GLP-1 and MACE reduction

Matthew Widdison, MD

Eastern Idaho Regional Medical Center Family Medicine Residency

New hit TV medical drama

Doctors on TV vs family medicine

- Medicine = Hot

Doctors on TV vs family mec

- Family medicine / primary care

Doctors on TV vs family mec

- Family medicine / primary care

= whatever this is

Preventative medicine is boring.

- What's better than good compression CPR?

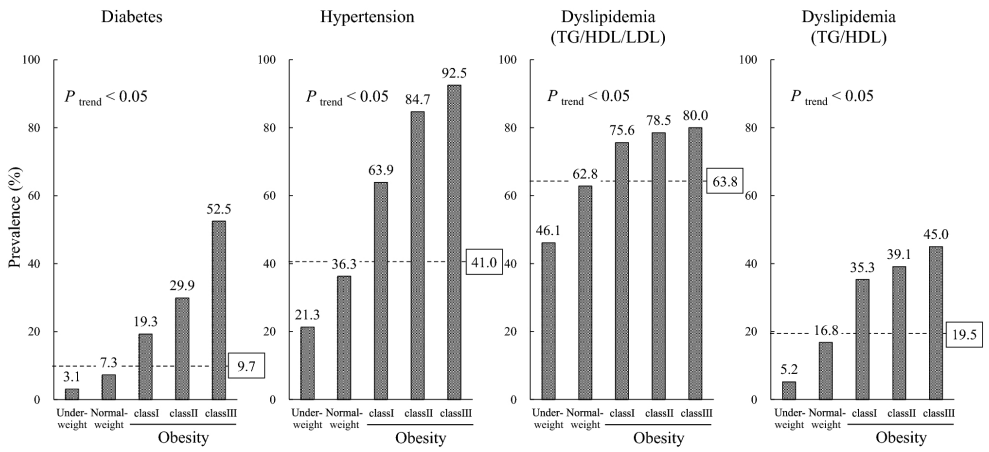
Preventative medicine is boring.

- What's better than good compression CPR?

- Not needing CPR.

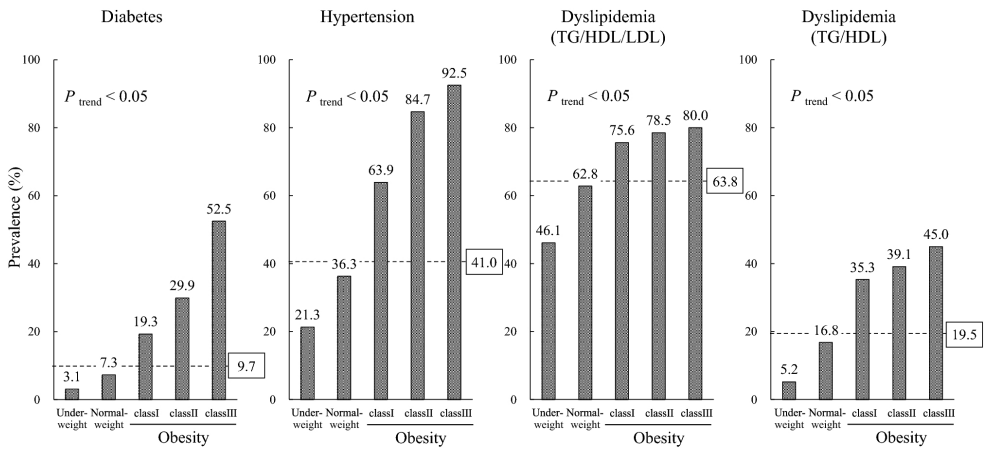
Relationship between diabetes, metabolic syndrome(s) and cardiovascular health.

