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Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

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La question clinique

Chez les personnes avec diabète type 2 et à risque cardiovasculaire élevé (MCAS, MVAS et/ou maladie rénale chronique), est-ce que le sémaglutide oral est efficace et sécuritaire pour diminuer les événements cardiovasculaires majeurs comparativement au placébo ?

Mise en contexte

Méthode

Devis : essai clinique randomisé (quadruple insu).

Population : 9 650 adultes de 50 ans et plus avec diabète type 2, avec une HbA1c 6,5-10 % et présentant une maladie cardiovasculaire athérosclérotique connue, une maladie rénale chronique, ou les deux, sans contre-indication (IM, AVC, hospitalisation pour AI ou AIT < 60 jours, revascularisation vasculaire planifiée).

Méthode

Intervention : Sémaglutide oral (3-7-14 mg die) à prendre le matin à jeun, combiné au traitement standard.

Comparateur : Placébo oral à prendre le matin à jeun, combiné au traitement standard.

Objectifs : critère de jugement principal : composite de décès d'origine cardiovasculaire, d'infarctus du myocarde non fatal et d'accident vasculaire cérébral non fatal.

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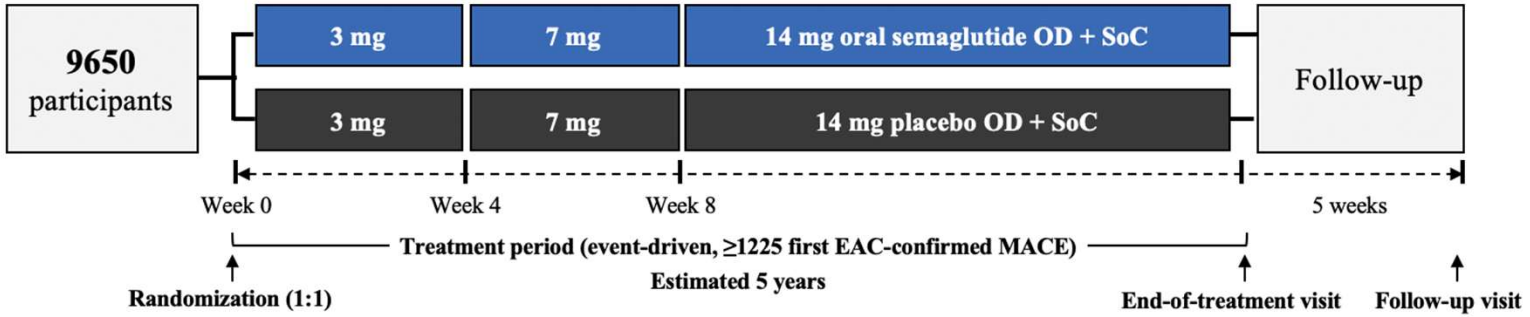
SOUL trial design

NCT03914326



Objective:
To assess the CV efficacy of oral semaglutide with regards to the risk of MACE compared with placebo in persons with T2D and at high risk of CV events

Key inclusion criteria*

- Age ≥50 years
- Diagnosed with T2D
- HbA_{1c} 6.5–10.0% (47–86 mmol/mol)
- History of ≥1 of the following conditions:
  - Coronary heart disease
  - Cerebrovascular disease
  - Symptomatic peripheral arterial disease
  - Chronic kidney disease†

Trial information

- Randomized, double-blind, parallel-group, placebo-controlled trial
- Group sequential design with one interim test for superiority
- Trial product added on top of SoC
- Dose reductions and treatment pauses allowed
- Selective safety reporting

*Established at screening.
†Defined as eGFR <60 mL/min/1.73 m² based on medical records ≤6 months old.
CV, cardiovascular; EAC, events adjudication committee; HbA_{1c}, glycated hemoglobin; MACE, major adverse cardiovascular event; OD, once daily; SoC, standard of care; T2D, type 2 diabetes

Analyses statistiques

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SOUL trial outcomes and testing hierarchy

Primary outcome: 3-point MACE
CV death, nonfatal myocardial infarction, nonfatal stroke

↓ Superiority if $p<0.02281^{*}$

First confirmatory secondary outcome: 5-point composite kidney outcome
eGFR <15 mL/min/1.73 m^2, chronic kidney replacement therapy

↓ Superiority if $p<0.02216^{*}$

Second confirmatory outcome: CV death†

↓ Superiority if $p<0.02245^{*}$

Third confirmatory outcome: Major adverse limb events
Acute or chronic limb ischemia requiring hospitalization

Superiority if $p<0.02267^{*}$

Supporting secondary outcomes included:

- Individual components of composite outcomes
- Coronary revascularization
- Hospitalization for unstable angina
- Death from non-CV causes
- Heart failure composite
- Metabolic parameters
- Inflammation markers
- Safety

*Limit determined by the Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries accounting for the group sequential design (interim analysis). The significance level depended on the exact number of events at interim and final analyses
†Includes undetermined cause of death
CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event

