Alternatives à la chirurgie dans la prise en charge de l'obésité

Prof. Claire CARETTE
Service de Nutrition – Centre Spécialisé Obésité
Hôpital Européen George Pompidou
APHP.Centre - Université Paris Cité

Liens d’intérêt

- Hospitalité/formation : Rythm, NovoNordisk, MSD, Novartis, Lilly, Sanofi, AstraZeneca, Servier, BMS, Abbott, Amgen, Vifor, Vitalaire, Fresenius Kabi

- Rémunération : NovoNordisk, AstraZeneca, Novartis, MSD, Lilly, Servier, Baxter, Publicis Health

Options thérapeutiques alternatives à la chirurgie bariatrique

- ✓Modifications du mode de vie
- ✓Endoscopie bariatrique (sleeve endoscopique)
- ✓Pharmacothérapie

Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial

Lancet 2017; 389: 2214–25

Amy L Ahern, Graham M Wheeler, Paul Aveyard, Emma J Boyland, Jason C G Halford, Adrian P Mander, Jennifer Woolston, Ann M Thomson, Melina Tsiountsioura, Darren Cole, Bethan R Mead, Lisa Irvine, David Turner, Marc Suhrcke, Laura Pimpin, Lise Retat, Abbygail Jaccard, Laura Webber, Simon R Cohn, Susan A Jebb

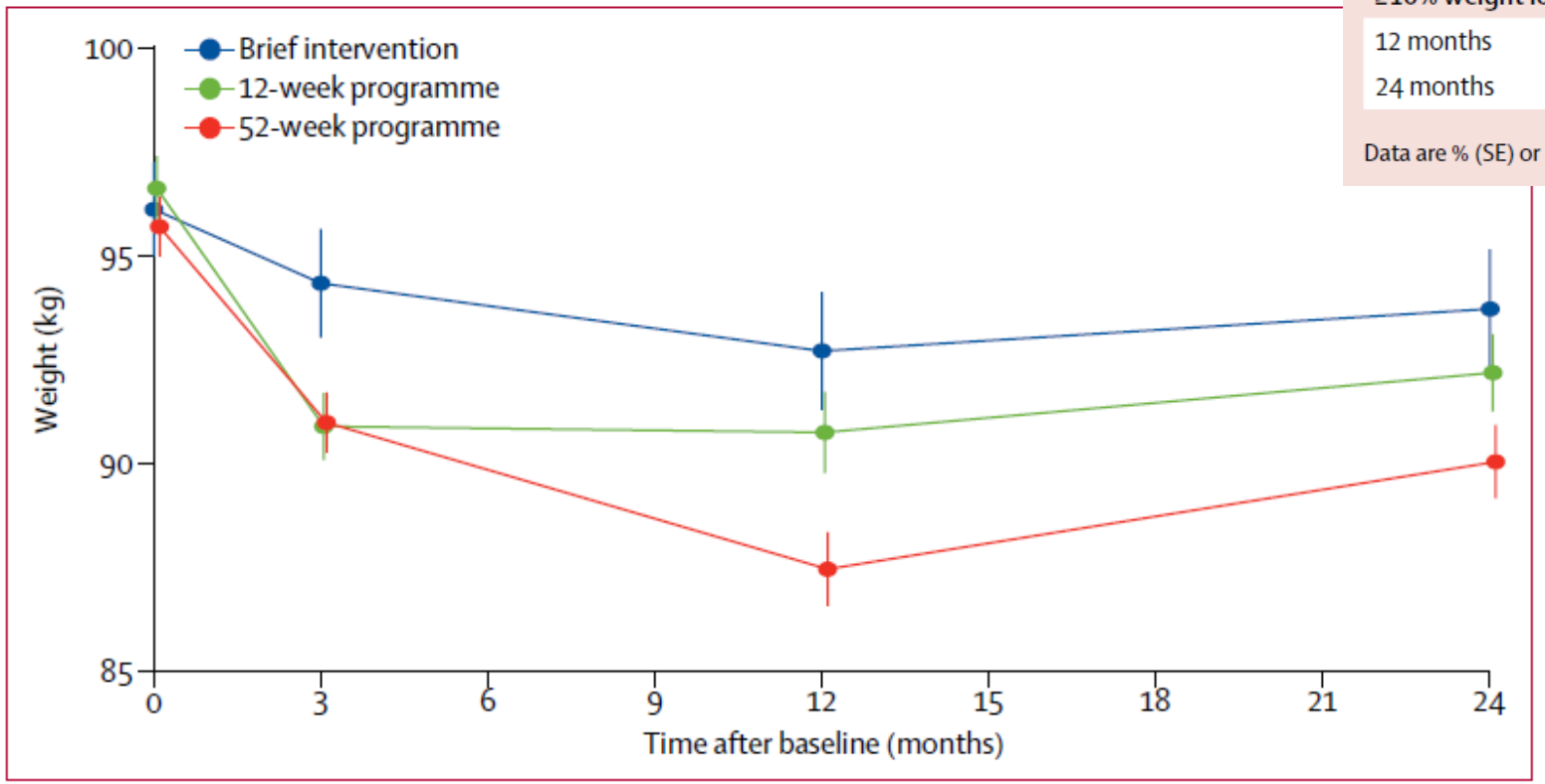


Figure 2: Bodyweight over 24 months of follow-up
Data are mean of all measured weights at each timepoint (SE).

	Proportion of participants losing at least 5% baseline weight		
	Brief intervention	12-week programme	52-week programme
≥5% weight loss			
12 months	25% (2·97)	42% (2·15)	57% (2·16)
24 months	22% (2·87)	27% (1·93)	39% (2·12)
≥10% weight loss			
12 months	9% (2·02)	15% (1·56)	30% (2·00)
24 months	9% (1·93)	12% (1·43)	18% (1·69)

Data are % (SE) or relative risk (95% CI).

RCT en soins primaires (UK)

- Conseils (N= 211)
- WW 12 semaines (n=528)
- WW 52 semaines (n=528)

Non aveugle

Suivi 2 ans

Interruptions (>30 %)

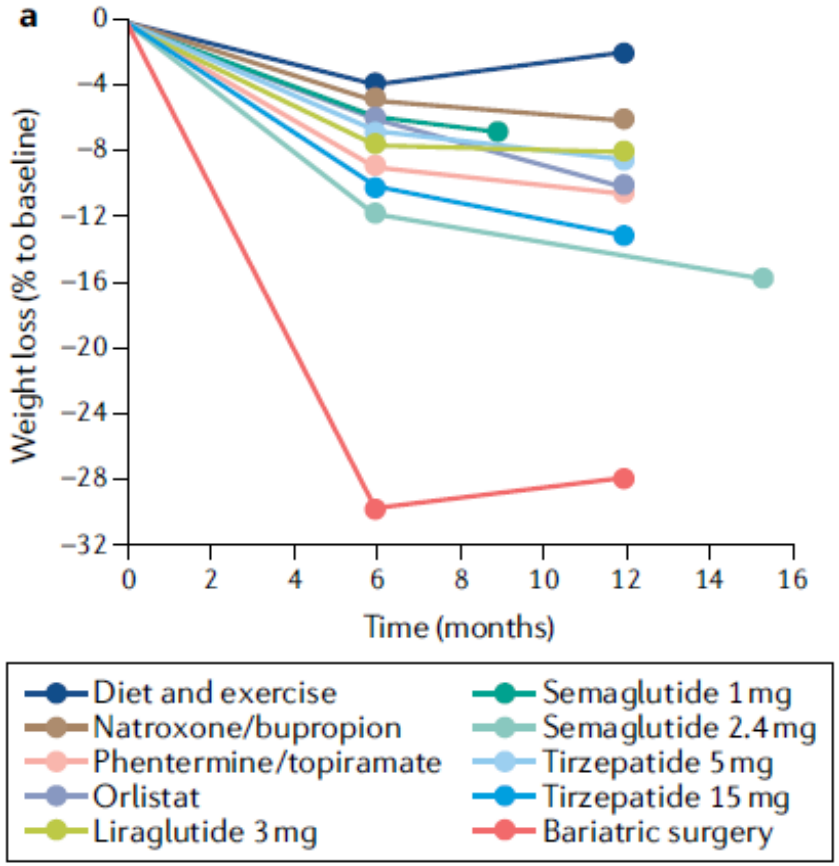
Amélioration des paramètres métaboliques (HbA1c, GAJ)

Les modifications du mode de vie

Component	Weight Loss	Weight-Loss Maintenance
Counseling	≥14 in-person counseling sessions (individual or group) with a trained interventionist during a 6-mo period; recommendations for similarly structured, comprehensive Web-based interventions, as well as evidence-based commercial programs	Monthly or more frequent in-person or telephone sessions for ≥1 yr with a trained interventionist
Diet	Low-calorie diet (typically 1200–1500 kcal per day for women and 1500–1800 kcal per day for men), with macronutrient composition based on patient's preferences and health status	Reduced-calorie diet, consistent with reduced body weight, with macronutrient composition based on patient's preferences and health status
Physical activity	≥150 min per week of aerobic activity (e.g., brisk walking)	200–300 min per week of aerobic activity (e.g., brisk walking)
Behavioral therapy	Daily monitoring of food intake and physical activity, facilitated by paper diaries or smart-phone applications; weekly monitoring of weight; structured curriculum of behavioral change (e.g., DPP), including goal setting, problem solving, and stimulus control; regular feedback and support from a trained interventionist	Occasional or frequent monitoring of food intake and physical activity, as needed; weekly-to-daily monitoring of weight; curriculum of behavioral change, including problem solving, cognitive restructuring, and relapse prevention; regular feedback from a trained interventionist

Heymsfield et al., NEJM 2017

Une place pour des techniques « mini-invasives » ?

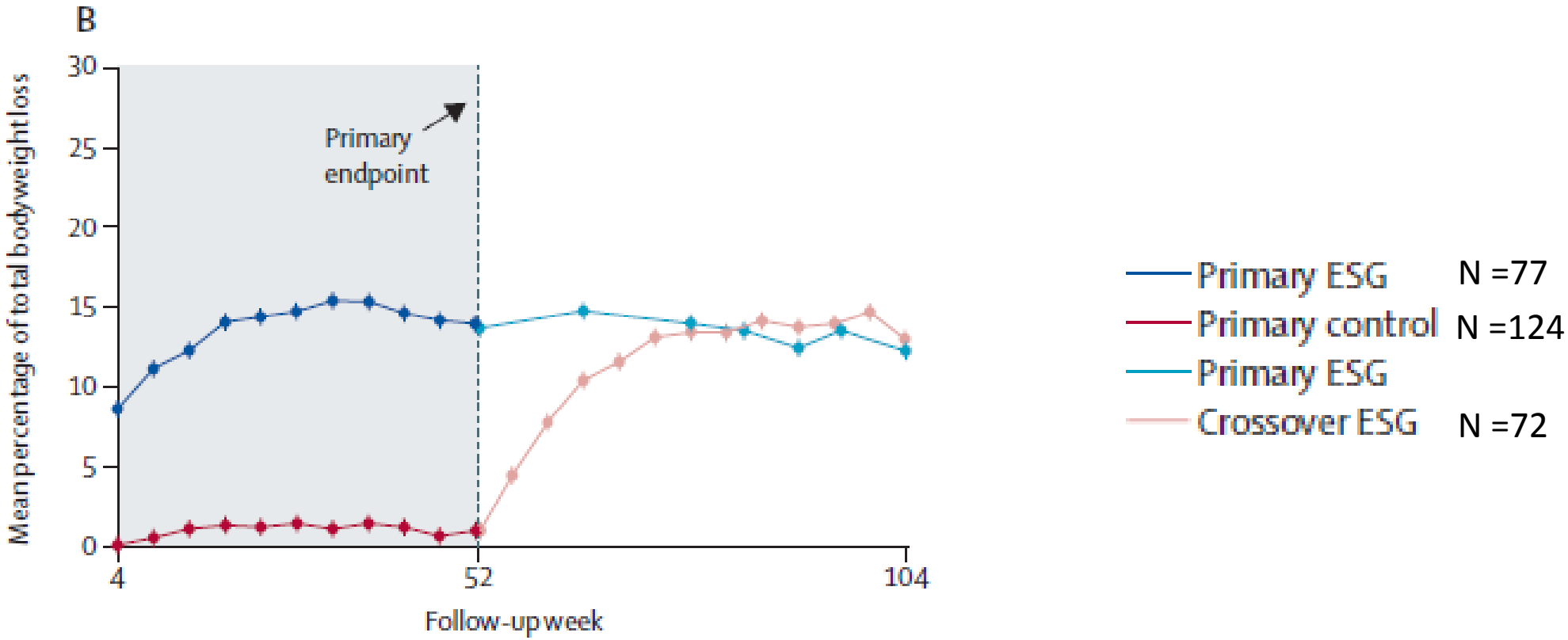


Müller et al., Nature Reviews 2021

Endoscopic sleeve gastroplasty for treatment of class 1 and 2 obesity (MERIT): a prospective, multicentre, randomised trial