- Framingham heart study (1948-)

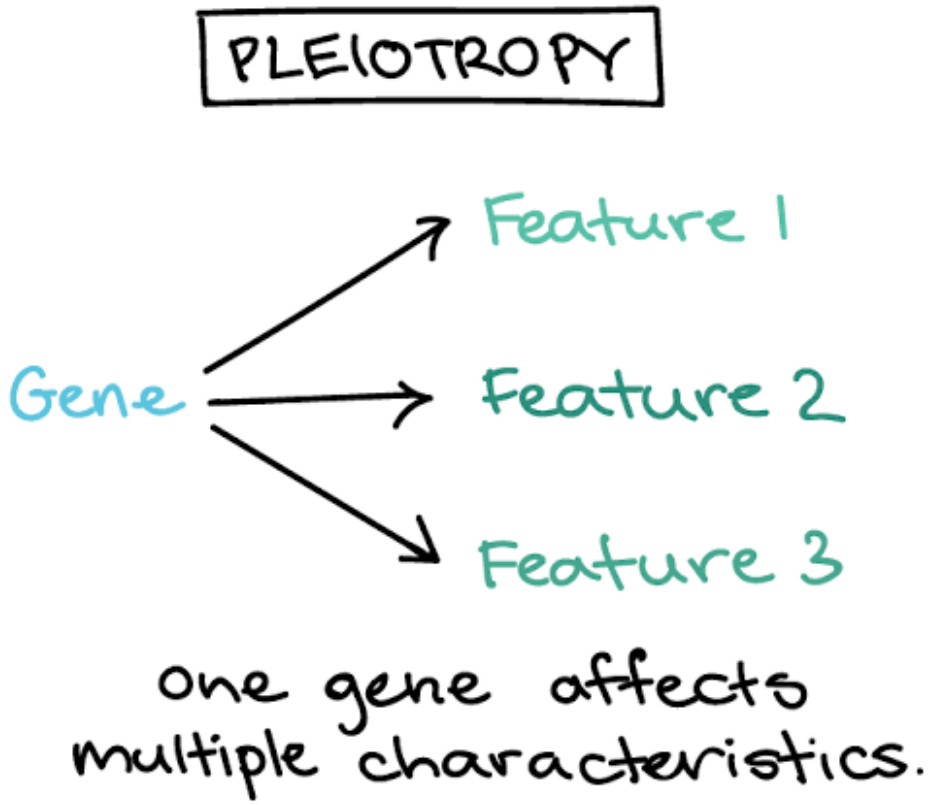


Relationship between diabetes, metabolic syndrome(s) and cardiovascular health.

- Framingham heart study (1948-)



Diabetes as more than just blood sugars



FDA NEWS RELEASE

FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight

More Press Announcements

For Immediate Release: March 08, 2024

Español

Today, the U.S. Food and Drug Administration approved a new indication for use for Wegovy (semaglutide) injection to reduce the risk of cardiovascular death, heart attack and stroke in adults with cardiovascular disease and either obesity or overweight. Wegovy should be used in addition to a reduced calorie diet and increased physical activity. Cardiovascular disease is a group of diseases of the heart and blood vessels.

"Wegovy is now the first weight loss medication to also be approved to help prevent life-threatening cardiovascular events in adults with cardiovascular disease and either obesity or overweight," said John Sharretts, M.D., director of the Division of Diabetes, Lipid Disorders, and Obesity in the FDA's Center for Drug Evaluation and Research. "This patient population has a higher risk of cardiovascular death, heart attack and stroke. Providing a treatment option that is proven to lower this cardiovascular risk is a major advance for public health."

