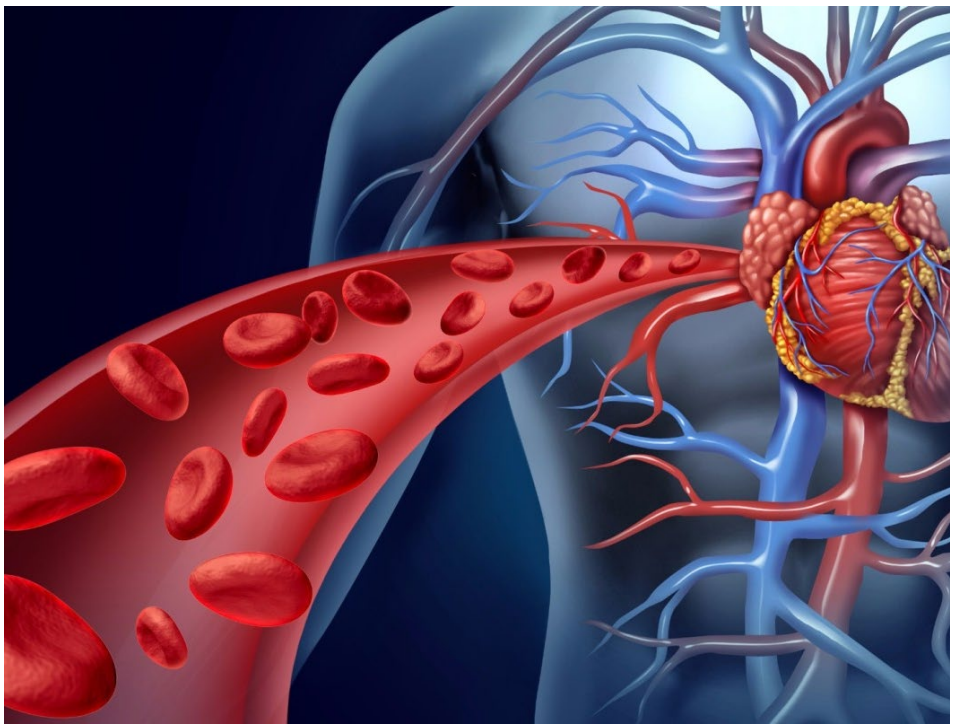
GLP-1 Receptor Agonists in Type 2 Diabetes and Heart Failure: Heart of Gold or Broken Hearted?



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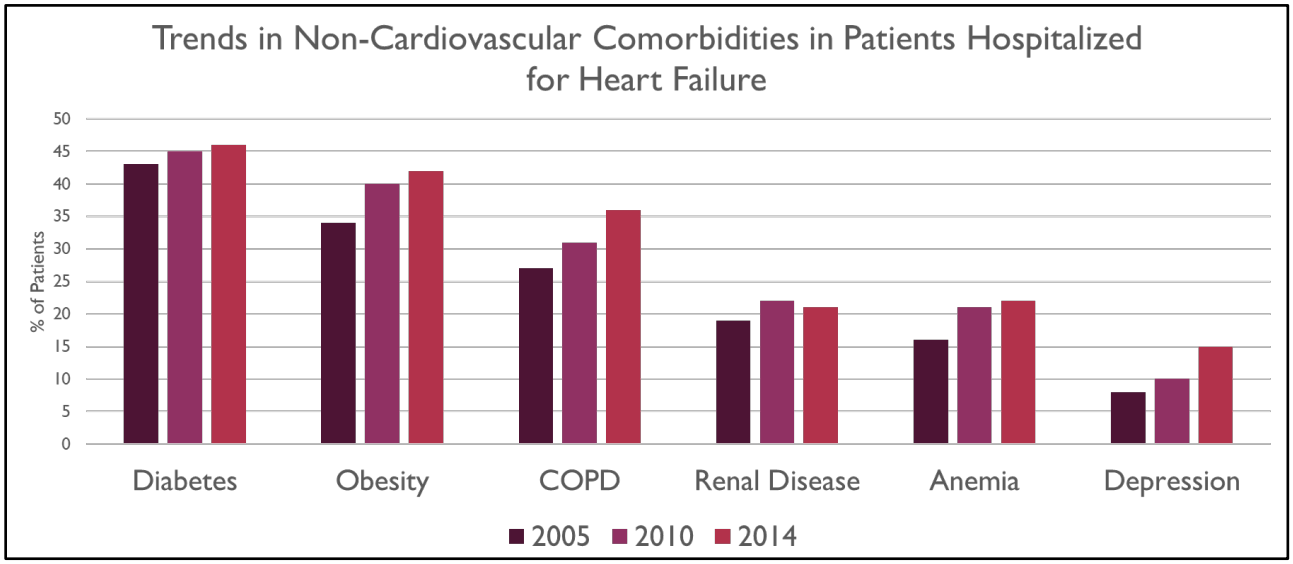
Learning Objectives

- Pharmacists:
  - Describe the pathophysiologic relationship between type 2 diabetes mellitus (T2DM) and heart failure (HF).
  - Compare and contrast the current guideline recommendations on the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with heart failure and T2DM.
  - Evaluate the effects of GLP-RAs on heart failure hospitalizations and mortality in patients with established heart failure.
- Pharmacy Technicians:
  - Describe the pathophysiologic relationship between type 2 diabetes mellitus (T2DM) and heart failure (HF).
  - Recall the current guideline recommendations on the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with heart failure and T2DM.
  - Describe the effects of GLP-RAs on heart failure hospitalizations and mortality in patients with established heart failure.

Background

- Epidemiology
  - Estimated 34.2 million people have diabetes with approximately 7.3 million people remaining undiagnosed.[1]
  - Patients with T2DM are 2x more likely to develop heart failure than patients without diabetes.[2]
    - Framingham Heart Study: Risk of HF is 2x more likely in men, 5x more likely in women.
    - The Framingham Heart Study followed 5,209 patients aged 30 to 62 for 18 years to assess cardiovascular risk factors. Risk of heart failure persisted after accounting for age, blood pressure, weight, and cholesterol levels.[2]
  - T2DM is a common comorbidity in patients with HF.[3]
    - Data from Get With the Guidelines-Heart Failure Registry reported that 45% (93,852 of 207,984) HF patients reported T2DM.[3]

Figure 1. Trends in Comorbidities HF Patients



- Consequences of Coexisting HF and T2DM
  - Increased risk of mortality and HF hospitalization[4-5]
    - In hospitalized patients:
      - The European Society of Cardiology and Heart Failure (ESC-HFA) registry found that in-hospital mortality (6.8 vs 4.4%; hazard ratio [HR] 1.77; 95% confidence interval [CI] 1.28-2.46, p<0.001), 1-year all-cause mortality (27.5 vs 24%; HR 1.16; 95% CI 1.02-1.33, p=0.024), and 1-year hospital re-admissions for HF (23.2 vs 18.5%; HR 1.32; 95% CI 1.14-1.53, p<0.001) were significantly increased in patients with diabetes.[4]
    - In ambulatory patients:
      - An ambulatory cohort of the ESC-HFA registry found higher rates of 1-year all-cause mortality (9.4% vs 7.2%; HR 1.28; 95% CI 1.07-1.54), cardiovascular death (4.8% vs 3.8%; HR 1.28; 95% CI 0.99-1.66), and HF hospitalization (13.8% vs 9.3%; 1.37; 95% CI 1.17-1.60) in diabetic patients.[5]
  - Increased risk of 30-day hospital readmission[6]
    - T2DM was associated with higher rates of 30-day readmission in HF patients (OR 1.06; 95% CI 1.03-1.08; p<0.001).
  - Worse quality of life[7]
    - HF patients with T2DM reported persistently unfavorable quality of life scores after hospital discharge (HR 1.18; 95% CI 1.101-1.39).

- Pathophysiology[8-9]
    - Shared pathophysiology of diabetes and heart failure
        - Ischemic Cardiomyopathy
            - Hyperglycemia, insulin resistance, and high amounts of insulin in the body increase atherosclerosis by causing vascular smooth muscle cell inflammation.
            - Additionally, T2DM can result in more atherogenic low-density lipoprotein cholesterol and promote endothelial dysfunction which leads to inflammation, platelet adhesion, and coronary plaque development.
        - Diabetic Cardiomyopathy
            - Defined as cardiovascular dysfunction in the presence of T2DM without other causes like coronary artery disease or hypertension.
            - Hyperglycemia, insulin resistance, and increased insulin production result in structural and functional changes within the heart.
            - **Left Ventricular Hypertrophy:** Left ventricular hypertrophy and cardiomyocyte hypertrophy are thought to be due to changes in extracellular matrix deposition and increased oxidative stress/ inflammation.
            - **Formation of AGEs:** Hyperglycemia causes the binding of proteins or lipids to sugars resulting in the formation of advanced glycation end products (AGEs). AGEs cross-link collagen and are resistant to proteolysis and may also bind to cardiac cell membranes which promotes fibrosis and inflammation.
            - **RAAS Activation:** Hyperglycemia causes the activation of the renin-angiotensin-aldosterone system (RAAS). This leads to the production of angiotensin II and aldosterone which causes cardiac hypertrophy and fibrosis.
            - **Free Fatty Acid Accumulation:** Heart tissue is unable to effectively use glucose (insulin resistance) and relies on free fatty acids for energy. Excessive high fatty acid oxidation results in lipid accumulation in cardiomyocytes and lipotoxicity. Eventually, cardiac myocytes undergo apoptosis.

