

Kidney and Survival Outcomes with Semaglutide by CKD Severity in the FLOW Trial

Katherine R. Tuttle^{1,2}, Johannes F.E. Mann^{3,4}, Manuel M. Mayrdorfer⁵, Brian Rayner⁶, Giuseppe Pugliese⁷, Richard E. Pratley⁸, Vlado Perkovic⁹, Kenneth W. Mahaffey¹⁰, Naoki Kashihara¹¹, Ole K. Jeppesen⁵, Janusz Gumprecht¹², Ricardo Correa-Rotter¹³, David Z.I. Cherney^{14,15}, Heidrun Bosch-Traberg⁵, Mustafa Arici¹⁶, and Peter Rossing^{17,18}, on behalf of the FLOW Trial Investigators*

Key Points

- Semaglutide reduced kidney outcome risk across broad CKD severity strata (eGFR; albuminuria).
- Reduced risk for all-cause death also carried through strata of CKD severity.
- In a population with type 2 diabetes, semaglutide improved kidney and survival outcomes irrespective of CKD severity, including advanced CKD.

Abstract

Background Semaglutide improved kidney and overall survival in participants with type 2 diabetes (T2D) and CKD in the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial. The aim of the present analyses was to quantify these benefits across broad strata of CKD severity.

Methods FLOW was a double-blind, randomized, placebo-controlled trial (median follow-up 3.4 [interquartile range, 2.9–4.0] years). Participants with T2D and eGFR 50–75 ml/min per 1.73 m² and urine albumin-to-creatinine ratio (UACR) >300 to <5000 mg/g, or eGFR 25 to <50 ml/min per 1.73 m² and UACR >100 to <5000 mg/g, were randomized to subcutaneous semaglutide 1 mg once-weekly or placebo. Subgroups were categorized by baseline eGFR (<30 to ≥60 ml/min per 1.73 m²) or UACR (<100 to ≥2000 mg/g) to assess the primary outcome and individual components (≥50% eGFR decline, eGFR <15 ml/min per 1.73 m², dialysis, kidney transplant, and death due to kidney or cardiovascular causes), all-cause death, eGFR, and UACR.

Results At baseline, the mean±SD eGFR was 47±15 ml/min per 1.73 m², and the median (5th–95th percentile) UACR was 568 (51–3225) mg/g. The primary outcome occurred in 19% (331 of 1767) versus 23% (410 of 1766) with semaglutide treatment versus placebo (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.66 to 0.88). Death occurred in 13% (227 of 1767) versus 16% (279 of 1766), respectively (HR, 0.80; 95% CI, 0.67 to 0.95). Across eGFR and UACR subgroups, HRs for the primary outcome remained consistent (*P* for interaction 0.83 and 0.42, respectively). For death, HRs were consistent among eGFR subgroups (*P* for interaction 0.54), but the HR was lowest (0.47; 95% CI, 0.31 to 0.70) for those with UACR ≥2000 mg/g (*P* for interaction 0.02). Estimated treatment effects on eGFR and UACR were generally consistent among subgroups.

Conclusions Semaglutide reduced risks of major kidney disease events and all-cause death across wide-ranging categories of baseline eGFR and UACR, supporting semaglutide treatment in T2D throughout the spectrum of CKD severity represented in FLOW, including advanced CKD. Clinical Trial registry name and registration number: [NCT03819153](https://clinicaltrials.gov/ct2/show/study/NCT03819153).

CJASN 21: 841–851, 2026. doi: <https://doi.org/10.2215/CJN.0000000974>

This is an open access article distributed under the [Creative Commons Attribution License 4.0 \(CCBY\)](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Prof. Katherine R. Tuttle, email: Katherine.Tuttle@providence.org

Received: October 3, 2025 **Accepted:** February 9, 2026

Published Online Ahead of Print: February 18, 2026

*The FLOW Trial Investigators list is extensive and can be found in the [Supplemental Material](#).

See related editorial, “Expanding Evidence for Glucagon-Like Peptide-1 Receptor Agonists in Those with Diabetes and Kidney Disease,” on pages 738–740.

Introduction

Diabetes has grown to pandemic proportions, with a global prevalence that is projected to become 783 million by 2045.¹ Type 2 diabetes (T2D) is responsible for >90% of diabetes cases. Living with T2D leads to serious complications, including CKD in nearly four of ten people.^{2,3} As a result, T2D is now the most common cause of kidney failure worldwide.^{4,5} The Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial comparing subcutaneous semaglutide 1.0 mg once-weekly with placebo—the first dedicated kidney outcomes trial of a glucagon-like peptide-1 (GLP-1) receptor agonist in T2D—showed a relative risk reduction for the primary kidney outcome of 24% over a median of 3.4 years.^{6,7} The relative risk of all-cause death was also reduced by 20%.

Whether the kidney protective effects of semaglutide vary by CKD severity is unclear. In cardiovascular outcomes trials, GLP-1 receptor agonists reduced albuminuria and slowed eGFR decline, even when used with other potentially protective therapies in populations with T2D or obesity and relatively low CKD risk.^{8–10} At the other end of the spectrum, preservation of eGFR and albuminuria lowering was observed in a population with moderate-to-severe CKD treated by dulaglutide versus insulin glargine for T2D.¹¹ Moreover, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes and Peptide Innovation for Early Diabetes Treatment trials, slower eGFR decline or Kidney Disease Improving Global Outcomes risk improvement was most evident in lower eGFR subgroups, pointing to kidney protection with advancing CKD.¹² Since death rates also escalate with eGFR decline,^{13–19} the aim of the present analyses was to quantify both kidney and survival benefits of semaglutide across discrete categories of eGFR and albuminuria representing the range of CKD severity in the FLOW trial.

Methods

Study Design and Participants

FLOW (ClinicalTrials.gov; [NCT03819153](#)) was a multicenter, double-blind, randomized (stratified according to the use of sodium-glucose cotransporter 2 [SGLT2] inhibitors at baseline), placebo-controlled clinical trial led by an academic steering committee and conducted at 387 international sites, with a median follow-up of 3.4 (interquartile range 2.9–4.0) years.^{6,7} Detailed inclusion and exclusion criteria have been published previously and are presented in [Supplemental Table 1](#).^{6,7} The trial protocol and statistical analysis plan are in the Supplement. Adult participants (18 years or older) with T2D and CKD (baseline eGFR 50–75 ml/min per 1.73 m² and urine albumin-to-creatinine ratio [UACR] >300 to <5000 mg/g, or eGFR 25 to <50 ml/min per 1.73 m² and UACR >100 to <5000 mg/g) were randomized (1:1) to treatment with subcutaneous semaglutide 1.0 mg once-weekly or placebo. Participants received study treatment on top of standard of care including an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker. The duration of FLOW was driven by the number of primary outcome events. Following an interim analysis, the Independent Data Monitoring

Committee recommended early trial cessation when 570 events had occurred, because of overwhelming benefits.

Outcomes

The primary outcome was a composite of $\geq 50\%$ eGFR decline from baseline, kidney failure (onset of persistent eGFR <15 ml/min per 1.73 m², initiation of chronic KRT by dialysis or kidney transplantation), and kidney or cardiovascular death.⁶ As prespecified secondary analyses, additional subgroups and outcomes are reported here: (1) The primary outcome by time-to-event analyses according to baseline eGFR (≥ 60 , ≥ 45 to <60, ≥ 30 to <45, and <30 ml/min per 1.73 m²) and more granular UACR (<100, ≥ 100 to <300, ≥ 300 to <1000, ≥ 1000 to <2000, ≥ 2000 mg/g) subgroups; (2) individual components of the primary outcome by these eGFR and UACR subgroups; (3) estimated treatment effects on eGFR (both creatinine and cystatin-C based) and UACR change over time by these eGFR and UACR subgroups, respectively; and (4) all-cause death was similarly assessed by these eGFR and UACR subgroups.

