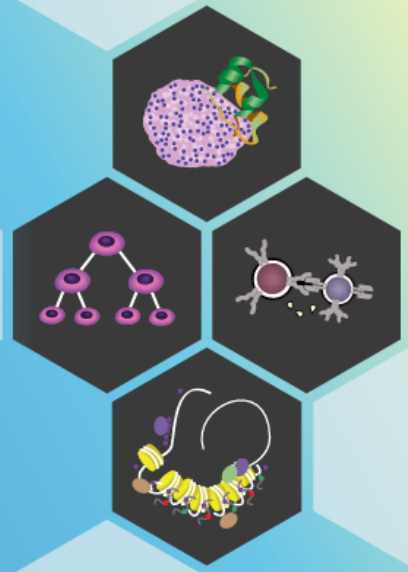
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Select Trial – New Insights into Obesity Treatment



Steven E. Kahn, MB, ChB

Professor of Medicine

Leonard L. Wright and Marjorie C. Wright Chair

VA Puget Sound Health Care System

University of Washington

Disclosures

- Consultant for Abarceo Pharma, AltPep, Amgen, Anji Pharmaceuticals, Biomea Fusion, Boehringer Ingelheim, Eli Lilly, Merck, Neurimmune, Novo Nordisk, and Oramed Pharmaceuticals.
- Grant/Research Support from Corcept Therapeutics.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Demographic and outcome commonalities and differences among individuals in this study.*
- *Disparities in health care coverage will affect the availability of treatments to all groups.*

Outline

1. Background
2. Study Design and Baseline Characteristics
3. Outcomes:
    a) Primary Outcome: Cardiovascular Events
    b) Secondary Outcomes: Weight, Glycemia, Renal
4. Implications

Outline

1. Background
2. Study Design and Baseline Characteristics
3. Outcomes:
    a) Primary Outcome: Cardiovascular Events
    b) Secondary Outcomes: Weight, Glycemia, Renal
4. Implications

The Link Between Obesity, CVD, and Death

In 2022, there were

813

million people aged ≥20 years living with obesity (BMI ≥30 kg/m^2)[2,3]

523

million people had **CVD** in 2019[4]

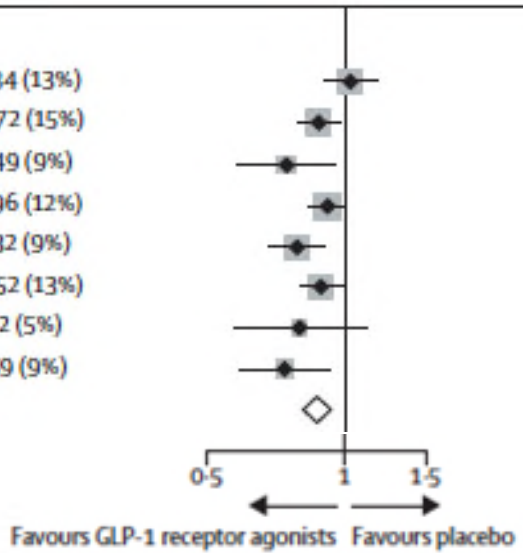
32%

of all global **deaths** are from **CVD**[5]

1. Yoo HJ Choi KM: World J Diabetes 5:357-363; 2014; 2. World Obesity Federation: World Obesity Atlas, 2023. Available at: https://www.worldobesityday.org/assets/downloads/World_Obesity_Atlas_2023_Report.pdf. Accessed June 2024; 3. World Obesity Federation: World Obesity Atlas, 2024. Available at: https://data.worldobesity.org/publications/WOF-Obesity-Atlas-v7.pdf. Accessed June 2024; 4. Roth GA et al: J Am Coll Cardiol 76:2982;3021; 2020
5. WHO. Fact sheet – CVDs. Available at: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed June 2024.

Meta-analysis of GLP-1 Receptor Agonist CVOTs: Three-Point MACE

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**



Sattar N et al: Lancet Diabetes Endocrinol 9: 653-622; 2021

Rationale for SELECT

Individuals with overweight or obesity and high cardiovascular risk, but without established diabetes, are candidates for heart disease secondary prevention.

Mediation by Weight Loss

+

Mediation by semaglutide

=

CV Event Reduction

SELECT was not a weight loss study, it was a heart disease prevention study.

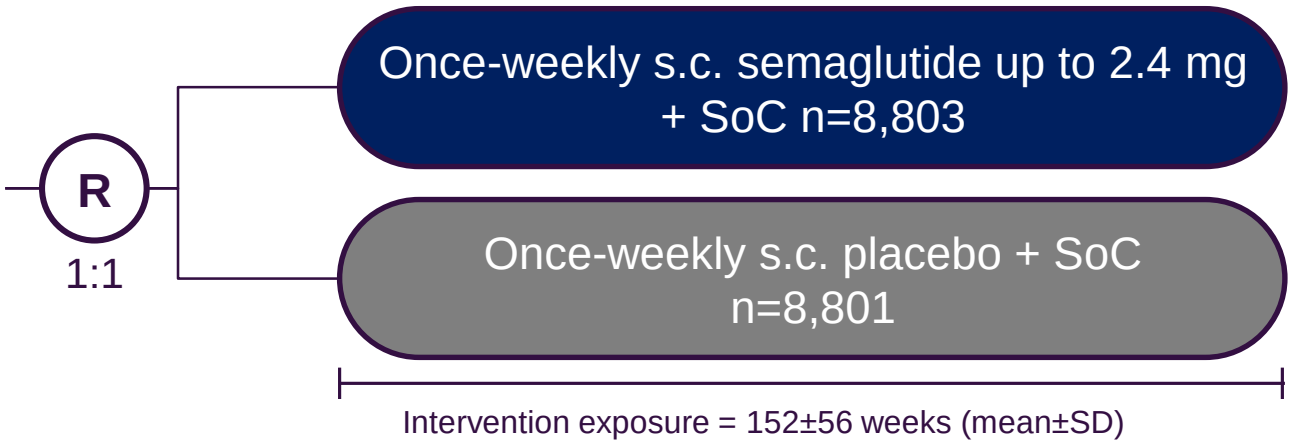
Ryan DH et al: Am Heart J 229:61-69; 2020

Outline

1. Background
2. Study Design and Baseline Characteristics
3. Outcomes:
    a) Primary Outcome: Cardiovascular Events
    b) Secondary Outcomes: Weight, Glycemia, Renal
4. Implications

SELECT: Study Design

- 17,604 patients
- ≥45 years of age
- BMI ≥27 kg/m^2
- CVD
- No diabetes (HbA_{1c} <6.5%)



Lingvay I et al: Obesity 31:111-122; 2023.

SELECT: Primary and Secondary Outcomes

Primary

Time from randomization to first occurrence of composite endpoint consisting of:

- CV death
- Non-fatal MI
- Non-fatal stroke

Confirmatory secondary

Time from randomization to first occurrence of:

- CV death
- Composite HF endpoint consisting of CV death or hospitalization or urgent medical visit for HF
- All-cause death

Supportive secondary

Change from randomization to Year 2 in:

- Body weight (%) and waist circumference (cm)
- Systolic blood pressure (mmHg)
- Lipids (mg/dL): total, HDL and LDL cholesterol, TG
- High-sensitivity C-reactive protein
- HbA_{1c} (%, mmol/mol)

Lincoff AM et al: N Engl J Med 389:2221-2232; 2023

Baseline Characteristics of SELECT Trial Participants

Demographics

Male | Female	Mean age	Asian|Black|White|Other
72.3 | 27.7%	**61.6 years**	**8.2 | 3.8 | 84.0 | 3.0%**

Participants by CV inclusion criteria




MI only	Stroke only	PAD only	≥2 CV inclusion criteria
67.6%	**17.8%**	**4.4%**	**8.2%**

n=17,604

Lincoff AM et al: N Engl J Med 389:2221-2232; 2023

Baseline Characteristics of SELECT Trial Participants

Clinical characteristics

Mean BMI

33.3 kg/m²

Distribution (kg/m²)
<30 | 30–<35 | 35–<40 | 40–<45 | ≥45

28.5 | 42.5 | 19.0 | 6.7 | 3.3%

Mean HbA_{1c}

5.8%

With prediabetes
(HbA_{1c} 5.7–6.4%)

