

Effect of semaglutide on COVID-19–related complications and all-cause death: Pooled analyses of the SELECT, FLOW, and SOUL trials

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This analysis was sponsored by Novo Nordisk A/S and the SELECT, FLOW, and SOUL trials are registered with ClinicalTrials.gov (NCT03574597, NCT03819153, and NCT03914326).

Editorial support was provided by Carolyn Bowler, PhD, CMPP, of Apollo, OPEN Health Communications, and funded by Novo Nordisk A/S, in accordance with Good Publication Practice (GPP) guidelines (www.ismpp.org/gpp-2022).

Scirica BM et al. Presented at the American Diabetes Association (ADA) 86th Scientific Sessions, June 5–8, 2026, New Orleans, LA, USA.



Presenter disclosures

Donna H. Ryan reports the following:

- Consulting honoraria from AbbVie, Altimune, Amgen, AstraZeneca, Biohaven, Boehringer Ingelheim, Calibrate, Carmot Therapeutics/Roche/Genentech, CINRx, Eli Lilly, eMed, Epitomee, Fractyl, i2o, Kailera, Novo Nordisk, Pfizer, Regeneron, Regor, Rhythm, Souffle, Source Bio, Structure Therapeutics, Tenvie, Viking, Wondr Health, WW, and Zealand Pharma
- Stock options from Calibrate, Epitomee, and Ro

Introduction

- Obesity and T2D increase the risk of both CV and non-CV deaths^{1,2}
- Semaglutide, a GLP-1RA, facilitates weight loss, lowers glycated hemoglobin levels and reduces CV events^{3,4}

This analysis aimed to evaluate the effect of semaglutide on all-cause death, CV death, and non-CV death, including infections and COVID-19–related complications

CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.

1. Afshin A et al. N Engl J Med 2017;377:13–27; 2. Carey IM et al. Lancet Reg Health Eur 2024;48:101147; 3. Badve SV et al. Lancet Diabetes Endocrinol 2025;13:15–28;

4. Lincoff AM et al. N Engl J Med 2023;389:2221–2232.

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Methods

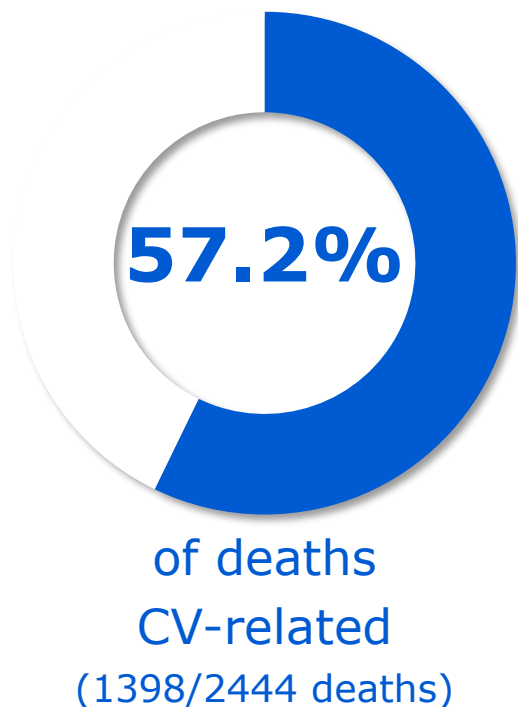
- SELECT (N=17,604),¹ FLOW (N=3533),² and SOUL (N=9650)³ randomized participants across a broad spectrum of cardio-kidney-metabolic diseases to semaglutide or placebo:
 - **SELECT**: overweight/obesity and ASCVD without T2D¹
 - **FLOW**: T2D and CKD²
 - **SOUL**: T2D with ASCVD and/or CKD³
- Mean follow-up ranged from **3.3–4.0 years, spanning the COVID-19 pandemic** (53% of participants were enrolled before Feb 2, 2020)
- Cause of death was adjudicated by an independent external event committee blinded to treatment
- Reported COVID-19–related infections, hospitalizations, and deaths were collected prospectively and included in this pooled analysis

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; T2D, type 2 diabetes.

