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The Effect of Semaglutide on Mortality and COVID-19–Related Deaths

An Analysis From the SELECT Trial

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ABSTRACT

BACKGROUND Patients with overweight and obesity are at increased risk of death from multiple causes, including cardiovascular (CV) death, with few therapies proven to reduce the risk.

OBJECTIVES This study sought to assess the effect of semaglutide 2.4 mg on all-cause death, CV death, and non-CV death, including subcategories of death and death from coronavirus disease-2019 (COVID-19).

METHODS The SELECT (Semaglutide Effects on Cardiovascular Outcomes in Patients With Overweight or Obesity) trial randomized 17,604 participants ≥45 years of age with a body mass index ≥27 kg/m^2 with established CV disease but without diabetes to once-weekly subcutaneous semaglutide 2.4 mg or placebo; the mean trial duration was 3.3 years. Adjudicated causes of all deaths, COVID-19 cases, and associated deaths were captured prospectively.

RESULTS Of 833 deaths, 485 (58%) were CV deaths, and 348 (42%) were non-CV deaths. Participants assigned to semaglutide vs placebo had lower rates of all-cause death (HR: 0.81; 95% CI: 0.71-0.93), CV death (HR: 0.85; 95% CI: 0.71-1.01), and non-CV death (HR: 0.77; 95% CI: 0.62-0.95). The most common causes of CV death with semaglutide vs placebo were sudden cardiac death (98 vs 109; HR: 0.89; 95% CI: 0.68-1.17) and undetermined death (77 vs 90; HR: 0.85; 95% CI: 0.63-1.15). Infection was the most common cause of non-CV death and occurred at a lower rate in the semaglutide vs the placebo group (62 vs 87; HR: 0.71; 95% CI: 0.51-0.98). Semaglutide did not reduce incident COVID-19; however, among participants who developed COVID-19, fewer participants treated with semaglutide had COVID-19-related serious adverse events (232 vs 277; $P = 0.04$) or died of COVID-19 (43 vs 65; HR: 0.66; 95% CI: 0.44-0.96). High rates of infectious deaths occurred during the COVID-19 pandemic, with less infectious death in the semaglutide arm, and resulted in fewer participants in the placebo group being at risk for CV death.

CONCLUSIONS Compared to placebo, patients treated with semaglutide 2.4 mg had lower rates of all-cause death, driven similarly by CV and non-CV death. The lower rate of non-CV death with semaglutide was predominantly because of fewer infectious deaths. These findings highlight the effect of semaglutide on mortality across a broad population of patients with CV disease and obesity. (Semaglutide Effects on Cardiovascular Outcomes in Patients With Overweight or Obesity [SELECT]; NCT03574597) (J Am Coll Cardiol 2024;■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

COVID-19 = coronavirus disease-2019

CV = cardiovascular

MI = myocardial infarction

Worldwide, the obesity epidemic has led to the rise of multiple obesity-related complications, and across multiple populations, obesity is closely associated with an increased risk of all-cause death.[1,2] Obesity exacerbates many cardiovascular (CV) risk factors, but obesity is itself an independent risk factor for CV death.[3] A higher body mass is also associated with the risk of other non-CV causes of death, such as infection or cancer. It has been estimated that a 5-kg/m^2 increase in body mass index (BMI) corresponds to an increased risk of all-cause death by 31%, CV death by 49%, respiratory-related death by 38%, and cancer-related death by 19%.[1]

Improving obesity-related mortality has been challenging because few interventions result in safe, clinically meaningful, and sustained weight loss.[1,4,5] Observational studies find an association between reduced mortality and bariatric surgery[6,7] or intentional weight loss,[8] but there have been no randomized clinical trials demonstrating that any weight loss therapies improve CV outcomes or mortality. Glucagon-like peptide-1 receptor agonists and dual-incretin agonists facilitate meaningful and sustained weight loss.[9-11] However, incretin-based therapies have many other benefits beyond weight loss and glycemic control[12] that may account for their observed effect on reducing CV events in patients with type 2 diabetes or obesity.[13,14]

In the SELECT (Semaglutide Effects on Cardiovascular Outcomes in Patients With Overweight or Obesity) trial, compared to placebo, once-weekly subcutaneous semaglutide 2.4 mg reduced the primary endpoint of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke in 17,604 patients who had pre-existing CV disease and overweight or obesity but without diabetes.[15] In addition, there was a 19% lower rate of all-cause death in patients assigned to semaglutide vs placebo. Among the results of the SELECT trial was an unexpected and transient convergence of the CV death event rates between the semaglutide and placebo arms. The coronavirus disease-2019 (COVID-19) pandemic occurred after the SELECT trial began, and the most severe periods were concurrent with the ongoing trial, thus providing the opportunity to evaluate the effect of COVID-19 on patients who were at high risk of COVID-19-related complications and death given their underlying comorbidities[16-18] and whether semaglutide modified that risk. This analysis investigates the effect of semaglutide 2.4 mg on all-cause death, CV death, and non-CV death related to different subgroups of patients and specific causes of death, including those related to COVID-19.