Figure 2. Pathophysiology of Diabetes and Heart Failure[8]

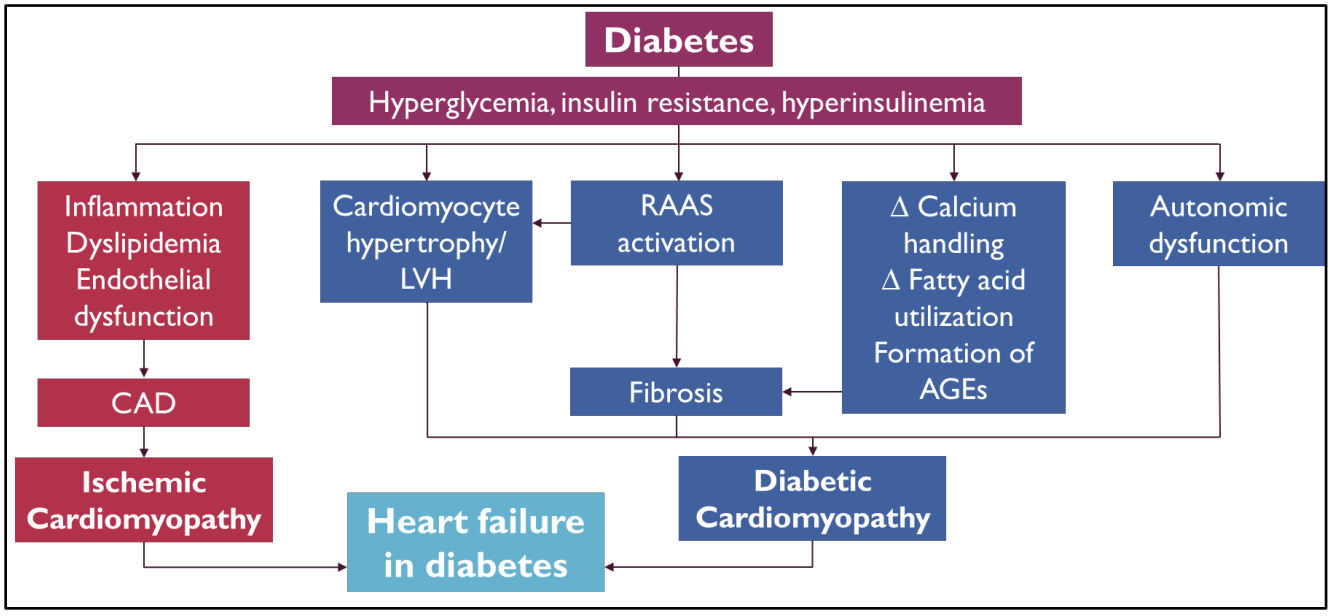
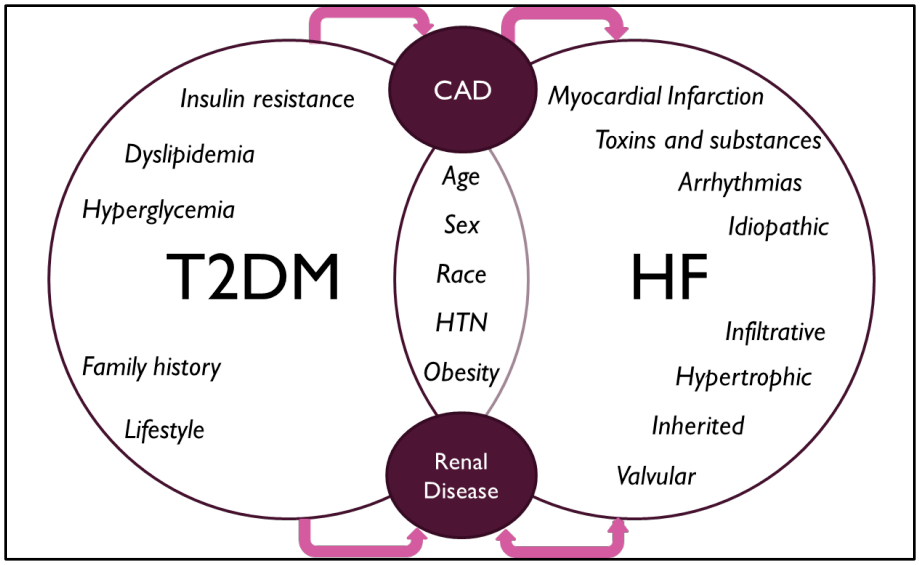
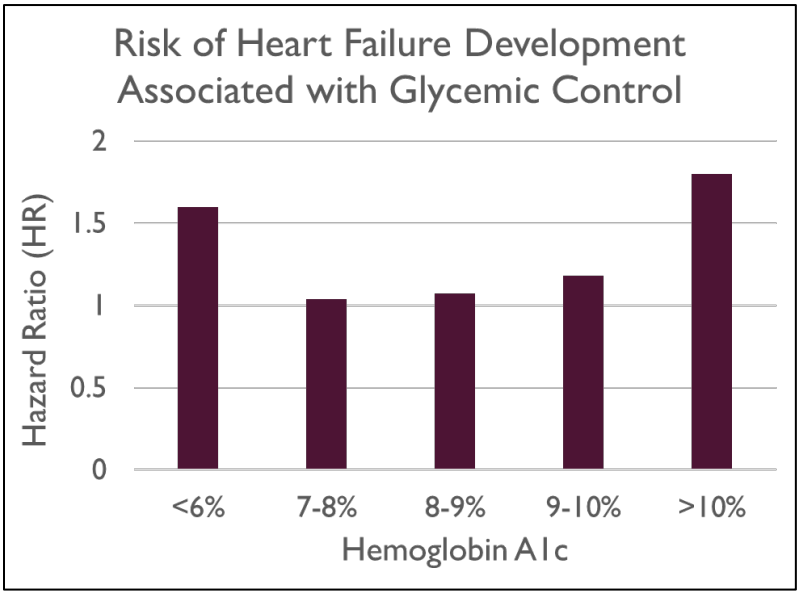


Figure 3. Risk Factors for Diabetes and Heart Failure[10]



- Treatment of T2DM and HF[11-12]
  - Hyperglycemia (and high hemoglobin A1c [HbgA1c] levels) associated with increased risk of developing HF.
    - Each 1% increase in HbgA1c associated with 8% increase in risk of HF.

Figure 4. Risk of HF Development Associated with Glycemic Control[11]



- Intensive versus Standard Glycemic Control[13]
  - Intensive treatment is generally associated with lower risk of microvascular complications of diabetes such as neuropathy, nephropathy, and retinopathy), however, macrovascular complications including cardiovascular death, stroke, all-cause mortality are not generally affected by intensive glucose control. An exception is nonfatal myocardial infarction which may be reduced with intensive glycemic control.
  - In terms of HF related events, intensive control does not reduce the risk of HF events based on a meta- analysis that pooled the data from 8 randomized controlled trials including 37,229 patients.

Figure 5. Probability of HF-related events with intensive glucose-lowering versus standard treatment[13]

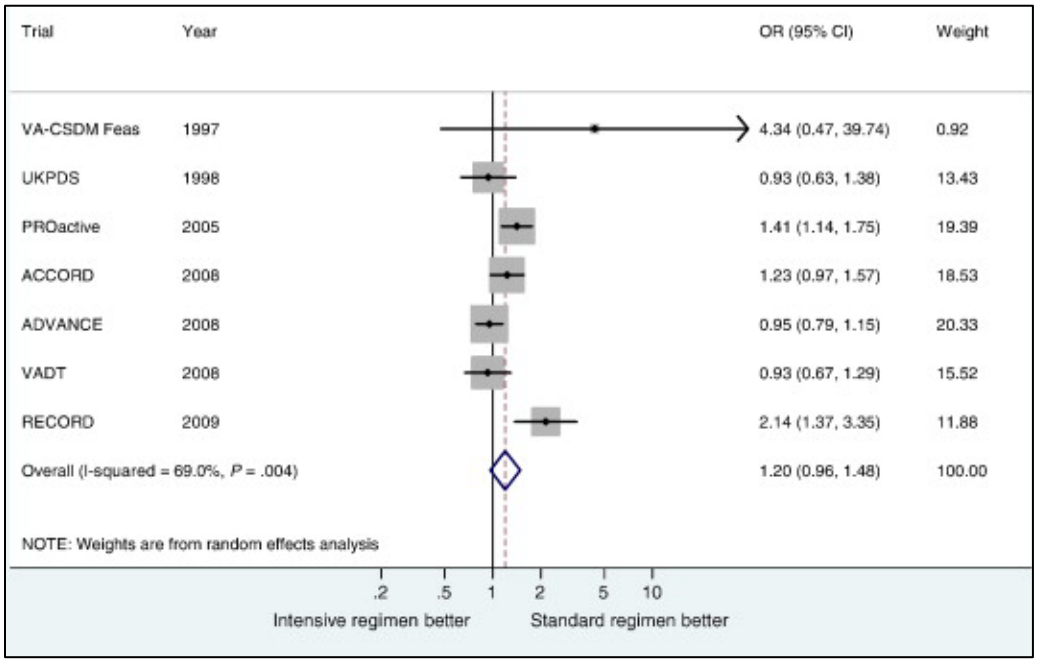


Figure 6. Hemoglobin A1c Goals in HF and T2DM [8,14]

