Application of GLP-RA Therapy for Cardiovascular Risk Reduction

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Disclosures

- None

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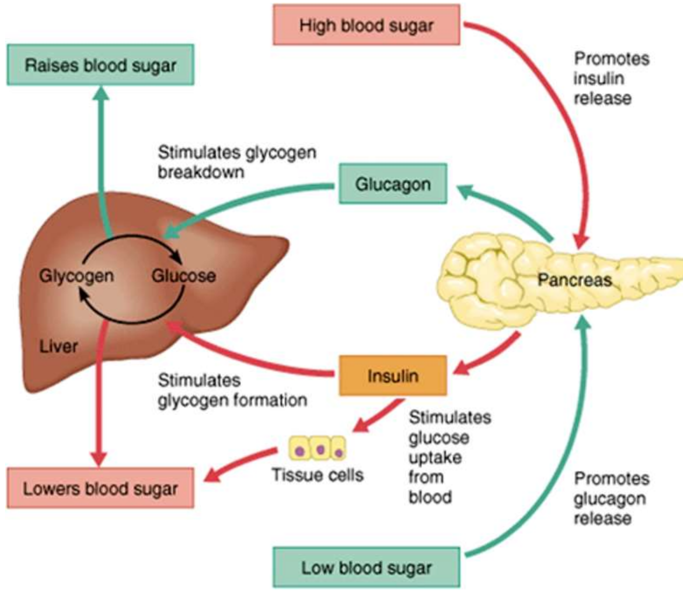
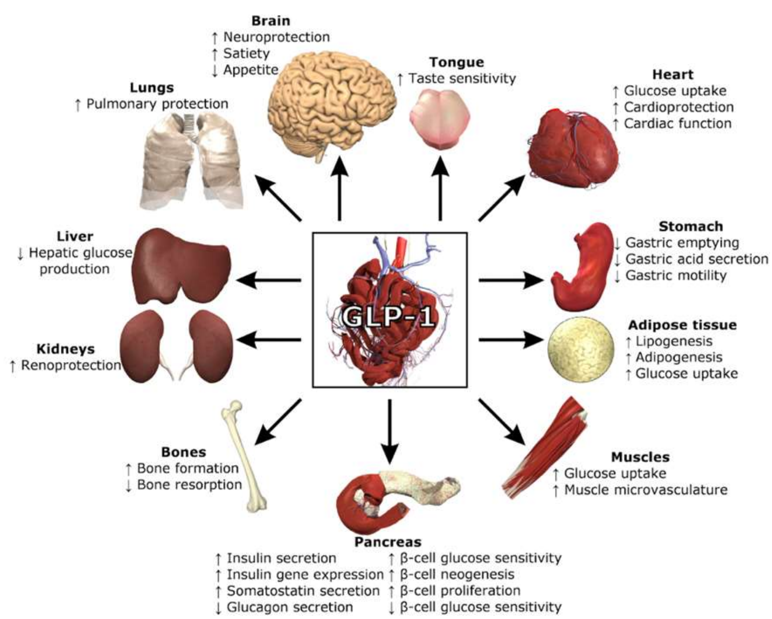
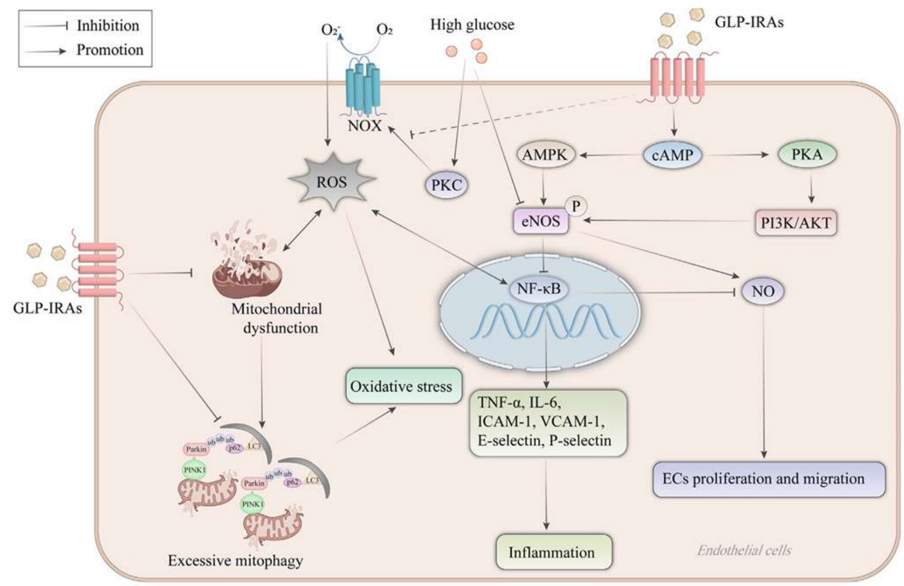