Lancet 2022; 400: 441–51

Barham K Abu Dayyeh, Fateh Bazerbachi, Eric J Vargas, Reem Z Sharaiha, Christopher C Thompson, Bradley C Thaemert, Andre F Teixeira, Christopher G Chapman, Vivek Kumbhari, Michael B Ujiki, Jeanette Ahrens, Courtney Day, the MERIT Study Group, Manoel Galvao Neto, Natan Zundel, Erik B Wilson



Amélioration des paramètres métaboliques

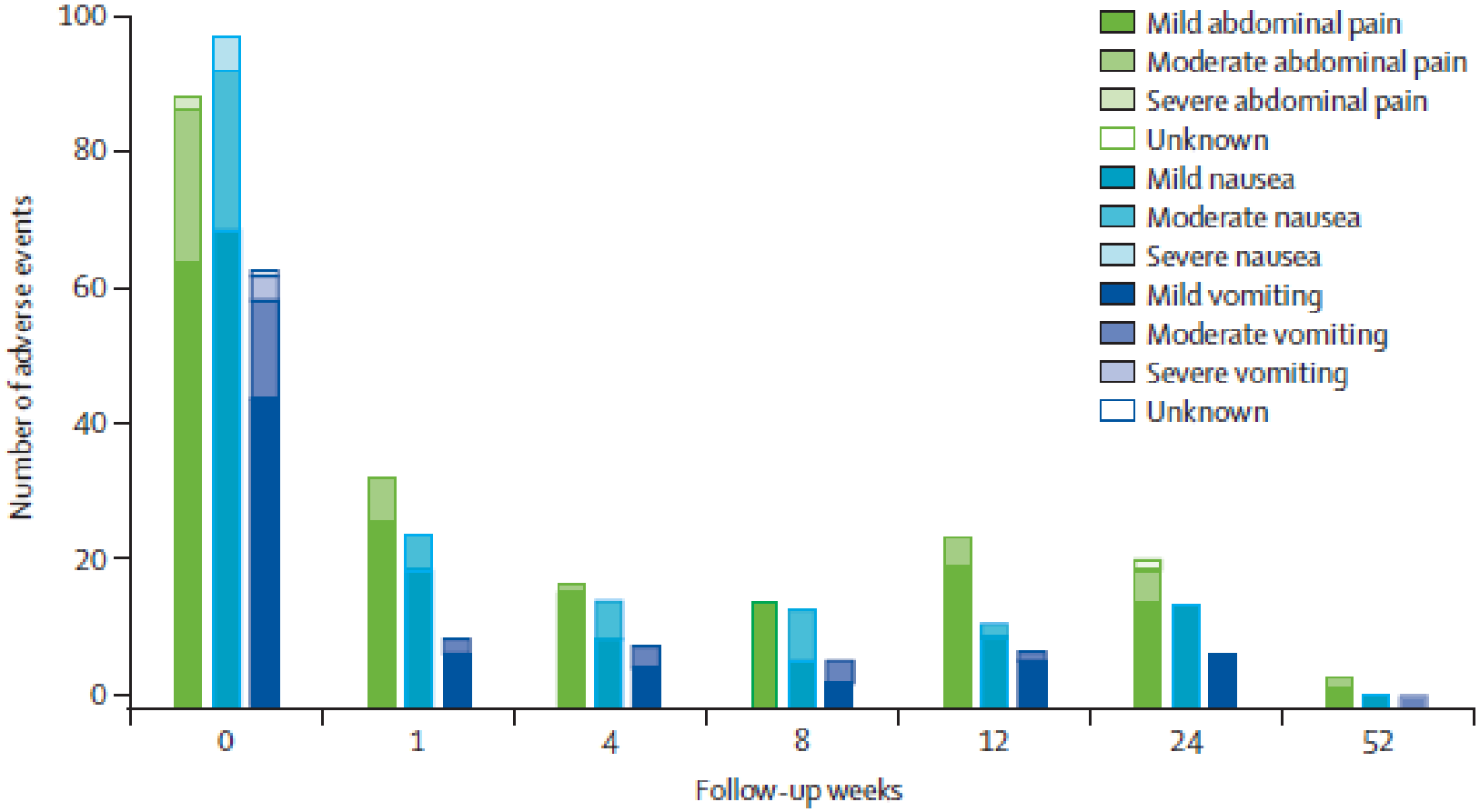
	ESG (primary)	Control	Rate difference*	p value†	ESG (primary and crossover)
Diabetes					
Improving	92% (12/13; 65 to 100)	15% (4/27; 5 to 33)	−77·5 (10·1; −91·4 to −47·4)	<0·0001	93% (25/27; 76 to 99)
Worsening	0% (0/13; 0 to 27)	44% (12/27; 28 to 63)	44·4 (9·6; 16·1 to 60·2)	0·0041	0% (0/27; 0 to 15)
Hyperlipidaemia					
Improving	40% (6/15; 20 to 64)	32% (8/25; 17 to 52)	8·0 (15·7; −37 to −22)	0·61	30% (7/23; 10 to 15)
Worsening	27% (4/15; 11 to 52)	28% (7/25; 14 to 48)	1·3 (14·9; −28 to 28)	0·93	30% (7/23; 10 to 15)
Hypertension					
Improving	67% (24/36; 50 to 80)	40% (19/48; 27 to 54)	−27·1 (10·6; −46·1 to 5·5)	0·014	60% (39/65; 48 to 71)
Worsening	6% (2/36; 1 to 19)	23% (11/48; 13 to 37)	17·4 (7·2; 1·5 to 30·7)	0·029	9% (6/65; 4 to 19)
Metabolic syndrome					
Improving	83% (24/29; 65 to 93)	35% (10/29; 20 to 53)	−48·3 (11·3; −67·0 to −23·3)	0·0002	83% (35/42; 69 to 92)
Worsening	0% (0/29; 0 to 14)	38% (11/29; 23 to 56)	37·9 (9·0; 17·2 to 53·7)	0·0002	5% (2/42; 1 to 17)
Effect on multiple comorbid conditions					
Improved at least 1 condition	41 (80%; n=51)	28 (45%; n=62)	..	..	70 (78%; n=90)
Worsened at least 1 condition	6 (12%; n=51)	31 (50%; n=62)	..	..	15 (17%; n=90)

Data are rate (n/N; 95% CI), rate difference (SE; 95% CI) or n (%; N). ESG=endoscopic sleeve gastroplasty. A negative rate difference indicates that the ESG rate was greater than the control rate. *Mean difference was calculated as the difference between the rate for the control group minus ESG group. †The p value was determined with an independent samples proportions test to evaluate differences between two rates.

Table 2: **Comorbidity 52-week change from baseline for randomly assigned participants**

Lancet 2022; 400: 441–51

Effets indésirables
en lien avec la procedure de sleeve endoscopique

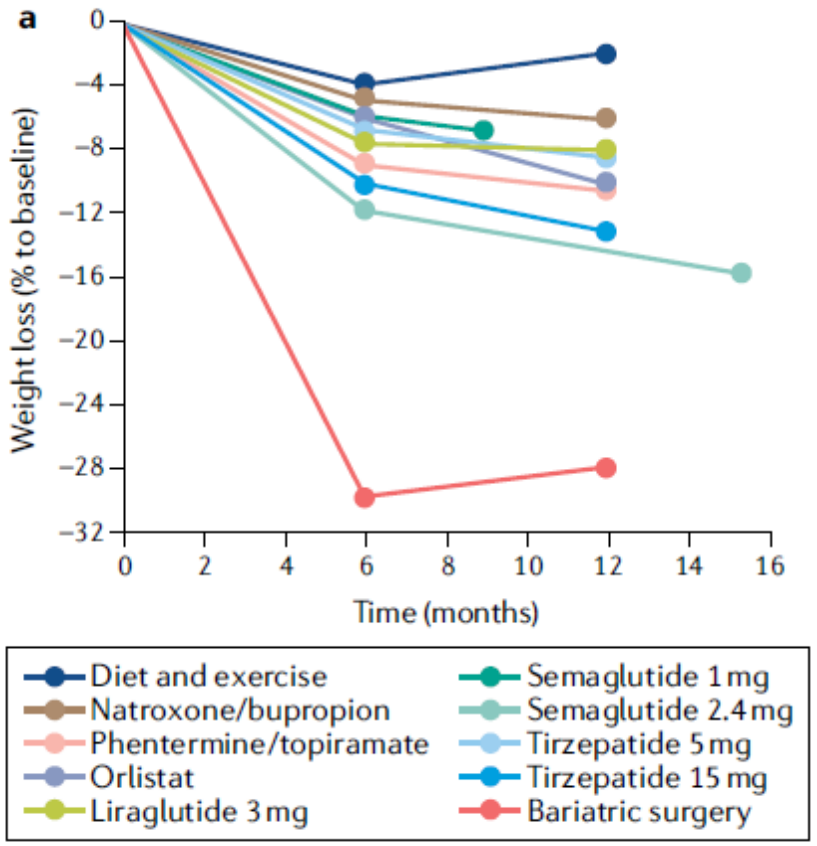


3 patients avec EI graves (2%) :

- 1 abcès
- 1 saignement
- 1 dénutrition

Lancet 2022; 400: 441-51

Une place pour la pharmacothérapie ?



