HEART FAILURE NETWORK

A Randomized Trial of Liraglutide for High-Risk Heart Failure Patients with Reduced Ejection Fraction (FIGHT)

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On behalf of the
NHLBI Heart Failure Clinical Research Network

U.S. Department of Health and Human Services
National Institutes of Health

NIH National Heart, Lung, and Blood Institute

Background: HF Bioenergetics

- The heart consumes more energy per gram than any organ and is continuously dependent on ATP synthesis
- As the heart fails, fatty acid metabolism is down-regulated, and ATP synthesis is more dependent on glucose
- In advanced heart failure, the myocardium also becomes insulin-resistant, which limits glucose uptake and further limits ATP production
- No current heart failure therapy directly targets these metabolic derangements

GLP-1 improves glucose utilization

- Glucagon-like peptide-1 (GLP-1) augments glucose uptake by increasing insulin secretion and insulin sensitivity
- In a pilot study of 12 patients with advanced HF and reduced EF, five weeks of therapy with continuous GLP-1 improved LVEF, exercise and quality of life compared with controls

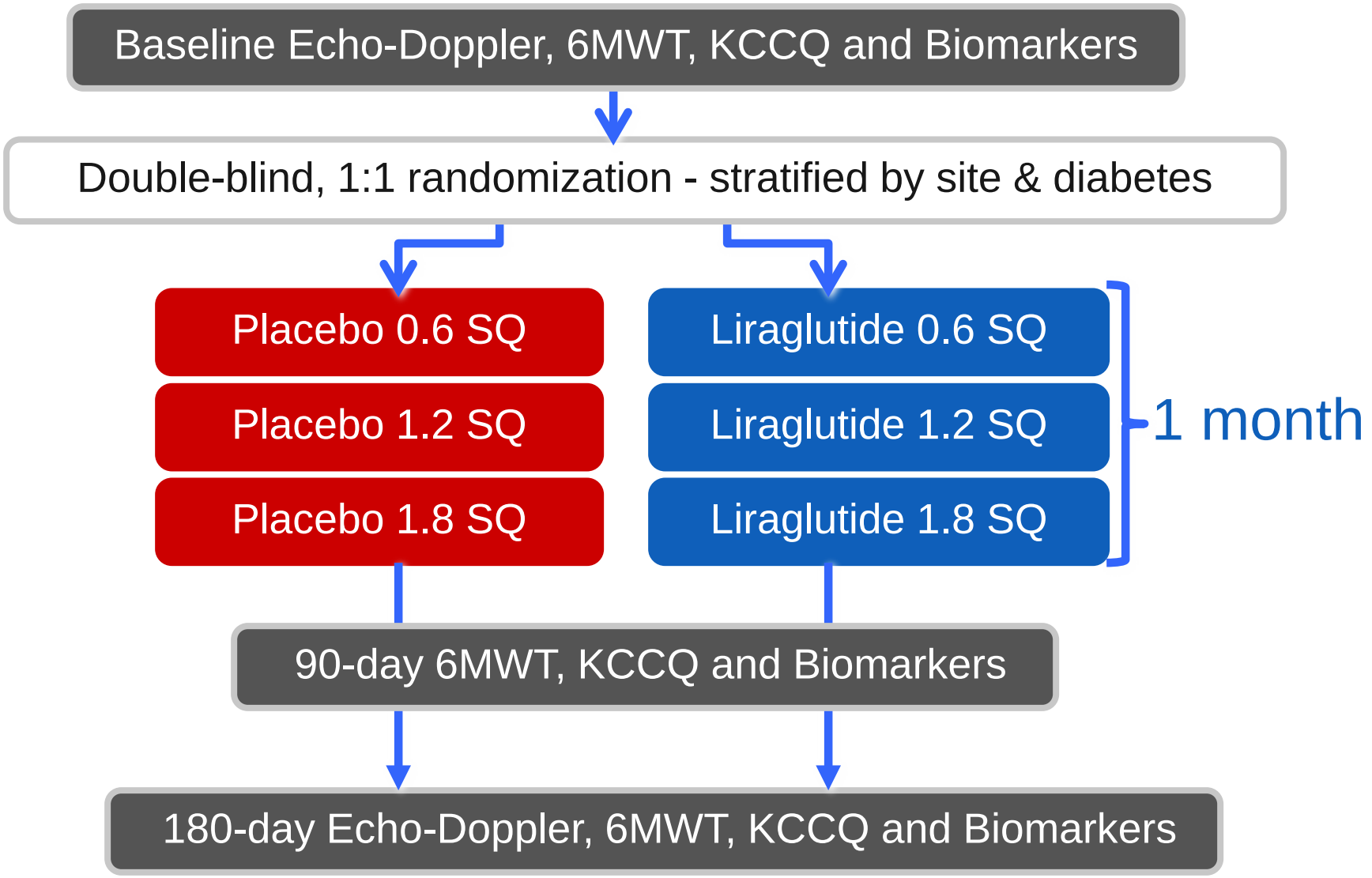
Hypothesis

Sustained therapy with the GLP-1 agonist liraglutide initiated during the post-acute HF discharge period will be associated with greater clinical stability through 180 days as assessed by a composite clinical endpoint.

Study Population

- 300 adults with a prior clinical diagnosis of HF who were hospitalized for an acute heart failure syndrome (AHFS)
- LVEF ≤ 40% during preceding 3 months