High blood sugar
Promotes insulin release
Raises blood sugar
Stimulates glycogen breakdown
Glucagon
Glycogen
Glucose
Liver
Pancreas
Stimulates glycogen formation
Insulin
Stimulates glucose uptake from blood
Tissue cells
Lowers blood sugar
Promotes glucagon release
Low blood sugar



Brain
↑ Neuroprotection
↑ Satiety
↓ Appetite
Tongue
↑ Taste sensitivity
Lungs
↑ Pulmonary protection
Heart
↑ Glucose uptake
↑ Cardioprotection
↑ Cardiac function
Liver
↓ Hepatic glucose production
Stomach
↓ Gastric emptying
↓ Gastric acid secretion
↓ Gastric motility
GLP-1
Kidneys
↑ Renoprotection
Adipose tissue
↑ Lipogenesis
↑ Adipogenesis
↑ Glucose uptake
Bones
↑ Bone formation
↓ Bone resorption
Muscles
↑ Glucose uptake
↑ Muscle microvasculature
Pancreas
↑ Insulin secretion
↑ Insulin gene expression
↑ Somatostatin secretion
↓ Glucagon secretion
↑ β-cell glucose sensitivity
↑ β-cell neogenesis
↑ β-cell proliferation
↓ β-cell glucose sensitivity



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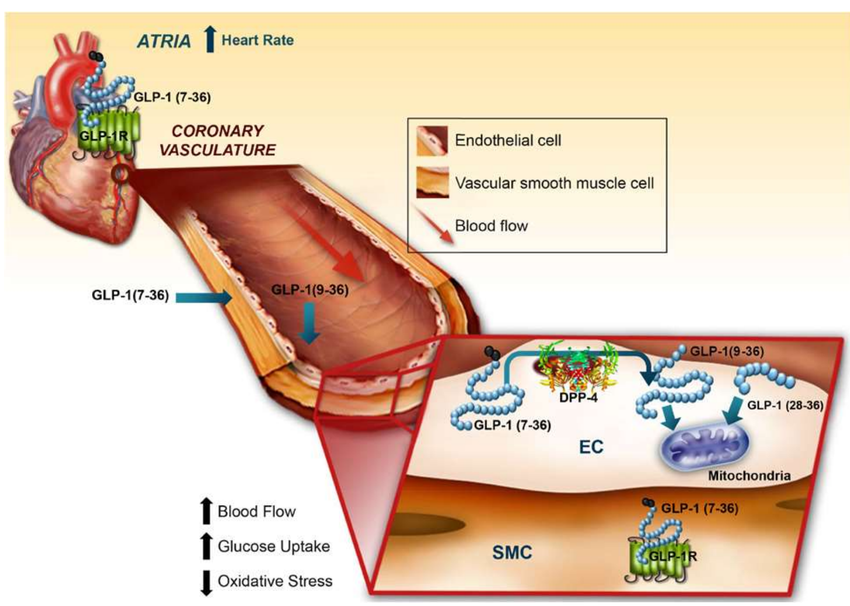

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LEADER
Liraglutide & CV Outcomes in T2DM

- Primary outcome – time to 1st occurrence of CV-related death, non-fatal MI or non-fatal CVA
  - Liraglutide 13% vs Placebo 15% (HR = 0.87)
- CV-related Death
  - Liraglutide 4.7% vs Placebo 6% (HR = 0.78)
- All-cause Death
  - Liraglutide 8.2% vs Placebo 9.6% (HR = 0.85)