METHODS

TRIAL DESIGN AND PARTICIPANTS. Details of the SELECT trial (NCT03574597), a multicenter, randomized, double-blind, placebo-controlled, event-driven phase 3 trial, have been reported previously.[15,19,20] The SELECT trial evaluated once-weekly subcutaneous semaglutide 2.4 mg vs placebo for reducing the risk of the primary endpoint, a composite endpoint of nonfatal MI, nonfatal stroke, or CV death in individuals with established CV disease and overweight or obesity but without type 2 diabetes. The protocol for SELECT was approved by the Institutional Review Board and ethics committee at each participating center. All patients provided written, informed consent before any trial-specific activity. Randomization in SELECT occurred from October 2018 through March 2021, with the last patient visit on June 29, 2023, thus overlapping with the most severe period of the COVID-19 pandemic (March 2020-March 2022).[21] Although the global COVID-19 pandemic was unexpected at the trial's start, protocol modifications were initiated with site procedures to document COVID-19 cases, collect associated adverse events with COVID-19 event terms, and adjudicate COVID-19-related deaths. Patient flow through the trial has been previously reported.[15]

Eligible patients were ≥45 years of age with a BMI ≥27 kg/m^2 with established CV disease defined as at least 1 of the following: prior MI, prior stroke, or symptomatic peripheral artery disease. The exclusion criteria included prior MI, stroke, hospitalization for unstable angina pectoris or a transient ischemic attack within 60 days before screening, glycated

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hemoglobin ≥6.5% (48 mmol/mol), history of type 1 or 2 diabetes, NYHA functional class IV heart failure, presence of end-stage kidney disease, or the need for chronic or intermittent dialysis. Patients were randomized (1:1) to receive escalating doses of once-weekly subcutaneous semaglutide over 16 weeks to a target dose of 2.4 mg or placebo.

OUTCOMES. The primary objective of SELECT was to demonstrate the superiority of semaglutide 2.4 mg vs placebo when given as an adjunct to standard of care with respect to reducing the incidence of a composite of CV death, nonfatal MI, or nonfatal stroke. Confirmatory secondary endpoints, tested in hierarchical order, were death from CV causes, a composite heart failure endpoint, and death from any cause. Because the results of the CV death comparison did not reach the prespecified statistical threshold, all subsequent analyses are considered hypothesis generating.

The present analysis examines the effect of semaglutide vs placebo on all-cause death, CV and non-CV death, and COVID-19-related death. An independent clinical events committee, blinded to trial group assignment, reviewed all deaths in accordance with prespecified criteria to determine the cause of death (CV vs non-CV) and then, if possible, subcategories of death (eg, sudden cardiac death, MI, infectious, and malignancy) (Supplemental Methods). Deaths with insufficient data to be categorized by the adjudication committee were classified as undetermined death and included in the analysis as CV deaths. Clinical details regarding COVID-19 treatment and outcomes, including COVID-19-related deaths, were prospectively collected in the SELECT trial soon after the onset of the pandemic in 2020.

The prespecified endpoints and analyses included in this analysis are non-CV death as a potential competing risk for the primary endpoint, assessing the impact of COVID-19 on the primary endpoint and specifically whether concurrent COVID-19 infections led to fewer CV deaths (eg, competing risk), and the time from randomization to non-CV death occurring concurrently with a COVID-19 serious adverse event. Subgroup analyses were prespecified to evaluate the consistency of the treatment effect based on baseline information (SELECT TRIAL Statistical Analysis Plan v.3.0[15]). Other analyses should be considered post hoc.

STATISTICAL METHODS. The statistical analyses were based on the intention-to-treat principle and included all randomized patients irrespective of adherence to semaglutide or placebo. Demographics and baseline characteristics were summarized according to the cause of death. Time-to-event outcomes were analyzed by presenting the HR for semaglutide vs placebo as estimated from a Cox proportional hazards model with the treatment group (semaglutide or placebo) as a fixed factor together with the 95% CI. Subgroup analyses for time-to-event endpoints were based on the same model by adding an interaction between the treatment group and the specific subgroup as a factor.

