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Safety of Semaglutide After Dialysis Initiation: An Individual-Level Pooled Analysis

Klara R. Klein, Anna Menacher, John B. Buse, Johannes F.E. Mann, Katherine R. Tuttle, Kajsa Kvist, Margit R. Andersen, Manuel Mayrdorfer, and Ildiko Lingvay

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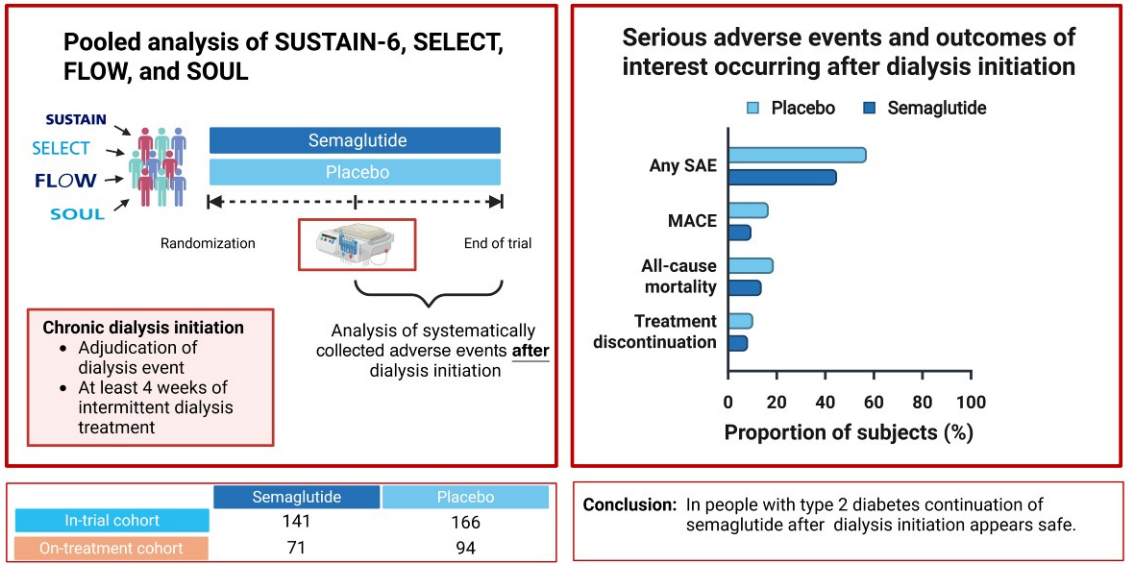
Treatment With Semaglutide Was Not Associated With a Higher Proportion of Serious Adverse Events (SAEs), including Major Adverse Cardiovascular Events (MACEs) and All-Cause Mortality, Among Those Initiating Dialysis



	Semaglutide	Placebo
In-trial cohort	141	166
On-treatment cohort	71	94

Conclusion: In people with type 2 diabetes continuation of semaglutide after dialysis initiation appears safe.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Semaglutide provides cardiovascular and mortality benefit in certain populations at high risk of cardiovascular events. Whether semaglutide is safe in people receiving dialysis, a population at very high risk for cardiovascular events and death, is not known.

- **What is the specific question we wanted to answer?**
  What is the safety of semaglutide after dialysis initiation among people initiating dialysis in SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes), SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity), FLOW (Evaluate Renal Function With Semaglutide Once Weekly), and SOUL (Semaglutide Cardiovascular Outcomes).

- **What did we find?**
  We found no difference in serious adverse events, and rates of cardiovascular events and death were lower in people randomized to semaglutide compared with placebo.

- **What are the implications of our findings?**
  Our analysis indicates that continuation of semaglutide in people initiating dialysis is safe and potentially beneficial, but further evidence is necessary.

Safety of Semaglutide After Dialysis Initiation: An Individual-Level Pooled Analysis

Klara R. Klein,[1] Anna Menacher,[2] John B. Buse,[1] Johannes F.E. Mann,[3,4] Katherine R. Tuttle,[5] Kajsa Kvist,[2] Margit R. Andersen,[2] Manuel Mayrdorfer,[2] and Ildiko Lingvay[6]

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ORIGINAL ARTICLE

OBJECTIVE

People receiving dialysis are at high risk of cardiovascular and all-cause mortality. Semaglutide reduces major adverse cardiovascular events (MACE) in people with type 2 diabetes (T2D) and those without T2D with obesity and high cardiovascular risk. Data to establish safety and efficacy in dialysis-dependent kidney failure are scarce. We aimed to assess the safety of semaglutide in people who initiate dialysis.