Contexte

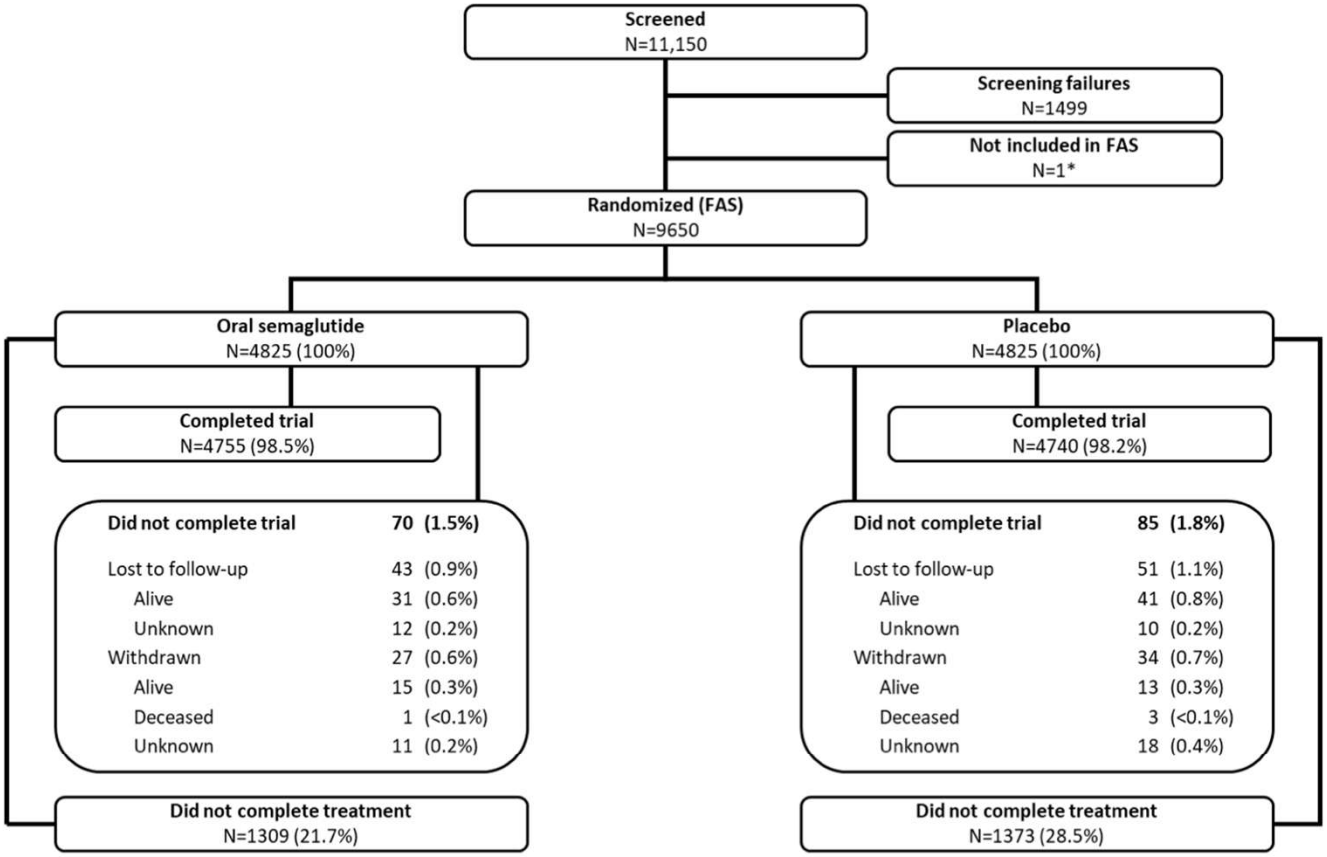
Suivi : 48 mois (4 ans) en moyenne

Suivi des patients = 98,4 %.

Sites : 444 sites de 33 pays (Canada, É-U, France, R-U...)

Financement : commandité par Novo Nordisk.

Flot des participants



*Randomization was removed due to one participant being randomized more than once.