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LEADER
Adverse Events

- Adverse events leading to permanent discontinuation of trial regimen
  - Liraglutide 9.5% vs Placebo 7.3% (p = < 0.001)
- Serious adverse events
  - Liraglutide 4.1% vs Placebo 5.2% (p = .01)
- Notable adverse event rates
  - Nausea – Liraglutide 1.6% vs Placebo 0.4%
  - Vomiting – 0.7% vs < 0.1%
  - Diarrhea – 0.6% vs 0.1%
  - Acute pancreatitis – 0.4% vs 0.5%
  - Acute gallstone disease – 3.1% vs 1.9%
  - Severe hypoglycemia – 2.4% vs 3.3%

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August 2017

FDA approves Liraglutide for CV risk reduction in adults with T2DM and established CVD

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SCALE Diabetes

Liraglutide for Weight Loss with T2DM

- Change in body weight
  - Liraglutide 3.0 mg -6% (14 lbs)
  - Liraglutide 1.8 mg -4.7% (11 lbs)
  - Placebo -2% (4.8 lbs)
- ≥ 5% body weight loss
  - Liraglutide 3.0 mg 54%
  - Liraglutide 1.8 mg 40%
  - Placebo 21%
- ≥ 10% body weight loss
  - Liraglutide 3.0 mg 25%
  - Liraglutide 1.8% 16%
  - Placebo 6.7%

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SCALE Obesity
Liraglutide for Weight Loss in NON-Diabetics

- Change in body weight
  - Liraglutide 3.0 mg -8% (18.5 lbs)
  - Placebo -2.6% (6.2 lbs)
- ≥ 5% body weight loss
  - Liraglutide 3.0 mg 63%
  - Placebo 27%
- ≥ 10% body weight loss
  - Liraglutide 3.0 mg 33%
  - Placebo 10.6%

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December 2014

FDA approves Liraglutide for adults with obesity (BMI ≥ 30) or overweight (BMI ≥ 27) with weight-related condition

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AWARD
Dulaglutide in Metformin-treated T2DM

- Change in A1C
  - Dulaglutide 1.5 mg -1.5%
  - Dulaglutide 3.0 mg -1.6%
  - Dulaglutide 4.5 mg -1.8%

- Change in weight
  - Dulaglutide 1.5 mg -4%
  - Dulaglutide 3.0 mg -4%
  - Dulaglutide 4.5 mg -5%

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REWIND
Dulaglutide & CV Benefits in T2DM

- Primary outcome – CV death, MI or CVA
  - Dulaglutide 1.5 mg 12%, Placebo 13.4% (HR = 0.88, p = 0.026)

- Primary outcome driven largely by significant reduction in non-fatal CVA
  - CV death – Dulaglutide 6.4%, Placebo (p = 0.21)
  - Non-fatal MI – Dulaglutide 4.1%, Placebo 4.3% (p = 0.46)
  - Non-fatal CVA – Dulaglutide 2.7%, Placebo 3.5% (p = 0.017)

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February 2020

FDA approves Dulaglutide for CV risk reduction in adults with T2DM with and without established CVD.

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SUSTAIN-6
Semaglutide & CV Outcomes WITH DM

- Primary outcome – time to 1st occurrence of CV death, non-fatal MI or non-fatal CVA
  - Semaglutide 6.6% vs Placebo 8.9% (HR = 0.74)
- Non-fatal MI
  - Semaglutide 2.9% vs Placebo 3.9% (HR = 0.74)
- Non-fatal CVA
  - Semaglutide 1.6% vs Placebo 2.7% (HR = 0.61)

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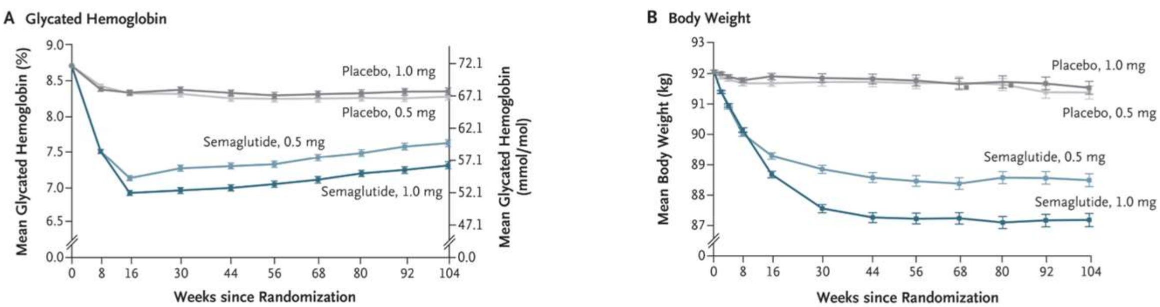
SUSTAIN
Semaglutide & CV Outcomes WITH DM



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December 2017

FDA approves Semaglutide for treatment of T2DM

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January 2020

FDA approves Semaglutide for CV risk reduction in adults with T2DM and known heart disease.