66.4%

Mean eGFR

82.5 mL/min/1.73 m²

Chronic HF

24.3%

Subclass[2]
HFpEF | HFrEF | Unknown

12.9 | 7.7 | 3.8%

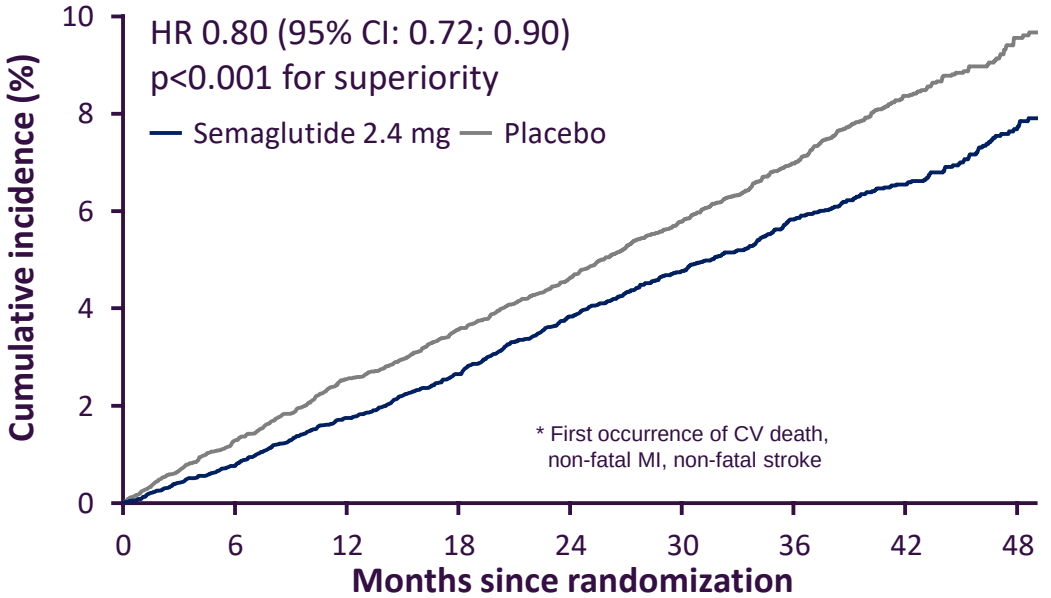
n=17,604

Lincoff AM et al: N Engl J Med 389:2221-2232; 2023

Outline

1. Background
2. Study Design and Baseline Characteristics
3. Outcomes:
    a) Primary Outcome: Cardiovascular Events
    b) Secondary Outcomes: Weight, Glycemia, Renal
4. Implications

SELECT: Major Adverse CV Outcomes (CV Death, Non-fatal MI, Non-fatal Stroke)

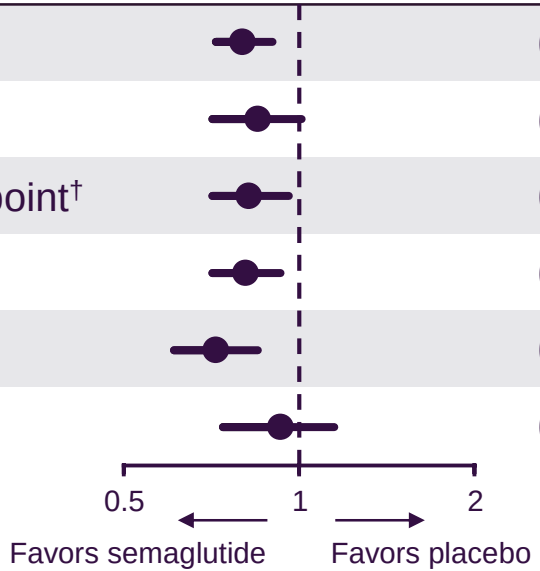


No. at risk									
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734
Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672

Lincoff AM et al: N Engl J Med 389:2221-2232; 2023

SELECT: Major Adverse Cardiovascular Outcomes

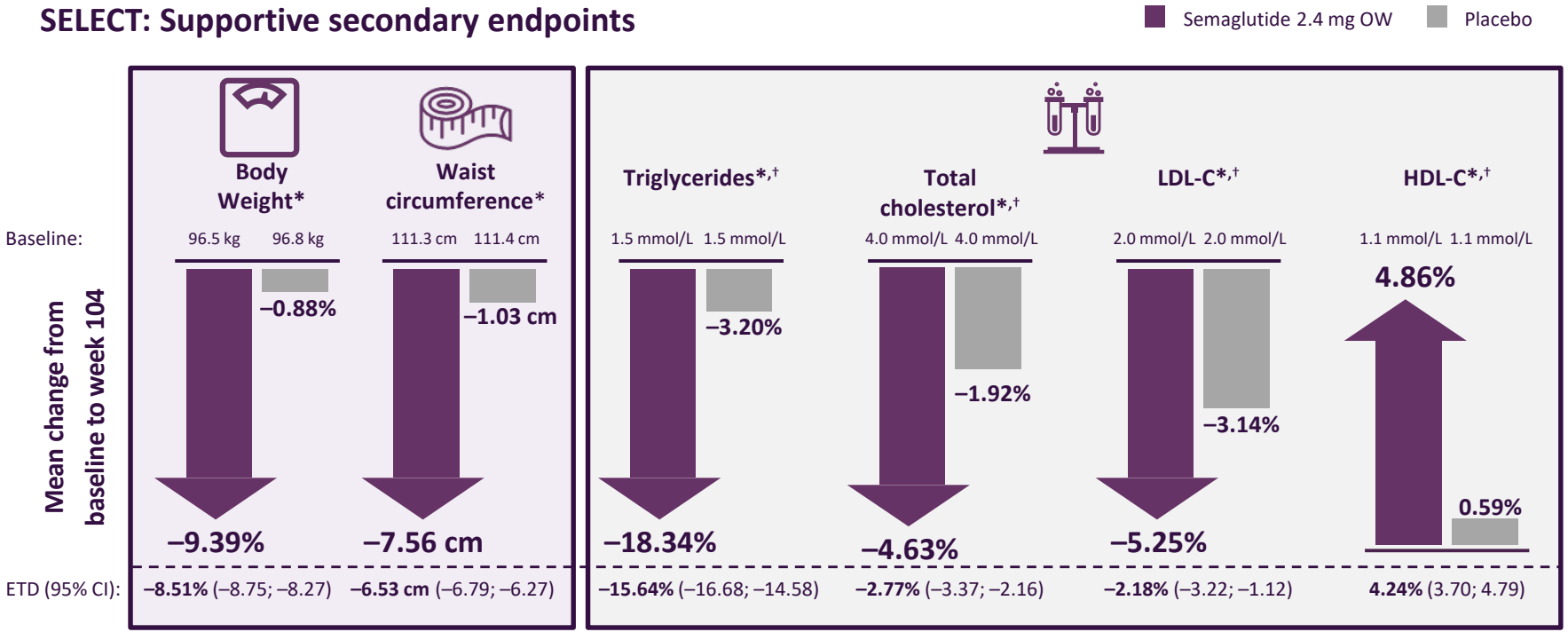
		HR (95% CI)
Primary endpoint	**MACE***	**0.80** (0.72; 0.90)
Confirmatory secondary endpoints	CV death	**0.85** (0.71; 1.01)
	HF composite endpoint†	**0.82** (0.71; 0.96)
	All-cause death	**0.81** (0.71; 0.93)
Supportive secondary endpoints	Non-fatal MI	**0.72** (0.61; 0.85)
	Non-fatal stroke	**0.93** (0.74; 1.15)



*First occurrence of CV death, non-fatal MI, non-fatal stroke. †Composite of HF hospitalization, urgent HF visit, or CV-related death