1. Lincoff AM et al. *N Engl J Med* 2023;389:2221–2232; 2. Perkovic V et al *N Engl J Med* 2024;391:109–121; 3. McGuire DK et al. *N Engl J Med* 2025;392:2001–2012.

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Causes of CV death by treatment group



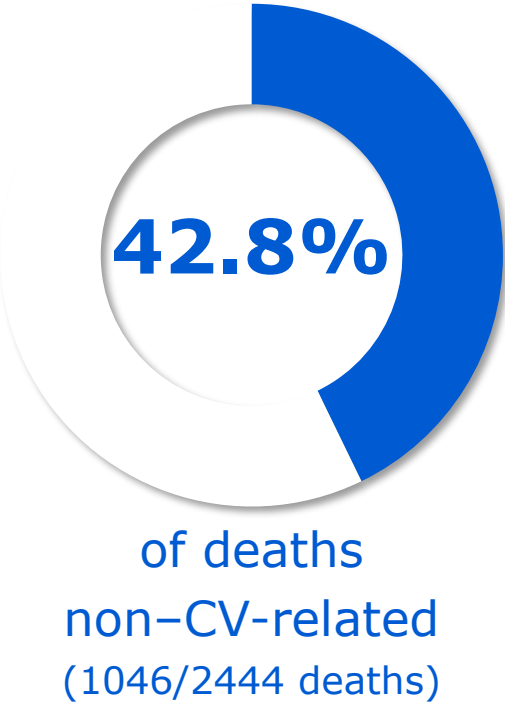
	Semaglutide (N=15,395)		Placebo (N=15,392)		HR (95% CI)	p value
	n (%)	IR	n (%)	IR		
All-cause death						
All causes	1130 (7.3)	0.7	1314 (8.5)	0.8	0.85 (0.78, 0.92)	<0.001
CV death						
CV causes	647 (4.2)	0.4	751 (4.9)	0.5	0.85 (0.77, 0.95)	0.003
Sudden cardiac death	276 (1.8)	0.2	302 (2.0)	0.2	0.90 (0.77, 1.06)	0.22
Undetermined cause of death	200 (1.3)	0.1	270 (1.8)	0.2	0.73 (0.61, 0.88)	<0.001
Acute MI	31 (0.2)	0.0	47 (0.3)	0.0	0.65 (0.41, 1.02)	0.06
Stroke	56 (0.4)	0.0	51 (0.3)	0.0	1.08 (0.74, 1.59)	0.68
Heart failure	50 (0.3)	0.0	47 (0.3)	0.0	1.05 (0.70, 1.57)	0.81
Other CV causes [†]	34 (0.2)	0.0	34 (0.2)	0.0	0.98 (0.61, 1.59)	0.94

Data are from the in-trial period. Estimated HRs and corresponding CIs were calculated using a Cox proportional hazards model with treatment group as a fixed factor and stratification by trial. p values are two-sided and correspond to tests of no difference. A cut-off of 30 events was used to decide which events should be pooled, corresponding to approximately 0.1% of the total population across the three trials.

[†]Other CV causes comprised CV hemorrhage, CV procedure, and other unspecified causes.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 years of observation; MI, myocardial infarction.