Creatinine-based eGFR and cystatin C–based eGFR were measured in a central laboratory and calculated using the CKD Epidemiology Collaboration 2009 formula.²⁰ UACR was also measured in a central laboratory and analyzed using spot urine samples.

Statistical Analysis

FLOW was designed for 90% power to detect a 20% relative risk reduction for the primary kidney outcome. There were no power estimates for the subgroup analyses by baseline eGFR and UACR categories.

Aalen-Johansen estimates analyzed the time from randomization to the first primary outcome event, with noncardiovascular and nonkidney death modeled as competing risks. A Cox proportional hazards model (with treatment group and interaction between treatment group and subgroup as a fixed factor and stratified by use of SGLT2 inhibitors at baseline) evaluated treatment effects (hazard ratios [HRs] and 95% confidence intervals [95% CIs]) for the time from randomization to the first primary outcome event; participants without a first primary outcome event were censored at the end of their in-trial period. Events not defined by eGFR or UACR were confirmed by the Event Adjudication Committee.

Changes in baseline eGFR-creatinine, eGFR-cystatin C, and UACR over time were analyzed using a linear random effects model with treatment, use of SGLT2 inhibitors (yes/no) at baseline, time (as a continuous variable), and treatment time interaction as fixed effects, and including participant effect as a random intercept and time as a random slope. UACR at 24 months was also analyzed using an analysis of covariance model with treatment, use of SGLT2 inhibitors (yes/no) at baseline, baseline UACR subgroup, and interaction between treatment and baseline UACR subgroup as fixed factors and baseline UACR as a covariate. The ratio to baseline and the corresponding baseline value were log-transformed before analysis. Missing data at 24 months were imputed using a multiple imputation model and done separately for each treatment group and included baseline value as a covariate and use of SGLT-2

Table 1. Baseline characteristics by baseline eGFR and urine albumin-to-creatinine ratio subgroups

Variable	Total (N=3533) ^a	eGFR Subgroup (ml/min per 1.73 m ²)				
		≥60 (n=719)	≥45 to <60 (n=1055)	≥30 to <45 (n=1358)	<30 (n=400)	
Age, yr	67±9	65±9	67±9	67±9	67±9	
Female sex	1069 (30)	212 (29)	320 (30)	412 (30)	125 (31)	
History of CVD						
ASCVD ^b	1198 (34)	239 (33)	385 (36)	446 (33)	128 (32)	
Heart failure	678 (19)	118 (16)	227 (22)	258 (19)	75 (19)	
HbA _{1c} , %	7.8±1.3	7.9±1.3	7.8±1.3	7.8±1.3	7.6±1.3	
Duration of diabetes, yr	17.4±9.3	16.0±8.5	17.2±9.2	17.7±9.6	18.9±9.5	
eGFR, ml/min per 1.73 m ²	47±15	70±9	51±4	37±4	26±2	
UACR, mg/g	568 (51 to 3225)	562 (49 to 2839)	520 (43 to 3143)	567 (51 to 3414)	848 (78 to 3320)	
ACE inhibitor/ARB use	3364 (95)	704 (98)	1023 (97)	1274 (94)	362 (91)	
SGLT2 inhibitor use	550 (16)	151 (21)	198 (19)	158 (12)	43 (11)	
Insulin use	2168 (61)	402 (56)	609 (58)	888 (65)	268 (67)	
	Total (N=3533) ^a	UACR subgroup (mg/g)				
		<100 (n=350)	≥100 to <300 (n=763)	≥300 to <1000 (n=1288)	≥1000 to <2000 (n=640)	≥2000 (n=491)
Age, yr	67±9	69±8	68±8	67±9	66±9	63±10
Female sex	1069 (30)	139 (40)	225 (29)	373 (29)	184 (29)	148 (30)
History of CVD						
ASCVD ^b	1198 (34)	104 (30)	267 (35)	446 (35)	215 (34)	166 (34)
Heart failure	678 (19)	81 (23)	134 (18)	250 (19)	119 (19)	94 (19)
HbA _{1c} , %	7.8±1.3	7.8±1.4	7.7±1.2	7.7±1.3	7.9±1.3	7.9±1.3
Duration of diabetes, yr	17.4±9.3	17.4±10.0	17.8±9.8	17.2±9.1	17.6±9.1	16.9±8.7
eGFR, ml/min per 1.73 m ²	47±15	47±14	47±15	48±15	47±16	43±15
UACR, mg/g	568 (51 to 3225)	50 (5 to 96)	187 (109 to 289)	564 (325 to 941)	1410 (1028 to 1928)	2897 (2067 to 5340)
ACE inhibitor/ARB use	3364 (95)	334 (95)	726 (95)	1233 (96)	610 (95)	460 (94)
SGLT2 inhibitor use	550 (16)	60 (17)	135 (18)	190 (15)	106 (17)	59 (12)
Insulin use	2168 (61)	199 (57)	473 (62)	771 (60)	395 (62)	329 (67)
Values are no. (%), mean±SD, or median (5th to 95th percentiles). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HbA _{1c} , glycated hemoglobin; SGLT2, sodium-glucose cotransporter 2; UACR, urine albumin-to-creatinine ratio.						
^a One participant in the semaglutide arm did not have baseline eGFR data available.						
^b Myocardial infarction, stroke, and peripheral arterial disease.						