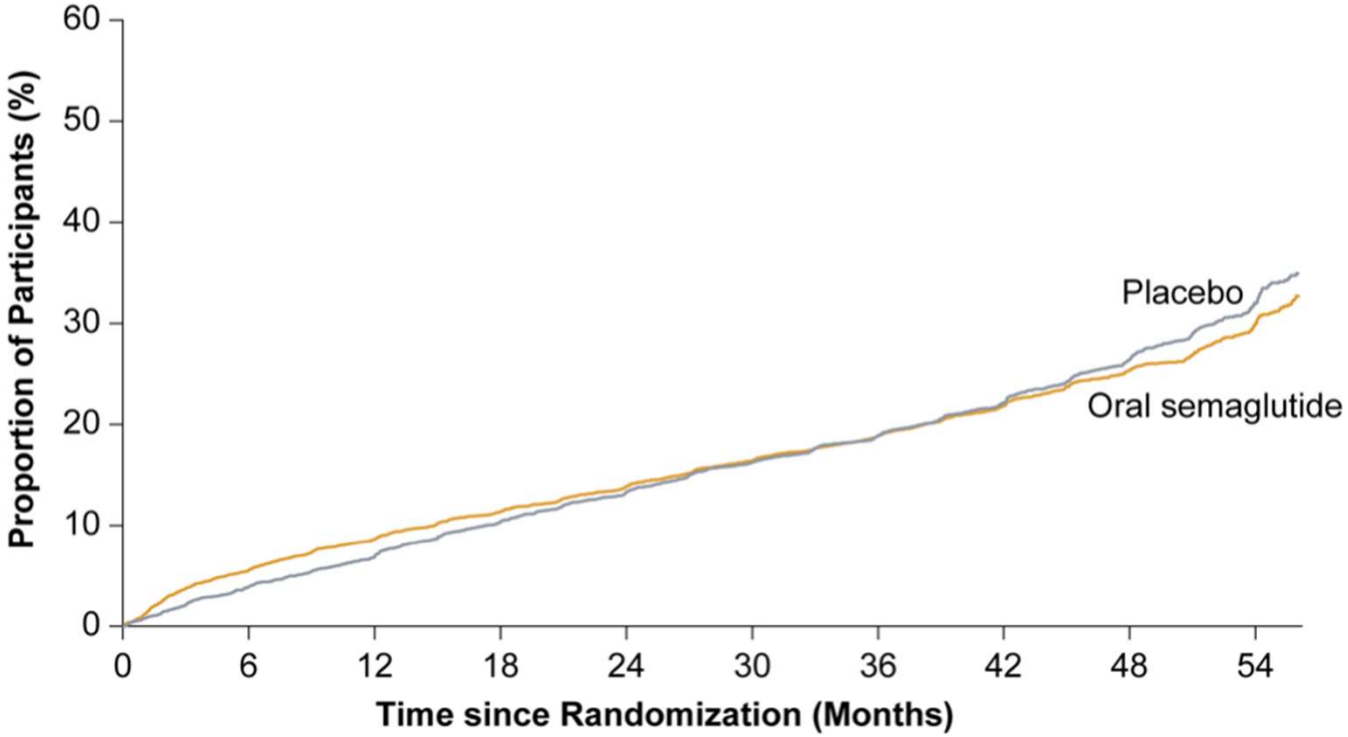
Participants who completed the trial were defined as those who attended the follow-up visit or died during the trial. Mean duration of exposure to treatment was 42.0±15.5 months overall (41.8±15.9 months for oral semaglutide and 42.1±15.1 months for placebo).

Caractéristiques des participants

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Oral Semaglutide (N=4825)	Placebo (N=4825)
Age — yr	66.1±7.6	66.1±7.5
Female sex — no. (%)	1376 (28.5)	1414 (29.3)
Race or ethnic group — no. (%)†		
White	3327 (69.0)	3321 (68.8)
Black	124 (2.6)	128 (2.7)
Asian	1134 (23.5)	1121 (23.2)
American Indian or Alaska Native	7 (0.1)	12 (0.2)
Native Hawaiian or Pacific Islander	4 (<0.1)	5 (0.1)
Other	185 (3.8)	192 (4.0)
Not reported	44 (0.9)	46 (1.0)
Hispanic or Latino ethnic group — no. (%)†	674 (14.0)	706 (14.6)
Body weight — kg	87.5±19.1	88.3±19.6
Body-mass index‡	31.0±5.7	31.2±5.9
Glycated hemoglobin level — mmol/mol	63.6±12.6	63.5±12.3
Glycated hemoglobin level — %	8.0±1.2	8.0±1.1
Median duration of diabetes (IQR) — yr	14.7 (9.0–20.8)	14.6 (8.9–20.8)
History of cardiovascular or kidney disease — no. (%)§		
Cardiovascular disease only	2730 (56.6)	2738 (56.7)
Chronic kidney disease only	632 (13.1)	609 (12.6)
Both cardiovascular and chronic kidney disease	1303 (27.0)	1317 (27.3)
Hypertension — no. (%)	4378 (90.7)	4381 (90.8)
Current smoking — no. (%)	545 (11.3)	584 (12.1)
Systolic blood pressure — mm Hg	134.6±16.3	134.7±16.4
Diastolic blood pressure — mm Hg	76.6±10.1	76.7±10.1
Pulse — beats/min	72.8±11.1	72.9±11.4
Median high-sensitivity C-reactive protein level (IQR) — mg/liter	2.0 (0.9–4.3)	2.0 (0.9–4.5)
eGFR — ml/min/1.73 m^2¶	74.0±22.6	73.6±22.6

B Cumulative Incidence Plot for Participants who Permanently Discontinued Treatment