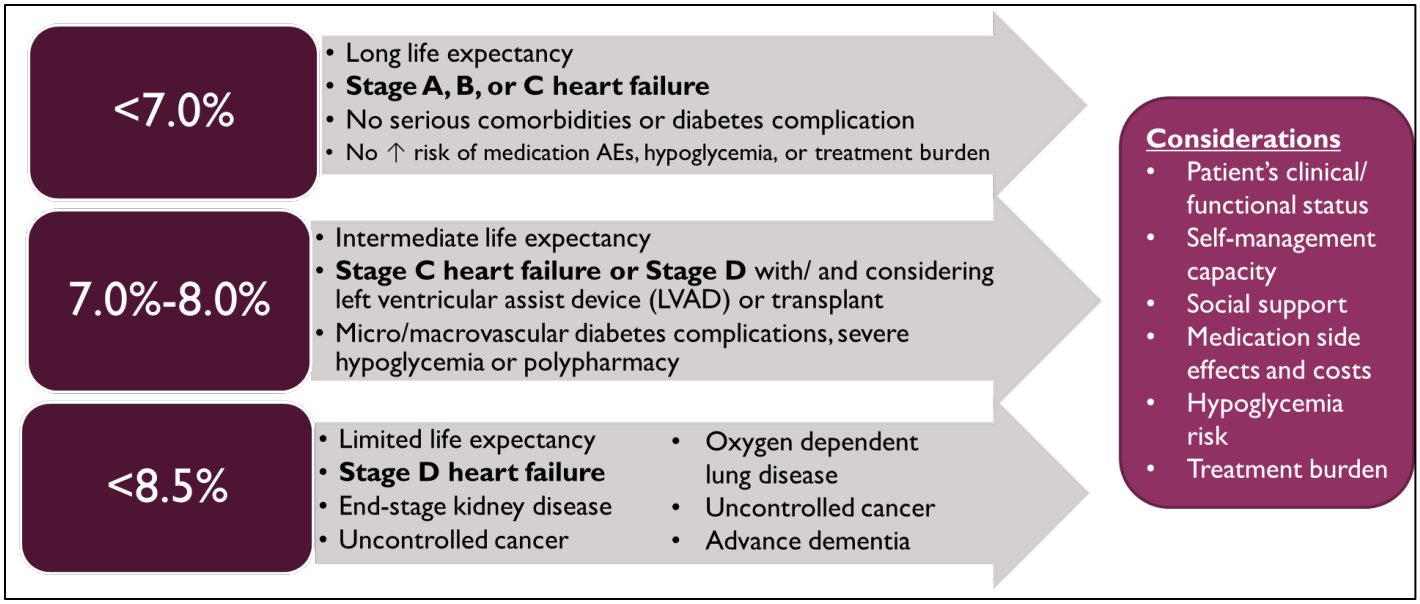
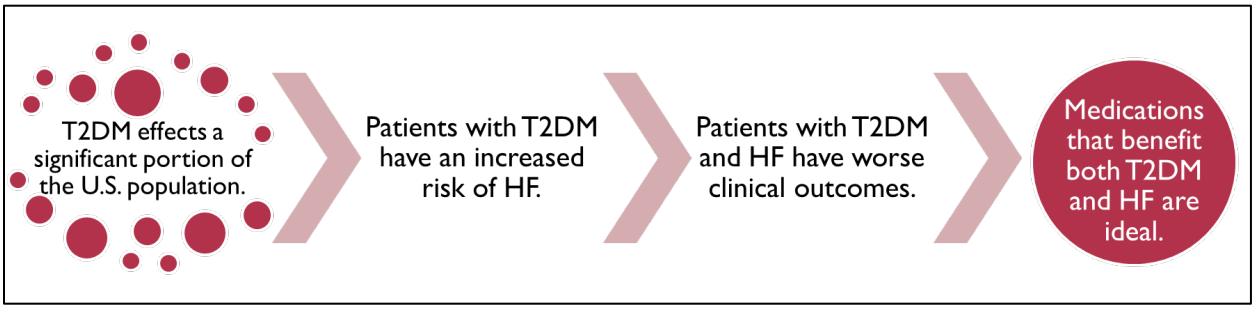
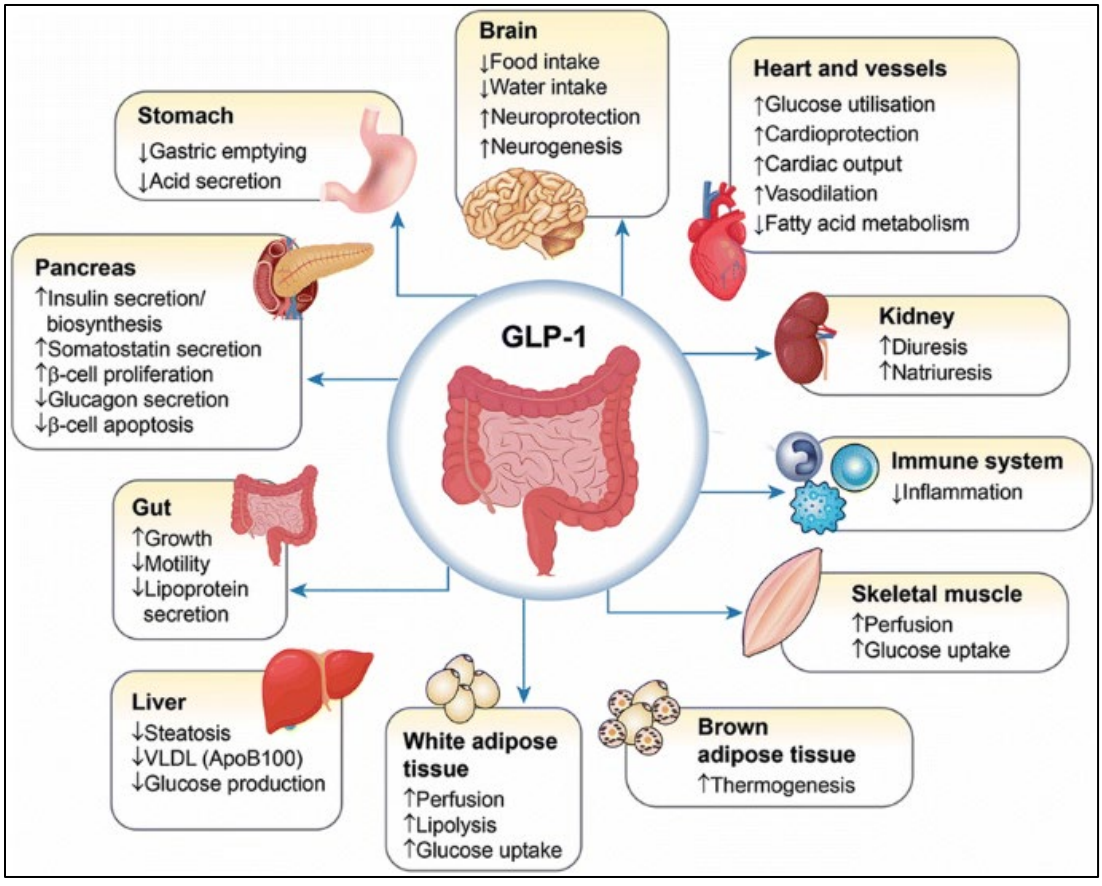


Figure 7. Treatment of T2DM and HF[15]



- T2DM Drug Therapy in Heart Failure[16-17]
    - Sodium Glucose Cotransporter-2 Inhibitor (SGLT-2i)
        - Decrease in mortality
        - Decrease in HF hospitalization
        - Improves cardiovascular risk factors (reduces weight and blood pressure)
    - Metformin
        - Better short-term and long-term prognosis
        - Decrease in mortality
        - Decrease in cardiac hypertrophy
        - Stimulates cardiac glucose uptake
    - Dipeptidyl peptidase-4 Inhibitor (DPP-4i)
        - Saxagliptin – significant increase in HF hospitalization
    - Sulfonylurea (SU)
        - Conflicting results – no definitive CVOT
    - Insulin
        - Observational data – possible increase risk of HF
        - Cardiovascular Outcome Trial (CVOT) data – no increase in CV or HF events
    - Thiazolidinedione (TZD)
        - Contraindicated in New York Heart Association (NYHA) Class III or IV HF
        - Black Box Warning: TZDs may cause or exacerbate HF; not recommended in symptomatic HF; monitor for HF symptoms after initiation; discontinue if HF develops
        - Increases fluid retention and weight gain
- Role of GLP-1 RAs in the Treatment of T2DM and HF[18-19]
    - Mechanism of Action: GLP-1 is a peptide hormone secreted by the small intestine in response to oral intake and binds to GLP-1 receptors in the pancreas. GLP-1 receptor activation stimulates insulin secretion and production while inhibiting glucagon secretion.

Figure 8. GLP-1 Mechanism of Action Overview[20]



- Cardiovascular Effects of GLP-1 RAs[18-24]
  - Anti-atherosclerotic effects
    - Decreased matrix metalloproteinase-2 (MMP-2) levels.
    - Decreased vascular smooth muscle cell proliferation.
    - Reductions in plaque size and foam cell formation.
  - Improved endothelial function
    - Increased nitric oxide production.
    - Decreased oxidative stress.
  - Decreased infarct/reperfusion injury
    - Maintains normal calcium levels in myocardial injury caused by oxidative stress in animal studies.
    - Improves infarct size and myocardial salvage in patients with STEMI after PCI.
    - Promote myocardial glucose uptake and decreased glucose induced apoptosis.
  - Increased cardiac output and heart rate
    - Exact mechanism is unclear (possibly unrelated to catecholamines due to similar increases in HR seen in rats pretreated with reserpine, propranolol, or phentolamine).
  - Anti-inflammatory
    - Decreased levels of inflammatory markers (C-reactive protein, plasminogen activator inhibitor-1, and vascular cell adhesion molecule).
  - Risk factor modification
    - Increased glycemic control and decreased insulin resistance.
    - Decreased body weight.
    - Decreased LDL and triglycerides.
    - Decreased blood pressure.

Table 1. GLP-1 RA Overview[25-31]

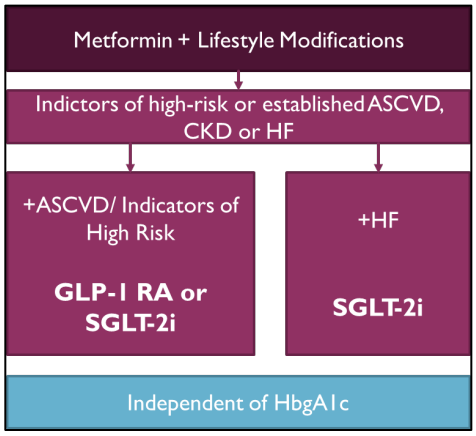
Drug	Dose	Frequency	Half Life	Average A1c Reduction	Weight Loss Effects	Side Effects
Short Acting						
Exenatide BID (Byetta)	5mcg SubQ for 1 month then increase to 10mcg SubQ based on response	Twice daily	2.4 hours	-0.8 to -1.7%	-1.1 to -3.0kg	Nausea (8%) Diarrhea (2%) Injection site reaction (17%)
Lixisenatide (Adlyxin)	10mcg SubQ for 14 days then 20mcg SubQ from day 15	Once daily	~3 hours	-0.6 to -0.9%	+0.3 to -2.7kg	Nausea (25%) Gastrointestinal symptoms (40%) Headache (9%)
Intermediate Acting						
Liraglutide (Victoza)	0.6mg SubQ for 1 week then 1.2mg (maximum dose = 1.8mg/day)	Once daily	~13 hours	-0.8 to -1.5%	-0.2 to 3.6kg	Increased heart rate (>10bpm from baseline: 34%; >20 bpm from baseline: 5%) Nausea (39%) Constipation (19%) Diarrhea (21%) Headache (14%)
Long Acting						
Semaglutide SubQ (Ozempic)	0.25mg SubQ for 4 weeks then 0.5mg escalated to 1mg after 4 weeks if needed	Once weekly	~7 days	-1.1 to -1.4%	-3.6 to 4.9kg	Increased amylase (10-13%) Increased lipase (PO: 30-34%; SubQ: 22%) GI adverse effects (32-41%) Nausea (11-20%)
Semaglutide PO (Rybelsus)	3mg PO for 30 days then 7mg escalated to 14mg after 30 days if needed	Once daily	~7 days	-1.0%	-4.2kg	

Exenatide QW (Bydureon)	2mg SubQ	Once weekly	7-14 days	-1.3 to -1.6%	-2.0 to -2.7kg	Nausea (8-11%) Diarrhea (4-11%) Injection site reaction (17%)
Albiglutide (Tanzeum)	30mg SubQ; may increase to 50mg SubQ if needed	Once weekly	~5 days	-0.6 to 0.9%	+0.3 to 1.1kg	Hypoglycemia (up to 17%) Diarrhea (13%), Nausea (11%) Upper respiratory tract infection (14%)
Dulaglutide (Trulicity)	0.75mg SubQ; may increase to 1.5mg SubQ if needed	Once weekly	~5 days	-0.7 to -1.6%	-0.9 to -3.1kg	Hypoglycemia (up to 77%) Diarrhea (9-13%), Nausea (12- 21%), Vomiting (6-13%)

Guideline Recommendations

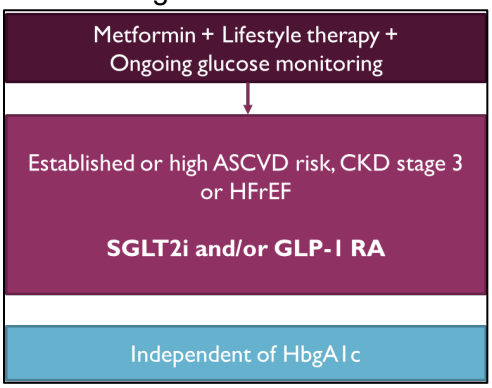
- *American Diabetes Association (ADA)*[32-34]
  - 2021
    - Pharmacologic Approaches to Glycemic Treatment – Recommend SGLT-2i or GLP-1 RA in patients with T2DM and atherosclerotic cardiovascular disease, kidney disease, or heart failure in addition to metformin. (Evidence Level: A)
    - Cardiovascular Disease and Risk Management – SGLT-2is are preferred if HF predominates. (Evidence Level: A)
  - 2020
    - If an SGLT-2i is not tolerated or is contraindicated, then add a GLP-1RA with proven CV benefit.