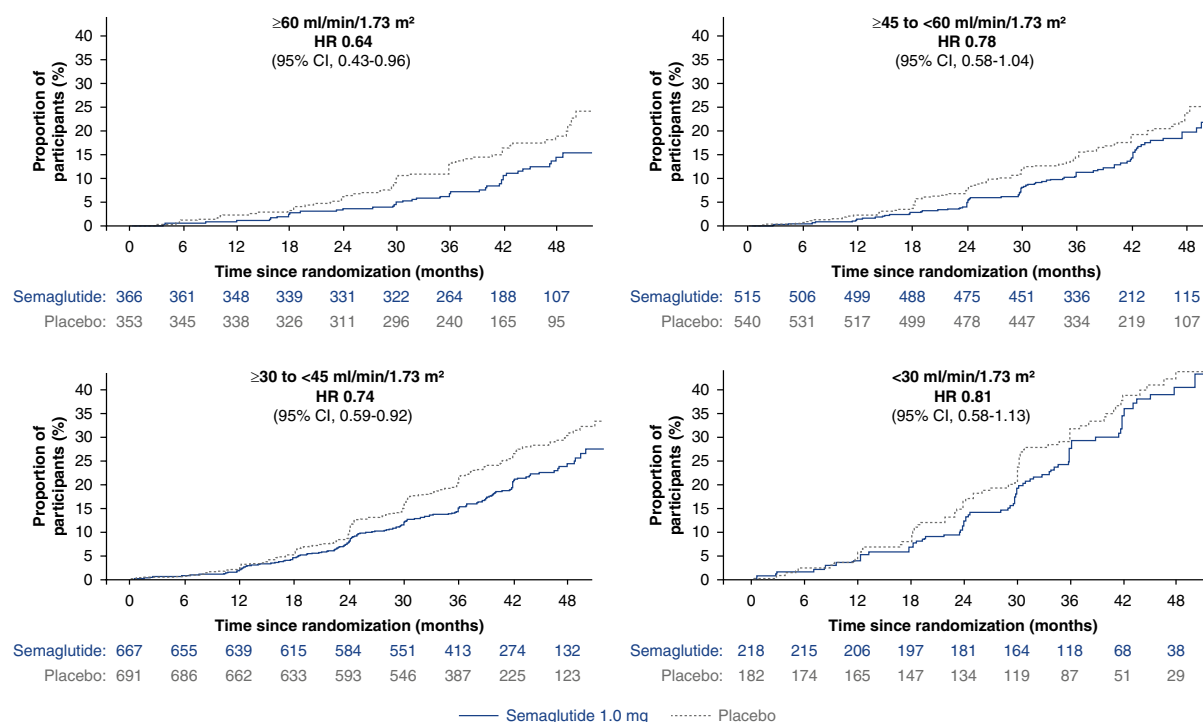


Figure 1. Time to the primary kidney outcome by baseline eGFR subgroup. *P* for interaction was 0.83. Cumulative incidence estimates based on time from randomization to first primary kidney outcome with noncardiovascular and nonkidney death modeled as competing risks during the in-trial period. CI, confidence interval; HR, hazard ratio.

inhibitor (yes/no) at baseline as a fixed factor and was fitted to all subjects with a measurement regardless of treatment status at 24 months. The fitted model was used to impute values for all patients with missing data at 24 months to create 500 complete data sets. Rubin's rules were used to combine the results.²¹

Time from randomization to all-cause death was analyzed using a Cox proportional hazards model with treatment as a categorical fixed factor and stratified by SGLT2 inhibitor use (yes versus no) at baseline. Participants without all-cause death were censored at the end of their in-trial period.

For subgroup analyses, estimated HRs and corresponding 95% CIs were calculated in a Cox proportional hazards model with treatment, subgroup, and interaction between treatment group and subgroup as fixed factors and stratified by SGLT2 inhibitor use (yes/no) at baseline. No adjustment for multiplicity or alpha-protection was performed and should therefore not be used to infer conclusive treatment effects. Two-sided *P* values <0.05 were considered significant. All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute).

Results

Participant Characteristics

Participant flow through the trial is shown in [Supplemental Figure 1](#), as reported previously.⁶ Among 3533 participants in the FLOW population, 30% (*n*=1069) were women, mean (SD) age was 67 (9) years, mean (SD) eGFR was

47 (15) ml/min per 1.73 m², and median (5th–95th percentile) UACR was 568 (51–3225) mg/g. Baseline characteristics were mostly balanced across eGFR subgroups ([Table 1](#)) with a few imbalances. The mean duration of diabetes in participants with eGFR <30 ml/min per 1.73 m² was longer (18.9 [SD 9.5] versus 16.0–17.7 [8.5–9.6] years), and the use of insulin was higher (67% versus 56%–65% of participants) in contrast to other eGFR subgroups, respectively. Conversely, participants with baseline eGFR ≥45 ml/min per 1.73 m² more frequently used angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (97%–98% versus 91%–94%, respectively) and SGLT2 inhibitors (19%–21% versus 11%–12%, respectively) than those with baseline eGFR <45 ml/min per 1.73 m². Similarly, baseline characteristics were mostly balanced across UACR subgroups ([Table 1](#)). With higher UACR levels, the proportion of participants using insulin was higher.

Primary Outcome and Individual Components by eGFR and UACR Subgroups

The primary kidney outcome was consistent across eGFR subgroups, reported by 11% (41 of 366) versus 17% (59 of 353) of participants receiving semaglutide versus placebo, respectively, with eGFR ≥60 ml/min per 1.73 m² (HR, 0.64; 95% CI, 0.43 to 0.96), 16% (80 of 515) versus 19% (103 of 540) with eGFR ≥45 to <60 ml/min per 1.73 m² (HR, 0.78; 95% CI, 0.58 to 1.04), 21% (137 of 667) versus 26% (181 of 691) with eGFR ≥30 to <45 ml/min per 1.73 m² (HR, 0.74; 95% CI, 0.59 to 0.92), and 33% (73 of 218)

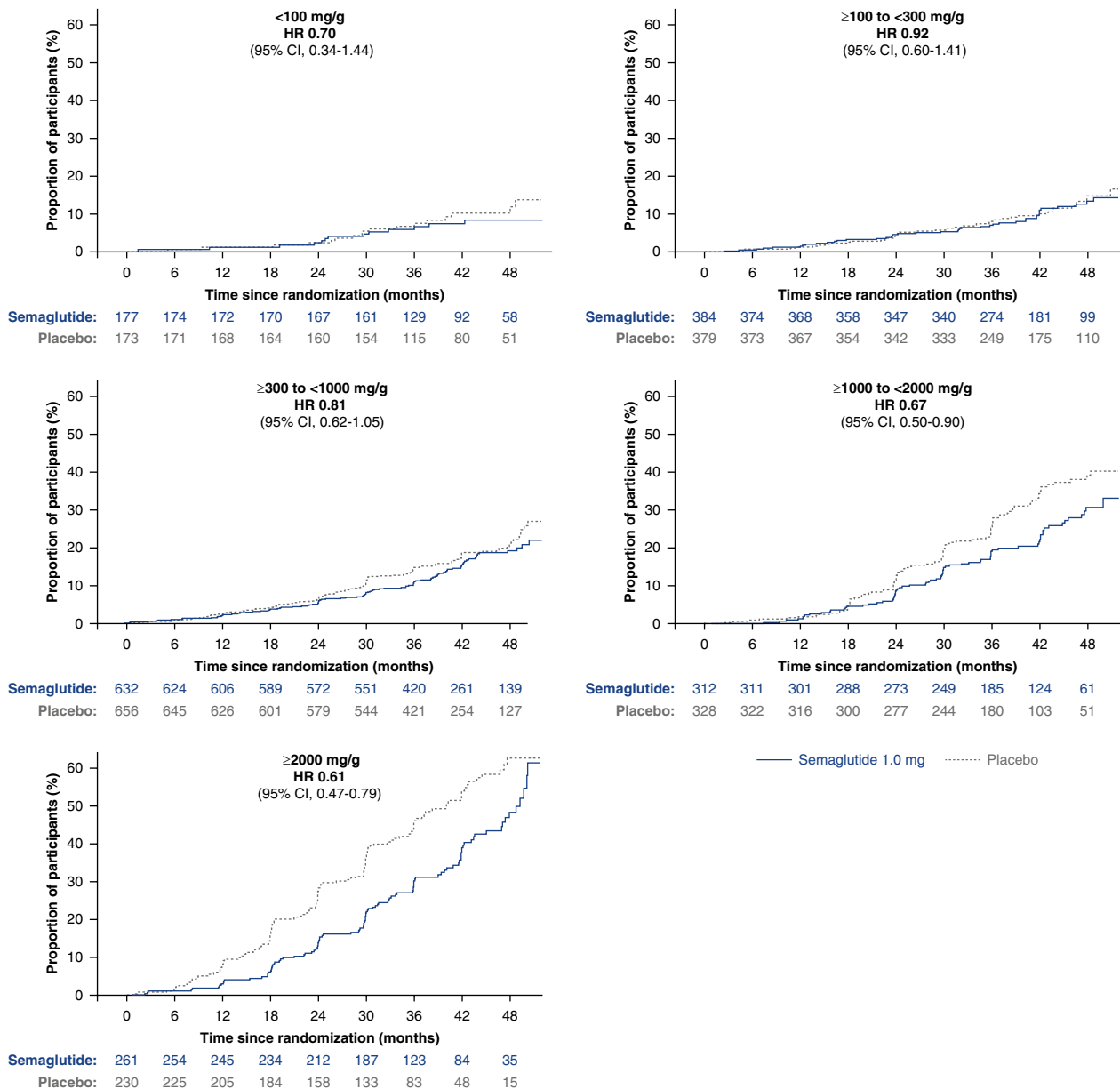


Figure 2. Time to the primary kidney outcome by baseline UACR subgroup. *P* for interaction was 0.42. Cumulative incidence estimates based on time from randomization to first primary kidney outcome with noncardiovascular and nonkidney death modeled as competing risks during the in-trial period. UACR, urine albumin-to-creatinine ratio.