- On evidence-based medication for HF
- Use of at least 40 mg of furosemide total daily (or equivalent) prior to admission for AHFS
- Both diabetics and non-diabetics were included (stratified to assure balanced treatment allocation)

Study Design



Endpoints

Primary Endpoint:

A hierarchical rank endpoint in which participants are ranked across three hierarchical groups:

Tier 1: Time to death,

Tier 2: Time to HF hospitalization

Tier 3: Time-averaged proportional change in NT-proBNP (baseline to 180 days)

Secondary Endpoints:

- Individual components of the primary endpoint
- Change in cardiac structure/function by echocardiography
- Quality of life scores
- Six minute walk

Tertiary Endpoints: Change in weight, glucose control, markers of cardiorenal function and lipid control

Hierarchical Composite Rank Score

At 180 Days, all patients ranked

1	**FIRST** Death
X	**LAST** Death
X+1	Alive with **FIRST** HF hospitalization
Y	Alive with **LAST** HF hospitalization
Y+1	**LEAST** favorable change in serial NTproBNPs
300	**MOST** favorable change in serial NTproBNPs

Mean rank score (lower worse) compared between groups
Anchor value (no treatment effect) = 300 / 2 = 150

Baseline Features (n=300)

Characteristic	Placebo (N=146)	Liraglutide (N=154)
Age	60±2	60±13
Female	23%	20%
Racial Minority	38%	47%
Years since HF Diagnosis	7.8±6.3	8.3±6.8
HF Hospitalization in past year	86%	89%
Ischemic etiology of HF	77%	86%
Hx Hypertension	78%	79%
Hx Atrial Fibrillation	48%	49%
Hx of Diabetes	60%	59%
Chronic Renal Insufficiency	36%	43%

There were no significant baseline differences between groups

Baseline Features (n=300)