Müller et al., Nature Reviews 2021

Un lourd passé/passif…

Hormones thyroïdiennes →

Amphétamines →

Isomeride et Mediator
(retrait en 2009 en France…) →

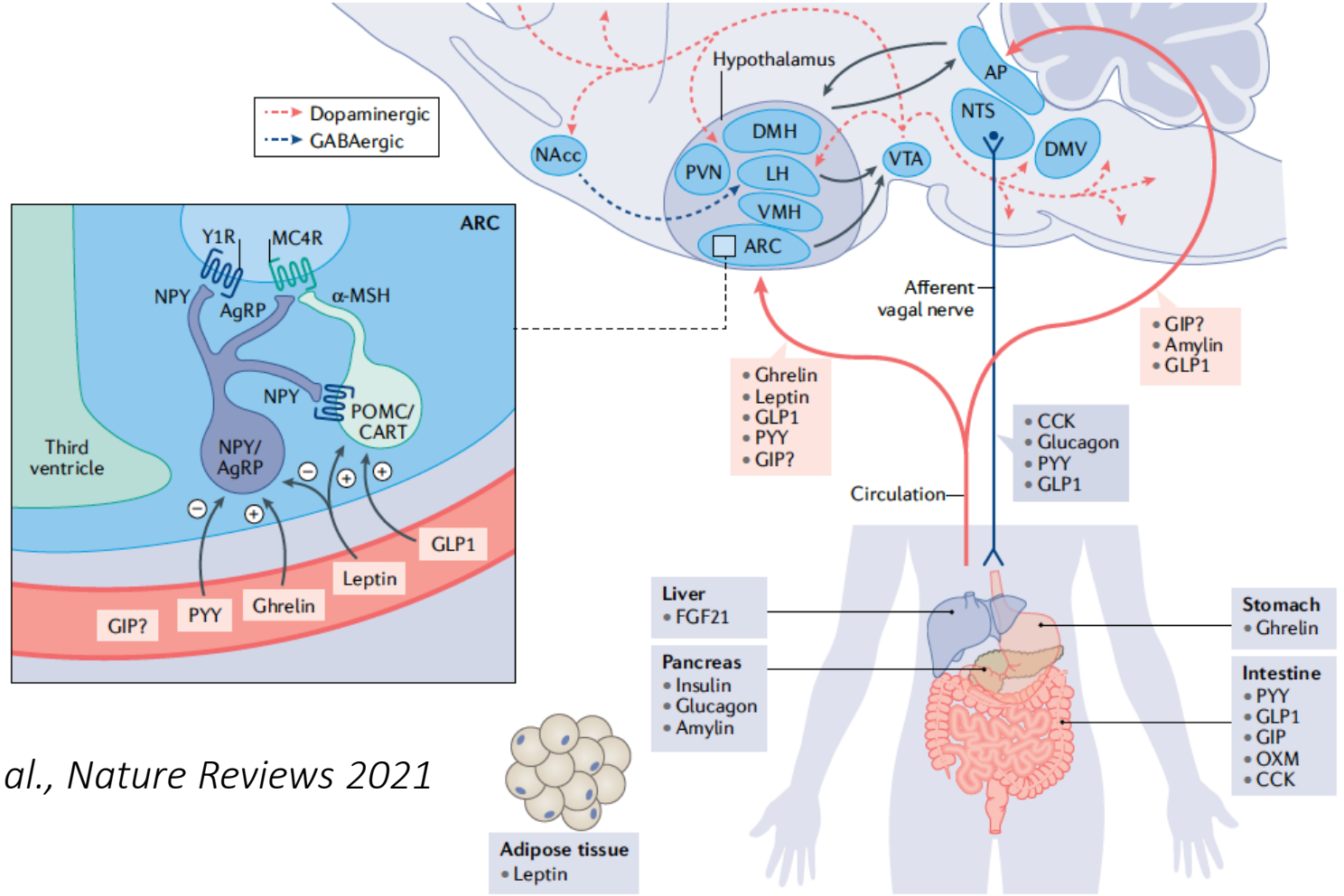
Acomplia →

Sibutral →

Drug	Year Introduced or Withdrawn	Comments
Thyroid	1892	Mimics endogenous thyroxine/triiodothyronine
		Associated with tachycardia and increase in metabolic rate
Dinitrophenol	1932	Uncouples oxidative phosphorylation
		Associated with cataracts, neuropathy, and death
Amphetamine	1937	Noradrenergic-dopaminergic drug
		Associated with recreational abuse and pulmonary hypertension
Aminorex	1965	Noradrenergic drug
		Associated with pulmonary hypertension
Fenfluramine, dexfenfluramine	1997	Serotonergic drugs
		Both associated with cardiac valvulopathy and primary pulmonary hypertension
Phenylpropanolamine	1998	Noradrenergic agonist
		Associated with strokes and cardiovascular deaths
Ephedra alkaloids	2003	Noradrenergic drugs
		Associated with heart attacks, strokes, and death
Rimonabant	2008	Cannabinoid receptor antagonist
		Associated with depression and suicidality
Sibutramine	2010	Norepinephrine-serotonin reuptake inhibitor
		Associated with elevated BP and death

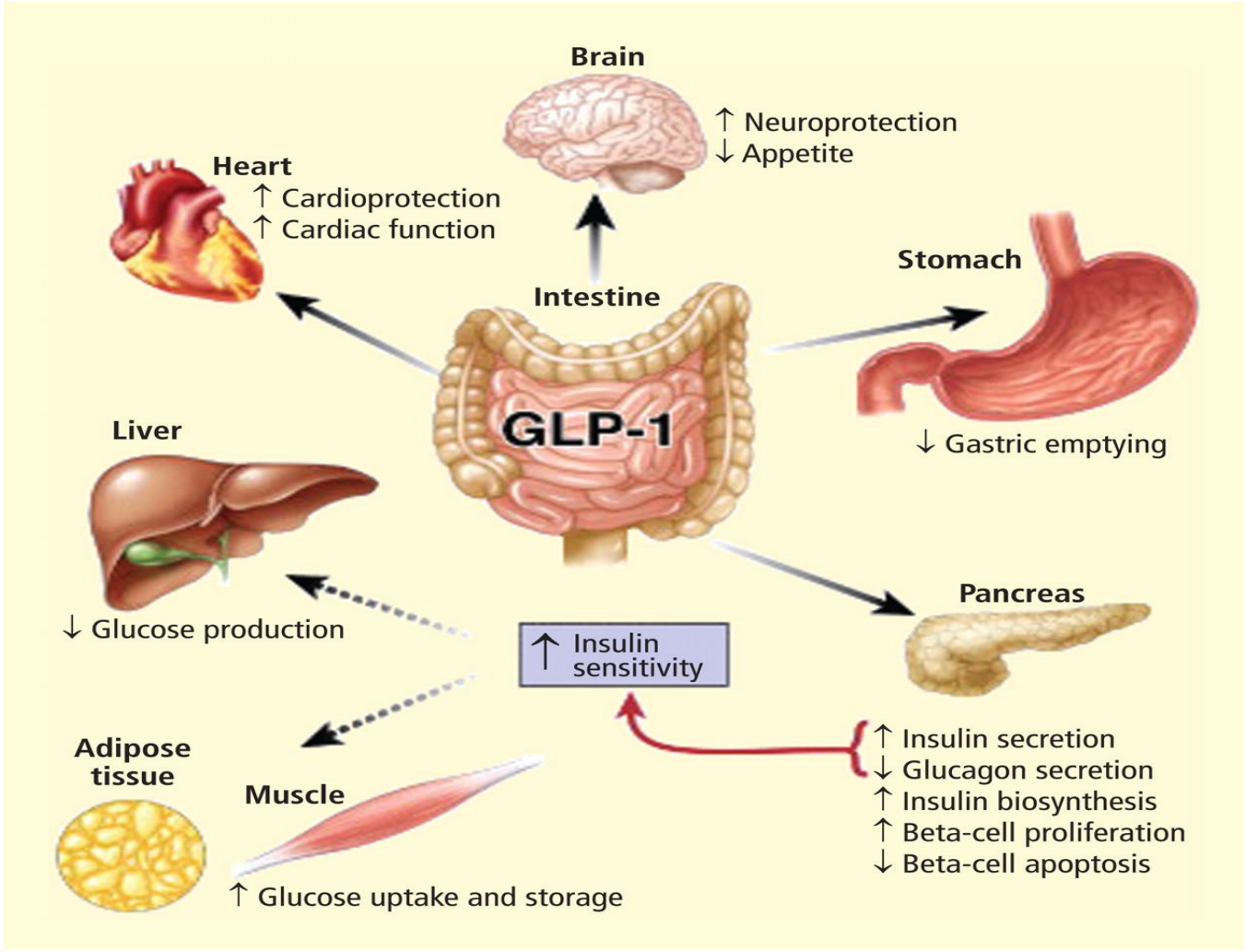
Bray et al, Endoc Rev 2018

Pharmacothérapie : le renouveau des agents et des cibles



Müller et al., Nature Reviews 2021

Analogues du GLP1 : mécanismes d'action

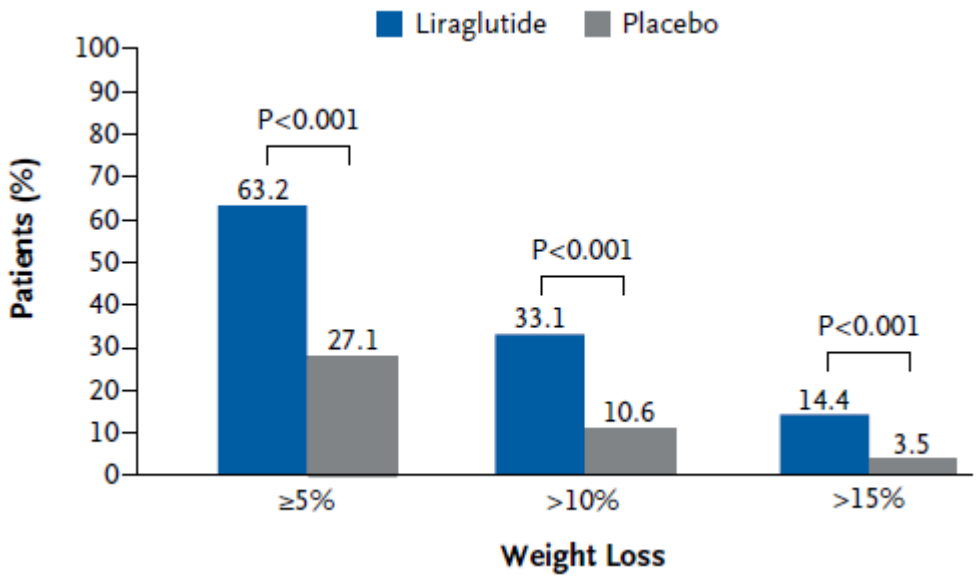


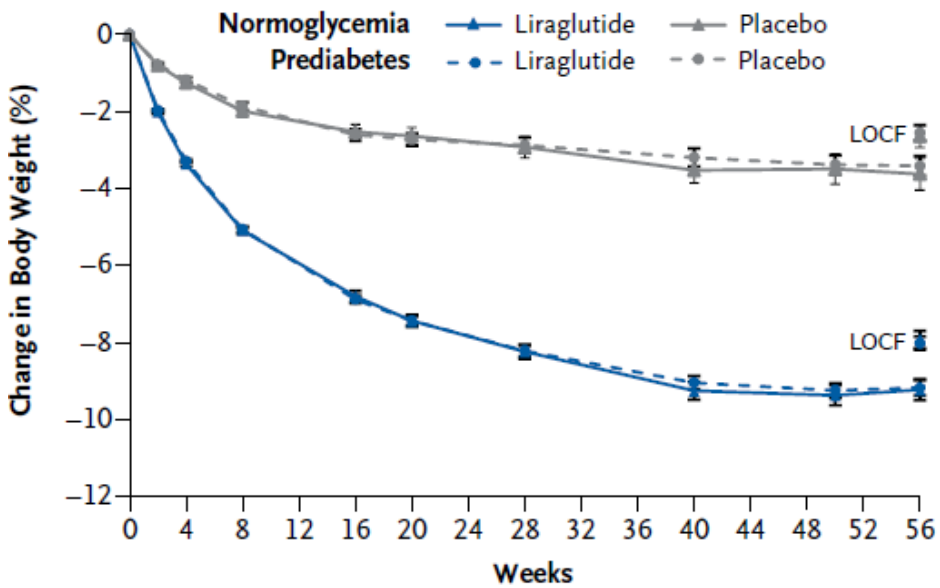
PETERS A L Cleveland Clinic Journal of Medicine 2009;76:S20-S27

