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Effects of Semaglutide With or Without Concomitant Mineralocorticoid Receptor Antagonist Use in Participants With Type 2 Diabetes and Chronic Kidney Disease: A FLOW Trial Prespecified Secondary Analysis

Peter Rossing, George Bakris, Vlado Perkovic, Richard Pratley, Katherine R. Tuttle, Kenneth W. Mahaffey, Thomas Idorn, Nicolas Belmar, Heidrun Bosch-Traberg, Søren Rasmussen, Robert S. Busch, Ronald E. Schmieder, Pieter Gillard, and Johannes F.E. Mann, on behalf of the FLOW Investigator Group

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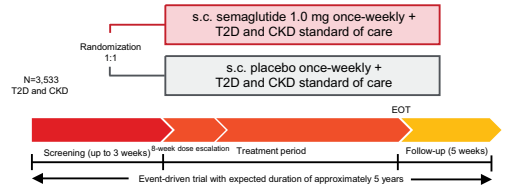
In FLOW, the GLP-1 RA semaglutide reduced the risk of major kidney outcomes, MACE, and all-cause mortality in people with T2D and CKD, irrespective of baseline mineralocorticoid receptor antagonist use

This prespecified analysis examined whether the kidney and CV benefits of semaglutide versus placebo in participants with T2D and CKD are influenced by the concomitant use of MRAs

STUDY DESIGN

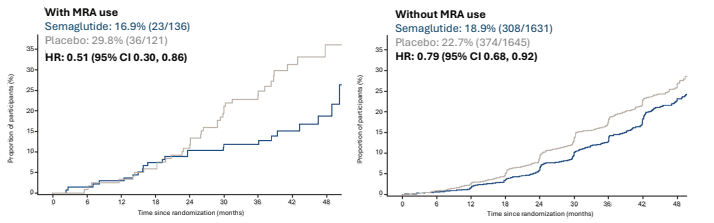


BASELINE CHARACTERISTICS

	With MRA use	Without MRA use
Participants (n)	257	3276
Age (mean, years)	66	68
Women (%)	28	30
Systolic blood pressure (median, mmHg)	141	138
eGFR (median, mL/min/1.74 m²)	46	44
UACR (median, mg/g)	563	569

PRIMARY OUTCOME

5-component composite of onset of a persistent ≥50% reduction in eGFR, kidney failure, or death due to kidney or CV causes



P-interaction = 0.12

SECONDARY OUTCOMES

	HR (95% CI) With MRA use	HR (95% CI) Without MRA use	P-interaction
MACE†	0.74 (0.42, 1.31)	0.82 (0.68, 1.00)	0.75
All-cause mortality	0.82 (0.49, 1.36)	0.79 (0.65, 0.95)	0.89

- In participants with T2D and CKD, similar benefits of semaglutide on major kidney outcomes, MACE, and all-cause mortality were observed regardless of baseline MRA use
- The safety profile of semaglutide was comparable between subgroups

†Composite of nonfatal myocardial infarction, nonfatal stroke, or CV death. CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; FLOW, Evaluate Renal Function With Semaglutide Once Weekly; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular events; MRA, mineralocorticoid receptor antagonist; s.c., subcutaneous; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Mineralocorticoid receptor antagonists (MRAs) are commonly used for the treatment of type 2 diabetes (T2D) with chronic kidney disease (CKD). Semaglutide (a glucagon-like peptide 1 receptor agonist) improves kidney and cardiovascular (CV) outcomes in T2D, but no dedicated trials have examined combination with MRAs.
- **What is the specific question we wanted to answer?**
  Does MRA use affect the benefits of semaglutide in T2D with CKD?
- **What did we find?**
  Consistent benefits of semaglutide on kidney outcomes, major adverse CV events, and all-cause mortality were observed regardless of baseline MRA use.
- **What are the implications of our findings?**
  Our study suggests that semaglutide and MRAs can be combined for a larger effect, but as the MRA-treated group was small, the results should be interpreted with caution.

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ORIGINAL ARTICLE

Effects of Semaglutide With or Without Concomitant Mineralocorticoid Receptor Antagonist Use in Participants With Type 2 Diabetes and Chronic Kidney Disease: A FLOW Trial Prespecified Secondary Analysis

Peter Rossing,[1,2] George Bakris,[3] Vlado Perkovic,[4] Richard Pratley,[5] Katherine R. Tuttle,[6,7] Kenneth W. Mahaffey,[8] Thomas Idorn,[9] Nicolas Belmar,[9] Heidrun Bosch-Traberg,[9] Søren Rasmussen,[9] Robert S. Busch,[10] Ronald E. Schmieder,[11] Pieter Gillard,[12] and Johannes F.E. Mann,[11,13] on behalf of the FLOW Investigator Group*

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OBJECTIVE

In the Evaluate Renal Function With Semaglutide Once Weekly (FLOW) trial, semaglutide reduced the risk of major kidney and cardiovascular (CV) outcomes and all-cause mortality in people with type 2 diabetes (T2D) and chronic kidney disease (CKD). This prespecified analysis assessed the effects of semaglutide on kidney, CV, and mortality outcomes by baseline mineralocorticoid receptor antagonist (MRA) use.

RESEARCH DESIGN AND METHODS

Participants were randomized to once-weekly subcutaneous semaglutide 1.0 mg or placebo. The primary kidney outcome was a composite of time to first persistent ≥50% eGFR reduction from baseline, kidney failure, or death from kidney/CV causes. Baseline MRA was predominantly spironolactone; finerenone was only available after recruitment ended.