RESEARCH DESIGN AND METHODS

In this post hoc analysis of four randomized, placebo-controlled trials (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6], Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity [SELECT], Evaluate Renal Function With Semaglutide Once Weekly [FLOW], and Semaglutide Cardiovascular Outcomes [SOUL]), we evaluated systematically collected adverse events (AEs) from participants who initiated dialysis during study follow-up. We compared the proportion and event rates of systematically collected serious AEs (SAEs), including adjudicated MACE, and AEs leading to permanent treatment discontinuation in participants originally randomized to semaglutide or placebo who remained on treatment after dialysis initiation.

RESULTS

Among 34,064 participants randomized across the trials, 307 initiated dialysis, of whom 165 participants randomized to semaglutide (*n* = 71) or placebo (*n* = 94) remained on treatment. After dialysis initiation, SAEs were reported in 32 of 71 (45%) and 54 of 94 (57%) participants, and the proportion of participants who permanently discontinued trial medication was 8.5% and 10.6% in the semaglutide and placebo groups, respectively. The MACE event rates were 9.7 and 16.1 events per 100 person-years, and all-cause mortality event rates were 13.8 and 18.1 events per 100 person-years, in the semaglutide and placebo groups, respectively.

CONCLUSIONS

Although more evidence is needed, continuation of semaglutide after dialysis initiation appears safe and warrants efficacy testing regarding reduction in MACE and death.

Currently, over 3.5 million people worldwide receive maintenance dialysis, with diabetes accounting for nearly half of all new cases of kidney failure (1,2). Driven largely by the global diabetes epidemic, the prevalence of kidney failure continues

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to rise, with over 5.4 million individuals projected to require kidney replacement therapy by 2030, most of whom will be treated with dialysis (3). Individuals receiving dialysis have a 5-year survival rate of less than 50%, primarily due to cardiovascular complications (4). To date, no pharmacotherapy has demonstrated a clear cardiovascular benefit in the dialysis population (5).

Glucagon-like peptide 1 receptor agonists (GLP-1 RA) reduce major adverse cardiovascular events (MACE) in people living with type 2 diabetes, those without type 2 diabetes with BMI $\geq$27 kg/m^2 and high cardiovascular risk, and those with high kidney risk who are not treated with dialysis (6–10). As such, both kidney and diabetes guideline bodies recommend GLP-1 RA for cardiovascular and kidney protection in people with type 2 diabetes and chronic kidney disease (CKD) (11–13). Early evidence also suggests that GLP-1 RA provide clinically meaningful kidney benefit in people without type 2 diabetes with BMI $\geq$27 kg/m^2 and CKD (14). Together, these data suggest an important role for GLP-1 RA for cardiovascular and kidney protection in people living with CKD not receiving dialysis regardless of diabetes status.

However, whether these benefits extend to people living with dialysis-dependent kidney failure is not known. Data to establish the safety and efficacy of GLP-1 RA in people living with dialysis-dependent kidney failure are scarce, and prescription of GLP-1 RA to people treated with dialysis remains limited (15). The lack of population-specific evidence has limited most major guideline bodies from strongly recommending GLP-1 RA use among people receiving dialysis (16,17). Instead, they call for more evidence to establish cardiovascular efficacy and mortality benefit in the dialysis population. Unfortunately, enrollment challenges have hindered efforts to conduct large-scale randomized controlled trials of GLP-1 RA in people treated with dialysis (18,19). Using data from four clinical trials, we therefore evaluated the safety of semaglutide in participants who initiated dialysis during study follow-up and explored the potential for efficacy with respect to cardiovascular outcomes and all-cause mortality.