Figure 9. ADA Algorithm for Glucose Lowering Medications in T2DM[32]



- *American Association of Clinical Endocrinologists (AACE)*[35]
  - 2020: Recommend SGLT-2i or long acting GLP-1 RA in patients with established ASCVD or at high risk, chronic kidney disease (CKD) stage 3, or heart failure with reduced ejection fraction (HFrEF) independent of glycemic control.

Figure 10. AACE Algorithm for Glucose Lowering Medications in T2DM[35]



- *American College of Cardiology (ACC)*[36]
    - 2020: Recommend SGLT-2i in patients with ASCVD, HF, or at high risk for ASCVD.
        - Consider the addition of GLP-1 RA if further CV risk reduction is indicated.
        - Recommend GLP-1 RA in patients with ASCVD or high risk of ASCVD.
- *American Heart Association/ Heart Failure Society of America (AHA/HFSA)*[37]
    - 2019: Recommend SGLT-2i in patients with T2DM at risk of HF and established HF.
        - GLP-1 RAs have no impact on risk of HF hospitalization.
        - Safe to use in but not beneficial in HF prevention.
        - Caution use in recent decompensation due to no benefit and possible worse outcomes.

Table 2. Summary of Current Recommendations[32-37]

Guideline or Statement	Year	SGLT-2i preferred in HF	GLP-1 RA as second line option in HF	Caution use in recently decompensated HF patients
American Diabetes Association (ADA)	2020	+	+	-
	2021	+	+/-	-
American Association of Clinical Endocrinologists (AACE)	2020	+	+	-
American College of Cardiology (ACC)	2020	+	+/-*	-
American Heart Association/ Heart Failure Society of America (AHA/HFSA)	2019	+	+/-^	+

*Consider addition of GLP-1 RA if further CV risk reduction indicated.
^GLP-1 RAs have no impact on the risk of HF hospitalization

Clinical Controversy

- Based on guideline recommendations, GLP-1 RAs are often used as a second line treatment for patients with HF and T2DM who cannot use SGLT-2 inhibitors.
- What is the evidence supporting the use of GLP-1 RAs in preventing HF hospitalization or mortality in patients with HF and T2DM?

Early Clinical Trials

- *Sokos, et al.*[38]
    - This single-center, open label, nonrandomized study investigated the use of a 5-week continuous SubQ infusion of GLP-1 (2.5 pmol/kg/min) in ambulatory patients with chronic NYHA class III/IV heart failure on guideline directed medical therapy (n=12).
    - Found LVEF improved from 21 ± 3% to 27 ± 3% ($p<0.001$) and quality of life (Minnesota Quality of Life score) improved from 64 ± 4 to 44 ± 5 ($p<0.001$) in patients receiving GLP-1 compared to control patients. Benefits seen in patients with and without diabetes.
- *Halbirk, et al.*[39]
    - This double-blinded, placebo-controlled, crossover study investigated the use of a 48 hour GLP-1 infusion (1.0pmol/kg/min) in hospitalized compensated HFrEF patients (NYHA class II and III) without diabetes (n=15).
    - Found cardiac index (1.5 ± 0.1 L/min/m2 vs. 1.7 ± 0.2 L/min/m2 P = 0.54) and LVEF LVEF (30 ± 2% vs. 30 ± 2%; P=0.93) did not improve while HR (67 ± 2 beats/min vs. 65 ± 2 beats/min; p=0.016) and diastolic blood pressure slightly increased (71 ± 2 mmHg vs. 68 ± 2 mmHg; p=0.008).

- *Velez, et al.*[40]
    - Retrospective cohort study in diabetic patients without a history of HF found that GLP-1 agents (GLP-1 RAs and DDP-IV inhibitors) were associated with a reduced risk of HF hospitalization (HR 0.51; 95% CI 0.34-0.77; p=0.002) and lower risk of mortality (HR 0.31; 95% CI 0.18 -0.53; p=0.001) compared to the control group.
    - When separated by agent, DDP-IV inhibitors (n=1,189) reported a significantly lower risk of HF hospitalization, all-cause mortality, and all-cause hospitalization. The GLP-1 RA group only reported 1 hospitalization out of 205 so a comparison could not be made.
- *Chen, et al.*[41]
    - Single center, randomized, double-blind, placebo-controlled trial in China investigated the use of liraglutide after PCI in STEMI patients with or without diabetes (n=92).
    - Patients were given 1.8mg of liraglutide before PCI, then 0.6mg daily for 2 days, 1.2 mg for 2 days, and then 1.8mg for 2 days (total 7 days) in addition to aspirin, statins, and beta blockers.
    - Found LVEF increased from 50.9 ± 7.9% to 60.2 ± 9.1% in patients without diabetes and 50.1 ± 7.3 to 62.8 ± 9.0% in patients with diabetes after 3 months. Compared to the control group, liraglutide increased LVEF by an additional 4.1% (95% CI +1.1% to 6.9%; p<0.001)

Randomized Controlled Trials in HFrEF

Table 3. Overview of the FIGHT Trial (2016)

<table>
<tr><th colspan="3">Margulies KB, Hernandez AF, Redfield MM, et al; NHLBI Heart Failure Clinical Research Network. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA. 2016;316(5):500-508.</th></tr>
<tr><td>Objective</td><td colspan="2">Determine the effect of liraglutide in patients with advance heart failure who have been recently hospitalized for acute decompensated heart failure.</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study Design</td><td colspan="2">Multicenter, double-blind, randomized, placebo-controlled, Phase 2 trial conducted from 2013 to 2015.
Patients were identified based on hospital admission records and enrolled in last 24 hours of hospitalization or within 2-weeks of discharge.</td></tr>
<tr><td>Population</td><td>Inclusion Criteria
Established HF with LVEF less than 40% within prior 3 months
Recent hospitalization within 14 days for acute HF exacerbation while receiving evidence-based medications (including ACE-inhibitor/ARB and beta-blocker)
Receiving at least 40mg of furosemide (or equivalent) prior to admission</td><td>Exclusion Criteria
Recent acute coronary syndrome or coronary intervention within 4 weeks of randomization
Primary infiltrative or restrictive cardiomyopathy
Ongoing hemodynamically significant arrhythmias
VAD or heart transplant likely within 6 months
Active infection driving HF hospitalization
Severe pulmonary, renal or hepatic disease
History of gastroparesis, pancreatitis, or medullary thyroid cancer</td></tr>
<tr><td>Intervention</td><td colspan="2">Intervention (n=154): liraglutide SubQ daily; initially started at 0.6mg/dL and then increased to 1.2mg/dL after 14 days if tolerated; increased to a maximum of 1.8mg/dL if tolerated after additional 14 days
Control (n=146): placebo SubQ daily
Randomized 1:1 to receive liraglutide or placebo. Performed follow up testing at 30-, 90-, and 180-days. Continued concomitant HF therapies and allowed for up titration of neurohormonal agents after hospitalization as tolerated. Continued T2DM drugs with adjustments made to sulfonylurea and insulin doses in combination with at least daily blood glucose monitoring to reduce the risk of hypoglycemia.</td></tr>
<tr><td>Outcomes</td><td colspan="2">Primary Outcome: global rank score (hierarchical arrangement based on 1) time to death, 2) time to HF hospitalization, and 3) time averaged proportional change in N-terminal pro-B-type natriuretic peptide [NT-proBNP] from baseline to 180 days)
Secondary Outcomes (selected): death, HF hospitalization, time averaged change in NT-proBNP, change in LVEF%, change in Kansas City Cardiomyopathy Questionnaire scores (KCCQ), and change in 6 min walk distance.
Safety Outcomes: collected by telephone at 210 days, reported by site investigators, not adjudicated</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">Estimated 150 subjects needed in each group to provide a power of 92% assuming a 25% reduction in clinical outcomes (mortality and HF hospitalizations)
Intention to treat analysis
Utilized Chi-square test and Fisher’s exact test for binary outcomes
Used general linear models and nonparametric approaches for continuous outcomes
Kaplan Meier survival estimates and log-rank tests used for unadjusted time-to-event comparison</td></tr>
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Results

Baseline Characteristics

Characteristic	Liraglutide (n=154)	Placebo (n=146)
Age, median (IQR), yr	62 (52-68)	61 (51-67)
Female, n (%)	31 (20)	33 (23)
White, n (%)	82 (53)	90 (62)
Body mass index, median (IQR), kg/m^2	31 (26-36)	33 (25-38)
NYHA classification, n (%)		
II	49 (32)	36 (25)
III	93 (60)	96 (66)
IV	8 (5)	6 (4)
NT-proBNP, pg/mL	1936 (1075-4231)	2083 (1020-4333)
Medical History, n (%)		
Ischemic heart disease	133 (86)	113 (77)
T2DM	91 (59)	87 (60)
HF hospitalization in past yr	137 (89)	125 (86)
LVEF, n (%)	25 (20-33)	25 (19-32)
Medications		
Beta blocker	143 (93)	139 (95)
ACEi or ARB	112 (73)	104 (71)
Aldosterone antagonist	88 (57)	89 (61)
Lipid lowering agent	110 (71)	110 (75)