RESULTS

Effects were analyzed by baseline MRA use (*n* = 257 [136 in the semaglutide group and 121 in the placebo group]) and nonuse (*n* = 3,276 [1,631 in the semaglutide group and 1,645 in the placebo group]). Semaglutide reduced the risk of the primary kidney outcome by 49% (59 events; hazard ratio [HR] 0.51 [95% CI 0.30, 0.86]) and 21% (682 events; HR 0.79 [95% CI 0.68, 0.92]; *P*-interaction = 0.12) versus placebo in MRA and non-MRA subgroups, respectively. There was no heterogeneity, favoring the effects of semaglutide on major adverse CV events (MACE) and all-cause mortality in both MRA subgroups (*P*-interaction > 0.7). Albuminuria at 104 weeks was reduced from baseline with semaglutide by 15% (95% CI −41, 31) in MRA users and 33% (26, 39) in nonusers versus placebo (*P*-interaction = 0.22). Estimated glomerular filtration rate decline was similarly reduced with semaglutide (*P*-interaction = 0.71). The safety profile of semaglutide was comparable between subgroups.

CONCLUSIONS

In participants with T2D and CKD, consistent benefits of semaglutide on major kidney outcomes, MACE, and all-cause mortality were observed regardless of baseline MRA use.

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*A complete list of the FLOW Investigator Group can be found in the supplementary material online.

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Between 2022 and 2025, estimates of the global prevalence of diabetes have ranged from 589 to 828 million people, with this number expected to increase to almost 1 billion by 2050 (1,2). Diabetes is the most common cause of chronic kidney disease (CKD), which affects ∼40% of people with type 2 diabetes (T2D). In 2017, >840 million people were estimated to have CKD, the prevalence of which is increasing in line with rising rates of diabetes, obesity, aging, and hypertension (3). By 2040, CKD is expected to have climbed from the 16th (in 2016) to the 5th most common cause of death (4). The combination of T2D and CKD is associated with an excess cardiovascular (CV) risk, with an estimated loss of life of up to 16 years (5) and a sixfold increase in CV mortality (6).

Standard of care for CKD in diabetes has for decades included renin-angiotensin system (RAS) inhibition. More recently, sodium–glucose cotransporter 2 inhibitors (SGLT2is) have been shown to reduce progression of CKD, CV events, and all-cause mortality and have become an additional first-line therapy (7,8). In people with CKD and T2D, first- and second-generation mineralocorticoid receptor antagonists (MRAs) have been used for resistant hypertension and heart failure with reduced ejection fraction. Short-term studies have shown kidney benefits with steroidal MRAs (spironolactone and eplerenone) on top of RAS inhibition in terms of a reduction in albuminuria, which is considered a surrogate for long-term kidney effects. However, long-term studies of the kidney benefits of steroidal MRAs have never been performed (7,9). Finerenone, a nonsteroidal MRA, was recently shown to safely reduce progression of CKD and CV events in T2D with CKD (10,11). Based on these findings, finerenone is now recommended in clinical practice guidelines for the treatment of T2D with CKD (12,13). Guidelines recommend glucagon-like peptide 1 receptor agonists (GLP-1RAs) for the management of hyperglycemia in CKD due to maintenance of efficacy in people with lower estimated glomerular filtration rate (eGFR), along with the CV benefit in people with T2D, demonstrated in CV outcome trials in CV high-risk populations with T2D (12).

The Evaluate Renal Function With Semaglutide Once Weekly (FLOW) trial examined subcutaneous semaglutide, a GLP-1RA, 1.0 mg once weekly in participants with T2D with CKD. This first large, dedicated, kidney outcomes trial showed significant kidney, CV, and survival benefits with semaglutide compared with placebo, supporting a fourth pillar in the management of CKD in addition to RAS inhibition, SGLT2 inhibition, and nonsteroidal MRAs (14). The most recent update of the American Diabetes Association (ADA) guidelines now recommends GLP-1RAs with their proven CKD benefit for T2D with CKD (15).

GLP-1RAs and MRAs work on the kidneys and heart through different and potentially complementary or interacting mechanisms (16), but no dedicated trials have examined the combination of GLP-1RAs and MRAs on major kidney and CV outcomes in participants with T2D and CKD. Therefore, we assessed, in a prespecified analysis, the efficacy and safety of semaglutide by baseline MRA use in the FLOW trial (ClinicalTrials.gov identifier: NCT03819153).

RESEARCH DESIGN AND METHODS

Participants and Trial Design

The design and main results of this randomized, double-blind, placebo-controlled, international, multicenter, kidney outcomes trial have been described in detail previously (14,17). The trial was overseen by an academic-led steering committee in partnership with the sponsor Novo Nordisk, who also managed trial operations. All participants provided written informed consent, and the protocol was approved by both national and institutional ethical and regulatory authorities.

In brief, participants with T2D and CKD were randomly assigned double blind in a 1:1 ratio to receive subcutaneous semaglutide 1.0 mg or matching placebo once weekly, using a central interactive web response system, between June 2019 and May 2021 and followed up until January 2024 (14). Participants included those with an eGFR of 25–75 mL/min/1.73 m^2 (calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation) (18) and a urine albumin-to-creatinine ratio (UACR) of >300 to <5,000 mg/g (if the eGFR was ≥50 mL/min/1.73 m^2) or a UACR of >100 to <5,000 mg/g (if the eGFR was 25 to <50 mL/min/1.73 m^2) while receiving a stable maximal labeled or tolerated dose of an RAS inhibitor. Individuals unable to tolerate RAS inhibitors or for whom such treatment is contraindicated were eligible for inclusion. Information on MRA use, including type of MRA, was collected at baseline and during study visits as concomitant medication, but information on the indication for MRA use was not collected.

Outcome Measures

The primary kidney outcome was a five-component composite of onset of a ≥50% reduction in eGFR from the baseline value sustained for at least 28 days, kidney failure (commencement of chronic dialysis, kidney transplant, or reduction in eGFR to <15 mL/min/1.73 m^2 sustained for at least 28 days), or death from kidney or CV causes. Three confirmatory secondary outcomes were hierarchically assessed. The first was rate of loss of kidney function, defined as total eGFR slope (annual rate of change in eGFR) based on serum creatinine. The second was time to first major adverse CV event (MACE), a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or CV death. The third was death from any cause. Other supportive and exploratory outcomes were also prespecified (see the FLOW protocol [14]), including a four-component kidney-specific composite outcome identical to the primary kidney outcome but excluding death from CV causes.