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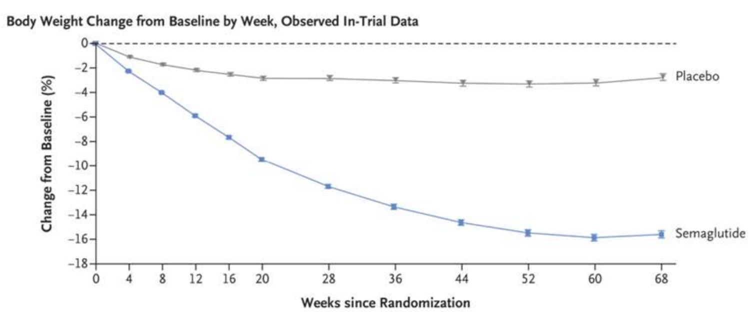
STEP
Semaglutide in Adults Overweight or Obese



- Mean change in body weight
    - Semaglutide 2.4 mg -14.9% vs Placebo -2.4%

- Number of patients achieving
    - ≥ 10% total body weight → Semaglutide 69% vs Placebo 12%
    - ≥ 15% total body weight → Semaglutide 50.5% vs Placebo 4.9%

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STEP
Adverse Events

- Adverse events leading to permanent discontinuation of treatment regimen
  - Semaglutide 7% vs Placebo 3%
- Nausea – Semaglutide 44%, Placebo 17%
- Diarrhea – Semaglutide 31%, Placebo 16%
- Constipation – Semaglutide 23%, Placebo 10%
- Gallbladder dysfunction – Semaglutide 2.6%, Placebo 1.2%
- Pancreatitis – Semaglutide 0.2% (3 patients), Placebo 0%

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June 2021

FDA approves Semaglutide for adults with obesity (BMI ≥ 30) or overweight (BMI ≥ 27) with weight-related condition

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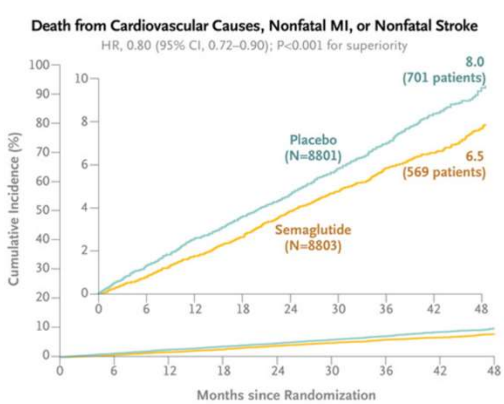
January 2020

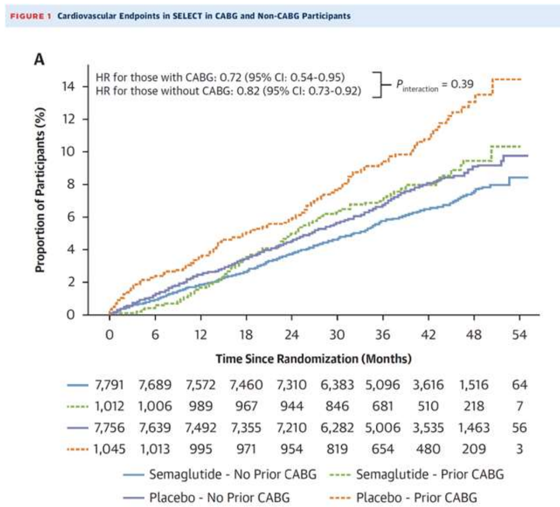
FDA approves Semaglutide for CV risk reduction in adults with T2DM and known heart disease.