RESEARCH DESIGN AND METHODS

We included all cardiovascular and kidney outcome trials examining semaglutide for which dialysis initiation was an adjudicated event (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6], Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity [SELECT], Evaluate Renal Function With Semaglutide Once Weekly [FLOW], and Semaglutide Cardiovascular Outcomes [SOUL]). Participants from Peptide Innovation for Early Diabetes Treatment [PIONEER-6], a cardiovascular outcome trial of oral semaglutide, were excluded because dialysis events were not adjudicated (20). The trial designs for SUSTAIN-6, SELECT, FLOW, and SOUL have been previously published (6,7,10,21). Briefly, these studies were randomized, double-blind, placebo-controlled clinical trials assessing the impact of semaglutide on cardiovascular and kidney outcomes. A type 2 diabetes diagnosis was required for all studies except for SELECT, and each trial used subcutaneous semaglutide (maximum dose: SUSTAIN-6 and FLOW = 1 mg/week, SELECT = 2.4 mg/week semaglutide) except SOUL, which evaluated oral semaglutide (maximum dose: 14 mg/day). The primary outcomes in SUSTAIN-6, SELECT, and SOUL were MACE (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). In FLOW, the primary outcome was major kidney disease events (a composite of kidney failure, $\geq$50% reduction in the estimated glomerular filtration rate from baseline, or death from kidney-related or cardiovascular causes).

In this individual-level pooled exploratory analysis, we evaluated systematically collected adverse events (AEs), serious AEs (SAEs), AEs that led to permanent treatment discontinuation, kidney transplantation, MACE, and all-cause mortality after participants initiated chronic dialysis, until the end of each study. A schematic of the study design, describing the postrandomized nature of the evaluated cohort, is provided in Supplementary Fig. 1, and a flowchart of the study and participant inclusion is provided in Fig. 1. Chronic dialysis was defined as any dialysis modality (peritoneal or hemodialysis) for at least 4 weeks. Four weeks of follow-up was not required if a competing event (e.g., death) occurred and there was no reason to believe that there was a reversible cause for dialysis initiation. Exact definitions from each trial protocol are provided in Supplementary Material, Section VII. MACE, all-cause mortality, and dialysis events were adjudicated by a blinded external committee. We analyzed individuals who initiated chronic dialysis (in-trial analysis), a subpopulation of participants who were on randomized treatment at and following dialysis initiation (on-treatment analysis and primary analysis), and a subpopulation of participants who discontinued treatment at or before dialysis initiation (discontinued-treatment analysis).

Because of breaking baseline randomization, our analysis is restricted to an exploratory descriptive analysis of baseline characteristics, as well as proportion and event rates of AEs, and does not entertain a causal analysis by reweighting the population to reflect balance between groups at the new baseline of dialysis initiation, because of low sample size and methodological constraints. Instead, we provide 95% CIs of the proportions and event rates in the Supplementary Material to highlight the variation from the mean for both descriptive statistics. We used event rates to account for the time spent treated with dialysis in each respective group. Results of the in-trial analysis are provided in Supplementary Tables 1–4. A sensitivity analysis that shifts follow-up start from 1 day to 7 days after dialysis initiation is provided in Supplementary Material, Section II to elucidate any systematic biases of early AEs that should be attributed to the initiation of dialysis itself.

Data and Resource Availability

All data that support the findings are included within the manuscript. Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in data sets in a deidentified and anonymized format. Data will be made available after research completion and approval of the product and product use in the European Union and the U.S. Information about data access request proposals can be found at www.novonordisk-trials.com.