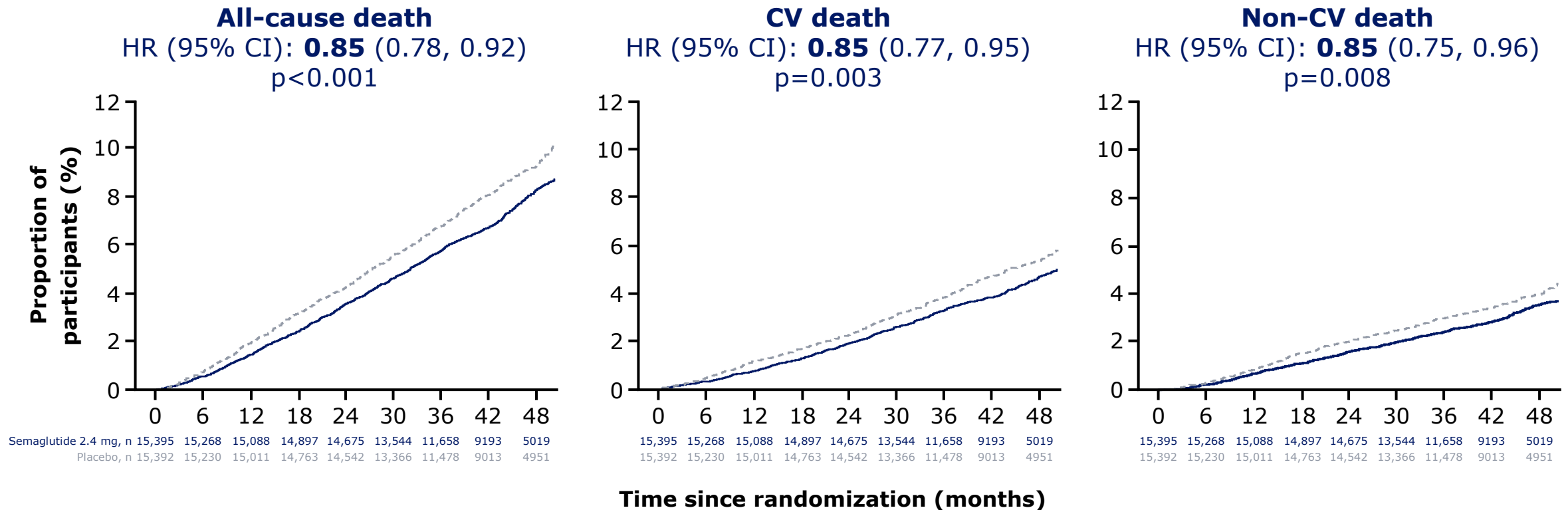
Causes of non-CV death by treatment group



	Semaglutide (N=15,395)		Placebo (N=15,392)		HR (95% CI)	p value
	n (%)	IR	n (%)	IR		
All-cause death						
All causes	1130 (7.3)	0.7	1314 (8.5)	0.8	0.85 (0.78, 0.92)	<0.001
Non-CV death						
Non-CV causes	483 (3.1)	0.3	563 (3.7)	0.3	0.85 (0.75, 0.96)	0.008
Infection	226 (1.5)	0.1	292 (1.9)	0.2	0.77 (0.64, 0.91)	0.003
Pulmonary causes	17 (0.1)	0.0	27 (0.2)	0.0	0.63 (0.33, 1.14)	0.13
Malignancy	161 (1.0)	0.1	147 (1.0)	0.1	1.08 (0.87, 1.35)	0.49
Pancreatic causes	0 (0.0)	0.0	3 (0.0)	0.0	0.00 (NE, 0.88)	0.08
Other non-CV causes [†]	79 (0.5)	0.0	94 (0.6)	0.1	0.83 (0.61, 1.12)	0.22