Content current as of:
03/08/2024

Regulated Product(s)
Drugs

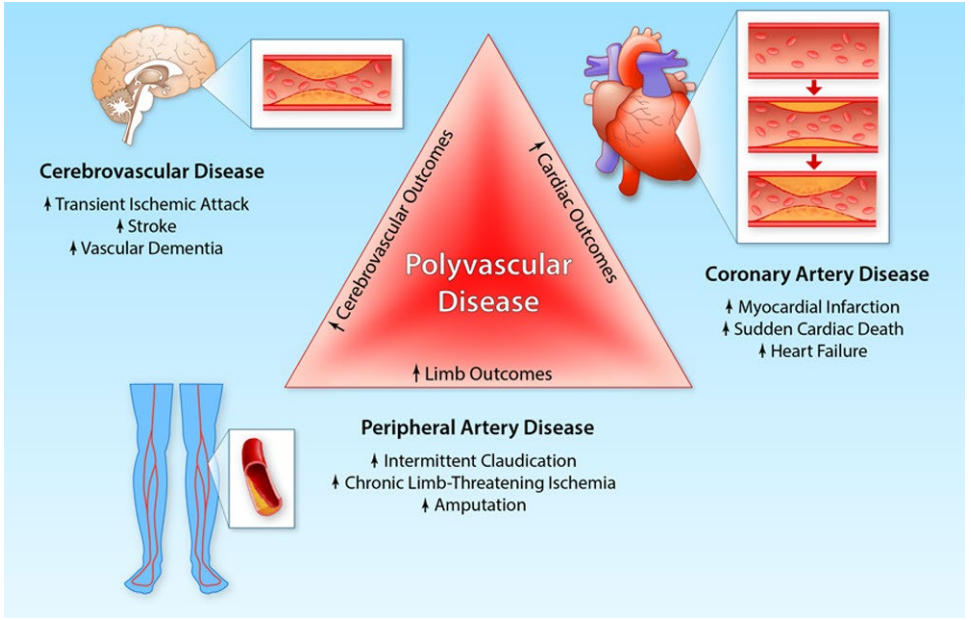
Follow FDA
Follow @US_FDA
Follow FDA
Follow @FDAMedia

Treating heart attacks with glucose lowering medication?

Terminology

MACE (major adverse cardiac events) =

- myocardial infarction
- Stroke
- peripheral arterial disease
- cardiovascular death.



Treating heart attacks with glucose lowering medication?

Yes.

But no.

But also, yes.

Knowledge up to this point:

- LEADER (2016)
- SUSTAIN (2016)
- REWIND (2019)
- SELECT (2023)
- SOUL (2025)
- SURPASS-CVOT (2025)

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilber
Johannes F.E. Mann,
Neil R. Poulter, F.Med.Sci
Bernard Zinma
for the LEADI

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

2023 nejm

- SELECT (2023)
  - No diabetes
  - 20% Risk reduction
  - NNT = 67
  - (NNT for statins 217-313 for 1° Prev)

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Lincoff AM et al. DOI: 10.1056/NEJMoa2307563

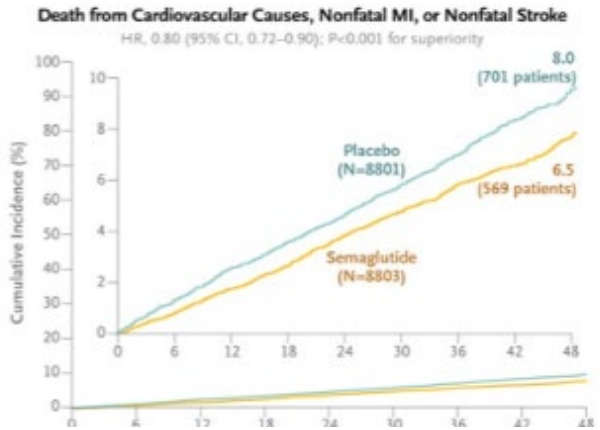
CLINICAL PROBLEM

Glucagon-like peptide-1 (GLP-1) receptor agonists can reduce the risk of adverse cardiovascular events in patients with diabetes. Whether the GLP-1 receptor agonist semaglutide can also reduce cardiovascular risk in patients with overweight or obesity but without diabetes is unknown.

CLINICAL TRIAL

Design: An international, double-blind, event-driven, randomized, placebo-controlled, superiority trial assessed the safety and efficacy of semaglutide in patients with preexisting cardiovascular disease, overweight or obesity (body-mass index, ≥27), and no history of diabetes.

Intervention: 17,604 adults ≥45 years of age were assigned to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo. The primary cardiovascular end point was a composite of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis.



