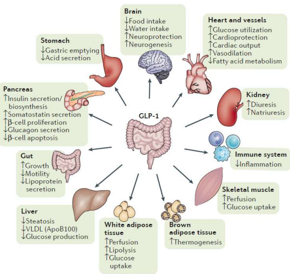
FLOW Study Review

Semaglutide and CKD Outcomes

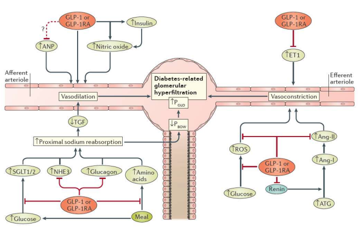
Alison Shipley, RPh

Role of Glucagon-like-Peptide-1



Muskiet et al. Nature Reviews Nephrology, 2017

GLP-1 and the Kidney

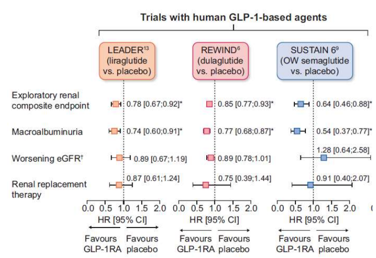


Direct Effects
- Proximal tubular natriuresis simulation
- Vasodilatory effects on the afferent arteriole
- Decreases glomerular hyperfiltration

Indirect Effects
- Weight loss
- Improved blood pressure control
- Improved glycemic control

Muskiet et al. Nature Reviews Nephrology, 2017

Trials of GLP-1 Receptor Agonists



LEADER
- Mean eGFR 79.1 ml/min/1.73m^2

REWIND
- Mean eGFR 74.9 ml/min/1.73m^2

SUSTAIN 6
- 30% eGFR > 90 ml/min/1.73m^2
- 41.5% eGFR 60-90 ml/min/1.73m^2
- 25.2% eGFR 30-60 ml/min/1.73m^2
- 2.9% eGFR 15-30 ml/min/1.73m^2

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The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

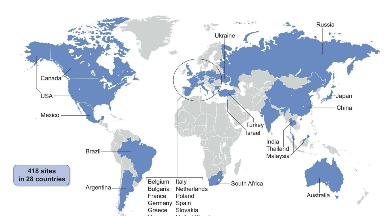
Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

FLOW = evaluate kidney Function with semagLutide Once Weekly

Methods

- International, double-blind, randomized, placebo-controlled trial
- 28 countries



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Study Population

Inclusion Criteria

- Adult patients
- Type 2 diabetes (HbA1c ≤ 10%)
- Stable maximum tolerated dose of a RAS inhibitor
- Renal impairment, defined as either:
  - eGFR ≥ 50 and ≤ 75 ml/min/1.73 m^2 and UACR > 300 and < 5000 mg/g (34 to 565 mg/mmol) or
  - eGFR ≥ 25 and ≤ 50 ml/min/1.73 m^2 and UACR > 100 and < 5000 mg/g (11 to 565 mg/mmol)

Exclusion Criteria

- Congenital or hereditary kidney disease
- History of malignancy within 5 years
- MI, stroke, hospitalization for unstable angina or TIA within 60 days
- Planned coronary, carotid or peripheral artery revascularization
- Uncontrolled proliferative diabetic retinopathy
- Current NYHA Class IV heart failure
- Pregnancy or breastfeeding
- Use of any GLP1-RA within 30 days prior to screening
- Combination use of ACEi and ARB
- Dialysis within 90 days prior to screening
- Prior solid organ transplant or awaiting transplant

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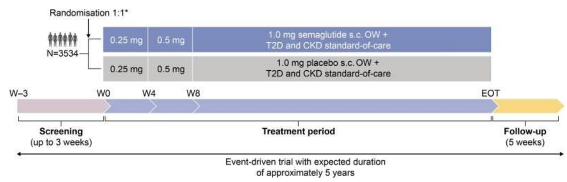
Intervention



SGLT2 inhibitors and MRA were permitted and randomization was stratified by use of SGLT2 inhibitors at baseline

Participants with eGFR ≥ 60 ml/min/1.73 m^2 were capped at 20%

Injection training was repeated at weeks 4, 26 and annually

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Outcome Measurements

Primary outcome

- **Time to first occurrence of major kidney events consisting of:**
- Kidney failure:
  - Onset of persistent eGFR <15 ml/min/1.73 m^2
  - Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)
- Onset of persistent >50% reduction in eGFR compared with baseline
- Death from kidney-related cause
- Death from cardiovascular cause

