Traitement médicamenteux de l'obésité et effets cardiovasculaires

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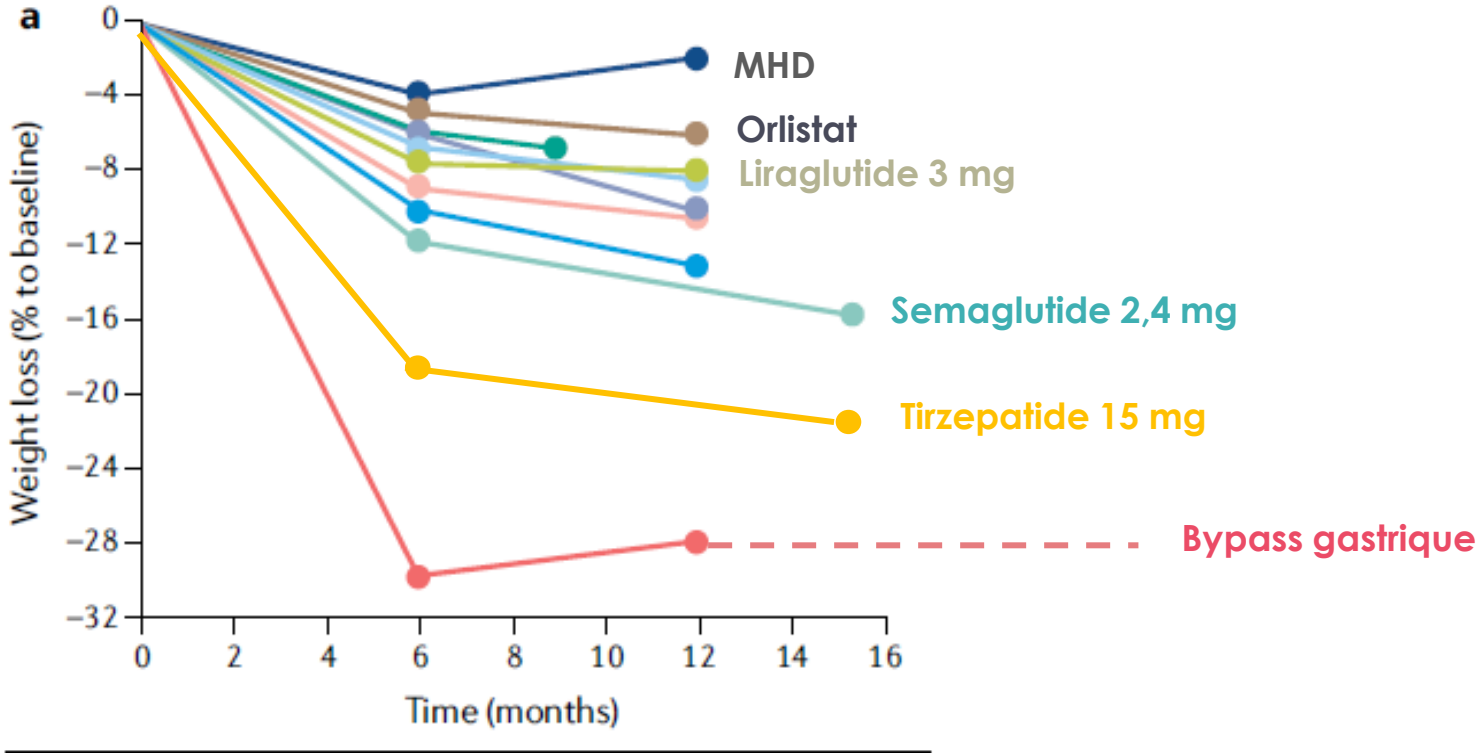
Conflits d’intérêts

