefore, regulatory agencies now require cardiovascular outcome data from randomized controlled trials prior to approving new agents for the treatment of diabetes. Many of the recent GLP-1 receptor agonist and analogues, as well as DPP-4 inhibitors, have been subject to such scrutiny. These studies have further informed the paradigm as to whether and to what extent incretin based therapies confer cardiovascular benefit.

Robust Pre-clinical Data

There have been promising preclinical studies of GLP-1 using conscious, chronically instrumented large animal models of myocardial ischemia and heart failure, as well as proof of concept studies in humans. The studies have looked at short term (48-72 hours) and intermediate term (4 weeks) infusions of native GLP-1 (7-36) amide. In conscious, chronically instrumented dogs, GLP-1 infusions (1.5pmol.kg.min) attenuated post ischemic contractile dysfunction after brief periods of myocardial ischemia [6,7]. In the same study, GLP-1 administration hastened the recovery of regional wall motion abnormalities and impaired isovolumic relaxation compared to control. In dogs with non-ischemic pacing induced cardiomyopathy, a 48 hour infusion of GLP-1 (7-36) increased stroke volume, left ventricular dP/dt, and left ventricular ejection fraction while decreasing left ventricular end diastolic pressure and systemic vascular resistance [8]. In senescent beagles, GLP-1 infusion for 4 weeks improved whole body and myocardial insulin resistance, and protected against the development of an accelerated course of heart failure following rapid pacing [9]. These promising studies in large animal models, together with vast literature demonstrating enhanced post ischemic recovery in mice and rats [10,11] led to early consideration of the use of GLP-1 in humans with heart failure and impaired LV systolic function.

Proof of Concept Trials in LV Systolic Dysfunction in Humans

Nikolaidis et al. [12] enrolled eleven patients status post reperfusion after acute myocardial infarction and reduced ejection fraction to receive a three day infusion of GLP-1. There was an increase in LVEF (from $29\pm 2\%$ to $39\pm 3\%$, $p < 0.01$) compared to controls and a shorter length of stay (6 versus 10 days, $p < 0.02$). In a double blind, randomized controlled clinical trial of safety and efficacy, Nathanson et al. [13] reported that the intravenous infusion of GLP analog exenatide significantly increased cardiac index and decreased pulmonary wedge pressure at 3 and 6 hours after infusion compared to placebo. This study was performed in diabetics with and LV EF $< 35\%$.

In a pilot study, Sokos et al. [14] showed that a five week infusion of recombinant GLP was associated with significant improvements in 12 patients with chronic severe HF (NYHA III-IV). There was improvement in LVEF, Minnesota Quality of Life score, 6 minute walk distance and exercise VO₂ max. There seems to be metabolic modulation with infusion of GLP beyond glycemic control given the

favorable effects in this study were similar in magnitude in diabetics and nondiabetics. However, Halbrik et al. [15] did not observe changes in cardiac index or LVEF during a limited 48 hour infusion of GLP-1 in nondiabetic patients with ischemic heart disease and NYHA II-III symptoms of HF. Note that the duration of exposure to treatment was substantially less (48 hours) compared to 5 weeks in the Sokos study.

The Results of Randomized Clinical Trials

Several different classes of incretin therapies have been examined in large randomized clinical trials of the gluco-regulatory effect and secondary cardiovascular outcomes data. The cardiovascular safety profile of DPP4 inhibitors showed an increased the risk of heart failure hospitalizations when Saxagliptin was used in SAVOR [16]. However, sitagliptin did not affect risk of heart failure hospitalizations in type 2 diabetics overall and among high risk patients in TECOS [17].

More recently, investigators have examined the impact of GLP-1 analogues directly in subjects with established heart failure. Margulies et al. [18] enrolled 300 patients in a phase II randomized, double blinded, placebo controlled clinical trial. The Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial enrolled hospitalized high risk patients with a reduced ejection fraction (LVEF $< 40\%$) and NYHA class 2 (30%) or 3 (60%). Liraglutide, a subcutaneous GLP-1 agonist, was initiated in the immediate discharge period. Patients were followed for 180 days and assessed for clinical stability by a composite clinical end point. On average, patients had HF for 8 years and 90% had been hospitalized with HF at least once in the year before the index hospitalization. Sixty percent had diabetes and the average LV EF was 26%. The primary endpoints were time to death, time to HF hospitalization and time averaged proportional change in NT-pro BNP from baseline to 180 days. Secondary end points included change in cardiac structure and function by echocardiogram from baseline to 180 days. Additional secondary end points were functional status based on the 6 minute walk distances at 30, 90 and 180 days, changes in symptoms, based on the Kansas City Cardiomyopathy Questionnaire from baseline to 180 days. Liraglutide produced no improvement in the primary composite endpoint with a trend toward increase adverse outcomes among diabetics treated with liraglutide.

LePore et al. [19] looked at the effects of 12 weeks of treatment of albiglutide, a long acting GLP -1 agonist in patients with stable, chronic heart failure with reduced LV EF $< 40\%$ and NYHA functional class II to III symptoms. A 30mg dose was compared with placebo in 81 randomized patients. There was a modest increase in peak oxygen consumption which was measured at the peak of exercise. However, LV EF, 6 minute walk test, myocardial glucose use and oxygen use, which were not measured at peak exercise, showed no improvement.