SELECT
Semaglutide & CV Outcomes in Obesity WITHOUT DM



- Primary outcome – Composite CV-related death, non-fatal MI or non-fatal CVA
  - Semaglutide 6.5% vs Placebo 8% (HR = 0.80)
- CV-related death
  - Semaglutide 2.5% vs Placebo 3% (HR = 0.85)
- Mean change in body weight
  - Semaglutide -9% vs Placebo -0.88%

SELECT
Semaglutide & CV Outcomes in Obesity WITHOUT DM
[sub-selected for prior CABG]

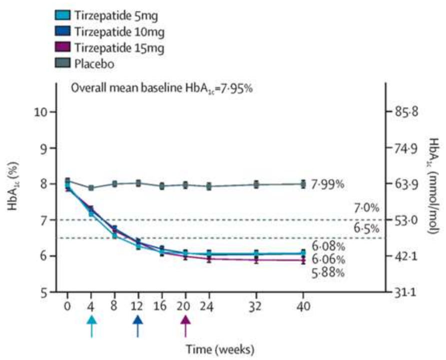


March 2024

FDA Approves Semaglutide for CV risk reduction in adults overweight or obese with established CVD

SURPASS - 1

Tirzepatide for T2DM (drug naïve)



Mean change in A1C:

- Tirzepatide 5 mg: - 1.78%
- Tirzepatide 10 mg: - 1.89%
- Tirzepatide 15 mg: - 2.1%
- Placebo: + 0.04%

* 87-92% of Tirzepatide patients reached an A1C < 7%

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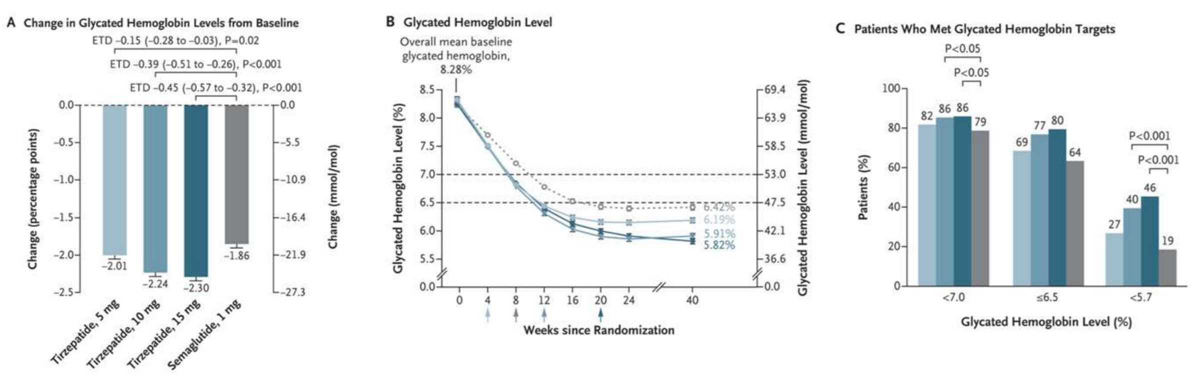
SURPASS

Tirzepatide vs Semaglutide WITH DM



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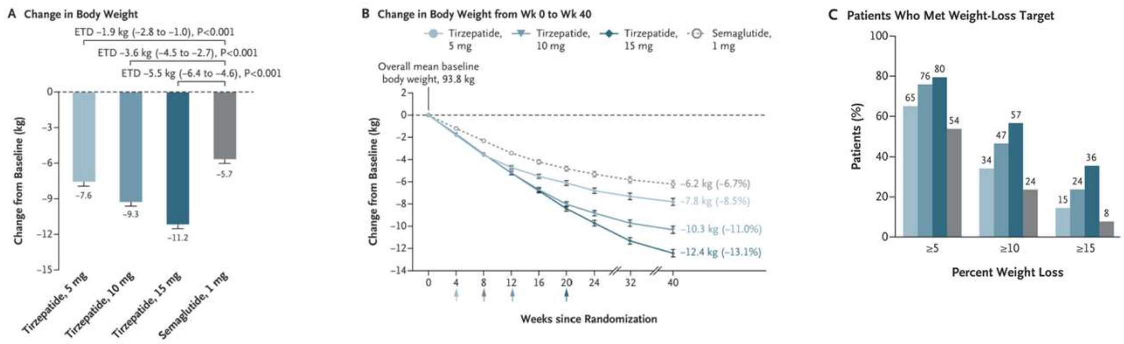
SURPASS
Tirzepatide vs Semaglutide WITH DM