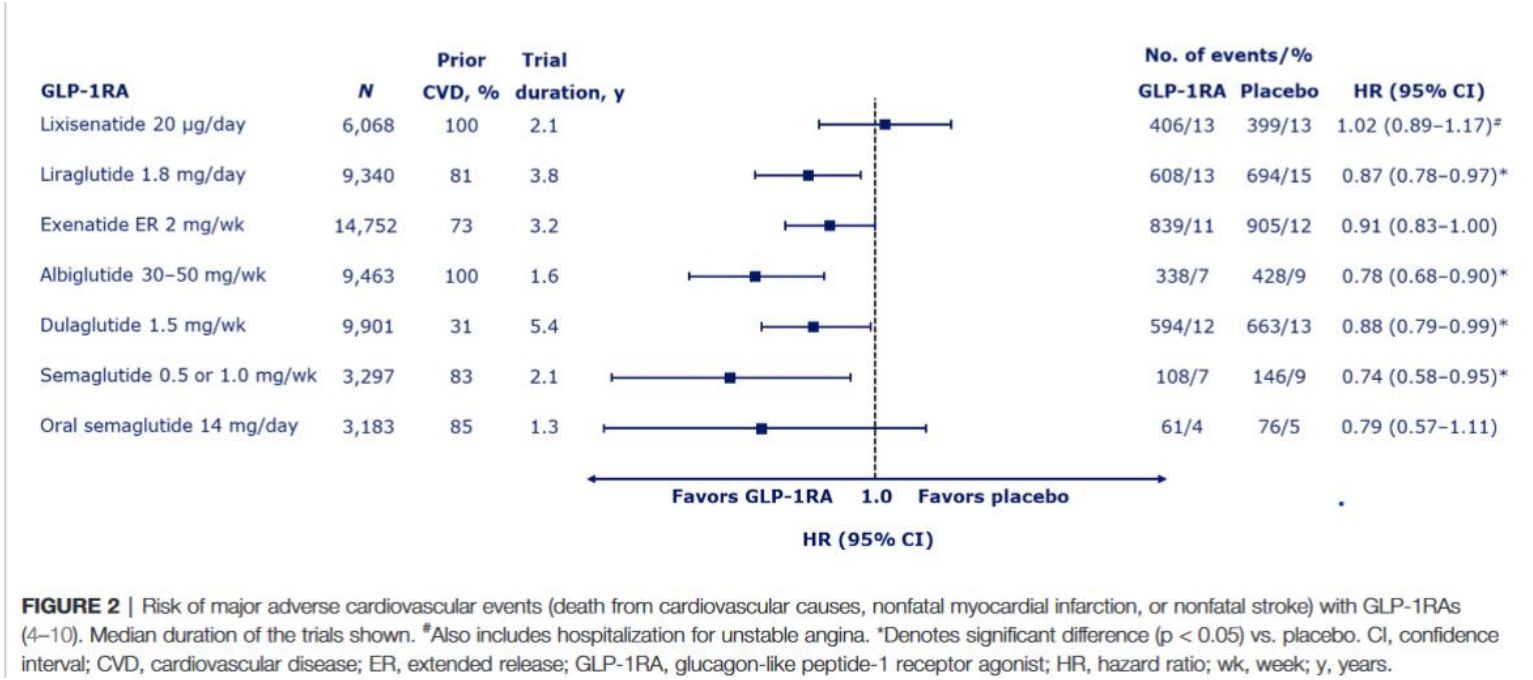
- Rémunérations : Boehringer Ingelheim, Axis Santé, Pfizer, Bioprojet Pharma, Novo Nordisk, AstraZeneca, Novartis, Ipsen, MSD, Eli Lilly et Publicis Health
- Hospitalités/formations : Rhythm, Novo Nordisk, MSD, Novartis, Eli Lilly, Sanofi, AstraZeneca, Bristol-Myers Squibb, Abbott, Amgen, Vifor et Fresenius Kabi

Le renouveau des médicaments anti-obésité



Adapted from Müller et al., Nature Reviews 2021

Bénéfice CV des analogues du GLP1 dans la population diabétique



GLP-1RA	N	Prior CVD, %	Trial duration, y	No. of events/% GLP-1RA	No. of events/% Placebo	HR (95% CI)
Lixisenatide 20 µg/day	6,068	100	2.1	406/13	399/13	1.02 (0.89–1.17)#
Liraglutide 1.8 mg/day	9,340	81	3.8	608/13	694/15	0.87 (0.78–0.97)*
Exenatide ER 2 mg/wk	14,752	73	3.2	839/11	905/12	0.91 (0.83–1.00)
Albiglutide 30–50 mg/wk	9,463	100	1.6	338/7	428/9	0.78 (0.68–0.90)*
Dulaglutide 1.5 mg/wk	9,901	31	5.4	594/12	663/13	0.88 (0.79–0.99)*
Semaglutide 0.5 or 1.0 mg/wk	3,297	83	2.1	108/7	146/9	0.74 (0.58–0.95)*
Oral semaglutide 14 mg/day	3,183	85	1.3	61/4	76/5	0.79 (0.57–1.11)

FIGURE 2 | Risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) with GLP-1RAs (4–10). Median duration of the trials shown. #Also includes hospitalization for unstable angina. *Denotes significant difference ($p < 0.05$) vs. placebo. CI, confidence interval; CVD, cardiovascular disease; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; wk, week; y, years.

