GLP1-RA e Dual Agonist-Tirzepatide nel pre-diabete

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CONFLICTS OF INTEREST

Il dott Stefano Ciardullo dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- AstraZeneca
- Boheringer Ingelheim
- Echosens
- Eli Lilly
- Guidotti
- MSD
- Novo Nordisk

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Table 1 **Biochemical diagnostic criteria for diabetes and pre-diabetes according to the World Health Organization and the American Diabetes Association (from ref. Marx *et al.*[2])**

Glycaemic maker	WHO criteria (2011, 2019)	ADA criteria (2021)
	Diabetes	
FPG	≥7.0 mmol/L (≥126 mg/dL)	
2hPG	≥11.1 mmol/L (≥200 mg/dL)	
HbA1c	>6.5% (>48 mmol?mol)	
RPG	≥11.1 mmol/L (≥200 mg/dL)	
	Pre-diabetes	
FPG	6.1–6.9 mmol/L (110–125 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)
2hPG (OGTT)	7.8–11.0 mmol/L (140–199 mg/dL)	
HbA1c	6.0%–6.4% (42–47 mmol/mol)	5.7%–6.4% (39–47 mmol/mol)

ADA, American Diabetes Association; 2hPG, 2 h plasma glucose; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; RPG, random plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization.

Table 2 **New diagnostic criteria of plasma glucose values proposed by the International Diabetes Federation for diagnosing pre-diabetes with the 1 h oral glucose tolerance test (OGTT; https://idf.org/news/idf-position-statement-1-hour-pg-test/)**

	Normal	Pre-diabetes	Diabetes
OGTT (1 h)	≤154 mg/dL	155–208 mg/dL	≥209 mg(dL)
	≤8.6 mmol/L	8.6–11.6 mmol/L	≥11.6 mmol/L

European Heart Journal (2024) 45, 5117–5126

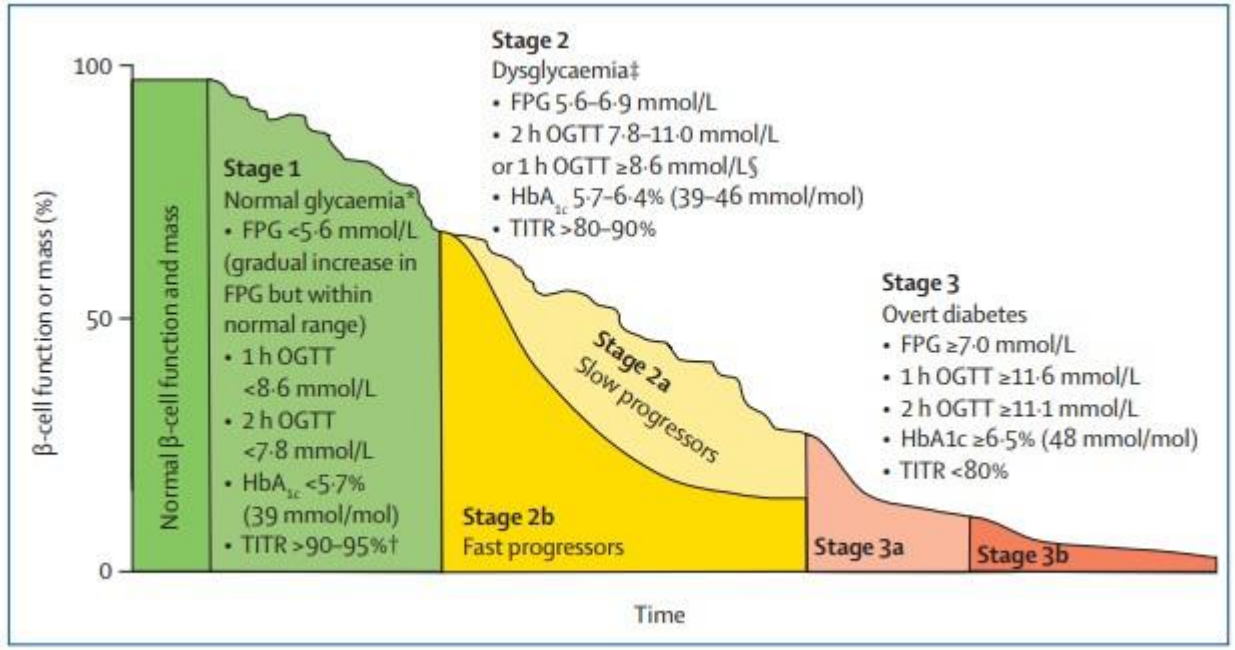
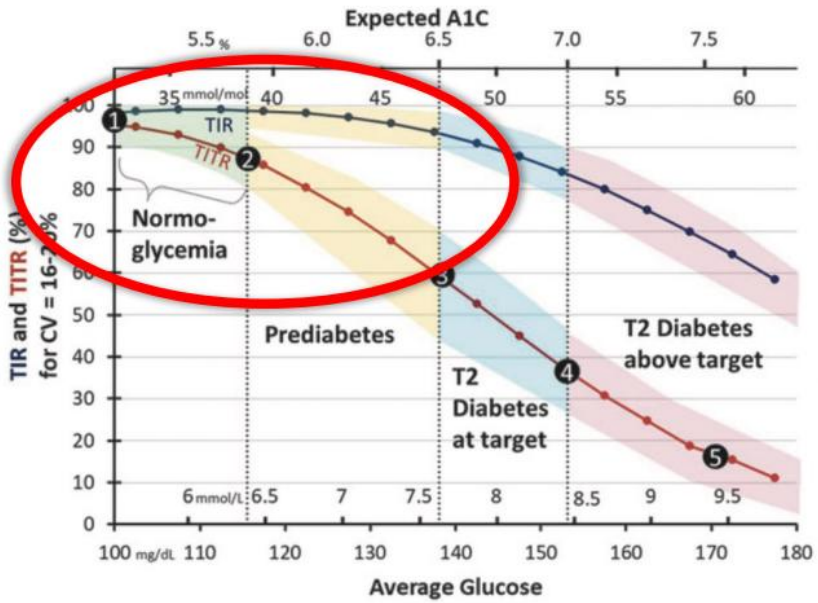


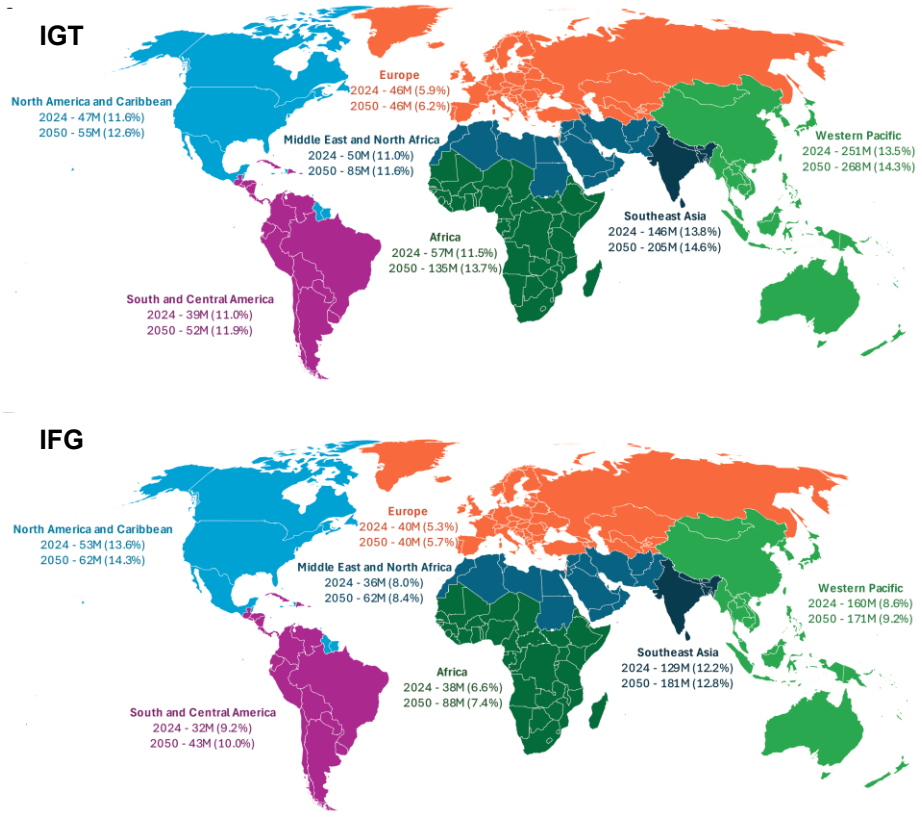
Figure: **Proposed staging of type 2 diabetes**



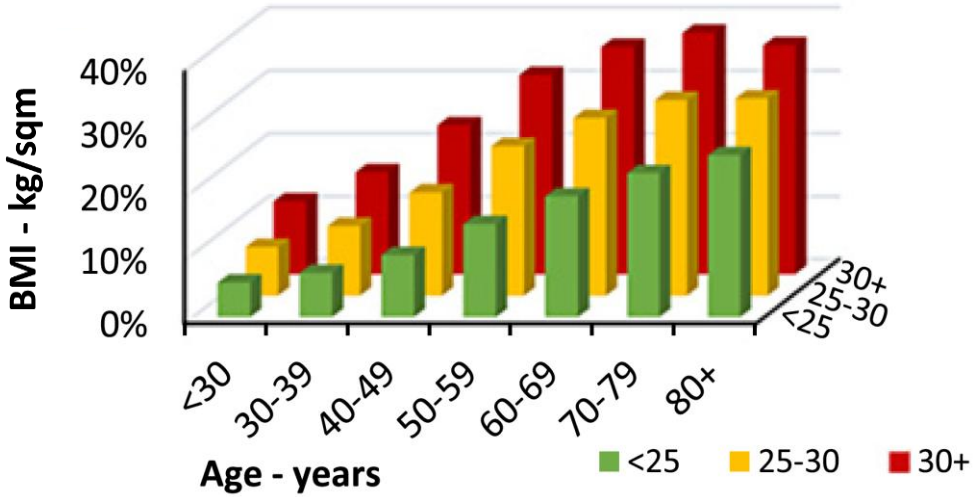
	❶	❷	❸	❹	❺
A1C, %	5.1	5.7	6.5	7.0	7.5
AG, mg/dL	100	117	138	154	170
CV, %	18	18	18	18	18
TIR, %	98	99	94	84	67
TITR, %	95	86	60	37	18
TIR-TITR, %	3	13	34	47	49

❶ → ❷ Normoglycemia → Prediabetes
❷ → ❸ Prediabetes → T2 diabetes
❸ → ❹ T2 diabetes → In target zone
❹ → ❺ In target zone → Above target zone

The global burden of prediabetes and obesity



A relentless escalation: from 580 to 750 million cases by 2050, with a projected global prevalence of 11%.