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SURPASS
Adverse Events

- Adverse events leading to discontinuation of treatment regimen
  - Tirzepatide: 6% @ 5 mg, 8.5% @ 10 mg, 8.5% @ 15 mg
  - Semaglutide: 4.1%
- Nausea – Tirzepatide 17% to 22%, Semaglutide 17.9%
- Diarrhea – Tirzepatide 13% to 16%, Semaglutide 11.5%
- Constipation – Tirzepatide 4.5% to 6.8%, Semaglutide 5.8%
- Cholelithiasis – Tirzepatide 0.9%, Semaglutide 0.4%

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May 2022

FDA approves Tirzepatide for adults with T2DM

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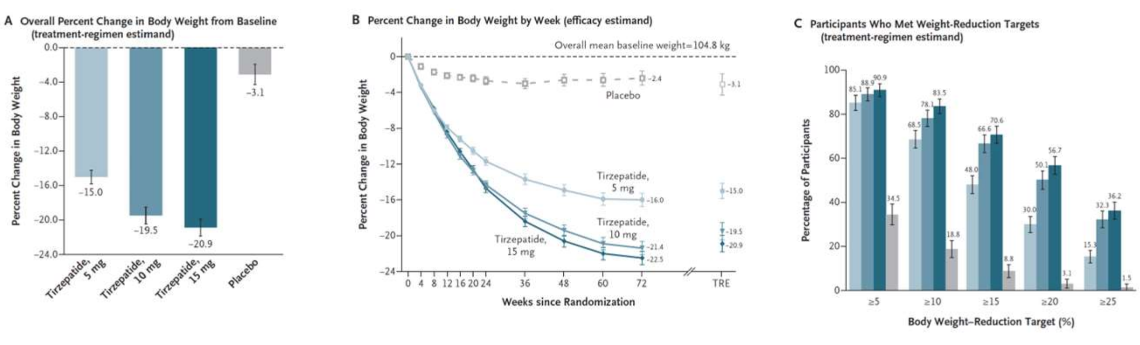
SURMOUNT
Tirzepatide for Obesity



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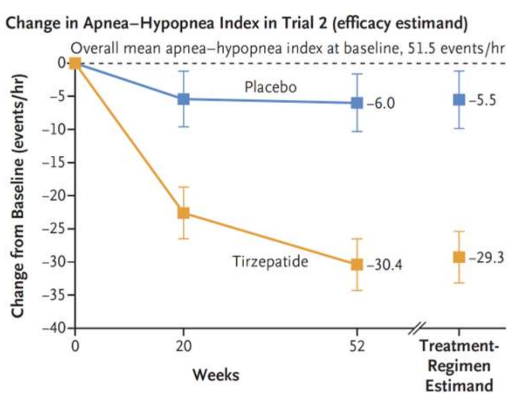
October 2022

FDA approves Tirzepatide for adults with obesity or overweight with weight-related conditions.

SURMOUNT-OSA

Tirzepatide for Treatment of OSA & Obesity



- With Tirzepatide → .
  - 25 fewer breathing disruptions per hour in patients NOT on PAP therapy.
  - 29 fewer breathing disruptions per hour in patient ON PAP.
- @ 1 year, 50% on Tirzepatide experienced remission or mild, non-symptomatic OSA.

* Tirzepatide patients lost on average 45 lbs (18%) of body weight

December 2024

FDA approves Tirzepatide as 1st and only prescription medicine for moderate-to-severe OSA in adults with obesity.

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STEP-HFpEF

Semaglutide with HFpEF & Obesity

- Change in KCCQ-CSS
  - Semaglutide 16.6 pts vs Placebo 8.7 pts
- Mean change in body weight
  - Semaglutide -13% vs Placebo -2.6%
- Mean change in 6-minute walk distance
  - Semaglutide 21.5 m vs Placebo 1.2 m
- Change in hsCRP
  - Semaglutide -43% vs Placebo -7%

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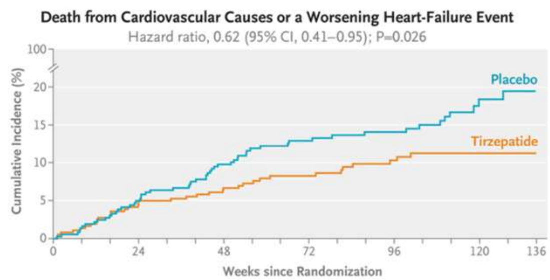
SUMMIT
Tirzepatide for HFpEF & Obesity



- Composite CV death or worsened HF events
  - Tirzepatide 9.9% vs Placebo 15.3% (HR = 0.62)

- Change in KCCQ-CSS
  - Tirzepatide 19.5 pts vs Placebo 12.7 pts

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FDA approval for Semaglutide & Tirzepatide for HFpEF indication…

TBD

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59 Y/O WM with PMH PAF, embolic CVA, HTN, HLD, Class III Obesity, OSA on CPAP , NAFLD with steatosis and mild sub-clinical CAD.

