Heart failure (HF) is a leading cause of mortality and morbidity in the industrialized world and imposes a substantial burden on public health. In the United States, HF is the primary cause of death for more than 60,000 people annually and a contributing factor in over 282,000 cases. Despite guideline-recommended therapy for patients with HF and reduced ejection fraction, the 1-year mortality in patients with New York Heart Association (NYHA) functional class III to IV HF on maximal medical therapy is 35% to 40%. Based on recent estimates, approximately 5.1 million adult Americans have HF, and projections show that by the year 2030 the prevalence of HF in the United States will increase by 25%. By any metric, HF imposes a major public health and financial burden on society. The lack of new disease-modifying pharmacological therapy for HF over the past 2 decades further amplifies these concerns.

Importance of Hospitalization for Acute HF Syndrome
Hospitalization for acute HF syndrome (AHFS) is a significant predictor of increased mortality, recurrent hospitalization, increased resource consumption, impaired functional status, and worsened quality of life. Even after excluding patients with shock, several recent studies indicate that the rate of the composite end point of death or rehospitalization at 60 days post discharge is consistently >30% among patients hospitalized for AHFS. Although studies have identified some patient characteristics affecting the risk of this composite end point, no widely accepted risk prediction model has emerged to date.

Failure of Short-Term Interventions
Previous large-scale studies have examined numerous interventions for preventing posthospitalization death or rehospitalization. Although some in-hospital treatments for AHFS have favorably affected in-hospital metrics, such as the rate of decongestion, or dyspnea scores, nearly all have failed to affect posthospitalization mortality or readmission or both. Included among these failed interventions are intravenous milrinone, hemodynamically guided therapy, tolvaptan, levosimendan, rolloffiline, nesiritide, and ultrafiltration. Currently, the lone exception is recombinant relaxin-2 therapy with the Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) trial reporting reduced 180-day mortality but no improvement in the rates of cardiovascular death or rehospitalization. Thus, while AHFS hospitalization identifies increased risk, it seems that sustained interventions during the vulnerable early months after a HF hospitalization will be required to affect the high rates of rehospitalization and mortality in this population.

Why Cardiac Metabolism as a Therapeutic Target for HF
Even in the absence of acute coronary insufficiency, an increasing body of literature supports the concept of the failing heart as an energy-starved organ. The heart consumes more energy per gram than any other organ, and myocardial metabolic demands are further increased in the setting of HF by pathological hypertrophy, increased wall stress, neurohormonal stimulation, and vasoconstriction. As illustrated in the Figure, cardiac myocytes can use a variety of substrates to generate ATP. Under normal circumstances, fatty acids constitute the predominant fuel for ATP generation by cardiac myocytes. In pathological cardiac hypertrophy, changes in transcription factors and cofactors reduce fatty acid oxidation by downregulating genes involved in fatty acid transport and utilization, resulting in an increased reliance on glucose metabolism. However, as HF continues to progress, the myocardium becomes progressively insulin-resistant, which limits uptake of vitally needed glucose by the plasma membrane glucose transporters 1 and 4. The net result of these metabolic
Glucagon-Like Peptide-1 Is a Metabolic Modulator with Therapeutic Potential in HF

Glucagon-like peptide-1 (GLP-1) is a naturally occurring incretin peptide released from intestinal L cells that enhances cellular glucose uptake by stimulating insulin secretion and by enhancing insulin sensitivity in target tissues. In normal physiology, endogenous GLP-1 is implicated in the control of appetite and satiety. Administration of exogenous GLP-1 as a continuous infusion in patients with type 2 diabetes mellitus causes an impressive increase in insulin sensitivity in both skeletal muscle and adipose tissue, with substantial improvements in insulin-mediated glucose uptake. Importantly, the insulin-stimulating actions of GLP-1 cease at glucose levels below 4 mmol/L (72 mg/dL), which mitigates the risk of hypoglycemia. GLP-1 also promotes increased glucose uptake in target tissues via mechanisms independent of increases in circulating insulin. Receptors for GLP-1 have been identified in rodent and human myocardium, thereby identifying myocardium as a direct target for GLP-1 action. As illustrated in the Figure, recent studies indicate that GLP-1 receptor binding activates adenylyl cyclase and phosphorylates (activates) the cAMP-dependent protein kinase (AMPK). In turn, activated AMPK enhances insulin-dependent signaling, increases glucose uptake and provides other cardioprotective actions. Recognizing that mitochondrial dysfunction contributes to defects in substrate utilization in HF, it is relevant that GLP-1 agonists improve mitochondrial function in vitro and reduce mitochondrial oxidative stress and damage within the hearts of rodents with type 2 diabetes mellitus.