In addition to serum creatinine at weeks 4, 12, and 26 and then every 26 weeks, serum cystatin C was measured centrally at randomization, weeks 12 and 52, and then every year after randomization and was used to calculate the eGFR to determine the rate of loss of kidney function and total eGFR slope.

Statistical Analysis

The FLOW trial was event driven and designed to provide 90% power to detect a 20% relative risk reduction for semaglutide versus placebo for the primary kidney outcome (17). Assuming an event rate for the primary outcome of 7.5% per year in the placebo group, a minimum of 3,508 participants were to be enrolled in the trial, requiring a minimum of 854 primary outcome events.

Time from randomization to each outcome was analyzed using a stratified Cox proportional hazards model with randomized treatment group (semaglutide or placebo) as a fixed factor and SGLT2i use at baseline (yes/no) as a stratification factor. For subgroup analyses, hazard ratios (HRs)

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(95% CIs) were estimated using the same model, with interaction between treatment group and subgroup (MRA use vs. MRA nonuse at baseline) as a fixed factor. Furthermore, two time-dependent Cox regression models were performed: one with MRA use as the time-dependent variable (yes/no) and randomized treatment as a fixed factor and the other with MRA use interacting with randomized treatment. A Wald χ^2 test was used to indicate whether there was heterogeneity of the semaglutide effect across MRA use. Estimation of the absolute risk difference (and 95% CI) at 3 years between semaglutide and placebo were based on the Aalen-Johansen estimator for the cumulative incidence function. Numbers needed to treat were calculated as the reciprocal to the absolute risk difference.

FLOW participants have an increased risk of mortality from both non-CV kidney causes and CV causes. We therefore performed a sensitivity analysis using the Fine-Gray subdistribution hazards model, with treatment by MRA use as a fixed factor and SGLT2i use at baseline as a stratification factor, for both the primary outcome and the four-component kidney-specific outcome, thereby accounting for these causes as competing risks. Results from this model were summarized with subdistribution HRs (sHRs) and corresponding 95% CIs together with the test for interaction between treatment and MRA use at baseline.

Log transformation was applied before analysis for parameters that were right-skewed (as specified in the statistical analysis plan), and treatment differences were expressed as a treatment mean ratio. Analyses of change in UACR evaluated before week 104 were performed using a mixed model for repeated measurements using in-trial data. A prespecified, single interim analysis was triggered in October 2023 after approximately two-thirds (n = 570) of the planned total primary outcomes had accrued. The independent data monitoring committee reviewed the data and recommended early completion of the trial for efficacy. This recommendation was accepted, and the trial was completed.

No adjustment for multiplicity or α-protection was performed in this exploratory analysis. Two-sided $P < 0.05$ was considered significant. All statistical analyses were performed using SAS 9.4 software (SAS Institute). Novo Nordisk maintained the clinical database and performed the statistical analyses. Further details of the statistical analyses are provided in the Supplementary Material.

Data and Resource Availability

Data will be shared with researchers who submit a research proposal approved by the independent review board. Individual participant 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 https://www.novonordisk-trials.com/.

RESULTS

Participant Characteristics

A total of 5,581 participants were screened between June 2019 and May 2021, and 3,533 were randomized (mean eGFR 47.0 mL/min/1.73 m^2, median UACR 568 mg/g, mean glycated hemoglobin [HbA_{1c}] 7.8%). Of these, 257 participants (7.3%) received an MRA at baseline, with similar proportions in the semaglutide (136 of 1,767 [7.7%]) and placebo (121 of 1,766 [6.9%]) groups (Supplementary Table 1 and Supplementary Fig. 1). Of the 257 participants, 218 (84.8%) were prescribed spironolactone, 38 (14.8%) were prescribed eplerenone, 1 (0.4%) was prescribed esaxerenone, and 0 received finerenone (first approved in July 2021 and later marketed after the recruitment period for FLOW had ended). Across semaglutide and placebo groups, ~80% of participants taking an MRA at baseline were still taking it after 24 months (Supplementary Fig. 2*A*).

Comparison of baseline demographics and participant characteristics for participants who did and did not report use of an MRA at baseline are shown overall and by treatment group in Table 1 and Supplementary Table 1, respectively. Overall, there were no differences in baseline eGFR and UACR values, history of hypertension, or ethnicity, but MRA users were more often White and less often Asian than nonusers. Participants receiving an MRA at baseline more often had a history of MI, heart failure, or stroke; marginally greater HbA_{1c} and systolic blood pressure; and higher BMI compared with those not receiving an MRA. Participants reporting use of an MRA at baseline were more likely to be taking a β-blocker or diuretic and less likely to be taking a dipeptidyl peptidase 4 inhibitor than participants not reporting use of an MRA. While the use of SGLT2is, insulin, metformin, sulfonylureas, and calcium channel blockers did not differ between MRA users and nonusers at baseline, there was a difference between subgroups in the use of lipid-lowering therapies (89.1% vs. 79.5%, respectively) (Table 1).