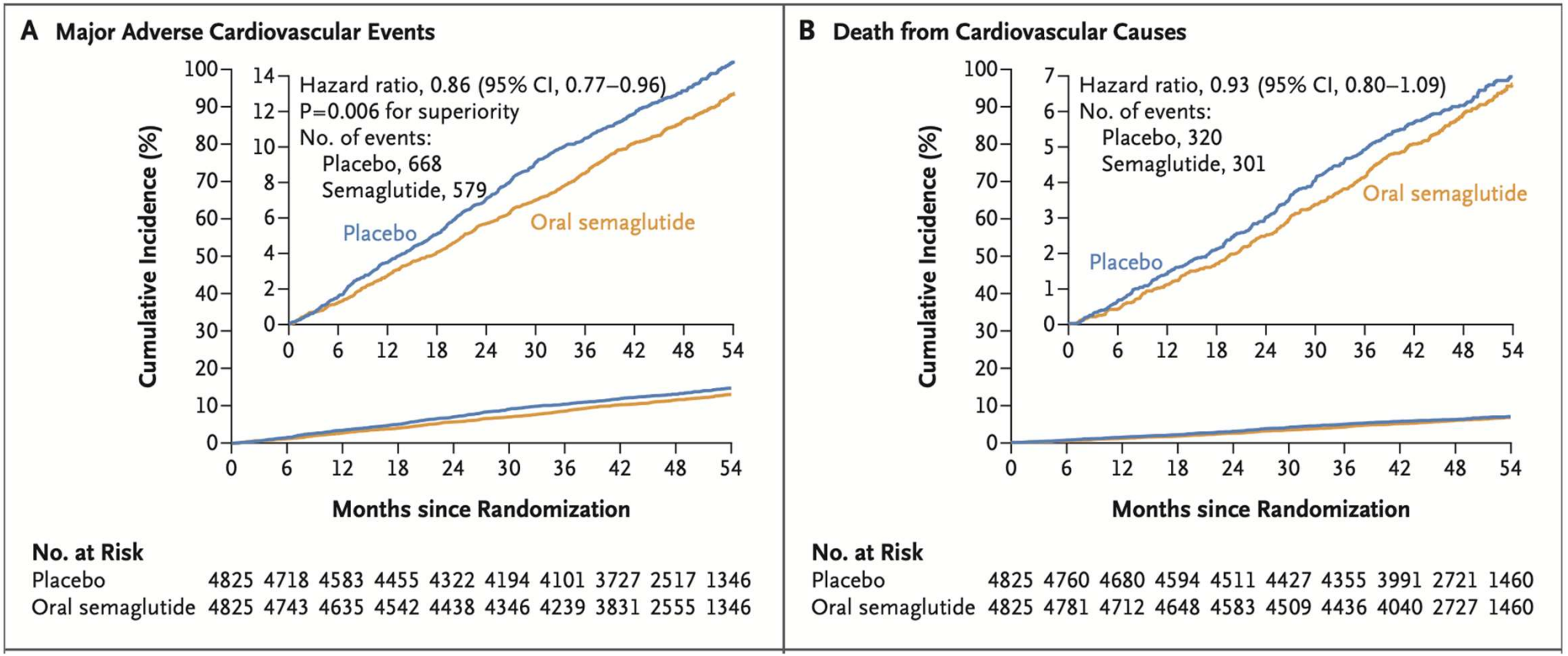
No. at Risk

Placebo	4825	4609	4438	4245	4073	3903	3753	3166	2011	751
Oral semaglutide	4825	4534	4364	4212	4070	3935	3792	3209	2058	789

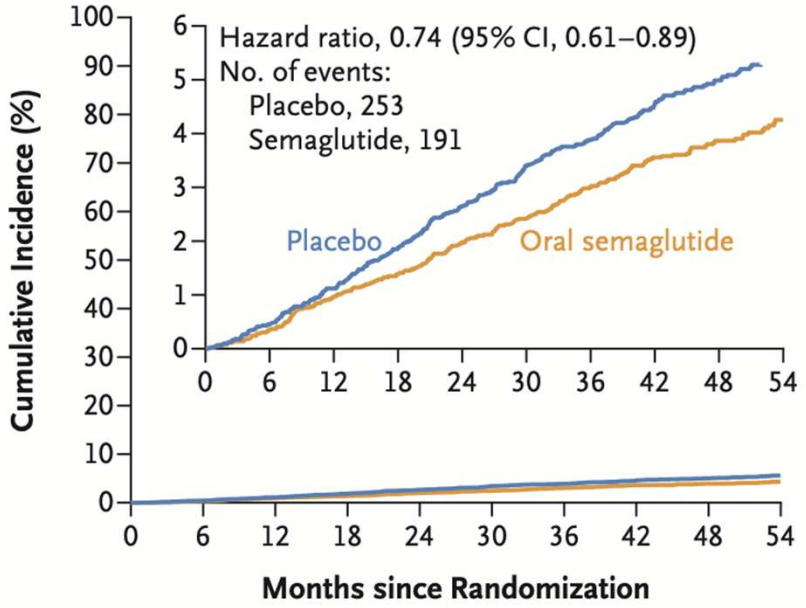
Résultats

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Oral Semaglutide (N=4825)		Placebo (N=4825)		Hazard Ratio (95% CI)	P Value†
	no. of participants with event (%)	*no. of events per 100 person-yr*	*no. of participants with event (%)*	*no. of events per 100 person-yr*		
Primary outcome						
Major adverse cardiovascular events, three-point composite‡	579 (12.0)	3.1	668 (13.8)	3.7	0.86 (0.77–0.96)	0.006
Confirmatory secondary outcomes						
Major kidney disease events, five-point composite§	403 (8.4)	2.1	435 (9.0)	2.3	0.91 (0.80–1.05)	0.19
Death from cardiovascular causes	301 (6.2)	1.6	320 (6.6)	1.7	0.93 (0.80–1.09)	—
Major adverse limb events, two-point composite¶	71 (1.5)	0.4	99 (2.1)	0.5	0.71 (0.52–0.96)	—
Supportive secondary outcomes						
Major adverse cardiovascular events, five-point composite‖	670 (13.9)	3.6	777 (16.1)	4.3	0.84 (0.76–0.93)	—
Nonfatal myocardial infarction	191 (4.0)	1.0	253 (5.2)	1.4	0.74 (0.61–0.89)	—
Fatal or nonfatal myocardial infarction	200 (4.1)	1.1	268 (5.6)	1.4	0.73 (0.61–0.88)	—
Nonfatal stroke	144 (3.0)	0.8	161 (3.3)	0.9	0.88 (0.70–1.11)	—
Fatal or nonfatal stroke	164 (3.4)	0.9	171 (3.5)	0.9	0.95 (0.76–1.17)	—
Coronary revascularization	200 (4.1)	1.1	263 (5.5)	1.4	0.75 (0.62–0.90)	—
Hospitalization for unstable angina pectoris	74 (1.5)	0.4	80 (1.7)	0.4	0.92 (0.67–1.26)	—
Death from any cause	528 (10.9)	2.8	577 (12.0)	3.0	0.91 (0.80–1.02)	—
Death from noncardiovascular causes	227 (4.7)	1.2	257 (5.3)	1.4	0.87 (0.73–1.04)	—
Heart failure events, three-point composite**	405 (8.4)	2.1	443 (9.2)	2.4	0.90 (0.79–1.03)	—
Heart failure	146 (3.0)	0.8	167 (3.5)	0.9	0.86 (0.69–1.08)	—
Major kidney disease events, four-point composite††	112 (2.3)	0.6	129 (2.7)	0.7	0.86 (0.66–1.10)	—
Death from kidney-related causes	1 (<0.1)	<0.1	7 (0.1)	<0.1	0.14 (0.01–0.79)	—
Severe hypoglycemic episode	76 (1.6)	0.5	84 (1.7)	0.6	0.90 (0.66–1.22)	—