These observations support GLP-1 as a potential pharmacological modulator to enhance myocardial glucose metabolism. In contrast to recombinant GLP-1 that requires continuous infusion due to rapid hydrolysis in vivo, degradation-resistant GLP-1 agonists permit intermittent subcutaneous administration with dosing intervals ranging from 12 hours to 1 week. Two GLP-1 agonists, exenatide and liraglutide, are currently available in both twice-daily and once-weekly formulations and offer interesting cardiovascular effects that may potentially be important in HF. Exenatide is available in both twice-daily and once-weekly formulations and liraglutide is administered once daily. More generally, though small molecules and devices have dominated HF therapeutics, protein-based therapies administered by subcutaneous injection expand the potential for pathophysiologic modulation.

Acute Effects of GLP-1 in HF

In both preclinical studies using animal models and clinical investigations, short-term GLP-1 infusions have demonstrated salutary cardiac effects. In conscious, chronically instrumented dogs, GLP-1 (1.5 pmol/kg/min) attenuated myocardial stunning after brief periods of myocardial ischemia with regional wall motion and isovolumic left ventricular relaxation recovering significantly earlier in treated versus control animals (6 versus 24 hours). GLP-1 induced equivalent protective effects in rat models of transient and sustained coronary occlusion. In dogs with pacing-induced cardiomyopathy, a 48-hour infusion of GLP-1 increased stroke volume, left ventricular dp/dt, and left ventricular ejection fraction (LVEF) while decreasing left ventricular end-diastolic pressure and systemic vascular resistance. Identical dosing of GLP-1 produced no changes in normal control normal dogs, demonstrating that GLP-1 specifically targets pathological processes. Likewise, in 11
patients with severe left ventricular dysfunction after acute myocardial infarction and reperfusion, subjects treated with a 3-day GLP-1 infusion had greater increase in LVEF (from 29±2% to 39±3%, P<0.01) compared with historical controls (28±2% to 29±2%) and GLP-1-treated patients had a shorter length of stay (6 versus 10 days, P<0.02). In a randomized, double-blinded, crossover clinical trial in 20 patients with a low LVEF (<35%) and NYHA III-IV HF symptoms, Nathanson et al reported that the GLP-1 agonist exenatide significantly increased cardiac index and decreased pulmonary wedge pressure at 3 and 6 hours after the infusion had begun, while placebo infusion induced no changes in these variables. In contrast, Halbirk et al did not observe change in LVEF or cardiac index during a 48-hour infusion of recombinant GLP-1 in nondiabetic patients with ischemic heart disease and NYHA II-III symptoms of HF. The predominance of data indicates that GLP-1 is neither a positive nor a negative inotrope.

Chronic GLP-1 Therapy in HF

Data supporting a therapeutic benefit for GLP-1 therapy in patients with chronic HF are derived from small pilot studies and retrospective analyses. In 12 patients with chronic severe HF (NYHA III-IV), a continuous, 5-week infusion of recombinant GLP-1 was associated with significant improvements in LVEF; Minnesota Quality of Life score, 6-minute walk distance, and exercise VO2max, while historical controls had no changes in these parameters. The favorable effects of GLP-1 therapy were similar in magnitude in diabetics and in nondiabetics, suggesting effects beyond glycemic control. Eight GLP-1-treated patients had reduced requirements for diuretics. Four patients in the GLP-1-treated group and 2 in the control group experienced asymptomatic hypoglycemia (plasma glucose 50–70 mg/dL). Nevertheless, the diabetic patients who received GLP-1 had better glycemic control and reduced requirements for insulin or oral hypoglycemic agents compared with diabetic patients in the control group. A subsequent exploratory study evaluated 3 different doses of the long-acting GLP-1 agonist (albiglutide) in a 12-week, randomized, double-blinded clinical trial including outpatients with stable NYHA class 2 or 3 HF and LVEF<40%. The administration of albiglutide up to 30 mg/wk for 12 weeks to subjects with mild-moderate HF was generally well-tolerated. Compared with placebo, peak VO2 improved significantly by 1.51 mL/kg/min (95% confidence interval, 0.21–2.82 mL/kg/min, P=0.024) in subjects on albiglutide 30 mg, but there were no treatment-related improvements in LV size, LV function, 6-minute walk, or quality of life scores (GlaxoSmithKline, unpublished data, posted at clinicaltrials.gov, NCT01357850, 2013).

