Médicaments contre l'obésité ?

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Médicaments contre l'obésité : pour quoi ?

- L'obésité est un FDR
- Mais le poids, l'IMC, l'obesité sévère, le syndrome métabolique ….. sont des critères intermédiaires, au mieux des biomarqueurs
- Traiter le poids est une condition nécessaire (peut être?) mais non suffisante
- Traiter le poids avec des effets indésirables graves est inacceptable
- Donc médicaments contre les complications attribuables à l'obésité:
  - Symptomatique
  - Morphologique
  - Pronostique (morbi - mortalité CV …)

Pour preuve

Il y'a des médicaments qui font ***perdre*** du poids et ***augmentent*** la MM CV
(Pr Drici : du rimonabant au MEDIATOR…)

Medication Name and Mechanism
Noradrenergic agents
Benzphetamine hydrochloride
Phendimetrazine tartrate
Diethylpropion hydrochloride
Mazindol
Phentermine
Resin
Hydrochloride
Hydrochloride
Phenylpropanolamine
Noradrenergic-serotonergic agents
Sibutramine hydrochloride
Other agents
Orlistat

March **1999**. Archives of Family Medicine 8(2):156-67

Il y'a des médicaments ***qui ne font pas perdre de poids*** mais ***réduisent*** la MM CV
ou qui ***augmentent*** le poids et ***reduisent*** la MM !

TABLE 2

Antihypertensives and weight[3]

Weight gain	Weight neutral
Alpha-adrenergic blockers	ACE inhibitors
Beta-adrenergic blockers (atenolol, metoprolol, nadolol, propranolol)	Angiotensin receptor blockers
	Beta-adrenergic blockers (carvedilol, nebivolol)
	CCBs
	Thiazides

ACE, angiotensin-converting enzyme; CCBs, calcium channel blockers.

J Fam Pract. 2016 November;65(11):780-782,784-786,788

Médicaments contre l’obésité : pour quoi ?

	Poids ↑	Poids ↓
Morbi moralité ↑		
Morbi moralité ↓		

Médicaments contre l'obésité : pour quoi ?

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- Donc médicaments contre les complications attribuables à l'obésité:
  - Symptomatique
  - Morphologique
  - Pronostique (morbi - mortalité CV …)
  - **Quelque soit le mécanisme**

Pourquoi ? Une obésité des obésités

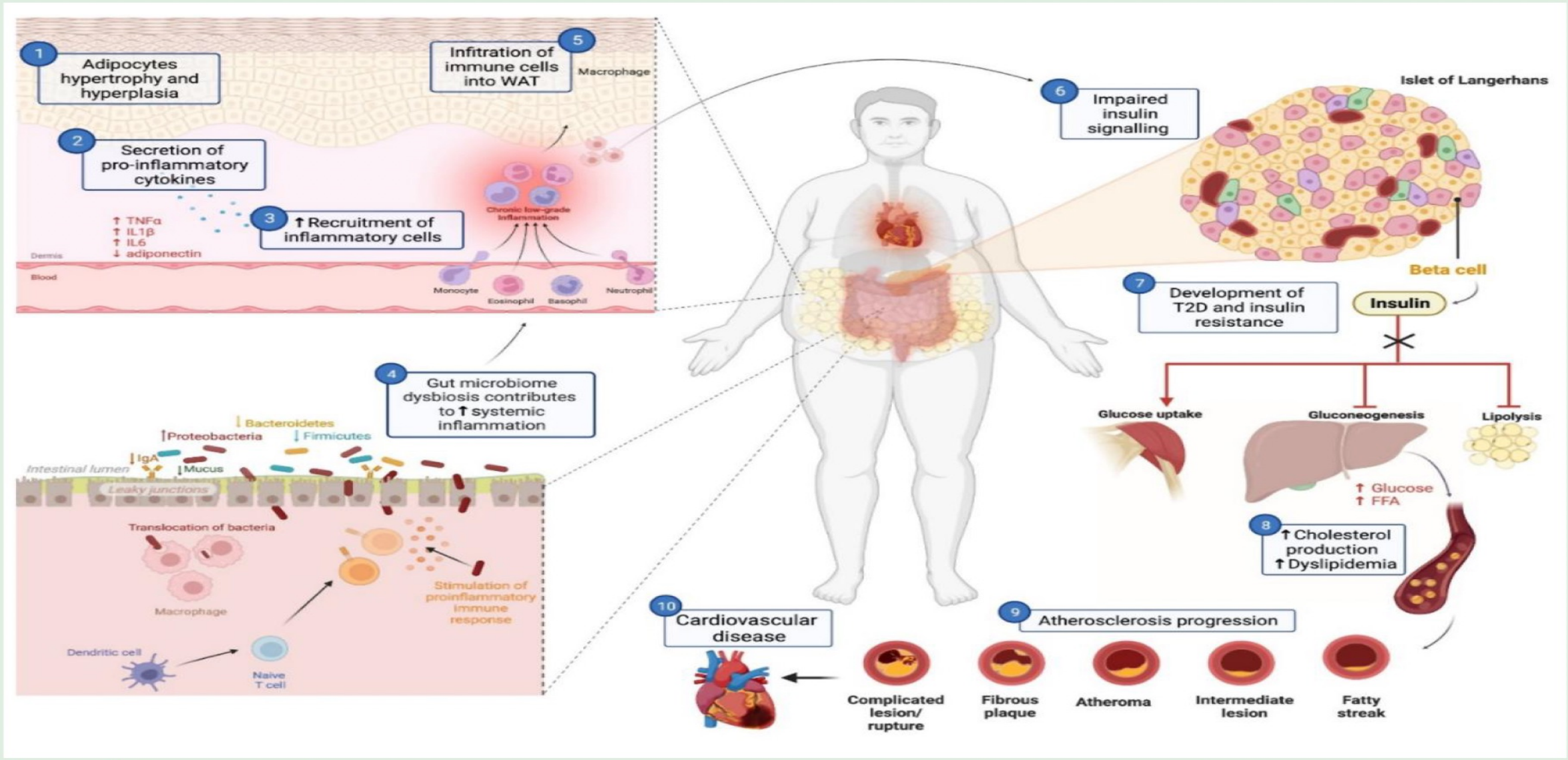
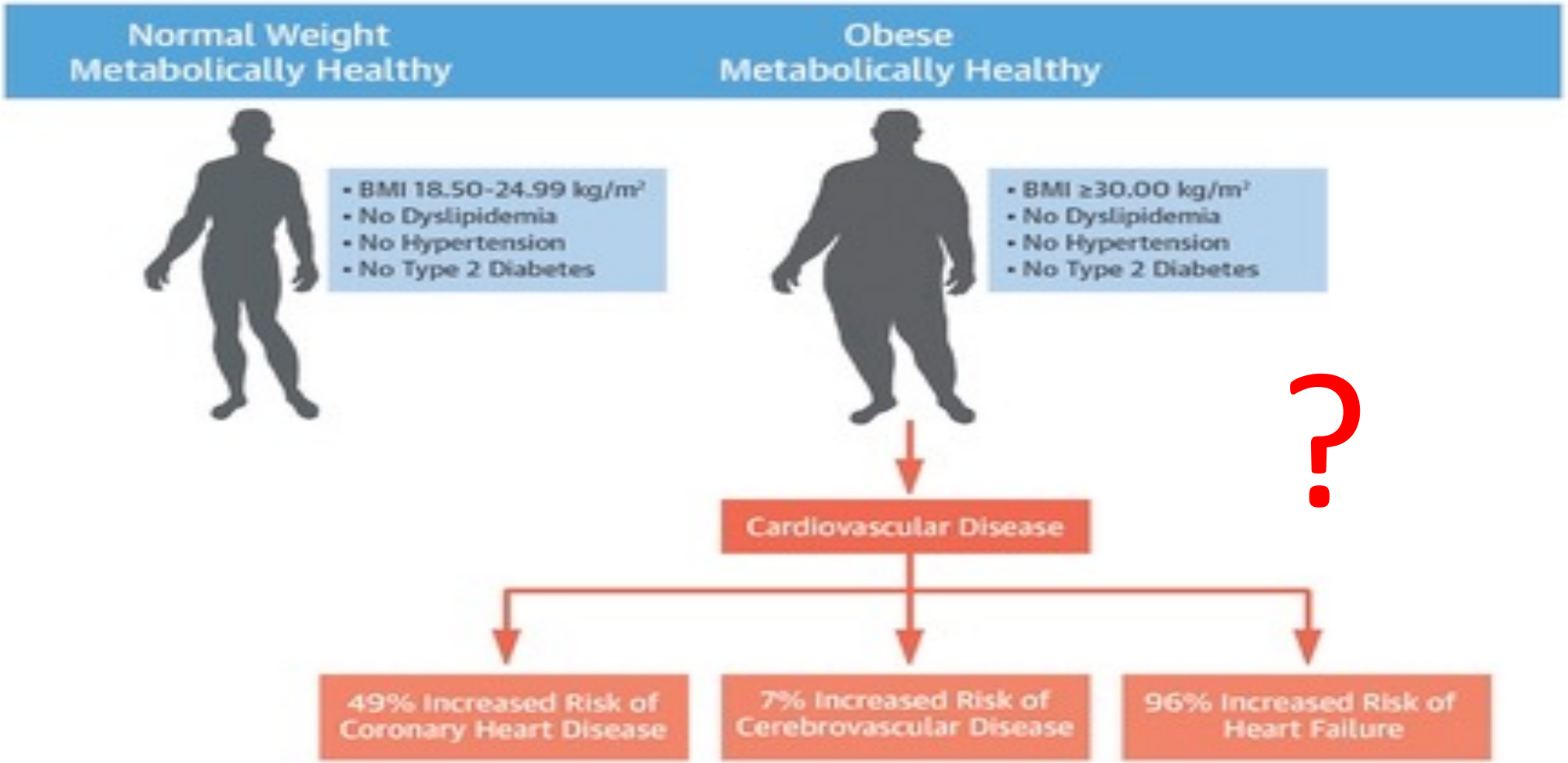