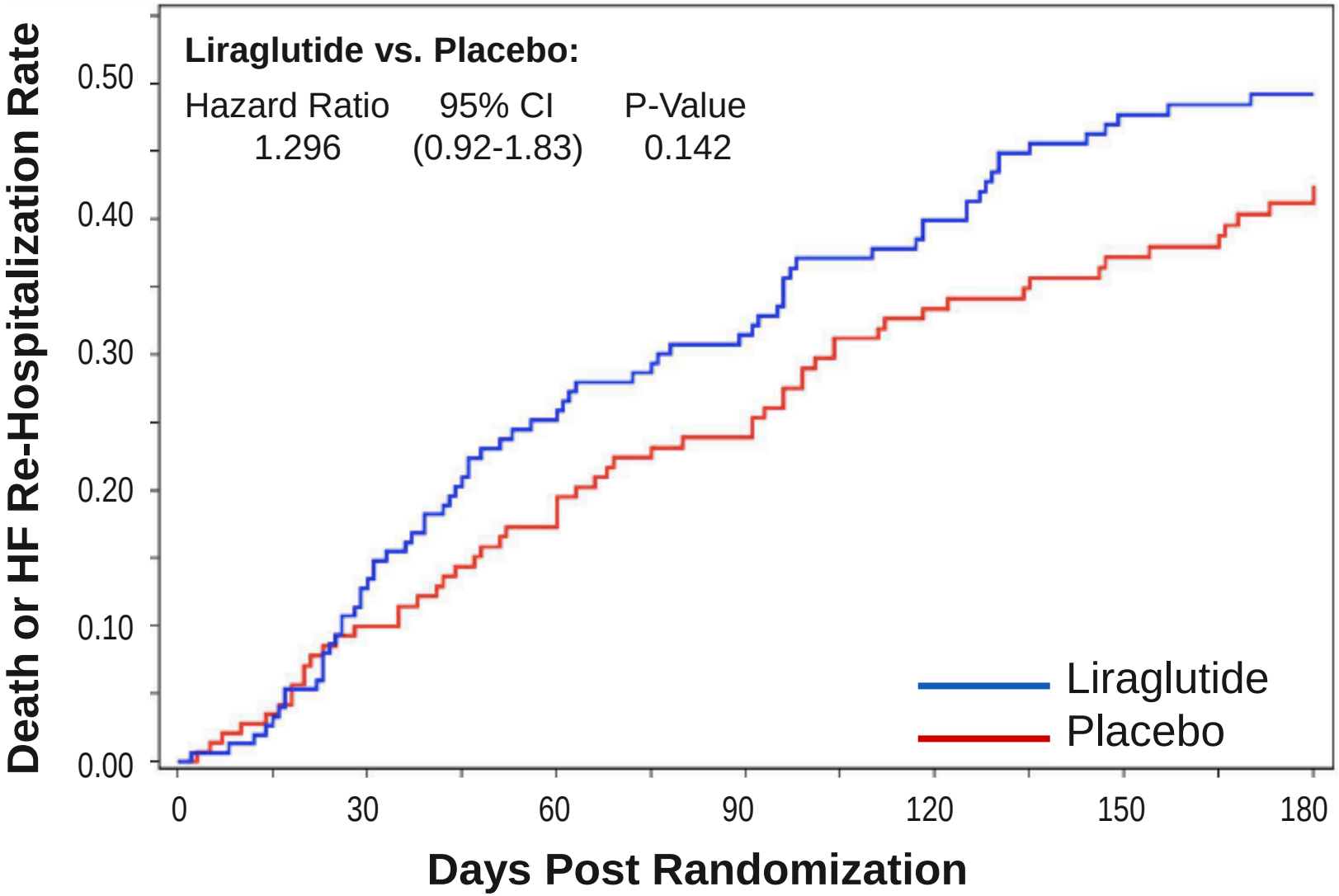
Characteristic	Placebo (N=146)	Liraglutide (N=154)
BMI	33±9	32±8
NYHA II/III	26%/68%	32%/61%
NTproBNP	3,807±5,059	3,875±5,464
LVEF (%)	26±9	26±9
Beta-blocker Rx	95%	93%
ACE-inhibitor or ARB Rx	72%	73%
Hydralazine Rx	32%	33%
Aldosterone Antagonist Rx	61%	58%