A Major Adverse Cardiovascular Events
Cumulative Incidence (%)
Hazard ratio, 0.86 (95% CI, 0.77–0.96)
P=0.006 for superiority
No. of events:
Placebo, 668
Semaglutide, 579
Placebo
Oral semaglutide
Months since Randomization
No. at Risk
Placebo 4825 4718 4583 4455 4322 4194 4101 3727 2517 1346
Oral semaglutide 4825 4743 4635 4542 4438 4346 4239 3831 2555 1346
B Death from Cardiovascular Causes
Cumulative Incidence (%)
Hazard ratio, 0.93 (95% CI, 0.80–1.09)
No. of events:
Placebo, 320
Semaglutide, 301
Placebo
Oral semaglutide
Months since Randomization
No. at Risk
Placebo 4825 4760 4680 4594 4511 4427 4355 3991 2721 1460
Oral semaglutide 4825 4781 4712 4648 4583 4509 4436 4040 2727 1460

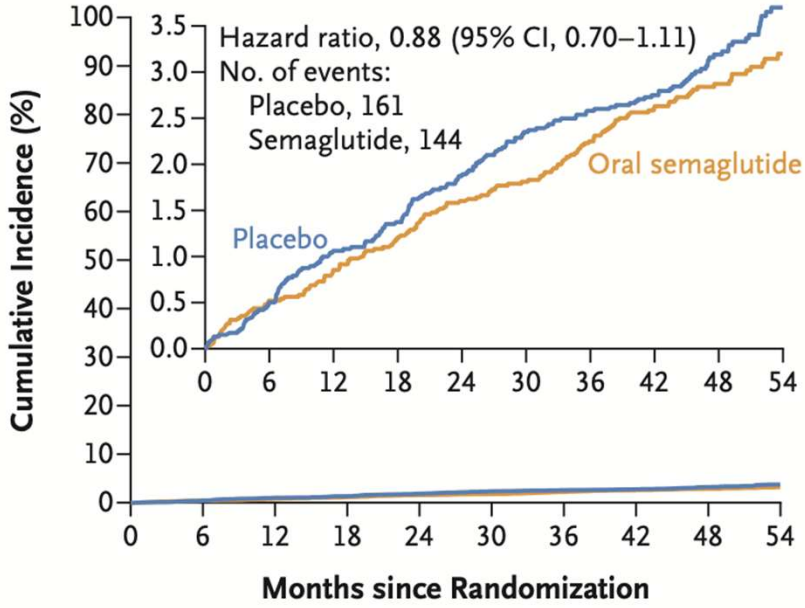
C **Nonfatal Myocardial Infarction**



No. at Risk

Placebo	4825	4739	4631	4511	4395	4284	4197	3821	2595	1390
Oral semaglutide	4825	4766	4672	4593	4505	4416	4322	3922	2638	1394

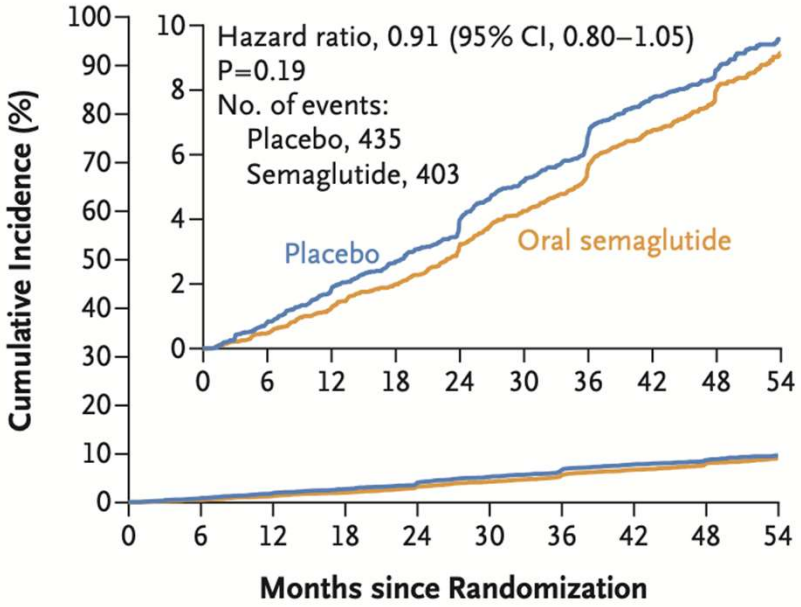
D **Nonfatal Stroke**



No. at Risk

Placebo	4825	4739	4631	4533	4432	4330	4254	3890	2636	1412
Oral semaglutide	4825	4758	4675	4595	4513	4434	4346	3943	2640	1408