On the basis of preclinical and early-phase clinical data supporting the concept that GLP-1 induces beneficial effects on myocardial glucose metabolism with a favorable safety profile in large numbers of patients with diabetes mellitus, we designed a randomized, blinded, proof-of-concept trial of GLP-1 therapy in HF patients already treated with evidence-based medications. Because preclinical data indicate that myocardial metabolism is particularly abnormal in more advanced HF (NYHA III-IV) and that GLP-1 seems more effective in high-risk settings (after ischemia and heart surgery), we postulate that patients with more advanced HF are most likely to benefit from GLP-1 agonist therapy. Moreover, because the months after AHFS hospitalization are a vulnerable period for adverse outcomes, we felt that patients hospitalized with AHFS are a particularly opportune group to target with sustained GLP-1 therapy. Accordingly, the National Heart, Lung, and Blood Institute HF Network has designed and initiated a trial to test the hypothesis that sustained therapy with a subcutaneous GLP-1 agonist initiated during the post-AHFS discharge period will be associated with greater clinical stability through 180 days as assessed by a composite clinical end point. While very long-acting GLP-1 agonists have the advantage of ease of administration (1 dose per week), a concern with these formulations is the long interval between their initiation and steady-state levels, particularly when incremental dose escalation is envisioned. Given the nontrivial risks of rehospitalization during the first 6 weeks after discharge, we selected liraglutide because of its once-daily dosing while allowing steady-state levels within a few days of initiating each dose.

Study Design and Patient Population

The Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study is a randomized, double-blinded, placebo-controlled clinical trial in high-risk patients with reduced ejection fraction (LVEF<40%) and AHFS who are treated for 180 days with placebo or a GLP-1 agonist delivered by daily subcutaneous injection (clinicaltrials.gov, NCT01880968). Recognizing that insulin resistance has been observed in advanced HF without diabetes mellitus, FIGHT includes both diabetics and nondiabetics and consists of screening, study drug titration, and follow-up phases. A total of 300 patients meeting eligibility criteria are being enrolled and randomized in the study. Patients admitted to the hospital because of AHFS are screened for basic inclusion and exclusion criteria (Table 1) and consenting patients meeting these criteria are enrolled either in the hospital shortly before their anticipated discharge or as an outpatient within 14 days of discharge.

Randomization, Stratification, and Blinding

After providing informed consent, subjects who fulfill all the inclusion criteria and none of the exclusion criteria are randomized. Randomization to GLP-1 agonist/placebo (1:1 allocation ratio) is stratified by site and presence or absence of diabetes mellitus, using a permuted block randomization scheme to ensure relatively equal distribution of subjects to each arm within each clinical site. Before study drug administration, patients undergo baseline laboratory evaluations (metabolic profiling, HF biomarkers), echocardiography, a 6-minute walk test, a quality-of-life assessment, and training in study drug self administration. Patients are observed as they self administer their first dose of study drug.

