Presenter:

Shiva Maleki, MD

Research assistant

Kidney diseases research center

Isfahan University of Medical Sciences

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

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*

Method

Aspect	Details
Number of Participants	3,533 total participants
Study Groups	Semaglutide group: 1,767 Placebo group: 1,766
Inclusion Criteria	Adults with Type 2 diabetes and CKD eGFR: 25–75 mL/min/1.73m^2 Albumin-to-creatinine ratio: >300 to <5000 mg/g (eGFR ≥50) Albumin-to-creatinine ratio: >100 to <5000 (eGFR <50)
Study Duration	Median follow-up: 3.4 years
Semaglutide Dose	1.0 mg subcutaneous weekly
Dosing Schedule	Week 1-4: 0.25 mg weekly Week 5-8: 0.5 mg weekly Maintenance: 1.0 mg weekly

Global Burden of CKD in Type 2 Diabetes

- Type 2 diabetes is the leading cause of CKD in many countries, accounting for a substantial proportion of kidney failure cases.

- Chronic kidney disease (CKD) affects over half a billion people globally, posing significant public health challenges.

- CKD in diabetic patients often progresses to end-stage kidney disease, requiring dialysis or transplantation, and significantly increases the risk of cardiovascular events and mortality.

Existing Therapies

Three medical therapies have been shown to have benefits in patients with type 2 diabetes and chronic kidney disease:

1. **Renin–angiotensin system (RAS) inhibitors**
2. **Sodium–glucose cotransporter 2 (SGLT2) inhibitors**
3. **Mineralocorticoid receptor antagonist**

Role: **Protect the kidneys and reduce the risk of adverse cardiovascular outcomes**

Many patients continue to lose kidney function and go on to have kidney failure or to die, most commonly from cardiovascular events. Thus, the effects of therapies such as glucagon-like peptide 1 (GLP-1) receptor agonists are of great interest.

GLP-1 receptor agonists

Use of GLP-1 receptor agonists in populations with type 2 diabetes:

Examples: Semaglutide, liraglutide, dulaglutide,...

Benefits:

1. Improve glycemic control

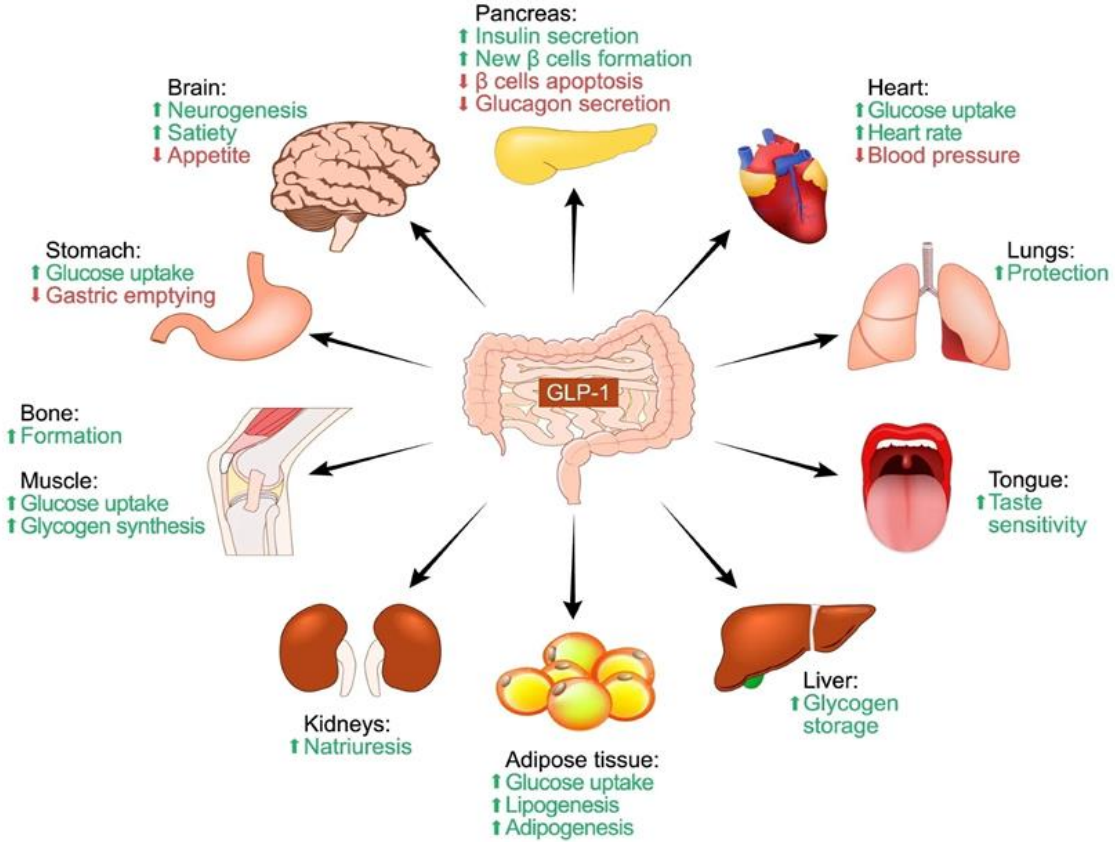
2. Decrease body weight

3. Reduce cardiovascular events

4. Reduced Kidney outcome

(worsening kidney function, end-stage kidney disease, kidney failure, and development of macroalbuminuria)

Functions of Glucagon-like peptide-1



The kidney benefits may be attributed to weight loss, improved glycemic control, and better blood pressure regulation induced by GLP-1 receptor agonists.

Semaglutide

- Glucagon-like peptide-1 receptor agonist (GLP-1 RA)

Roles:

1. Glycemic control

Pancreatic actions:

- Stimulates glucose-dependent insulin secretion from pancreatic beta cells

- Suppresses inappropriate glucagon release from alpha cells

- reducing hepatic glucose production.

2. Weight loss:

• Slow Gastric Emptying:

leading to slower glucose absorption and reduced postprandial glucose spikes.

• Appetite Suppression:

Acts on hypothalamic centers to reduce appetite.

3. Reduced major adverse cardiovascular events

4. Reduced major Kidney disease events:

Semaglutide reduced the risk of major kidney disease events by 24% compared to placebo.

- **Major kidney disease events include:**

Primary outcome: major kidney disease events — no. (%)
Components of primary outcome — no. (%)
Persistent ≥50% reduction from baseline in eGFR
Persistent eGFR <15 ml/min/1.73 m^2
Initiation of kidney-replacement therapy
Death from kidney-related causes
Death from cardiovascular causes

Secondary outcome:

1. total eGFR slope (the annual rate of change in eGFR from randomization to the end of the trial)
2. major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes)

• Improved eGFR Slope:

slowing the annual loss of kidney function by a mean of 1.16 ml per minute per 1.73 m2.

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m²	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001

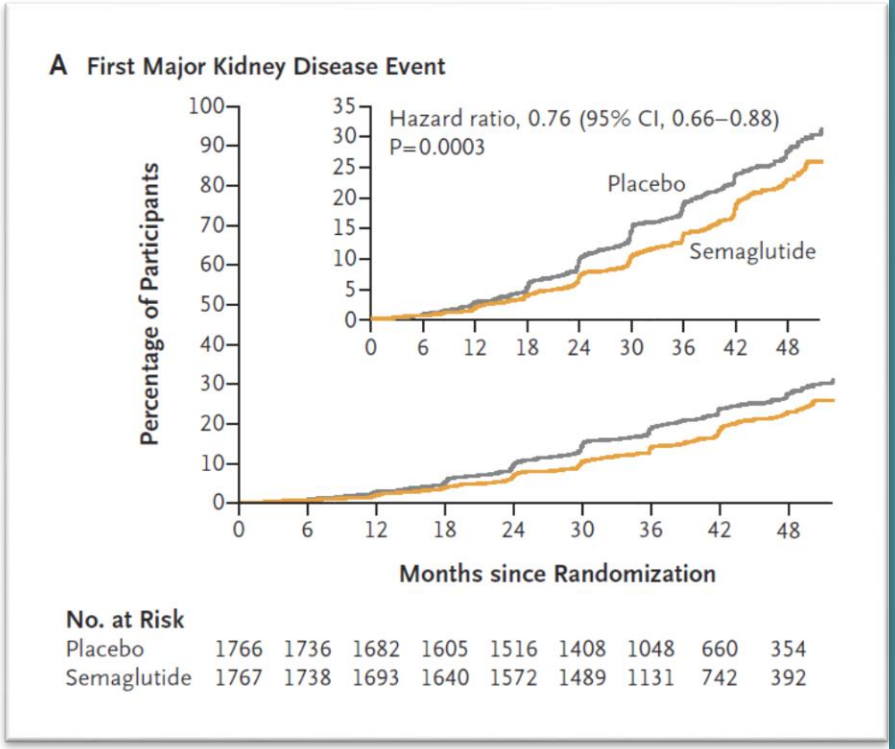
Comparison of semaglutide and placebo groups

A: First Major Kidney Disease Event

1. Onset of kidney failure (requiring dialysis or transplantation).
2. Sustained reduction in eGFR by ≥50%.
3. Death due to kidney-related or cardiovascular causes.