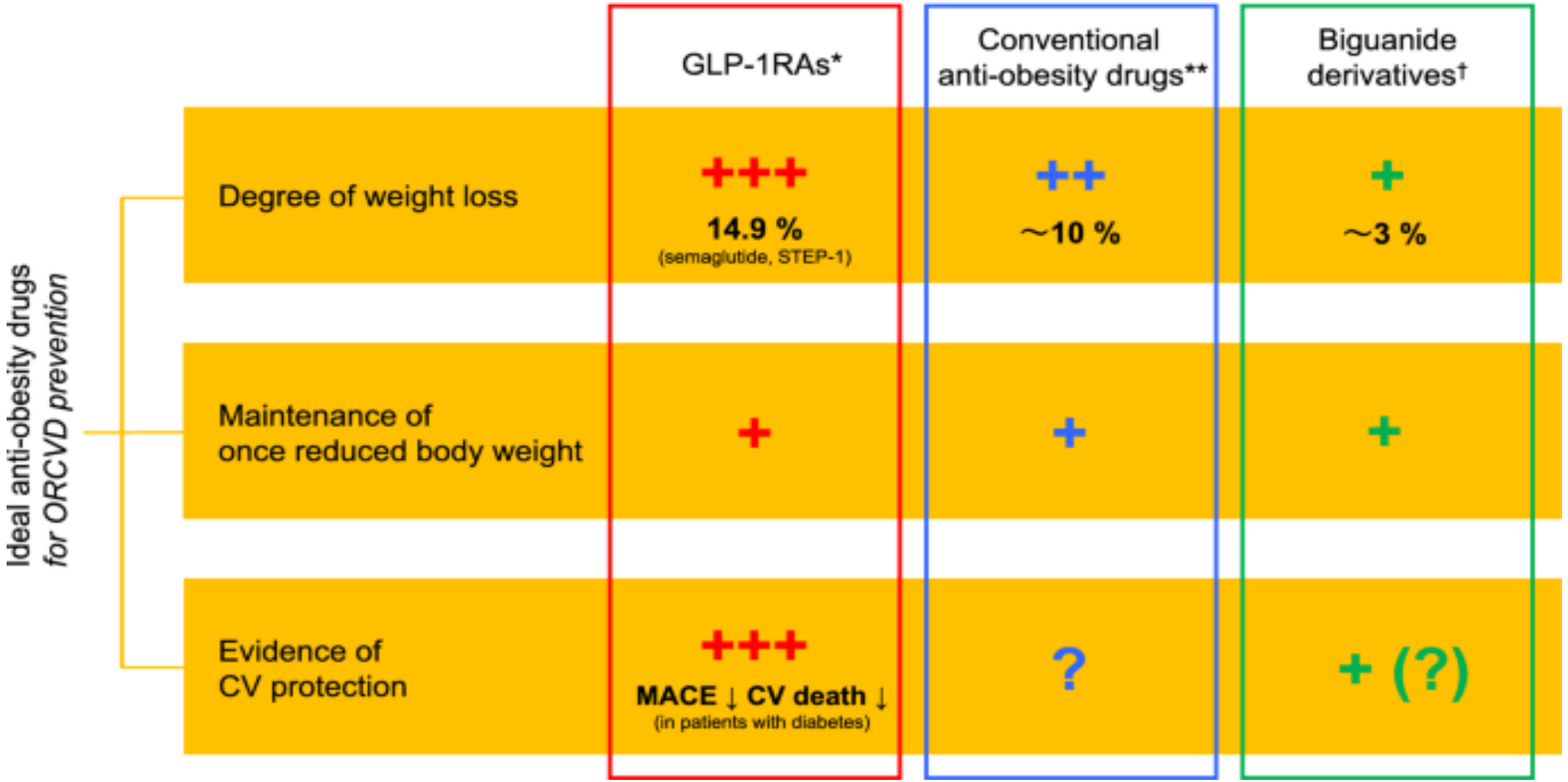
Figure 1 The pathophysiology underlying the link between excessive fat accumulation and the development of cardiovascular disease.

CENTRAL ILLUSTRATION: Metabolically Healthy Obese and Incident Cardiovascular Disease



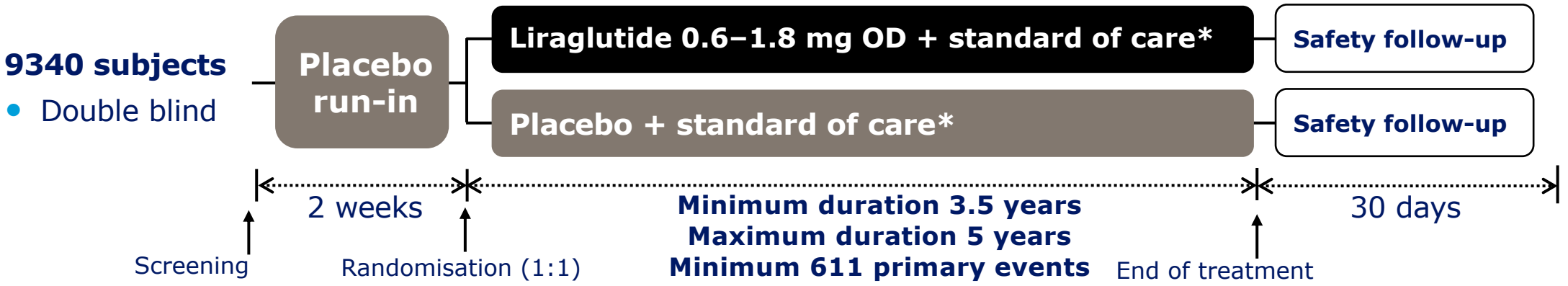
Caleyachetty, R. et al. J Am Coll Cardiol. 2017;70(12):1429-37.

Et puis ….


Ideal anti-obesity drugs
for ORCVD prevention
GLP-1RAs*
Conventional anti-obesity drugs**
Biguanide derivatives†
Degree of weight loss
+++
14.9 %
(semaglutide, STEP-1)
++
~10 %
+
~3 %
Maintenance of once reduced body weight
+
+
+
Evidence of CV protection
+++
MACE ↓ CV death ↓
(in patients with diabetes)
?
+ (?)

LEADER

Study design



Key inclusion criteria

- T2D, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

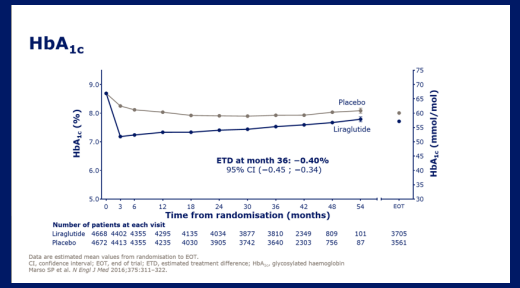
- T1D
- Use of GLP-1RAs, DPP-4i, pramlintide or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

*Medication intensification to achieve HbA_{1c} ≤7.0% when appropriate; add-on medications were TZDs, SUs, alpha glucosidase inhibitors (DPP-4 and incretin medications were not allowed)
CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; MEN-2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer; OAD, oral antidiabetic drug; OD, once daily; SU, sulphonylurea; T1D, type 1 diabetes; T2D, type 2 diabetes; TZD, thiazolidinedione
Marso SP et al. *N Engl J Med* 2016;375:311–322

LEADER

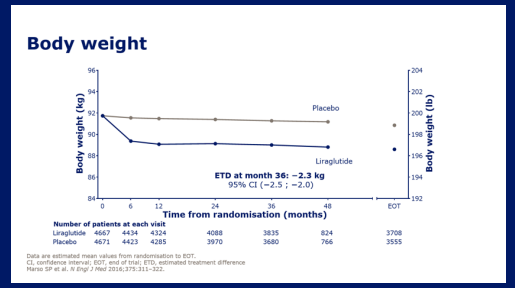
Impact on HbA_{1c}, weight, blood pressure and lipids