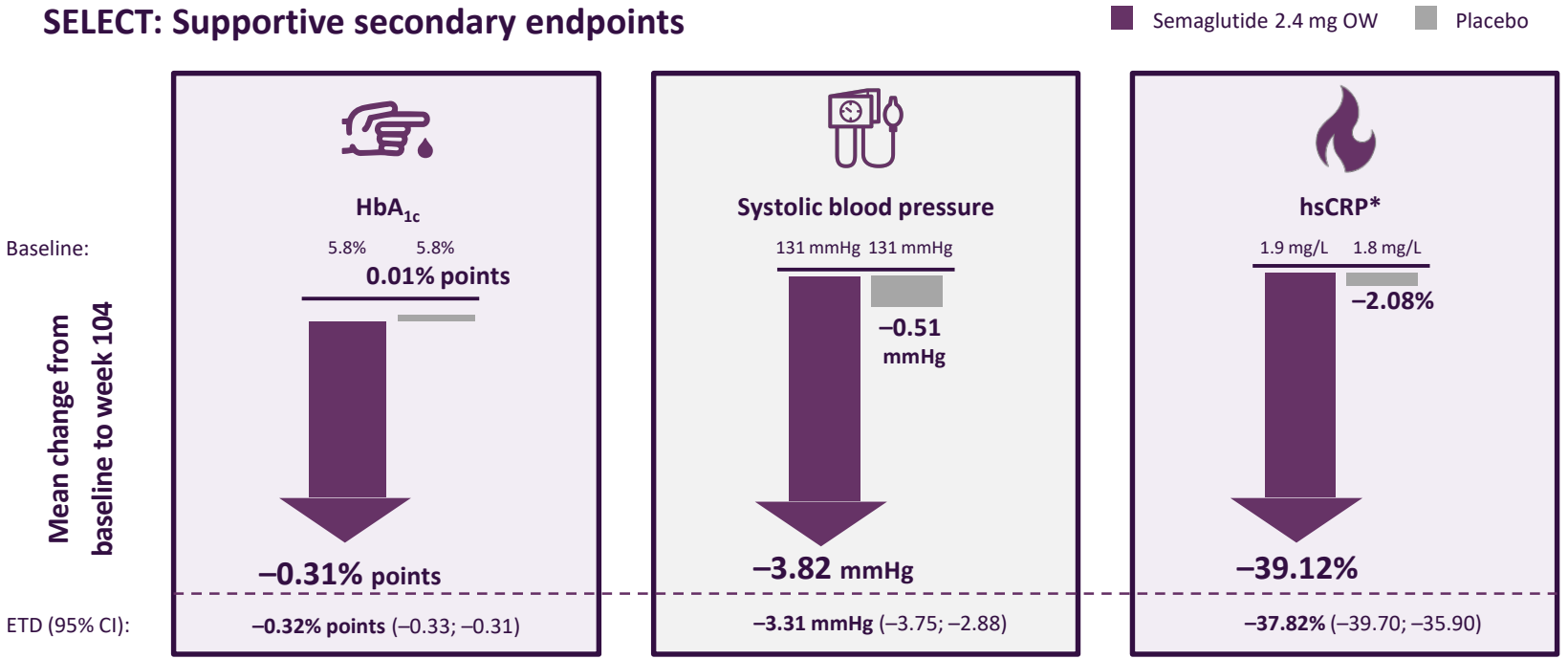
Lincoff AM et al: N Engl J Med 389:2221-2232; 2023

Modifiable Risk Factors Underlying Cardiovascular Disease in SELECT



Lincoff AM et al: N Engl J Med 389:2221-2232; 2023

Modifiable Risk Factors Underlying CVD in SELECT

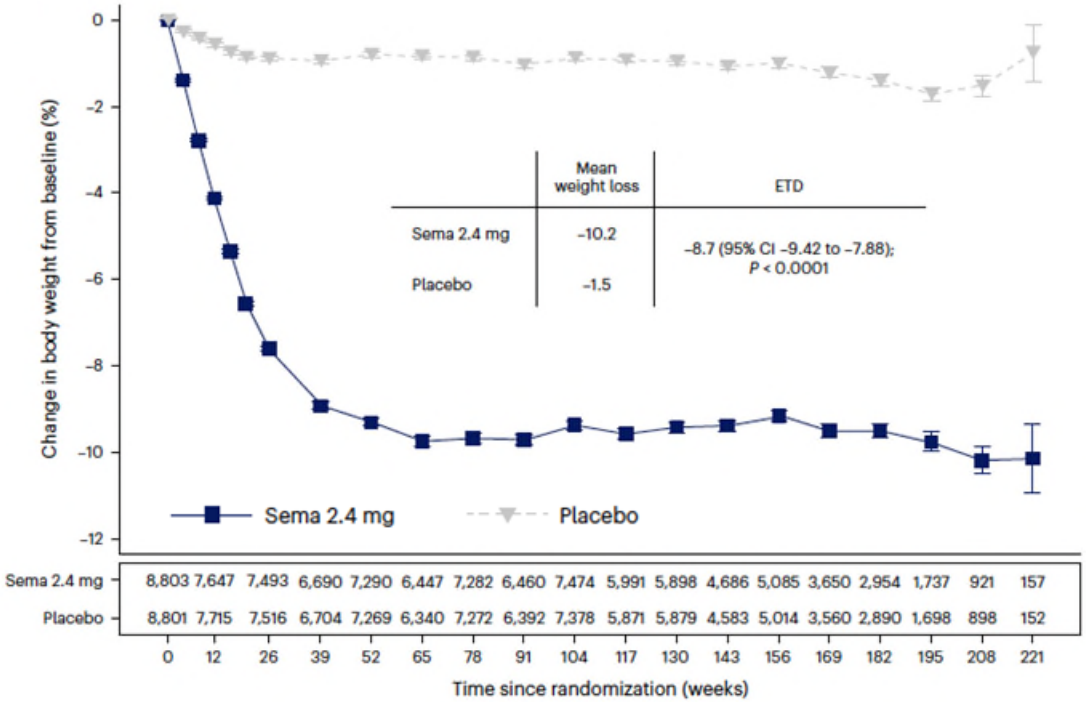


Lincoff AM et al: N Engl J Med 389:2221-2232; 2023

Outline

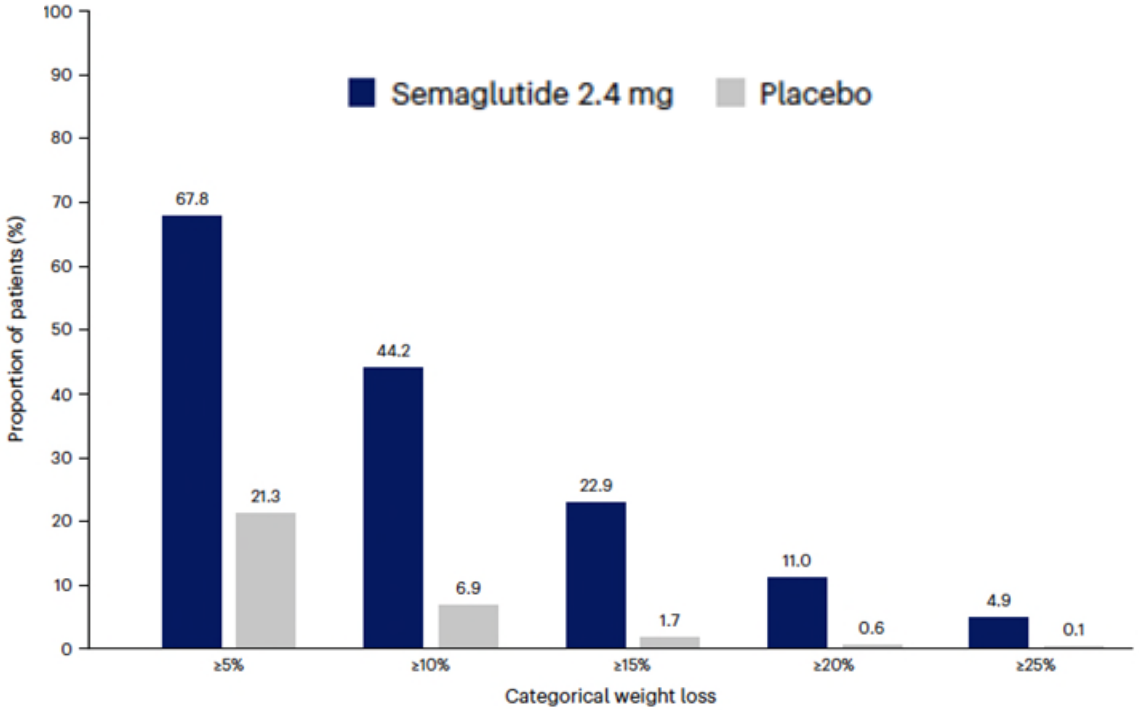
1. Background
2. Study Design and Baseline Characteristics
3. Outcomes:
    a) Primary Outcome: Cardiovascular Events
    b) Secondary Outcomes: Weight, Glycemia, Renal
4. Implications