Outcomes

Outcome	Liraglutide (n=154)	Placebo (n=146)	Treatment Effect (95% CI)	P value
Primary Endpoint				
Mean global rank score	146	156	-	0.31
Secondary Endpoints				
Death, n (%)	19 (12)	16 (11)	1.10 (0.57-2.14)	0.78
Rehospitalization for HF, n (%)	63 (41)	50 (34)	1.30 (0.89-1.88)	0.17
Time averaged proportional change in NT-proBNP, mean	1.9 (1.4- 2.3)	1.8 (1.4-2.1)	0.1 (-0.4-0.7)	0.65
KCCQ score, overall	13 (10 to 17)	13 (9 to 17)	0.6 (-4.5-5.8)	0.81
LVEF, %	1.1 (-0.7-2.8)	1.4 (-0.4-3.2)	-0.1 (-2.3-2.1)	0.85
Safety Events				
Hypoglycemia, n (%)	2 (1)	4 (3)	-	-
Change in heart rate, beats/min	1.0 (-1.72-3.63)	1.2 (-1.5-3.8)	-1.6 (-4.8-1.6)	0.33

- **Dose Titration:** In the liraglutide group, 60% reached the maximum dose (1.8mg/day), 21% reached 1.2mg/day, and 16% reached 0.6mg/day. Placebo group achieved 71%, 19%, and 10% proportions, respectively.
- **Duration:** Median duration for liraglutide group was 25.0 weeks (IQR 8.6-25.9). Median duration for placebo group was 25.0 weeks (IQR 11.4-26.0)
- **Tertiary Endpoints:** Liraglutide group reported greater weight loss at 30 days and 90 days but no significant different at 180 days.
- **T2DM Subgroup**: No statistically significant difference in global rank scores between liraglutide and placebo (85 vs 94, p = 0.27). However, reported higher risk of death or rehospitalization with liraglutide compared to placebo (HR 1.54; 95% CI 0.97-2.46; p = 0.07)

Author's Conclusion

"Among patients recently hospitalized with heart failure and reduce LVEF, the use of liraglutide did not lead to greater posthospitalization clinical stability. These findings do not support the use of liraglutide in this clinical situation."

Critique

Strengths

- Prospective, randomized, double blinded, placebo-controlled trial.
- Multicenter trial conducted in the United States.
- Inclusion and exclusion criteria of patients with recent HF exacerbation appropriate for objective of the trial.
- Outcomes were clinically relevant and included measurements of clinical and functional status.
- Met power needed to assess HF hospitalizations and mortality in statistical analysis.

Limitations

- Global rank score not validated in heart failure trials and does not predict success in phase III trial.
- Not powered to detect statistically significant differences in individual clinical outcomes and safety outcomes.
- Used a different titration strategy than clinical practice and did not report rate of GI adverse effects.
- Changes in baseline guideline directed medical therapy for HF undocumented.
- Adherence to GLP-1 RA not measured.

Take Home Points

Liraglutide does not result in improved clinical stability compared to placebo in patients with advance heart failure who have been recently hospitalized for acute heart failure. Liraglutide may lead to worse clinical outcomes in patients with T2DM and HF with a recent HF exacerbation.

Table 4. Overview of the LIVE Trial (2017)

Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail.* 2017;19(1):69-77.

Objective	Determine the effects of liraglutide on left ventricular function in stable HFrEF with and without diabetes.
Methods	
Study Design	Investigator initiated, multicenter, randomized, double-blind, placebo controlled trial • Patients identified at heart failure and diabetes clinics at 4 Danish centers from 2012 to 2015
Population	Inclusion Criteria • Age 30 to 85 years old • HF NYHA class I, II, III • LVEF ≤ 45% • Stable HF treatment (using ESC guidelines) for 3 months prior to randomization Exclusion Criteria • MI or coronary revascularization within 3 months • Hospitalization due to uncompensated heart disease within 30 days • NYHA class IV • Atrial Fibrillation with ventricular rate >100/min at rest • Other: T1DM, HbA1c >10%, use of GLP-1 RA or DDPIV within 30 days, liver disease with ALT> 3x ULN, IBD, pancreatitis, gastroparesis, eGFR < 30, thyroid adenoma/carcinoma
Intervention	**Intervention (n=122):** liraglutide SubQ daily; initially started at 0.6mg and then increased to 1.2mg after 1 week if tolerated; increased to a maximum of 1.8mg if tolerated after additional 7 days – **Control (n=119):** placebo SubQ daily • Randomized 1:1 to receive liraglutide or placebo. • Performed follow up assessment at baseline, week 3, week 12, and at the conclusion. • Continued concomitant HF therapies. • Continued T2DM drugs with sulfonylurea and insulin doses initially decreased to avoid hypoglycemia. Reduced non study T2DM drug before study drug if recurrent hypoglycemia occurred.
Outcomes	**Primary Outcome:** change in LVEF% from randomization to conclusion of the study • ECHOs performed by one experienced, blinded technician **Secondary Outcomes:** change in peak systolic longitudinal tissue velocity, LV end-systolic volume, LV end-diastolic volume, diastolic function, global longitudinal strain, functional status (6MWT), NT-proBNP, quality of life (Minnesota Living with Heart Failure Questionnaire) **Safety Outcomes:** Senior specialist validated suspected cardiac related events. Evaluated by unblinded, independent committee comprised of cardiologist and endocrinologist
Statistical Analysis	• Estimated 192 patients needed to provide 90% power to observe a 2.5% change in LVEF (as seen in LVEF trials with ACEis and beta blockers.) • Alpha of 0.05 • Used intention to treat and per protocol analysis. • Used unpaired t-test or ANOVA for normal distributed data. • Used Mann-Whitney U-test for non-normally distributed data. • Used Chi square and Fisher's exact test for categorical data.
Results	

Baseline Characteristics

Characteristic	**Liraglutide (n=122)**	**Placebo (n=119)**
Age, mean (SD), yr	65 (9.2)	65 (10.7)
Female, n (%)	13 (10.6)	13 (10.9)
Body mass index, mean (SD), kg/m^2	28.0 (3.8)	29.8 (4.6)
NYHA classification, n (%)		
I	36 (31)	35 (30)
II	65 (55)	64 (56)
III	17 (14)	16 (14)
NT-proBNP, pg/mL	413 (208-926)	388 (153-880)
Medical History, n (%)		
Ischemic heart disease	72 (59)	73 (62)
T2DM	39 (32)	35 (29)
LVEF, n (%)	33.7 (7.6)	35.4 (9.4)
Medications		
Beta blocker	113 (93)	108 (91)
ACEi or ARB	118 (97)	115 (97)
Aldosterone antagonist	59 (48)	54 (45)
Statin	96 (79)	92 (77)

Outcomes

Outcome	Liraglutide (n=122)	Placebo (n=119)	Delta Estimate (95% CI)	P value	NNT/ NNH
Primary Endpoint (Change from Baseline)					
LVEF, %	0.7 (5.4)	1.5 (5.0)	-0.8 (-2.1, 0.5)	0.24	-
Secondary Endpoints (Change from Baseline)					
6MWT, m, median (IQR)	28 (65)	3 (89)	24 (2, 47)	0.04	4.2
MLHFQ, grade	-2.7 (12)	-1.1	-1.6 (-5.3, 2.0)	0.39	-
Heart Rate, bpm	6 (9)	-1 (8)	7 (5,9)	<0.0001	100
BMI, kg/m^2	-0.7 (1.0)	0.1 (1.1)	-0.8 (-1.1, -0.4)	<0.0001	1000
Plasma NT-proBNP, pg/mL	-62 (735)	78 (524)	-140 (-137, 37)	0.12	-
Safety Outcomes					
Serious cardiovascular AE (death due to VT, VT, AF requiring intervention, ACS, worsening of HF), n (%)	12 (10)	3 (3)	-	0.04	14
Non serious cardiovascular events (non-sustained VT, supraventricular tachycardia, AF, and worsening HF), n (%)	13 (11)	9 (8)	-	0.14	-
GI events (nausea, constipation), n (%)	80 (66)	19 (16)	-	<0.0001	2
CNS events (dizziness, fatigue), n (%)	38 (31)	15 (13)	-	0.002	5
Hypoglycemia in T2DM, n (%)	4 (10)	3 (9)	-	0.73	-

- **Duration**: 24 weeks
- **Adherence**: estimated to be 90% between both groups.
- **Titration:** reported average liraglutide dose of 1.4mg (1.3, 1.5) and placebo dose 1.6mg (1.5, 1.7).
- **Dropout rate:** 29 (12%) dropped out after randomization. Although the dropout rate did not significantly differ between the two groups, the primary reason for drop out in the liraglutide group was GI side effects.
- **T2DM:** The primary conclusion was consistent when adjusted for T2DM (p=0.59).
- **AE:** Significantly more adverse events seen with liraglutide (HR 3.9; 95% CI 1.1, 13.8; p = 0.029). One death due VT occurred shortly after increase in liraglutide dose.

Author's Conclusion

"Liraglutide did not affect left ventricular systolic function compared with placebo in stable chronic heart failure patients with and without diabetes. Treatment with liraglutide was associated with an increase in heart rate and more serious cardiac adverse events, and this raises some concern with respect to the use of liraglutide in patients with chronic heart failure and reduced left ventricular function."

Critique

Strengths

- Prospective, randomized, double blind, placebo-controlled trial.
- Reported comprehensive safety data in patients with HF.
- Estimated compliance between both groups.
- Optimal background treatment for heart failure and did not differ between groups.
- Outcomes included measurements of clinical and functional status.

Limitations

- Variations in LVEF measurement may obscure the effects of GLP-1 RA treatment due to type 2 error, however, results were consistent across multiple measurements of LV indices.
- LVEF is a surrogate measure for clinical outcomes and the study was not powered to detect differences in HF hospitalization or mortality.
- Small portion of population was female compared to male.
- The study was conducted in Denmark, which limits external validity.
- Did not report baseline T2DM medications used.
- Treatment duration potentially too short to show changes in LVEF and cardiac remodeling. (although previous studies indicate treatment with ACEi or beta blocker results in changes in cardiac modeling after 3 months)

Take Home Points

Treatment with liraglutide in ambulatory HF patients (with and without T2DM) did not result in significant improvement in LVEF and was associated with a significant increase in adverse effects. More data is required to establish the safety and efficacy of liraglutide in patients with HF.