versus 37% (67 of 182) with eGFR <30 ml/min per 1.73 m² (HR, 0.81; 95% CI, 0.58 to 1.13; *P* value for interaction 0.83; Figure 1 and Supplemental Figure 2). Comparing semaglutide to placebo for the individual components⁶: eGFR decline of ≥50% was 9% (165 of 1766) versus 12% (213 of 1766) with a HR of 0.73 (95% CI, 0.59 to 0.89); sustained eGFR <15 ml/min per 1.73 m² was 5% (92 of 1767) versus 6% (110 of 1766) with a HR of 0.80 (95% CI, 0.61 to 1.06); KRT occurred in 5% (87 of 1767) versus 6% (100 of 1766) with a HR of 0.84 (95% CI, 0.63 to 1.12); cardiovascular death occurred in 7% (123 of 1767) versus 10% (169 of 1766) with a HR of 0.71 (95% CI, 0.56 to 0.89). When the individual components were analyzed by eGFR subgroups, *P* values for interaction ranged between 0.28 and 0.86

(Supplemental Figure 2). The outcome of kidney death by eGFR subgroups could not be assessed because the number of events (ten cases) was too small.

Similarly consistent results for the primary kidney outcome were observed in the UACR subgroups (Figure 2 and Supplemental Figure 3), occurring in 7% (13 of 177) versus 10% (17 of 173) of participants receiving semaglutide versus placebo with UACR <100 mg/g (HR, 0.70; 95% CI, 0.34 to 1.44), 11% (42 of 384) versus 12% (45 of 379) with UACR ≥100 to <300 mg/g (HR, 0.92; 95% CI, 0.60 to 1.41), 15% (97 of 632) versus 18% (120 of 656) with UACR ≥300 to <1000 mg/g (HR, 0.81; 95% CI, 0.62 to 1.05), 24% (75 of 312) versus 33% (107 of 328) with UACR ≥1000 to <2000 mg/g (HR, 0.67; 95% CI, 0.50 to 0.90), and

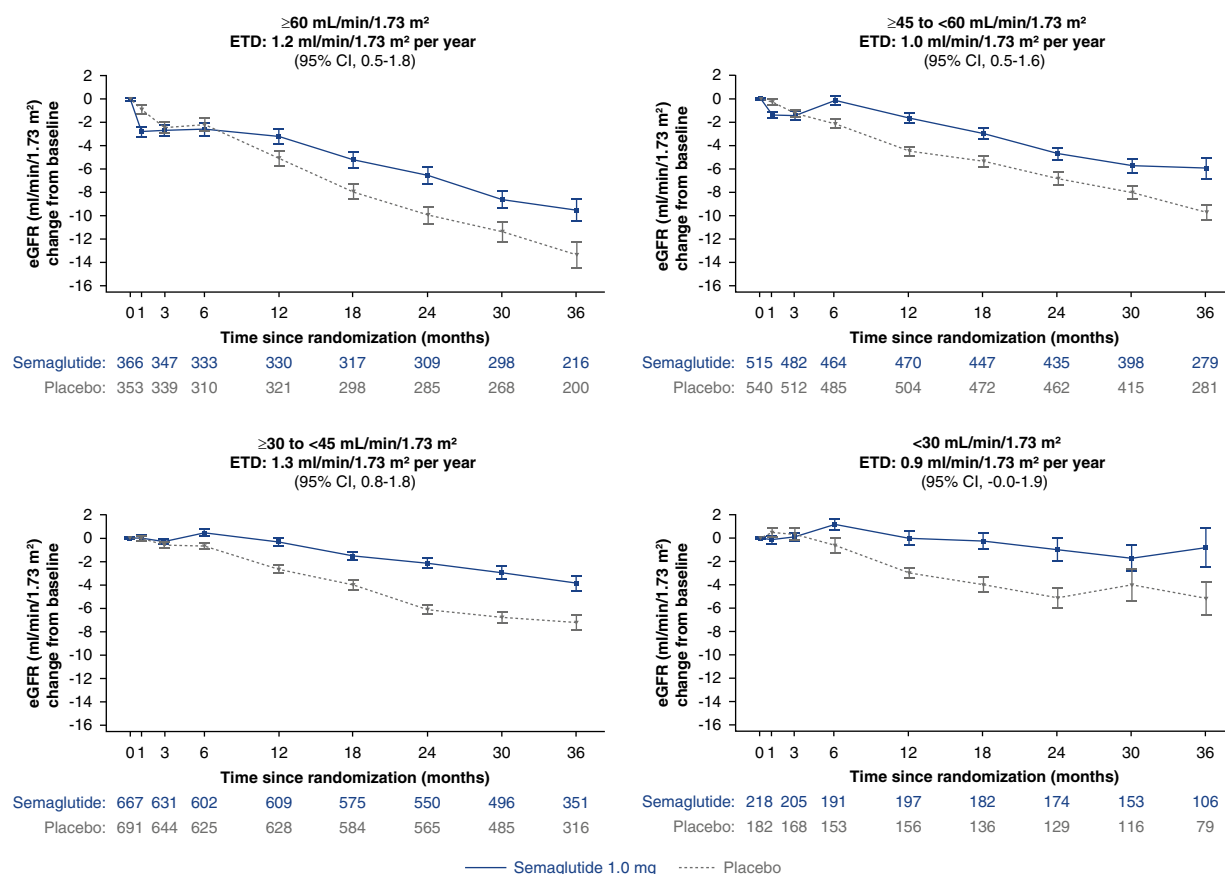


Figure 3. Change in eGFR relative to baseline over time by eGFR subgroup. *P* for interaction was 0.81. ETDs (mL/min per 1.73 m² per year) between treatment with semaglutide and placebo are illustrated. Data are from the in-trial period. Error bars are $\pm$ SEM. Numbers shown in lower panels represent the number of participants contributing to the analysis at that time point. Change in eGFR was analyzed using a linear random effects model with treatment, use of SGLT2 inhibitors (yes/no) at baseline, time (as a continuous variable), and treatment time interaction as fixed effects, and including participant effect as a random intercept and time as a random slope. ETD, estimated treatment difference; SGLT2, sodium-glucose cotransporter 2.