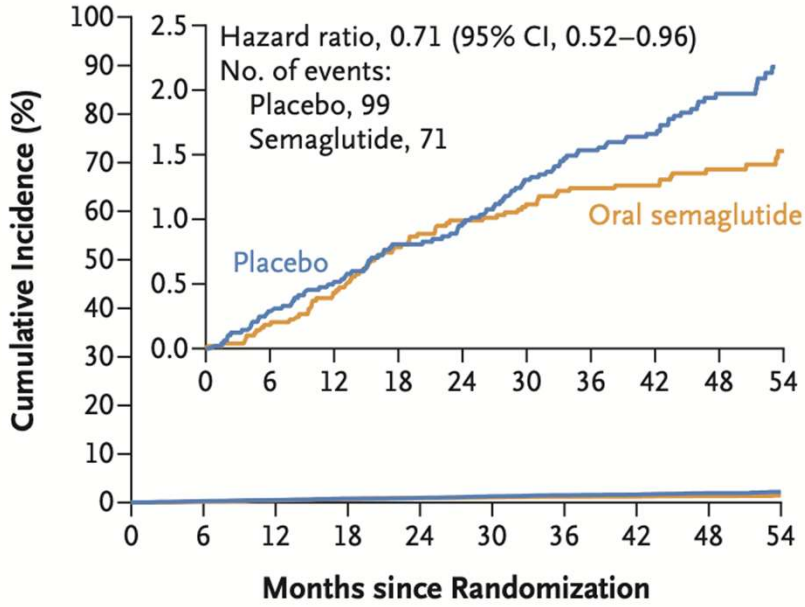
E **Major Kidney Disease Events**



No. at Risk

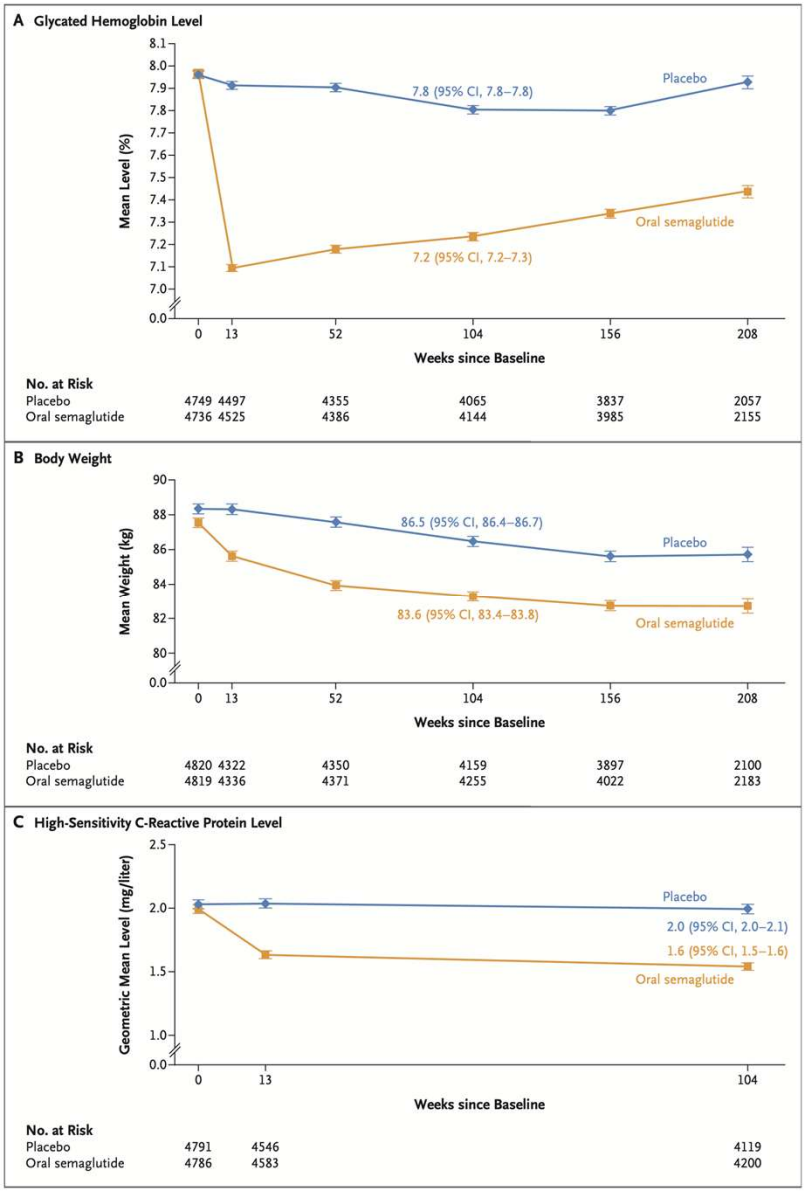
Placebo	4825	4753	4661	4570	4469	4378	4282	3911	2658	1429
Oral semaglutide	4825	4778	4704	4636	4551	4469	4372	3973	2681	1430