Nauck et al, Front Endoc 2023

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

nature medicine

Article https://doi.org/10.1038/s41591-023-02526-x

Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial

Caractéristiques des participants à l'inclusion

Characteristic	Semaglutide (N = 263)	Placebo (N = 266)	Total (N = 529)
Female sex — no. (%)	149 (56.7)	148 (55.6)	297 (56.1)
Median age (IQR) — yr	70 (62–75)	69 (62–75)	69 (62–75)
Ethnic group — no. (%)†			
Hispanic or Latino	15 (5.7)	21 (7.9)	36 (6.8)
Not Hispanic or Latino	248 (94.3)	245 (92.1)	493 (93.2)
Race — no. (%)†			
Black	8 (3.0)	13 (4.9)	21 (4.0)
White	255 (97.0)	252 (94.7)	507 (95.8)
Other	0	1 (0.4)	1 (0.2)
Median body weight (IQR) — kg	104.7 (92.4–120.1)	105.3 (92.4–122.0)	105.1 (92.4–120.8)
Median BMI (IQR)	37.2 (33.9–41.1)	36.9 (33.3–41.6)	37.0 (33.7–41.4)
BMI stratum — no. (%)			
30 to <35	89 (33.8)	91 (34.2)	180 (34.0)
≥35	174 (66.2)	175 (65.8)	349 (66.0)
Median waist circumference (IQR) — cm	119.0 (110.5–127.1)	120.0 (110.5–129.0)	119.4 (110.5–128.0)
Median systolic blood pressure (IQR) — mm Hg	133 (122–145)	132 (120–142)	133 (121–144)
Median NT-proBNP level (IQR) — pg/ml	414.4 (229.2–1014.0)	499.8 (204.7–1025.0)	450.8 (218.2–1015.0)
Median CRP level (IQR) — mg/liter	3.8 (1.9–7.0)	3.9 (2.0–8.4)	3.8 (1.9–7.7)
Median LVEF (IQR) — %	57.0 (50.0–60.0)	57.0 (50.0–60.0)	57.0 (50.0–60.0)
LVEF stratum — no. (%)			
45 to <50%‡	37 (14.1)	48 (18.0)	85 (16.1)
50 to 59%	113 (43.0)	102 (38.3)	215 (40.6)
≥60%	113 (43.0)	116 (43.6)	229 (43.3)
Median KCCQ-CSS (IQR) — points§	59.4 (42.7–72.9)	58.3 (40.5–72.9)	58.9 (41.7–72.9)
Median 6-minute walk distance (IQR) — m	316.0 (251.0–386.0)	325.8 (232.4–392.0)	320.0 (240.0–389.0)
Hospitalization for heart failure within 1 year — no. (%)	42 (16.0)	39 (14.7)	81 (15.3)
Coexisting conditions at screening — no. (%)			
Atrial fibrillation	135 (51.3)	140 (52.6)	275 (52.0)
Hypertension	216 (82.1)	217 (81.6)	433 (81.9)
Coronary artery disease	53 (20.2)	45 (16.9)	98 (18.5)
NYHA functional class — no. (%)			
II	183 (69.6)	167 (62.8)	350 (66.2)
III or IV	80 (30.4)	99 (37.2)	179 (33.8)

Koziborod et al. NEJM 2023

Résultats

Table 2. Efficacy End Points.*

End Point	Semaglutide (N=263)	Placebo (N=266)	Estimated Difference or Ratio (95% CI)	P Value
Dual primary end points				
Change in KCCQ-CSS from baseline to week 52 — points	16.6	8.7	7.8 (4.8 to 10.9)†	<0.001
Percentage change in body weight from baseline to week 52	–13.3	–2.6	–10.7 (–11.9 to –9.4)†	<0.001
Confirmatory secondary end points				
Change from baseline to week 52 in 6-minute walk distance — m	21.5	1.2	20.3 (8.6 to 32.1)†	<0.001
Change from baseline to week 52 in CRP level — %	–43.5	–7.3	0.61 (0.51 to 0.72) ‡§	<0.001
Hierarchical composite end point — crude percentage of wins¶	60.1	34.9	1.72 (1.37 to 2.15)‖	<0.001

CONCLUSIONS

In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo. (Funded by Novo Nordisk; STEP-HFpEF ClinicalTrials.gov number, NCT04788511.)

Koziborod et al. NEJM 2023

Effets indésirables

Table 3. Reportable Adverse Events during the Treatment Period.*

Adverse Event	Semaglutide (N = 263)			Placebo (N = 266)			P Value†
	no. of participants (%)	*no. of events*	*events/100 person-yr*	*no. of participants (%)*	*no. of events*	*events/100 person-yr*	
Serious adverse event	35 (13.3)	60	23.4	71 (26.7)	133	50.1	<0.001
Serious adverse event leading to discontinuation of semaglutide or placebo	6 (2.3)	7	2.7	6 (2.3)	7	2.6	—
Gastrointestinal disorder	1 (0.4)	1	0.4	1 (0.4)	1	0.4	—
Adverse events leading to discontinuation of semaglutide or placebo	35 (13.3)	47	18.4	14 (5.3)	17	6.4	—
Gastrointestinal disorder	25 (9.5)	33	12.9	7 (2.6)	9	3.4	—
Fatal event	3 (1.1)	3	1.2	4 (1.5)	5	1.9	—
Most frequent serious adverse events‡							—
Cardiac disorder	7 (2.7)	8	3.1	30 (11.3)	43	16.2	<0.001
Atrial fibrillation	3 (1.1)	3	1.2	9 (3.4)	12	4.5	—
Cardiac failure	0	0	0	12 (4.5)	13	4.9	—
Atrial flutter	0	0	0	3 (1.1)	5	1.9	—
Congestive cardiac failure	0	0	0	3 (1.1)	3	1.3	—

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

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*

- ✓ **17 604 adultes >45 ans**
- ✓ **Prévention secondaire**
- ✓ **IMC ≥ 27 kg/m²**
- ✓ **39,8 mois de suivi**

Exclusion: DT2, IC, IRT, CV<60j

Lincoff AM et al. NEJM 2023

Caractéristiques des participants à l'inclusion

Démographie

Male | Female

72.3 | 27.7%

Mean age

61.6 years

Asian|Black|White|Other

8.2 | 3.8 | 84.0 | 3.0%

Participants by CV inclusion criteria

MI only

67.6%

Stroke only

17.8%

PAD only

4.4%

≥2 CV inclusion criteria

8.2%

Number of enrolled participants differs from number reported in baseline publication (17,605) as one participant was randomised twice in error and subsequently removed for the primary analysis.
CV, cardiovascular; MI, myocardial infarction; PAD, peripheral arterial disease.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Caractéristiques des participants à l'inclusion