40% (104 of 261) versus 53% (121 of 230) with UACR ≥ 2000 mg/g (HR 0.61; 95% CI, 0.47 to 0.79; *P* value for interaction 0.42). When analyzed by UACR subgroups, the results were also consistent for eGFR decline of $\geq 50\%$, dialysis or kidney transplant, and cardiovascular death in the full analysis set, with *P* values for interaction ranging between 0.17 and 0.96 (Supplemental Figure 3). The outcomes of onset of persistent eGFR <15 mL/min per 1.73 m² and kidney death could not be analyzed because of the low number of events in one or more UACR subgroups.

Changes in eGFR Over Time by eGFR Subgroups

The estimated treatment difference in mean creatinine-based eGFR at 24 months was 3.3 mL/min per 1.73 m² (95% CI, 2.4 to 4.2) in the semaglutide versus placebo groups based on the full analysis set.⁶ Across eGFR subgroups, the rate of decline in eGFR was slower in participants receiving semaglutide than in those receiving placebo, with the following estimated treatment differences in mean eGFR slope (mL/min per 1.73 m² per year): 1.2 (95% CI, 0.5 to 1.8) for eGFR ≥ 60 mL/min per 1.73 m², 1.0 (95% CI, 0.5 to 1.6) for ≥ 45 to <60 mL/min per 1.73 m², 1.3 (95% CI, 0.8 to 1.8)

for ≥ 30 to <45 mL/min per 1.73 m², and 0.9 (95% CI, -0.0 to 1.9) for <30 mL/min per 1.73 m² (interaction *P* = 0.81; Figure 3). Consistent benefits for semaglutide were also observed when evaluating rate of change in cystatin C-based eGFR (Supplemental Figure 4), with the estimated treatment differences in mean eGFR ranging between 1.1 and 1.8 mL/min per 1.73 m² per year across the eGFR subgroups (interaction *P* = 0.34).

Changes in Albuminuria Over Time by UACR Subgroups

Participants with albuminuria in the two lowest categories at baseline (<100 mg/g and ≥ 100 to <300 mg/g) had smaller changes in UACR relative to baseline at 24 months with semaglutide treatment compared with placebo (UACR geometric means at 24 months for semaglutide were 242.0 and 279.0 mg/g, respectively, and for placebo they were 347.2 and 402.0 mg/g, respectively) but had estimated treatment ratios of 0.70 and 0.69 on a relative scale, respectively (Supplemental Figure 5). For those with higher baseline albuminuria categories (≥ 300 to <1000 mg/g, ≥ 1000 to <2000 mg/g, and ≥ 2000 mg/g), semaglutide similarly decreased UACR compared with placebo on a relative scale (estimated treatment ratios of

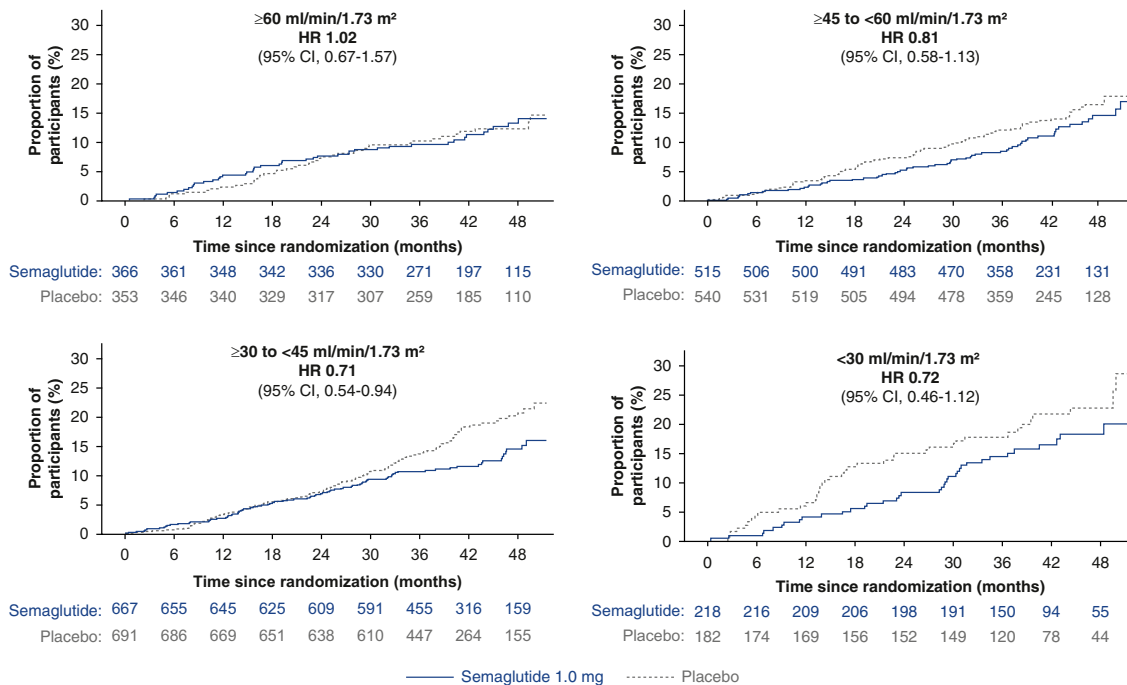


Figure 4. Time to all-cause death by baseline eGFR subgroup. *P* for interaction was 0.54. Time from randomization to all-cause death was analyzed using a Cox proportional hazards model with treatment as a categorical fixed factor and stratified by SGLT2 inhibitor use (yes/no) at baseline during the in-trial period.

0.70, 0.65, and 0.62, respectively) but with larger reductions (UACR geometric means at 24 months for semaglutide were 287.7, 338.6, and 344.2 mg/g, respectively, and for placebo, they were versus 409.1, 517.3, and 552.3 mg/g, respectively). The *P* for interaction was 0.94 across UACR subgroups.

All-Cause Death by eGFR and UACR Subgroups

All-cause death was a confirmatory secondary outcome in the FLOW trial.⁶ In eGFR subgroups, all-cause death occurred in 12% (44 of 366) versus 12% (42 of 353) of participants receiving semaglutide versus placebo with eGFR ≥ 60 ml/min per 1.73 m² (HR, 1.02; 95% CI, 0.67 to 1.57), 12% (63 of 515) versus 15% (79 of 540) with eGFR ≥ 45 to <60 ml/min per 1.73 m² (HR, 0.81; 95% CI, 0.58 to 1.13), 12% (83 of 667) versus 17% (118 of 691) with eGFR ≥ 30 to <45 ml/min per 1.73 m² (HR, 0.71; 95% CI, 0.54 to 0.94), and 17% (37 of 218) versus 22% (40 of 182) with eGFR <30 ml/min per 1.73 m² (HR, 0.72; 95% CI, 0.46 to 1.12; *P* for interaction 0.54; Figure 4 and Supplemental Table 2).

Across UACR subgroups, all-cause death outcome occurred in 12% (22 of 177) versus 12% (21 of 173) of participants receiving semaglutide versus placebo with UACR <100 mg/g (HR, 0.97; 95% CI, 0.53 to 1.77), 13% (48 of 384) versus 10% (38 of 379) with UACR ≥ 100 to <300 mg/g (HR, 1.28; 95% CI, 0.84 to 1.97), 12% (78 of 632) versus 16% (103 of 656) with UACR ≥ 300 to <1000 mg/g (HR, 0.78; 95% CI, 0.58 to 1.04), 14% (43 of 312) versus 17% (55 of 328) with UACR ≥ 1000 to <2000 mg/g (HR, 0.79; 95% CI, 0.53 to 1.18), and 14% (36 of 261) versus 27% (62 of 230) with

UACR ≥ 2000 mg/g (HR, 0.47; 95% CI, 0.31 to 0.70) (Figure 5 and Supplemental Table 2). The *P* for interaction among UACR subgroups was 0.02, due to a greater benefit of semaglutide in the UACR ≥ 2000 mg/g subgroup versus the other UACR subgroups.