Confirmatory secondary outcomes

- Annual rate of change in eGFR (total eGFR slope)
- Time to first occurrence of a composite MACE outcome consisting of CV death, non-fatal MI or non-fatal stroke
- Time to occurrence of all-cause death

Supportive secondary outcomes

- Time to occurrence of each of the individual components of the primary composite outcome, and of the confirmatory secondary MACE outcomes
- Change in eGFR, UACR, body weight, HbA1C, blood pressure

*eGFR was calculated using both creatinine (CKD-EPI) and cystatin C to account for any change weight loss could have on creatinine measurement

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Sample Size, Analytic Plan, and Funding

- This trial was event-driven, with a minimum of 854 primary outcome events (including 515 kidney events) which would provide 90% power to detect a 20% risk reduction
  - Based on a 8.5% annual event rate in the placebo arm, this would require about 3508 participants to be enrolled
- The trial used an intention-to-treat principle
- An interim analysis was planned after two thirds of the total events had accrued with clear stopping rules
- Funding was provided by Novo Nordisk, which manufactured semaglutide

Results

June 2019 to May 2021

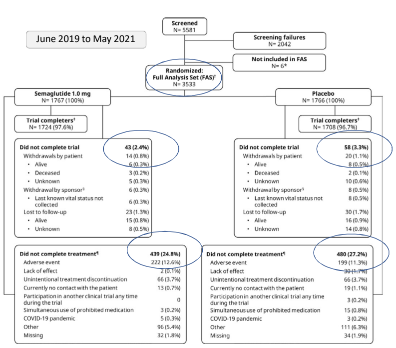

Figure S1. Perkovic et al. NEJM 2024

Interim Analysis

- The trial was halted early in October 2023 after the Data Safety and Monitoring Board performed an interim analysis after 570 events had accrued and stopping rules were met
  - By the time all follow up visits were completed, 741 events had occurred
- Mean follow-up duration was 3.4 years
- A total of 3472 (98.6%) patients completed follow-up or died during this period

Baseline Characteristics

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Age — yr	66.6±9.0	66.7±9.0	66.6±9.0
Female sex — no. (%)	519 (29.4)	550 (31.1)	1069 (30.3)
Geographic region — no. (%)			
Asia	478 (27.1)	434 (24.6)	912 (25.8)
Europe	472 (26.7)	491 (27.8)	963 (27.3)
North America	423 (23.9)	442 (25.0)	865 (24.5)
Other	394 (22.3)	399 (22.6)	793 (22.4)
Race or ethnic group — no. (%)†			
White	1155 (65.4)	1168 (66.1)	2323 (65.8)
Asian	439 (24.8)	407 (23.0)	846 (23.9)
Black	78 (4.4)	82 (4.6)	160 (4.5)
Other	95 (5.4)	109 (6.2)	204 (5.8)
Hispanic or Latinx ethnic group — no. (%)†			
Yes	273 (15.4)	283 (16.0)	556 (15.7)
No	1421 (80.4)	1411 (79.9)	2832 (80.2)
Not reported	73 (4.1)	72 (4.1)	145 (4.1)
Glycated hemoglobin level — %	7.8±1.3	7.8±1.3	7.8±1.3
Body-mass index‡	31.9±6.1	32.0±6.5	32.0±6.3
Body weight — kg	89.5±19.8	89.8±21.2	89.6±20.5
Systolic blood pressure — mm Hg	138.9±16.1	138.4±15.4	138.6±15.8
Diastolic blood pressure — mm Hg	76.8±10.0	76.1±10.0	76.4±10.0