N: 6,412,591 (3,556,116 females)

Health check-ups from 2017 to 2023

Mary R. Rooney et al. Diabetes Care 2025; Caren Sourij et al. Obes Facts 2025

Association between prediabetes and mortality

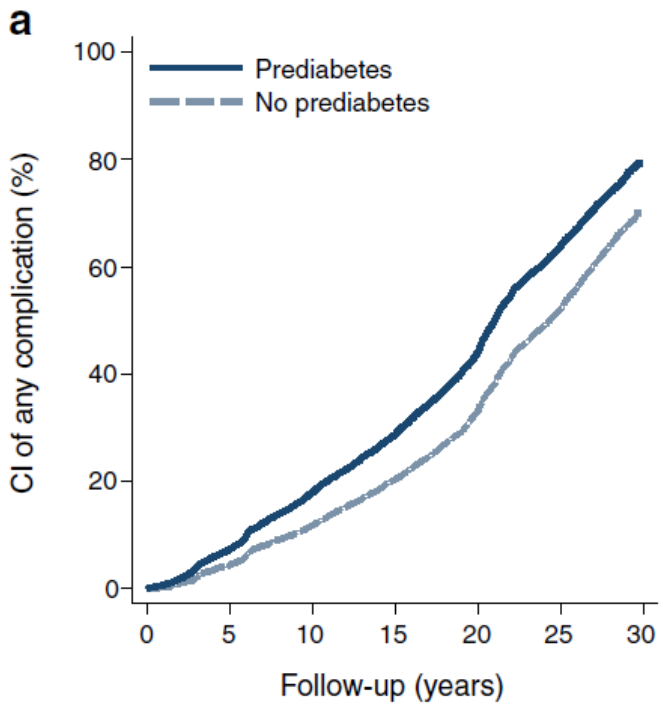
Model[a]	HR (95% CI)	*P* value
Overall		
Unadjusted	1.58 (1.43-1.74)	<.001
Adjusted for demographics	0.88 (0.80-0.98)	.02
Adjusted for demographics and lifestyle factors	0.92 (0.82-1.04)	.17
Adjusted for demographics, lifestyle factors, and comorbidities (fully adjusted)	1.05 (0.92-1.19)	.47
Stratified by age group		
20-54 y	1.68 (1.25-2.20)	<.001
55-74 y	0.87 (0.69-1.09)	.22
≥75 y	0.97 (0.83-1.12)	.66
Stratified by race and ethnicity		
Non-Hispanic Black	1.02 (0.80-1.30)	.86
Non-Hispanic White	1.06 (0.91-1.23)	.45
Other[b]	0.81 (0.56-1.19)	.29

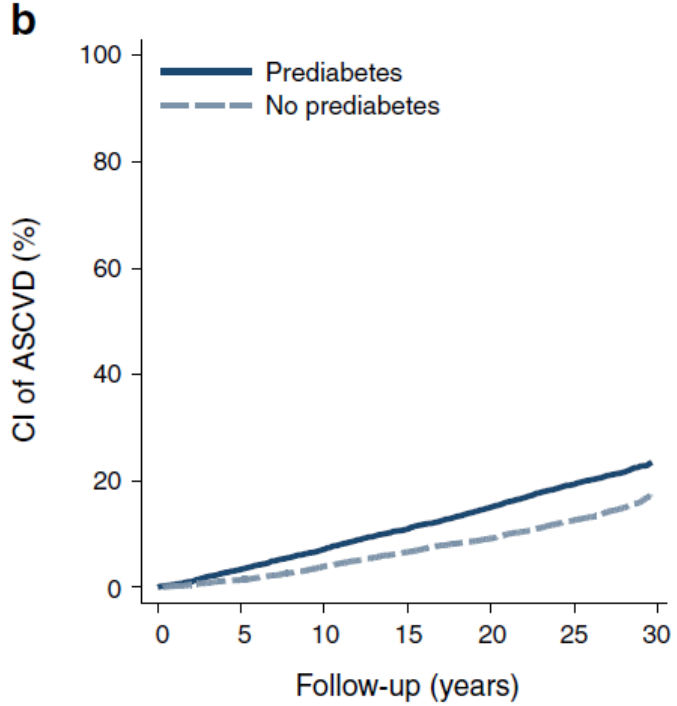
Prediabetes significantly increases mortality risk only in younger adults (20–54 years), emphasizing the need for age-targeted interventions (NHANES cohort study)

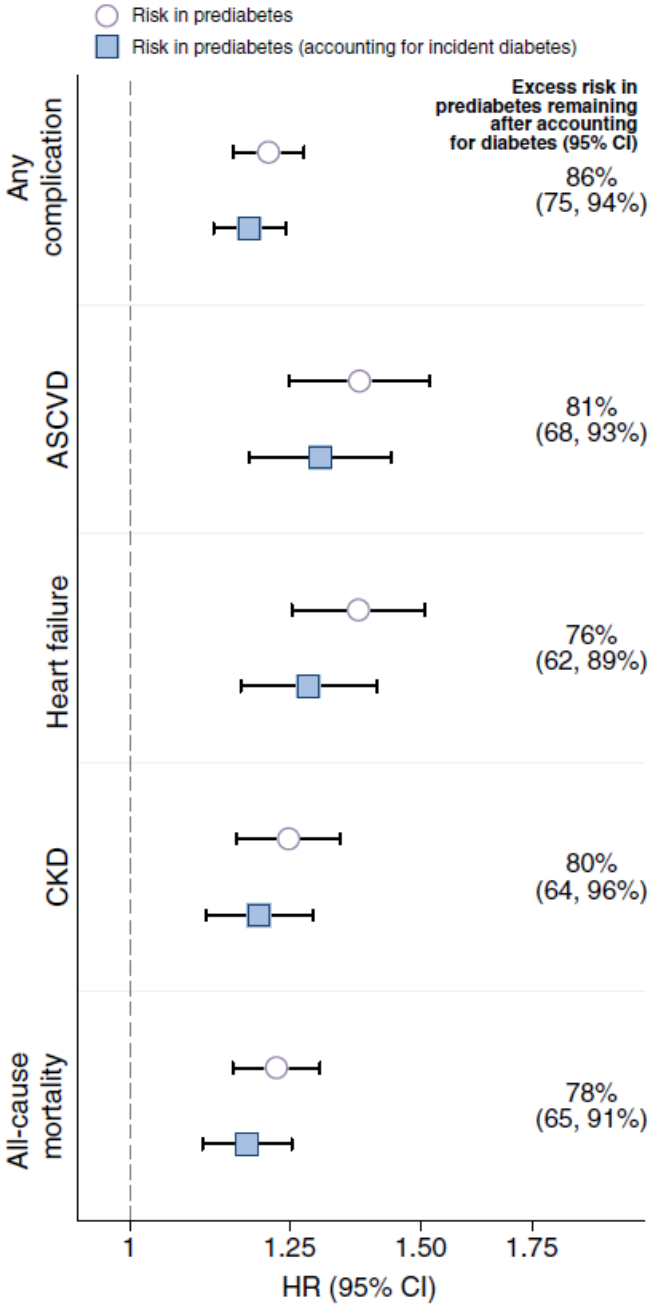
Obinna Ekwunife et al. JAMA Network Open. 2025

Prediabetes is associated with elevated risk of clinical outcomes even without progression to diabetes

Mary R. Rooney[1,2] · Amelia S. Wallace[1,2] · Justin B. Echouffo Tcheugui[2,3] · Michael Fang[1,2] · Jiaqi Hu[1,2,4] · Pamela L. Lutsey[5] · Morgan E. Grams[6] · Josef Coresh[7] · Elizabeth Selvin[1,2]



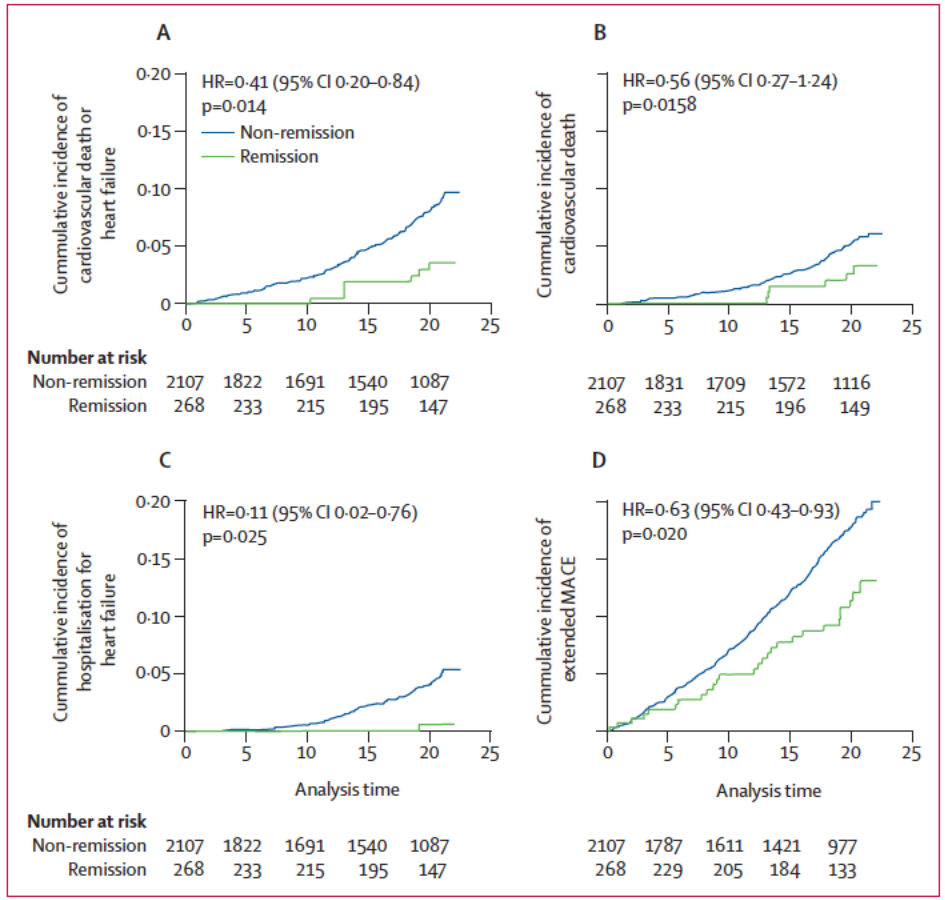




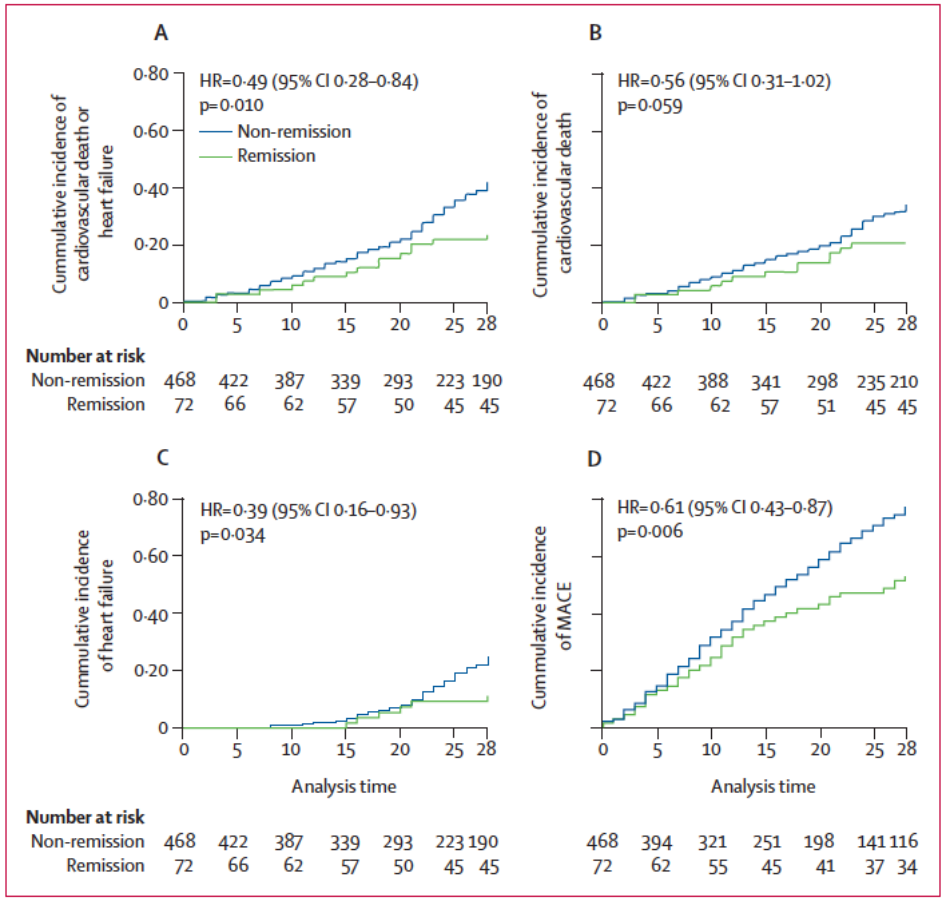
Diabetologia 2025

Prediabetes remission and cardiovascular morbidity and mortality

DPPOS (20 anni)