HbA_{1c}



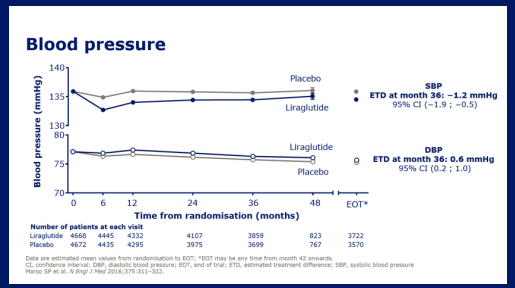
Treatment difference
–0.4%
95% CI (–0.45 ; –0.34)
p<0.001

Body weight



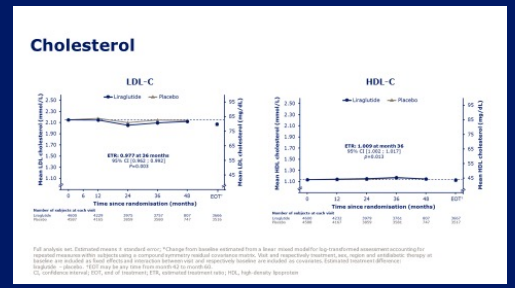
Treatment difference
–2.3 kg
95% CI (–2.54 ; –1.99)
p<0.001

SBP



Treatment difference
–1.2 mmHg
95% CI (–1.9 ; –0.5)
p<0.001

Lipids



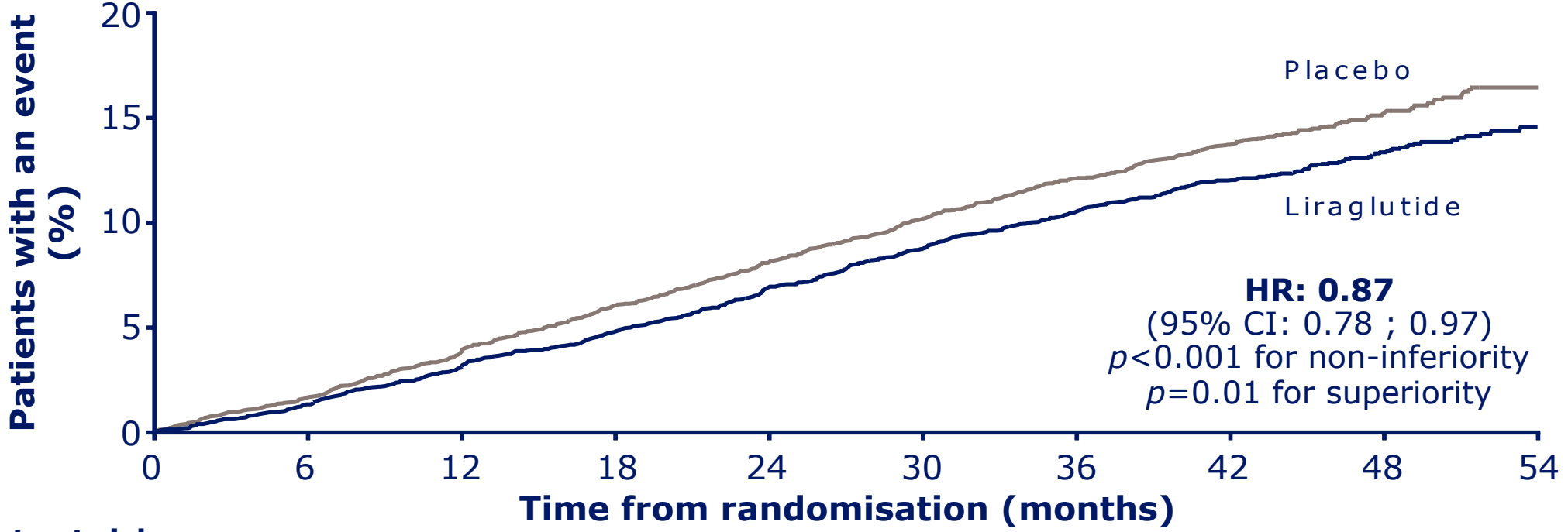
Small decrease
TC LDL-C and TGs

Small increase
HDL-C

CI, confidence interval; HbA_{1c}, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol ; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides
Marso SP et al. *N Engl J Med* 2016;375:311–322

LEADER: Primary outcome

CV death, non-fatal MI or non-fatal stroke



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from CV causes, non-fatal MI or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months

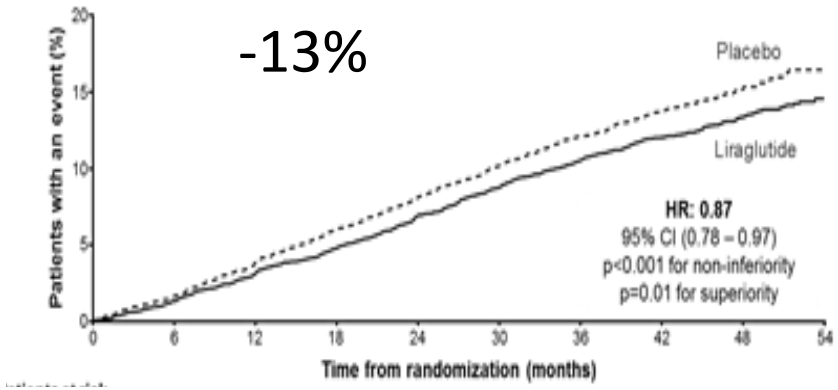
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction

Marso SP et al. *N Engl J Med* 2016;375:311–322

Résumé des résultats CV

Critère primaire
Mortalité CV, IDM non-fatal, ou AVC non-fatal

-13%

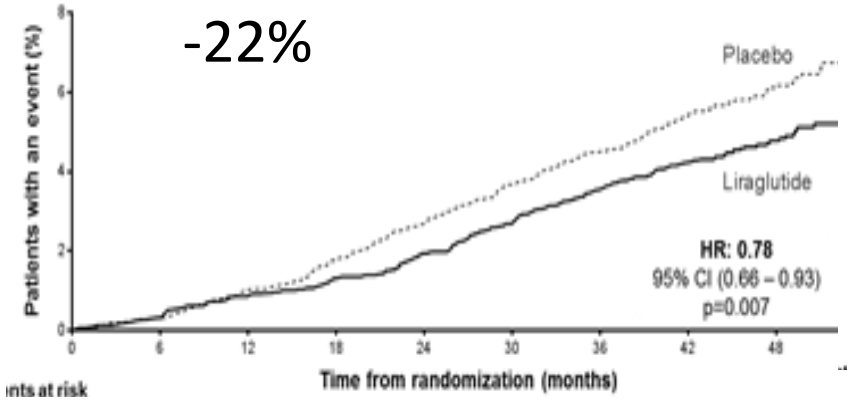


HR: 0.87
95% CI (0.78 ; 0.97)

P<0,001 for inferiority
p=0.01 for superiority

Mortalité CV

-22%

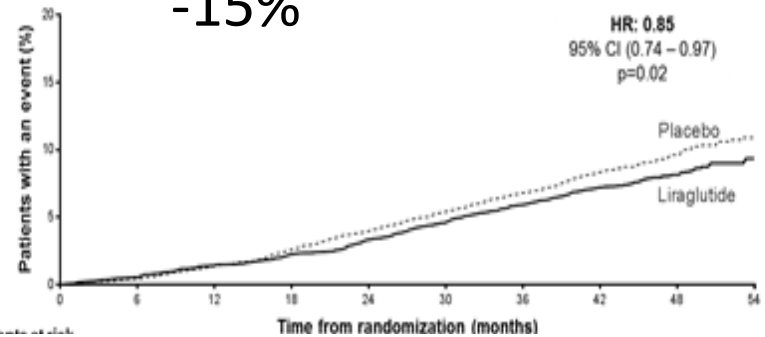


HR: 0.78
95% CI (0.66 ; 0.93)

p=0.007

Mortalité toutes causes

-15%



HR: 0.85
95% CI (0.74 ; 0.97)

p=0.02

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Leader

	All (n = 9340)	No prior CVD group (n = 1748)	Prior CVD group (n = 7592)
Age (years)	64.3 ± 7.2	65.8 ± 5.2	63.9 ± 7.6
Gender			
Female	3337 (35.7 %)	793 (45.4 %)	2544 (33.5 %)
Male	6003 (64.3 %)	955 (54.6 %)	5048 (66.5 %)
BMI (kg/m^2)			
<25.0	865 (9.3 %)	172 (9.8 %)	693 (9.1 %)
25 to <30	2671 (28.6 %)	520 (29.7 %)	2151 (28.3 %)
30 to <35	2987 (32.0 %)	535 (30.6 %)	2452 (32.3 %)
35 to <40	1715 (18.4 %)	310 (17.7 %)	1405 (18.5 %)
≥40.0	1092 (11.7 %)	210 (12.0 %)	882 (11.6 %)
WC ATIII target			

Donc LEADER: liraglutide

	Poids ↑	Poids ↓
Morbi moralité ↑		
Morbi moralité ↓		Liraglutide 1.8 mg **(obese DT2 à haut risque CV)**

Liraglutide 3.0 mg once-daily (SCALE)
(Obesity and pre-diabetes)
MAIS PAS une ETUDE DE MM CV