Cardiovascular Outcome Trials (CVOTs)[42-44]

- In the 2000s, the approval of T2DM drugs was largely based on improvement in glycemic control and the safety data from phase 2 and 3 clinical trials.
- In 2007, a meta-analysis of 43 relatively small trials revealed that rosiglitazone increased the risk of myocardial infarction which sparked a controversy regarding the cardiovascular safety of T2DM drugs.
- In 2008, the FDA published guidance that required new T2DM drugs to prove they did not unreasonably increase cardiovascular risk.
- As a result, new T2DM medications were required to establish cardiovascular safety through large cardiovascular outcome trials (CVOTs) which included high risk populations (advanced disease, older patients, and renal impairment).
- CVOTs focus on the impact of the T2DM drug on major adverse cardiovascular events (MACE) including cardiovascular death, nonfatal myocardial infarction or nonfatal stroke with HF hospitalization as a secondary outcome.

Table 5. Overview of Cardiovascular Outcome Trials (CVOTs)[8,15]

Trial	Population	N	% HF	Median Follow Up, years	Primary Outcome	Impact on Primary CV Outcome	Impact on HF Hospitalization
ELIXA	Recent ACS	6068	22.4	2.1	CVD, MI, UA, stroke	No difference in risk (HR 1.02; 95% CI 0.89-1.17)	No difference in risk (HR 0.96; 95% CI 0.75-1.23)
LEADER	CVD or high risk	9340	17.8	3.8	CVD, MI, stroke	Decreased risk (HR 0.87; 95% CI 0.78-0.97)	No difference in risk (HR 0.87; 95% CI 0.73-1.05)
SUSTAIN-6	CVD or high risk	3297	23.6	2.1	CVD, MI, stroke	Decreased risk (HR 0.74; 95% CI 0.58-0.95)	No difference in risk (HR 1.11; 95% CI 0.77-1.61)
EXSCEL	With or without CVD	14752	16.2	3.2	CVD, MI, stroke	No significant difference (HR 0.74; 95% CI 0.83-1.00)	No difference in risk (HR 0.94; 95% CI 0.78-1.13)
HARMONY	CVD	9463	20.3	1.5	CVD, MI, stroke	Decreased risk (HR 0.78; 95% CI 0.68-0.90)	Decreased risk (HR 0.71; 95% CI 0.53-0.94)
PIONEER-6	CVD or high risk	3183	12.2	1.3	CVD, MI, stroke	No significant difference (HR 0.79; 95% CI 0.57-1.11)	No significant difference (HR 1.11; 95% CI 0.77-1.61)
REWIND	CVD or high risk	9901	8.6	5.4	CVD, MI, stroke	Decreased risk (HR 0.88; 95% CI 0.79-0.99)	No significant difference (HR 0.93; 95% CI 0.77-1.12)
Kristensen, et al.	N/A	56004	N/A	N/A	N/A	Decreased risk (HR 0.88; 95% CI 0.82-0.94)	Decreased risk (HR 0.91; 95% CI 0.83-0.99)

Table 6. LEADER Post Hoc Analysis in Patients With or Without Heart Failure

Marso SP, Baeres FMM, Bain SC, Goldman B, Husain M, Nauck MA, Poulter NR, Pratley RE, Thomsen AB, Buse JB; LEADER Trial Investigators. Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure. *J Am Coll Cardiol.* 2020;75(10):1128-1141.

Objective	Determine the effects of liraglutide on cardiovascular outcomes in patients with T2DM and HF	
Methods		
Study Design	Multicenter, double-blind, randomized, placebo-controlled trial post-hoc analysis	

Population	Inclusion Criteria
	• T2DM
	• Hbg A1c ≥ 7.0%
	• ≥50 years of age with established CVD:
	  ○ Prior MI, stroke, or TIA
	  ○ Prior coronary, carotid, or peripheral arterial revascularization
	  ○ Chronic HF (NYHA Class II–III)
	  ○ Chronic renal impairment (eGFR <60ml/min)
	• OR ≥60 years of age with at least one CV risk factor:
	  ○ Persistent microalbuminuria or proteinuria
	  ○ Hypertension and left ventricular hypertrophy
	  ○ Left ventricular systolic or diastolic dysfunction by imaging
	  ○ Ankle brachial index <0.9
		Exclusion Criteria
		• Use of a GLP-1 receptor agonist (exenatide, liraglutide or other) or pramlintide or any DPP-4 inhibitor within the 3 months prior to screening
		• Acute decompensation of glycemic control
		• Acute coronary or cerebrovascular event in the previous 14 days
		• Chronic HF (NYHA class IV)

Intervention	**Intervention:** liraglutide SubQ daily (n=4668); started at 0.6mg and increased to 1.2mg after one week and 1.8mg after one week as tolerated (maximum dose = 1.8mg/day) **Control:** placebo SubQ daily (n=4672) • Randomized 1:1 to receive the intervention or control • Follow up: 3.5 to 5 years • Additional glucose controlling agents could be added based on investigator's discretion.	
Outcomes	**Primary Outcome:** first occurrence of composite MACE (including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) **Secondary Outcomes:** coronary revascularization, HF hospitalization, unstable angina hospitalization, all-cause death. • HF hospitalizations were adjudicated by an independent, external, blinded committee.	
Statistical Analysis	Calculated 8754 patients would need to be randomized to reach 90% power with an alpha of 0.025. Used Cox regression model to analyze interactions between treatment and HF history. Used time to event analysis in the primary composite outcome of the overall population. Intention to treat analysis was used.	
Results		

Baseline Characteristics

Characteristic	**Patients with HF at baseline**		**Patients without HF at baseline**	
	Liraglutide (n=835)	**Placebo (n=832)**	**Liraglutide (n=3,833)**	**Placebo (n=3,840)**
Age, mean ± SD, yr	63.5 ± 7.8	64.0 ± 7.8	64.4 ± 7.1	64.5 ± 7.1
Female, n (%)	352 (42.2)	332 (39.9)	1,305 (34.0)	1,348 (35.1)
Body mass index, mean ± SD, kg/m^2	34.2 ± 6.9	33.9 ± 6.8	32.2 ± 6.1	32.2 ± 6.1
NYHA classification, n (%)				
I	179 (21.4)	169 (20.3)	-	-
II	545 (65.3)	546 (65.6)	-	-
III	108 (12.9)	106 (12.7)	-	-
Diabetes duration, yrs	11.6 ± 7.6	11.8 ± 8.1	13.0 ± 8.0	13.1 ± 8.0
HF Medication, n (%)				
Beta blocker	635 (76)	576 (69)	2,017 (53)	1,953 (51)
ACEi or ARB	728 (87)	721 (87)	3,167 (83)	3,115 (81)
Aldosterone antagonist	133 (16)	129 (16)	121 (3)	122 (3)
Statin	582 (70)	567 (68)	2,823 (74)	2,769 (72)
Antithrombotic Medications (Vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors)	130 (16)	123 (15)	179 (5)	191 (5)

<table>
<tr><td>Outcomes</td><td>
<table>
<tr><th>Outcomes</th><th>Liraglutide, N (%)</th><th>Placebo, N (%)</th><th>HR (95% CI)</th><th>P value</th></tr>
<tr><td colspan="5">Primary Endpoint</td></tr>
<tr><td>MACE
- NYHA Class I-III
- No HF</td><td>
142 (17.0)
466 (12.2)</td><td>
170 (20.4)
524 (13.6)</td><td>
0.81 (0.65; 1.02)
0.88 (0.78; 1.00)</td><td>0.53</td></tr>
<tr><td colspan="5">Secondary Endpoints</td></tr>
<tr><td>CV death
- NYHA Class I-III
- No HF</td><td>
76 (9.1)
143 (3.7)</td><td>
88 (10.6)
190 (4.9)</td><td>
0.85 (0.63; 1.16)
0.75 (0.60; 0.93)</td><td>0.50</td></tr>
<tr><td>Non-fatal MI
- NYHA Class I-III
- No HF</td><td>
54 (6.5)
227 (5.9)</td><td>
71 (8.5)
246 (6.4)</td><td>
0.74 (0.52; 1.06)
0.92 (0.77; 1.10)</td><td>0.29</td></tr>
<tr><td>Non-fatal stroke
- NYHA Class I-III
- No HF</td><td>
27 (3.2)
132 (3.4)</td><td>
30 (3.6)
147 (3.8)</td><td>
0.89 (0.53; 1.50)
0.89 (0.71; 1.13)</td><td>0.99</td></tr>
<tr><td>Hospitalization for HF
- NYHA Class I-III
- No HF</td><td>
108 (12.9)
110 (2.9)</td><td>
108 (13.0)
140 (3.6)</td><td>
0.98 (0.75; 1.28)
0.78 (0.61; 1.00)</td><td>0.22</td></tr>
</table>

Median follow up: 3.8 years
Median daily dose: 1.78mg (IQR 1.54 to 1.79)
Median Time of Exposure to Liraglutide or Placebo: 3.5 years
Mean Percentage of Time Receiving Trial Regimen: 84% for liraglutide and 83% for placebo.
AE: No statistically significant change in heart rate (HR) from baseline between patients with or without HF. Change in HR after 3 years of liraglutide was estimated to be 2.3 beats/min (95% CI 1.2-3.4) in patients with HF and 3.1 beats/min (95% CI 2.6-3.6) in patients without HF.

</td></tr>
<tr><td>Author’s Conclusion</td><td>“There was no increased risk of HF hospitalization with liraglutide versus placebo in patients with or without HF at baseline. … Overall, results from this analysis of LEADER data indicate that liraglutide should be considered a suitable treatment option for patients with T2D, either with or without a history of HF (NYHA functional class I to III).”</td></tr>
<tr><td>Critique</td><td>Strengths

Prospective, multicenter, randomized, double blind, placebo-controlled trial.
Used titration schedule recommended by package insert.
Large, multinational population.
Adjudicated HF hospitalizations.

Limitations

Based on exploratory analyses.
History of HF assessed by medical history. Less accurate than using ECHO imaging and did not provide ejection fraction. Biomarker data (NT-proBNP) not collected.
Limited to patients with NYHA class I to III; Results not applicable to patients with NYHA class IV or patients at lower risk for cardiovascular disease.
Use of other T2DM used in HF patients not reported.

</td></tr>
<tr><td>Take Home Points</td><td>

HF patients were more likely to experience cardiovascular events and all-cause death than patients without HF (except stroke).
GLP-1 RAs reduce the risk of MACE in patients with or without HF.
GLP-1 RAs do not increase the risk of HF hospitalization in patients with or without HF.