DaQingDPOS (30 anni)



Arreola et al. Lancet Diabetes Endocrinol 2026

Argomento	Contro (Supportano l'omissione dalle linee guida ESC)	Pro (Contestano l'omissione dalle linee guida ESC)
Entità del rischio	Il rischio assoluto è significativamente inferiore rispetto al DM.	Il glucosio è un fattore di rischio continuo **senza effetto soglia**.
Meccanismo del rischio	Il rischio cardiovascolare sembra mediato principalmente dalla **sindrome metabolica associata** piuttosto che dall'iperglicemia stessa.	2-hPG è un **predittore indipendente** di mortalità e infarto, spesso superiore alla sola glicemia a digiuno o all'HbA1c.
Evidenze dai trial	Molti studi dimostrano la prevenzione del diabete, ma **non una riduzione significativa** della mortalità o di eventi CV "hard".	**IGT ha una prognosi sfavorevole quasi quanto il diabete**, con eventi che compaiono precocemente (entro un anno).
Strategia clinica	La priorità è **trattare i singoli fattori di rischio (pressione, lipidi**) e prevenire il diabete tramite lo stile di vita.	L'omissione del pre-diabete riduce la possibilità di **identificare precocemente pazienti ad alto rischio** e di utilizzare strumenti terapeutici (es. semaglutide nello studio SELECT)
Ruolo dell'OGTT	Il test da carico (OGTT) è considerato **dispendioso** in termini di tempo e con un valore aggiunto limitato.	L'OGTT è un test **economico e fondamentale** per identificare l'IGT, che altrimenti verrebbe persa.

European Heart Journal (2024) 45, 5117–5126

GLP1-RA

Efficacy and safety of once-weekly semaglutide 2.4 mg in people with **obesity and prediabetes (STEP 10)**: A randomised, double-blind, placebo-controlled, multi-centre phase 3 trial

Barbara M. McGowan, MD[1], Jens M. Bruun, MD[2], Matt Capehorn, MB[3],
Sue D. Pedersen, MD[4], Kirsi H. Pietiläinen, MD[5,6], Hanna Angelene Kudiyanur Muniraju, MSc[7], Maria Quiroga, MD[8],
Anette Varbo, MD[8], David C.W. Lau, MD[9], for the STEP 10 Study Group

[1]Department of Diabetes and Endocrinology, Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark; [3]Rotherham Institute for Obesity, Clifton Medical Centre, Rotherham, UK; [4]C-endo Diabetes and Endocrinology Clinic, Calgary, Canada; [5]Obesity Research Unit, Research Program for Clinical and Molecular Metabolism, University of Helsinki, Helsinki, Finland; [6]Healthy Weight Hub, Endocrinology, Abdominal Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [7]Novo Nordisk Global Business Services, Bangalore, India; [8]Novo Nordisk A/S, Søborg, Denmark; [9]Department of Medicine, University of Calgary Cumming School of Medicine, Calgary, Canada

McGowan B et al. *Lancet Diabetes Endocrinol* 2024; https://doi.org/10.1016/S2213-8587(24)00182-7

STEP 10 trial design

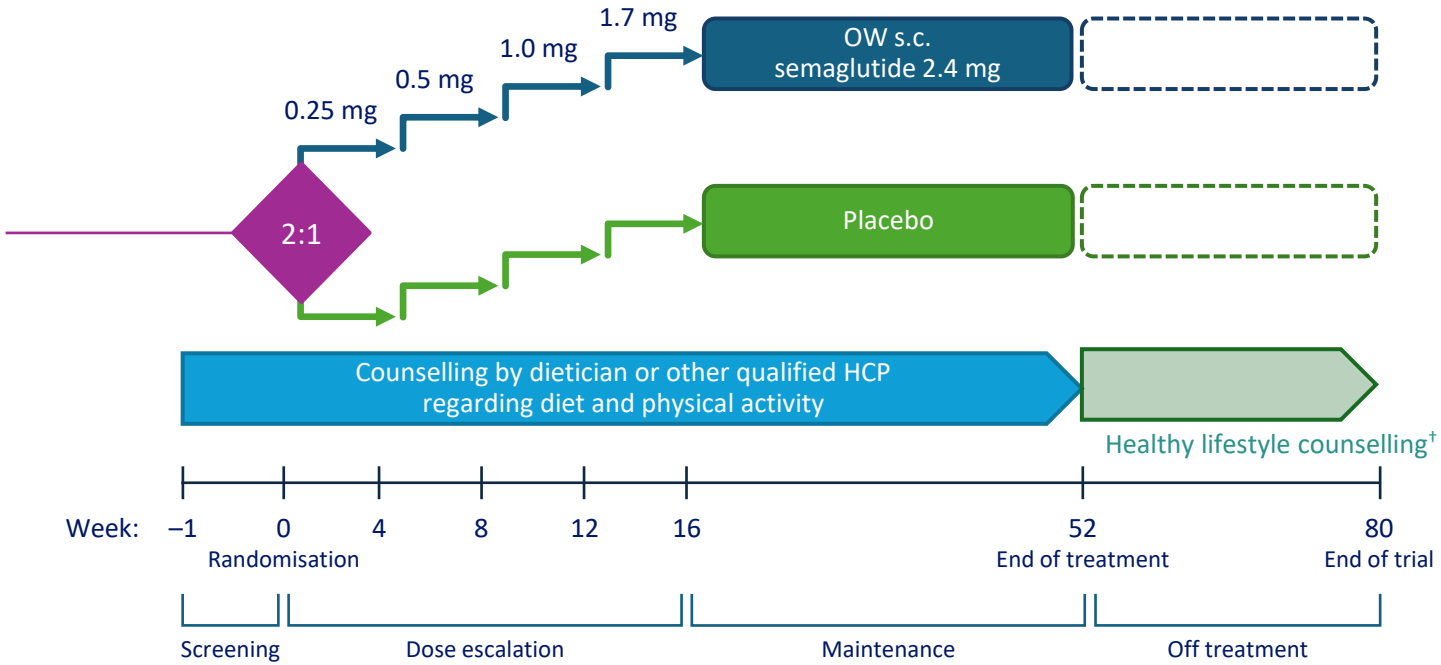
Randomised, double-blind multicentre, placebo-controlled trial

Key inclusion criteria

- Age ≥18 years old
- BMI ≥30 kg/m^2
- Prediabetes (NICE*) defined at screening as:
  - HbA_{1c} of 6.0–6.4% (42–46 mmol/mol)
    and/or
  - FPG 5.5–6.9 mmol/L

Key exclusion criteria

- HbA_{1c} ≥6.5% (≥48 mmol/mol) and/or FPG ≥7.0 mmol/L at screening
- Treatment with medication for obesity, glucose-lowering agents or self-reported change in body weight >5 kg in the 90 days prior to screening



Trial objective

To evaluate the efficacy and safety of once-weekly s.c. semaglutide 2.4 mg versus placebo as an adjunct to lifestyle intervention on body weight and reversion to normoglycaemia in participants with obesity and prediabetes at baseline