2023 nejm

- SELECT (2023)
  - No diabetes
  - 20% Risk reduction
  - NNT = 67
  - (NNT for statins 217-313 for 1° Prev)

CLINICAL TRIAL

Design: An international, double-blind, event-driven, randomized, placebo-controlled, superiority trial assessed the safety and efficacy of semaglutide in patients with preexisting cardiovascular disease, overweight or obesity (body-mass index, ≥27), and no history of diabetes.

Intervention: 17,604 adults ≥45 years of age were assigned to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo. The primary cardiovascular end point was a composite of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis.

2023 nejm

- SELECT (2023)
  - No diabetes
  - 20% Risk reduction
  - NNT = 67
  - (NNT for statins 217-313 for 1° Prev)
  - Follow up time 40 months

RESULTS

Efficacy: Semaglutide was superior to placebo in reducing the incidence of primary end-point events during a mean follow-up of approximately 40 months.

Safety: More patients discontinued semaglutide than placebo because of adverse events, a result driven largely by a higher incidence of gastrointestinal symptoms with semaglutide.

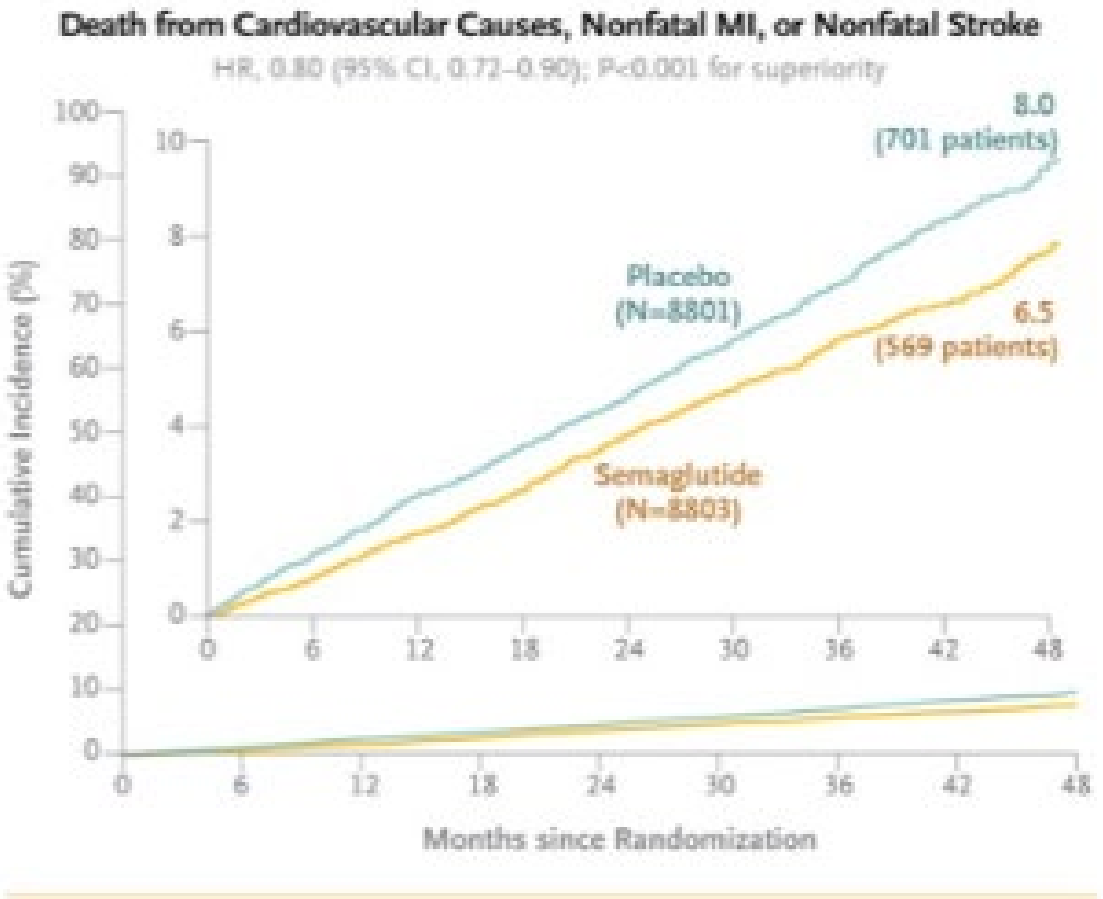
SELECT Study

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

2023 nejm

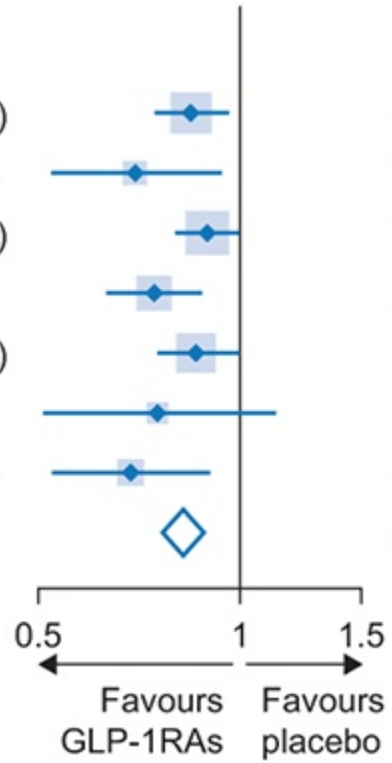
- SELECT (2023)
  - No diabetes
  - 20% Risk reduction
  - NNT = 67

  - MACE reduction happened almost immediately after starting



Other studies