SUSTAIN 6 : semaglutide sous cutané

- Patient LEADER – like

(DT2 haut risque CV)

- Weight loss (placebo-controlled weight loss of 2.9 and 4.3 kg) with 0.5 and 1mg dose in SUSTAIN 6

Trial	SUSTAIN 6 [Marso 2016a]
Comparison	Once-weekly subcutaneous semaglutide 0.5/1.0 mg vs. placebo
N	3,297
Age, y	65 ± 7
Female sex, %	39.3
Diabetes duration, y	13.9 ± 8.1
HbA_{1c}, %	8.7 ± 1.5
Body weight, kg	92.1 ± 20.6
Body mass index, kg/m^2	32.8 ± 6.2
Age ≥50 years and presence of CVD and/or CKD*, %	83.0
Age ≥60 years and presence of CV risk factors only, %	17.0
Established CVD without CKD, %	58.8
CKD without CVD, %	10.7
Established CVD with CKD, %	13.4
Prior myocardial infarction, %	32.5
Prior heart failure (NYHA class II or III), %	23.6
Prior moderate renal impairment, %	25.2

Mean values ± standard deviation unless otherwise stated.
**CKD was taken as an equivalent to existing CVD.*
CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovas
glycated hemoglobin; NA, not available; NYHA, New York Heart As

Front. Endocrinol., 29 March 2021

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

Donc SUSTAIN 6 < LEADER

	Poids ↑	Poids ↓
Morbi moralité ↑		
Morbi moralité ↓		Liraglutide 1.8 mg **(obese DT2 à haut risque CV)** Semaglutide **(obese DT2 à haut risque CV)**

PIONEER 6: semaglutide oral

- Patient LEADER – like

(DT2 haut risque CV)

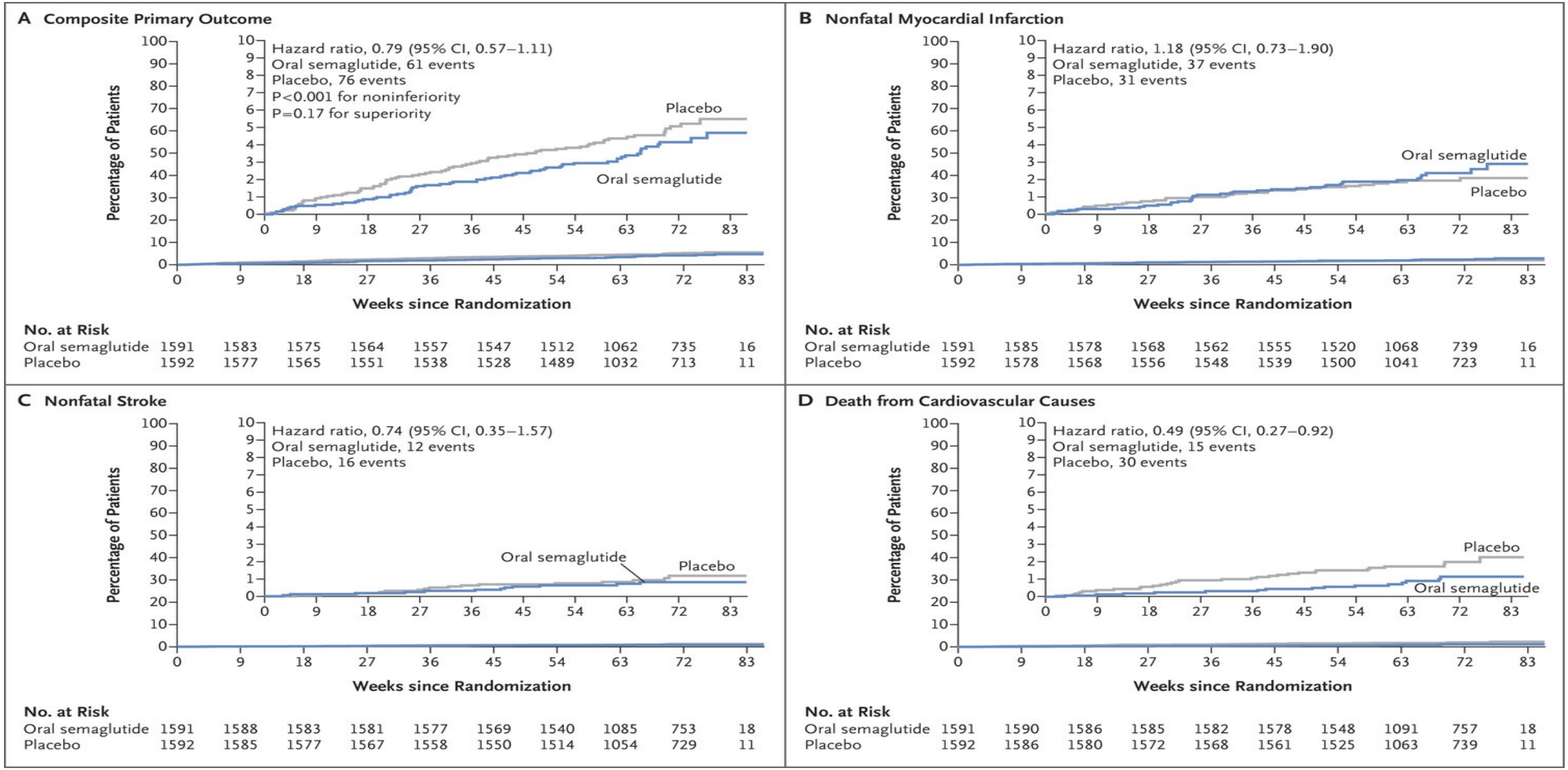
- Weight loss (placebo-controlled weight loss of 3.4 kg) in PIONEER 6.

Trial	SUSTAIN 6 [Marso 2016a]	PIONEER 6 [Husain 2019]
Comparison	Once-weekly subcutaneous semaglutide 0.5/1.0 mg vs. placebo	Once-daily oral semaglutide 14 mg vs. placebo
N	3,297	3,183
Age, y	65 ± 7	66 ± 7
Female sex, %	39.3	31.6
Diabetes duration, y	13.9 ± 8.1	14.9 ± 8.5
HbA_{1c}, %	8.7 ± 1.5	8.2 ± 1.6
Body weight, kg	92.1 ± 20.6	90.9 ± 21.2
Body mass index, kg/m^2	32.8 ± 6.2	32.3 ± 6.5
Age ≥50 years and presence of CVD and/or CKD*, %	83.0	84.7
Age ≥60 years and presence of CV risk factors only, %	17.0	15.3
Established CVD without CKD, %	58.8	NA
CKD without CVD, %	10.7	NA
Established CVD with CKD, %	13.4	NA
Prior myocardial infarction, %	32.5	36.1
Prior heart failure (NYHA class II or III), %	23.6	12.2
Prior moderate renal impairment, %	25.2	28.2

Mean values ± standard deviation unless otherwise stated.
**CKD was taken as an equivalent to existing CVD.*
CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin; NA, not available; NYHA, New York Heart Association; y, years.