Key result:

- The semaglutide group had a significantly lower cumulative incidence compared to the placebo group.



B: First Kidney-Specific Component Event

1. Sustained ≥50% reduction in eGFR.
2. Sustained eGFR of <15 mL/min/1.73 m^2
3. Initiation of long-term dialysis or renal replacement therapy
4. Death from kidney-specific causes.

Key Results:

• Semaglutide reduced the cumulative incidence of these events compared to placebo.

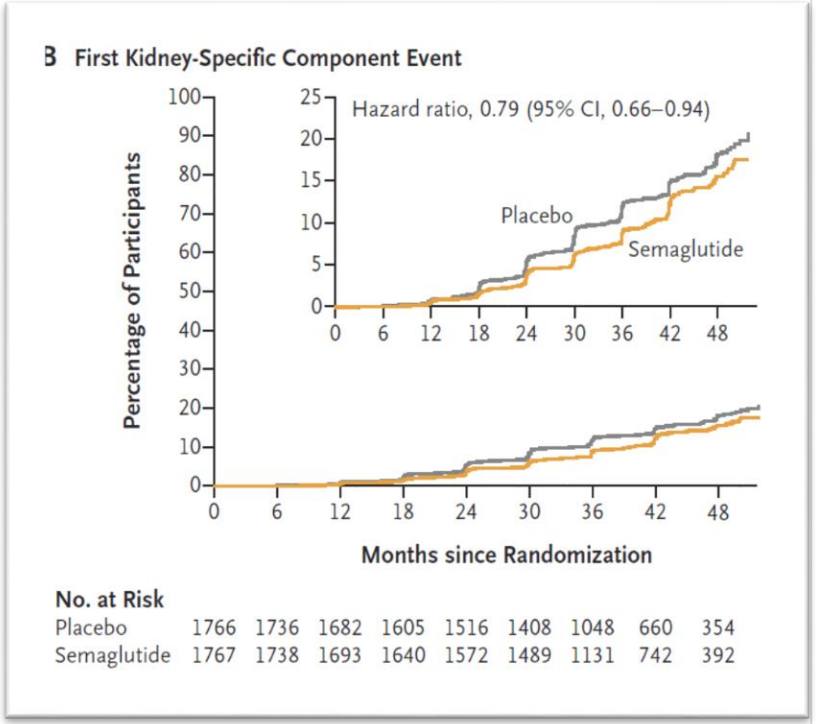


Table 2. Efficacy and Safety Outcomes.*

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 m²	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 m²	−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)	—	—
Death from any cause — no. (%)	227 (12.8)	279 (15.8)	0.80 (0.67 to 0.95)	—	0.01
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 m²	−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 m²	−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 m²	−2.01	−5.41	—	3.39 (2.63 to 4.15)	—

Gourdy *et al. Cardiovascular Diabetology* (2023) 22:79
https://doi.org/10.1186/s12933-023-01798-4