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2015 VOL. 373 NO. 1

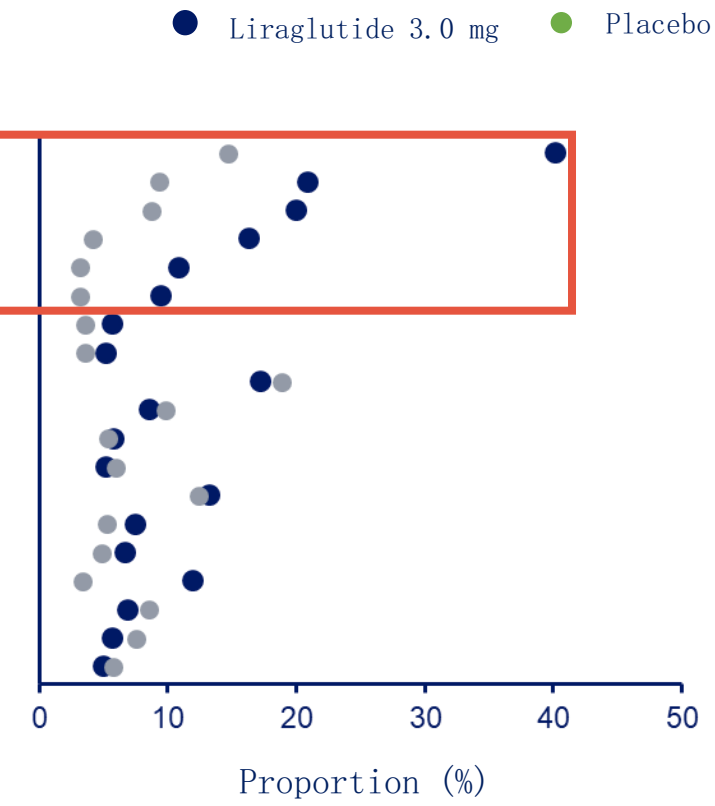
A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management





Effets secondaires chez ≥ 5% des participants

	Liraglutide 3.0 mg %	Placebo %
Nausea	40.2	14.7
Diarrhoea	20.9	9.3
Constipation	20.0	8.7
Vomiting	16.3	4.1
Decreased appetite	10.8	3.1
Dyspepsia	9.5	3.1
Abdominal pain upper	5.7	3.5
Abdominal pain	5.2	3.5
Nasopharyngitis	17.2	18.8
Upper respiratory tract infection	8.6	9.8
Influenza	5.8	5.3
Sinusitis	5.2	5.9
Headache	13.2	12.4
Fatigue	7.5	5.2
Dizziness	6.7	4.8
Hypoglycaemia	11.9	3.3
Back pain	6.9	8.5
Injection site haematoma	5.7	7.5
Arthralgia	5.0	5.7

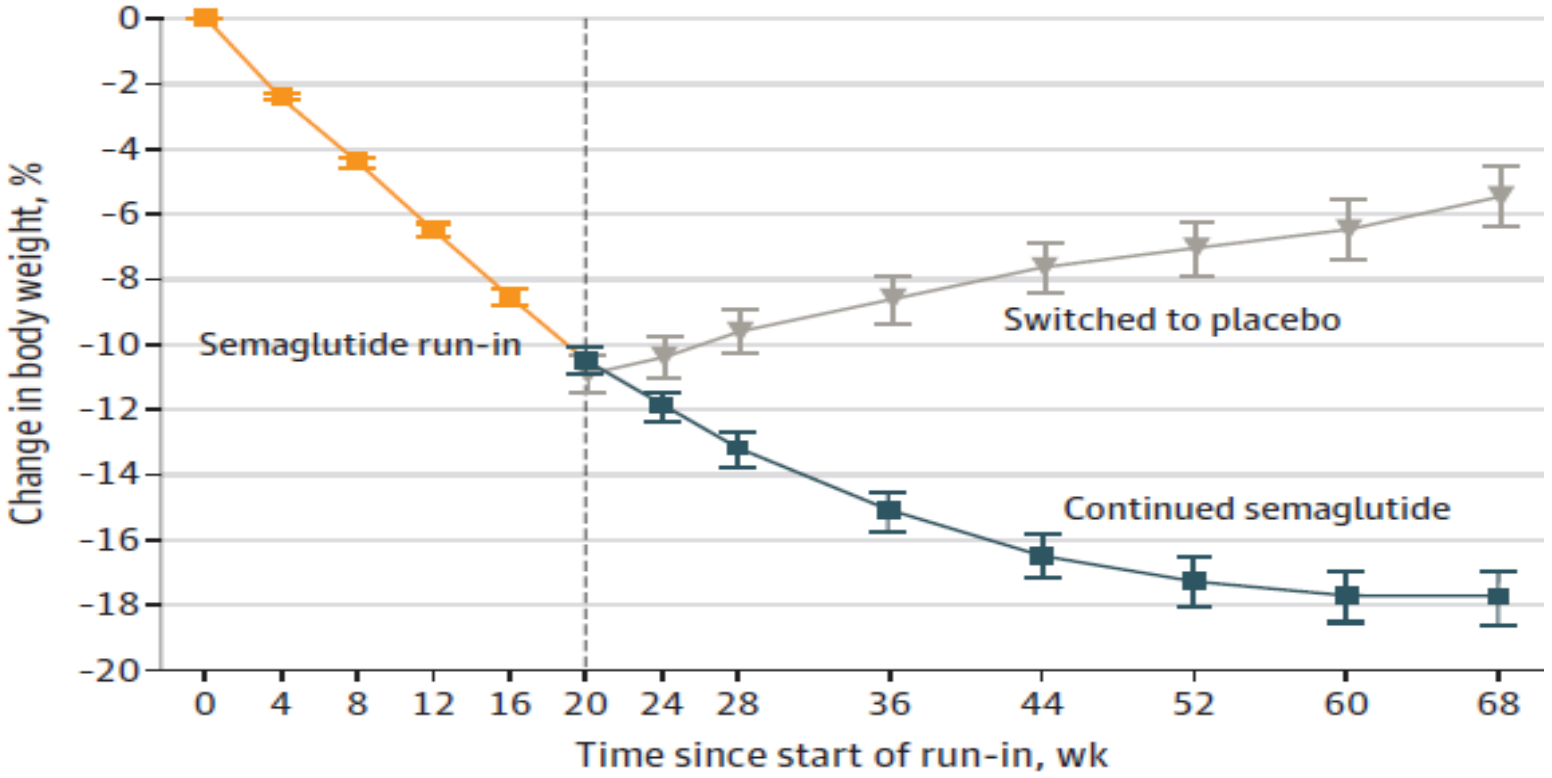


Pi-Sunyer et al. N Engl J Med 2015

JAMA | Original Investigation

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity

The STEP 4 Randomized Clinical Trial



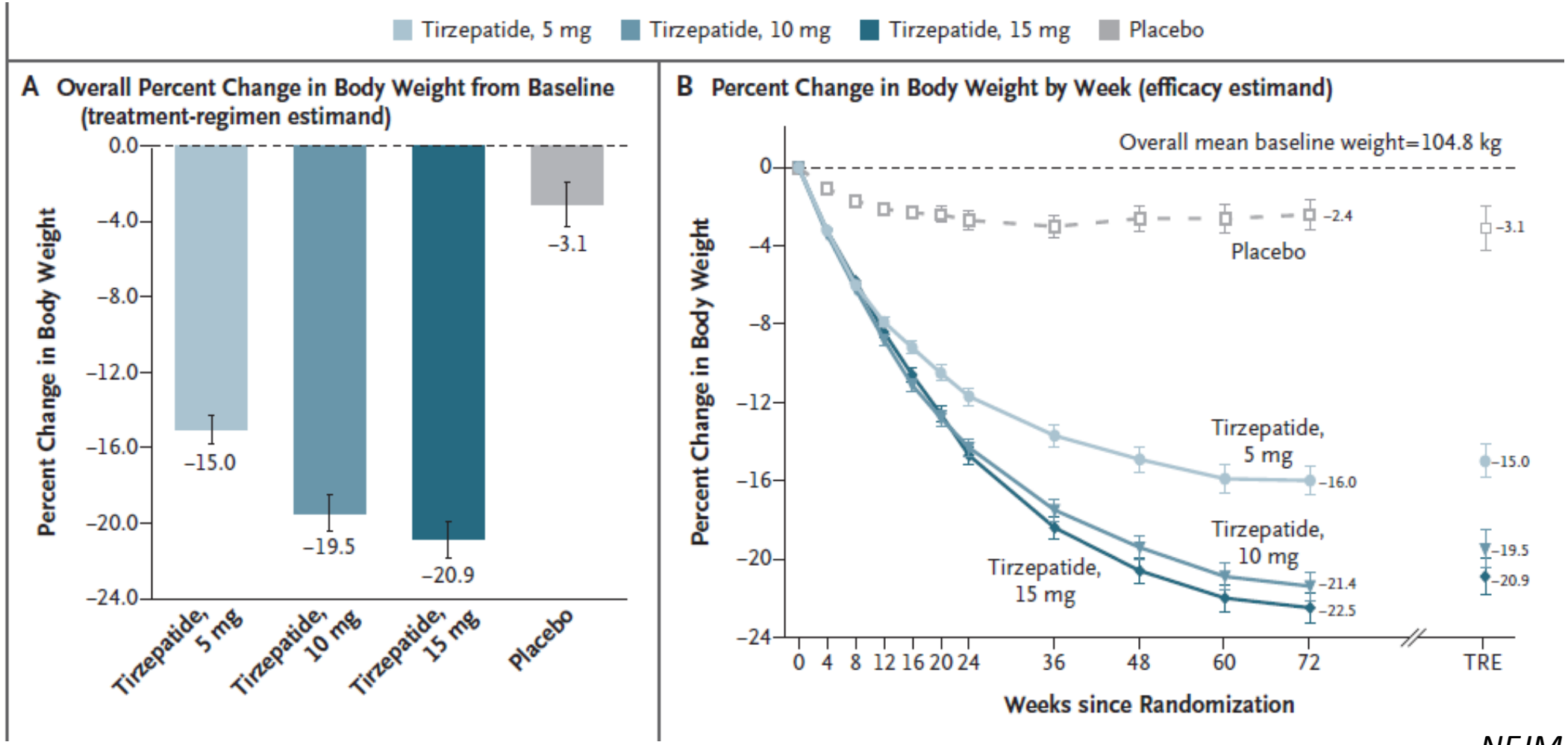
No. of participants

Semaglutide run-in	803	803	803	802	801			
Continued semaglutide	535	527	531	525	523	521	516	520
Switched to placebo	268	267	265	258	260	254	246	250

All participants received a lifestyle intervention from week 0 to week 68, including monthly counseling by qualified health care professionals, in person or by telephone. Participants were prescribed a reduced-calorie diet (500-kcal/d deficit relative to estimated energy expenditure calculated at week 0) and increased physical activity (150 min/wk), recorded daily by participants (using paper diaries, apps, or other tools) and reviewed during counseling visits.

Rubino et al. JAMA, 2021

TIRZEPATIDE : bi-analogue GLP1/GIP
Etude SURMOUNT-1



NEJM 2022

Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

End Points	Pooled Tirzepatide Groups†	Placebo (N = 643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

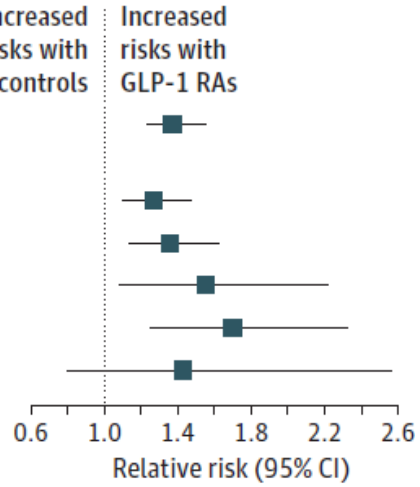
NEJM 2022

Effets indésirables essentiellement digestifs

Table 4. Adverse Events and Safety.

Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
		number (percent)		
Participants with ≥1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death*	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events leading to discontinuation of trial drug or placebo†	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0

Outcomes	No. of studies	No. of events/total: GLP-1 RAs groups	No. of events/total: Control groups	ARD (95% CI) per 10 000 persons/year	I^2, % (95% CI)	Relative risk (95% CI)
Gallbladder or biliary disease	76	916/57 856	544/45 515	27(17 to 38)	0 (0-27)	1.37 (1.23-1.55)
Cholelithiasis	61	454/53 674	287/42 212	14 (5 to 24)	0 (0 to 30)	1.27 (1.10 to 1.47)
Cholecystitis	53	302/49 491	187/40 574	10 (4 to 18)	0 (0 to 32)	1.36 (1.14 to 1.62)
Biliary disease	21	77/36 225	41/32 741	2 (0 to 5)	0 (0 to 48)	1.55 (1.08 to 2.22)
Cholecystectomy	7	125/13 690	61/11 479	9 (3 to 17)	0 (0 to 71)	1.70 (1.25 to 2.32)
Biliary cancer	12	25/31 010	15/30 026	5 (-3 to 20)	0 (0 to 58)	1.43 (0.80 to 2.56)



Factor	No. of patients	No. of trials	Relative risks (95% CI)	Heterogeneity: I^2 %	Heterogeneity: P value	P value for interaction[a]
Treatment						
Dose[b]						
High	61 962	54	1.56 (1.36-1.78)	0	.99	.006
Low	16 952	33	0.99 (0.74-1.33)	0	.67	
Duration, wk						
≤26	13 401	24	0.79 (0.48-1.31)	0	.97	.03
>26	90 417	53	1.40 (1.26-1.56)	0	.64	
Indication[c]						
Weight loss	11 282	13	2.29 (1.64-3.18)	0	.85	<.001
T2D/other	92 090	63	1.27 (1.14-1.43)	0	.94	
Baseline BMI[d]						
High	25 275	33	1.49 (1.20-1.84)	0	.50	.36
Low	77 530	42	1.33 (1.18-1.50)	0	.89	
Type of control						
Placebo	80 281	45	1.41 (1.26-1.58)	0	.83	.08
Active comparator	25 433	36	1.03 (0.74-1.44)	0	.93	

Lithiase biliaire

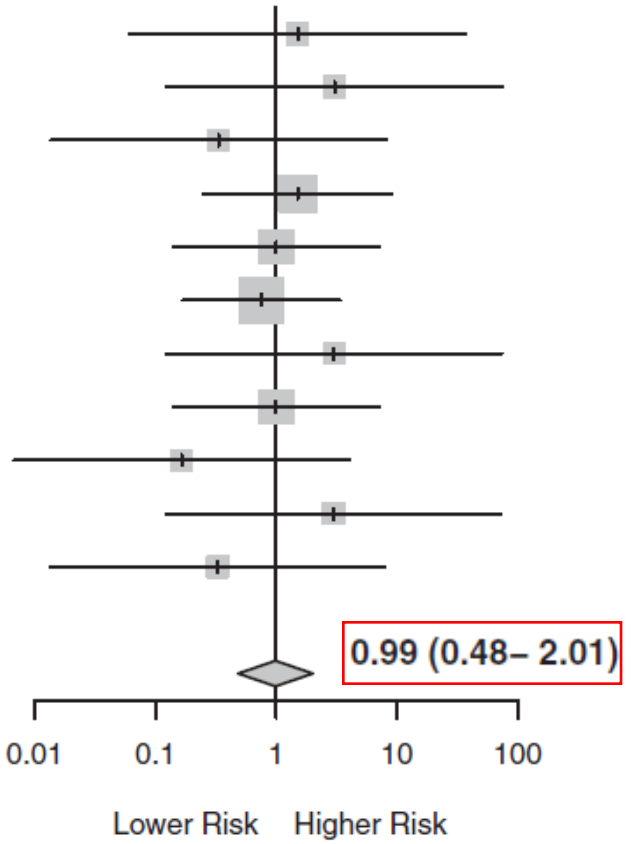
He et al. JAMA Inter Med 2022

Do GLP-1 Receptor Agonists Increase the Risk of Breast Cancer? A Systematic Review and Meta-analysis

	GLP–1RA		Control		Weight
	Events	Total	Events	Total	(%)
DUAL II China	1	301	0	151	5.0
DURATION–NEO–2	1	181	0	183	5.0
ELIXA	0	3031	1	3032	5.0
EXSCEL	3	7344	2	7372	15.9
Harmony Outcomes	2	4717	2	4715	13.3
LEADER	3	4668	4	4672	22.7
LixiLan–L	1	365	0	365	5.0
REWIND	2	4943	2	4949	13.3
SCALE (prediabetes subset)	0	1524	1	755	5.0
SCALE Maintenance	1	212	0	210	5.0
Unnamed (NCT00082407)	0	253	1	248	5.0
Overall	**14**	**27539**	**13**	**26652**	**100.0**

Heterogeneity: $I^2 = 0\%$, $p = 0.95$

Test for overall effect: $p = 0.97$



RCT 2020 et 2021

Piccoli et al. JCEM 2021

GLP-1 Receptor Agonists and the Risk of Thyroid Cancer

	All thyroid cancer			Medullary thyroid cancer		
	Case subjects, *n* = 2,562	Control subjects, *n* = 45,184	Adjusted HR (95% CI)*	Case subjects, *n* = 398	Control subjects, *n* = 6,993	Adjusted HR (95% CI)*
Current exposure model						
GLP-1 RA						
Nonuser	2,255 (88.0)	40,836 (90.4)	Reference	343 (86.2)	6,347 (90.8)	Reference
Past user	100 (3.9)	1,628 (3.6)	1.20 (0.96–1.50)	20 (5.0)	237 (3.4)	1.45 (0.84–2.50)
Current user	207 (8.1)	2,720 (6.0)	1.46 (1.23–1.74)	35 (8.8)	409 (5.9)	1.76 (1.16–2.69)
DPP4 inhibitors						
Nonuser	1,522 (59.4)	27,406 (60.7)	Reference	231 (58.0)	4,217 (60.3)	Reference
Past user	387 (15.1)	6,462 (14.3)	1.07 (0.94–1.22)	66 (16.6)	999 (14.3)	1.12 (0.81–1.55)
Current user	653 (25.5)	11,316 (25.0)	1.10 (0.99–1.22)	101 (25.4)	1,777 (25.4)	1.15 (0.88–1.50)
Cumulative exposure model						
GLP-1 RA						
Nonuser	2,255 (88.0)	40,836 (90.4)	Reference	343 (86.2)	6,347 (90.8)	Reference
≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99–1.50)	23 (5.8)	278 (4.0)	1.57 (0.96–2.55)
1–3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27–1.95)	20 (5.0)	203 (2.9)	1.78 (1.04–3.05)
>3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05–1.74)	12 (3.0)	165 (2.4)	1.61 (0.85–3.06)
DPP4 inhibitors						
Nonuser	1,522 (59.4)	27,406 (60.7)	Reference	231 (58.0)	4,217 (60.3)	Reference
≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99–1.28)	58 (14.6)	798 (11.4)	1.33 (0.97–1.84)
1–3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84–1.10)	48 (12.1)	882 (12.6)	0.98 (0.69–1.39)
>3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04–1.35)	61 (15.3)	1,096 (15.7)	1.11 (0.79–1.55)

*Adjustment for social deprivation index, goiter, hypo- and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered by therapeutic class.

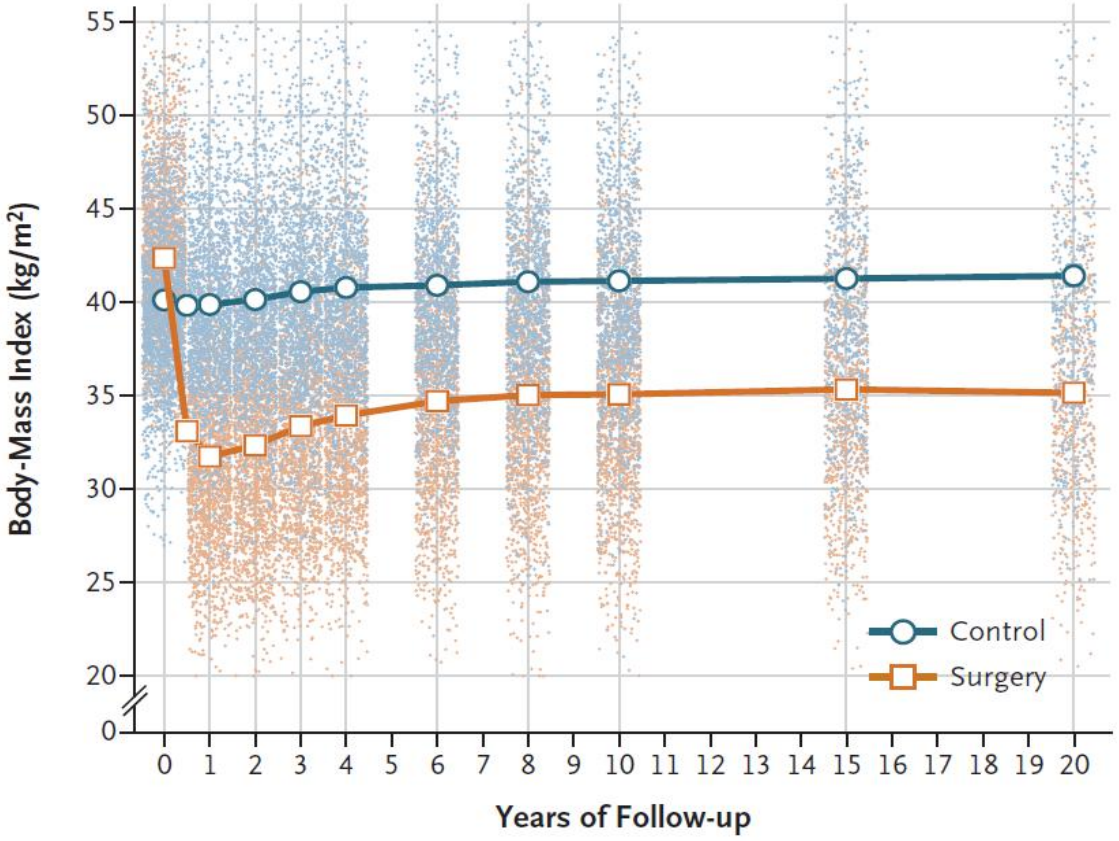
Bezin et al. diab Care 2022

Décision thérapeutique basée sur la balance bénéfice/risque long terme

Substantial bodyweight loss by any means[53]	Pharmacotherapy[54]	Bariatric surgery[55]
• Constipation • Cold intolerance • Fatigue • Hair loss • Dizziness • Postural hypotension • Cholelithiasis • Transient hyperuricaemia • Loose excess skin • Reduced bone-mineral density	**Phentermine–topiramate** • Insomnia • Irritability • Tachycardia • Constipation • Hypertension • Dry mouth • Dysgeusia • Paraesthesia **Orlistat** • Steatorrhoea • Oily spotting and leakage • Reduced absorption of fat-soluble vitamins **Naltrexone–bupropion** • Headache • Nausea • Dizziness • Constipation • Hypertension • Anxiety **GLP1R agonists** • Nausea • Vomiting • Constipation • Diarrhoea • Hypoglycaemia	**Short-term effects (of any procedure)** • Postoperative surgical complications (eg, bleeding, infection, leaks, etc) **Long-term effects (of sleeve gastrectomy, gastric bypass, and biliopancreatic diversion)** • Dumping syndrome • Micronutrient deficiencies **Sleeve gastrectomy** • Gastro-oesophageal reflux disease **Gastric bypass** • Hernia • Stricture • Obstruction • Ulcers **Adjustable gastric banding** • Slippage • Erosion • Pouch dilatation