F **Major Adverse Limb Events**

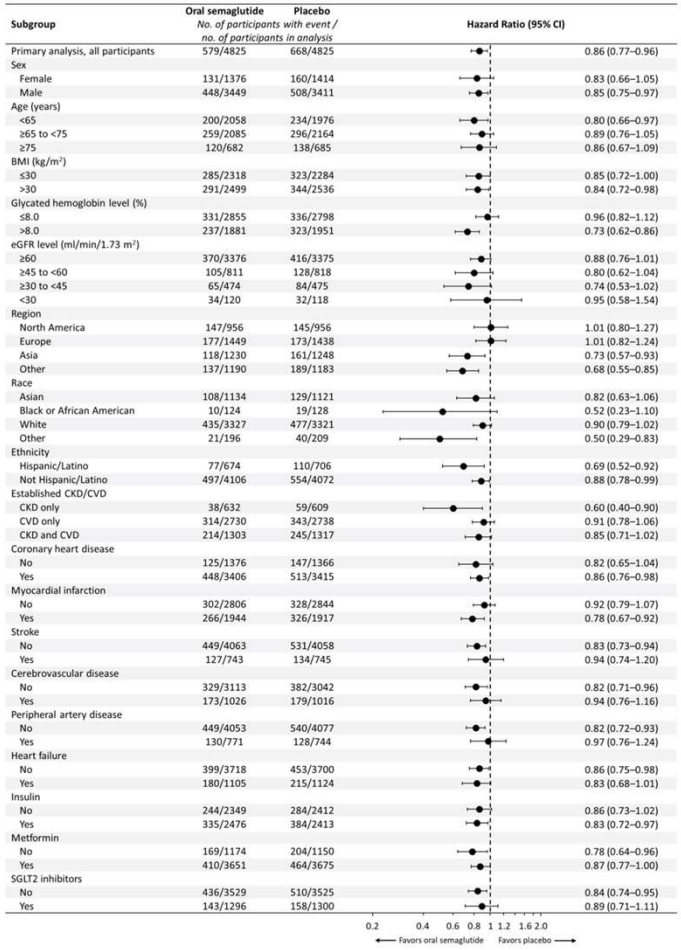


No. at Risk

Placebo	4825	4746	4655	4459	4470	4376	4296	3940	2678	1436
Oral semaglutide	4825	4772	4691	4612	4540	4463	4388	3999	2696	1439


A Glycated Hemoglobin Level
Mean Level (%)
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
0.0
Placebo
7.8 (95% CI, 7.8–7.8)
Oral semaglutide
7.2 (95% CI, 7.2–7.3)
0
13
52
104
156
208
Weeks since Baseline
No. at Risk
Placebo 4749 4497 4355 4065 3837 2057
Oral semaglutide 4736 4525 4386 4144 3985 2155
B Body Weight
Mean Weight (kg)
90
88
86
84
82
80
0.0
86.5 (95% CI, 86.4–86.7)
Placebo
83.6 (95% CI, 83.4–83.8)
Oral semaglutide
0
13
52
104
156
208
Weeks since Baseline
No. at Risk
Placebo 4820 4322 4350 4159 3897 2100
Oral semaglutide 4819 4336 4371 4255 4022 2183
C High-Sensitivity C-Reactive Protein Level
Geometric Mean Level (mg/liter)
2.5
2.0
1.5
1.0
0.0
Placebo
2.0 (95% CI, 2.0–2.1)
1.6 (95% CI, 1.5–1.6)
Oral semaglutide
0
13
104
Weeks since Baseline
No. at Risk
Placebo 4791 4546 4119
Oral semaglutide 4786 4583 4200