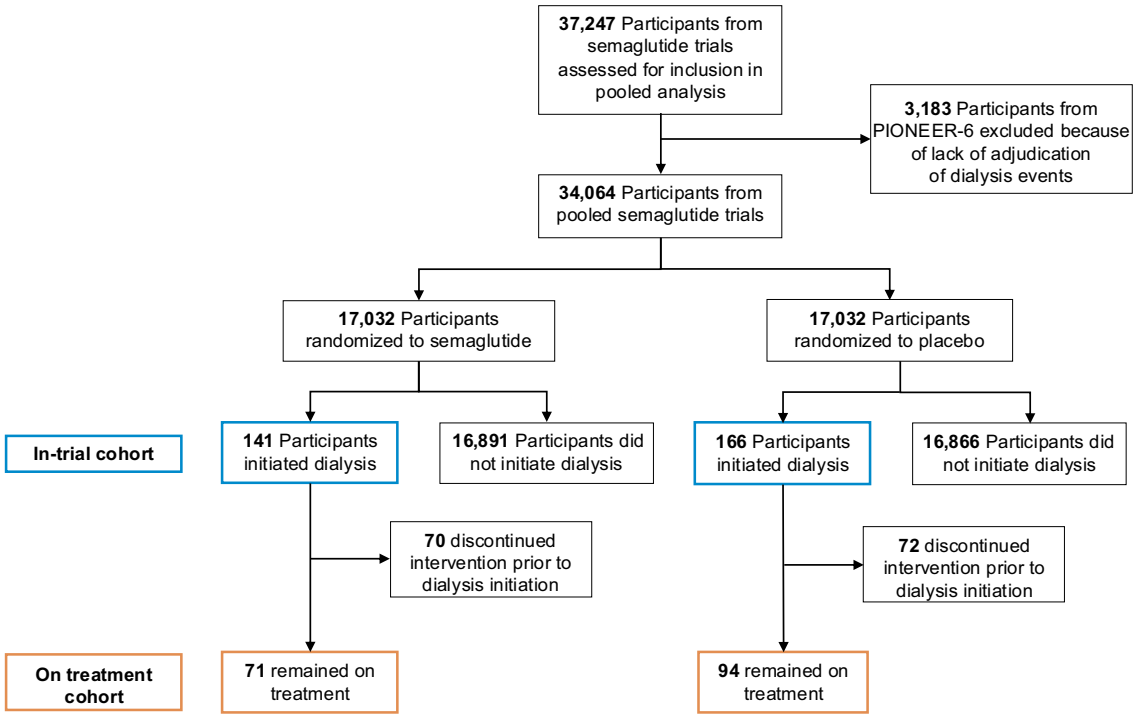

Figure 1—Participant flow diagram of the pooled analysis of SUSTAIN-6, SELECT, FLOW, and SOUL.

RESULTS

Among 34,064 participants randomized across four trials, 307 initiated dialysis (0.90%) (Fig. 1 and Supplementary Tables 1 and 2), of whom 165 were on treatment (semaglutide: *n* = 71; placebo: *n* = 94) at the time of dialysis initiation. The in-trial analysis consists of 23 participants from SUSTAIN-6, 10 participants from SELECT, 187 participants from FLOW, and 87 participants from SOUL (Supplementary Table 2). The on-treatment analysis set consists of 10 participants from SUSTAIN-6, 3 participants from SELECT, 105 participants from FLOW, and 47 participants from SOUL. The characteristics of the on-treatment cohort at the time of dialysis initiation are presented in Table 1. Concomitant medications used at the time of dialysis initiation are provided in Supplementary Table 5. At dialysis initiation, those originally randomized to semaglutide had a lower weight and insulin use. In the semaglutide group (*n* = 71), 76% were treated with the maximum dose of semaglutide allowed in each respective trial (Supplementary Table 6). Prior to dialysis initiation, 74.6% in the semaglutide group and 76.6% in the placebo group experienced at least one SAE. The distribution of SAEs occurring before dialysis initiation is provided in Supplementary Fig. 2. Mean follow-up time after dialysis initiation was 1.29 and 1.34 years in the semaglutide and placebo groups, respectively.

The counterpart to the on-treatment cohort, consisting of participants that discontinued treatment prior to dialysis initiation, consisted of 70 participants originally randomized to semaglutide and 72 participants originally randomized to placebo. The discontinued-treatment cohort tended to be older at dialysis start than the on-treatment cohort, with 66.9% vs. 48.5%, respectively, being >65 years of age. Likewise, 90.8% of participants in the discontinued-treatment cohort experienced at least one SAE prior to dialysis initiation, whereas only 75.6% of participants in the on-treatment cohort experienced at least one SAE prior to dialysis initiation (Supplementary Tables 7–9 and Table 1). The distribution of time between treatment discontinuation and dialysis initiation in the discontinued-treatment cohort is provided in Supplementary Fig. 3.