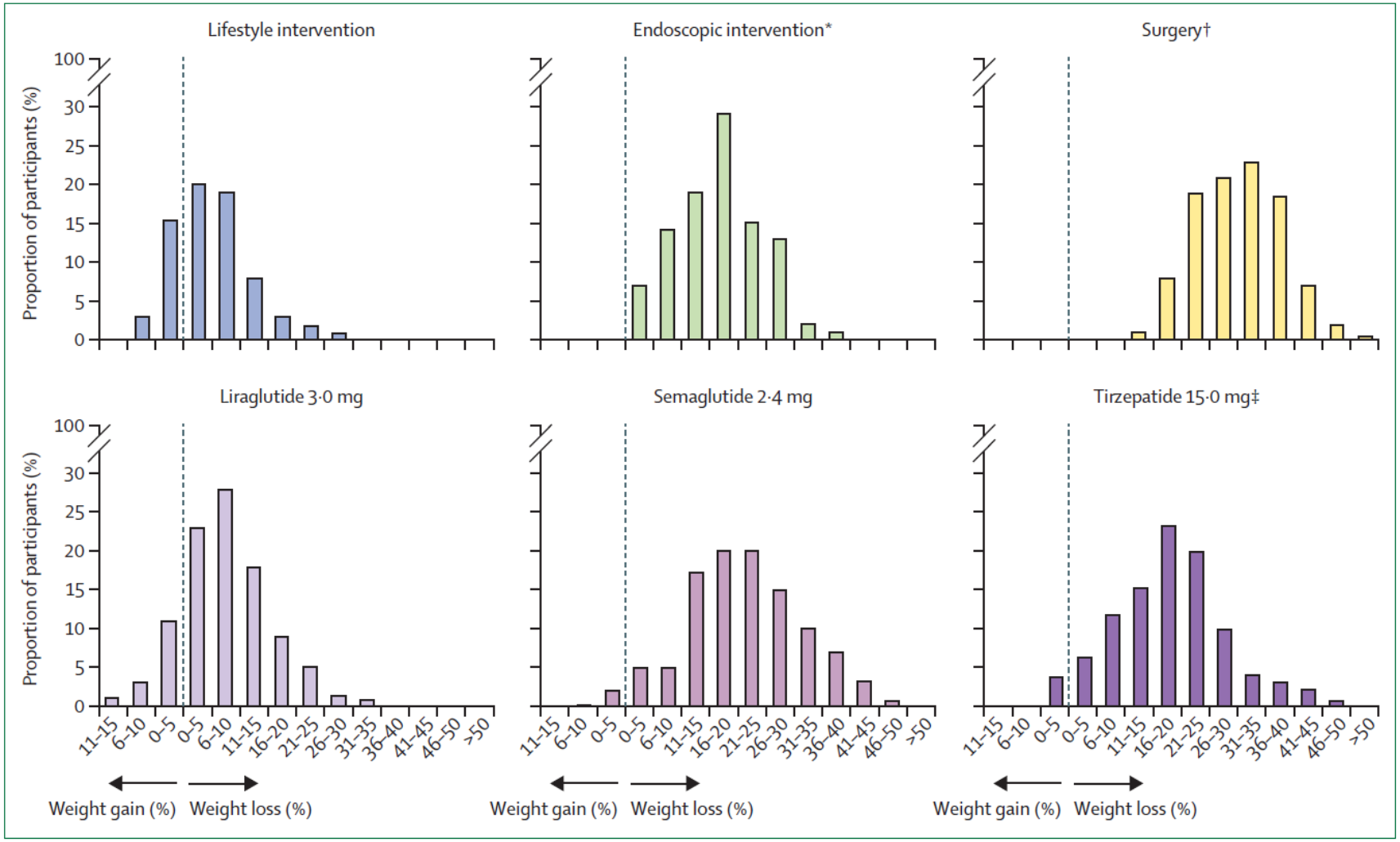
Figure 3: **Most common adverse effects of substantial weight loss by any means, pharmacotherapy, and bariatric surgery**

Linqvay et al, Lancet 2022



Carlsson et al, NEJM 2020

Variabilité de la réponse quelle que soit la pec



Perdomo et al Lancet 2023

Médicaments disponibles en France

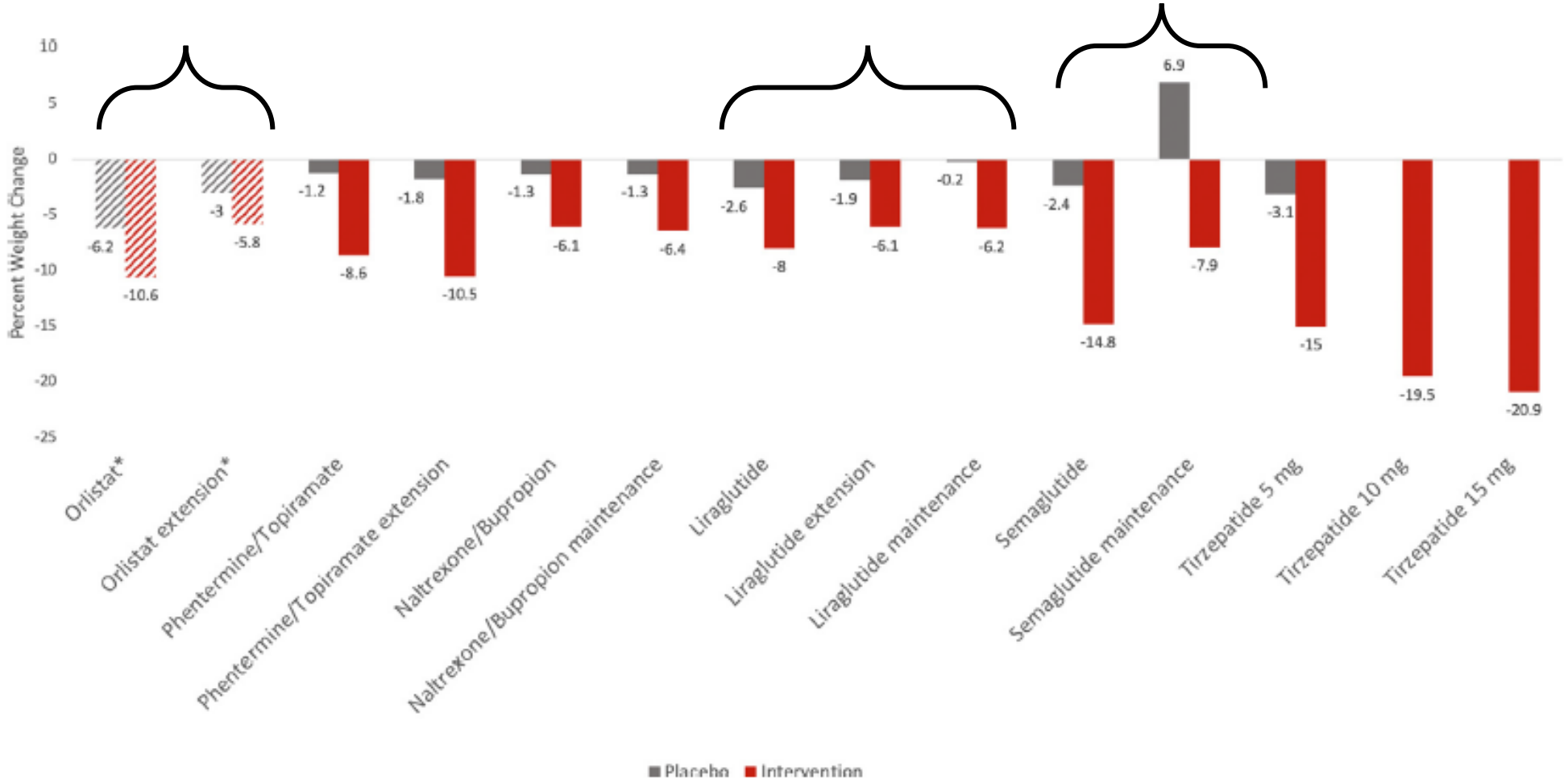
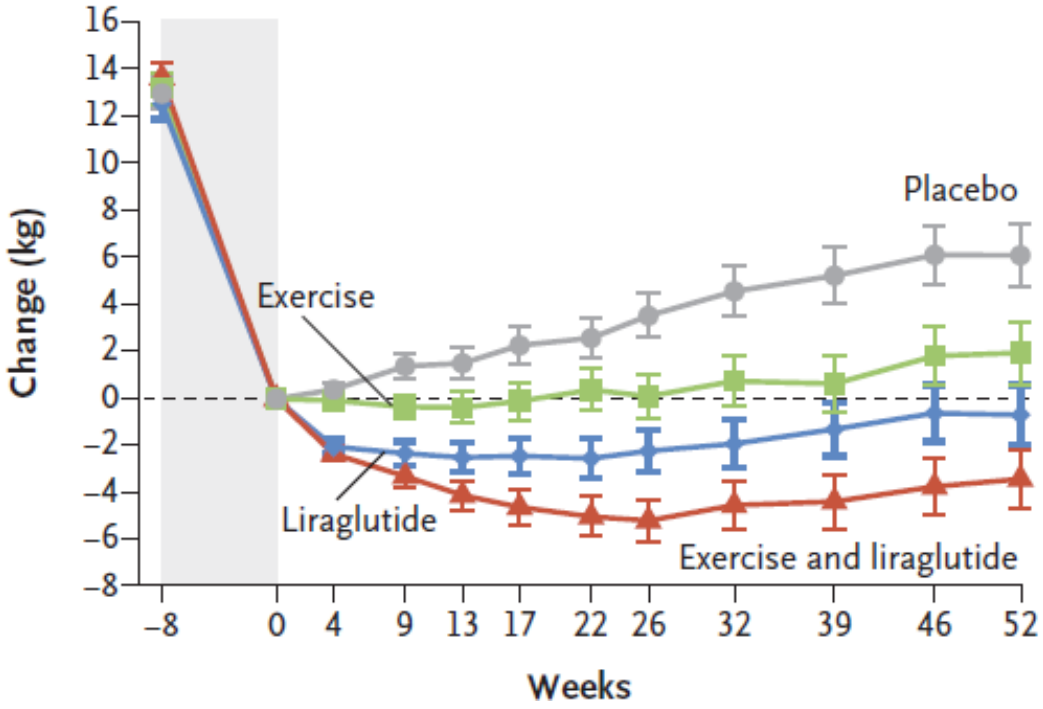
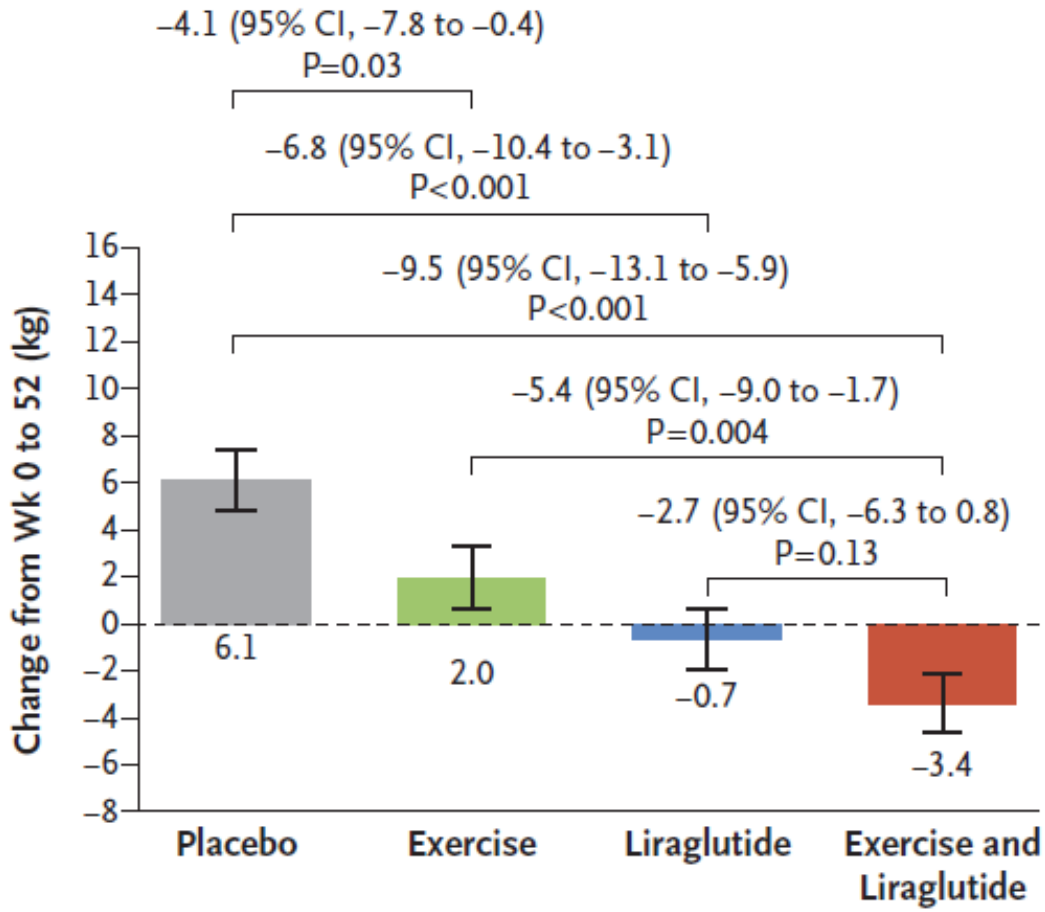