Analyses de sous-groupes



Subgroup	Oral semaglutide *No. of participants with event / no. of participants in analysis*	Placebo	Hazard Ratio (95% CI)
Primary analysis, all participants	579/4825	668/4825	0.86 (0.77–0.96)
Sex			
Female	131/1376	160/1414	0.83 (0.66–1.05)
Male	448/3449	508/3411	0.85 (0.75–0.97)
Age (years)			
<65	200/2058	234/1976	0.80 (0.66–0.97)
≥65 to <75	259/2085	296/2164	0.89 (0.76–1.05)
≥75	120/682	138/685	0.86 (0.67–1.09)
BMI (kg/m^2)			
≤30	285/2318	323/2284	0.85 (0.72–1.00)
>30	291/2499	344/2536	0.84 (0.72–0.98)
Glycated hemoglobin level (%)			
≤8.0	331/2855	336/2798	0.96 (0.82–1.12)
>8.0	237/1881	323/1951	0.73 (0.62–0.86)
eGFR level (ml/min/1.73 m^2)			
≥60	370/3376	416/3375	0.88 (0.76–1.01)
≥45 to <60	105/811	128/818	0.80 (0.62–1.04)
≥30 to <45	65/474	84/475	0.74 (0.53–1.02)
<30	34/120	32/118	0.95 (0.58–1.54)
Region			
North America	147/956	145/956	1.01 (0.80–1.27)
Europe	177/1449	173/1438	1.01 (0.82–1.24)
Asia	118/1230	161/1248	0.73 (0.57–0.93)
Other	137/1190	189/1183	0.68 (0.55–0.85)
Race			
Asian	108/1134	129/1121	0.82 (0.63–1.06)
Black or African American	10/124	19/128	0.52 (0.23–1.10)
White	435/3327	477/3321	0.90 (0.79–1.02)
Other	21/196	40/209	0.50 (0.29–0.83)
Ethnicity			
Hispanic/Latino	77/674	110/706	0.69 (0.52–0.92)
Not Hispanic/Latino	497/4106	554/4072	0.88 (0.78–0.99)
Established CKD/CVD			
CKD only	38/632	59/609	0.60 (0.40–0.90)
CVD only	314/2730	343/2738	0.91 (0.78–1.06)
CKD and CVD	214/1303	245/1317	0.85 (0.71–1.02)
Coronary heart disease			
No	125/1376	147/1366	0.82 (0.65–1.04)
Yes	448/3406	513/3415	0.86 (0.76–0.98)
Myocardial infarction			
No	302/2806	328/2844	0.92 (0.79–1.07)
Yes	266/1944	326/1917	0.78 (0.67–0.92)
Stroke			
No	449/4063	531/4058	0.83 (0.73–0.94)
Yes	127/743	134/745	0.94 (0.74–1.20)
Cerebrovascular disease			
No	329/3113	382/3042	0.82 (0.71–0.96)
Yes	173/1026	179/1016	0.94 (0.76–1.16)
Peripheral artery disease			
No	449/4053	540/4077	0.82 (0.72–0.93)
Yes	130/771	128/744	0.97 (0.76–1.24)
Heart failure			
No	399/3718	453/3700	0.86 (0.75–0.98)
Yes	180/1105	215/1124	0.83 (0.68–1.01)
Insulin			
No	244/2349	284/2412	0.86 (0.73–1.02)
Yes	335/2476	384/2413	0.83 (0.72–0.97)
Metformin			
No	169/1174	204/1150	0.78 (0.64–0.96)
Yes	410/3651	464/3675	0.87 (0.77–1.00)
SGLT2 inhibitors			
No	436/3529	510/3525	0.84 (0.74–0.95)
Yes	143/1296	158/1300	0.89 (0.71–1.11)

Effets indésirables

Table S4. Adverse Events Summary

Event	Oral semaglutide (N = 4825)	Placebo (N = 4825)	
	Number of participants (%)		P value
Serious adverse events* — n (%)	2312 (47.9)	2427 (50.3)	0.02
Cardiac disorders	861 (17.8)	954 (19.8)	0.02
Infections and infestations	726 (15.0)	797 (16.5)	0.05
Nervous system disorders	382 (7.9)	387 (8.0)	0.88
Neoplasms benign, malignant, and unspecified	330 (6.8)	274 (5.7)	0.02
Renal and urinary disorders	249 (5.2)	287 (5.9)	0.10
Gastrointestinal disorders	239 (5.0)	210 (4.4)	0.18
Vascular disorders	237 (4.9)	222 (4.6)	0.50
Injury, poisoning and procedural complications	218 (4.5)	304 (6.3)	<0.001
General disorders and administration-site conditions	206 (4.3)	184 (3.8)	0.28
Respiratory, thoracic, and mediastinal disorders	185 (3.8)	217 (4.5)	0.11
Metabolism and nutrition disorders	182 (3.8)	219 (4.5)	0.07
Musculoskeletal and connective tissue disorders	161 (3.3)	169 (3.5)	0.70
Hepatobiliary disorders	115 (2.4)	101 (2.1)	0.37
Eye disorders	102 (2.1)	97 (2.0)	0.77

Conclusion des auteurs

Chez les personnes atteintes de diabète de type 2 et de maladie cardiovasculaire athérosclérotique, de maladie rénale chronique, ou des deux, le sémaglutide oral a diminué le risque d'événements cardiovasculaires majeurs comparativement au placebo, sans augmentation d'effets indésirables graves.

Critique

Forces :

Limitations :

Implications cliniques

Autres articles récents

Bi Y, Li M, Liu Y, Li T, Lu J, Duan P, et al. Intensive Blood-Pressure Control in Patients with Type 2 Diabetes. N Engl J Med. 2025;392(12):1155-67.

Couturaud F, Schmidt J, Sanchez O, Ballerie A, Sevestre MA, Meneveau N, et al. Extended treatment of venous thromboembolism with reduced-dose versus full-dose direct oral anticoagulants in patients at high risk of recurrence: a non-inferiority, multicentre, randomised, open-label, blinded endpoint trial. Lancet. 2025;405(10480):725-35.

Vodstrcil LA, Plummer EL, Fairley CK, Hocking JS, Law MG, Petoumenos K, et al. Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis. N Engl J Med. 2025;392(10):947-57.

Veltkamp R, Korompoki E, Harvey KH, Harvey ER, Fiessler C, Malzahn U, et al. Direct oral anticoagulants versus no anticoagulation for the prevention of stroke in survivors of intracerebral haemorrhage with atrial fibrillation (PRESTIGE-AF): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2025;405(10482):927-36.

Guides de pratique récents

Advani SD, Thaden JT, Perez R, Stair SL, Lee UJ, Siddiqui NY. State-of-the-Art Review: Recurrent Uncomplicated Urinary Tract Infections in Women. Clin Infect Dis. 2025;80(3):e31-e42.