Front. Endocrinol., 29 March 2021

PIONEER 6: semaglutide oral



N Engl J Med 2019;381:841-851

Donc PIONEER 6 : non !
SUSTAIN 6 < LEADER

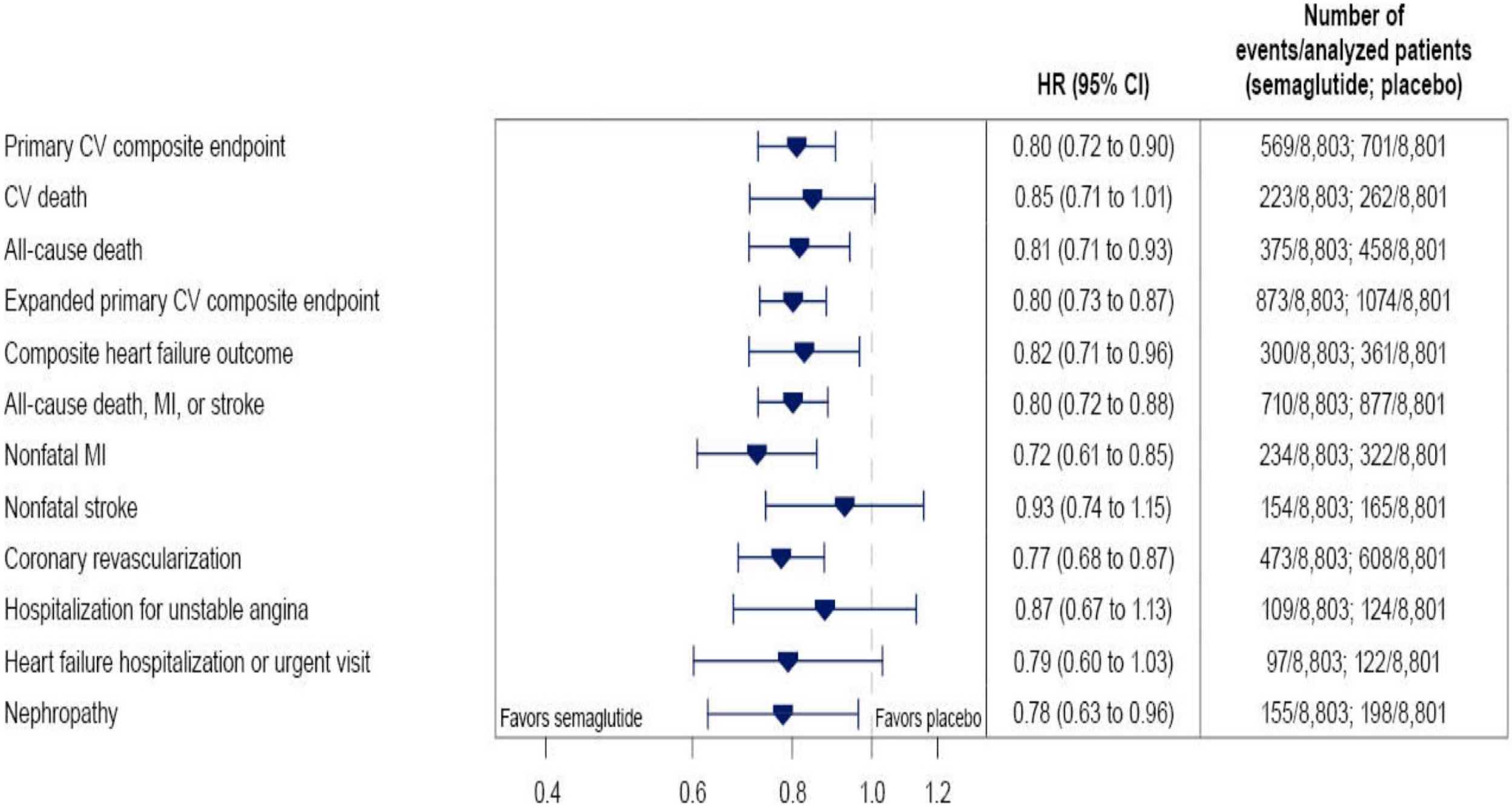
	Poids ↑	**Poids** ↓
Morbi moralité ↓		Liraglutide 1.8 mg **(obese DT2 à haut risque CV)** Semaglutide **0.5-1 mg s.s cut (obese DT2 à haut risque CV)**
Morbi moralité ↔		Semaglutide **0.5-1 mg s.s cut (obese DT2 à haut risque CV)**

SELECT : semaglutide sous cut.

- Patient obèse ou en surpods
- Absence de diabète
- En prévention secondaire

BMI‡		
Mean – kg/m^2	33.3 ± 5.0	33.4 ± 5.0
Distribution, kg/m^2 – no. (%)		
<30	2,555 (29.0)	2,469 (28.1)
30 to <35	3,693 (42.0)	3,781 (43.0)
35 to <40	1,687 (19.2)	1,659 (18.9)
40 to <45	579 (6.6)	595 (6.8)
≥45	289 (3.3)	297 (3.4)

History of CVD – no. (%)		
Coronary heart disease	7,234 (82.2)	7,218 (82.0)
MI	6,729 (76.4)	6,709 (76.2)
Coronary revascularization	5,933 (67.4)	5,916 (67.2)
Stroke	2,058 (23.4)	2,052 (23.3)
Symptomatic PAD	754 (8.6)	771 (8.8)
Chronic heart failure	2,155 (24.5)	2,131 (24.2)
Hypertension	7,206 (81.9)	7,186 (81.6)

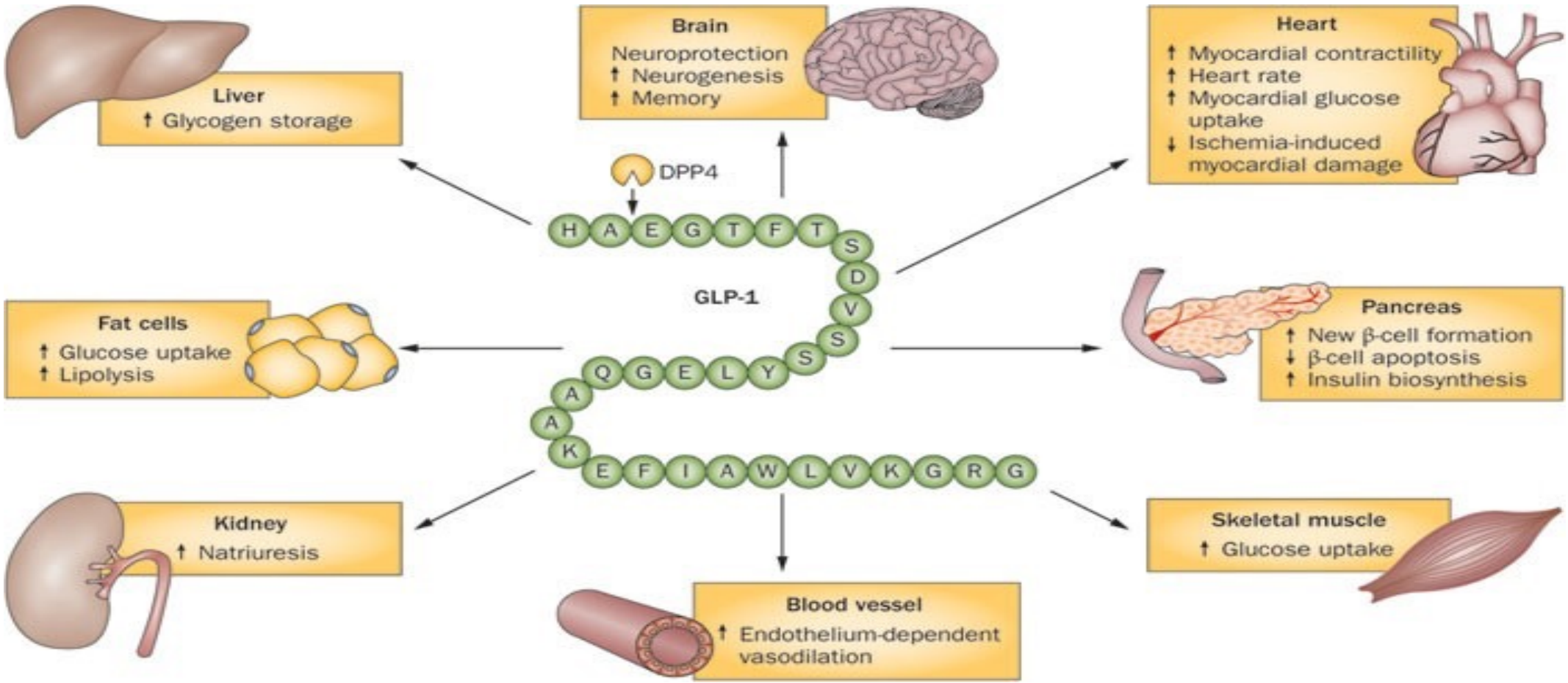

HR (95% CI)
Number of events/analyzed patients (semaglutide; placebo)
Primary CV composite endpoint
0.80 (0.72 to 0.90)
569/8,803; 701/8,801
CV death
0.85 (0.71 to 1.01)
223/8,803; 262/8,801
All-cause death
0.81 (0.71 to 0.93)
375/8,803; 458/8,801
Expanded primary CV composite endpoint
0.80 (0.73 to 0.87)
873/8,803; 1074/8,801
Composite heart failure outcome
0.82 (0.71 to 0.96)
300/8,803; 361/8,801
All-cause death, MI, or stroke
0.80 (0.72 to 0.88)
710/8,803; 877/8,801
Nonfatal MI
0.72 (0.61 to 0.85)
234/8,803; 322/8,801
Nonfatal stroke
0.93 (0.74 to 1.15)
154/8,803; 165/8,801
Coronary revascularization
0.77 (0.68 to 0.87)
473/8,803; 608/8,801
Hospitalization for unstable angina
0.87 (0.67 to 1.13)
109/8,803; 124/8,801
Heart failure hospitalization or urgent visit
0.79 (0.60 to 1.03)
97/8,803; 122/8,801
Nephropathy
0.78 (0.63 to 0.96)
155/8,803; 198/8,801
Favors semaglutide
Favors placebo
0.4
0.6
0.8
1.0
1.2

Donc PIONEER 6 : non !

SUSTAIN 6 < LEADER= SELECT (non diabetique! en prevention secondaire !)

	Poids ↑	**Poids** ↓
Morbi moralité ↑		
Morbi moralité ↓		Liraglutide 1.8 mg **(obese DT2 à haut risque CV)** Semaglutide **0.5-1 mg s.s cut (obese DT2 à haut risque CV)**
Morbi moralité ↓		Semaglutide **s.s cut (surpoids ou obese en prévention secondaire)**

Ca marche comment ?