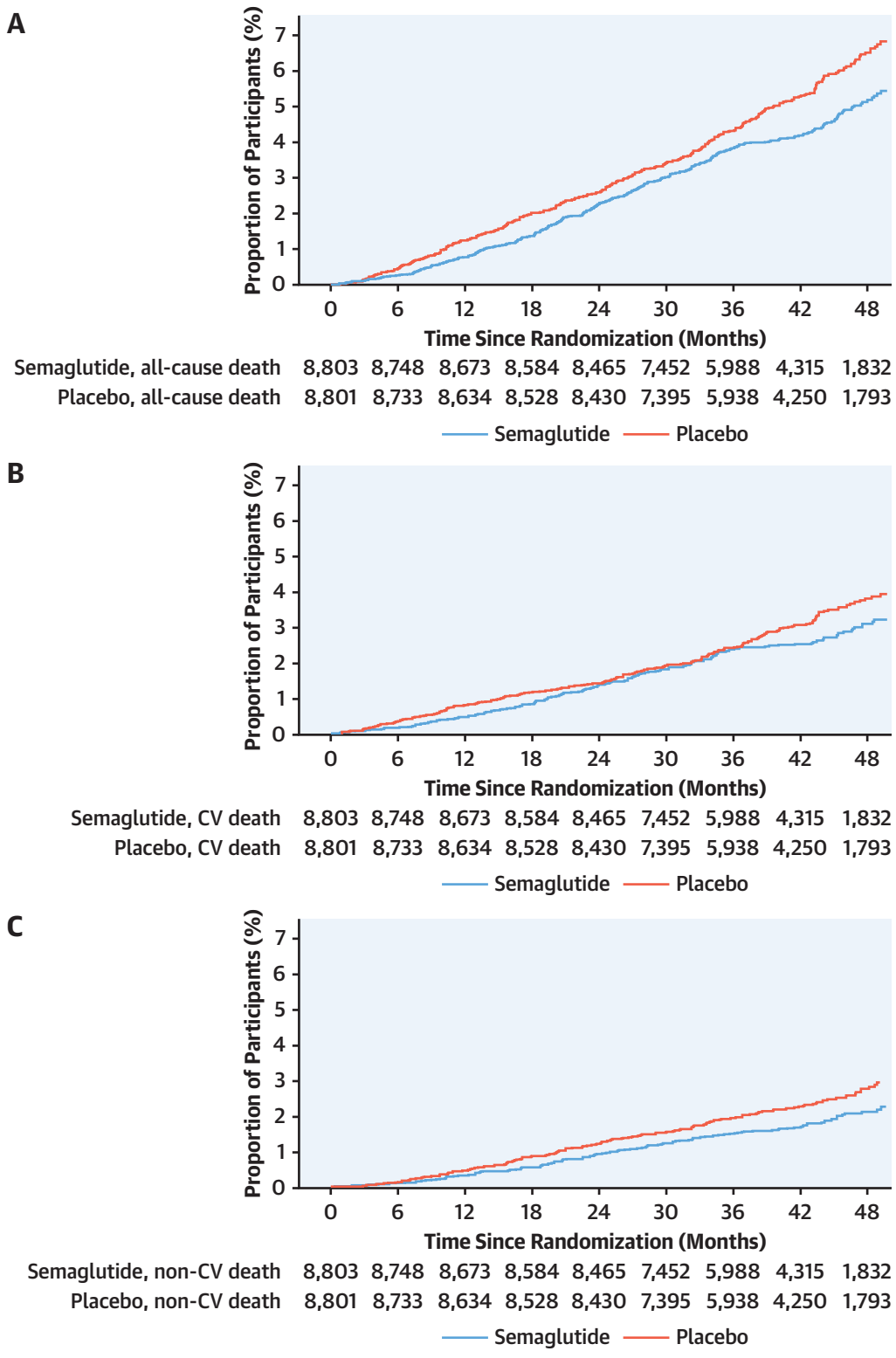
Time-to-event outcomes were plotted by treatment arm using the Aalen-Johansen method,[22] a cumulative incidence estimator that minimizes bias by considering non-CV death or all-cause death as competing events dependent on the outcome. In the presence of competing risks in time-to-event endpoints, the Kaplan-Meier estimator will result in biased (too high) incidence rate estimates, which can result in estimating the risk for a hypothetical population in which no one can die from the competing cause. The cumulative incident function curve estimated with the Aalen-Johansen estimator provides less biased estimates. *P* values from proportions of patients with adverse events are 2-sided and were calculated with the Fisher exact test for the test of no difference. CIs were not adjusted for multiplicity, and as stated previously, all comparisons are considered hypothesis generating.

ROLE OF THE FUNDING SOURCE. The funder was responsible for the study design in collaboration with the academic steering committee and contributed to data collection, analysis, and interpretation and participated in the preparation and review of the manuscript in collaboration with the authors. All authors had full access to the data and final responsibility for the decision to submit for publication.

RESULTS

Over a median follow-up of 3.3 years, there were 833 deaths in the SELECT trial, 485 (58%) of which were CV deaths and 348 (42%) were non-CV deaths. Baseline characteristics of patients according to cause of death are presented in Supplemental Table 1. Compared to placebo, patients assigned to semaglutide had lower rates of all-cause death (375 [4.3%] vs 458 [5.2%]; HR: 0.81; 95% CI: 0.71-0.93), CV death (223 [2.5%] vs 262 [3.0%]; HR: 0.85; 95% CI: 0.71-1.01), and non-CV death (152 [1.7%] vs 196 [2.2%]; HR: 0.77; 95% CI: 0.62-0.95) (**Figure 1**). In general, there were consistently lower rates of all-cause death, CV death, and non-CV death in patients assigned to semaglutide compared with placebo across major subgroups, including by age, sex, race, region, atherosclerotic disease areas, renal function, or heart failure. There

FIGURE 1 Cumulative Incidence of All-Cause Death, CV Death, and Non-CV Death by Treatment



Cumulative incidence of (A) all-cause death, (B) cardiovascular (CV) death, and (C) non-CV death by treatment group. Data are for the full analysis set and from the in-trial observation period. Cumulative incidence estimates for time to CV death are modeled with all-cause death as competing risk, and time to non-CV death is modeled with CV death as competing risk using the Aalen-Johansen estimator. Deaths with insufficient data to be categorized were labeled as undetermined cause of death and considered as CV death.