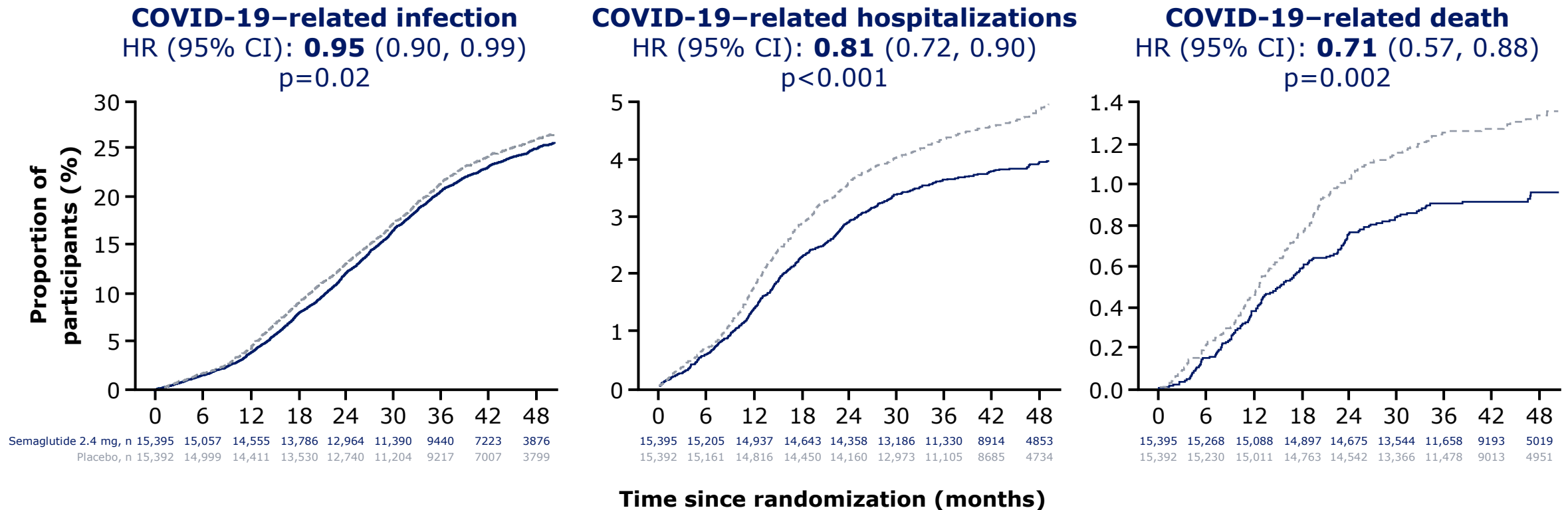
Data are from the in-trial period. Estimated HRs and corresponding CIs were calculated using a Cox proportional hazards model with treatment group as a fixed factor and stratification by trial. p values are two-sided and correspond to tests of no difference. A cut-off of 30 events was used to decide which events should be pooled, corresponding to approximately 0.1% of the total population across the three trials. [†]Other non-CV causes comprised renal, gastrointestinal, hepatobiliary, hemorrhage, inflammatory/immune, procedure/surgery, trauma, suicide, prescription drug reaction/overdose, neurologic, and other unspecified causes.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 years of observation; NE, not evaluable.

Time from randomization to all-cause death, CV death, and non-CV death



Data are from the in-trial period. Cumulative incidence estimates are based on time from randomization to the outcome of interest, using the Aalen-Johansen estimator. Time to CV death was modeled with non-CV death as competing risk. Time to non-CV death was modeled with CV death as competing risk. Participants without events of interest were censored at the end of their in-trial observation period. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Time from randomization to COVID-19-related infection, hospitalizations, and death



Data are from the in-trial period. Cumulative incidence estimates are based on time from randomization to the outcome of interest, using the Aalen-Johansen estimator. Time to COVID-19-related adverse events and serious adverse events were modeled with all-cause death as competing risk. Participants without events of interest were censored at the end of their in-trial observation period. CI, confidence interval; HR, hazard ratio.

Conclusions

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In this study of **>30,000 participants**, semaglutide reduced the risk of all-cause death, with similar reductions in CV and non-CV death (**15%**)



Effects on non-CV death were driven by **fewer infectious deaths**, predominantly through COVID-19–associated complications

Non-CV deaths related to:

Infections

–23%

COVID-19

–29%



Among participants who reported COVID-19–related infections (~23% of all participants), **non-CV death was more frequent than CV death**



The GLP-1RA semaglutide may **improve survival rate** through its **benefits on multiple disease processes in addition to ASCVD, particularly infection and associated complications**, which are common in patients with multiple comorbidities

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist.

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