Discussion

The FLOW trial enrolled a population with T2D across a range of CKD severity strata. Risk of the primary kidney outcome was consistently reduced throughout these strata determined by eGFR or UACR with semaglutide treatment versus placebo.⁶ Risks of primary outcome components inclusive of eGFR decline $\geq 50\%$, eGFR <15 ml/min per 1.73 m², KRT by dialysis or transplant, or death due to cardiovascular causes were also consistently reduced by semaglutide in both eGFR and more granular UACR subgroups than previously reported. The evidence for kidney protection by semaglutide was further strengthened by findings of slower rates of eGFR decline (approximately 1 ml/min per 1.73 m² per year or more compared with placebo) and reduced albuminuria (estimated treatment ratios of approximately 30%–40% compared with placebo) from the least to the most severe CKD subgroups. Moreover, time-to-event analyses revealed that benefits of semaglutide on the primary kidney outcome were evident early, at just 12–18 months, in the subgroup with UACR ≥ 2000 mg. In contrast to other subgroups, this UACR subgroup and the subgroup with eGFR <30 ml/min per 1.73 m² appear to have similarly early overall survival benefits. Notably, participants with UACR ≥ 2000 mg had a $>50\%$ relative risk reduction for all-cause death.

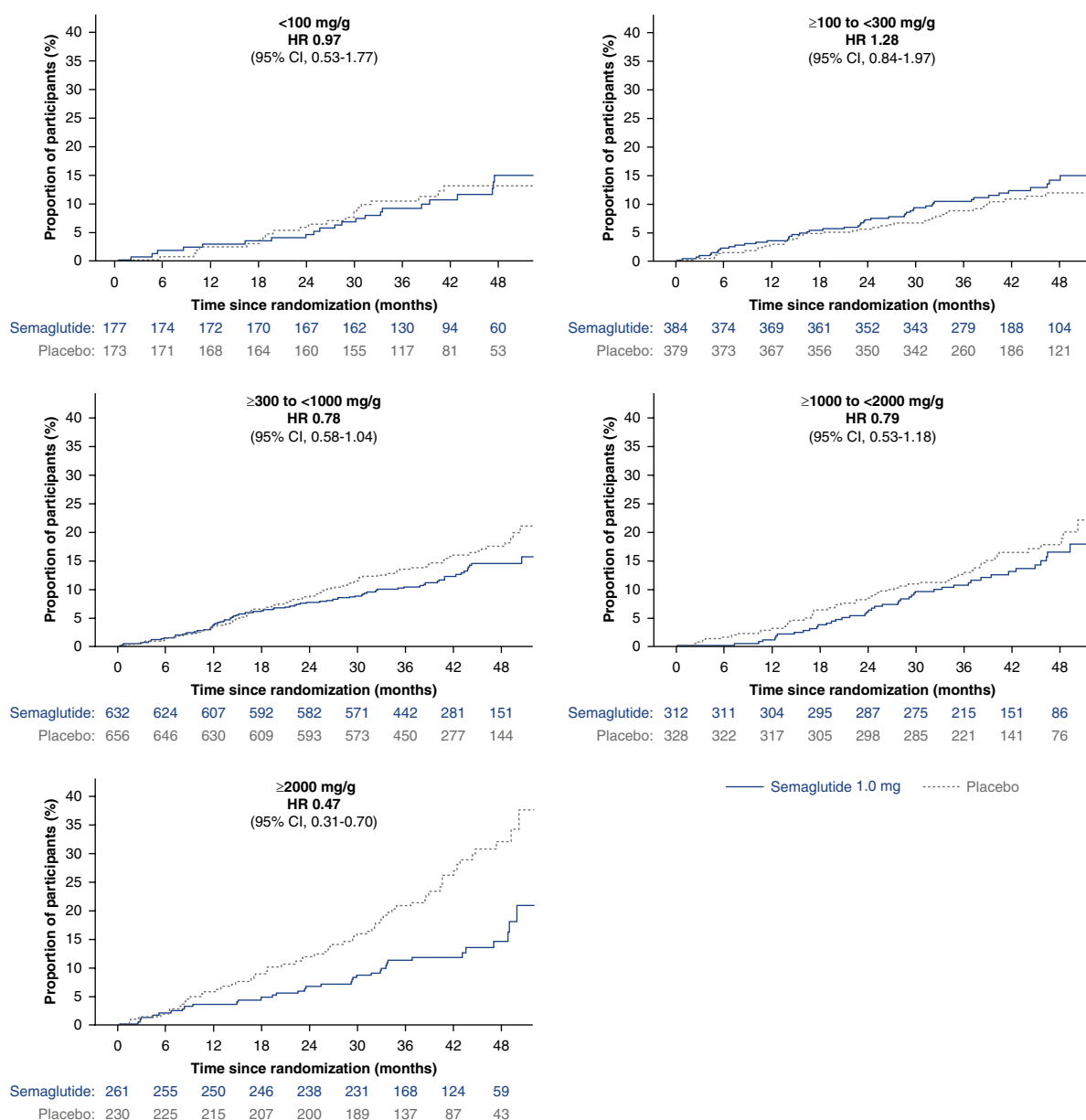


Figure 5. Time to all-cause death by baseline UACR subgroup. *P* for interaction was 0.02. Time from randomization to all-cause death was analyzed using a Cox proportional hazards model with treatment as a categorical fixed factor and stratified by SGLT2 inhibitor use (yes/no) at baseline during the in-trial period.

Most FLOW participants (93%) had high-risk or very-high-risk CKD at baseline by the Kidney Disease Improving Global Outcomes classification.^{6,22} Lower eGFR and higher albuminuria independently and additively increase risks of cardiovascular and all-cause deaths.¹⁶ However, the risks of death and kidney failure in the diabetes population vary such that death is more common than kidney failure with eGFR >45 ml/min per 1.73 m², but once eGFR is <30 ml/min per 1.73 m², these trends reverse, although both rates remain exceedingly high.¹⁹ The present data support the use of semaglutide to preserve life, particularly in people with T2D and UACR >2000 mg/g, and perhaps in those with eGFR <30 ml/min per 1.73 m². Indeed, such very-high-risk groups should be prioritized for implementation efforts, especially in the current

scenario of high drug cost, limited access, and resource constraints.

The clinical benefits of semaglutide on CKD in T2D are likely to be multifactorial. Improvements in glycemic control, BP control, or weight loss may provide indirect effects to reduce these risks. However, in a mediation analysis for kidney outcomes in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results and Semaglutide in Subjects with Type 2 Diabetes-6 trials, only 9% and 22% of risk reduction was attributable to lower BP or glycemia, respectively, with no relationship to body weight.²³ In addition, no relationship between change in body weight and eGFR was observed in clinical trials of a conventional GLP-1 receptor agonist, dulaglutide, or a dual GLP-1 and

gastrointestinal insulintropic peptide agonist, tirzepatide, in study populations with T2D.^{24,25} Therefore, direct protective effects by GLP-1 receptor agonists acting through other mechanisms are likely.