There were no significant baseline differences between groups

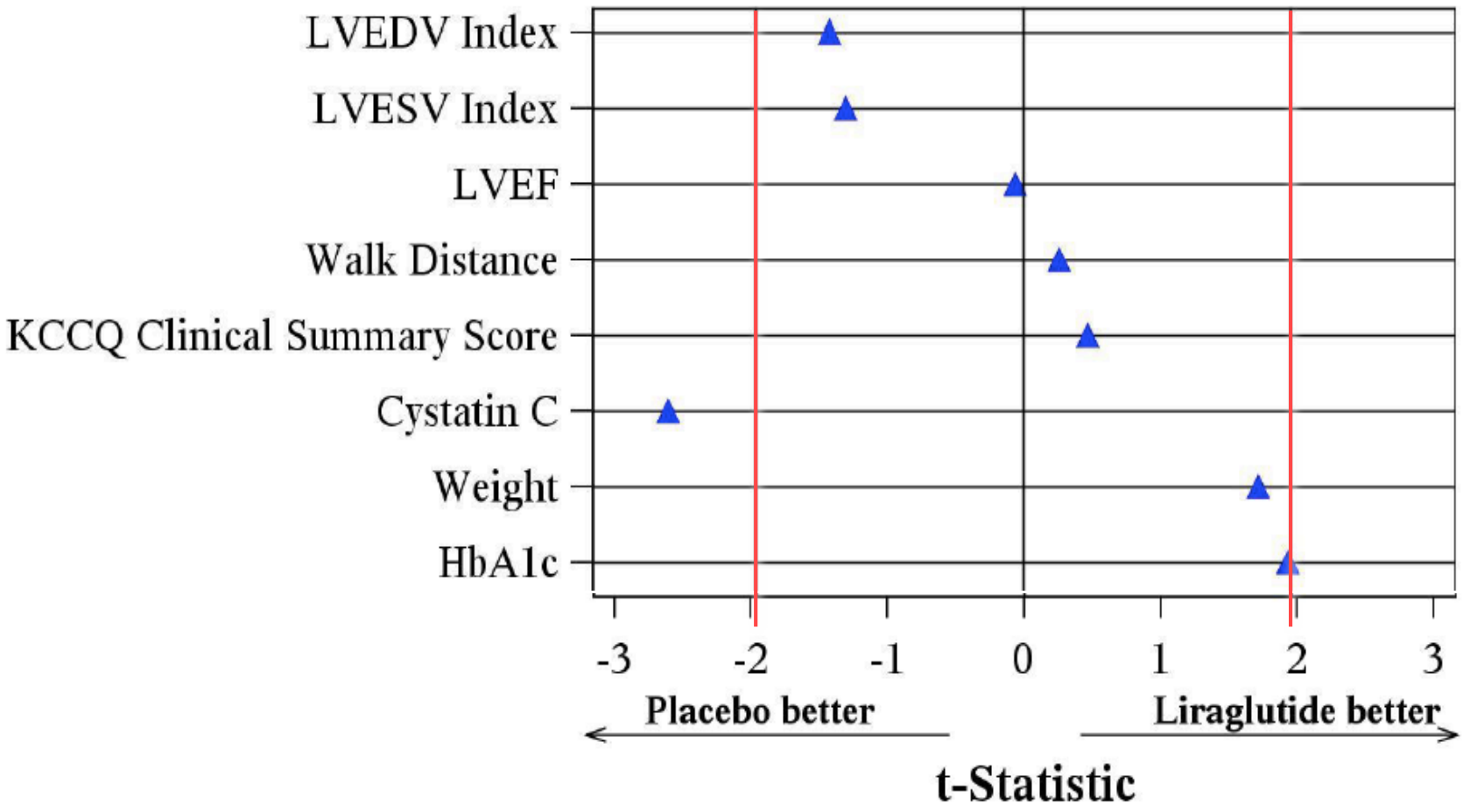
Results: Primary Endpoint

	Placebo (N=146)	Liraglutide (N=154)
Global Rank Score (Mean)	**155**	**146**
	p=0.309 (ns)	
Tier 1 Patients (Death)	16 (11%)	19 (12%)
Tier 2 Patients (Hosp. w/o death)	41 (28%)	53 (34%)