Outcomes With and Without MRA Use at Baseline

Primary Kidney Outcome

The primary kidney outcome in participants with or without MRA use at baseline is shown in Fig. 1. Over a median follow-up of 3.4 years, in participants reporting use of an MRA at baseline, there were 23 of 136 (16.9%) primary outcome events with semaglutide vs. 36 of 121 (29.8%) events with placebo (HR 0.51; 95% CI 0.30, 0.86; P = 0.012) (Supplementary Table 2). In participants not reporting MRA use at baseline, those numbers were 308 of 1,631 (18.9%) vs. 374 of 1,645 (22.7%) for the semaglutide and placebo groups, respectively (HR 0.79; 95% CI 0.68, 0.92; P = 0.002; P for interaction = 0.12) (Supplementary Table 2). This corresponds to an absolute difference of −0.11 (95% CI −0.20, −0.01) at 3 years, corresponding to a number needed to treat of 9 in participants with baseline MRA use, and an absolute difference of −0.04 (95% CI −0.07, −0.02), corresponding to a number needed to treat of 23 in participants without baseline MRA use. The treatment effects of semaglutide for the individual components of the primary outcome and CV outcomes according to MRA use at baseline are depicted in Fig. 2. A significant interaction (P = 0.027) was seen for renal replacement therapy with MRA use (HR 0.18; 95% CI 0.03, 0.71) without MRA use (HR 0.91; 95% CI 0.68, 1.23) but in the context of only 11 events among participants with MRA use at baseline. Results from the sensitivity analysis (in which non-CV death and nonkidney death were considered as competing risks) were comparable with the overall analysis (sHRs 0.51 [95% CI 0.30, 0.86] and 0.80 [95% CI 0.68, 0.92] for MRA users and nonusers, respectively; P-interaction = 0.11).

Four-Component Kidney-Specific Composite

Treatment with semaglutide also reduced the risk of the four-component kidney-specific composite outcome (excluding CV death from the five-component primary

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Table 1—Baseline characteristics according to MRA use at baseline

Characteristic	MRA use at baseline (n = 257)	No MRA use at baseline (n = 3,276)
Age (years)	66 (60–71)	68 (62–73)
Female sex	73 (28.4)	996 (30.4)
Region		
Asia	32 (12.5)	880 (26.9)
Europe	98 (38.1)	865 (26.4)
North America	49 (19.1)	816 (24.9)
Other	78 (30.4)	715 (21.8)
Ethnicity		
Hispanic or Latino	38 (14.8)	518 (15.8)
Other	207 (80.5)	2,625 (80.1)
Not reported	12 (4.7)	133 (4.1)
Race		
White	203 (79.0)	2,120 (64.7)
Asian	27 (10.5)	819 (25.0)
Black or African American	11 (4.3)	149 (4.5)
American Indian or Alaska Native	0 (0.0)	25 (0.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	5 (0.2)
Other	6 (2.3)	89 (2.7)
Not reported	10 (3.9)	69 (2.1)
Smoking status		
Current	29 (11.3)	400 (12.2)
Never	111 (43.2)	1,636 (49.9)
Previous	117 (45.5)	1,240 (37.9)
Duration of diabetes (years)	16.8 (11.2–21.8)	16.2 (10.7–22.6)
HbA_{1c} (%)	8.0 (7.1–9.1)	7.6 (6.8–8.6)
BMI (kg/m^2)	33.6 (30.1–38.3)	31.1 (27.3–35.3)
Body weight (kg)	97.6 (84.5–110.7)	87.0 (74.4–101.3)
SBP (mmHg)	141.0 (128.0–150.0)	138.0 (128.0–148.0)
DBP (mmHg)	78.0 (71.0–84.0)	77.0 (70.0–83.0)
Serum potassium (mmol/L)	4.8 (4.4–5.2)	4.7 (4.3–5.0)
History of a CV event		
No prior MI or stroke	165 (65.0)	2,523 (77.8)
Prior MI or stroke	89 (35.0)	719 (22.2)
History of heart failure	113 (44.0)	565 (17.3)
History of hypertension	254 (98.8)	3,206 (97.9)
eGFR (mL/min/1.73 m^2)	46.0 (37.0–56.0)	44.0 (35.0–56.5)
eGFR distribution (mL/min/1.73 m^2)		
<30	25 (9.8)	375 (11.4)
≥30 to <45	93 (36.3)	1,265 (38.6)
≥45 to <60	91 (35.5)	964 (29.4)
≥60	47 (18.4)	672 (20.5)
UACR (mg/g)	536.3 (201.7–1,254.1)	569.0 (232.8–1,313.9)
UACR distribution (mg/g)		
<30	7 (2.7)	102 (3.1)
≥30 to <300	73 (28.5)	931 (28.4)
≥300	176 (68.8)	2,243 (68.5)
Medication use at baseline		
RAASi	245 (95.3)	3,119 (95.2)
β-Blockers	184 (71.6)	1,659 (50.6)
Calcium channel blockers	147 (57.2)	1,886 (57.6)
Diuretics	257 (100.0)	1,523 (46.5)
Lipid-lowering therapies	229 (89.1)	2,605 (79.5)

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outcome) compared with placebo, irrespective of MRA use at baseline (HRs 0.38 [95% CI 0.15, 0.84] and 0.82 [95% CI 0.68, 0.99] with and without MRA use, respectively; P-interaction = 0.068) (Fig. 1*B* and Supplementary Table 2). Results from the sensitivity analysis (in which all-cause mortality excluding kidney death was considered as a competing risk) were comparable with the overall analysis (sHRs 0.38 [95% CI 0.17, 0.88] and 0.85 [95% CI 0.71, 1.02] for MRA users and nonusers, respectively; P-interaction = 0.07).

Initiation of MRA Use During the Trial

Following randomization, 113 (6.4%) participants in the semaglutide group and 160 (9.1%) in the placebo group initiated new treatment with any MRA at any time concomitant with study treatment (Supplementary Table 3 and Supplementary Fig. 2*B*). In participants not receiving an MRA at baseline, spironolactone was the most commonly initiated MRA in both treatment groups (initiated in 94 [5.3%] and 131 [7.4%] participants receiving semaglutide and placebo, respectively). Finerenone was initiated in 22 (1.2%) participants in the semaglutide group and 28 (1.6%) in the placebo group, and eplerenone was initiated in 14 (0.8%) and 22 (1.2%) participants, respectively.