Mean HbA_{1c}[1]

5.8%

With prediabetes[1]

66.4%

Mean BMI[1]

33.3 kg/m²

Distribution (kg/m²)[1]
<30 | 30–<35 | 35–<40 | 40–<45 | ≥45

28.5 | 42.5 | 19.0 | 6.7 | 3.3%

Mean eGFR[2]

82.5 mL/min/1.73 m²

Chronic heart failure[1]

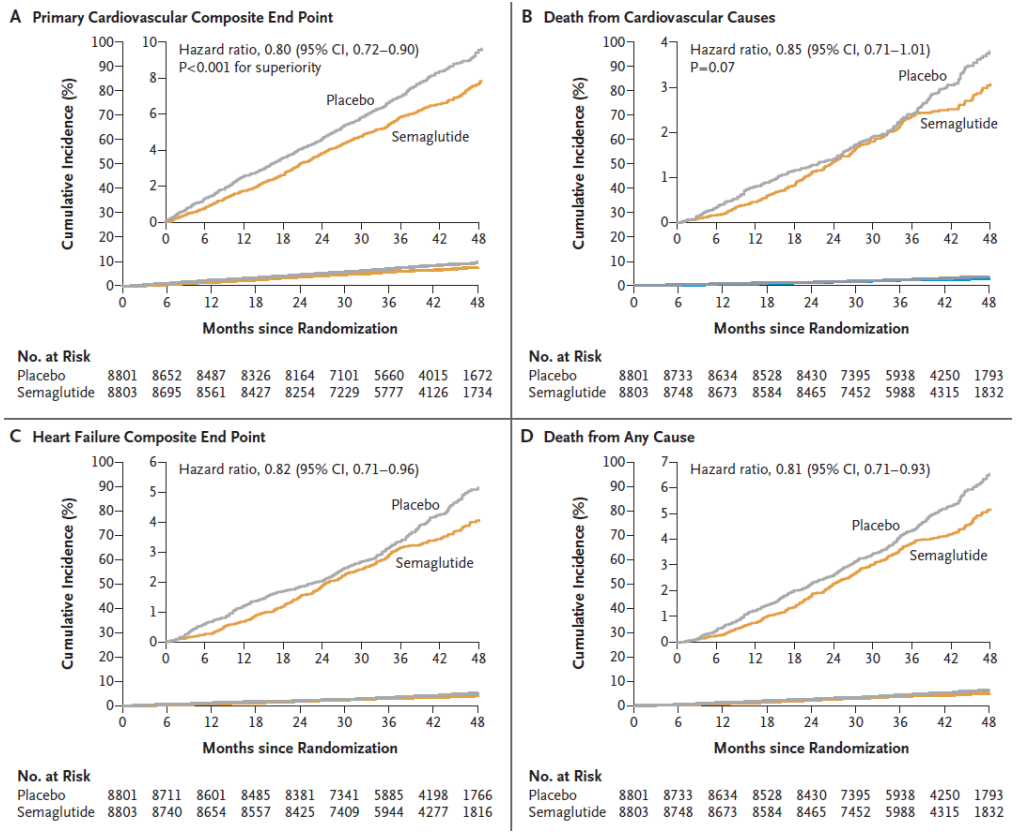
24.3%

Subclass[2]
HFpEF| HFrEF | Unknown

12.9 | 7.7 | 3.8

Number of enrolled participants differs from number reported in baseline publication (17,605) as one participant was randomised twice in error and subsequently removed for the primary analysis.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.
1. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. Novo Nordisk. Data on file.

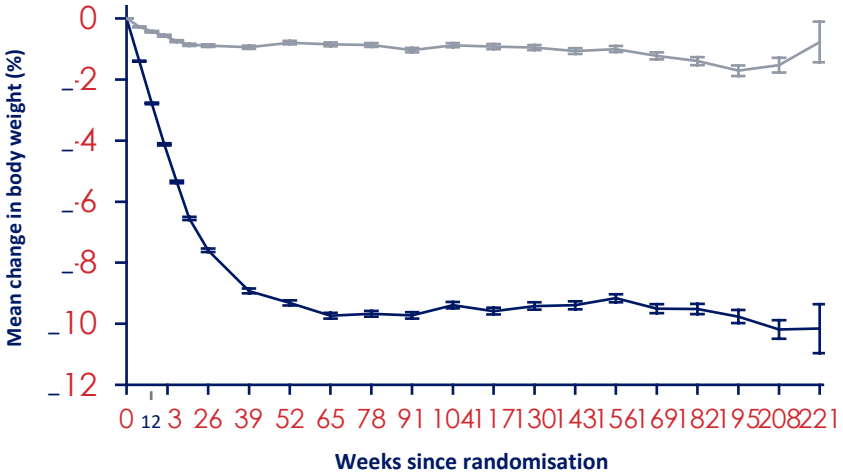
Résultats



Lincoff AM et al. NEJM 2023

Variation de poids (%)