Change in Body Weight Over Time: All Participants



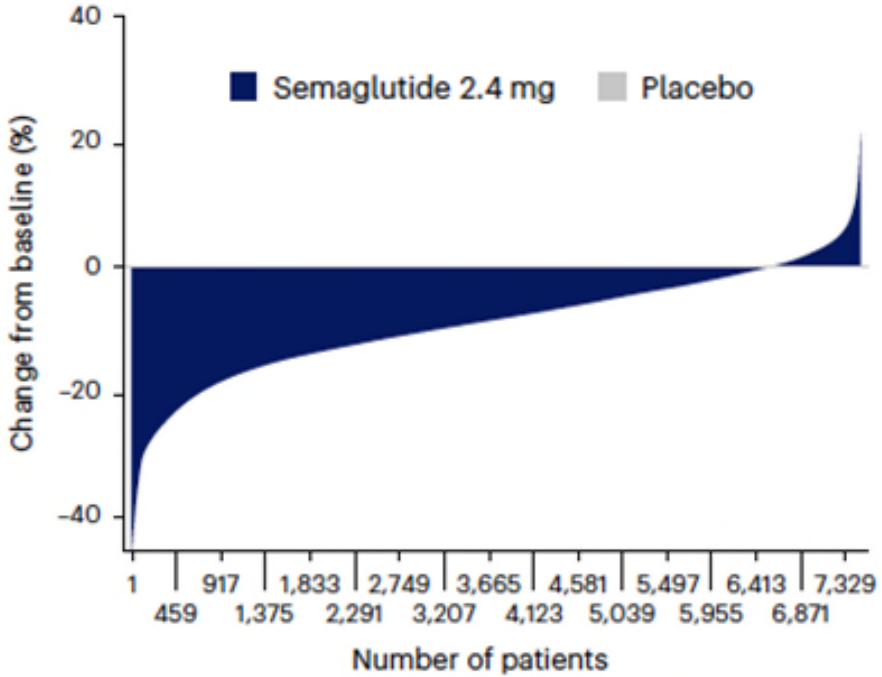
Ryan DH et al: Nat Med 30:2049-2057; 2024

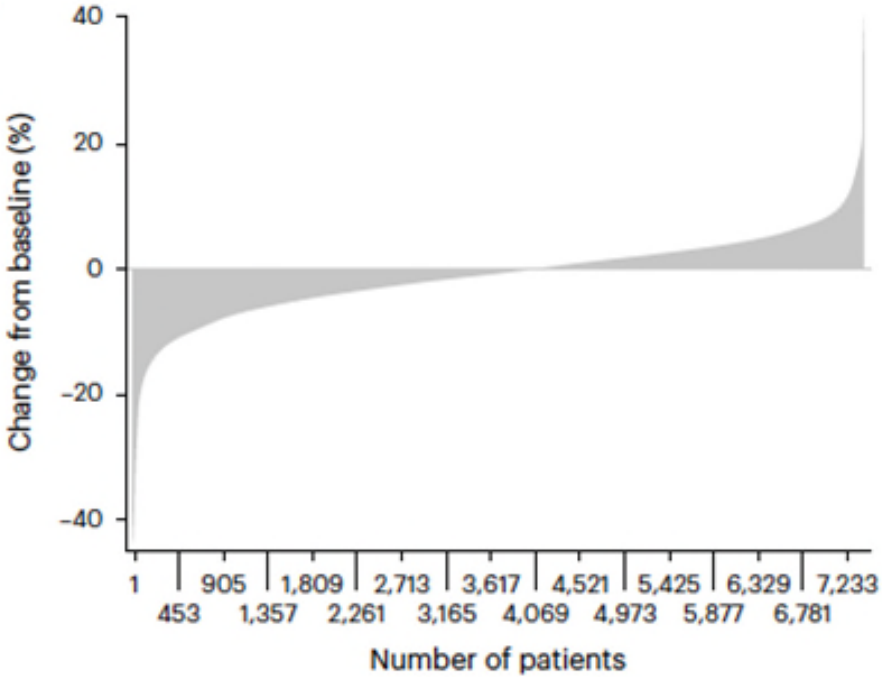
Variation in the Weight Loss Response: Categorical Weight Loss



Ryan DH et al: Nat Med 30:2049-2057; 2024

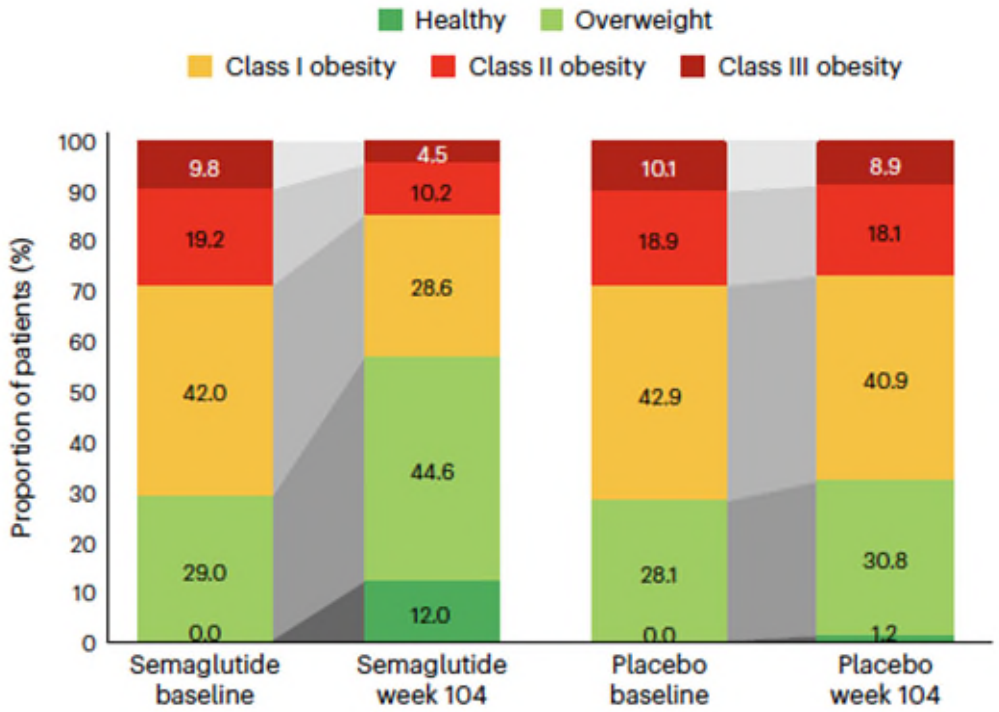
Variation in the Weight Loss Response: Percentage Change for Each Individual





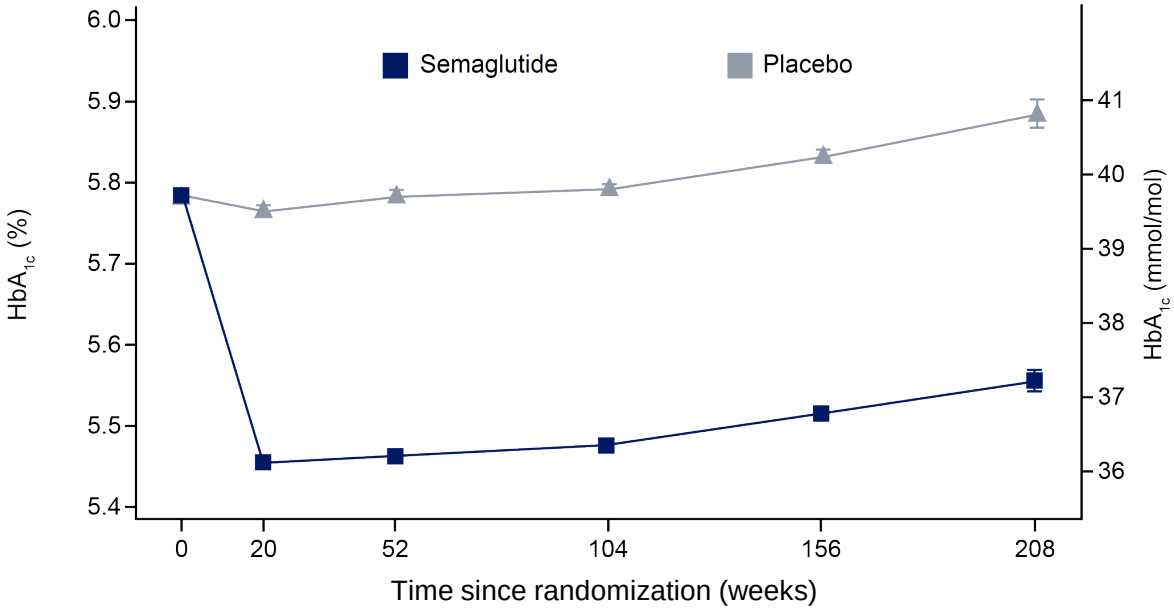
Ryan DH et al: Nat Med 30:2049-2057; 2024