GLP-1 receptors are expressed throughout the body.²⁶ In the kidney, endothelial cells and vascular smooth muscle cells of the juxtaglomerular apparatus are the main location where GLP-1 receptors have been detected.²⁷ As this is a relatively small cell population, nonintrinsic kidney cells could also be involved. Macrophages and T lymphocytes promote inflammation and fibrosis within organs throughout the body, including the kidney and heart.^{28–30} These immune cells contain GLP-1 receptors, that when activated, convert them to less or anti-inflammatory phenotypes.²⁸ Mouse and rat models show that signals through proinflammatory receptors, such as the receptor for advanced glycation end products and Toll-like receptors, are suppressed by GLP-1 receptor agonists, possibly by central nervous system GLP-1 actions resulting in immunomodulation through parasympathetic and opioid efferent activity.^{31–33} Accordingly, GLP-1 receptor agonists reduce kidney inflammation and fibrosis in mouse and rat models of CKD with or without diabetes.^{31,32} In humans with T2D and CKD, dulaglutide correspondingly reduced profibrotic biomarkers in blood and urine.³⁴ Interestingly, in a mouse model of sepsis, liraglutide decreased lung injury and reduced the death rate,³³ suggesting that resistance to severe illness could be another potential mechanistic link to improved overall survival as well as fewer serious infections and coronavirus disease 2019–related adverse events in FLOW.⁶

The present analyses have strengths and limitations. We assessed the primary kidney outcome, other secondary kidney outcomes, and all-cause death in subgroups defined according to eGFR and UACR categories. Although these subgroups were prespecified, they were not powered for these outcomes, and some had wide CIs giving uncertainty to individual estimates. In addition, some were too small to assess, *i.e.*, kidney death by either eGFR or UACR categories and eGFR <15 ml/min per 1.73 m² for UACR categories. The all-cause death analyses by CKD severity were conducted *post hoc*, which limits interpretability to exploratory observations. Nevertheless, statistical heterogeneity was not observed for eGFR categories, and the greatest benefit on all-cause death was seen in the highest UACR subgroup. At a minimum, this high-risk group benefits at least as much as others, and the benefit appears early when death is a major risk. Finally, the FLOW population was comprised of mostly older people, men, and those who identified as White race. To better align with representation of T2D and CKD populations, studies of diverse groups are needed to more fully understand the kidney and survival benefits of semaglutide.

In conclusion, semaglutide meaningfully reduced risks of major kidney disease events and all-cause death across multiple strata of CKD severity, on top of the current standard of care, in the FLOW population with T2D, including those with low levels of eGFR or high levels of albuminuria. Semaglutide is an important therapeutic consideration for improving kidney and survival outcomes for people with T2D and CKD including those with advanced CKD.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/CJN/C640>.

Author Contributions

Conceptualization: Kenneth W. Mahaffey, Johannes F. E. Mann, Vlado Perkovic, Richard E. Pratley, Peter Rossing, Katherine R. Tuttle.

Data curation: Ole K. Jeppesen.

Formal analysis: Ole K. Jeppesen, Katherine R. Tuttle.

Methodology: Ole K. Jeppesen, Kenneth W. Mahaffey, Johannes F. E. Mann, Vlado Perkovic, Richard E. Pratley, Peter Rossing, Katherine R. Tuttle.

Validation: Ole K. Jeppesen.

Visualization: Ole K. Jeppesen, Katherine R. Tuttle.

Writing – original draft: Katherine R. Tuttle.

Writing – review & editing: Mustafa Arici, Heidrun Bosch-Traberg, David Z. I. Cherney, Ricardo Correa-Rotter, Janusz Gumprecht, Ole K. Jeppesen, Naoki Kashihara, Kenneth W. Mahaffey, Johannes F. E. Mann, Manuel M. Mayrdorfer, Vlado Perkovic, Richard E. Pratley, Giuseppe Pugliese, Brian Rayner, Peter Rossing, Katherine R. Tuttle.

Funding

The FLOW trial was funded by Novo Nordisk A/S.

Acknowledgments

The FLOW Steering Committee comprised academic members who are authors of this paper (Katherine R. Tuttle, Vlado Perkovic, Johannes F.E. Mann, Richard E. Pratley, Kenneth W. Mahaffey, Peter Rossing), and George L. Bakris. Florian M.M. Baeres, Thomas Idorn, and Peter Schelde were FLOW Steering Committee members from Novo Nordisk. With oversight from the FLOW Steering Committee, Novo Nordisk representatives were involved in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; in the review and approval of the manuscript; and in the decision to submit the manuscript for publication.

The authors thank all the participants of this trial, the site investigators, and the staff. Editorial assistance in the form of drafting technical portions of the Methods and Results sections, redrawing figures and formatting was provided by Carolyn Bowler, PhD, CMPP, of Apollo, OPEN Health Communications, funded by Novo Nordisk A/S, in accordance with Good Publication Practice (GPP) guidelines (www.ismpp.org/gpp-2022). Professor George L. Bakris sadly passed away during the publication process. The authors thank him for his invaluable contribution to the FLOW trial and to this publication. This article is dedicated to his memory.

Because Katherine Tuttle is an author of this paper and an editor of the *Clinical Journal of the American Society of Nephrology*, she was not involved in the peer review process for this manuscript. Another editor oversaw the peer review and decision-making process for this manuscript.

Declarative Statements

This study includes clinical experimentation, and the FLOW trial was conducted in accordance with the Declaration of Helsinki and received Institutional Review Board or Ethics Committee approval. All patients provided written informed consent.

Data Sharing Statements

Data belong to a third party, and authors are not authorized to share the data. Identity of Third Party: Novo Nordisk A/S. Reason for Restriction: An authorised researcher can request access to

clinical study data by submitting a research proposal for review and approval by Novo Nordisk and an internal independent review panel. Requests are usually considered after the research is finished and the main results have been published. If the research supports a regulatory application, requests will be considered after the product and its intended use are approved in both the European Union and the United States of America. Participants' clinical data will be anonymised, following an approved internal process, before data are shared to external third parties. For details on how to request access to clinical data, visit novonordisk-trials.com.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/CJN/C641>.

Supplemental Table 1. Inclusion and exclusion criteria (as described previously^{1,2}).

Supplemental Table 2. All-cause death by baseline eGFR and UACR subgroup.

Supplemental Figure 1. Participant flow through the FLOW trial.¹

Supplemental Figure 2. The primary kidney outcome and its individual components by baseline eGFR subgroup.

Supplemental Figure 3. The primary kidney outcome and its individual components by baseline UACR subgroup.

Supplemental Figure 4. Change in eGFR (cystatin C) relative to baseline over time by eGFR subgroup.

Supplemental Figure 5. Change in UACR relative to baseline over time by UACR subgroup.

Supplemental References.

FLOW Trial Investigators List.