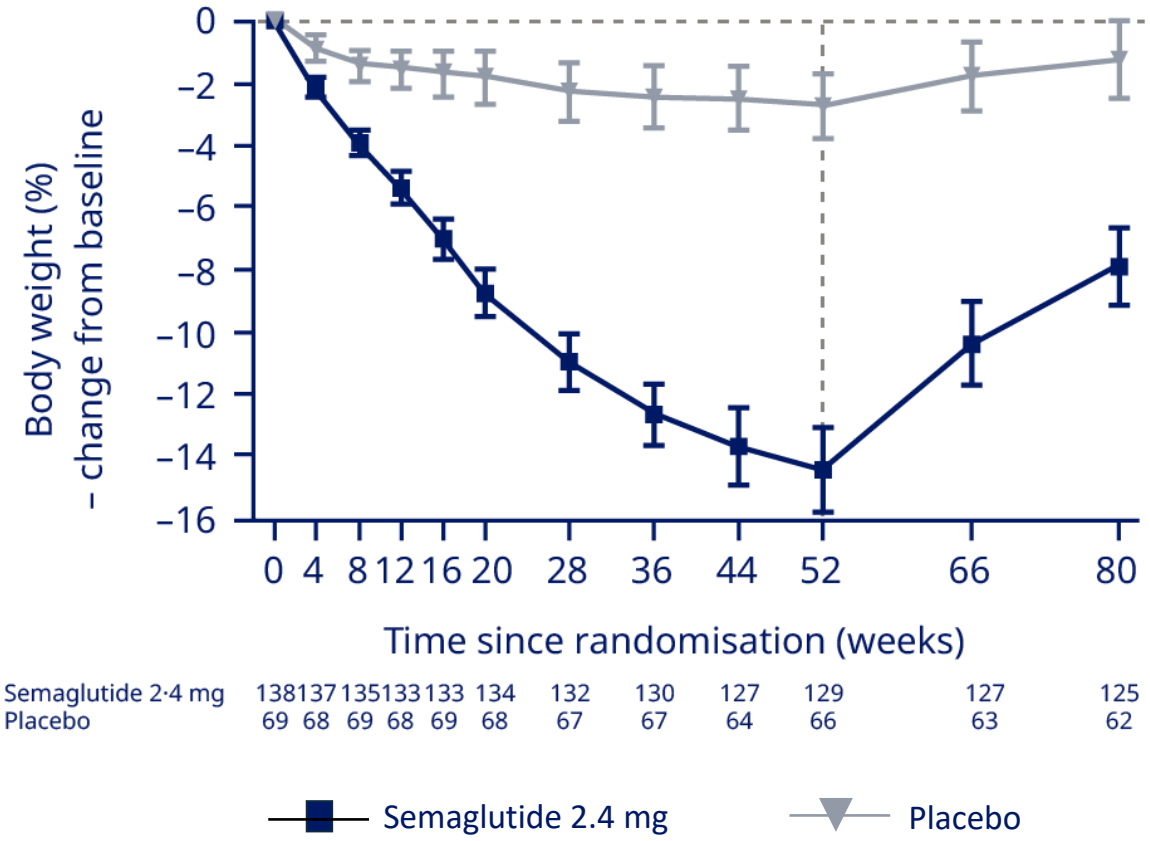
Key endpoints

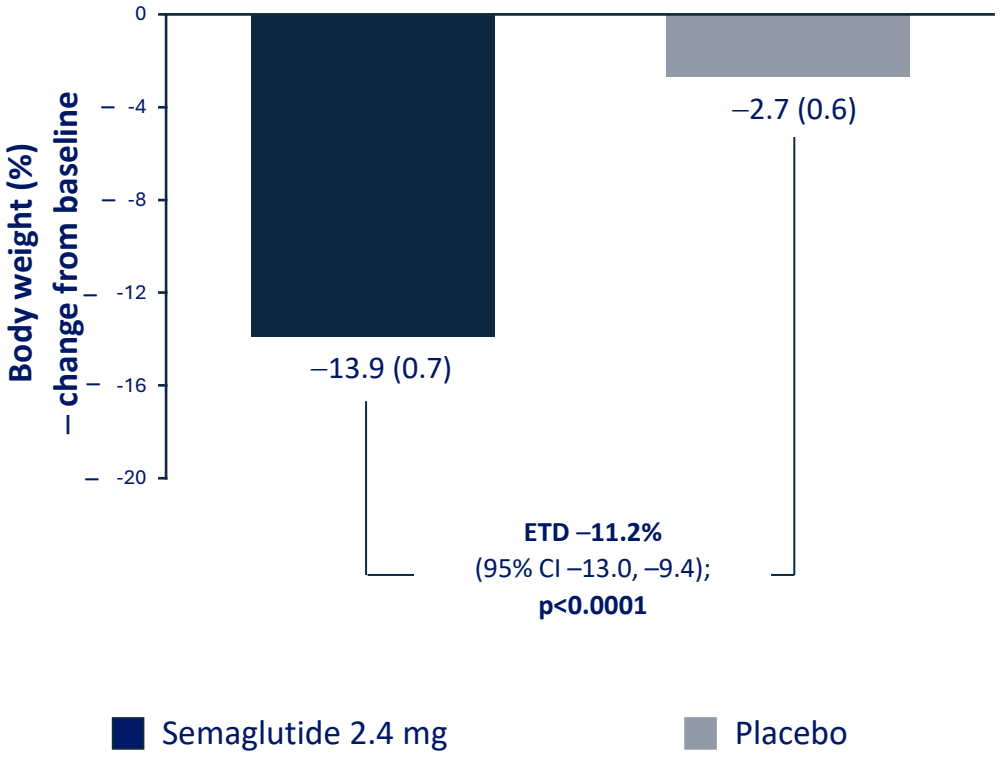
- Change in body weight (%) from baseline to week 52
- Proportion of participants who reverted to normoglycaemia at week 52

*National Institute for Health and Care Excellence. Public health guideline PH38. Type 2 diabetes: Prevention in people at high risk. July 2012. https://www.nice.org.uk/Guidance/PH38.
†Healthy lifestyle counselling as per normal clinical practice and country-specific guidelines.
BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; HCP, healthcare professional; NICE, National Institute for Health and Care Excellence; OW, once weekly; s.c., subcutaneous.
Adapted from Figure S1: Trial design of STEP 10.

Change in body weight from baseline to week 52

Treatment policy estimand

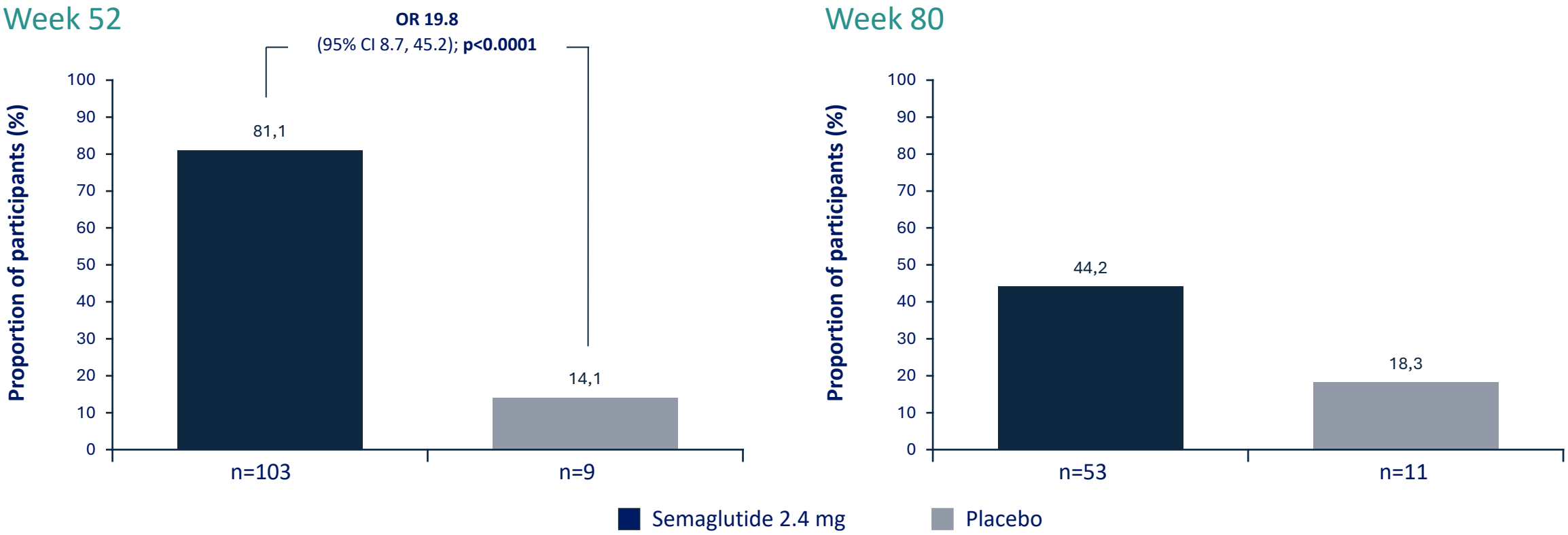




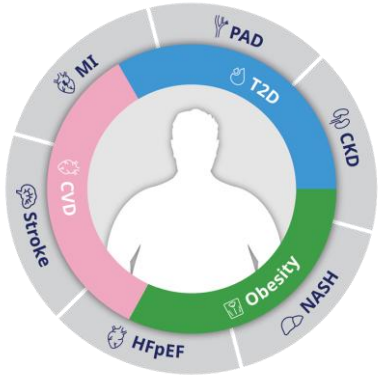
Observed mean (standard error of mean) percentage change for participants in the full analysis set during the in-trial observation period in body weight over time (error bars are +/– 95% CI of the mean; numbers below the panels are the number of participants contributing to the mean; dashed vertical line indicates end of treatment and the start of the off-treatment period), and from baseline to week 52. ETDs are for the treatment policy estimand.
CI, confidence interval; ETD, estimated treatment difference; N, number of participants.
Adapted from Figure 2A+B: Comparison of body weight parameters for semaglutide 2.4 mg versus placebo (full analysis set).

Reversion to normoglycaemia

Treatment policy estimand



Observed proportions of participants during the in-trial observation period in the full analysis set who reverted to normoglycaemia from baseline at week 52 and week 80. OR is for the treatment policy estimand.
Normoglycaemia was defined as having both HbA_{1c} <6.0% (<42 mmol/mol) and FPG <5.5 mmol/L.
CI, confidence interval; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; N, number of participants; OR, odds ratio; T2D, type 2 diabetes.
Adapted from Figure 3A+B: Proportion of participants who reverted to normoglycaemia or progressed to T2D for semaglutide 2.4 mg versus placebo (full analysis set).



SELECT CVOT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

- Diagnosed with overweight or obesity (BMI ≥27 kg/m^2)
- Age ≥45 years and established CVD*
- No prior history of diabetes (HbA1c <6.5%)

Randomisation (1:1)

N=17,604

Semaglutide 2.4 mg — Off-treatment follow-up

Placebo — Off-treatment follow-up

Event-driven treatment period (≥1225 first MACE)

Week:	–3	0	16	+5
	Screen		End of dose escalation	Maintenance dose†

Trial information

- Double-blind, parallel group, placebo-controlled superiority trial

Trial objective

To show that semaglutide 2.4 mg OW lowers the incidence risk of MACE vs placebo both added to SoC in participants with established CVD and overweight or obesity

Key endpoints

Primary: Time from randomisation to first occurrence of MACE (non-fatal MI, non-fatal stroke, CV death)

Secondary: Time from randomisation to:
CV death; HF composite‡ and all-cause death

*Established CVD: MI ≥60 days ago, stroke ≥60 days ago, or symptomatic peripheral artery disease. †Dose escalation is from week 4 to 16 with intervals of 4 weeks, and maintenance dose is event-driven to end of treatment period. ‡Heart failure hospitalisation, urgent heart failure visit or CV death.

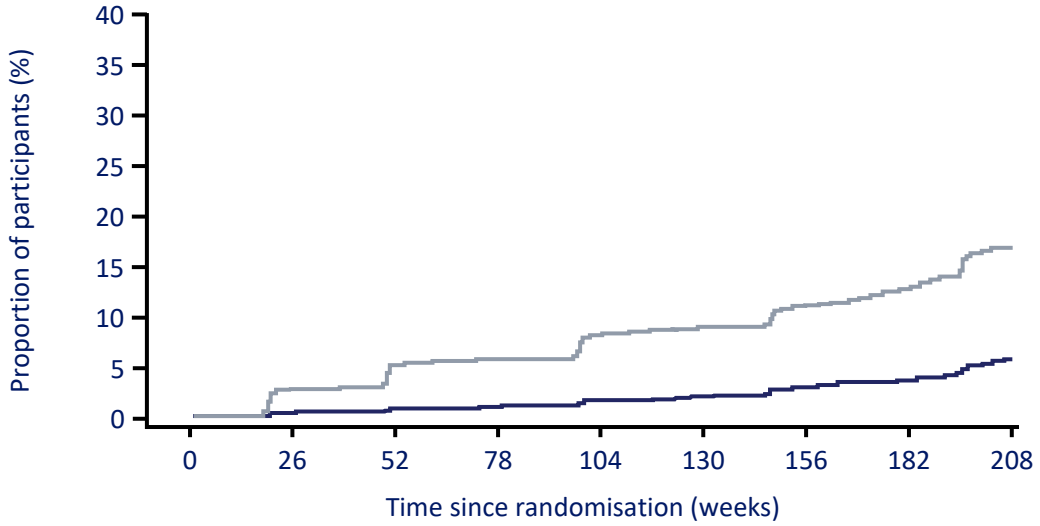
CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; MACE, major adverse cardiovascular events; MI, myocardial infarction; OW, once weekly; SoC, standard of care.

Available at: https://www.clinicaltrials.gov/ct2/show/NCT03574597 (accessed September 2022).
Design published in Ryan DH et al. Am Heart J 2020;229:61–9.