Change in BMI Category from Baseline to Week 104



Ryan DH et al: Nat Med 30:2049-2057; 2024

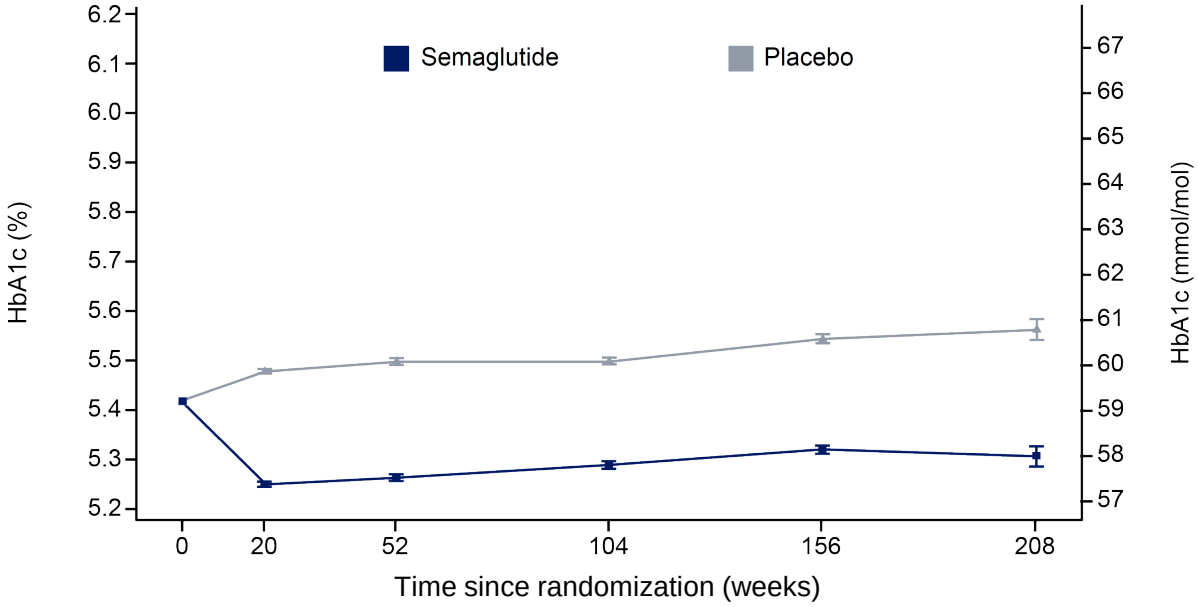
Change in Glycemia Over Time: All Participants



Semaglutide	8802	7993	7641	7439	4977	875
Placebo	8799	7998	7649	7351	4912	852

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

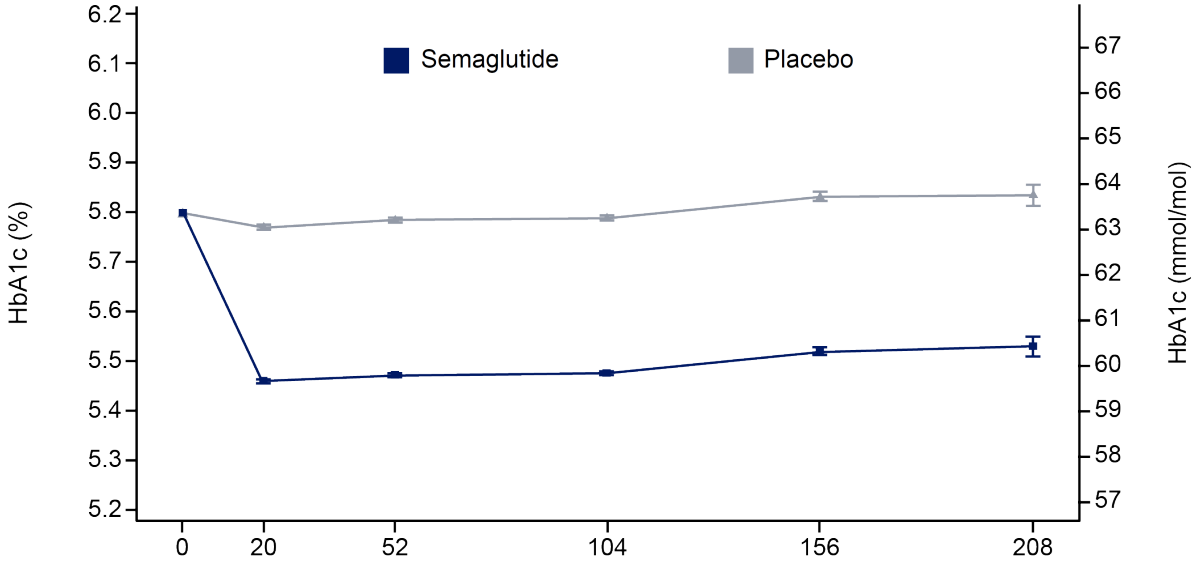
Change in Glycemia Over Time: Baseline HbA1c <5.7%



Semaglutide	2925	2666	2528	2468	1676	211
Placebo	2980	2715	2571	2487	1690	217

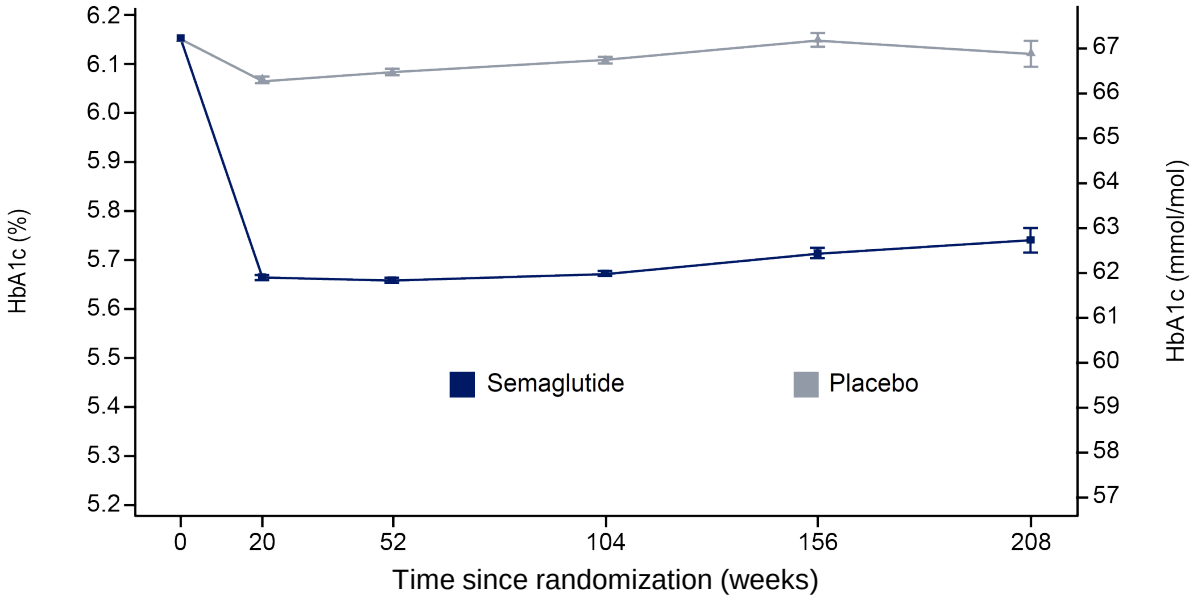
Kahn SE et al: Diabetes Care 47:1350-1359; 2024