After dialysis initiation, 32 (45%) and 54 (57%) participants in the semaglutide and placebo groups, respectively, reported SAEs (Table 2). The SAE event rate was higher in the semaglutide group, secondary to a single participant who reported 43 SAEs (including six gastrointestinal and 10 infectious events) yet remained on treatment (Fig. 2). This participant initiated chronic dialysis after 2.66 years of trial participation and experienced four SAEs prior to dialysis initiation. After the adjudicated dialysis initiation event, this participant remained on treatment for an additional 1.89 years until the conclusion of the study. When this outlier data point was excluded, SAE event rates were numerically lower in the semaglutide group in contrast to the placebo group (Table 2). Supplementary Table 10 shows the magnitude of the difference in proportions for any reported SAE between the groups. For those originally randomized to semaglutide, the proportion experiencing any SAE is 45.1% (95% CI 33.2–57.3) compared with 57.4% (95% CI 46.8–67.6) for placebo.

The proportion of participants experiencing serious gastrointestinal disorders was 2.8% in the semaglutide group and 7.4% in the placebo group, and the event rates were similar (9.7 and 9.1 events per 100 person-years for semaglutide and placebo, respectively). When the outlier data point was excluded, serious gastrointestinal disorder event rates were lower in the semaglutide group than in the placebo group (1.4 vs. 9.1 events per 100 person-years, respectively).

Table 1—Characteristics of the on-treatment cohort at the time of dialysis initiation by randomization group (semaglutide versus placebo)

	Semaglutide	Placebo	Total
n	71	94	165
Duration of follow-up (years), mean (SD)*	1.29 (0.912)	1.34 (0.809)	1.31 (0.852)
Sex, *n* (%)			
Male	49 (69.0)	70 (74.5)	119 (72.1)
Female	22 (31.0)	24 (25.5)	46 (27.9)
Age (years), mean (SD)	64.4 (10.0)	65.1 (8.53)	64.8 (9.19)
Age-group (years), *n* (%)			
<45	3 (4.2)	1 (1.1)	4 (2.4)
45 to <55	11 (15.5)	10 (10.6)	21 (12.7)
55 to <65	20 (28.2)	40 (42.6)	60 (36.4)
65 to <75	30 (42.3)	32 (34.0)	62 (37.6)
75 to <85	7 (9.9)	11 (11.7)	18 (10.9)
≥85	0 (0)	0 (0)	0 (0)
Race, *n* (%)			
Asian	19 (26.8)	25 (26.6)	44 (26.7)
Black or African American	4 (5.6)	7 (7.4)	11 (6.7)
White	44 (62.0)	54 (57.4)	98 (59.4)
Not reported	0 (0)	3 (3.2)	3 (1.8)
Other	4 (5.6)	5 (5.3)	9 (5.5)
Ethnicity, *n* (%)			
Hispanic/Latino	18 (25.4)	23 (24.5)	41 (24.8)
Not Hispanic/Latino	53 (74.6)	67 (71.3)	120 (72.7)
Not reported	0 (0)	4 (4.3)	4 (2.4)
Region, *n* (%)			
North America	25 (35.2)	29 (30.9)	54 (32.7)
South America	5 (7.0)	8 (8.5)	13 (7.9)
Europe	9 (12.7)	21 (22.3)	30 (18.2)
Africa	1 (1.4)	0 (0)	1 (0.6)
Asia	20 (28.2)	24 (25.5)	44 (26.7)
Other	11 (15.5)	12 (12.8)	23 (13.9)
Diabetes, *n* (%)†	70 (98.6)	92 (97.9)	162 (98.2)
CKD, *n* (%)	71 (100)	92 (97.9)	163 (98.8)
Coronary heart disease, *n* (%)	23 (32.4)	30 (31.9)	53 (32.1)
Cerebrovascular disease, *n* (%)	14 (19.7)	20 (21.3)	34 (20.6)
Heart failure, *n* (%)	20 (28.2)	35 (37.2)	55 (33.3)
Weight (kg), mean (SD)	84.5 (22.9)	90.3 (22.7)	87.9 (22.9)
HbA_{1c} (%), mean (SD)	6.81 (1.30)	7.12 (1.36)	6.99 (1.34)
Insulin use, *n* (%)	41 (57.7)	70 (74.5)	111 (67.3)
SAEs prior to dialysis initiation, *n* (%)	53 (74.6)	72 (76.6)	125 (75.6)

*The duration of follow-up for the dialysis cohort is measured as the difference between the end of study and the dialysis initiation. †A diagnosis of type 2 diabetes was required for inclusion in SUSTAIN-6, FLOW, and SOUL. A diagnosis of diabetes was exclusionary in SELECT.