Drug Intervention, Dose Titration, and Follow-Up

Participants are started on placebo or GLP-1 agonist (liraglutide; at 0.6 mg subcutaneous daily for 7 days). Liraglutide (Victoza®) is an FDA-approved human GLP-1 analog with
Table 1. FIGHT Inclusion and Selected Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Age ≥ 18 y</td>
<td>Acute coronary syndrome or percutaneous coronary intervention within the past 4 wk</td>
</tr>
<tr>
<td>AHFS (defined by both symptoms and signs) is the primary cause of hospitalization</td>
<td>Ongoing hemodynamically significant arrhythmias</td>
</tr>
<tr>
<td>Prior clinical diagnosis of HF</td>
<td>Ventricular assist device or heart transplant likely within the next 6 mo</td>
</tr>
<tr>
<td>LVEF &lt; 40% during the preceding 3 mo</td>
<td>Severe anemia (Hgb &lt; 8.0 g/dL)</td>
</tr>
<tr>
<td>On evidence-based medication for HF (including β-blocker and angiotensin</td>
<td>Severe renal, hepatic or pulmonary disease</td>
</tr>
<tr>
<td>converting enzyme-inhibitor/angiotensin receptor blocker) or previously deemed</td>
<td>Primary infiltrative or restrictive cardiomyopathy</td>
</tr>
<tr>
<td>intolerant</td>
<td>Severe aortic or mitral stenosis</td>
</tr>
<tr>
<td>Use of at least 40 mg of furosemide total daily dose (or equivalent) prior to</td>
<td>Active infection driving AHFS hospitalization</td>
</tr>
<tr>
<td>admission for AHFS</td>
<td>Terminal illness (other than HF) with expected survival of less than 1 y</td>
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<tr>
<td></td>
<td>Previous adverse reaction to or ongoing treatment with GLP-1 agonist Rx</td>
</tr>
<tr>
<td></td>
<td>Type 1 diabetes mellitus or very poor glycemic control at the time of randomization</td>
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<tr>
<td></td>
<td>History of gastroparesis, pancreatitis, or medullary thyroid cancer</td>
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AHFS indicates acute HF syndrome; GLP-1, glucagon-like peptide-1; HF, heart failure; and LVEF, left ventricular ejection fraction.

97% homology to native GLP-1. To enhance patient tolerance and allow adjustments in other diabetes mellitus treatments as needed, the dose is increased to 1.2 mg after 1 week of therapy and then the target dose of 1.8 mg at day 30. The 1.8 mg dose continues from day 30 through day 180. All participants receive study visits at 30, 90, and 180 days postrandomization and study phone calls at intervening times. Repeat echocardiography and metabolic profiling will be performed at the 180 day visit. Participants are called at day 210±7 to determine their adverse event status.

The most common adverse effects of liraglutide are gastrointestinal related and include nausea, vomiting, diarrhea, dyspepsia, weight loss, and constipation. Gastrointestinal adverse reactions are dose-related and typically decrease over time. The hypoglycemic effects of GLP-1 agonists are glucose-dependent and effectively nil in the presence of a normal circulating glucose. Accordingly, the risk of hypoglycemia with study drug is low in nondiabetics. Nevertheless, all participants are counseled on the signs and symptoms of hypoglycemia and the appropriate treatment prior to discharge. In diabetic patients, plans for hypoglycemia risk reduction include adjustments to insulin or insulin secretagogues (sulfonylureas or meglitinide) dosing at the time of study drug initiation or up-titration, at least daily monitoring of blood sugar, and close follow-up with the provider managing the subject’s diabetes mellitus.

The FIGHT protocol allows adjustment of standard HF therapies, including attempted up-titration of neurohumoral antagonists if not at goal or maximally tolerated doses, during and after the subjects’ initial hospitalization. There are no established guidelines for the treatment of diabetes mellitus in patients with AHFS. However, thiazolidinedione use is not recommended in patients with symptomatic HF in the American Diabetes Association 2012 Standards of Medical Care in Diabetes.41 Metformin may be used in patients with stable HF provided that renal function is normal. However, it should be avoided in unstable or hospitalized patients with HF.