TABLE 1 Causes of CV and Non-CV Death by Treatment Group

	Semaglutide 2.4 mg (n = 8,803)		Placebo (n = 8,801)			
	n (%)	Events/100 y	n (%)	Events/100 y	HR (95% CI)	*P* Value
EAC-confirmed CV death	223 (2.5)	0.8	262 (3.0)	0.9	0.85 (0.71-1.01)	0.07
CV death	146 (1.7)	0.5	172 (2.0)	0.6	0.84 (0.68-1.05)	0.13
Acute MI	12 (0.1)	<0.1	15 (0.2)	<0.1	0.80 (0.36-1.70)	0.55
Heart failure	14 (0.2)	<0.1	16 (0.2)	<0.1	0.87 (0.42-1.78)	0.70
Sudden cardiac death	98 (1.1)	0.3	109 (1.2)	0.4	0.89 (0.68-1.17)	0.42
Stroke	15 (0.2)	<0.1	21 (0.2)	<0.1	0.71 (0.36-1.37)	0.31
CV procedure	2 (<0.1)	<0.1	4 (<0.1)	<0.1	0.50 (0.07-2.54)	0.41
CV hemorrhage	2 (<0.1)	<0.1	0 (0)	–	–	–
Other causes	3 (<0.1)	<0.1	7 (<0.1)	<0.1	0.43 (0.09-1.53)	0.20
Undetermined cause of death	77 (0.9)	0.3	90 (1.0)	0.3	0.85 (0.63-1.15)	0.29
EAC-confirmed non-CV death	152 (1.7)	0.5	196 (2.2)	0.7	0.77 (0.62-0.95)	0.02
Pulmonary causes	8 (<0.1)	<0.1	12 (0.1)	<0.1	0.66 (0.26-1.60)	0.36
Gastrointestinal causes	3 (<0.1)	<0.1	5 (<0.1)	<0.1	0.60 (0.12-2.43)	0.47
Hepatobiliary causes	1 (<0.1)	<0.1	3 (<0.1)	<0.1	0.33 (0.02-2.58)	0.31
Infections[a]	62 (0.7)	0.2	87 (1.0)	0.3	0.71 (0.51-0.98)	0.04
Hemorrhage[b]	1 (<0.1)	<0.1	4 (<0.1)	<0.1	0.25 (0.01-1.68)	0.18
Non-CV procedure/surgery	0 (0)	–	1 (<0.1)	<0.1	–	–
Trauma	11 (0.1)	<0.1	19 (0.2)	<0.1	0.58 (0.26-1.19)	0.14
Suicide	5 (<0.1)	<0.1	3 (<0.1)	<0.1	1.66 (0.41-8.07)	0.49
Prescription drug reaction/overdose[c]	0 (0)	–	1 (<0.1)	<0.1	–	–
Neurologic	4 (<0.1)	<0.1	1 (<0.1)	<0.1	3.97 (0.59-77.66)	0.18
Malignancy	55 (0.6)	0.2	60 (0.7)	0.2	0.91 (0.63-1.31)	0.61
Other	2 (<0.1)	<0.1	0 (0)	–	–	–

Data are for the full analysis set and from the in-trial observation period. The HR and *P* value are for the time from randomization to the outcome for semaglutide vs placebo analyzed using a Cox proportional hazards model with treatment as a categorial fixed factor. EAC-confirmed CV death includes CV death and undetermined cause of death. [a]Infections including sepsis. [b]Hemorrhage that is neither CV bleeding nor stroke. [c]May include anaphylaxis.

CV = cardiovascular; EAC = event adjudication committee; MI = myocardial infarction.

was a trend toward a greater treatment effect with semaglutide compared to placebo in patients with glycated hemoglobin levels ≥6% for all-cause death[10] and non-CV death (Supplemental Figures 1 to 3).

The most common causes of CV death numerically were sudden cardiac death (98 in semaglutide vs 109 in placebo; HR: 0.89; 95% CI: 0.68-1.17) and deaths with insufficient data to adjudicate (undetermined) (77 vs 90; HR: 0.85; 95% CI: 0.63-1.15). The most common causes of non-CV death were infections (62 in semaglutide vs 87 in placebo; HR: 0.71; 95% CI: 0.51-0.98) and malignancy (55 vs 60; HR: 0.91; 95% CI: 0.63-1.31) (Table 1).

