Title: The Effect of Semaglutide on Mortality And COVID-19-Related Deaths - A Pre-Specified Analysis From The SELECT Trial

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Background: In the SELECT trial, in patients with established cardiovascular (CV) disease and BMI ≥27 kg/m^2, once weekly (OW) semaglutide 2.4 mg reduced the risk of the composite endpoint (CV death, myocardial infarction, and stroke) and reduced the risk of all-cause mortality versus placebo. This analysis investigated the effect of semaglutide 2.4 mg OW on all-cause mortality, CV and non-CV death, including subcategories of death and death from COVID-19.

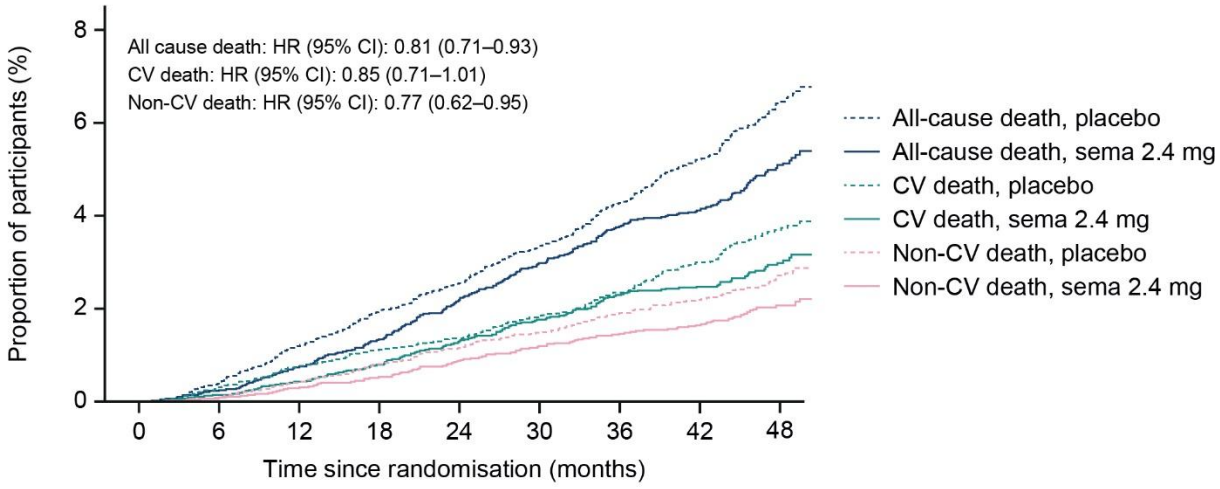
Methods: SELECT enrolled 17,604 participants with pre-existing CV disease without diabetes. An independent committee, blinded to treatment, determined causes of death including COVID-19. Deaths with insufficient data were undetermined and included as CV death; all described endpoints were considered exploratory.

Results: There were 833 deaths (58% CV-related) over a 3.3-year mean follow-up. Semaglutide reduced the risk of all-cause mortality (HR 0.81, 95% CI 0.71–0.93), CV death (0.85, 0.71–1.01), and non-CVD death (0.77, 0.62–0.95) vs placebo (Figure A). The most common causes of CV deaths were sudden cardiac death (0.89, 0.68–1.17) and undetermined death (0.85, 0.63–1.15), vs. non-CV deaths which were infections (0.71, 0.51–0.98). Fewer semaglutide treated patients had serious COVID-19-related adverse events (232 vs 277; p=0.04) or died from COVID-19 (0.66, 0.44–0.96) (Figure B).

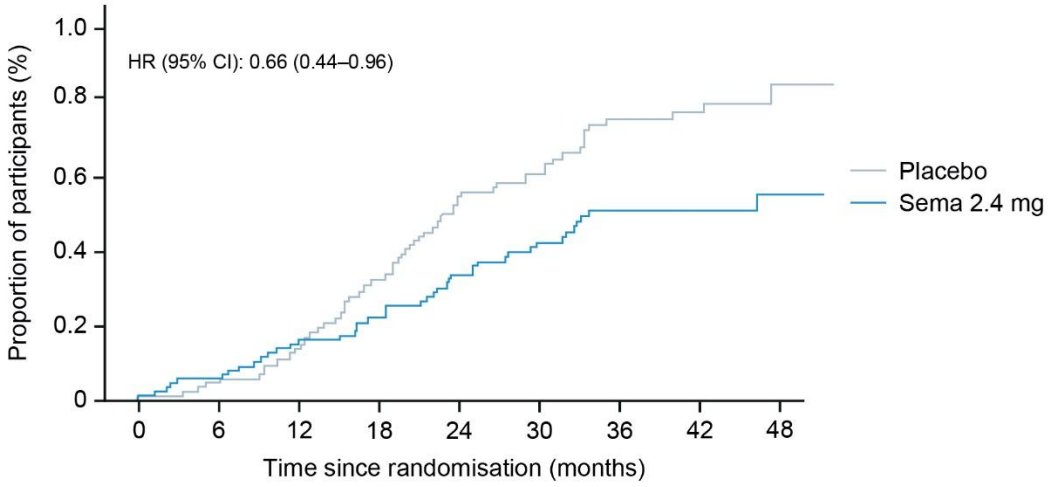
Conclusion: Semaglutide 2.4 mg OW reduced all-cause mortality, driven by similar reductions in both CV and non-CV death, with the latter predominately due to fewer infectious (COVID-19) deaths. These findings support the hypothesis that several mechanisms led to these reductions and highlight the effect of semaglutide on mortality in SELECT.

Figure. Cumulative incidence of A) all-cause mortality, CV death, and non-CV death and B) death due to COVID-19

A) All-cause mortality, CV death and non-CV death



B) Death due to COVID-19



Data are for the full analysis set and from the in-trial observation period. Cumulative incidence estimates are based on time from randomisation to death with all-cause death as competing risk using the Aalen-Johansen estimator. Deaths with insufficient data to be categorised were labelled as undetermined cause of death and considered as CV death.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; sema, semaglutide.

Financial support: Research relating to this abstract was funded by Novo Nordisk A/S.

Conflict of interest: David C. W. Lau has received research grants from Amgen, Boehringer Ingelheim, Novo Nordisk; serves as a consultant for Amgen, Eli Lilly, Novo Nordisk, Viatris, Zealand Pharma; received speakers' bureau from Boehringer Ingelheim, Novartis, Novo Norilsk, CME at Sea.