Cumulative incidence of diabetes over time

Participants with baseline HbA_{1c} <6.5%

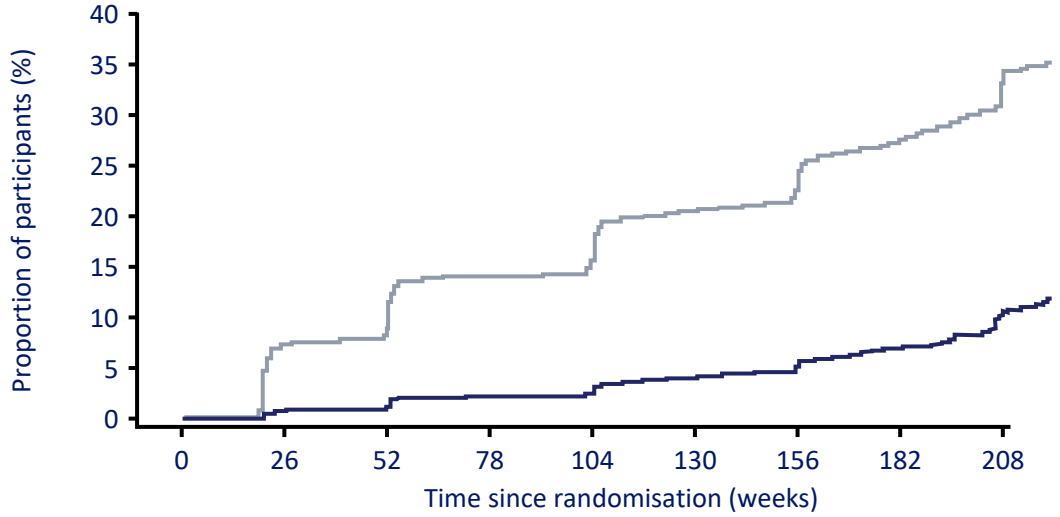
HR 0.27 (95% CI 0.24, 0.31)
p<0.0001



Sema 2.4 mg	8800	8713	8609	8494	8340	7312	5853	4210	1767
Placebo	8797	8487	8248	8050	7805	6792	5353	3789	1577

Participants with baseline HbA_{1c} 6.0% to <6.5%

HR 0.23 (95% CI 0.19, 0.26)
p<0.0001



Sema 2.4 mg	2809	2776	2728	2686	2629	2300	1799	1296	574
Placebo	2794	2568	2416	2311	2171	1857	1379	933	442

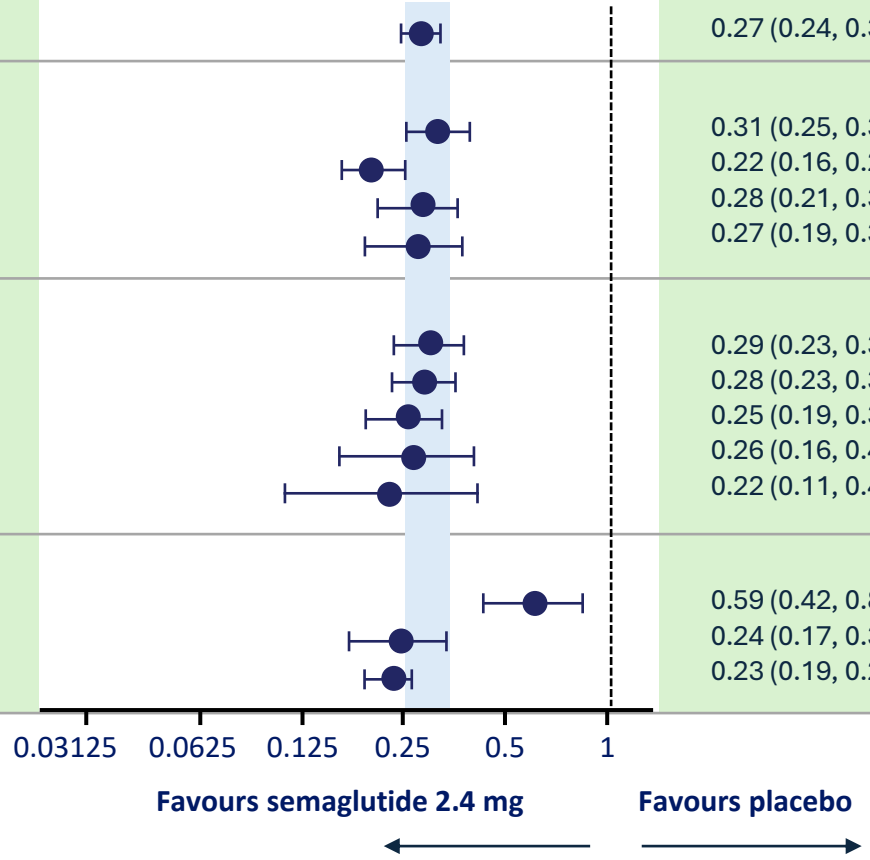
Semaglutide 2.4 mg **Placebo**

Diabetes defined as an HbA1c ≥6.5% (≥48 mmol/mol).
CI, confidence interval; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; sema, semaglutide.
Kahn SE, et al. Diabetes Care 2024. doi: 10.2337/dc24-0491.

Progression to diabetes

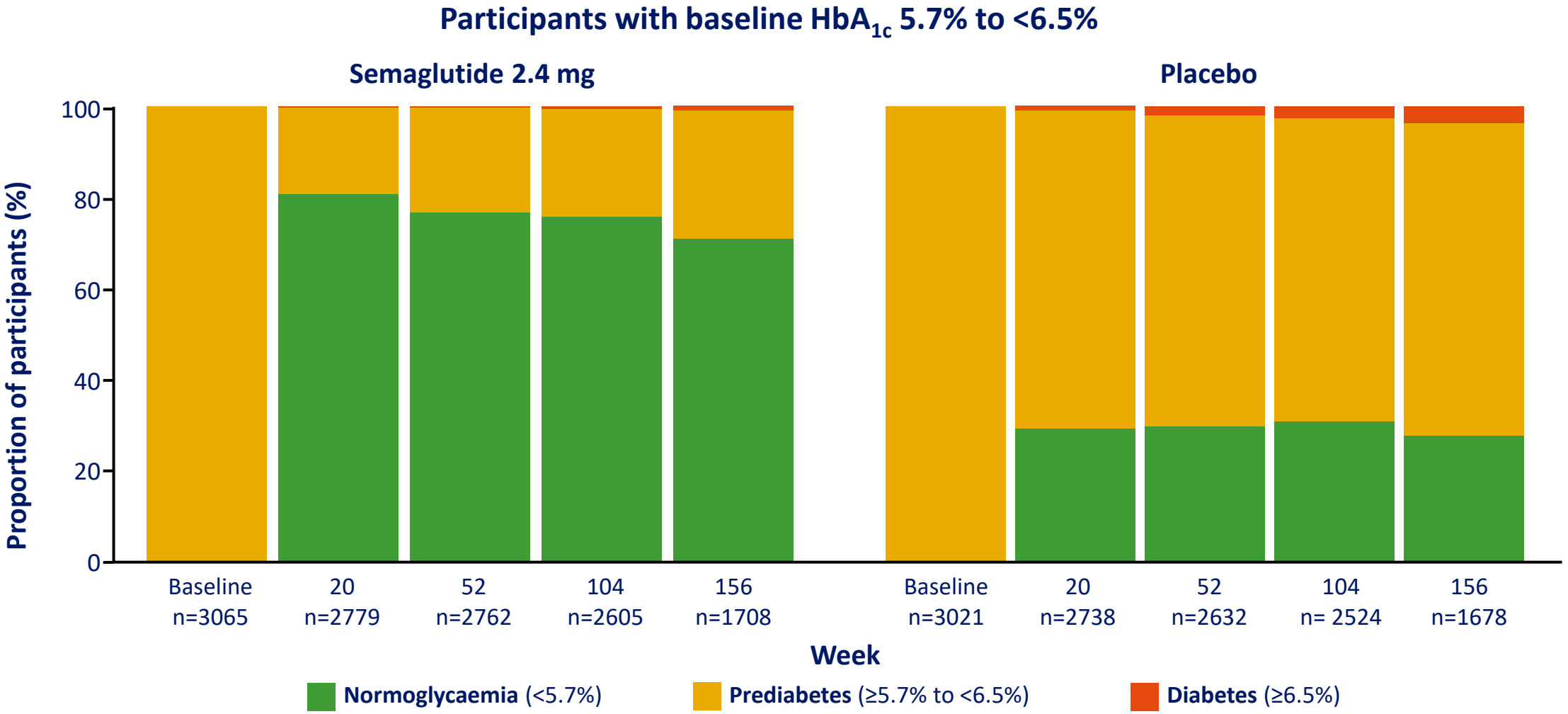
At week 156

	Semaglutide 2.4 mg Events / analyzed participants	Placebo Events / analyzed participants	Hazard ratio	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)	0.3038
≥90 to <100	55/2157	227/2048		0.22 (0.16, 0.29)	
≥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)	0.8397
≥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)	
≥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)	<0.0001
≥5.7 to <6.0	49/3065	196/3021		0.24 (0.17, 0.33)	
≥6.0	207/2809	778/2794		0.23 (0.19, 0.26)	



Diabetes defined as an HbA1c ≥6.5% (≥48 mmol/mol).
BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated haemoglobin; HR, hazard ratio.
Kahn SE, et al. Diabetes Care 2024. doi: 10.2337/dc24-0491. Supplementary Material

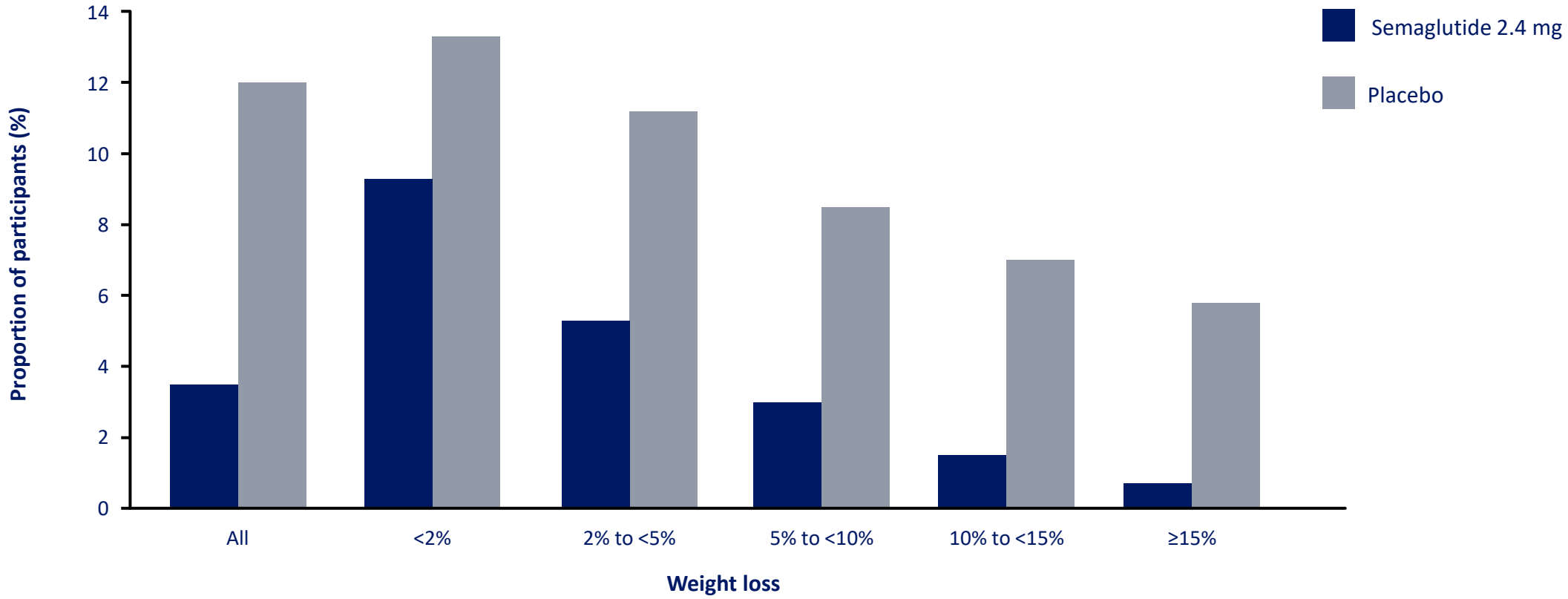
Change in glycaemic categories over time



Kahn SE, et al. Diabetes Care 2024. doi: 10.2337/dc24-0491.

Progression to diabetes by degree of weight loss

At 156 weeks



Semaglutide 2.4 mg	8799	1402	1173	2423	2002	1799
Placebo	8795	5687	1659	1060	286	103

Adapted from Kahn SE, et al. Diabetes Care 2024. doi: 10.2337/dc24-0491.