***Fig. 2:* Mean percent (%) weight change reported in the main phase 3 and extension trials of the FDA approved anti-obesity medications.** Orlistat: XENDOS trial (years 1 and 4). Phentermine/topiramate: CONQUER and SEQUEL trials. Naltrexone/bupropion: COR-I and COR-II trials. Liraglutide: SCALE Obesity, SCALE Obesity and Prediabetes Extension, and SCALE maintenance trials. Semaglutide: STEP 1 and STEP 4 trial. All trials are listed in order as seen in the figure from left to right. The grey color represents placebo arms; the red color represents intervention arms. [a]The mean weight change in the orlistat group is in kg not in percent (stripped bar charts). [b]Under expedited consideration for FDA approval.

Chacktoura et al. eClinical Medicine 2023

Une molécule ne remplace pas l'activité physique





Lundgren et al NEJM 2021

HAS
HAUTE AUTORITÉ DE SANTÉ

FFN
FÉDÉRATION FRANÇAISE DE NUTRITION

RECOMMANDER
LES BONNES PRATIQUES

RECOMMANDATION

Obésité de l'adulte : prise en charge de 2e et 3e niveaux

PARTIE I : PRISE EN CHARGE MÉDICALE
Cette RBP sera complétée en 2023 avec le travail sur la chirurgie bariatrique en cours.

Saxenda® (liraglutide 3mg/jour)

- AMM= en complément d'un régime hypocalorique et d'une augmentation de l'activité physique, dans le contrôle du poids chez des patients adultes ayant
  - IMC initial : ≥ 30 kg/m^2 (obésité), ou ≥ 27 kg/m^2 et < 30 kg/m^2 (surpoids)
  - + au moins 1 comorbidité liée au poids, telle que prédiabète ou diabète de type 2, une HTA, une dyslipidémie ou un SAOS.
- Le traitement par SAXENDA à la dose de 3 mg/jour doit être interrompu après 12 semaines si les patients n'ont pas perdu au moins 5 % de leur poids initial.
- AMM, reco HAS, mais pas de remboursement par l'AM
- **Non recommandé chez les patients présentant une insuffisance rénale sévère (clairance de la créatinine < 30 ml/min), y compris les patients présentant une insuffisance rénale terminale. (FDA jusque 15 ml/min)**

Wegovy® (semaglutide 2,4 mg/sem) en ATU

- AMM = en complément d'un régime hypocalorique et d'une augmentation de l'activité physique dans le contrôle du poids, notamment pour la perte de poids et le maintien du poids, chez des adultes avec
  - IMC initial ≥ 40 kg/m²
  - + au moins 1 comorbidité liée au poids : HTA traitée, dyslipidémie traitée, maladie cardiovasculaire établie ou SAOS appareillé.
- Lorsqu'il n'y a pas d'alternative thérapeutique disponible.
- Délivrance hospitalière mensuelle
- ATU de cohorte - accès précoce / cohorte SEMASEARCH

- **Non recommandé chez les patients présentant une insuffisance rénale sévère (clairance de la créatinine < 30 ml/min), y compris les patients présentant une insuffisance rénale terminale. (FDA jusque 15 ml/min)**

Effets cardio et rénoprotecteurs des analogues GLP1

- **Effets cardioprotecteurs** très bien démontrés dans le DT2 (diminution de la mortalité CV et des événements CV) notamment via la baisse de la PA
- Doute sur l'inocuité des analogues GLP1 en cas d'insuffisance cardiaque sévère (effet chronotrope, études FIGHT et LIVE)
- **Effets rénoprotecteurs** bien démontrés dans le DT2 : notamment via diminution de la microalbuminurie
- Quelques études d'efficacité/tolérance chez les **patients dialysés** avec de très petits effectifs et des doses/objectifs DT2, attention aux **EI plus marqués**
- **Dans l'obésité sans DT2,** les doses d'analogues GLP1 sont bcp plus élevées SANS bénéfice démontré pour le moment sur des critères durs (Résultats très attendus de l'étude SELECT)

Diabetes Care 2023;46(4):801–810 | https://doi.org/10.2337/dc22-1889

Effects of Semaglutide on Albuminuria and Kidney Function in People With Overweight or Obesity With or Without Type 2 Diabetes: Exploratory Analysis From the STEP 1, 2, and 3 Trials

Hiddo J.L.Heerspink, Ellen Apperloo, Melanie Davies, Dror Dicker, Kristian Kandler, Julio Rosenstock, Rasmus Sørrig, Jack Lawson, Niels Zeuthen, and David Cherney

Semaglutide improves albuminuria in people with overweight or obesity and type 2 diabetes

Context and Objective(s)

STEP 1–3 post hoc analyses explored the effects of semaglutide 1.0 mg and 2.4 mg versus placebo on kidney function

Design and Methods

Participants:

STEP 1 and 3: adults with overweight or obesity

STEP 2: adults with overweight or obesity and type 2 diabetes

Treatment arms:

1.0 mg semaglutide (STEP 2)
2.4 mg semaglutide
Placebo

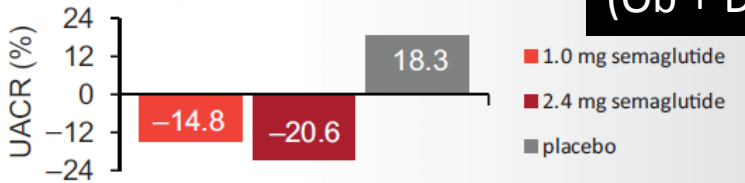
End points assessed:

Changes in urine albumin-to-creatinine ratio (UACR) and UACR status (STEP 2)

Changes in estimated glomerular filtration rate (eGFR) (STEP 1–3 pooled)

Results

UACR changes at week 68:



58.6% of the UACR-lowering effect was statistically independent of changes in glycated hemoglobin (HbA_{1c}) or body weight

The effect of semaglutide versus placebo was consistent across subgroups by baseline BMI, HbA_{1c}, eGFR, or use of renin–angiotensin system or sodium–glucose cotransporter-2 inhibitors

eGFR changes at week 68:

No difference between semaglutide 1.0 mg and 2.4 mg semaglutide and placebo

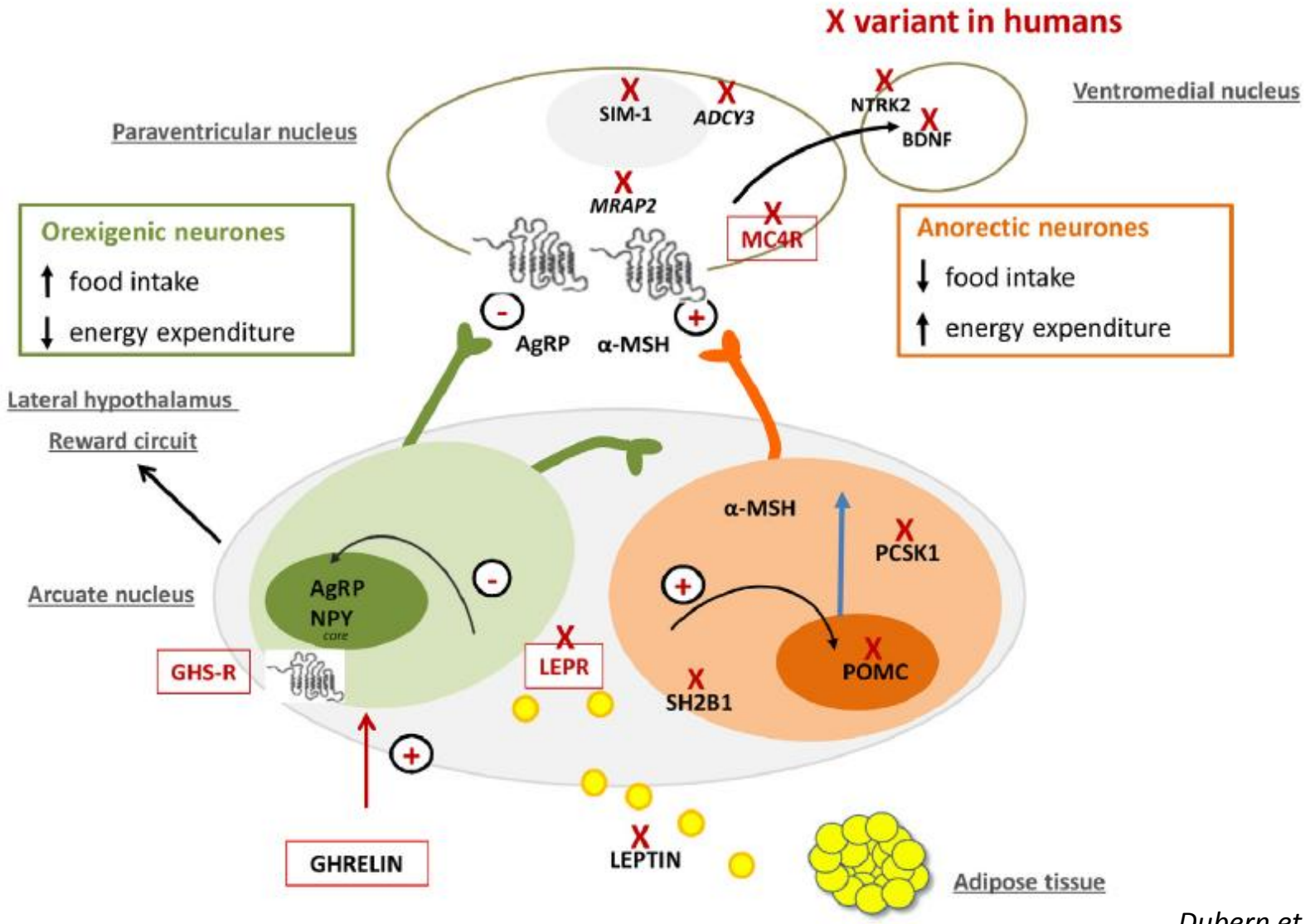
UACR - Post hoc STEP 2 (Ob + DT2)

eGFR - Post hoc STEP 1-3 (Ob +/- DT2)