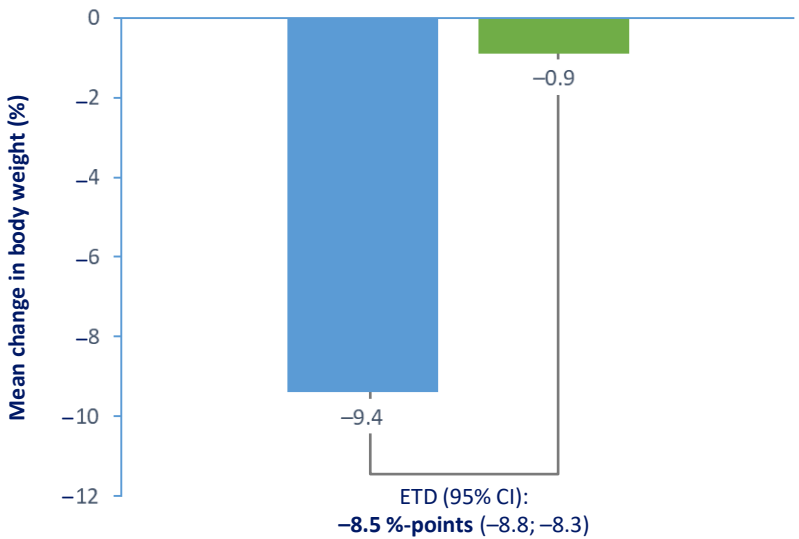
Mean baseline body weight, kg:
Semaglutide 2.4 mg: 96.5 Placebo: 96.8



No. of participants

Semaglutide	8,803	7,647	7,493	6,690	7,290	6,447	7,282	6,460	7,474	5,991	5,898	4,686	5,085	3,650	2,954	1,737	921	157
Placebo	8,801	7,715	7,516	6,704	7,269	6,340	7,272	6,392	7,378	5,871	5,879	4,583	5,014	3,560	2,890	1,698	898	152

Estimated change from baseline to week 104*



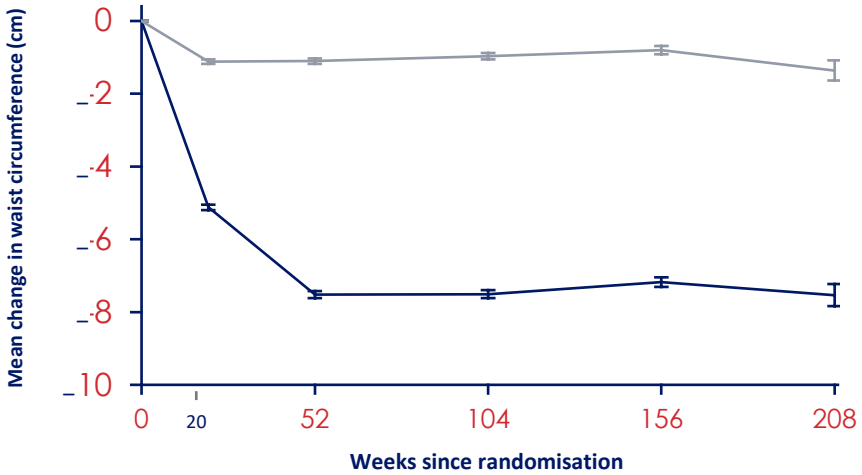
Semaglutide 2.4 mg Placebo

Error bars in the left-hand figure are 95% CI as calculated by 1.96 times the standard error. **Estimated using an ANCOVA with treatment as factor and the baseline value as covariate, using multiple imputation for missing values under a missing-at-random assumption. CIs have not been adjusted for multiplicity. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; SD, standard deviation.*
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Modification du tour de taille

Observed change from baseline over time

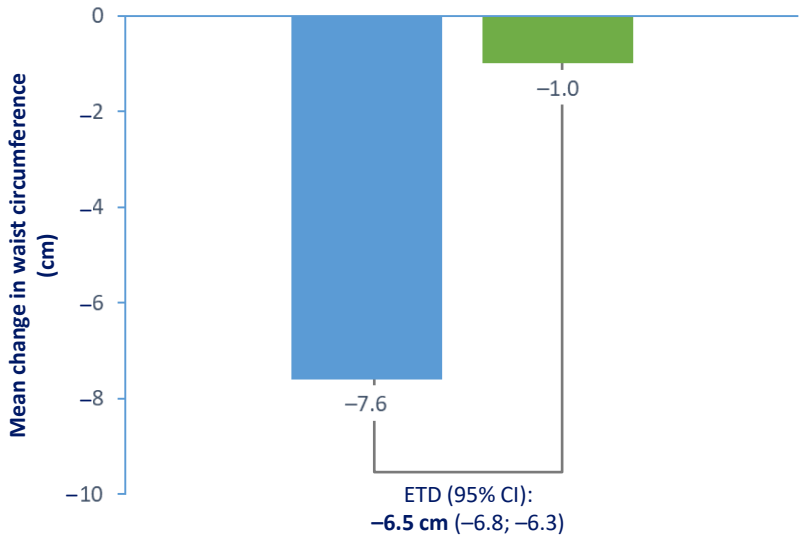
Mean (SD) baseline waist circumference, cm:
Semaglutide 2.4 mg: 111.3 (13.1) Placebo: 111.4 (13.1)