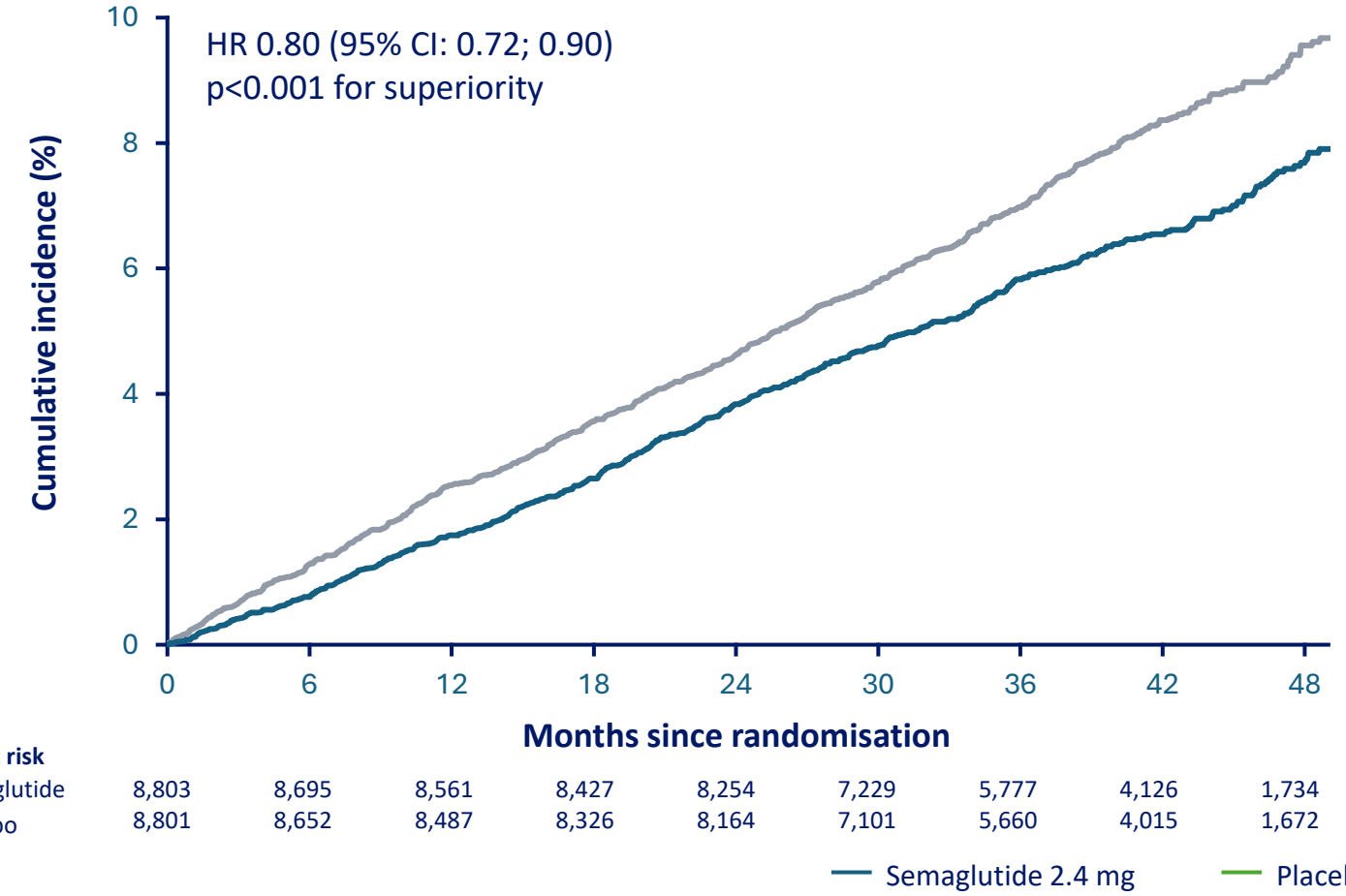
Mediation by body weight of time to regression and progression

At week 156

	Probability of no event at 156 weeks			Total effect (95% CI)	Direct effect (95% CI)	Percentage mediation (95% CI)
	Semaglutide 2.4 mg	Semaglutide 2.4 mg (adjusted)	Placebo			
Time to regression to normoglycaemia (HbA_{1c} <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)
Time to progression to diabetes (HbA_{1c} ≥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)

CI, confidence interval; K HbA_{1c}, glycated haemoglobin.
ahn SE, et al. Diabetes Care 2024. doi: 10.2337/dc24-0491. Supplementary Material

Cumulative incidence of MACE
SELECT: Primary cardiovascular composite endpoint



No. at risk									
Semaglutide	8,803	8,695	8,561	8,427	8,254	7,229	5,777	4,126	1,734
Placebo	8,801	8,652	8,487	8,326	8,164	7,101	5,660	4,015	1,672

Semaglutide 2.4 mg — Placebo

20%
reduction in risk of MACE*

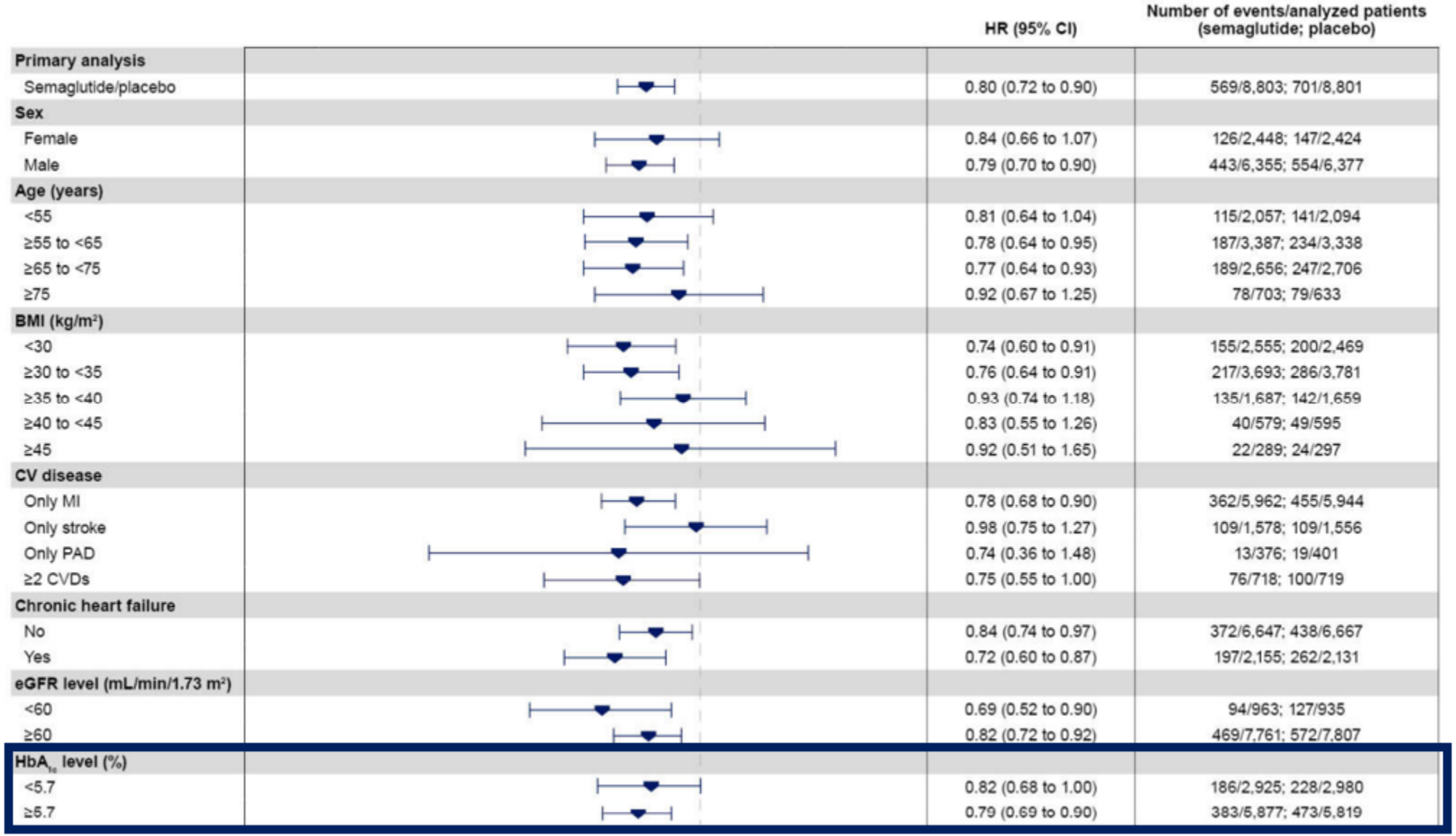
Semaglutide 2.4 mg significantly reduced
the risk of MACE by 20%
compared with placebo in people with obesity and established CVD, without T2D[1,2]

All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

Mean follow-up time was 39.8 months

Cumulative incidence (using the Aalen–Johansen method) of the composite MACE primary endpoint. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with MACE was 6.5% with semaglutide 2.4 mg and 8.0% with placebo. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.
1. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. American College of Cardiology, SELECT: Semaglutide Reduces Risk of MACE in Adults With Overweight or Obesity, Accessed October 2023, https://www.acc.org/Latest-in-Cardiology/Articles/2023/08/10/14/29/SELECT-Semaglutide-Reduces-Risk-of-MACE-in-Adults-With-Overweight-or-Obesity