ELIXA (Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome) compared Lixisenatide with placebo in $> 6,000$ patients for a median of 25 months with diabetes and a recent acute coronary event, including 22% with a history of heart failure [20]. Lixisenatide had no effect on the primary composite endpoint (death, myocardial infarction, stroke, or hospitalization for unstable angina) or the rates of hospitalization for heart failure.

The LEADER (Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation) trial investigated the cardiovascular safety of liraglutide in >9000 adults with type 2 diabetes [21]. LEADER enrolled two distinct populations of high risk patients (1) patients with prior CVD were >50 years old and had one or more of the following cardiovascular comorbidities: concomitant CVD, cerebrovascular disease, peripheral vascular disease, chronic renal failure or chronic heart failure (2) patients without prior CVD were >60 years old at screening and had one or more cardiovascular risk factors including LV systolic or diastolic dysfunction. There were 1599 patients with CHF. NYHA class IV excluded and most were AHA/ACC stage A or B. The patients enrolled in this phase 3B, multicenter, international, randomized, double-blind, placebo controlled clinical trial received liraglutide administered at 0.6mg daily for one week, 1.2mg, for an additional week and a potential maximum dosage thereafter of 1.8mg based on tolerance. Compared with placebo, the addition of liraglutide reduced the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke during a follow up period of 5 years.

In SUSTAIN-6, semaglutide significantly improved HbA1c and bodyweight in patients with type 2 diabetes compared with placebo [22]. This was a multicenter phase 3A trial evaluating the efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes. Marso et al. [23] reported that in 3260 patients with type 2 diabetes and high cardiovascular risk, semaglutide reduced risk for composite cardiovascular outcome at a median of 2 years when compared with placebo. In this non-inferiority trial, the primary outcomes were: CV death, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included an expanded CV composite: primary composite components, revascularization, or hospitalization for heart failure or unstable angina.

Thus, the impact of DPP-4 inhibition or the use of long-acting GLP-1 analogues on cardiovascular outcomes varies with the agent employed, the power of the trial design, and the cardiovascular outcome of interest.

Is the Bloom off the Rose?

Despite compelling preclinical data and early proof of concept in humans, the results to date are mixed and disappointing with respect to the effects of long acting GLP-1 receptor agonists and DPP-4 inhibitors in heart disease, particularly in heart failure. What might explain these results? In the studies reviewed above, while there is variation in the CV outcomes, GLP-1 analogs reduce weight; improve blood pressure and diabetic control. These effects will in turn, lower risk of cardiovascular disease in the long term. However, the direct effects to improve symptoms of heart failure have not been observed. So why have the results of relevant large animal models of heart failure not translated into benefits in humans? First, incretin based therapy may have its most favorable effects in acute decompensated heart failure in earlier stages. The positive signals in Leader in contrast to FIGHT support the importance of study in earlier stages of heart failure. Secondly, the acute metabolic derangements in ischemic heart disease may be more amenable to metabolic modulation with incretins than LV dysfunction associated with non-ischemic etiologies. Thirdly, there may be important pharmacologic differences

in the cardiovascular actions of native GLP-1 compared to DPP-4 inhibitors and long acting analogues.

These may include important differences in the affinity and binding characteristics of the GLP-1 analogs at the GLP-1 receptor as well as the effective concentrations at the GLP-1 receptor whose density may be significantly less in cardiovascular tissues. In both the FIGHT and LEADER trials, the GLP-1 analogue liraglutide was used as the therapeutic agent. Like most of the synthetic analogues developed principally for the treatment of diabetes, liraglutide is DPP-4 resistant in an attempt to maximize its effects as a glucose-dependent insulin secretagogue. However, the density of GLP-1 receptors on pancreatic beta cells is a log order greater than on cardiac myocytes. As such, the dose and binding kinetics at the receptor may vary for large analogues like liraglutide. DPP-4 inhibitors result in increasing endogenous levels of GLP-1 but only within the physiological range of 20-30 pM. While these doses elaborated in proximity to pancreatic beta cells are sufficient to elicit an insulinotropic response, they are below the 100-120pM level required to observe a cardiovascular response. By contrast, prior studies in both large animal models and proof of concept trials in humans in which GLP-1 was found to be salutary employed the continuous infusion of native GLP-1 (7-36) amide which is the natural receptor agonist. Secondly, there is a growing body of evidence that the metabolites of native GLP-1 [GLP-1 (9-36) and GLP-1 (32-36)] have important cardiovascular effects [8,24,25]. These metabolites appear to be responsible for vasoactive properties of the peptide which may be particularly beneficial in heart failure [26]. DPP-4 resistant analogues will not generate these metabolites and may therefore be devoid of their putative vascular benefits. Thus, while the findings to date in large clinical trials have been disappointing, these large clinical trials have not directly tested the efficacy of native GLP-1 and its active metabolites which proved effective in relevant large animal models and in proof of concept studies in human. As such, it may be premature to close the books on this class of agents with respect to their putative cardiovascular benefits in heart failure.

A Call for Comparative Effectiveness Trials

The findings from this review suggest that it will be important to conduct a comparative effectiveness trial of classes of incretins (native GLP-1 (7-36) amide, DPP-4 inhibitors, and GLP-1 analogues) to determine whether and to what extent the native peptide and its active metabolites are critical to the cardiovascular effects. Alternatively, clinical trials designed to use short term IV infusion of GLP-1 (7-36) amide in acute decompensated heart failure, particularly of ischemic etiology, may be insightful. The fact that a chronic oral preparation is not available should not preclude prematurely the potential biological benefits of this class of agents.

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