No. of participants

Semaglutide	8,759	7,507	7,193	7,373	5,013	912
Placebo	8,756	7,533	7,182	7,273	4,950	887

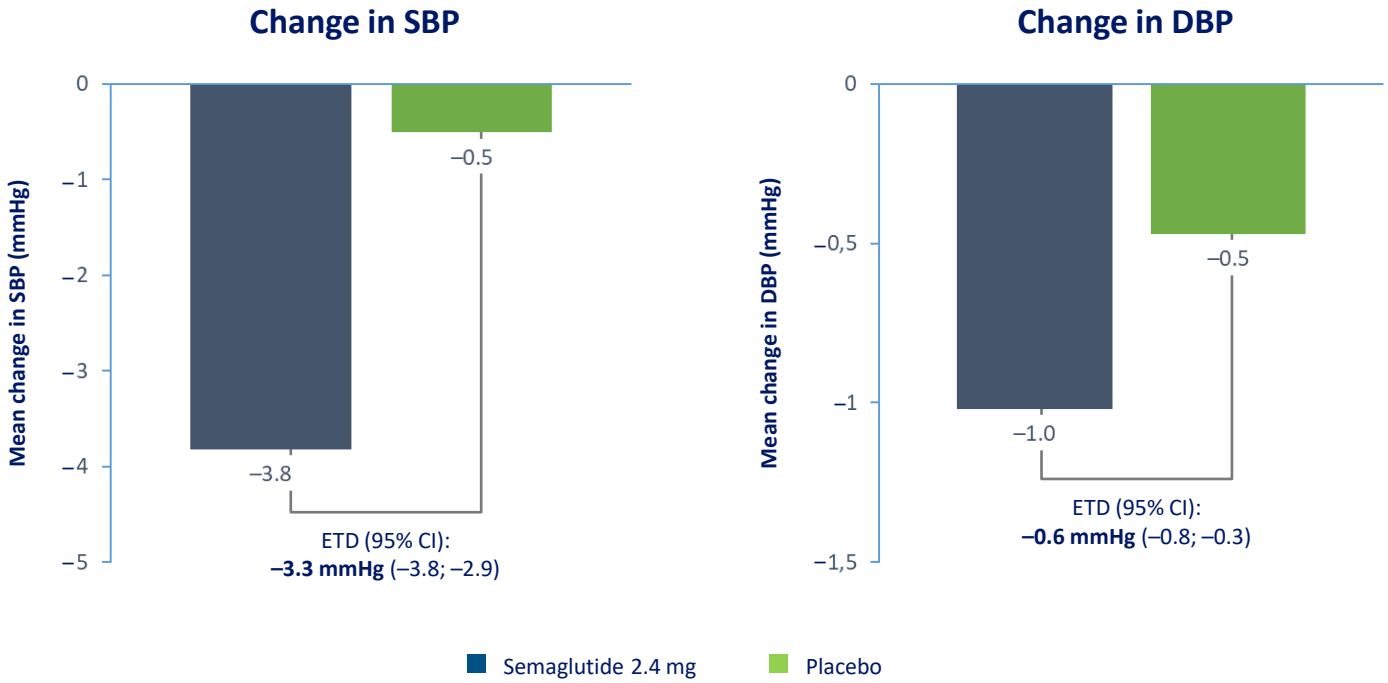
Estimated change from baseline to week 104*