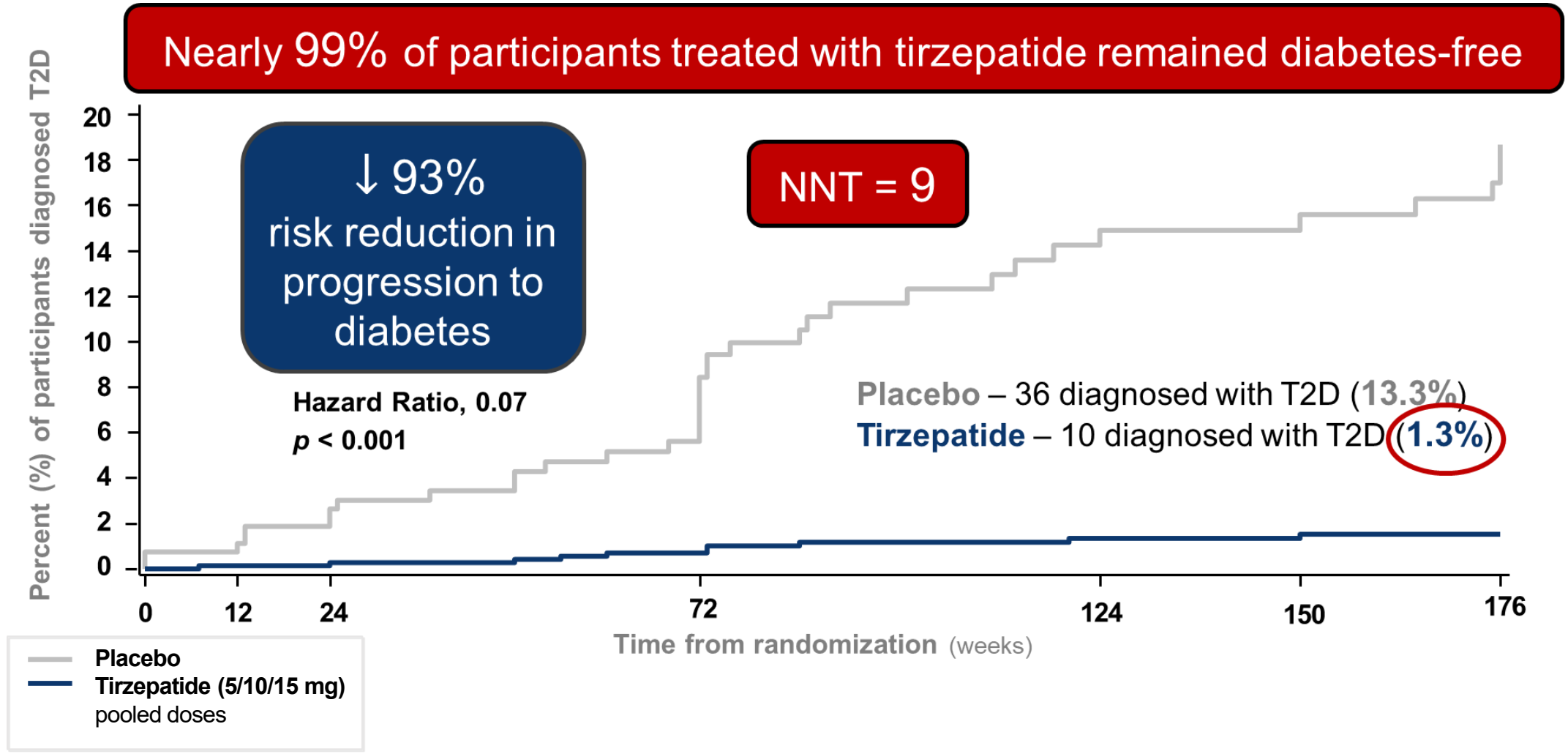
MACE in SELECT Trial



	HR (95% CI)	Number of events/analyzed patients (semaglutide; placebo)
Primary analysis		
Semaglutide/placebo	0.80 (0.72 to 0.90)	569/8,803; 701/8,801
Sex		
Female	0.84 (0.66 to 1.07)	126/2,448; 147/2,424
Male	0.79 (0.70 to 0.90)	443/6,355; 554/6,377
Age (years)		
<55	0.81 (0.64 to 1.04)	115/2,057; 141/2,094
≥55 to <65	0.78 (0.64 to 0.95)	187/3,387; 234/3,338
≥65 to <75	0.77 (0.64 to 0.93)	189/2,656; 247/2,706
≥75	0.92 (0.67 to 1.25)	78/703; 79/633
BMI (kg/m²)		
<30	0.74 (0.60 to 0.91)	155/2,555; 200/2,469
≥30 to <35	0.76 (0.64 to 0.91)	217/3,693; 286/3,781
≥35 to <40	0.93 (0.74 to 1.18)	135/1,687; 142/1,659
≥40 to <45	0.83 (0.55 to 1.26)	40/579; 49/595
≥45	0.92 (0.51 to 1.65)	22/289; 24/297
CV disease		
Only MI	0.78 (0.68 to 0.90)	362/5,962; 455/5,944
Only stroke	0.98 (0.75 to 1.27)	109/1,578; 109/1,556
Only PAD	0.74 (0.36 to 1.48)	13/376; 19/401
≥2 CVDs	0.75 (0.55 to 1.00)	76/718; 100/719
Chronic heart failure		
No	0.84 (0.74 to 0.97)	372/6,647; 438/6,667
Yes	0.72 (0.60 to 0.87)	197/2,155; 262/2,131
eGFR level (mL/min/1.73 m²)		
<60	0.69 (0.52 to 0.90)	94/963; 127/935
≥60	0.82 (0.72 to 0.92)	469/7,761; 572/7,807
HbA_{1c} level (%)		
<5.7	0.82 (0.68 to 1.00)	186/2,925; 228/2,980
≥5.7	0.79 (0.69 to 0.90)	383/5,877; 473/5,819

Dual Agonist-Tirzepatide

SURMOUNT-1 Proportion of participants diagnosed with T2D over time (pooled tirzepatide doses)



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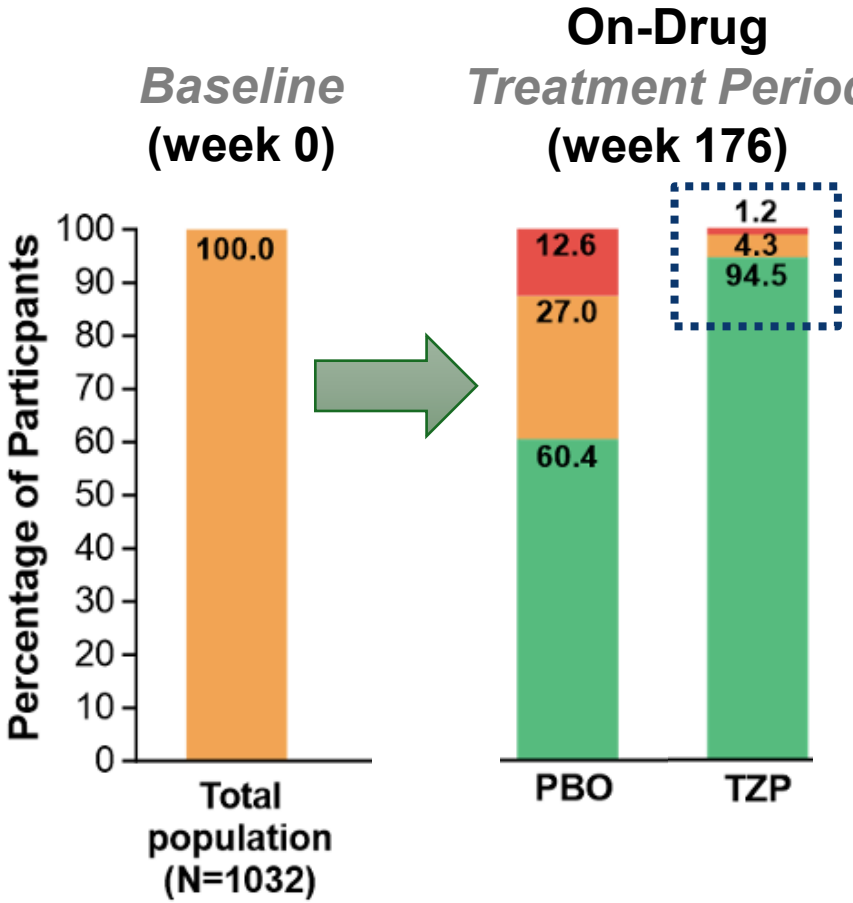
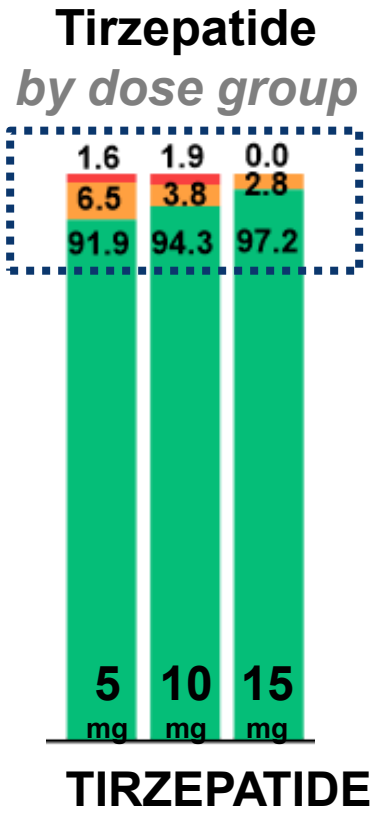
Changes in Glycemic Status at week 176

Normoglycemia
Prediabetes
Type 2 diabetes

On Treatment
Efficacy Estimand



Reversion to normoglycemia was demonstrated in nearly 95% of those who received tirzepatide vs. 60% of those who received placebo



with **15 mg** dose

no participants developed diabetes and 97% reverted from prediabetes to normoglycemia

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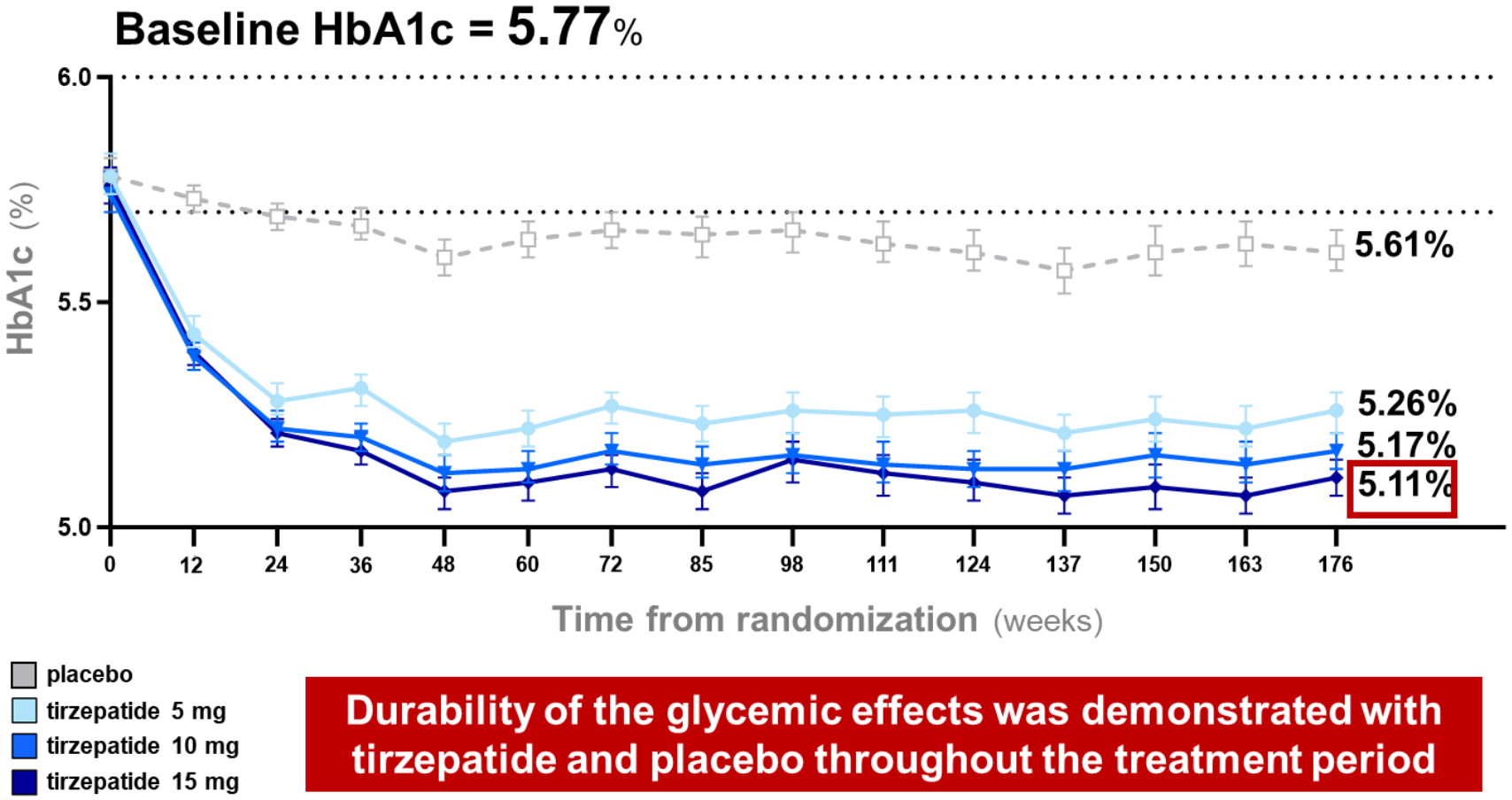
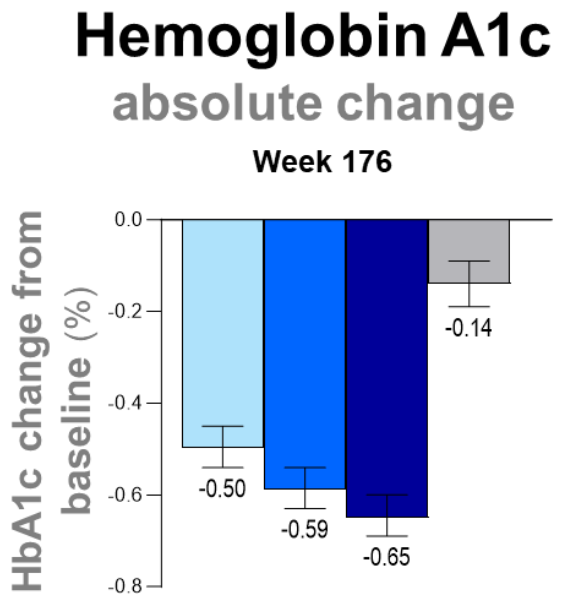
HbA1c: change over 176 weeks