The proportion of participants reporting AEs that led to permanent discontinuation of investigational product was similar between groups (semaglutide: 8.5%; placebo: 10.6%) (Table 2). No participants randomized to semaglutide received a kidney transplant, while two randomized to placebo received a kidney transplant. Severe hypoglycemic episode event rates were similar between randomized treatment groups.

The proportion of participants experiencing MACE was lower in the semaglutide group than in the placebo group (Table 2) (9.9% vs. 17%, respectively). The MACE event rate was 9.7 events per 100 person-years with semaglutide and 16.1 events per 100 person-years for placebo. The all-cause mortality rate was also lower in the semaglutide group than the placebo group (13.8 and 18.1 events per 100 person-years, respectively). The 95% CI for proportion of participants experiencing MACE and all-cause mortality for semaglutide is 9.9% (95% CI 4.1–19.3) and 14.1% (95% CI 7.0–24.4), respectively, compared with 17% (95% CI 10.1–26.2) and 19.1% (95% CI 11.8–28.6), respectively, for placebo (Supplementary Table 10).

CONCLUSIONS

In this post hoc, individual-level pooled analysis of four international, randomized placebo-controlled clinical trials with systematically collected outcomes and AEs, semaglutide was not associated with a higher proportion of SAEs in participants initiating dialysis. The proportion and event rates of adjudicated MACE and all-cause mortality events were numerically lower among those originally randomized to semaglutide. Additionally, there was no evidence of an increased risk of serious gastrointestinal or hypoglycemic events, nor a higher permanent treatment discontinuation rate with semaglutide when compared with placebo after initiation of dialysis. As people treated with dialysis frequently experience gastrointestinal symptoms and high risk of hypoglycemia (22–24), these data provide reassurance that continued use of semaglutide does not exacerbate these concerns.

Prospective studies of GLP-1 RA in the dialysis population are limited (16). Only one randomized, placebo-controlled trial has been conducted in the outpatient setting (25,26). In this study, 24 participants with type 2 diabetes and dialysis-dependent kidney failure and 23 participants with type 2 diabetes and normal kidney function were randomized to liraglutide or placebo to compare the plasma concentrations of liraglutide in people treated with dialysis to those with normal kidney function. Secondarily, the study assessed the preliminary safety and efficacy of liraglutide in people treated with dialysis compared with those with normal glomerular filtration rate. Among those treated with dialysis, 10 of 14 participants randomized to liraglutide completed the 12-week study compared with all participants randomized to placebo. Plasma liraglutide concentrations were higher in people treated with dialysis, and nausea and vomiting occurred more frequently in people treated with dialysis randomized to liraglutide than the other three arms.

Table 2—Serious adverse events and adverse events of interest occurring after initiation of dialysis in the on-treatment cohort

	Semaglutide				Placebo			
	Participants	Proportion (%)	No. of events	Event rate[1,2]	Participants	Proportion (%)	No. of events	Event rate[1,2]
On-treatment cohort								
Any SAE	32	45.1	117	161.6	54	57.4	110	110.8
Serious infections and infestations	11	15.5	24	33.1	20	21.3	28	28.2
Serious gastrointestinal disorders	2	2.8	7	9.7	7	7.4	9	9.1
All-cause mortality	10	14.1	10	13.8	18	19.1	18	18.1
MACE[3]	7	9.9	7	9.7	16	17	16	16.1
AEs leading to permanent IP discontinuation	6	8.5	6	8.3	10	10.6	10	10.1
Severe hypoglycemic episodes	1	1.4	1	1.4	2	2.1	2	2.0
Kidney transplant	0	0.0	0	0.0	2	2.1	2	2.0
On-treatment cohort excluding the outlier participant[4]								
Any SAE	31	44.3	74	105.1	54	57.4	110	110.8
Serious infections and infestations	10	14.3	14	19.9	20	21.3	28	28.2
Serious gastrointestinal disorders	1	1.4	1	1.4	7	7.4	9	9.1
All-cause mortality	10	14.3	10	14.2	18	19.1	18	18.1
MACE[3]	7	10.0	7	9.9	16	17.0	16	16.1
AEs leading to permanent IP discontinuation	6	8.6	6	8.5	10	10.6	10	10.1
Severe hypoglycemic episodes	0	0.0	0	0.0	2	2.1	2	2.0
Kidney transplant	0	0.0	0	0.0	2	2.1	2	2.0