Change in Glycemia Over Time: Baseline HbA1c 5.7% to <6.0%



Kahn SE et al: Diabetes Care 47:1350-1359; 2024

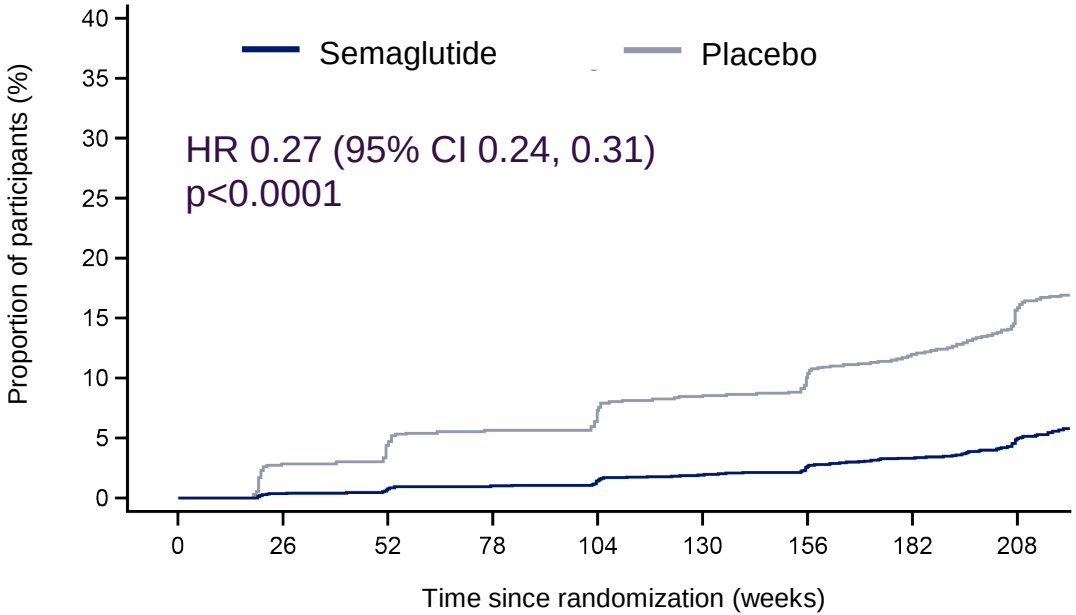
Change in Glycemia Over Time: Baseline HbA1c 6.0% to ≤6.5%



Semaglutide	2812	2547	2440	2366	1593	337
Placebo	2798	2544	2446	2340	1544	355

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

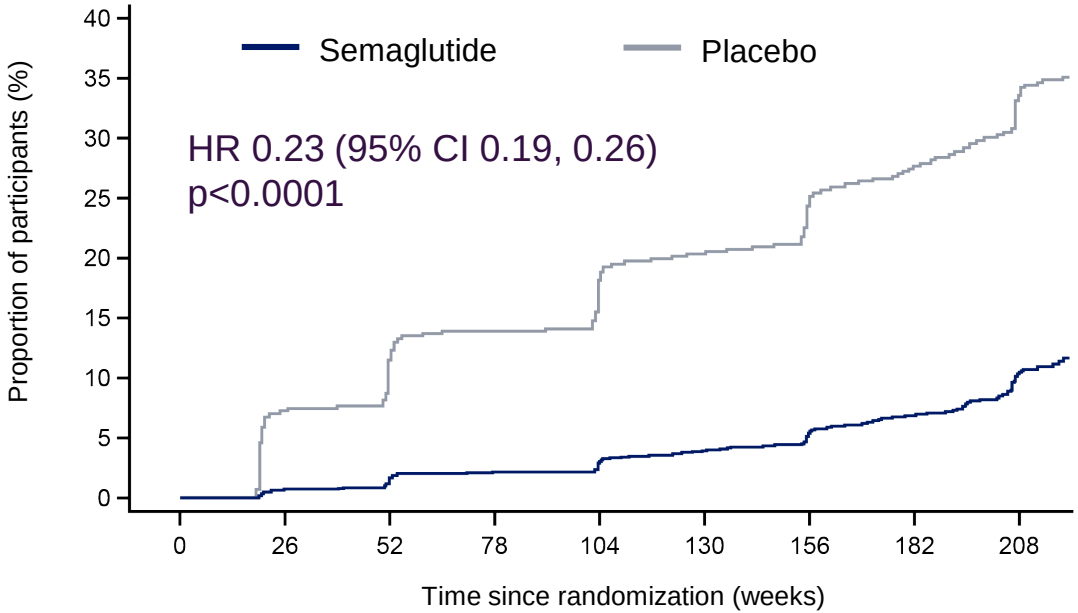
Cumulative Incidence of Diabetes: Baseline HbA1c <6.5%



Semaglutide	8800	8713	8609	8494	8340	7312	5853	4210	1767
Placebo	8797	8487	8248	8050	7805	6792	5353	3789	1577

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

Cumulative Incidence of Diabetes: Baseline HbA1c 6.0% to <6.5%

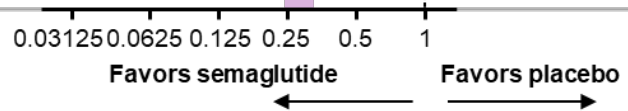


Semaglutide	2809	2776	2728	2686	2629	2300	1799	1296	574
Placebo	2794	2568	2416	2311	2171	1857	1379	933	442

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

Progression to Diabetes at Week 156: Baseline Body Weight and Glycemia

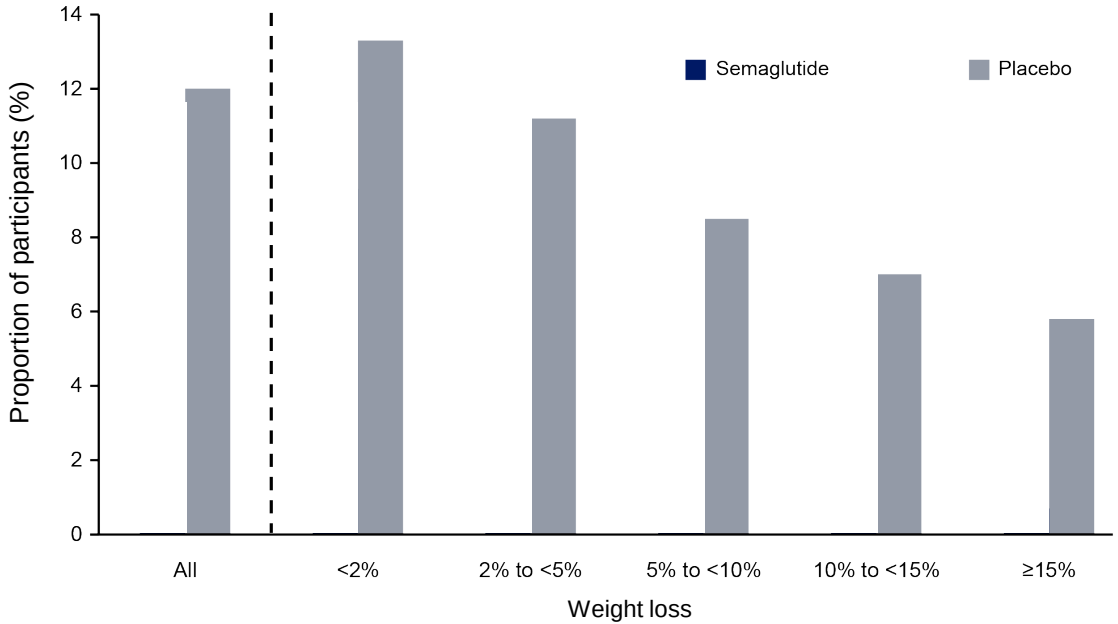
	Semaglutide Events / analyzed participants	Placebo Events / analyzed participants	HR (95% CI)	p-value
Primary analysis	306/8799	1059/8795	0.27 (0.24, 0.31)	
Body weight group, kg				
<90	122/3428	376/3454	0.31 (0.25, 0.38)	
≥90 to <100	55/2157	227/2048	0.22 (0.16, 0.29)	0.3038
≥100 to <115	77/2011	266/2041	0.28 (0.21, 0.35)	
≥115	52/1203	190/1252	0.27 (0.19, 0.36)	
BMI group, kg/m^2				
<30	80/2555	251/2468	0.29 (0.23, 0.37)	
≥30 to <35	124/3691	422/3780	0.28 (0.23, 0.35)	
≥35 to <40	66/1686	248/1655	0.25 (0.19, 0.32)	0.8397
≥40 to <45	25/579	92/595	0.26 (0.16, 0.40)	
≥45	11/288	46/297	0.22 (0.11, 0.41)	
HbA_{1c} group (%)				
<5.7	50/2925	85/2980	0.59 (0.42, 0.84)	
≥5.7 to <6.0	49/3065	196/3021	0.24 (0.17, 0.33)	<0.0001
≥6.0	207/2809	778/2794	0.23 (0.19, 0.26)	



All randomized patients (intention-to-treat) analyzed using a Cox proportional hazards model with treatment, subgroup, and interaction between treatment and subgroup as fixed factors.