Nature Reviews Endocrinology **volume 8**, pages 728–742 (2012)

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trial of Lixisenatide in Early Parkinson's Disease

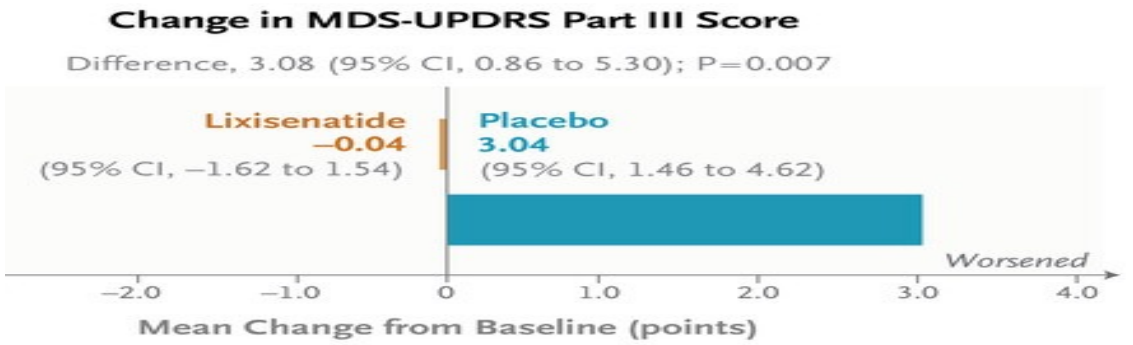
Meissner WG et al. DOI: 10.1056/NEJMoa2312323

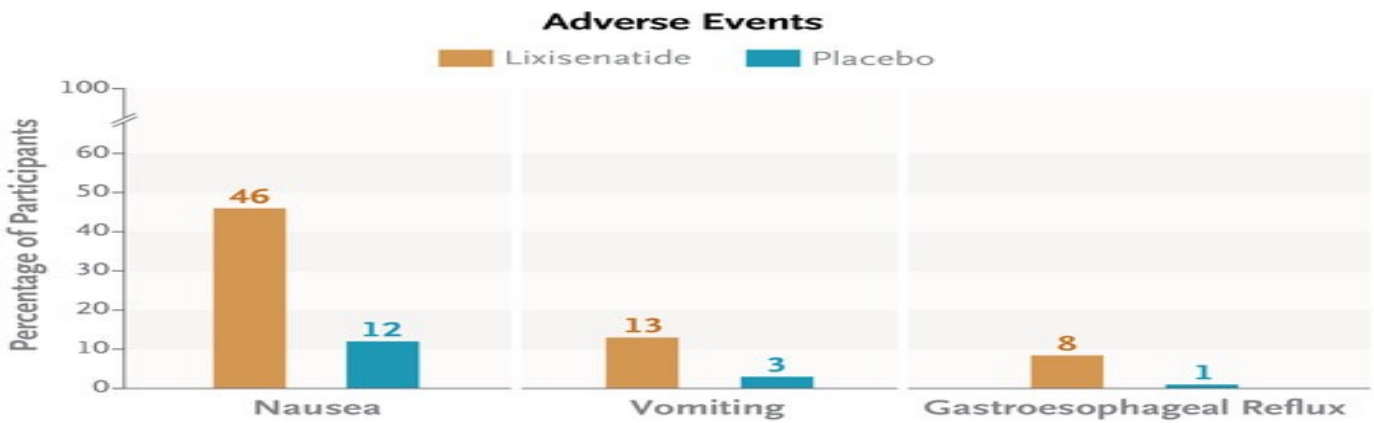
Participants with Parkinson's disease diagnosed <3 yr earlier

Administered subcutaneously every day for 12 mo

CONCLUSIONS

In participants with early Parkinson's disease, add-on treatment with lixisenatide for 12 months limited motor disability progression but was associated with gastrointestinal side effects.





N Engl J Med 2024;390:1176-1185

En pratique 1: validité externe.

	Liraglutide	Semaglutide s/s cut	Semaglutide per os
Obese DT2 haut risque CV (prevention I et II)	LEADER +++	SUSTAIN 6 ++	PIONEER 6 NON
Surpoids ou Obèse Non diabetique En prevention secondaire		SELECT +++	

En pratique 2: extrapolation des données.

Dapagliflozin for heart failure according to body mass index: A prespecified analysis of the DELIVER trial

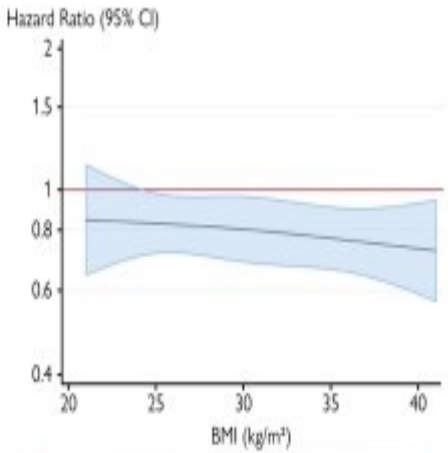
6257 patients in DELIVER trial with a recorded BMI measurement at baseline

- HFpEF or HFmrEF
- Randomized to dapagliflozin or matched placebo

- 45% patients were obese
- 78% were obese or overweight

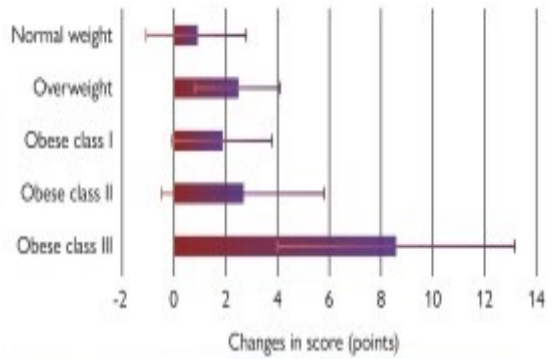
Prespecified analysis by baseline BMI

Primary outcome (worsening HF or CV death)

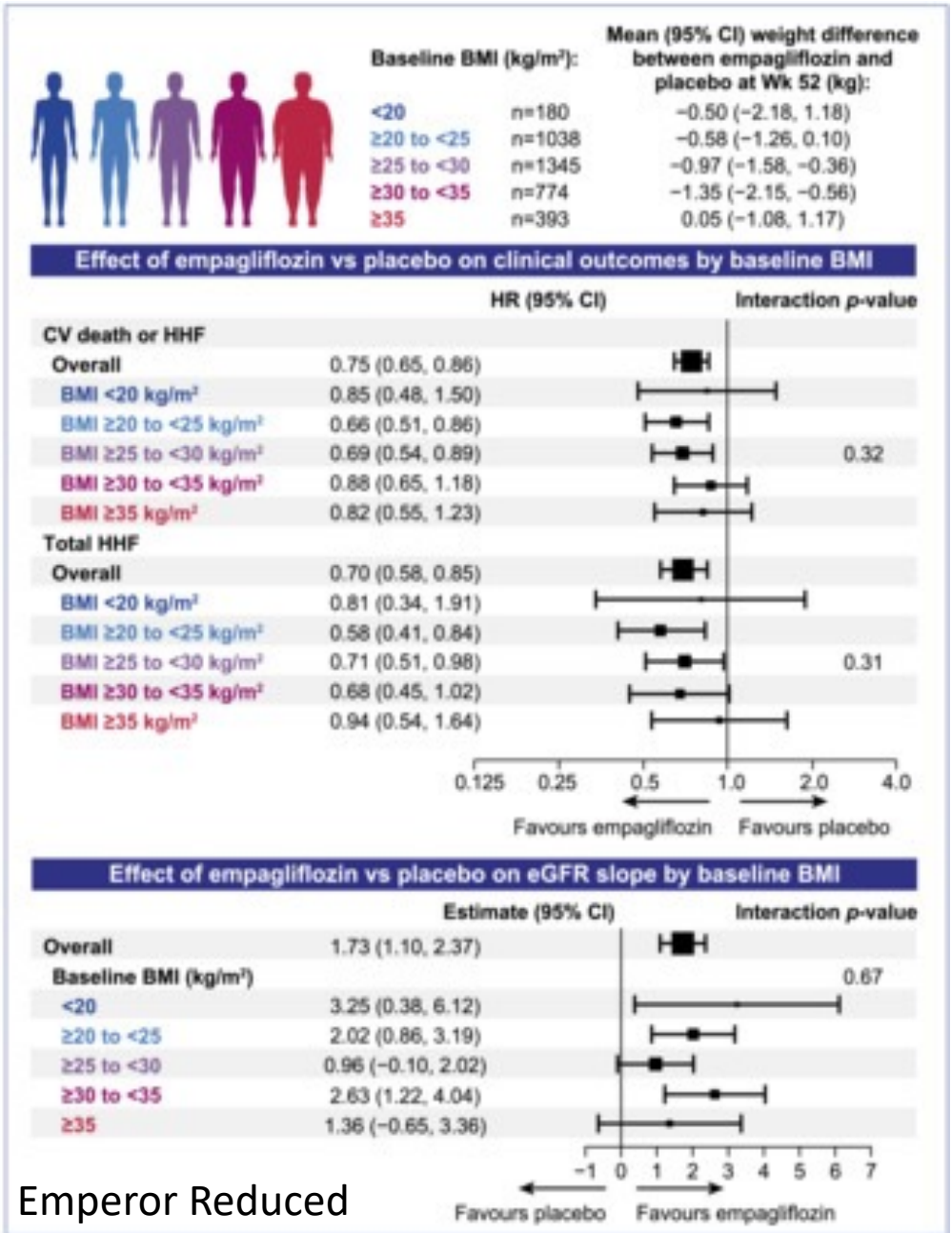


Dapagliflozin reduced the incidence of primary outcome, regardless of baseline BMI