Analyzing the primary kidney outcome in participants who reported MRA use at baseline or who initiated an MRA during the study (249 in the semaglutide group and 281 in the placebo group), there were 53 (21.3%) and 82 (29.2%) primary outcomes with semaglutide and placebo, respectively (HR 0.66; 95% CI 0.47, 0.94) (Supplementary Table 4). The corresponding numbers of participants who did not use an MRA at any time (1,518 in the semaglutide group and 1,485 in the placebo group) were 278 (18.3%) and 328 (22.1%), respectively (HR 0.79; 95% CI 0.67, 0.93; P-interaction = 0.37) (Supplementary Table 4). The sensitivity analysis conducted using the Fine-Gray model showed a similar result (P-interaction = 0.32). When MRA use during the study was treated as a time-dependent covariate in a Cox regression analysis, the HR for the primary outcome was 0.77 (95% CI 0.66, 0.89). Using a time-dependent Cox regression analysis with MRA use by randomized treatment as a fixed factor, the HRs for the primary outcome were 0.54 (95% CI

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Table 1—Continued

Characteristic	MRA use at baseline (n = 257)	No MRA use at baseline (n = 3,276)
Glucose-lowering therapies		
Insulin	168 (65.4)	2,000 (61.1)
Metformin	144 (56.0)	1,688 (51.5)
Sulfonylureas	65 (25.3)	826 (25.2)
SGLT2is	42 (16.3)	508 (15.5)
DPP-4is	47 (18.3)	858 (26.2)
Thiazolidinediones	4 (1.6)	141 (4.3)

Data are median (interquartile range) or *n* (%). DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase 4 inhibitor; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure.

0.34, 0.84) in participants using an MRA during the study (either from baseline or initiation during study) and 0.80 (95% CI 0.69, 0.93) in participants never using an MRA. Corresponding cumulative incidence plots are provided in Supplementary Fig. 3.

Secondary Outcomes

eGFR Based on Creatinine. The eGFR over time according to MRA use at baseline is displayed in Fig. 3. The annual rate of change in eGFR, measured by total eGFR slope based on serum creatinine, in the subgroup with MRA use at baseline was −2.20 mL/min/1.73 m^2 with semaglutide vs. −3.58 mL/min/1.73 m^2 with placebo. In the subgroup without MRA use at baseline, the rate was −2.19 vs. −3.34 mL/min/1.73 m^2 for semaglutide versus placebo, respectively. The between-group differences for semaglutide versus placebo were a 1.38 mL/min/1.73 m^2 per year (95% CI 0.21, 2.54) and 1.15 mL/min/1.73 m^2 per year (95% CI 0.83, 1.46) less decline with and without MRA use, respectively (P-interaction = 0.71).

eGFR Based on Cystatin C. The annual rate of change in eGFR, measured by total eGFR slope based on serum cystatin C, in the subgroup with MRA use at baseline was −1.61 vs. −2.86 mL/min/1.73 m^2 with semaglutide versus placebo, respectively. The rate in the subgroup without MRA use at baseline was −1.23 vs. −2.69 mL/min/1.73 m^2 for semaglutide versus placebo, respectively. The between-group differences for semaglutide versus placebo were a 1.25 mL/min/1.73 m^2 per year (95% CI 0.07, 2.42) and 1.46 mL/min/1.73 m^2 per year (95% CI 1.14, 1.78) less eGFR decline with and without MRA use, respectively (P for interaction = 0.73). Calculating the decline in eGFR from baseline to week 104 after randomization, based on both serum creatinine and serum cystatin C, as prespecified, gave consistent results with the slope analysis; that is, eGFR decline was less with semaglutide than with placebo, with no statistical interaction for MRA use (Supplementary Table 5).

MACE and All-Cause Mortality. Composite MACE outcome events were less frequent with semaglutide versus placebo, and there was no difference between subgroups with or without MRA use at baseline (P-interaction = 0.75) (Fig. 2 and Supplementary