End Points

Primary End Point

End-point selection for high-risk HF populations is critical and often debated. During the course of the study, we expect that a certain number of subjects will achieve a clinical end point such as death or HF hospitalization. These clinically meaningful events must be included in the study end point, but relying on such events alone will not provide sufficient power in a phase 2 study of 300 subjects. As recently highlighted,45 there is increasing evidence that relative change in circulating natriuretic peptides over time helps stratify risk and provides a surrogate measure of HF severity, with decreases associated with improvement in clinical outcomes and responses to therapy.46-48 As such, we are measuring serial amino-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in all subjects after discharge and using the proportional change in NT-proBNP over time to contribute to the study end point for subjects who do not experience a clinical event. Thus, the primary end point of FIGHT is a global rank end point in which all participants, regardless of treatment assignment, are ranked across 3 hierarchical groups: (1) time to death, (2) time to HF hospitalization, and (3) time-averaged proportional change in NT-proBNP (from baseline to 180 days). We will then compare the distribution of the ranks in the active and placebo arms to determine the overall effect of liraglutide on HF stability. Hospitalization for HF is distinguished from hospitalizations due to other causes based on the presence of both clinical manifestations of worsening HF and additional or increased therapy specifically for the treatment of worsening HF. An adjudication committee assesses the cause of hospitalizations in a uniform manner.

Secondary End Points

The principal secondary end points in this study include change in cardiac structure and function (by echocardiography) from baseline to 180 days. The most important metrics are left ventricular end-systolic volume, left ventricular end-diastolic volume, left-ventricular ejection fraction, and E/E′ ratio. Additional secondary end points include 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, and individual components of the primary end point at 30, 90, and 180 days after randomization.

Tertiary End Points

Additional parameters assessed for efficacy include the change in AHFS biomarker panel (including aldosterone, cystatin C, high-sensitivity C-reactive protein from baseline to 30, 90,
Statistical Considerations

The primary analysis will be conducted on an intention-to-treat basis. The intention-to-treat population includes all participants who are randomized. The analysis of the primary end point will be based on the Wilcoxon test statistic. For the primary comparison, participants randomized to liraglutide will be compared with placebo subjects, using a Type I error rate of 0.05. For secondary and tertiary end points, general linear models and nonparametric approaches will be used to analyze the continuous outcomes. For binary outcomes, chi-square tests and Fisher exact test will be used for unadjusted comparisons. For adjusted comparisons, logistic regression analysis will be used to compare liraglutide versus placebo with the estimated 6-month all-cause mortality rates.

Sample Size and Power Calculation

Data from the Diuretic Optimization Strategies Evaluation trial were used to estimate 60-day event rates for clinical end points, including death, all-cause hospitalization, and HF hospitalization, and composite end points, including death or all-cause hospitalization and death or HF hospitalization (see Table 2). Data from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial also provided relevant information regarding 6-month all-cause mortality and HF hospitalization event rates. In that population, the estimated 6-month all-cause mortality rate and HF hospitalization or all-cause mortality rates were 13% and 30%, respectively. To account for the possible higher-risk patient population in FIGHT, we have assumed 180-day event rates of 15% for all-cause mortality and 35% for the composite of HF hospitalization or all-cause mortality.

To estimate the power of the primary end point for the FIGHT study, we have conducted a simulation study where the clinical events and biomarker changes were varied across a range of parameters. For the clinical events of all-cause death and HF hospitalizations, we assumed 20% and 25% reductions for the active treatment groups compared with the placebo group. For the NT-proBNP components, we assumed 0.4 to 0.6 SD reductions compared with the placebo group. The estimated power shown in Table 2 was based on 1000 simulated data sets for each parameter setting. All simulations used 145 subjects per treatment group and assumed no missing data. Each computed test statistic was compared with the 2-sided 0.05 level. To allow for <3% to 5% missing data for the time-averaged NT-proBNP component, the total sample size for FIGHT was increased to 300 subjects or 150 subjects per treatment group. This sample size provides 92% power under the assumptions of a 25% reduction in clinical events (both mortality and HF-hospitalizations) along with a 0.5 SD reduction in time-averaged NT-proBNP from the time of enrollment to 180 days. With a 25% reduction in clinical events and a 0.4 SD reduction in NT-proBNP, the estimated power would still be in excess of 80%.

Safety

Interim data analysis for efficacy and futility will not be conducted because of relatively small size and short duration of this phase-II clinical trial. Safety data, summarized at the treatment level, will be assessed approximately every 6 months by the National Heart, Lung, and Blood Institute–appointed Data and Safety Monitoring Board. The safety analyses will be based on the entire intention-to-treat population. Safety will be evaluated by comparing the occurrence of adverse events and changes in laboratory values of the active arm compared with placebo. The number and percentage of participants experiencing treatment emergent adverse events will be tabulated by treatment group, body system, and preferred term. The percentages between treatment groups will be compared using Fisher exact test.