On Treatment
Efficacy Estimand



Durability of the glycemic effects was demonstrated with tirzepatide and placebo throughout the treatment period



Decrease in HbA1c up to 0.65%

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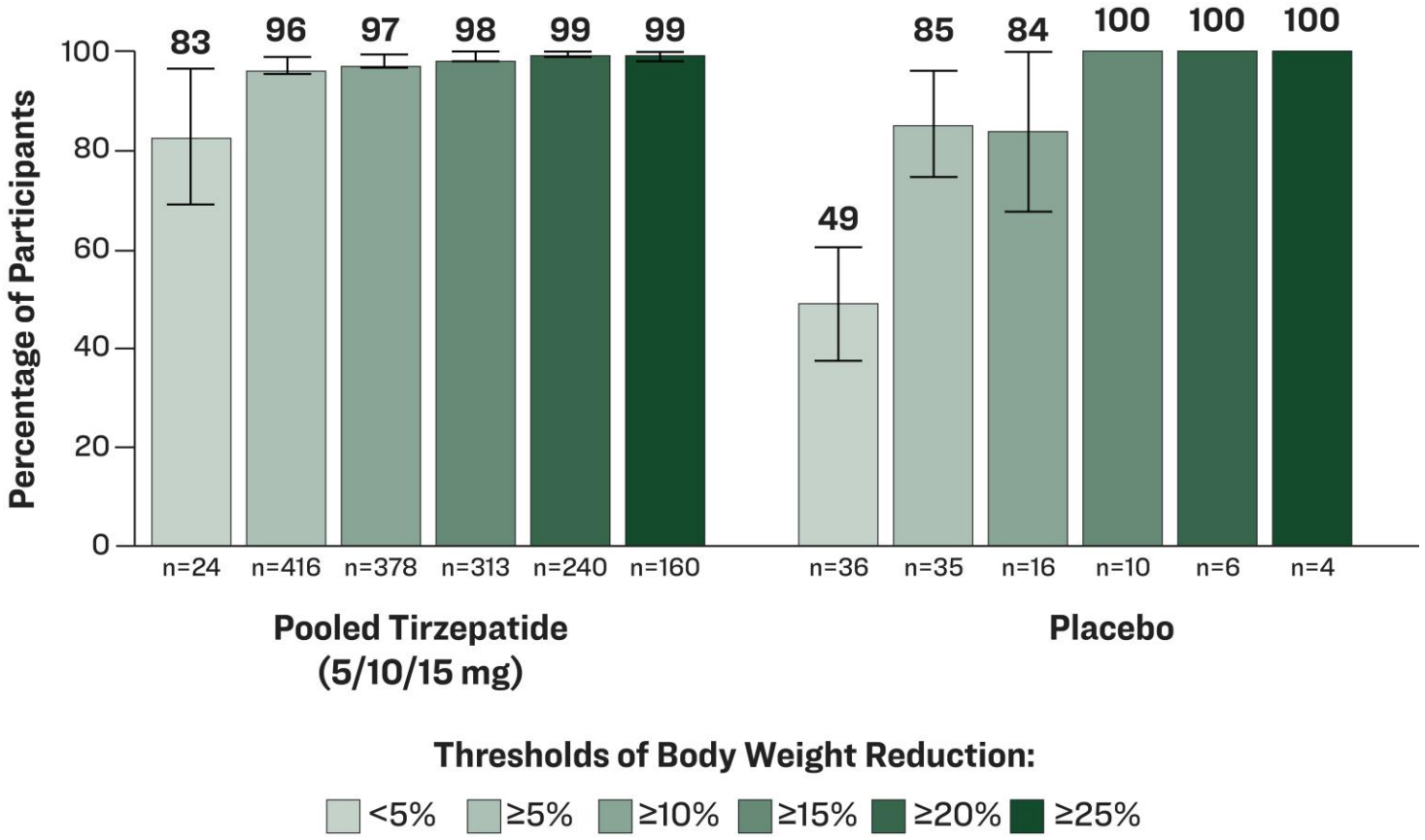
SURMOUNT-1 Three-Year Study

- Proportion of Participants Achieving Normoglycemia by Body Weight-Reduction Thresholds at Week 176



Efficacy Estimand

Note: Error bars indicate 95% confidence interval. The <5% weight-reduction subgroup included participants who gained body weight or lost <5% during the 176-week treatment period. Not tested under a type 1 error–control procedure. Only participants with non-missing weight measures at Week 176 were included in the analysis.
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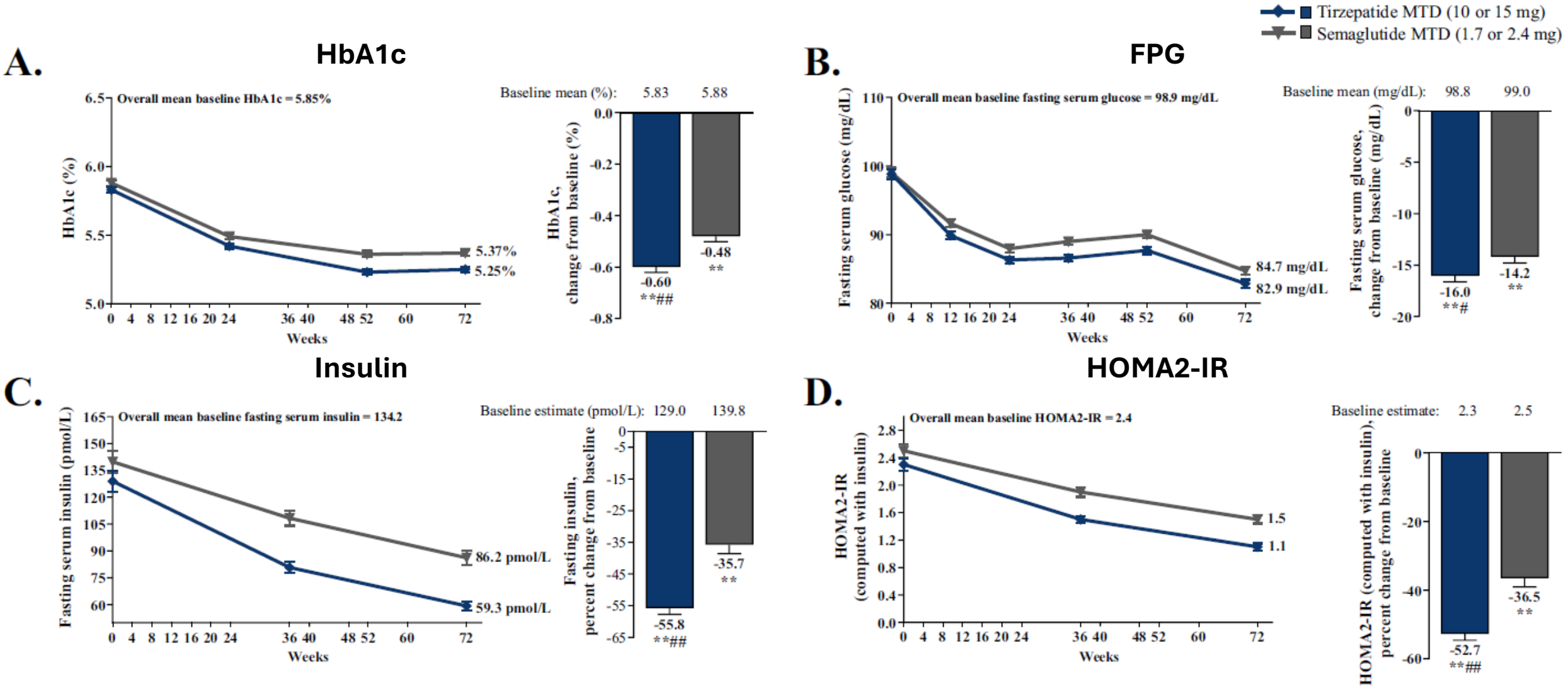
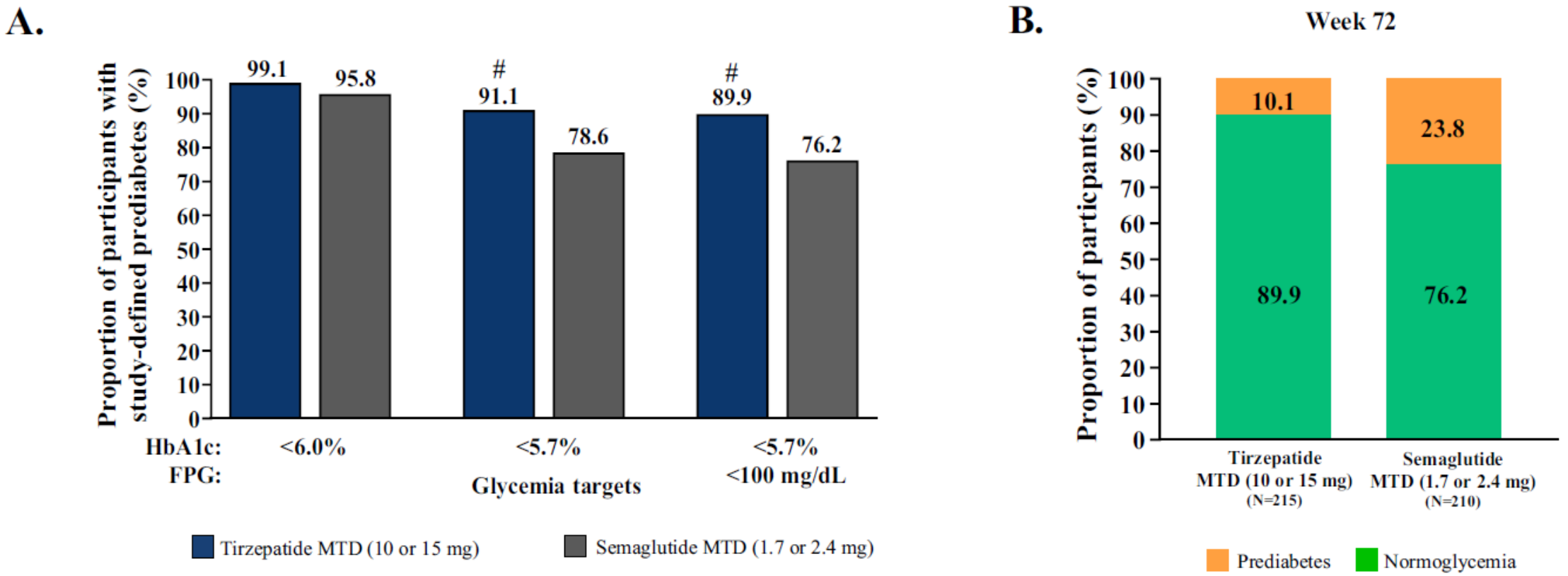
Direct Comparison – SURMOUNT 5



Galindo RJ JEI 2026

Direct Comparison – SURMOUNT 5



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Grazie dell’attenzione