Mean change in KCCQ-TSS from baseline to 8 months according to BMI category



Larger increases (improvement) in KCCQ-TSS were seen in patients with obesity



Emperor Reduced

Baseline Characteristics

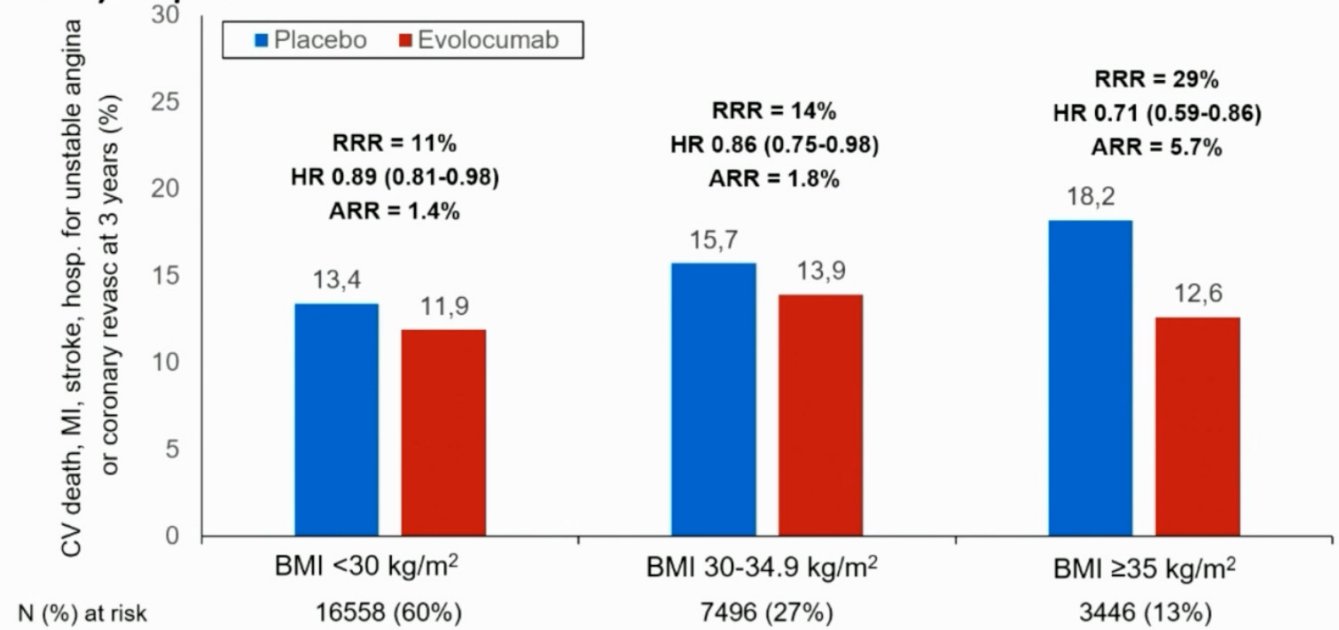
Characteristic	BMI Categories (kg/m²) BMI <25.0 N=5,012 (18%)	BMI 25.0-29.9 N=11,546 (42%)	BMI 30-34.9 N=7,496 (27%)	BMI ≥35 N=3,446 (13%)
Age (years)	64	64	62	60
Male	72%	80%	76%	65%
Region				
Asia Pacific	26%	14%	9%	7%
Europe	55%	66%	67%	57%
Latin America	7%	7%	6%	5%
North America	11%	14%	18%	31%
Prior coronary artery disease	83%	87%	87%	86%
Diabetes mellitus	25%	32%		
Multivessel disease	21%	22%		
High-intensity statin use	62%	69%		
Baseline LDL-C (mg/dL)	92	92		
Baseline lipoprotein(a) (nmol/L)	42	37		
Baseline hsCRP (mg/L)	1.3	1.5		