COVID-19, DEATH, AND SEMAGLUTIDE. A total of 4,258 patients (24.2%) reported a diagnosis of COVID-19. Overall, baseline characteristics in patients who did or did not report COVID-19 were generally similar. Patients who reported a COVID-19 event were slightly more likely to be female or have a history of MI as the basis for inclusion in the study, but both groups had similar age, renal function, and glycemic indexes (Supplemental Table 2). The median time from randomization to the first COVID-19 adverse event was 752 days in both arms (IQR: 511-999 days in the semaglutide arm and 499-1,000 days in the placebo arm). Compared with placebo, semaglutide did not reduce the number of patients with a reported case of COVID-19 (2,108 vs 2,150 events; $P = 0.46$). However, among patients who reported a diagnosis of COVID-19, fewer patients treated with semaglutide had serious COVID-19-related adverse events (232 [2.6%] vs 277 [3.1%]; $P = 0.04$). The change in weight between randomization and reported COVID-19 in patients who died of COVID-19 according to treatment was −6.4 kg in the semaglutide group vs −0.9 kg in the placebo ($P < 0.001$) group and −8.4 kg vs −1.25 kg ($P < 0.001$), respectively, in patients who did not die.

Patients who developed COVID-19 were more likely to die from non-CV causes compared with CV causes (137 non-CV deaths [74.5%] vs 47 CV deaths [25.5%]), whereas the relationship was the inverse in patients without any reported COVID-19 (211 [32.5%] non-CV deaths vs 438 CV deaths [67.5%]) (Table 2, top). Excluding the 50 deaths that occurred before COVID-19 did not meaningfully change that ratio (Table 2, bottom). Over the entire trial, there were 137 non-CV deaths in patients with a reported COVID-19 event,

TABLE 2 CV and Non-CV Death in Participants Who Did or Did Not Report COVID-19

	COVID-19			No COVID-19		
	Total	Semaglutide	Placebo	Total	Semaglutide	Placebo
All randomized patients	4,258	2,150	2,108	13,346	6,695	6,651
CV death	47 (1.1)	21 (1.0)	26 (1.2)	438 (3.3)	202 (3.0)	236 (3.5)
Non-CV death	137 (3.2)	57 (2.7)	80 (3.7)	211 (1.6)	95 (1.4)	116 (1.7)
Total	184 (4.3)	78 (3.7)	106 (4.9)	649 (4.9)	297 (4.4)	352 (5.3)
Patients alive on February 1, 2020 (start of COVID-19 pandemic)	4,258	2,150	2,108	13,296	6,676	6,620
CV death	47 (1.1)	21 (1.0)	26 (1.2)	399 (3.0)	186 (2.8)	213 (3.2)
Non-CV death	137 (3.2)	57 (2.7)	80 (3.7)	200 (1.5)	92 (1.4)	108 (1.6)
Total	184 (4.3)	78 (3.7)	106 (4.9)	599 (4.5)	278 (4.2)	321 (4.8)

Values are N or n (%).
COVID-19 = coronavirus disease-2019; CV = cardiovascular.

with the most common adjudicated cause being infectious (109 cases).

Fewer deaths were adjudicated as directly related to COVID-19 in the semaglutide arm compared with the placebo arm (43 vs 65; HR: 0.66; 95% CI: 0.44-0.96) (Supplemental Figure 4). Similarly, the rate of all-cause death concurrent with COVID-19 serious adverse events was also lower in the semaglutide arm compared with the placebo arm (46 vs 69; HR: 0.66; 95% CI: 0.45-0.96).

The event curves and treatment effect of semaglutide vs placebo on CV and non-CV death in patients who did or did not report any COVID-19 are presented in Supplemental Figure 5. There were numerically fewer deaths in the semaglutide arm in each COVID-19 subgroup, although the largest difference between semaglutide and placebo was for non-CV deaths in patients with a COVID-19 event (**Table 2**). Landmarking death analysis at the time of the first COVID-19 adverse event shows that most non-CV deaths occurred soon after the onset of COVID-19, with fewer non-CV deaths occurring in patients assigned to semaglutide (**Figure 2**).

An illness-death model was performed to evaluate the interaction between semaglutide, COVID-19, and all-cause death and found a similar relationship between semaglutide vs placebo with respect to those who had COVID-19 (HR for semaglutide vs placebo: 0.84 [95% CI: 0.72-0.98] in patients without COVID-19 and HR: 0.74 [95% CI: 0.55-0.99] in patients with COVID-19; *P* interaction = 0.46) even though the ratio of CV to non-CV death was the opposite in patients who did or did not report COVID-19.