Numerous ED presentations / hospitalizations for AF. Multiple attempts at rate / rhythm control, most recently via Sotalol + Cardizem.

Dec 2023: 342 lbs, BMI 48 kg/m^2

Started Semaglutide 0.25 mg Jan 2024 (compounded) → 0.5 mg Feb 2024

May 2024: 295 lbs, BMI 41 kg/m^2

Sep 2024: 284 lbs, BMI 39 kg/m^2

Exercise capacity / QOL markedly improved. Zero AF recurrences to date.

No intolerable GLP-related A/Es.

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57 Y/O WM PMH PAF, HFpEF, HTN, NIDDM, NAFLD w/ steatosis, OSA on CPAP and Class III Obesity.

Mar 2024: A1C 9.1%, 318 lbs, , BMI 48 kg/m^2

Started on Metformin 500 mg XR QD + Semaglutide 0.5 mg/wk (titrated to 2 mg/wk)

Jan 2025: A1C 6.5%, 253 lbs, BMI 38 kg/m^2

No intolerable GLP-related A/Es.

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57 Y/O WM PMH PAF, HFpEF, HTN, NIDDM, NAFLD w/ steatosis, OSA on CPAP and Class III Obesity.

Mar 2024: A1C 9.1%, 318 lbs, , BMI 48 kg/m^2

Started on Metformin 500 mg XR QD + Semaglutide 0.5 mg/wk (titrated to 2 mg/wk)

Jan 2025: A1C 6.5%, 253 lbs, BMI 38 kg/m^2

No intolerable GLP-related A/Es.

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45 Y/O WM PMH HFpEF, PAF, HTN, OSA on CPAP, lymphedema and Class V Obesity.

HFpEF complicated by multiple hospitalizations for acute decompensation, most recently April 2024 when diuresed ~ 30 lbs.

Rx: Torsemide 100 mg QD +/- Metolazone PRN, Empagliflozin 10 mg QD, Sacubitril/Valsartan 49-51 mg BID, Metoprolol Succinate ER 150 mg BID, Diltiazem 180 mg QD, Apixaban 5 mg BID

July 2024: 475 lbs, BMI 66 kg/m^2

Started on Tirzepatide 5 mg/wk

Jan 2025: 425 lbs, BMI 57 kg/m^2

Functional capacity / QOL improved. No recurrent HF decompensations.

No intolerable GLP-related A/Es.

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References

- Marso, et al. "Liraglutide & CV Outcomes in Type II Diabetes." NEJM. 2016.
- Garvey, et al. "Efficacy of Liraglutide in Individuals with Type II Diabetes." JAMA. 2015.
- Davies, et al. "Efficacy of Liraglutide for Weight Loss Among Patients with Type II Diabetes." JAMA. 2015.
- Gerstein, et al. "Dulaglutide & CV Outcomes in Type II Diabetes." The Lancet. 2019.
- Frias, et al. "Efficacy of Dulaglutide in Metformin-treated Patients with Type II Diabetes." Diabetes Care. 2021.
- Marso, et al. "Semaglutide & CV Outcomes in Patients with Type II Diabetes." NEJM. 2016.
- Wilding, et al. "Semaglutide in Adults with Overweight or Obesity." NEJM. 2021.
- Lincoff, et al. "Semaglutide & CV Outcomes in Obesity without Diabetes." NEJM. 2023.
- Kosiborod, et al. "Semaglutide in Patients with Heart Failure preserved Ejection Fraction." NEJM. 2023.
- Rosenstock, et al. "Efficacy of Tirzepatide in Patients with Type II Diabetes." The Lancet. 2021.
- Jastreboff, et al. "Tirzepatide for Treatment of Obesity." NEJM. 2022.
- Malhotra, et al. "Tirzepatide for Treatment of OSA." NEJM. 2024.
- Packer, et al. "Tirzepatide for HFpEF." NEJM. 2024.

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