For on-treatment cohort, number of participants on semaglutide was 71, and number on placebo was 94; for on-treatment cohort excluding the outlier participant, there was one less participant on semaglutide. Participants: number in on-treatment cohort experiencing at least one event after dialysis initiation; Proportion (%): percentage in on-treatment cohort experiencing at least one event after dialysis initiation; No. of events: total number of events in on-treatment cohort after dialysis initiation. IP, investigational product. [1]Event rate for on-treatment analysis: all collected adverse events occurring after initiation of dialysis and while being on treatment divided over person-years calculated for all participants in each trial group until discontinuation of trial medication, death, loss-to-follow up, withdrawal, or end of treatment, whichever came first. On-treatment periods are defined as observed on-treatment period with intended study product plus a 35-day washout period. [2]Event rate [(no. of events divided by sum of person-years) × 100]: event rates are defined per 100 person-years. The sum of person-years was 72.4 or 70.4 years for the on-treatment analysis for the semaglutide (with or without outlier participant) and 99.3 years for the placebo group. [3]MACE is defined as nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, or undetermined death. [4]The outlier participant reported 43 serious adverse events while remaining on medication.

Notably, rates of nausea and vomiting in participants treated with dialysis randomized to placebo were similar to participants with normal kidney function randomized to liraglutide, highlighting the high burden of gastrointestinal symptoms at baseline in people treated with dialysis (26).

Mild hypoglycemia measured by continuous glucose monitoring increased in participants receiving dialysis who were randomized to liraglutide compared with placebo (25). Eight of 12 participants with continuous glucose monitoring data were treated with insulin, and three were treated with oral glucose-lowering medications. Glucose-lowering medication reduction was not protocolized at randomization. As such, proactive management of glucose-lowering therapies with addition of GLP-1 RA may be necessary to reduce hypoglycemia risk.

Nonrandomized studies have also raised concerns regarding fat and skeletal muscle loss with GLP-1 RA (27), as GLP-1 RA–induced weight loss may be detrimental to people with dialysis-dependent kidney failure (16). Observational data suggest lighter body weight associates with worse survival in the dialysis population (28). As a result, concerns related to GLP-1 RA–induced weight loss, especially with more potent agents, may contribute to hesitancy for broad use of GLP-1 RA in the dialysis population. Indeed, in the U.S. dialysis population, few people who may benefit are prescribed GLP-1 RA (15,16). In our pooled analysis, people who were originally randomized to semaglutide had, on average, a lower weight than people in the placebo group at dialysis initiation; nevertheless, people who initiated dialysis in the semaglutide group did not experience more SAEs, including gastrointestinal events, MACE, all-cause mortality, or hypoglycemia, than people who initiated dialysis in the placebo group, who had, on average, a higher weight at dialysis initiation.

Observational studies indicating potential for benefit are also emerging. One such study suggested that GLP-1 RA use conferred MACE and all-cause mortality risk reduction in people living with type 2 diabetes at dialysis initiation when compared with basal insulin (29). Similarly, a more recent study demonstrated that GLP-1 RA use in people receiving dialysis associated with a decreased risk of mortality compared with GLP1-RA nonusers (30). However, both studies need to be interpreted within the context of their constructed cohort and potential biases (e.g., immortal time bias, reverse causation, or competing risks). Regardless of these limitations, consistent with the present results, these observational