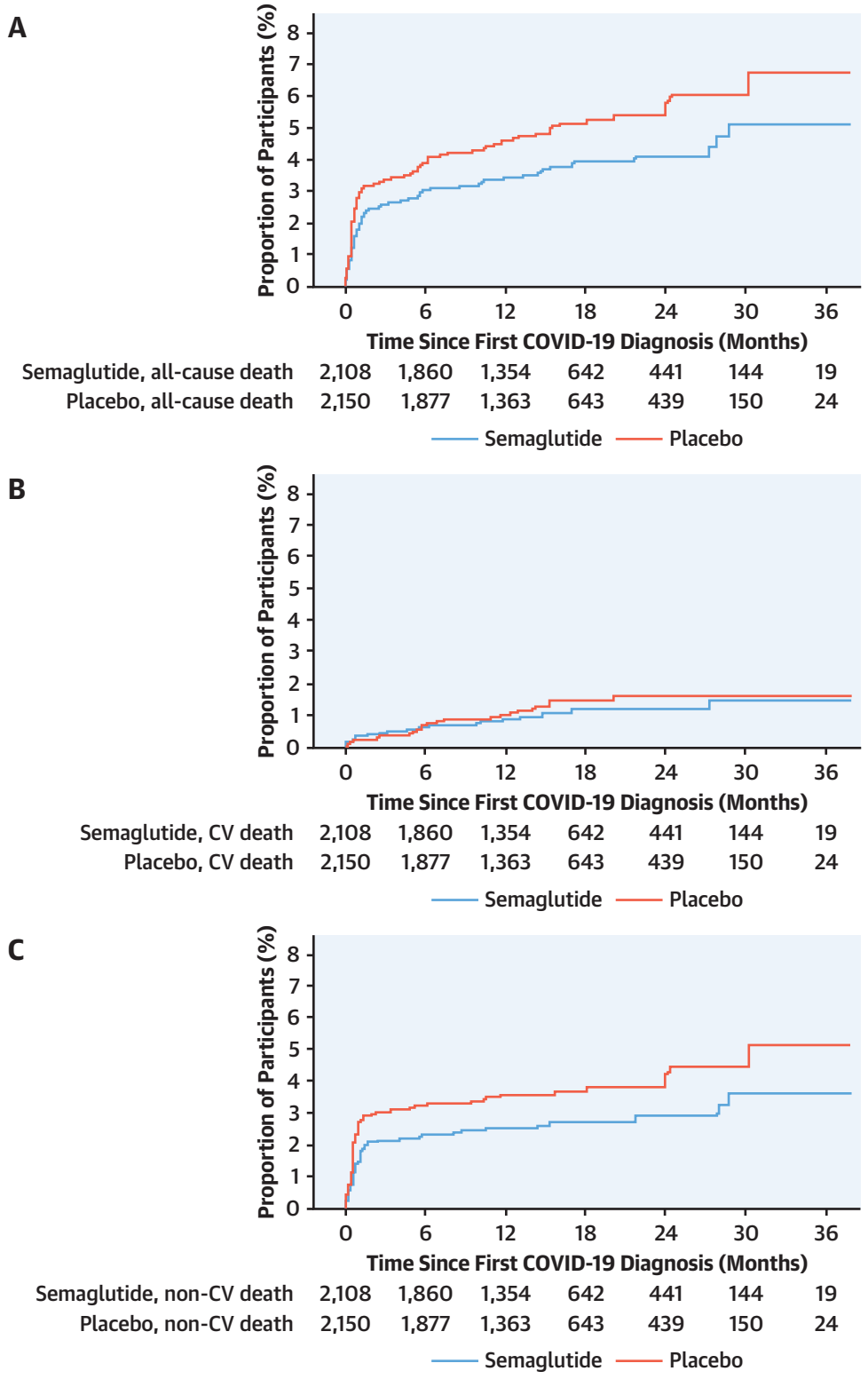
The rates of death over 6-month intervals of calendar time are plotted in **Figure 3** to illustrate the changes related to the COVID-19 pandemic from March 2020 to March 2022. Infectious deaths peaked during the pandemic and were lower in the semaglutide vs the placebo arm. In contrast, although rates of CV death were lower in the semaglutide vs the placebo arm in the periods before and after the COVID-19 pandemic, the rates of CV death did not increase and were similar in the semaglutide and placebo arms during the COVID-19 pandemic. Supplemental Figure 6 shows the cumulative proportion of all-cause deaths, CV deaths, and non-CV deaths based on calendar time, with a peak in non-CV deaths and a separation of non-CV death event curves between semaglutide and placebo during the pandemic, although there are wide CIs around these observations.

DISCUSSION

In 17,604 patients with established CV disease and overweight or obesity but without diabetes in the SELECT trial, semaglutide 2.4 mg reduced ACM by 19%, driven by similar reductions in CV death (15% reduction) and non-CV death (23% reduction). The lower rate of non-CV death with semaglutide vs placebo was predominantly because of fewer infectious deaths, in particular COVID-19-related deaths, supporting the hypothesis that there may be several mechanisms that led to the reduction in CV and non-CV death, some of which may be unrelated to atherothrombosis.