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Diabetes duration — no. (%)			
<15 yr	774 (43.8)	753 (42.6)	1527 (43.2)
≥15 yr	992 (56.1)	1013 (57.4)	2005 (56.8)
Previous myocardial infarction or stroke — no. (%)	405 (22.9)	403 (22.8)	808 (22.9)
Chronic heart failure — no. (%)	342 (19.4)	336 (19.0)	678 (19.2)
Smoking status — no. (%)§			
Current smoker	223 (12.6)	206 (11.7)	429 (12.1)
Previous smoker	661 (37.4)	696 (39.4)	1357 (38.4)
Never smoked	883 (50.0)	864 (48.9)	1747 (49.4)
eGFR — ml/min/1.73 m^2¶	46.9±15.6	47.1±14.7	47.0±15.2
eGFR distribution — no. (%)¶			
≥60 ml/min/1.73 m^2	366 (20.7)	353 (20.0)	719 (20.4)
≥45 to <60 ml/min/1.73 m^2	515 (29.1)	540 (30.6)	1055 (29.9)
≥30 to <45 ml/min/1.73 m^2	667 (37.7)	691 (39.1)	1358 (38.4)
<30 ml/min/1.73 m^2	218 (12.3)	182 (10.3)	400 (11.3)
Median urinary albumin-to-creatinine ratio‖	582.3	557.8	567.6
Category of albuminuria — no. (%)**			
A1, normoalbuminuria	52 (2.9)	57 (3.2)	109 (3.1)
A2, microalbuminuria	509 (28.8)	495 (28.0)	1004 (28.4)
A3, macroalbuminuria	1205 (68.2)	1214 (68.7)	2419 (68.5)

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Baseline Characteristics

Table 1. (Continued.)

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Medication use — no. (%)			
SGLT2 inhibitor	277 (15.7)	273 (15.5)	550 (15.6)
ACE inhibitor	625 (35.4)	615 (34.8)	1240 (35.1)
ARB	1066 (60.3)	1061 (60.1)	2127 (60.2)
Lipid-lowering drug	1418 (80.2)	1416 (80.2)	2834 (80.2)
Diuretic agent	870 (49.2)	910 (51.5)	1780 (50.4)
Insulin	1083 (61.3)	1085 (61.4)	2168 (61.4)

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Baseline Characteristics

UACR categories (mg/g)

eGFR categories (ml/min/1.73 m^2)	<30	≥30 to <300	≥300
≥90	1 (<0.1)	7 (0.2)	23 (0.6)
≥60 to <90	24 (0.7)	173 (4.9)	491 (13.9)
≥45 to <60	37 (1.0)	324 (9.2)	694 (19.6)
≥30 to <45	40 (1.1)	414 (11.7)	905 (25.6)
≥15 to <30	7 (0.2)	87 (2.5)	306 (8.6)

Low risk n=25 (0.7%)
High risk n=878 (24.8%)
Moderate risk n=217 (6.1%)
Very high risk n=2413 (68.2%)

Majority were high or very high risk CKD

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Results

Primary outcome: 24% risk reduction

Table 2. Efficacy and Safety Outcomes.*

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m^2	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m^2	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001
Major cardiovascular events — no. (%)	212 (12.0)	254 (14.4)	0.82 (0.68 to 0.98)	—	0.029
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Nonfatal myocardial infarction	52 (2.9)	64 (3.6)	0.80 (0.55 to 1.15)	—	—
Nonfatal stroke	63 (3.6)	51 (2.9)	1.22 (0.84 to 1.77)	—	—

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Table 2. Efficacy and Safety Outcomes.*

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Supportive secondary outcomes					
Ratio of urinary albumin-to-creatinine ratio at week 104 to urinary albumin-to-creatinine ratio at baseline	0.60	0.88	0.68 (0.62 to 0.75)‡	—	—
Mean change in body weight from baseline to week 104 — kg	−5.55	−1.45	—	−4.10 (−4.56 to −3.65)	—
Mean change in glycated hemoglobin level from baseline to week 104 — percentage points	−0.87	−0.06	—	−0.81 (−0.90 to −0.72)	—
Mean change in systolic blood pressure from baseline to week 104 — mm Hg	−3.79	−1.55	—	−2.23 (−3.33 to −1.13)	—
Mean change in diastolic blood pressure from baseline to week 104 — mm Hg	−0.23	−1.01	—	0.78 (0.16 to 1.41)	—
Mean change in eGFR from baseline to week 12 — ml/min/1.73 m^2	−1.07	−1.05	—	−0.03 (−0.56 to 0.51)	—
Mean annual rate of change in eGFR from week 12 to end of trial — ml/min/1.73 m^2	−2.36	−3.30	—	0.94 (0.62 to 1.26)	—
Mean change in eGFR by the cystatin C equation from baseline to week 104 — ml/min/1.73 m^2	−2.01	−5.41	—	3.39 (2.63 to 4.15)	—