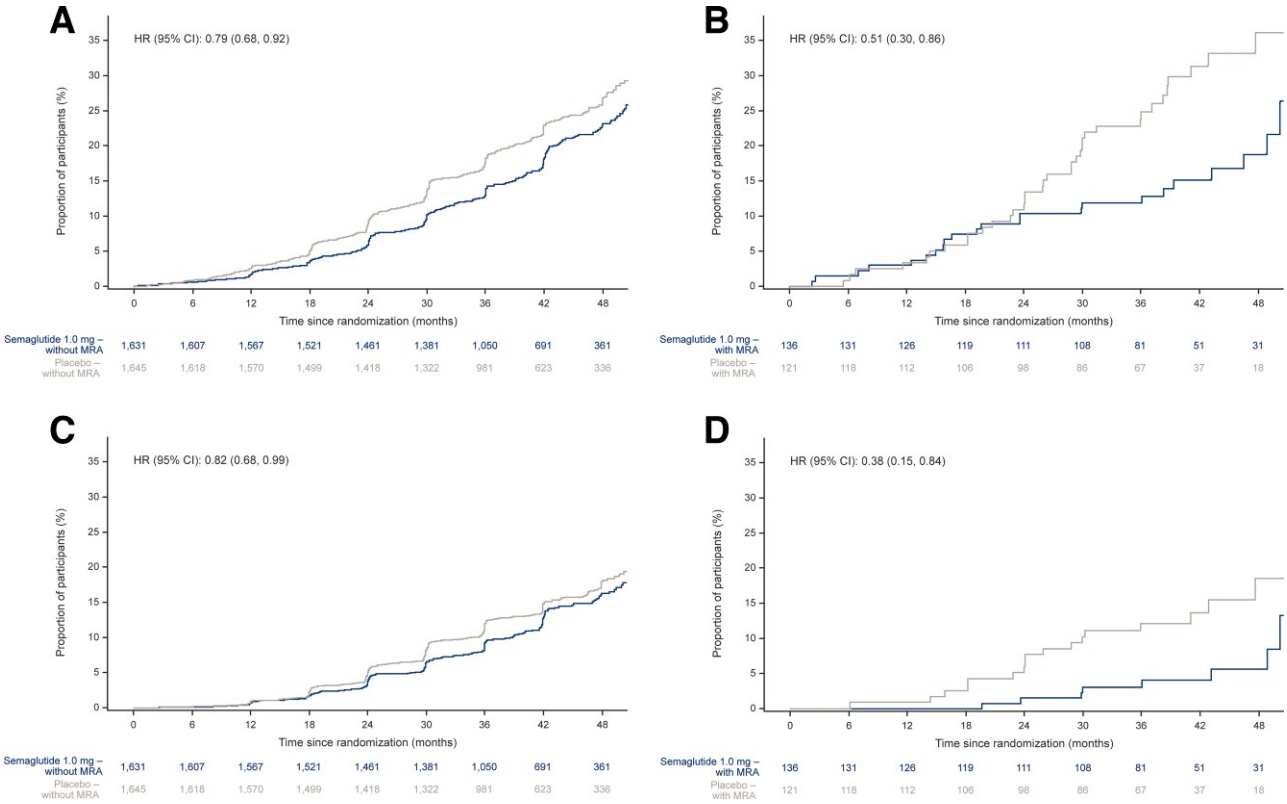

Figure 1—Time from randomization to first primary kidney outcome event without (*A*) and with (*B*) MRA use at baseline and time to first secondary four-component composite outcome event without (*C*) and with (*D*) MRA use at baseline. The cumulative incidence rate was calculated using the Aalen-Johansen method with nonkidney and non-CV death (*A* and *B*) and nonkidney death (*C* and *D*) as a competing risk.

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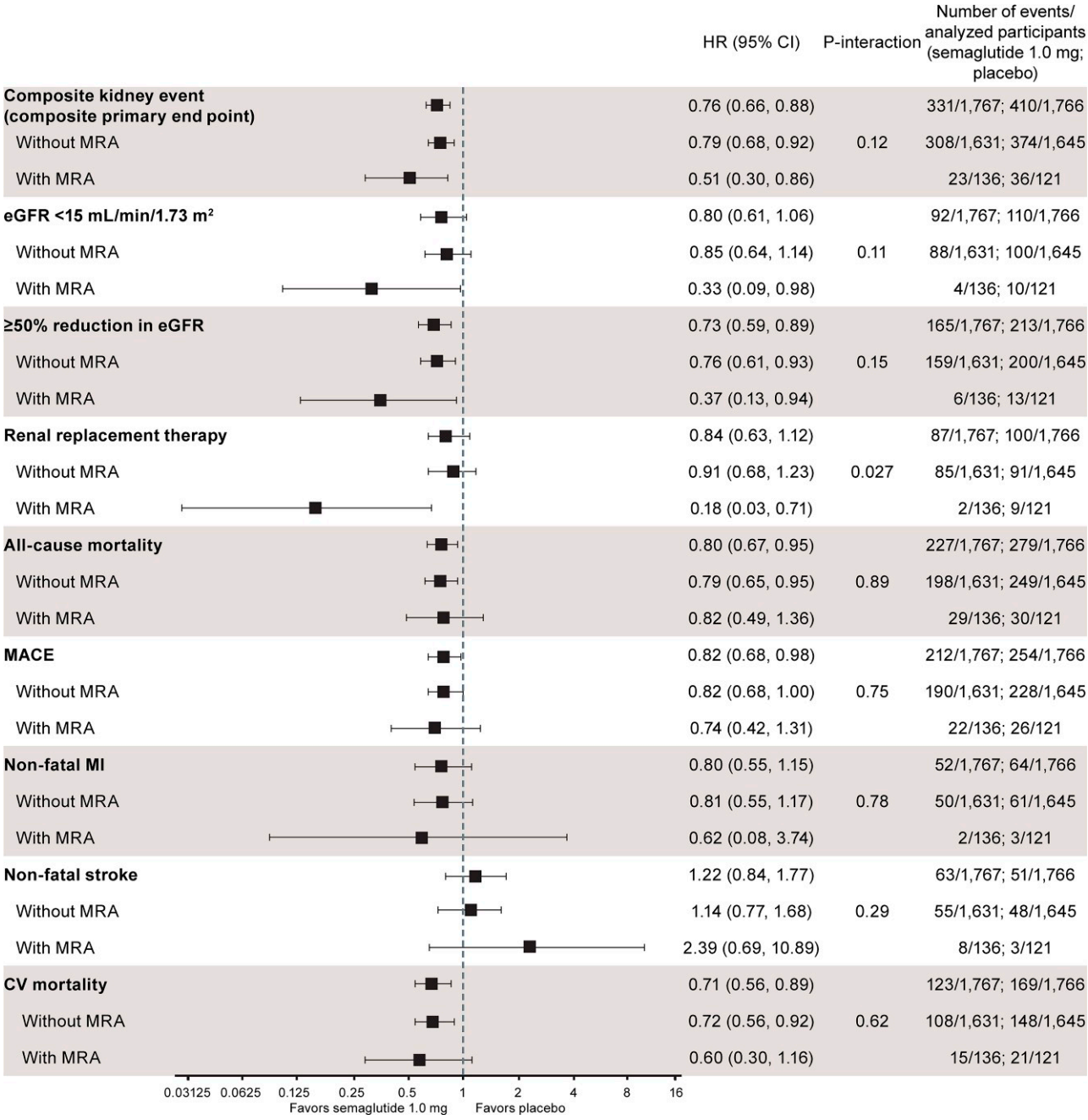

Figure 2—Major kidney outcomes, all-cause mortality, and CV outcomes by MRA use at baseline. Data from the in-trial period (full analysis set). Time from randomization to each outcome was analyzed using a stratified Cox proportional hazards model with treatment as a categorical fixed factor and two-sided *P* values. Participants without events of interest were censored at the end of their in-trial period. For the subgroup analyses, estimated HRs and corresponding CIs were calculated in a Cox proportional hazards model with interaction between treatment groups and subgroup as a fixed factor. *P* values for the test of no interaction effect between MRA use and treatment using a score test are shown. There was no kidney death in the MRA use subgroup, which is not displayed here. Renal replacement therapy includes dialysis initiation or kidney transplant.