Diabetes Care

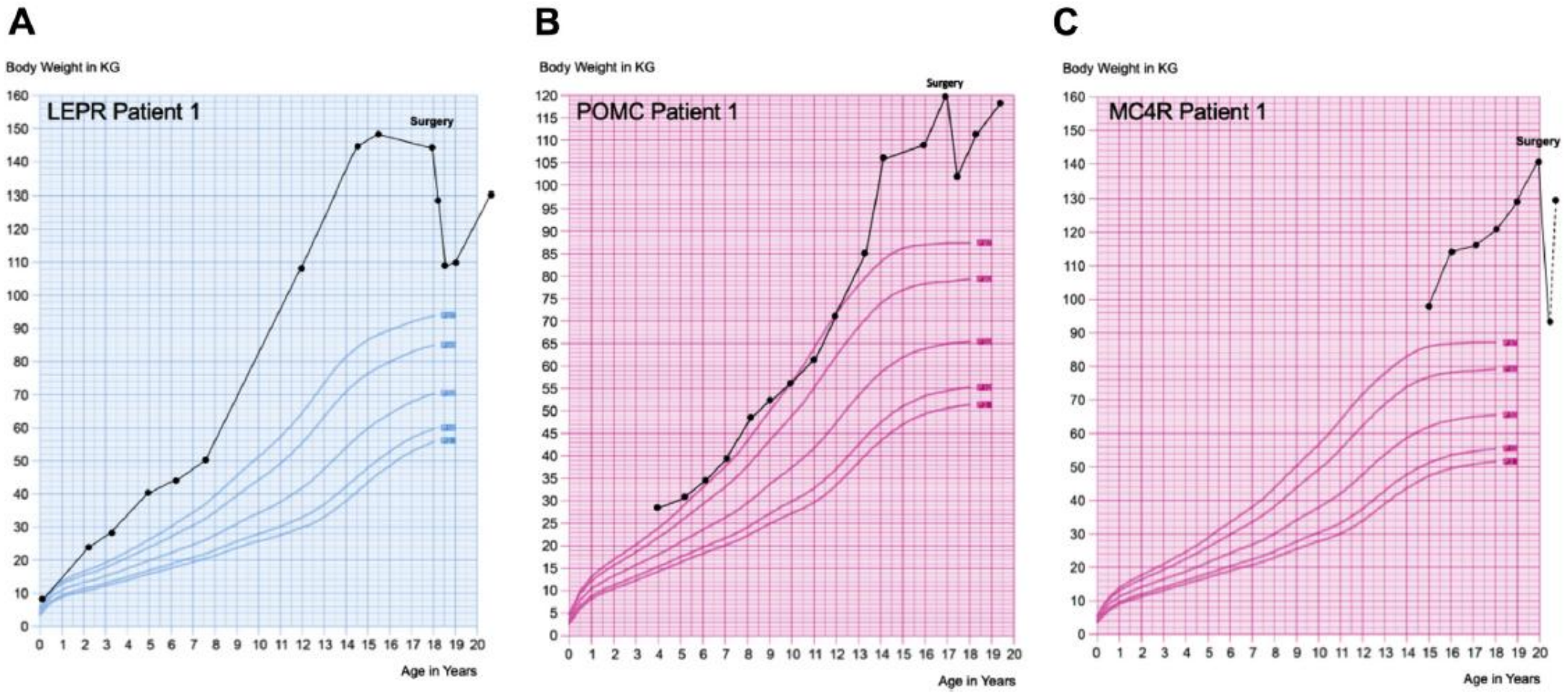
The STEP 1–3 trials (NCT03548935, NCT03552757, and NCT03611582) were funded by Novo Nordisk A/S. The authors thank the trial participants, the investigators, and trial site staff who conducted the trial.

Le cas particulier des obésités monogéniques



Dubern et al Ann Endoc 2022

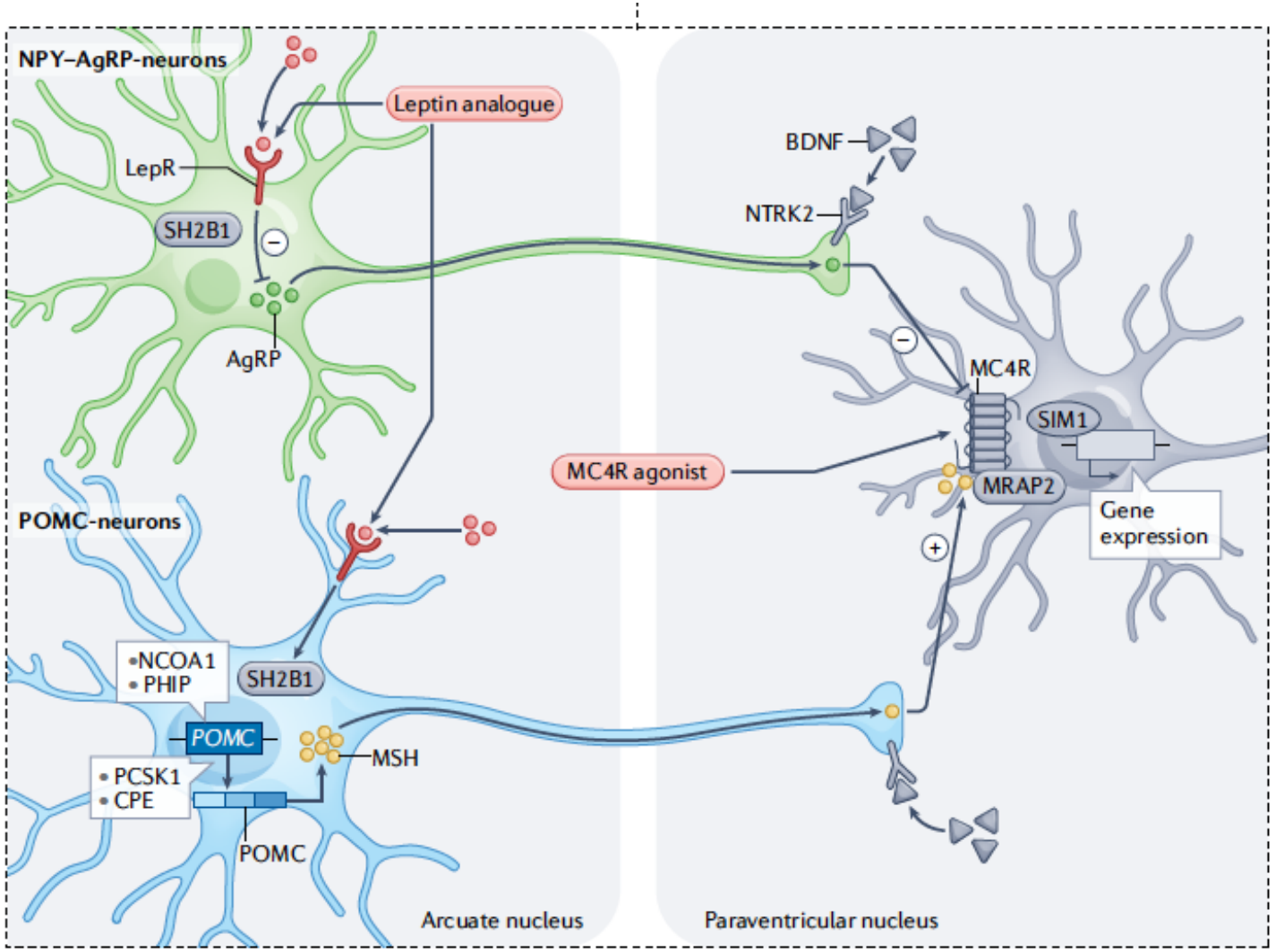
Réponse très transitoire à la chirurgie bariatrique



Mutations bialléliques des gènes de la voie leptine mélanocortine

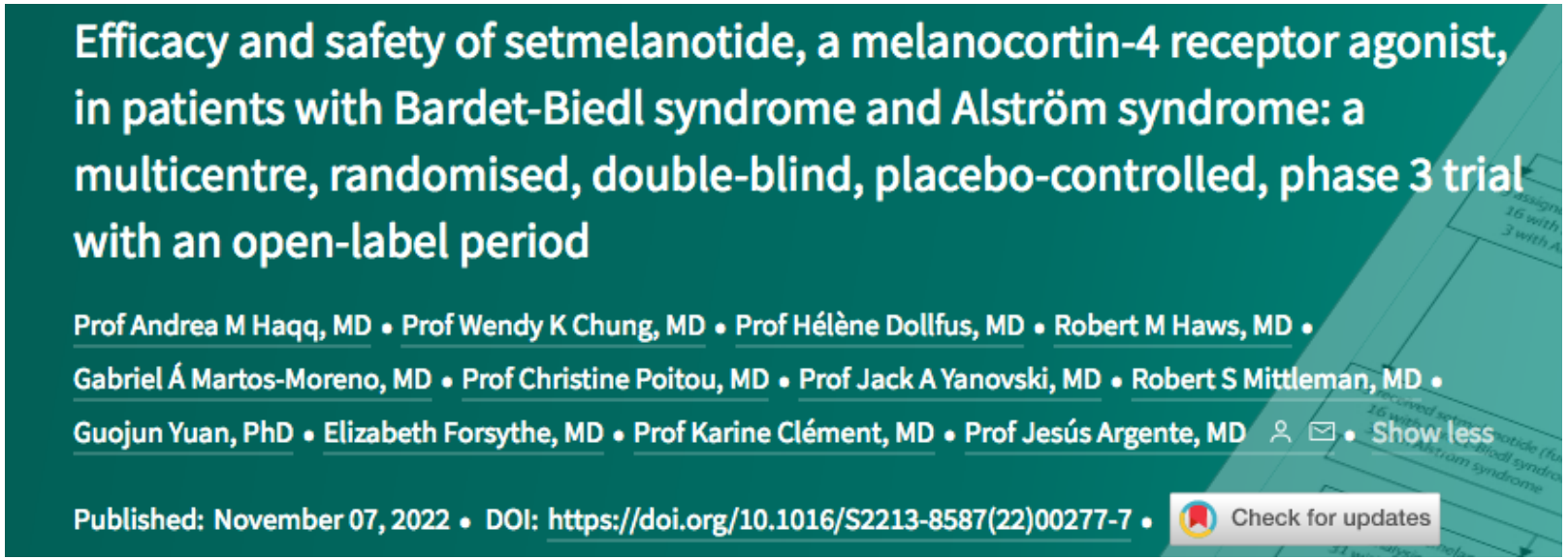
Poitou et al SOARD 2021

Avènement de traitements spécifiques



- Analogue de la leptine : mutation LEP
- Agoniste MC4R (setmelanotide) : mutations LEPR et POMC, et même dans le BBS

Hinney et al Nat Rev Endoc 2022



Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period

Prof Andrea M Haqq, MD • Prof Wendy K Chung, MD • Prof Hélène Dollfus, MD • Robert M Haws, MD • Gabriel Á Martos-Moreno, MD • Prof Christine Poitou, MD • Prof Jack A Yanovski, MD • Robert S Mittleman, MD • Guojun Yuan, PhD • Elizabeth Forsythe, MD • Prof Karine Clément, MD • Prof Jesús Argente, MD • Show less

Published: November 07, 2022 • DOI: https://doi.org/10.1016/S2213-8587(22)00277-7 • Check for updates

THE LANCET
Diabetes & Endocrinology

- 38 patients traités randomisés contre pcb
- 32 BBS et 6 Alstrom
- Chez les 16 BBS traités par setmelanotide, 32 % ont obtenu une perte de poids > 10 % après 52 semaines de traitement
- EI les plus fréquents : hyperpigmentation et erythème au site d'injection
- Alstrom : résultats non concluants

Conclusion

- ✓ OBÉSITÉ = MALADIE CHRONIQUE hétérogène et récidivante
- ✓ Tous les traitements doivent être évalués avec la perspective d'un rapport bénéfice/risque acceptable au long terme
- ✓ **Traitement médical**
  - ✓ Semaglutide 2,4 mg AMM et accès précoce possible hors DFG < 30 ml/min
  - ✓ Bénéfice CV et rénal bien démontré dans le DT2, à venir dans l'obésité
  - ✓ Efficacité/tolérance mal évaluées dans l'IR terminale ou TR
- ✓ **Traitement chirurgical**
  - ✓ Bénéfice pondéral majeur, bénéfice CV et rénal bien démontré y compris sur le devenir post TR
  - ✓ Risque de complications augmenté en cas d'IR terminale