Results: Death or HF Hospitalization

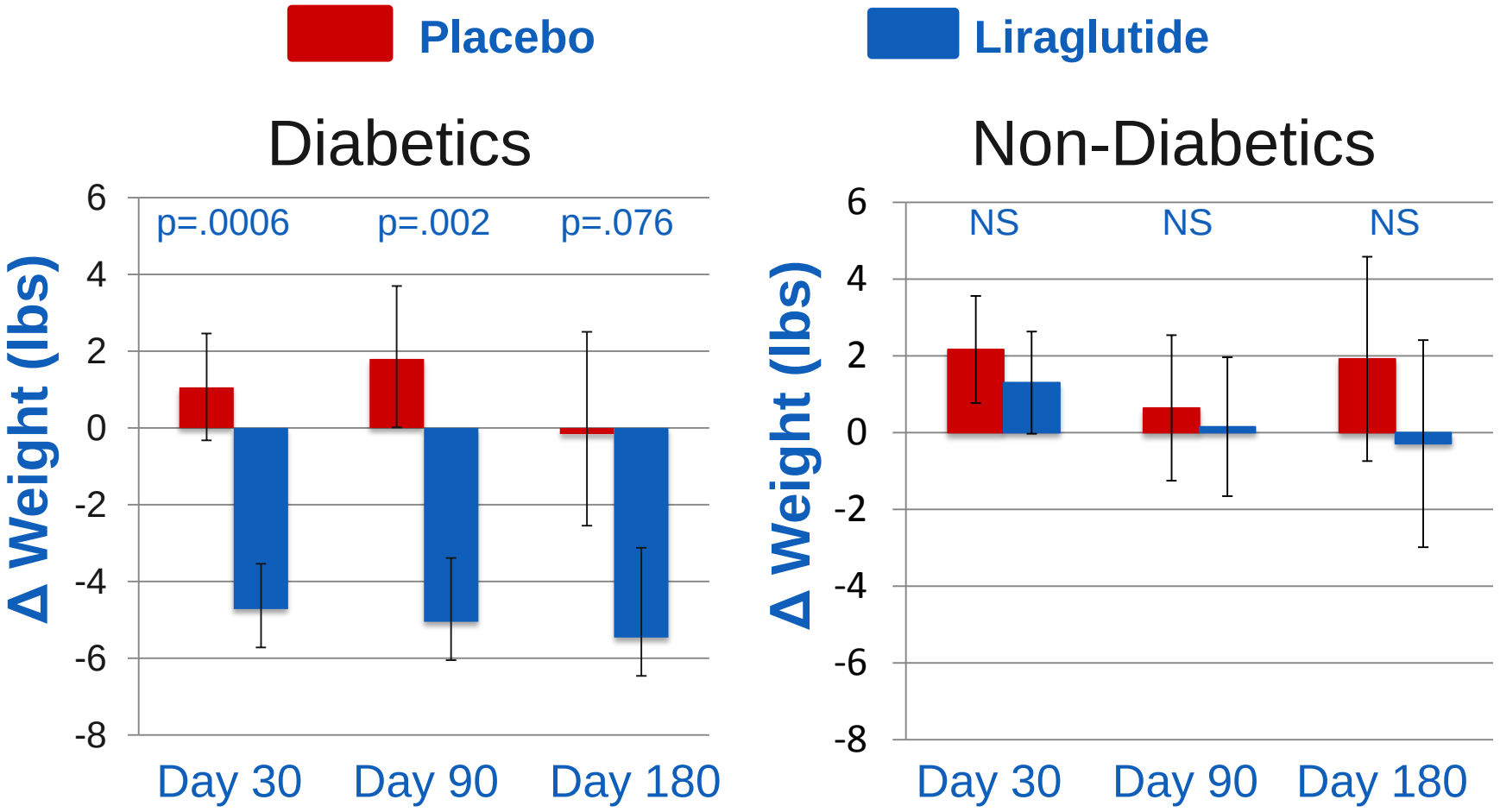


Results: Other Endpoints



All results based on changes from Baseline → 180 days

Results: Weight Changes



Data are changes from Baseline (mean±SEM)

Results: Safety

Adverse Event	Placebo	Liraglutide	O.R.	p-Value
Severe Hypoglycemic Event	6%	8%	1.29	0.582
Any Hyperglycemic Event	18%	10%	0.51	0.048
Arrhythmia	11%	17%	1.65	0.229
Sudden Cardiac Death	1%	1%	0.95	0.749
Acute Coronary Syndrome	1%	1%	1.91	0.807
Worsening Heart Failure	40%	47%	1.33	0.223
Cerebrovascular Event	3%	3%	0.75	0.624
Venous Thromboembolism	3%	1%	0.23	0.132
Lightheadedness, presyncope or syncope	14%	16%	1.22	0.539
Worsened Renal Function	10%	18%	1.86	0.073
Acute Pancreatitis	2%	0%		0.057

Summary and Conclusions

- The GLP-1 agonist liraglutide does not improve post-hospital clinical stability in patients with advanced HF and reduced LVEF
- Among diabetics with advanced HF, liraglutide was associated with a mild reduction in weight and improved blood glucose control
- Though not statistically significant, the composite of death or HF hospitalization and some renal function metrics, numerically favored placebo vs. liraglutide
- Larger studies are needed to establish the safety of liraglutide or other GLP-1 agonists for diabetes management or weight loss in patients with advanced HF