Fig. 4). Results for the three individual components of the composite MACE outcome consistently showed interaction *P* values that indicated no signs of heterogeneity (*P*-interaction = 0.29–0.78). All-cause mortality was less frequent with semaglutide versus placebo, with no difference between participants reporting and not reporting MRA use at baseline (*P*-interaction = 0.89) (Fig. 2 and Supplementary Fig. 5).

Exploratory Outcomes and Safety. UACR over time in participants with and without MRA use at baseline is shown in Supplementary Fig. 6. Semaglutide lowered UACR compared with placebo at week 104 (15% [95% CI −41, 31] and 33% [95% CI 26, 39] in the subgroups with and without MRA use at baseline, respectively; *P*-interaction = 0.22).

Hyperkalemia based on laboratory reports (>5.5 mEq/L) was similar with semaglutide compared with placebo (22.1% vs. 19.0% and 13.6% vs. 17.6% in those

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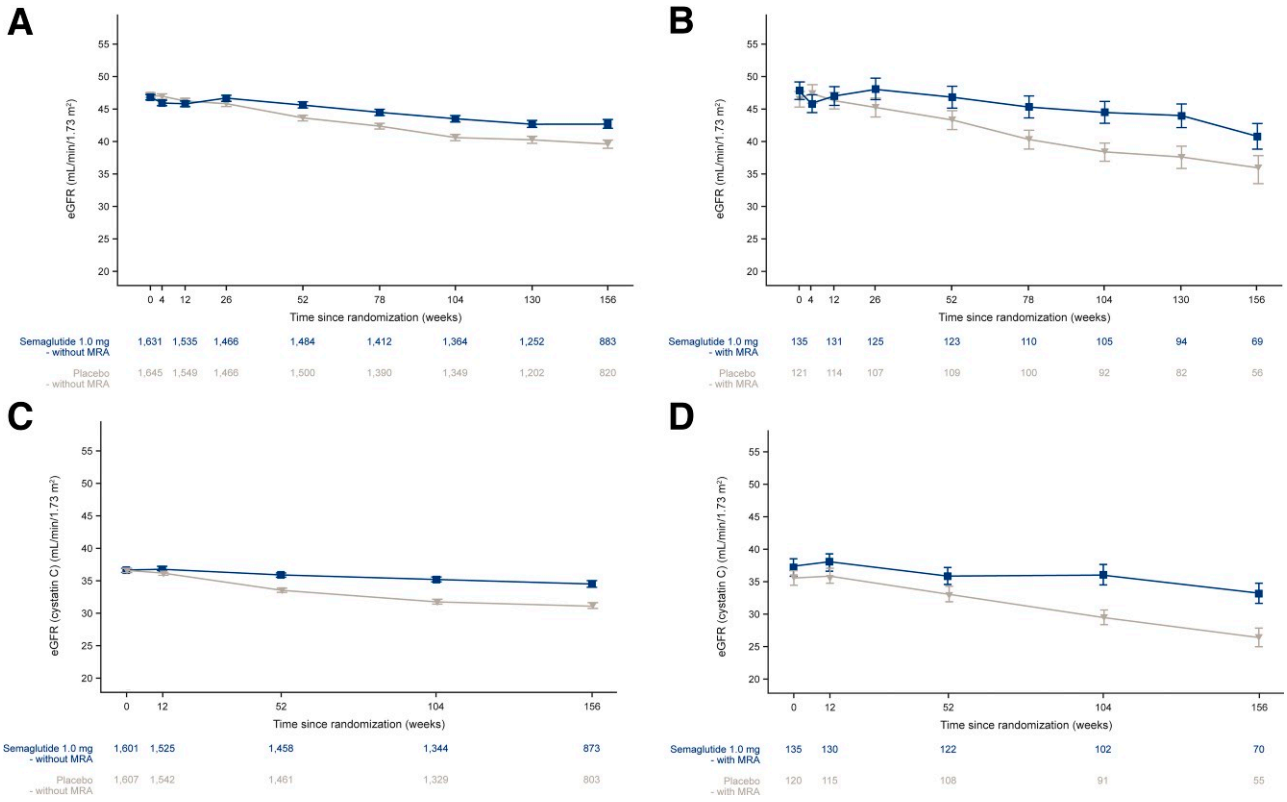

Figure 3—eGFR over time based on serum creatinine in participants without (*A*) and with (*B*) MRA use at baseline and based on serum cystatin C in participants without (*C*) and with (*D*) MRA use at baseline. Observed data from the in-trial period are shown. Error bars are SEM. Numbers shown under the plots represent the number of participants contributing to the means.

with and without MRA use at baseline, respectively; *P*-interaction = 0.12). Change in median serum potassium levels over the course of the study is shown in Supplementary Fig. 7. In the subgroup of participants with MRA use at baseline, serious adverse events were reported at a frequency of 55.1% vs. 66.9% for semaglutide versus placebo, and at a frequency of 49.2% vs. 52.8% in the subgroup without MRA use at baseline. The most frequent serious adverse events were infections and cardiac- and kidney-related disorders. Details are shown in Supplementary Fig. 8.

CONCLUSIONS

This prespecified FLOW subgroup analysis showed consistent kidney, CV, and mortality benefits with semaglutide compared with placebo in participants with T2D and CKD, irrespective of whether they were using an MRA at baseline or at any time concomitant with study medication. The concomitant use of semaglutide with an MRA was associated with fewer serious adverse events with semaglutide compared with placebo, again independent of the use of an MRA. These findings add to the body of evidence regarding the additive treatment effect of the combination of semaglutide and an MRA on kidney and CV events and mortality.