Semaglutide 2.4 mg Placebo

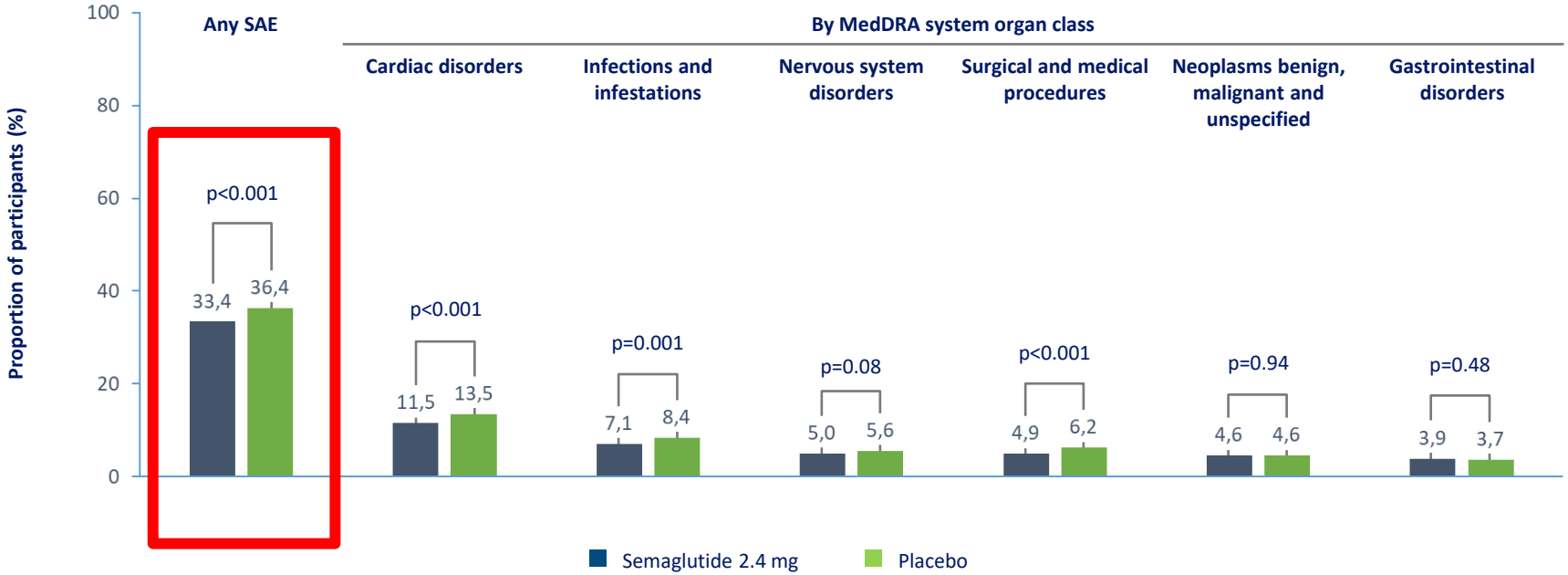
Error bars in the left-hand figure are 95% CI as calculated by 1.96 times the standard error. **Estimated using an ANCOVA with treatment as factor and the baseline value as covariate, using multiple imputation for missing values under a missing-at-random assumption. CIs have not been adjusted for multiplicity. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; SD, standard deviation.*
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Modification de la tension artérielle (mmHg)



Change from baseline to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.
ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic blood pressure.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Effets indésirables graves

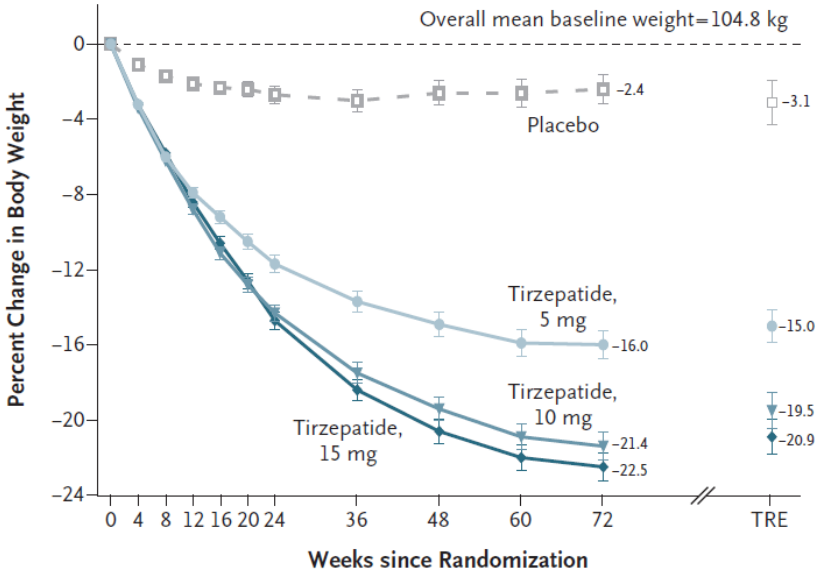


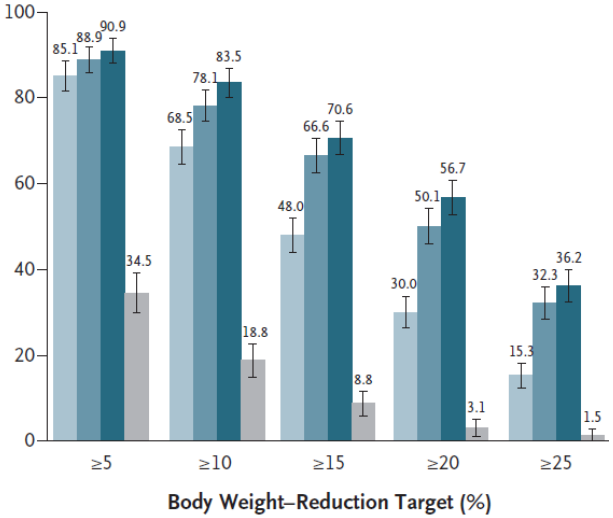
Two-sided p-values from Fisher's exact test for test of no difference.
MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

SURMOUNT-1

Tirzepatide Once Weekly for the Treatment of Obesity

- ✓ **N=2539, 72 semaines**
- ✓ **IMC>30 ou >27kg/m² avec fdr**
- ✓ **Non diabétiques**
- ✓ **IMC : 38 kg/m²**