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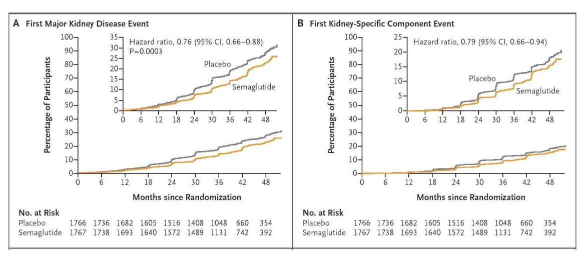
Primary Outcome



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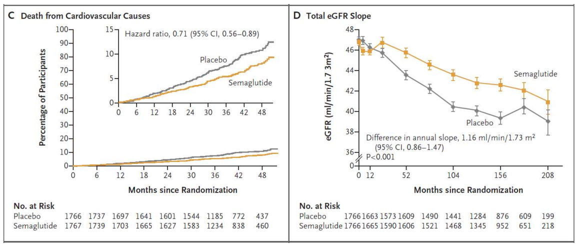
Secondary Outcomes



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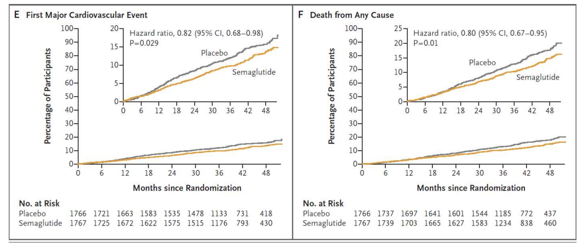
Secondary Outcomes



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Safety Outcomes

Table 3. Safety Outcomes.

Adverse Event	Semaglutide (N=1767)	Placebo (N=1766)
	no. of participants (%)	
Serious adverse event	877 (49.6)	950 (53.8)
Adverse event leading to permanent discontinuation of semaglutide or placebo	233 (13.2)	211 (11.9)
Prespecified adverse events of special interest		
Diabetic retinopathy*	402 (22.8)	398 (22.5)
Covid-19–related disorder	358 (20.3)	404 (22.9)
Serious adverse event: cardiovascular disorder	273 (15.4)	319 (18.1)
Heart failure*	133 (7.5)	175 (9.9)
Acute kidney failure*	172 (9.7)	182 (10.3)
Malignant tumor*	120 (6.8)	104 (5.9)
Serious adverse event: gastrointestinal disorder	95 (5.4)	94 (5.3)
Serious adverse event: rare event	48 (2.7)	57 (3.2)
Acute gallbladder disease*	32 (1.8)	39 (2.2)
Severe hypoglycemia*	37 (2.1)	37 (2.1)
Medication error*	15 (0.8)	13 (0.7)
Serious adverse event: hepatic disorder	18 (1.0)	20 (1.1)
Acute pancreatitis*	10 (0.6)	7 (0.4)
Serious adverse event: allergic reaction	6 (0.3)	9 (0.5)
Serious adverse event: abuse and misuse	1 (0.1)	4 (0.2)
Serious adverse event: suspected transmission of infectious agent through semaglutide or placebo	0	1 (0.1)

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Conclusion

The authors conclude that among patients with Type 2 diabetes and high-risk chronic kidney disease, semaglutide reduced the risk of major kidney disease events

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Discussion

Strengths

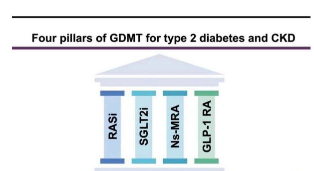
- FLOW is the first trial looking at the primary renoprotective effects of a GLP1-RA down to an eGFR of 25 ml/min/1.73 m^2
- Compared to other landmark cardio-renal trials, FLOW trial included a higher-risk population
- Overall good generalizability of results because it was conducted in a wide geographical area

Limitations

- Type 1 diabetics excluded
- Low proportion of Black patients (< 5%)
- SGLT2i therapy was not a requirement
  - There were a larger number of 'drop in' patients in the placebo group, presumably due to proteinuria and hyperglycemia, making the benefits of semaglutide even more impressive

Summary

The FLOW trial showed that semaglutide significantly decreased the risk of progression of kidney disease in T2DM, without significant increases in serious adverse events



Agarwal R, Fouque D. NDT 2023

Thank you!