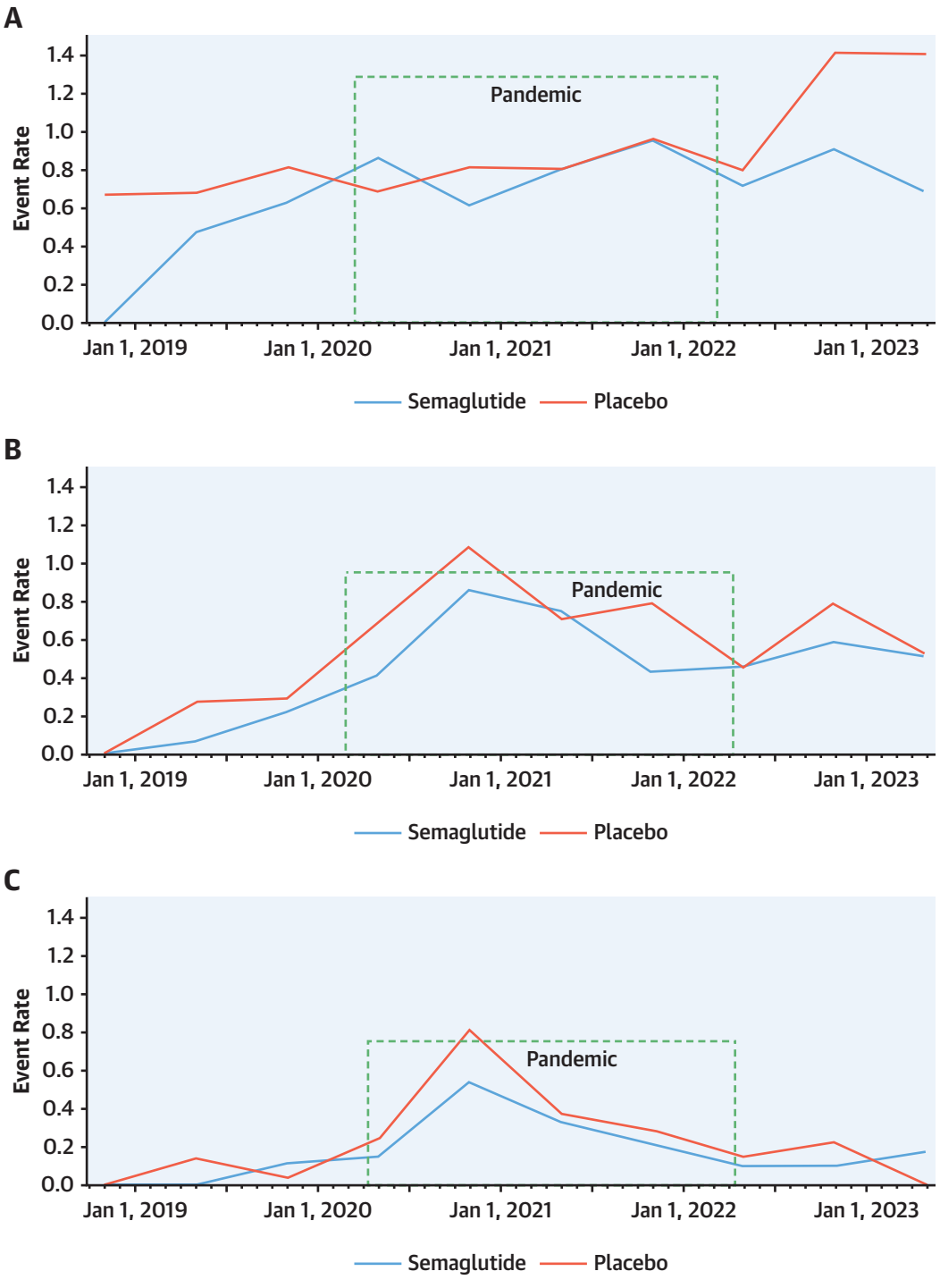
Obesity is independently associated with increased CV and non-CV death.[1,2,23] The SELECT trial is the first randomized study to demonstrate that a specific therapy that acts through multiple potential metabolic pathways[12] and induces meaningful weight loss also reduces all-cause death and does so consistently across multiple different populations.[15] Before the SELECT trial, no randomized study of any therapy that promoted weight loss demonstrated any benefit on mortality, although observational studies found that bariatric surgery is associated with a lower risk of

FIGURE 2 Time From COVID-19 Onset to All-Cause Death, CV Death, and Non-CV Death by Treatment



Time from coronavirus disease-2019 (COVID-19) diagnosis to (A) all-cause mortality, (B) cardiovascular (CV) death, and (C) non-CV death.