Continuous variables are presented as the median, and

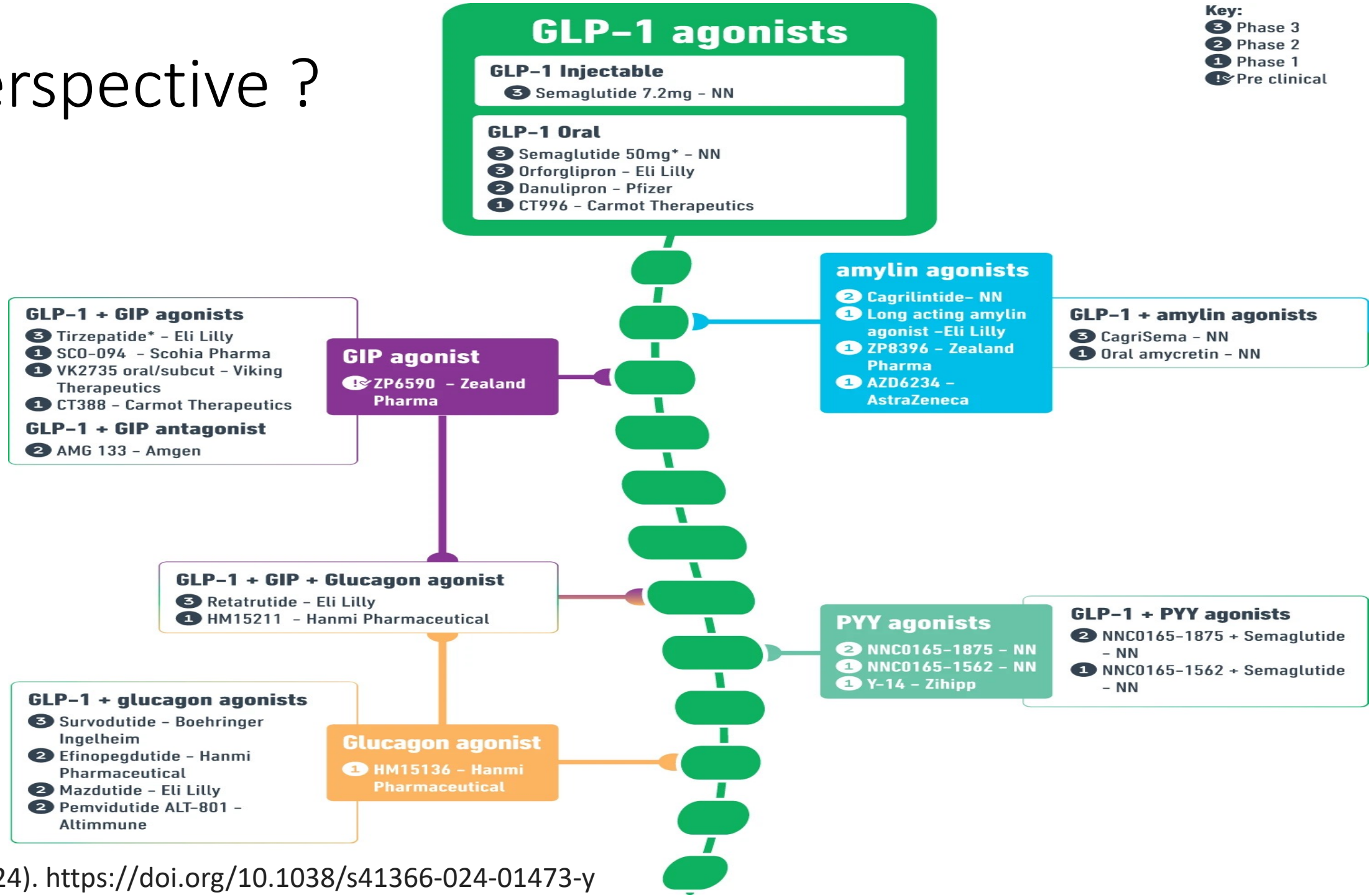
P-Trend < 0.01 for

Efficacy of Evolocumab by Baseline BMI

Primary endpoint

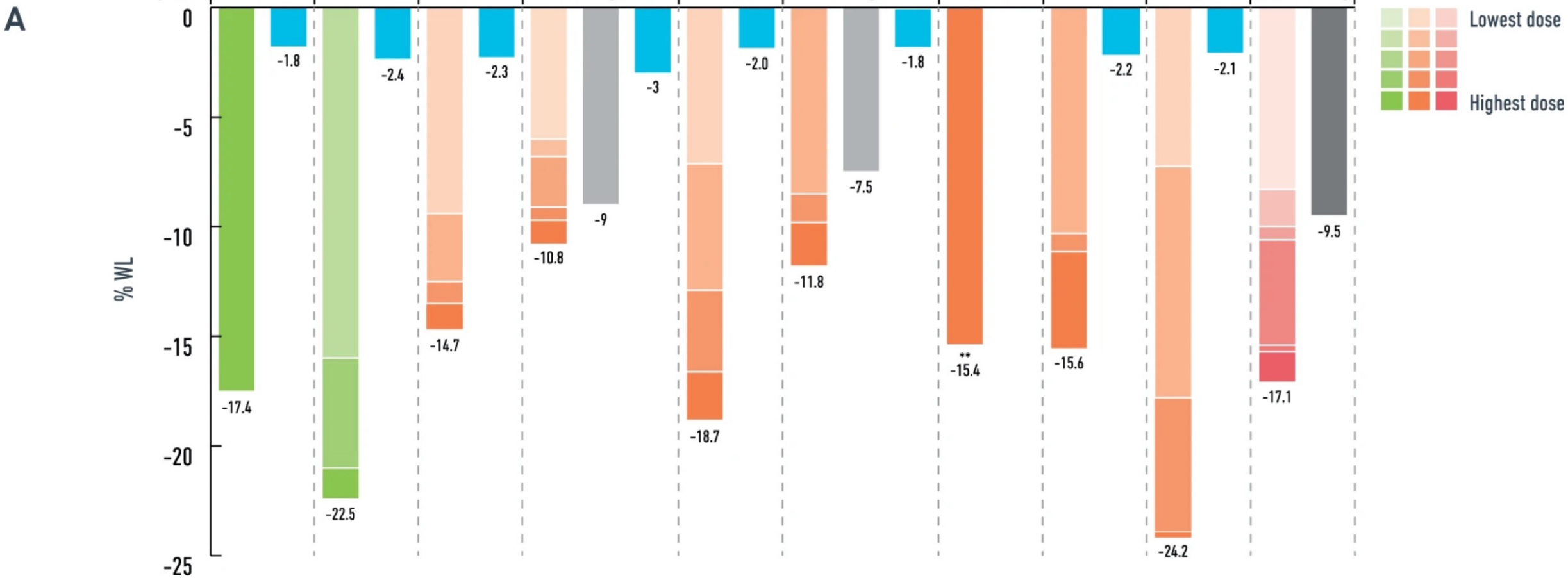


En perspective ?



Int J Obes (2024). https://doi.org/10.1038/s41366-024-01473-y

	Oral Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Cagrilintide[A]	Survodutide[A*]	Efinopegdutide[B]	Mazdutide[C**]	Pemvidutide[A*]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.4/10mg OW	9mg OW	1.2/1.8/2.4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Number of participants	667	2539	272	706	387	474	80	391	338	95
Timepoint (weeks)	68	72	36	26	46	26	24	48	48	20
Baseline weight (kg)	105.4	104.8	108.7	107.4	105.7	113.3	96.9	104	107.7	95.7 - 99.6
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg



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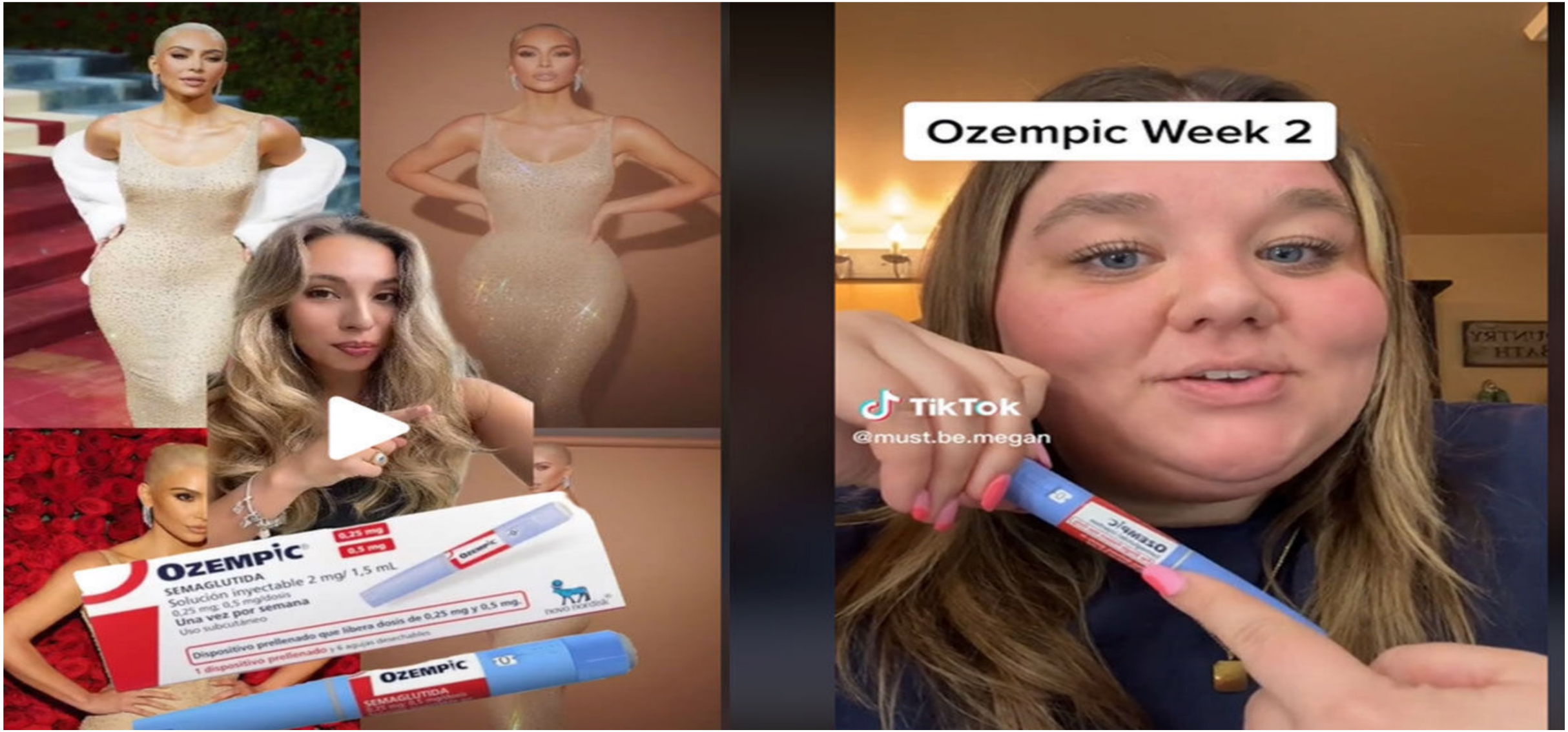
Pharmacologie sociale: médicamentation de la société ?



Pharmacologie sociale: médicamentation de la société ?

QUE CHOISIR

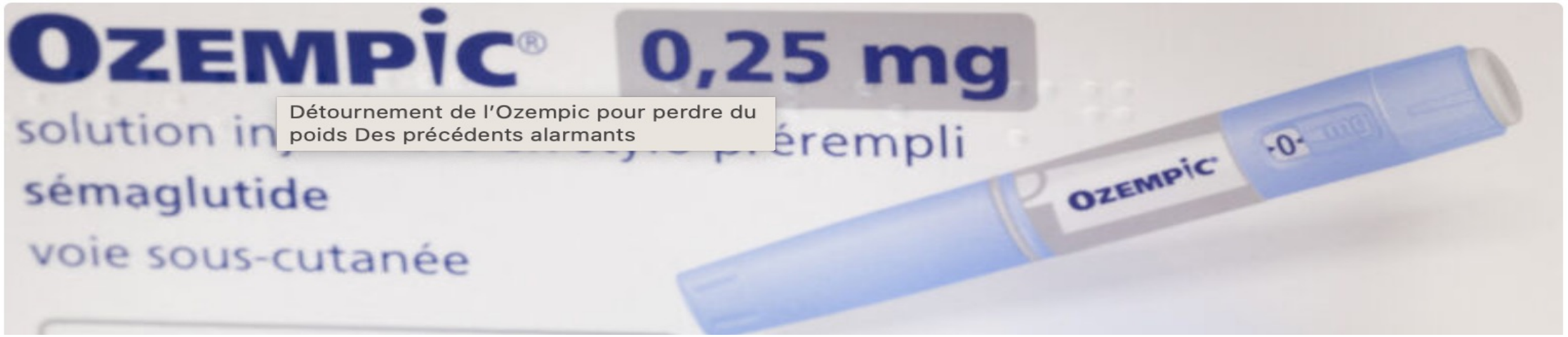
Tests Actualités Services Nos combats

Alimentation > Nutrition > Obésité

ACTUALITÉ

Détournement de l'Ozempic pour perdre du poids

Des précédents alarmants



Détournement de l'Ozempic pour perdre du poids Des précédents alarmants

Conclusions

- Peut on (Doit on?) traiter une maladie sans modifier le comportement
- Médicaments améliorent le pronostic CV des patients obèses
- Médicament spécifique des patients obèses ? Ou inclure des patients obèses dans tous les essais
- Tous égaux face à l'obésité ?
- Effet yoyo
- Bénéfices à long terme et Risques à long terme
- siRNA ?