Trial name (GLP-1RA)	GLP-1RA n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*P* value
LEADER (liraglutide)	608/4668 (13%)	694/4672 (15%)	0.87 (0.78-0.97)		.01
SUSTAIN 6 (semaglutide)	108/1648 (7%)	146/1649 (9%)	0.74 (0.58-0.95)		.016
EXSCEL (exenatide)	839/7356 (11%)	905/7396 (12%)	0.91 (0.83-1.00)		.061
Harmony Outcomes (albiglutide)	338/4731 (7%)	428/4732 (9%)	0.78 (0.68-0.90)		.0006
REWIND (dulaglutide)	594/4949 (12%)	663/4952 (13%)	0.88 (0.79-0.99)		.026
PIONEER 6 (oral semaglutide)	61/1591 (4%)	76/1592 (5%)	0.79 (0.57-1.11)		.17
AMPLITUDE-O (efpeglenatide)	189/2717 (7%)	125/1359 (9%)	0.73 (0.58-0.92)		.069
Subtotal (I^2 = 14.9%, *P* = .316)			**0.85 (0.80-0.90)**	**61 (46-92)**	**< .0001**



Smart people:

AHA/ACC (2023)	GLP-1 RA with proven CV benefit recommended for chronic coronary disease + T2D to reduce MACE	Class I, LOE A
ADA (2026)	GLP-1 RA recommended for T2D + ASCVD, high CV risk, HF, or CKD — **independent of HbA1c**	Strong recommendation
ESC (2019)	GLP-1 RA recommended for T2D + ASCVD or high/very high CV risk; can be **first-line before metformin**	Class I, LOE A
ACC (2020 ECDP)	GLP-1 RA or SGLT2i with proven CV benefit for T2D + established ASCVD, regardless of HbA1c	Expert consensus

Getting this medicine paid for.

- FDA approved medications ≠ insurance approval
- >1% of private insurers cover GLP-1's for MACE
- Clarifications:
  - Medicare
  - Bridge program

How can I get coverage for my patients through Medicare GLP-1 Bridge starting July 1?