Cardiovascular Diabetology

REVIEW Open Access

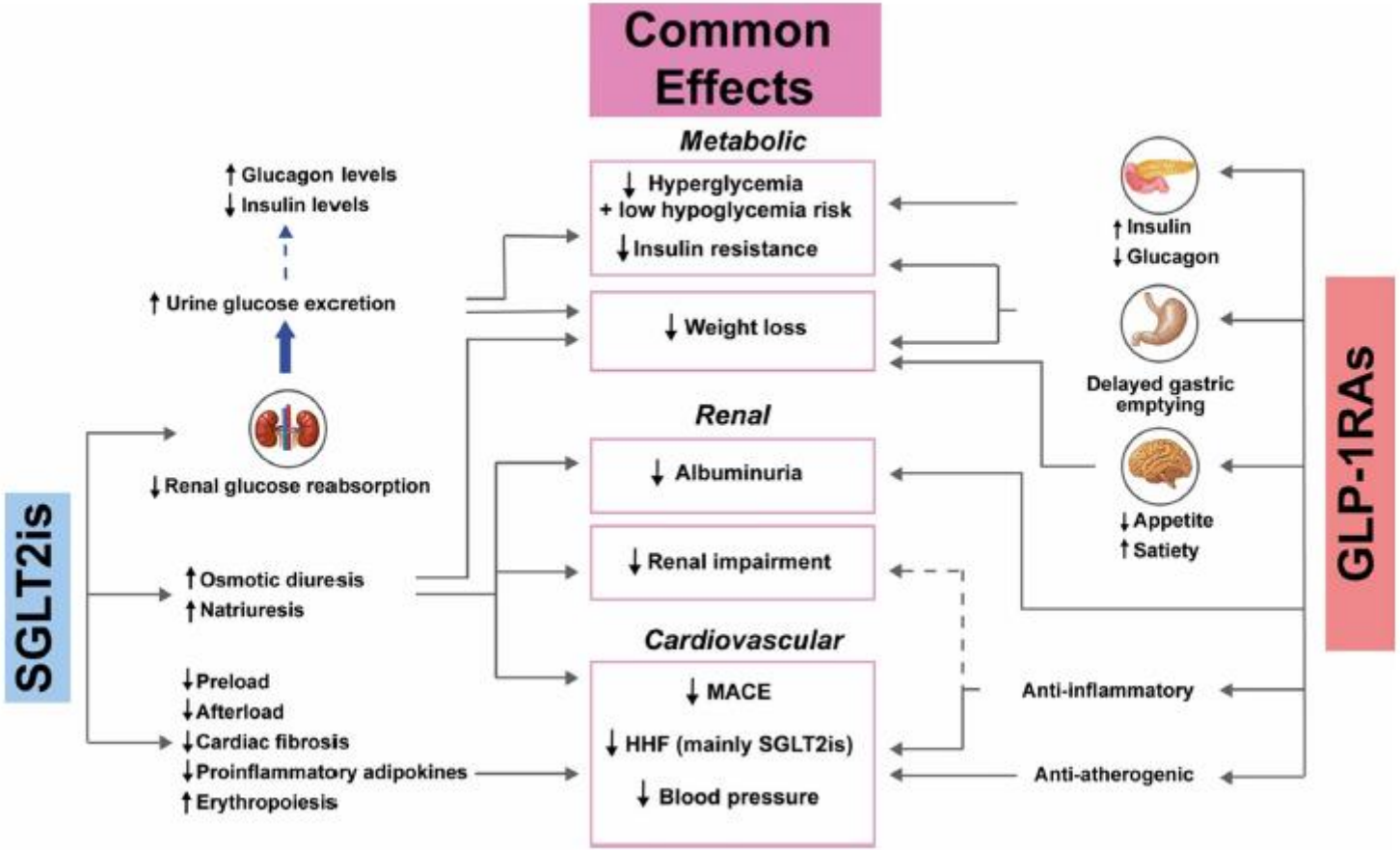
Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM)

Pierre Gourdy[1,2*], Patrice Darmon[3], François Dievart[4], Jean-Michel Halimi[5,6] and Bruno Guerci[7]

Combination therapy of GLP-1 RA and SGLT2i

Both glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) have individually been shown to reduce cardiovascular and kidney outcomes in patients with T2DM,with a low hypoglycemia risk.

combination therapy of GLP-1 receptor agonists (GLP-1RAs) and SGLT2 inhibitors (SGLT2is) offers significant potential benefits for patients with type 2 diabetes mellitus (T2DM), particularly in addressing metabolic, cardiovascular, and renal diseases.


Common Effects
Metabolic
↓ Hyperglycemia + low hypoglycemia risk
↓ Insulin resistance
↓ Weight loss
Renal
↓ Albuminuria
↓ Renal impairment
Cardiovascular
↓ MACE
↓ HHF (mainly SGLT2is)
↓ Blood pressure
↑ Glucagon levels
↓ Insulin levels
↑ Urine glucose excretion
↓ Renal glucose reabsorption
↑ Osmotic diuresis
↑ Natriuresis
↓ Preload
↓ Afterload
↓ Cardiac fibrosis
↓ Proinflammatory adipokines
↑ Erythropoiesis
SGLT2is
↑ Insulin
↓ Glucagon
Delayed gastric emptying
↓ Appetite
↑ Satiety
Anti-inflammatory
Anti-atherogenic
GLP-1RAs


Thank you
for your attention