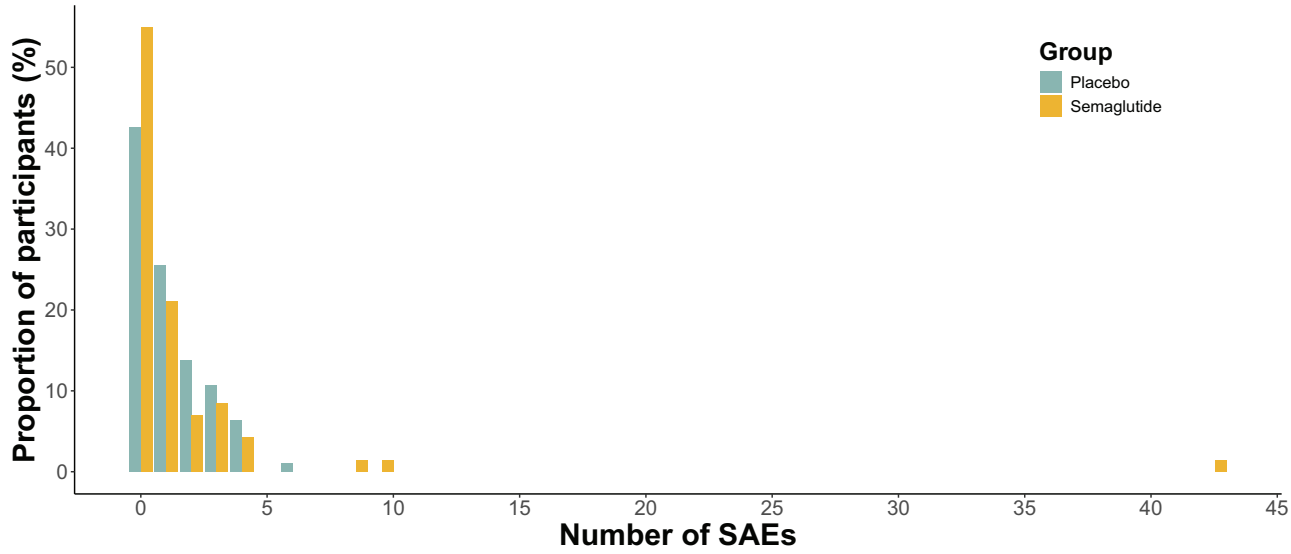

Figure 2—Distribution of serious adverse events occurring after dialysis initiation in the on-treatment cohort by treatment group.

data suggest potential for MACE and mortality benefit with GLP-1 RA use in the dialysis population, necessitating future study of their potential benefit.

Several important study limitations are noteworthy in our work as well. Few participants initiated dialysis, and they were randomized at study start rather than at dialysis initiation, thus limiting our evaluation to an exploratory analysis with descriptive assessments. The follow-up time for each participant in the pooled analysis varied based on trial length and time of dialysis initiation, although the follow-up duration after dialysis initiation was comparable between randomized groups and exceeds, on average, 1 year. Additionally, differences in AE collection across the trials prevented comparison of nonserious AEs; however, that fewer permanent treatment discontinuations occurred in those treated with semaglutide is reassuring regarding tolerance.

It is worth commenting on the selection bias in this analysis, which has been induced by creating a cohort of people initiating dialysis after randomization. Because semaglutide reduces risks of MACE, all-cause mortality, and loss of kidney function and kidney failure in people with CKD (10), semaglutide use prior to dialysis may have introduced unidentifiable differences between the cohorts at dialysis initiation. Given that, in semaglutide outcomes trials, a higher mortality rate was observed in people randomized to placebo, differential survivor bias has been introduced by treatment assignment, thus disrupting the equipoise of risks provided by randomization into the trials. While our analyses suggest a potential for benefit, a study that randomizes people treated with dialysis to semaglutide or placebo is required to fully elucidate the risks and benefits. Unfortunately, thus far, randomized studies of GLP-1 RA in dialysis have proven challenging (18,19). As such, these data are likely to be the most robust prospective evidence available for some time.

The present observations represent the largest prospective report of people receiving dialysis treated with GLP-1 RA and support the safety of semaglutide continuation in people initiating dialysis. Further, the available data highlight potential for benefits on MACE and all-cause mortality. In the absence of randomized trials in dialysis-dependent kidney failure, these new insights into the safety of GLP-1 RA use highlight the need to test GLP-1 RA as potential therapies to improve cardiovascular and survival outcomes in this high-risk population and should encourage continuation of GLP-1 RA after dialysis initiation.

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