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

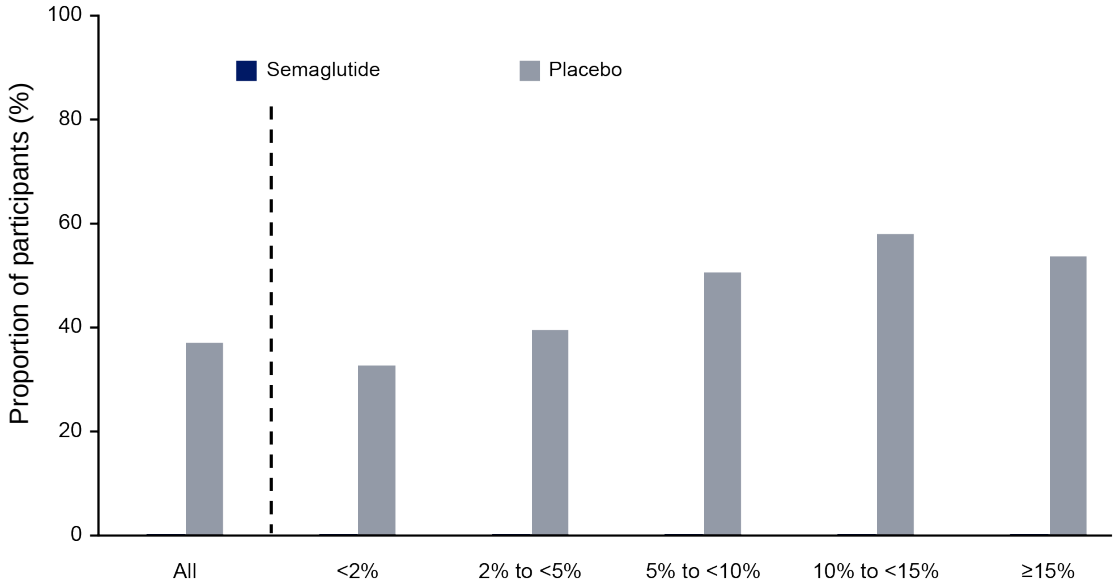
Progression to Diabetes at 156 Weeks by Degree of Weight Loss



	All	<2%	2% to <5%	5% to <10%	10% to <15%	≥15%
Semaglutide, n	8799	1402	1173	2423	2002	1799
Placebo, n	8795	5687	1659	1060	286	103

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

Regression to Normoglycemia at 156 Weeks by Degree of Weight Loss



	All	<2%	2% to <5%	5% to <10%	10% to <15%	≥15%
Semaglutide, n	5877	949	804	1589	1341	1194
Placebo, n	5819	3790	1091	697	174	67

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

Mediation by Body Weight of Time to Regression and Progression at Week 156

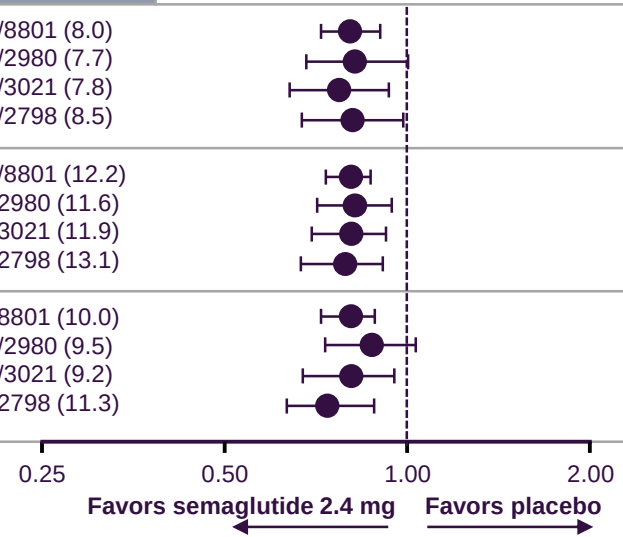
	Probability of no event at 156 weeks			Total effect (95% CI)	Direct effect (95% CI)	Percentage mediation (95% CI)
	Semaglutide	Semaglutide (adjusted)	Placebo			
Time to progression to diabetes (HbA1c ≥6.5%)						
Body weight (kg)	0.972	0.946	0.895	0.077 (0.069, 0.085)	0.051 (0.038, 0.061)	34.5 (25.2, 45.7)
Time to regression to normoglycemia (HbA1c <5.7%)						
Body weight (kg)	0.205	0.323	0.638	-0.433 (-0.449, -0.415)	-0.316 (-0.338, -0.291)	27.1 (23.3, 31.1)

Modeling approach – Vansteelandt S et al: Stat Med 38:4828-4840; 2019

Kahn SE et al: Diabetes Care 47:1350-1359; 2024

Risk of Cardiovascular Events by Baseline HbA1c Category

Endpoint	Baseline HbA_{1c} (%)	Semaglutide Events / analyzed participants (%)	Placebo Events / analyzed participants (%)	HR (95% CI)	Interaction p-value
MACE	All participants	569/8803 (6.5)	701/8801 (8.0)	0.80 (0.72, 0.90)	0.89
	<5.7	186/2925 (6.4)	228/2980 (7.7)	0.82 (0.68, 1.00)	
	5.7–<6.0	186/3065 (6.1)	235/3021 (7.8)	0.77 (0.64, 0.93)	
	≥6.0–<6.5	197/2812 (7.0)	238/2798 (8.5)	0.81 (0.67, 0.98)	
Expanded MACE*	All participants	873/8803 (9.9)	1074/8801 (12.2)	0.80 (0.73, 0.87)	0.93
	<5.7	281/2925 (9.6)	346/2980 (11.6)	0.82 (0.70, 0.95)	
	5.7–<6.0	298/3065 (9.7)	361/3021 (11.9)	0.80 (0.69, 0.93)	
	≥6.0–<6.5	294/2812 (10.5)	367/2798 (13.1)	0.78 (0.67, 0.91)	
MACE with all-cause mortality	All participants	710/8803 (8.1)	877/8801 (10.0)	0.80 (0.72, 0.88)	0.45
	<5.7	243/2925 (8.3)	283/2980 (9.5)	0.87 (0.73, 1.03)	
	5.7–<6.0	227/3065 (7.4)	278/3021 (9.2)	0.80 (0.67, 0.95)	
	≥6.0–<6.5	240/2812 (8.5)	316/2798 (11.3)	0.74 (0.63, 0.88)	

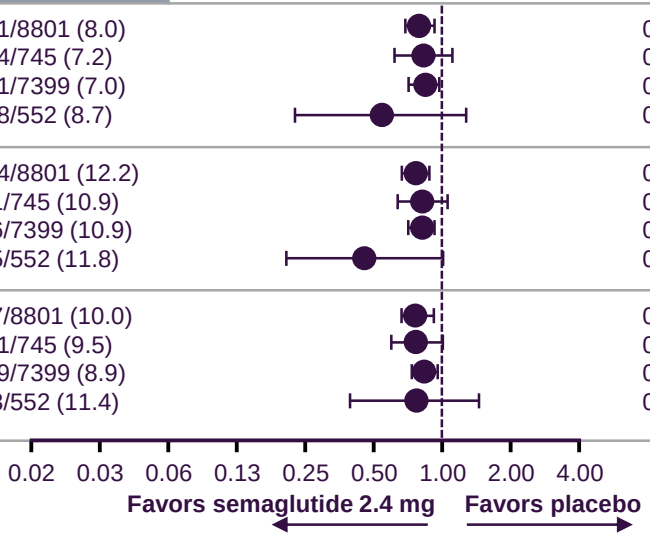


*MACE plus revascularization or hospitalization for unstable angina.
The full analysis set from the in-trial period analyzed using a Cox proportional hazards model with interaction between treatment groups and the relevant HbA_{1c} subgroup as fixed factors.