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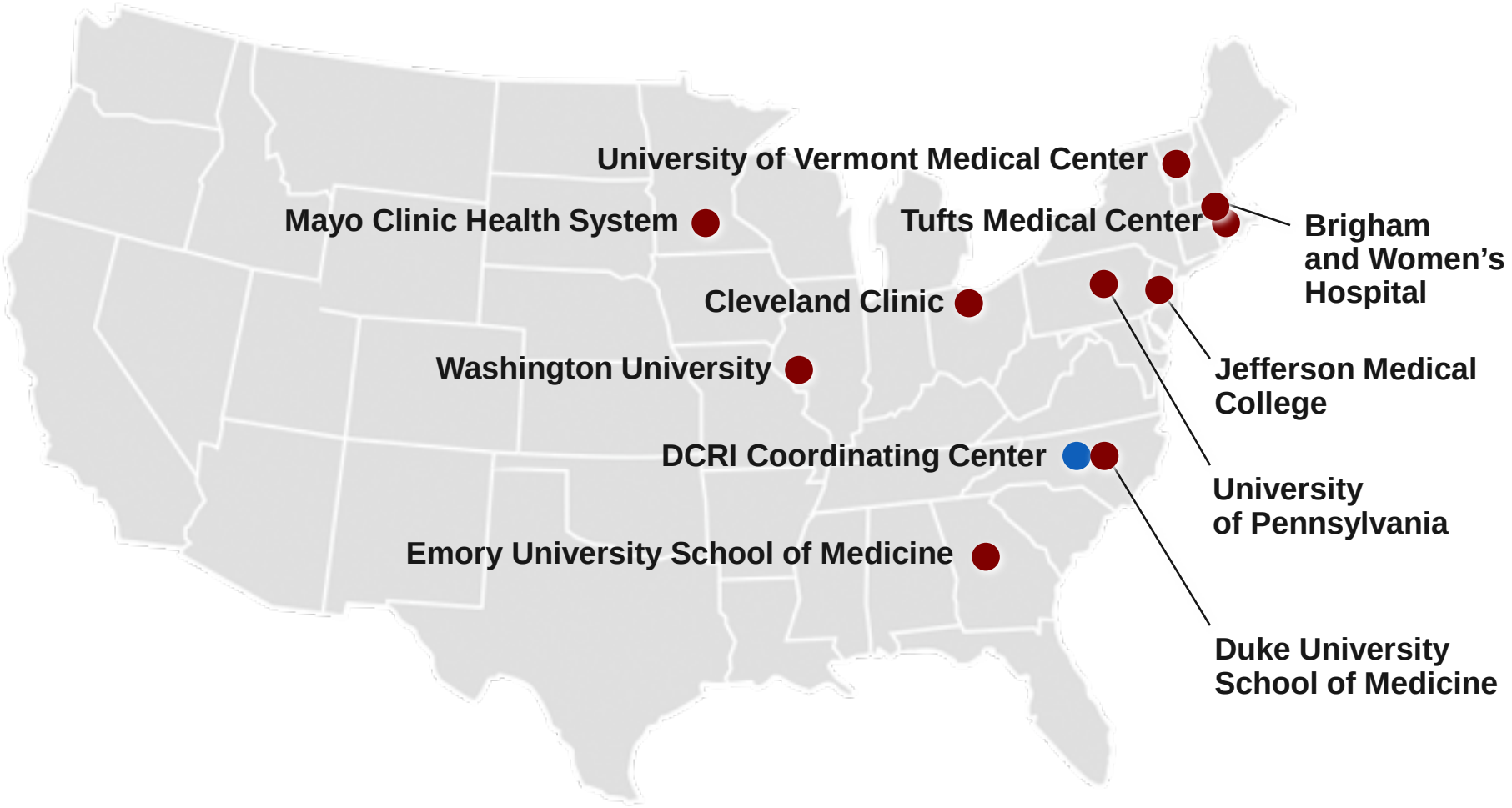

- Regional Clinical Centers
- Coordinating Center

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