1. While CMS will confirm whether a patient is eligible for Bridge, providers can help expedite the process by asking these questions.	• **Does my patient have eligible Medicare Part D plan coverage?** If yes, then the patient might qualify for Bridge. Most people with Medicare Part D coverage are eligible. People enrolled in private fee-for-service plans, section 1876 cost contract plans, section 1833 health care prepayment plans, PACE organizations, fallback plans, and religious fraternal benefit plans aren't eligible, unless they're also enrolled in a standalone prescription drug plan (PDP). • **Has my patient received a GLP-1 through their Part D plan?** If yes, your patient isn't eligible for coverage under Medicare GLP-1 Bridge and you must submit any request for GLP-1 coverage to the patient's Part D plan. • **Does my patient have type 2 diabetes, moderate-to-severe sleep apnea, or metabolic dysfunction-associated steatohepatitis (MASH)?** If yes, your patient isn't eligible for coverage under Medicare GLP-1 Bridge and you must submit any request for GLP-1 coverage to the patient's Part D plan. • **Does my patient meet the Medicare GLP-1 Bridge clinical criteria?** ○ My patient is at least 18 years of age ○ I'm prescribing the GLP-1 to reduce excess body weight and maintain weight reduction and not for any other approved indication ○ At the time my patient starts GLP-1 therapy, at least one of these is true: ■ My patient has a body mass index (BMI) of at least 35 ■ My patient has a BMI of at least 30 AND a diagnosis of one or more of the following: (A) heart failure with preserved ejection fraction, (B) uncontrolled hypertension (defined as systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg, despite concurrent treatment with two antihypertensive medications), or (C) chronic kidney disease stage 3a or above; ■ My patient has a BMI of at least 27 AND a diagnosis of one or more of the following: (A) pre-diabetes (B) previous myocardial infarction, (C) previous stroke, or (D) symptomatic peripheral artery disease

How can I get coverage for my patients through Medicare GLP-1 Bridge starting July 1?

1. While CMS will confirm whether a patient is eligible for Bridge, providers can help expedite the process by asking these questions.	• **Does my patient have eligible Medicare Part D plan coverage?** If yes, then the patient might qualify for Bridge. Most people with Medicare Part D coverage are eligible. People enrolled in private fee-for-service plans, section 1876 cost contract plans, section 1833 health care prepayment plans, PACE organizations, fallback plans, and religious fraternal benefit plans aren't eligible, unless they're also enrolled in a standalone prescription drug plan (PDP). • **Has my patient received a GLP-1 through their Part D plan?** If yes, your patient isn't eligible for coverage under Medicare GLP-1 Bridge and you must submit any request for GLP-1 coverage to the patient's Part D plan. • **Does my patient have type 2 diabetes, moderate-to-severe sleep apnea, or metabolic dysfunction-associated steatohepatitis (MASH)?** If yes, your patient isn't eligible for coverage under Medicare GLP-1 Bridge and you must submit any request for GLP-1 coverage to the patient's Part D plan. • **Does my patient meet the Medicare GLP-1 Bridge clinical criteria?** ○ My patient is at least 18 years of age ○ I'm prescribing the GLP-1 to reduce excess body weight and maintain weight reduction and not for any other approved indication ○ At the time my patient starts GLP-1 therapy, at least one of these is true: ■ My patient has a body mass index (BMI) of at least 35 ■ My patient has a BMI of at least 30 AND a diagnosis of one or more of the following: (A) heart failure with preserved ejection fraction, (B) uncontrolled hypertension (defined as systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg, despite concurrent treatment with two antihypertensive medications), or (C) chronic kidney disease stage 3a or above; ■ My patient has a BMI of at least 27 AND a diagnosis of one or more of the following: (A) pre-diabetes (B) previous myocardial infarction, (C) previous stroke, or (D) symptomatic peripheral artery disease

Bridge


Eligibility & Clinical Criteria
Plan Eligibility Requirements
Must be enrolled in a standalone Part D plan or a Medicare Advantage MA-PD plan.
BMI Qualifications
BMI 35+
BMI 30+
BMI 27+
Data
Required Clinical Conditions
BMI Tier
Heart failure (HFpEF), uncontrolled hypertension, or stage 3a+ kidney disease.
Data
Required Clinical Conditions
BMI Tier
Pre-diabetes, previous heart attack, stroke, or peripheral artery disease.
Historical BMI Consideration: Qualifications can be based on your BMI at the start of your therapy.