Lingvay I et al: Diabetes Care 47:1360-1369; 2024

Risk of Cardiovascular Events by Change in HbA1c at Week 20

Endpoint	HbA_{1c} change from baseline to week 20 (%-points)	Semaglutide Events / analyzed participants (%)	Placebo Events / analyzed participants (%)	HR (95% CI)	Interaction p-value
MACE	All participants	569/8803 (6.5)	701/8801 (8.0)	0.80 (0.72, 0.90)	0.62
	<-0.3	265/4461 (5.9)	54/745 (7.2)	0.83 (0.62, 1.11)	
	-0.3 to 0.3	246/4419 (6.0)	521/7399 (7.0)	0.84 (0.72, 0.97)	
	>0.3	6/131 (4.6)	48/552 (8.7)	0.55 (0.23, 1.27)	
Expanded MACE*	All participants	873/8803 (9.9)	1074/8801 (12.2)	0.80 (0.73, 0.87)	0.35
	<-0.3	398/4461 (8.9)	81/745 (10.9)	0.82 (0.65, 1.05)	
	-0.3 to 0.3	375/4119 (9.1)	806/7399 (10.9)	0.82 (0.72, 0.93)	
	>0.3	7/131 (5.3)	65/552 (11.8)	0.46 (0.21, 1.01)	
MACE or all-cause mortality	All participants	710/8803 (8.1)	877/8801 (10.0)	0.80 (0.72, 0.88)	0.81
	<-0.3	324/4461 (7.3)	71/745 (9.5)	0.77 (0.60, 1.00)	
	-0.3 to 0.3	314/4119 (7.6)	659/7399 (8.9)	0.84 (0.74, 0.96)	
	>0.3	11/131 (8.4)	63/552 (11.4)	0.76 (0.40, 1.45)	

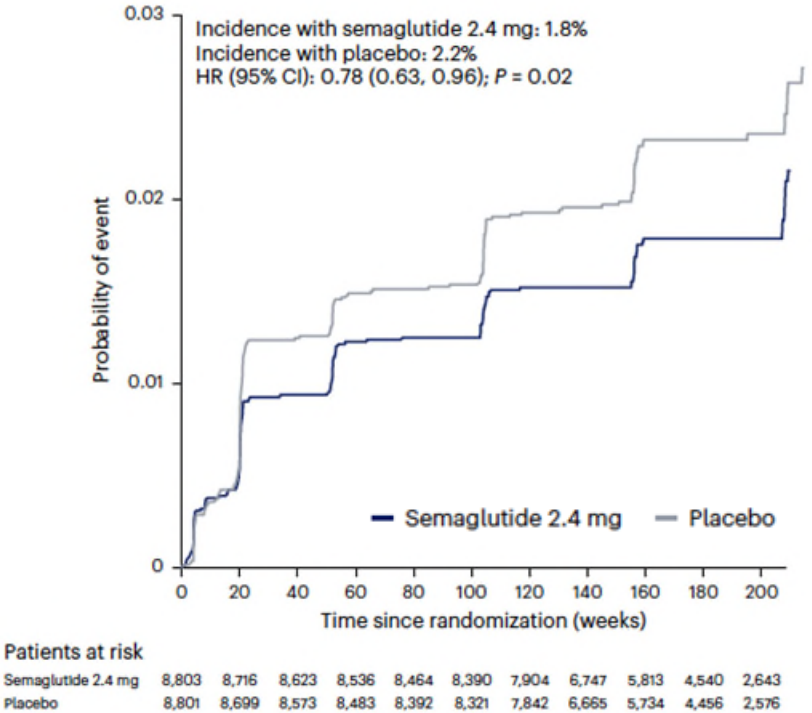


*MACE plus revascularization or hospitalization for unstable angina.

The full analysis set from the in-trial period. Subgroups were defined by changes in HbA_{1c} from baseline to 20 weeks of treatment. Only individuals who reached the week 20 visit are included in this analysis. HRs and 95% CIs were calculated using a Cox proportional hazards model with interaction between treatment groups and the relevant HbA_{1c} subgroup as fixed factors..

Lingvay I et al: Diabetes Care 47:1360-1369; 2024

SELECT: Cumulative Incidence of Main 5-Component Kidney Composite Endpoints

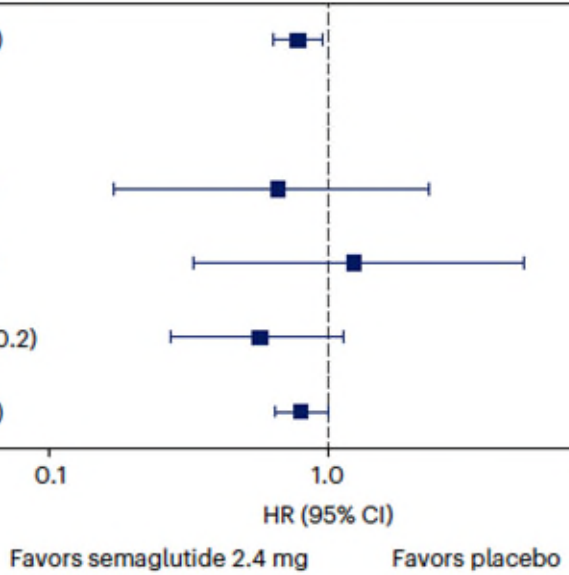


- Death from kidney causes
- Initiation of chronic kidney replacement therapy (dialysis or transplantation)
- Onset of persistent eGFR <15 ml min^{-1} 1.73 m^{-2}
- Persistent ≥50% reduction in eGFR compared to baseline
- Onset of persistent macroalbuminuria

Colhoun HM et al: Nat Med 30:2058-2066; 2024

SELECT: Effect of Semaglutide on the Main 5-Component Kidney Composite Endpoint

	Semaglutide 2.4 mg (*N* = 8,803), *n* (%)	Placebo (*N* = 8,801), *n* (%)	HR (95% CI); *P* value
5-component kidney composite endpoint	155 (1.8)	198 (2.2)	0.78 (0.63, 0.96); 0.02
Death due to kidney disease	0	0	N/A
Initiation of chronic kidney replacement therapy[a]	4 (0.0)	6 (0.1)	0.66 (0.17, 2.32); 0.52
Onset of persistent eGFR <15 ml min^{-1} 1.73 m^{-2}	5 (0.1)	4 (0.0)	1.24 (0.33, 5.02); 0.74
Onset of persistent ≥50% reduction in eGFR	12/8,724[b] (0.1)	21/8,742[b] (0.2)	0.57 (0.27, 1.14); 0.11
Onset of persistent macroalbuminuria	144 (1.6)	179 (2.0)	0.80 (0.64, 1.00); 0.05



Colhoun HM et al: Nat Med 30:2058-2066; 2024

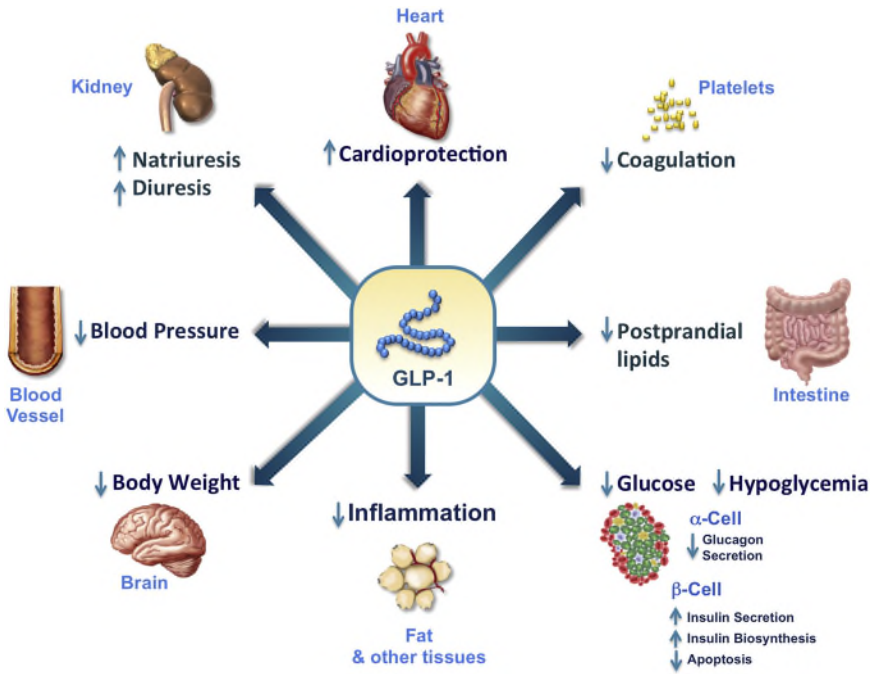
Outline

1. Background
2. Study Design and Baseline Characteristics
3. Outcomes:
    a) Primary Outcome: Cardiovascular Events
    b) Secondary Outcomes: Weight, Glycemia, Renal
4. Implications

Conclusions

- Semaglutide positively impacts the progression of diabetes and regression of normoglycemia in people with prediabetes as well as reducing adverse renal outcomes.
- Thus, in people with overweight or obesity and CVD, treatment with semaglutide would be expected to positively impact glycemia and renal function in addition to CV outcomes.

Glucagon-like Peptide-1 (GLP-1) Has Pleiotropic Effects



Drucker DJ: Cell Metab 24:15-30; 2016

Projected Impact of Overweight and Obesity in the United States

What are we going to do to stem the obesity epidemic?

And if GLP-1 receptor agonists provide an approach to reduce body weight and the risks associated with obesity, how are we going to ensure that all those needing them getting access?

World Obesity Federation: World Obesity Atlas 2023. https://data.worldobesity.org/publications/?cat=19