Jastreboff et al, NEJM 2022

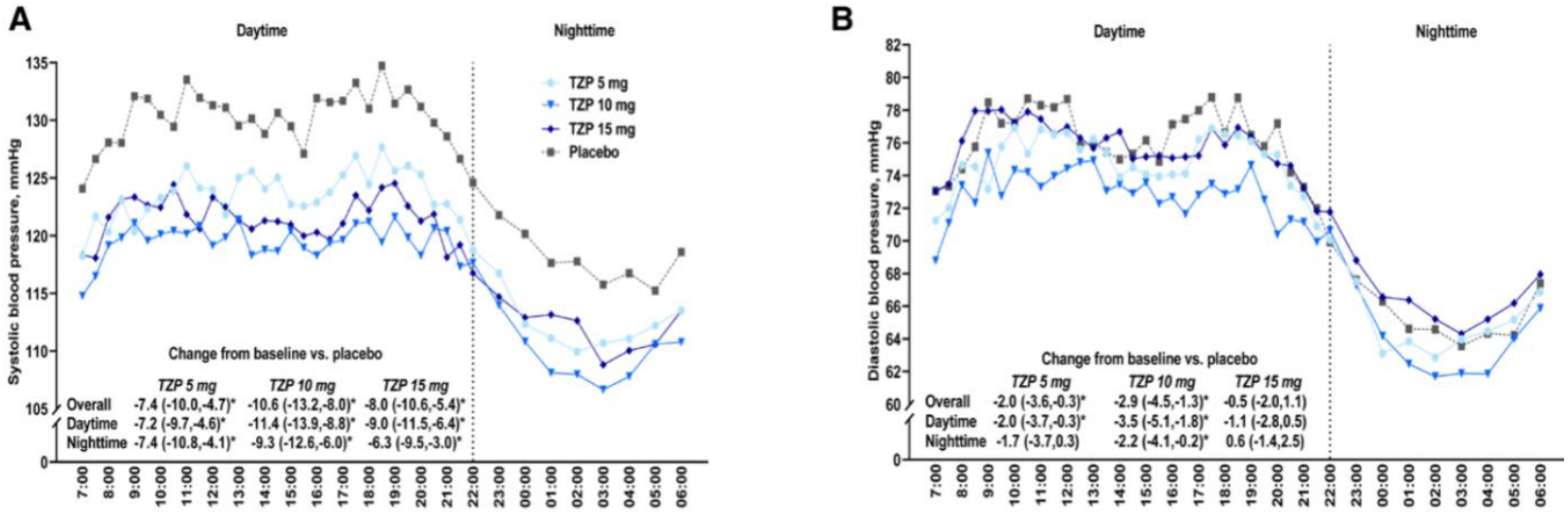
SURMOUNT-1 : analyse post hoc du score ASCVD

TABLE 2 Shift in atherosclerotic cardiovascular disease risk categories from baseline to weeks 24 and 72

Visit/time	Outcome	Observed proportion, n (%)		Odds ratio (vs. placebo)	
		Placebo	Pooled TZP	Estimate (95% CI)	*P* value
All participants					
Week 24	Improved	16 (2.9)	116 (6.9)	2.2 (1.6, 3.0)	<0.001
	Stable	495 (91.0)	1528 (90.7)		
	Worsened	33 (6.1)	41 (2.4)		
	Total, N	544	1685		
Week 72	Improved	14 (3.1)	111 (7.3)	2.4 (1.7, 3.5)	<0.001
	Stable	391 (87.9)	1336 (88.0)		
	Worsened	40 (9.0)	72 (4.7)		
	Total, N	445	1519		
Participants with intermediate-to-high risk at baseline					
Week 24	Improved	8 (13.3)	57 (31.5)	2.8 (1.4, 5.6)	0.003
	Stable	51 (85.0)	122 (67.4)		
	Worsened	1 (1.7)	2 (1.1)		
	Total, N	60	181		
Week 72	Improved	6 (12.8)	52 (31.9)	2.9 (1.3, 6.2)	0.008
	Stable	40 (85.1)	105 (64.4)		
	Worsened	1 (2.1)	6 (3.7)		
	Total, N	47	163		

Hankosky et al, Diab Obes Metab 2024

SURMOUNT-1 : mesure de la PA sur 24h ambulatoire dans une sous population (n=600)



De Lemos et al, Hypertension 2024

A Study of Tirzepatide (LY3298176) on the Reduction on.Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)

Study Overview

Brief Summary

This study will investigate the effect of tirzepatide on the reduction of morbidity and mortality in adults living with obesity and provide additional evidence for the potential clinical benefits of tirzepatide in this population.

Official Title

A Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Investigate the Effect of Tirzepatide on the Reduction of Morbidity and Mortality in Adults With Obesity

Conditions

Obesity | Overweight

Intervention / Treatment

- Drug: Tirzepatide
- Drug: Placebo

Other Study ID Numbers

Study Start (Actual)

2022-10-11

Primary Completion (Estimated)

2027-10-07

Study Completion (Estimated)

2027-10-07

Enrollment (Actual)

15374

Study Type

Interventional

Phase

Phase 3

Conclusion

- Bénéfice majeur au-delà du poids sur tous les FDR CV notamment la PAS avec le semaglutide (agoniste GLP1 R) et le tirzepatide (biagoniste GLP1 R + GIP R)
- Bénéfice CV démontré en prévention secondaire et dans l'IC à FE préservée avec le semaglutide
- Quid de l'IC à FE altérée ?