Currently, steroidal MRAs such as spironolactone and eplerenone are recommended in the ADA and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for individuals with T2D and resistant hypertension and an eGFR >45 mL/min/1.73 m^2 (7,12) and for the management of heart failure with reduced ejection fraction independent of diabetes and CKD (19). In short-term studies of <6 months as a rule, the steroidal MRAs reduced albuminuria but did not prevent progression of CKD in T2D (20). In elderly patients with stage 3 CKD, there was no effect of MRA on CV outcomes, potentially because two-thirds of patients stopped spironolactone treatment within 6 months predominantly because they met safety stopping rules (21). Similarly, spironolactone did not reduce the number of CV events in patients receiving dialysis (22). Further development of steroidal MRAs for the treatment of CKD was stopped because of hyperkalemia risk, and thus, it is not clear whether the short-term changes in albuminuria translate to long-term preservation of kidney function in CKD. Recently, nonsteroidal MRAs, including finerenone, have been developed for the treatment of CKD, starting in the population with T2D in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) (11) and the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) (10) studies, combined in the FIDELIO-DKD and FIGARO-DKD trial program analysis FIDELITY (23), which collectively included ∼13,000 participants with T2D and CKD. The effects on kidney and CV events with finerenone treatment compared with placebo in the FIDELITY analysis were similar in 944 users of GLP-1RAs at baseline and in 12,082 nonusers of GLP-1RAs, with no significant interaction, thus supporting their combined use (24). Any potential additive effect could be attributable to differential mechanisms of action of the two classes of medication, and mechanistic interaction was suggested in an experimental study of diabetic mice in

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which finerenone prevented downregulation of GLP-1 receptors in the kidney (16,25). In the current analysis, the benefits of semaglutide are seen irrespective of the use of MRAs, but finerenone was not used at baseline, only steroidal MRAs. Numerically, semaglutide reduced the primary end point to a greater extent in users of MRAs than in nonusers, which is in line with a significantly larger reduction in albuminuria with finerenone on a background of GLP-1RAs compared with those not using MRAs (24). In the current study, the interaction was not significant, and numbers were small, so further large-scale studies are required.

For the management of T2D with CKD, GLP-1RAs with demonstrated CV benefit, such as semaglutide, are recommended to reduce CV risk by the European Society of Cardiology (26), the European Association for the Study of Diabetes/ADA (27), and KDIGO (7). In the FLOW trial, in participants with T2D and CKD, semaglutide 1.0 mg once weekly reduced the risk of major kidney disease events by 24% and blunted eGFR decline by 1.16 mL/min/1.73 m^2 per year (14). There was also an 18% reduction in three-point MACE and a 20% reduction in all-cause mortality. As individuals with diabetes and CKD are at exceedingly high risk for kidney failure, CV events, and death, these results support a clinically meaningful benefit of semaglutide, with or without MRA therapy, for this population. A recent meta-analysis included 11 trials with GLP-1RAs, involving 85,373 participants, of whom 67,769 were diagnosed with T2D. In those with T2D, GLP-1RAs reduced the composite kidney outcome by 18% compared with placebo (HR 0.82; 95% CI 0.73, 0.93; I^2 = 26.4%), kidney failure by 16% (HR 0.84; 95% CI 0.72, 0.99; I^2 = 0%), MACE by 13% (HR 0.87; 95% CI 0.81, 0.93; I^2 = 49.8%), and all-cause mortality by 12% (HR 0.88; 95% CI 0.83, 0.93; I^2 = 0%), and similar results were seen when participants without diabetes from the Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) study were included (28). New guidelines recommend GLP-1RAs with proven CKD benefit for T2D with CKD (15).

Recently, we demonstrated that the benefit of semaglutide in FLOW was similar regardless of baseline use of SGLT2is (29), and in a meta-analysis of SGLT2i studies from SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists Consortium (SMART-C), the benefit of SGLT2is was also similar, regardless of baseline use of GLP-1RAs (30). This supports the concept of four pillars for optimal management of CKD in T2D targeting multiple different underlying pathophysiologic pathways with RAS blockade, SGLT2is, a nonsteroidal MRA (finerenone), and a GLP-1RA (semaglutide) (31). A modeling simulation analysis from different studies supported that the more pillars implemented, the greater the CV and kidney benefits (32).

There were no safety signals or concerns with concomitant use of MRAs and semaglutide, although numbers were small and duration of treatment short. Of relevance for the use of MRAs, there was no interaction with semaglutide use and the risk for hyperkalemia.

There are several limitations to this exploratory subgroup analysis. There were differences in baseline characteristics between subgroups across the study population, although important factors such as eGFR, UACR, and SGLT2i use were similar. Importantly, finerenone only became available late during the FLOW trial, and its use was very limited. Additionally, it is not known whether MRAs were used in FLOW for the treatment of hypertension, heart failure, CKD, or other conditions. The higher blood pressure and prevalence of heart failure or prior CV disease might suggest that some participants receiving an MRA were being treated with these agents for hypertension or heart failure. This was a prespecified analysis but with limited statistical power based on 257 users of MRAs at baseline with 59 primary outcomes, while there were 3,276 without MRA use and 682 outcomes in total. This analysis should be considered exploratory, as participants included in this analysis were not stratified by baseline MRA use at study initiation. Participants included in the analyses determining the effect of postbaseline initiation of MRAs were not randomized; therefore, these can only be considered hypothesis generating. Potential strengths of FLOW included its consistent enrollment and retention during the coronavirus 2019 pandemic, the high adherence (adherence to the trial regimen averaged 89% of the planned time during the trial period), and the lower-than-expected number of dropouts.

In conclusion, semaglutide reduced risks of kidney, CV, and all-cause mortality outcomes without heterogeneity of those benefits by baseline MRA use in participants with T2D and CKD. Given the substantial benefits of both semaglutide and MRAs and the acceptable safety profile of their combination, this option may be considered when treating persons with T2D and CKD.

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