Conclusions

A growing evidence base indicates that myocardial metabolic abnormalities, including reduced fatty acid oxidation and myocardial insulin resistance impairing glucose utilization, contribute to the syndrome of HF with reduced ejection fraction. Recognizing that no currently used HF therapy directly targets these fundamental metabolic derangements, the FIGHT study is designed to test the hypothesis that sustained therapy with a subcutaneous GLP-1 agonist will improve clinical stability in patients with advanced HF by improving myocardial glucose utilization. This phase II proof-of-concept trial uses a randomized, placebo-controlled, double-blinded design, a hierarchical composite end point, and an intention-to-treat
analysis framework. We note that a particular novel aspect of the design is the targeting of patients hospitalized for AHFS to identify patients at high risk while facilitating enrollment, baseline testing, and research subject training. Another novel feature of this study is its primary end point, which integrates clinically meaningful events as well as longitudinal measures of HF severity in subjects who do not experience events into a single hierarchical end point. We submit that positive results demonstrating an efficacy signal should motivate a Phase 3 study of GLP-1 agonists in high-risk patients with heart failure and reduced ejection fraction that is powered for clinical events. A negative result will strongly suggest that such agents are ineffective in this population.

Sources of Funding
This work was supported by grants from the National Heart, Lung, and Blood Institute (co-ordinating center: U10 HL084904; regional clinical centers: U10 HL110312, U10 HL110337, U10 HL110342, U10 HL110262, U10 HL110297, U10 HL110302, U10 HL110309, U10 HL110336, U10 HL110338).

Disclosures
Dr Margulies reports unpaid advisory committee membership for Novo Nordisk and research grant support from Juventis Therapeutics, Celladon Corporation, Thoratec Corporation, and Innolign Biomedical, LLC. Dr Anstrom has received research support from AstraZeneca, Lilly Company, and Medtronic; has served as a consultant for Abbott Vascular, AstraZeneca, Bristol-Myers Squibb, Pfizer (modest), GSK, and Ikaria; and has served on Data Monitoring Committees for Pfizer and Vertex. Dr Hernandez reports consulting for Novartis, Janssen, and Bristol-Myers Squibb and that his institution has received grants from Novartis, Janssen, and Bristol-Myers Squibb. Dr Redfield reports receiving royalties from Anexon and payment for educational presentations from the Heart Failure Society of America and reports unpaid advisory committee membership for Novartis. Dr Braunwald reports grants to his institution from AstraZeneca, Johnson & Johnson, Merck, sanofi-aventis, and membership for Novartis. Dr Braunwald reports grants to his institution from AstraZeneca, Lilly Company, and reports unpaid advisory committee membership for Novartis. Dr Braunwald reports grants to his institution from AstraZeneca, Johnson & Johnson, Merck, sanofi-aventis, Daiichi Sankyo, GlaxoSmithKline, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics, and Pfizer; uncompensated personal fees from Merck; consulting for Genzyme, Amoyce, Medicines Co, CardioRentis, and sanofi-aventis; uncompensated lectures for Merck & CVRx; and payment for lectures from Eli Lilly, Daiichi Sankyo, Menarini International, Medscape, and Bayer, outside the submitted work. Dr Cappola reports consulting for TEVA Pharmaceuticals and being a coinventor on pending patents for neuregulin and soluble fms-like tyrosine kinase-1 as heart failure biomarkers and inventor on a patent for gene expression biomarkers of heart transplant rejection.

References

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Key Words: clinical trial - glucagon-like peptide-1 - heart failure - insulin resistance
GLP-1 Agonist Therapy for Advanced Heart Failure With Reduced Ejection Fraction: Design and Rationale for the Functional Impact of GLP-1 for Heart Failure Treatment Study

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_Circ Heart Fail._ 2014;7:673-679
doi: 10.1161/CIRCHEARTFAILURE.114.000346

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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