References

- Sun H, Saeedi P, Karuranga S, et al. Erratum to IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2023;204:110945. doi:10.1016/j.diabres.2023.110945
- Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol.* 2017;12(12):2032–2045. doi:10.2215/CJN.11491116
- Tuttle KR, Jones CR, Daratha KB, et al. Incidence of chronic kidney disease among adults with diabetes, 2015–2020. *N Engl J Med.* 2022;387(15):1430–1431. doi:10.1056/NEJMc2207018
- Bello AK, Okpechi IG, Levin A, et al. An update on the global disparities in kidney disease burden and care across world countries and regions. *Lancet Glob Health.* 2024;12(3):e382–e395. doi:10.1016/s2214-109x(23)00570-3
- Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl (2011).* 2022;12(1):7–11. doi:10.1016/j.kisu.2021.11.003
- Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med.* 2024;391(2):109–121. doi:10.1056/NEJMoa2403347
- Rossing P, Baeres FMM, Bakris G, et al. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. *Nephrol Dial Transplant.* 2023;38(9):2041–2051. doi:10.1093/ndt/gfad009
- Badve SV, Bilal A, Lee MMY, et al. Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol.* 2025;13(1):15–28. doi:10.1016/s2213-8587(24)00271-7
- Neuen BL, Fletcher RA, Heath L, et al. Cardiovascular, kidney, and safety outcomes with GLP-1 receptor agonists alone and in combination with SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis. *Circulation.* 2024;150(22):1781–1790. doi:10.1161/circulationaha.124.071689
- Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9(10):653–662. doi:10.1016/s2213-8587(21)00203-5
- Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol.* 2018;6(8):605–617. doi:10.1016/s2213-8587(18)30104-9
- Tuttle KR, Bosch-Traberg H, Cherney DZI, et al. Post hoc analysis of SUSTAIN 6 and PIONEER 6 trials suggests that people with type 2 diabetes at high cardiovascular risk treated with semaglutide experience more stable kidney function compared with placebo. *Kidney Int.* 2023;103(4):772–781. doi:10.1016/j.kint.2022.12.028
- Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol.* 2013;24(2):302–308. doi:10.1681/ASN.2012070718
- Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA.* 2014;311(24):2518–2531. doi:10.1001/jama.2014.6634
- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351(13):1296–1305. doi:10.1056/NEJMoa041031
- Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80(1):17–28. doi:10.1038/ki.2010.483
- Adler AI, Stevens RJ, Manley SE, et al.; on behalf of the UKPDS Group. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int.* 2003;63(1):225–232. doi:10.1046/j.1523-1755.2003.00712.x
- Dalrymple LS, Katz R, Kestenbaum B, et al. Chronic kidney disease and the risk of end-stage renal disease versus death. *J Gen Intern Med.* 2011;26(4):379–385. doi:10.1007/s11606-010-1511-x
- Tuttle KR, Kornowski LM, Jones CR, et al. A real-world cohort study of the risks of kidney failure and death in diabetes. *Clin J Am Soc Nephrol.* 2026;21(1):83–94. doi:10.2215/CJN.0000000857
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–612. doi:10.7326/0003-4819-150-9-200905050-00006
- Rubin DB. *Multiple Imputation for Nonresponse in Surveys.* Wiley Series in Probability and Statistics. John Wiley & Sons; 1987.
- Stevens PE, Ahmed SB, Carrero JJ, et al.; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* 2024;105(4S):S117–S314. doi:10.1016/j.kint.2023.10.018
- Mann JFE, Buse JB, Idorn T, et al. Potential kidney protection with liraglutide and semaglutide: exploratory mediation analysis. *Diabetes Obes Metab.* 2021;23(9):2058–2066. doi:10.1111/dom.14443
- Tuttle KR, Lakshmanan MC, Rayner B, Zimmermann AG, Woodward B, Botros FT. Body weight and eGFR during dulaglutide treatment in type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7). *Diabetes Obes Metab.* 2019;21(6):1493–1497. doi:10.1111/dom.13668
- Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on cystatin C-based kidney function: a SURPASS-4 post hoc analysis. *Diabetes Care.* 2023;46(8):1501–1506. doi:10.2337/dc23-0261
- Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology.* 2007;132(6):2131–2157. doi:10.1053/j.gastro.2007.03.054
- Hviid AVR, Sørensen CM. Glucagon-like peptide-1 receptors in the kidney: impact on renal autoregulation. *Am J Physiol*

- Renal Physiol.* 2020;318(2):F443–F454. doi:[10.1152/ajprenal.00280.2019](https://doi.org/10.1152/ajprenal.00280.2019)
28. Alicic RZ, Cox EJ, Neumiller JJ, Tuttle KR. Incretin drugs in diabetic kidney disease: biological mechanisms and clinical evidence. *Nat Rev Nephrol.* 2021;17(4):227–244. doi:[10.1038/s41581-020-00367-2](https://doi.org/10.1038/s41581-020-00367-2)
 29. Michos ED, Bakris GL, Rodbard HW, Tuttle KR. Glucagon-like peptide-1 receptor agonists in diabetic kidney disease: a review of their kidney and heart protection. *Am J Prev Cardiol.* 2023;14:100502. doi:[10.1016/j.ajpc.2023.100502](https://doi.org/10.1016/j.ajpc.2023.100502)
 30. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. *Nat Rev Cardiol.* 2023;20(7):463–474. doi:[10.1038/s41569-023-00849-3](https://doi.org/10.1038/s41569-023-00849-3)
 31. Fujita H, Morii T, Fujishima H, et al. The protective roles of GLP-1R signaling in diabetic nephropathy: possible mechanism and therapeutic potential. *Kidney Int.* 2014;85(3):579–589. doi:[10.1038/ki.2013.427](https://doi.org/10.1038/ki.2013.427)
 32. Sourris KC, Ding Y, Maxwell SS, et al. Glucagon-like peptide-1 receptor signaling modifies the extent of diabetic kidney disease through dampening the receptor for advanced glycation end products-induced inflammation. *Kidney Int.* 2024;105(1):132–149. doi:[10.1016/j.kint.2023.09.029](https://doi.org/10.1016/j.kint.2023.09.029)
 33. Wong CK, McLean BA, Baggio LL, et al. Central glucagon-like peptide 1 receptor activation inhibits toll-like receptor agonist-induced inflammation. *Cell Metab.* 2024;36(1):130–143.e5. doi:[10.1016/j.cmet.2023.11.009](https://doi.org/10.1016/j.cmet.2023.11.009)
 34. Tuttle KR, Wilson JM, Lin Y, et al. Indicators of kidney fibrosis in patients with type 2 diabetes and chronic kidney disease treated with dulaglutide. *Am J Nephrol.* 2023;54(1-2):74–82. doi:[10.1159/000529374](https://doi.org/10.1159/000529374)

AFFILIATIONS

¹Division of Nephrology, University of Washington School of Medicine, Seattle, Washington

²Providence Medical Research Center, Providence Inland Northwest Health, Spokane, Washington

³KfH Kidney Centre, München, Germany

⁴University Hospital, Friedrich-Alexander University, Erlangen, Germany

⁵Novo Nordisk A/S, Bagsvaerd, Denmark

⁶Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

⁷University of Rome La Sapienza, Rome, Italy

⁸AdventHealth Translational Research Institute, Orlando, Florida

⁹University of New South Wales, Sydney, New South Wales, Australia

¹⁰Department of Medicine, Stanford Center for Clinical Research (SCCR), Stanford, California

¹¹Kawasaki Ika Daigaku, Kurashiki, Okayama, Japan

¹²Medical University of Silesia, Katowice, Poland

¹³Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

¹⁴Toronto General Hospital, Toronto, Ontario, Canada

¹⁵University of Toronto, Toronto, Ontario, Canada

¹⁶Hacettepe University Faculty of Medicine, Ankara, Turkey

¹⁷Steno Diabetes Center Copenhagen, Herlev, Denmark

¹⁸Kobenhavns Universitet, Kobenhavn, Denmark