FIGURE 3 Event Rates of CV Death, Non-CV Death, and Death From Infectious Causes by Calendar Date



Event rates over calendar time for (A) cardiovascular (CV) death, (B) non-CV death, and (C) non-CV death caused by infection. Data are for the full analysis set and from the in-trial observation period. The event rates are calculated per 6 months as the number of deaths divided by the time at risk.

all-cause death after an average of 10.9 years of follow-up.[6] Despite the long follow-up and adjustment for comorbidities, observational studies likely have residual confounding, including confounding by indication, which will bias in favor of bariatric surgery. Whether the benefit of semaglutide on non-CV mortality was because of weight loss or other incretin-mediated pathways is not known. However, the reduction in CV death, MI, and ischemic stroke with semaglutide in SELECT does not appear to have been mediated through weight loss.[19]

The response to the COVID-19 pandemic in the SELECT trial was to amend the protocol to collect data regarding this unexpected event. The study documented that approximately one-fourth of participants reported a COVID-19 infection, with similar rates in both groups. There were several unexpected observations in the SELECT trial regarding the causes and timings of death, which largely corresponded with the most severe periods of the COVID-19 pandemic (March 2020-March 2022). The first observation is that non-CV death may have acted as a "competing risk" for CV death. Patients who reported a COVID-19 infection were more likely to die from non-CV causes, whereas patients without a COVID-19 event died, as expected in this population, predominantly from CV causes. The relatively high number of non-CV deaths in patients with COVID-19 combined with fewer non-CV deaths with semaglutide vs placebo meant that more patients in the semaglutide arm than in the placebo arm survived to remain "at risk" for CV death. Competing risks occur frequently in the analysis of survival data.[24,25] A competing risk is an event whose occurrence precludes the occurrence of the primary event of interest. In the SELECT trial, the competing risk of non-CV death (which prevents the occurrence of CV death) combined with the lower rates of non-CV death in the semaglutide arm may have resulted in the unanticipated convergence of survival curves for CV death observed during the COVID-19 pandemic.

The second unexpected observation was the lower rate of non-CV death with semaglutide vs placebo, particularly infectious deaths, including in patients with reported cases of COVID-19. The mechanism by which semaglutide is associated with lower CV or non-CV mortality is unknown. Weight loss improves traditional cardiometabolic and kidney risk factors,[3] such as hypertension, dyslipidemia, renal function,[26] and dysglycemia. However, the blood pressure and lipid reductions in SELECT with semaglutide were relatively small compared with those in dedicated risk factor-lowering trials, and the observed reduction in major adverse cardiovascular events is more than would be expected based on those changes. Moreover, there is often a delay before the benefit of improved risk factors manifests into fewer clinical events.[27-29] In the Swedish Obese Subjects study, the risk of death associated with bariatric surgery was only apparent 5 years after surgery, although patients in this cohort were lower risk than patients in SELECT.[6]

Epidemiologic studies report a U-shaped relationship between non-CV death and BMI and even suggest an "obesity paradox" whereby increased BMI is associated with better outcomes. In a randomized clinical trial, many of the confounding comorbidities associated with poorer outcomes and lower BMI are excluded. There was an associated increased risk of respiratory decompensation and mortality in patients with COVID-19 and obesity[16,17] and plausible biologic hypotheses associating obesity with adverse COVID outcomes, including impaired respiratory status, lower cardiometabolic reserve, or immune hyperreactivity or dysregulation.[18]

Weight reduction reduces inflammation, as reflected by the lower levels of high-sensitivity C-reactive protein in patients treated with semaglutide compared to placebo. Whether this is through reductions in visceral (especially epicardial or pericardial) adiposity[30] or other pathways is not known. Other direct effects of Glucagon-like peptide-1 receptor agonism are also possible. A matched cohort study of patients who underwent surgical bariatric surgery found that substantial weight loss was associated with lower rates of more severe COVID-19 complications.[31] Accordingly, it is plausible that the decreased risk of infectious deaths is caused by weight loss, which was 5 kg greater in patients assigned to semaglutide compared to placebo by 1 year, the average time to COVID-19 diagnosis after randomization.

STUDY LIMITATIONS. There are several limitations to this analysis. According to the prespecified testing hierarchy, all comparisons following CV death should be treated as hypothesis generating because CV death did not meet the prespecified *P* value. Moreover, testing subgroups and different components of endpoints can result in underpowered analyses and chance findings. Although there is a possibility of adjudication misclassifications between CV and non-CV deaths, the likelihood of such errors influencing the results is minimal because both investigators and adjudicators were blinded, eliminating potential bias

toward either treatment arm that could account for the nonlinear cumulative incidence rates. Deaths during the COVID-19 pandemic were at times more challenging to adjudicate because of limited medical information; however, unknown deaths were conservatively categorized as CV death and should not have led to any treatment bias. Formal testing demonstrating the presence of competing risks can be challenging because, compared to the overall trial size, the proportion of participants who had non-CV deaths was relatively low. Regardless, we used the Aalen-Johansen method to estimate event rates rather than the Kaplan-Meier estimator, which is known to bias upward with time when competing risks are present.[25] Whether the effect of semaglutide on non-CV death would have been the same without a global respiratory pandemic is unknown but must be considered when planning future outcome trials with incretin therapies.

CONCLUSIONS

These findings highlight the mortality benefit of semaglutide across a broad population of patients with CV disease and obesity. The robust reduction in non-CV death, particularly infectious deaths, was surprising and perhaps only detectable because of the COVID-19-related surge in non-CV deaths; however, these findings reinforce that overweight and obesity increase the risk of death because of many etiologies, which can be modified with potent incretin-based therapies like semaglutide.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.