</td></tr>
</table>

Table 7. EXSCEL Post Hoc Analysis in Patients With or Without Heart Failure

Fudim M, White J, Pagidipati NJ, et al. Effect of Once-Weekly Exenatide in Patients With Type 2 Diabetes Mellitus With and Without Heart Failure and Heart Failure-Related Outcomes: Insights From the EXSCEL Trial. *Circulation.* 2019;140(20):1613-1622.

Objective	Determine the effects of once weekly exenatide on cardiovascular outcomes in patients with and without heart failure compared to placebo
Methods	
Study Design	Multicenter, double-blind, randomized, placebo-controlled trial post-hoc analysis
Population	**Inclusion Criteria** • Age ≥ 18 years old • T2DM with Hbg A1c of 6.5 -10.0% • With or without history or previous cardiovascular events (clinical manifestation of CAD, ischemic cerebrovascular disease, atherosclerotic peripheral arterial disease) • May have received up to 3 oral glucose lowering agents, or insulin (alone or with 2 or less glucose lowering agents) **Exclusion Criteria** • Two or more severe hypoglycemia episodes (received assistance from a third party) within past year • End stage renal disease or EGFR <30mL/min/1.73 m2 • Personal or family history of medullary thyroid carcinoma • Multiple endocrine neoplasia type 2 • Baseline calcitonin > 40ng/L • Previous treatment with GLP-1 RA • History of gastroparesis or pancreatitis
Intervention	**Intervention:** exenatide 2mg SubQ weekly (n=7,356) **Control:** placebo SubQ weekly (n=7,396) • Randomized 1:1 to receive the intervention or control. • Patients discontinued trial if developed two or more episodes of severe hypoglycemia, irreversible kidney dysfunction (two consecutive eGFR measurements <30mL/min/1.73m2), received renal replacement therapy, reported calcitonin levels (>50ng/L). • Additional glucose controlling agents could be added based on investigator's discretion to achieve the patient's glycemic goal.
Outcomes	**Primary Outcome:** first occurrence of composite MACE (including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) **Secondary Outcomes:** all-cause death, separate components of MACE, HF hospitalization, ACS hospitalization. • HF hospitalizations were adjudicated by an independent, blinded committee.
Statistical Analysis	Estimated 1360 patients with a primary event would be needed to detect a 15% reduction in the primary outcome with exenatide compared to placebo. Alpha of 0.05. Used Cox regression analysis to determine treatment effects of exenatide on secondary endpoints. Used intention to treat analysis
Results	

Baseline Characteristics

Characteristic	History of HF (n=2,389)		No History of HF (n=12,362)	
	Exenatide (n=1,161)	Placebo (n=1,228)	Exenatide (n=6,194)	Placebo (n=6,168)
Age, median (IQR), yr	64 (58, 69)	62 (55, 68)	62.0 (56.0, 68.0)	62.0 (55.0, 68.0)
Female, n (%)	849 (35.5)	4,753 (38.4)		
White, n (%)	1036 (89.2)	1084 (88.3)	4518 (73.0)	4537 (73.6)
Body mass index, median (IQR), kg/m^2	33.0 (29.3, 37.5)	32.8 (29.4, 37.3)	31.6 (28.1, 35.9)	31.6 (28.1, 35.9)
NYHA classification, n (%) I II III IV	 365 (31.5) 628 (54.1) 162 (14.0) 5 (0.4)	 373 (30.4) 705 (57.5) 141 (11.5) 8 (0.7)	 - - - -	 - - - -
LV Assessment/ Ejection Fraction Normal (>55%) Mild Dysfunction (40-55%) Moderate Dysfunction (25-39%) Severe Dysfunction (<25%) Unknown	 241 (20.8) 273 (23.5) 139 (12.0) 32 (2.8) 476 (41.0)	 275 (22.4) 301 (24.5) 108 (8.8) 24 (2.0) 520 (42.3)	 1206 (19.5) 470 (7.6) 71 (1.1) 10 (0.2) 4437 (71.6)	 1203 (19.5) 454 (7.4) 70 (1.1) 15 (0.2) 4426 (71.8)
Coronary artery disease, n (%)	840 (72.4)	893 (72.7)	3057 (49.4)	3003 (48.7)
Cerebrovascular disease, n (%)	239 (20.6)	261 (21.3)	994 (16.1)	1015 (16.5)
Peripheral arterial disease, n (%)	195 (16.8)	230 (18.7)	1205 (19.5)	1170 (19.0)
Prior MI, n (%)	613 (52.8)	645 (52.5)	1734 (28.0)	1686 (27.3)

Duration of T2DM, median (IQR), yr	12.0 (7.0, 18.0)	12.0 (7.0, 18.0)	12.0 (7.0, 17.0)	12.0 (7.0, 18.0)
Cardiovascular Medications				
Beta blockers	870 (74.9)	932 (75.9)	3211 (51.8)	3197 (51.8)
ACEi or ARB	1026 (88.4)	1075 (87.5)	4842 (78.2)	4844 (78.6)
Aldosterone antagonists	221 (19.0)	210 (17.1)	235 (3.8)	246 (4.0)
Statin	920 (79.2)	979 (79.7)	4544 (73.4)	4401 (71.4)
Antihyperglycemic Therapy				
Oral agents	914 (78.7)	990 (80.6)	5299 (85.6)	5288 (85.7)
Insulin	610 (52.5)	612 (49.8)	2786 (45.0)	2827 (45.8)
DPP-IV inhibitor	143 (12.3)	137 (11.2)	975 (15.7)	948 (15.4)

Outcomes

	Exenatide, N (%)	**Placebo, N (%)**	**HR (95% CI)**	**P-value**
Primary Endpoint				
MACE				
- No Prior HF (n= 6,194)	612 (9.9)	668 (10.8)	0.91 (0.83; 1.00)	0.505
- Prior HF (n=1,161)	227 (19.6)	237 (19.3)	0.97 (0.81; 1.16)	
Secondary Endpoints				
All-cause death				
- No Prior HF	328 (5.3)	410 (6.6)	0.79 (0.68; 0.98)	0.031
- Prior HF	179 (15.4)	174 (14.2)	1.05 (0.95; 1.29)	
CV death				
- No Prior HF	212 (3.4)	256 (4.2)	0.82 (0.68; 0.98)	0.147
- Prior HF	128 (11.0)	127 (10.3)	1.03 (0.80; 1.31)	
All MI				
- No Prior HF	372 (6.0)	375 (6.1)	0.97 (0.84; 1.13)	0.898
- Prior HF	111 (9.6)	118 (9.6)	0.96 (0.74; 1.24)	
All stroke				
- No Prior HF	140 (2.3)	176 (2.9)	0.78 (0.62; 0.97)	0.114
- Prior HF	47 (4.0)	42 (3.4)	1.14 (0.75; 1.73)	
Hospitalization for HF				
- No Prior HF	129 (2.1)	144 (2.3)	0.88 (0.69; 1.11)	0.329
- Prior HF	90 (7.8)	87 (7.1)	1.06 (0.79; 1.42)	

- **Hospitalization for Heart Failure (regardless of HF status):** Although the time to first adjudicated hHF was not different between exenatide and placebo groups, first plus recurrent hHF was lower in the patients who received exenatide (HR 0.82; 95% CI 0.68-0.99; p = 0.038).
- **Median Follow Up:** 3.2 years (IQR 2.2-4.4)
- **Drop Out:** In the exenatide group, 255 (3.5%) did not complete the study. Primarily due to withdrawal of consent (n=217).
- **Premature Permanent Discontinuation:** 43% of patients (3164/7356) discontinued exenatide before the end of the trial mainly due to patient decision (30.3%) or patient died (3.1%).
- **AE:** Changes in HR were not reported in the HF specific group but increased by 2.51 bpm in the overall population who received exenatide (95% CI 2.28-2.74; p<0.001).

Author's Conclusion

"In EXSCEL, the use of EQW in patients with or without HF was well tolerated, but benefits of EQW on reduction in all-cause death and first hospitalization for HF were attenuated in patients with baseline HF."

Critique

Strengths

- Prospective, multicenter, randomized, double blind, placebo-controlled trial.
- HF status determined by investigator using available clinical data including subjective measurements (signs and symptoms of HF) and objective data (echocardiography and natriuretic peptide levels).
- Reported LVEF and classified patients based on mild to severe dysfunction.
- Included very small number of NYHA Class IV patients previously excluded from other CVOTs.
- Largest HF population among major CVOTs.

Limitations

- Based on exploratory analyses.
- Substantial number of HF patients did not report level of LV dysfunction and baseline HF was not formally adjudicated.
- Missing break down of oral antihyperglycemic agents used.
- Guideline directed medical therapy for heart failure potentially not optimized.
- Shorter duration of follow up compared to other CVOTs.
- High rate of premature permanent discontinuation.

Take Home Points

- Although exenatide appears to be safe and well tolerated, exenatide does not appear to have the same cardiovascular benefits in patients with HF compared to patients with no prior HF.

Table 8. SUSTAIN and PIONEER Post Hoc Analysis Across CV Risk Subgroups

Husain M, Bain SC, Jeppesen OK, et al. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. *Diabetes Obes Metab.* 2020;22(3):442-451.

Objective	Determine the effects of semaglutide on MACE and HF hospitalization in T2DM patients and across CV risk subgroups.
Methods	
Study Design	Multicenter, randomized, double-blind, placebo-controlled trial (SUSTAIN: parallel group)

Population	Inclusion Criteria
	• HbgA1c ≥ 7% (SUSTAIN only)
	• ≥50 years of age with established CVD:
	  ○ Prior MI, stroke, or TIA
	  ○ Prior coronary, carotid, or peripheral arterial revascularization
	  ○ Chronic HF (NYHA Class II–III)
	  ○ Chronic renal impairment (eGFR <60ml/min in SUSTAIN 6 or ≥30–<59 mL/min in PIONEER 6)
	• OR ≥60 years of age with at least one CV risk factor:
	  ○ Persistent microalbuminuria or proteinuria
	  ○ Hypertension and left ventricular hypertrophy
	  ○ Left ventricular systolic or diastolic dysfunction by imaging
	  ○ Ankle brachial index <0.9
	
	Exclusion Criteria
	• Chronic (or intermittent in PIONEER 6) haemodialysis or peritoneal dialysis
	• Chronic HF (NYHA Class IV)
	• Treatment with DPP-IV inhibitor, GLP-1 RA or insulin other than basal or premixed insulin (SUSTAIN)
	SUSTAIN
	• Acute coronary or cerebrovascular event within 90 days before randomization; planned revascularization of a coronary, carotid, or peripheral artery; or long-term dialysis
	PIONEER
	• MI, stroke or hospitalization for unstable angina or TIA within 60 days prior to screening
	• Proliferative retinopathy or maculopathy requiring acute treatment
	• eGFR <30 mL/min/1.73 m^2

Intervention	SUSTAIN • Semaglutide 0.5mg (n=826), 1mg (n=822) SubQ weekly • Placebo 0.5mg (n=824), 1mg (n=825) SubQ weekly • Randomized 1:1:1:1 • **Titration Schedule:** Started at 0.25mg SubQ weekly for 4 weeks then increased to 0.5mg for 4 weeks until maintenance dose reached (0.5mg or 1.0). No changes in maintenance dose were allowed. • **Monitoring:** quarterly visits, used local guidelines to manage T2DM. PIONEER • Semaglutide 14mg PO daily (n=1,591) • Placebo PO daily (n=1,592) • Randomized 1:1 • **Titration Schedule:** Started at 3mg for 4 weeks then increased to 7mg for 4 weeks. Increased to 14mg (maximum dose) as tolerated. Dose could be de-escalated to reduce GI side effects but investigators were encouraged to escalate dose once GI side effects resolved. • **Monitoring:** in person or telephone visits, used local guidelines to manage T2DM.
Outcomes	Primary Outcome • First occurrence of MACE (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) Secondary Outcomes • Death from cardiovascular causes, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, HF hospitalization, unstable angina hospitalization, retinopathy, nephropathy
Statistical Analysis	SUSTAIN-6: time and event driven trial to continue until at least 122 primary outcome events occurred or 104 weeks of exposure. PIONEER-6: event driven trial assessing noninferiority to placebo to continue until at least 122 primary outcome events occurred. Post Hoc Analysis: used stratified Cox proportional hazards model
Results	
Baseline Characteristics	

Characteristic	**Semaglutide (n=3,239)**	**Placebo (n=3,241)**
Age, mean (SD), yr	65.3 (7.2)	65.5 (7.4)
Female, n (%)	1142 (35.3)	1160 (35.8)
Body mass index, mean (SD), kg/m^2	32.5 (6.4)	32.5 (6.3)
NYHA classification, n (%)		
II/III	473 (14.6)	488 (15.1)
Medical History, n (%)		
Prior MI	1090 (33.7)	1131 (34.9)
Prior stroke or TIA	499 (15.4)	522 (16.1)
CKD (eGFR <60mL/min)	849 (26.2)	844 (26.0)
Medications, n (%) (SUSTAIN-6 ONLY)		

<table>
<tr><td></td><td>
<table>
<tr><td>Beta blocker</td><td>934/1648 (56.7)</td><td>960/1649 (58.2)</td></tr>
<tr><td>ACEi or ARB</td><td>1377/1648 (83.6)</td><td>1376/1649 (83.4)</td></tr>
<tr><td>Aldosterone antagonist</td><td>97/1648 (5.9)</td><td>97/1649 (5.9)</td></tr>
<tr><td>Statin</td><td>1199/1648 (72.8)</td><td>1200/1649 (72.8)</td></tr>
<tr><td>Insulin</td><td>956/1648 (58.0)</td><td>957/1649 (58.0)</td></tr>
<tr><td>Sulfonylurea</td><td>698/1648 (42.4)</td><td>712/1649 (43.2)</td></tr>
<tr><td>Thiazolidinedione</td><td>35/1648 (2.1)</td><td>41/1649 (2.5)</td></tr>
</table>

Patients with HF (n=961/6,480) reported shorter duration of T2DM and higher rates of CVD at baseline compared to patients without HF.

Duration of DM: 12.8 years (8.3) vs 14.6 years (8.3)
Prior MI: 419 (43.6%) vs 1787 (32.6%)
Prior stroke or TIA: 142 (14.8%) vs 870 (15.9%)
CKD: 262 (27.3) vs 1420 (25.9%)

SGLT-2i Use: SUSTAIN reported that 1 patient (0.1%) in the semaglutide group and 4 (0.2%) in the placebo group used an SGLT-2 inhibitor at baseline. PIONEER reported that 165 (10.4%) in the semaglutide group and 140 (8.8%) used an SGLT-2 inhibitor at baseline.

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<tr><td>Outcomes</td><td>
<table>
<tr><th>SUSTAIN-6 and PIONEER-6</th><th>Semaglutide (n=3239)</th><th>Placebo (n=3241)</th><th>HR (95% CI)</th></tr>
<tr><td colspan="4">Primary Endpoint</td></tr>
<tr><td>MACE, n (%)</td><td>169 (3.1)</td><td>222 (4.2)</td><td>0.76 (0.62-0.92)</td></tr>
<tr><td colspan="4">Secondary Endpoint</td></tr>
<tr><td>CV death, n (%)</td><td>59 (1.1)</td><td>76 (1.4)</td><td>0.78 (0.56-1.10)</td></tr>
<tr><td>Non-fatal MI, n (%)</td><td>84 (1.5)</td><td>95 (1.8)</td><td>0.88 (0.66-1.18)</td></tr>
<tr><td>Non-fatal stroke, n (%)</td><td>39 (0.7)</td><td>60 (1.1)</td><td>0.65 (0.43-0.97)</td></tr>
<tr><td>Hospitalization for HF, n (%)</td><td>80 (1.5)</td><td>78 (1.4)</td><td>1.03 (0.75-1.40)</td></tr>
</table>

Subgroup analysis for MACE in patients with prior HF: semaglutide 51/473 vs placebo 49/488; HR 1.06 (95% CI 0.72-1.57; p =0.046)
Median follow-up: SUSTAIN – 2.1 years; PIONEER – 1.3 years

</td></tr>
<tr><td>Author’s Conclusion</td><td>“In SUSTAIN and PIONEER combined, glucagon-like peptide-1 analogue semaglutide showed consistent effects on MACE versus comparators across varying CV risk. No effect of semaglutide on MACE was observed in subjects with prior HF.”
“Taken together, these data suggest that GLP-1 RAs have a consistent effect on MACE in subjects with T2D and CVD, there are no overall safety concerns regarding their effects on HF, and they should be considered in those with T2D and HF as suggested in recent guidelines.”</td></tr>
<tr><td>Critique</td><td>Strengths

Prospective, multicenter, randomized, double blind, placebo-controlled trial.
Combined data from two randomized controlled trials with similar designs.

Limitations

Based on exploratory analyses.
History of HF assessed by medical history. Less accurate than using ECHO imaging and did not provide ejection fraction.
Limited to patients with NYHA class II to III; did not determine how many have class II vs III.
Low event rate in HF subgroup.
Missing baseline guideline directed medical therapy for HF in PIONEER trial.
</td></tr>
<tr><td>Take Home Points</td><td>

No differences in HF hospitalizations in total population (T2DM w/ or w/out HF)
HF + T2DM patients reported no difference in MACE between semaglutide and placebo
</td></tr>
</table>

Table 9. Summary of the Literature

Final Recommendation

Characteristic	FIGHT	LIVE	LEADER (Post Hoc)	EXSCEL (Post Hoc)	PIONEER-6/ SUSTAIN-6 (Post Hoc)
N	154	122	835	1,161	473
Population (HF specific)	NYHA Class II-IV Recent HF hospitalization	NYHA Class I-III Stable HF	NYHA Class I-III CVD or high risk	NYHA Class I-IV With or without CVD	NYHA Class II-III CVD or high risk
Agent	Liraglutide	Liraglutide	Liraglutide	Exenatide	Semaglutide
How was HF determined?	Used ECHO imaging	Used ECHO imaging	Reported by patient	Used ECHO imaging	Reported by patient
Decreased risk of MACE?	-	-	**Y**	**N**	**N**
Increased risk of HF hospitalizations?	**Y***	-	**N**	**N**	**N**

*Not statistically significant

Figure 11. Role of GLP-1 RAs in the Treatment of T2DM and HF[16]

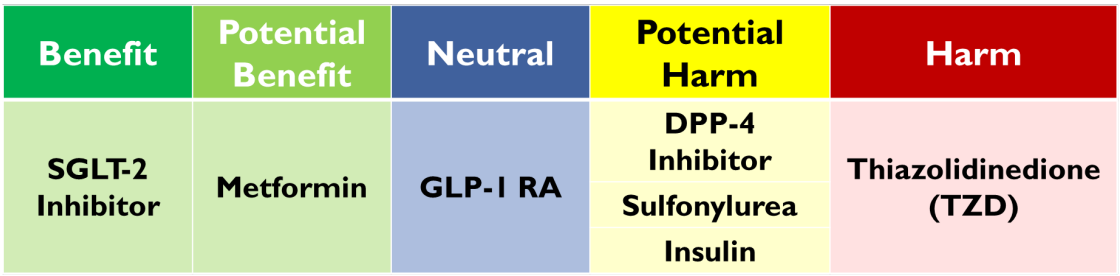
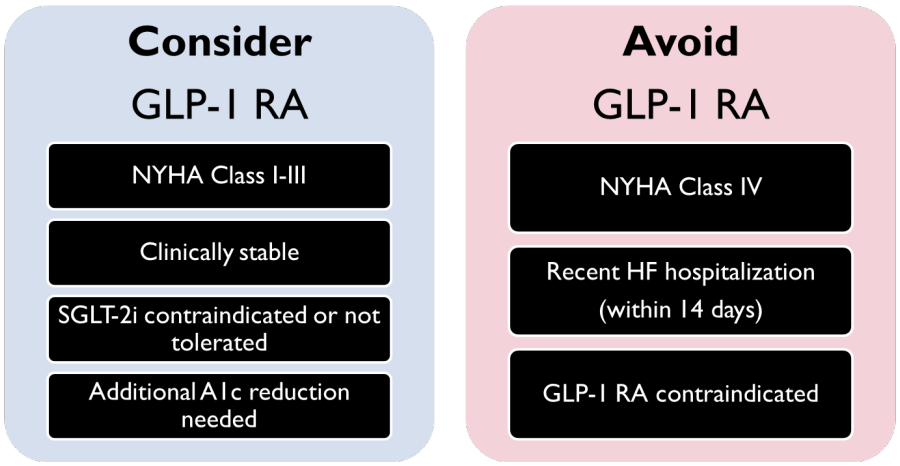


Figure 12. Considerations When Using GLP-1 RAs in T2DM and HF



- **Conclusion:** Although initial studies in HFrEF patients (FIGHT and LIVE trial) indicated that GLP-1 RAs may lead to worse clinical outcomes, CVOTs indicate that GLP-1 RAs do not increase HF hospitalizations. However, post hoc analysis of CVOTs suggest that GLP-1 RAs do not reduce the risk of MACE in patients with T2DM and HF. Additional studies are needed to fully characterize the role of GLP-1 RAs in patients with HF and T2DM.

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