Extracorporeal Nephrology Group

Journal Review

FLOW Trial

Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease

Compiled by

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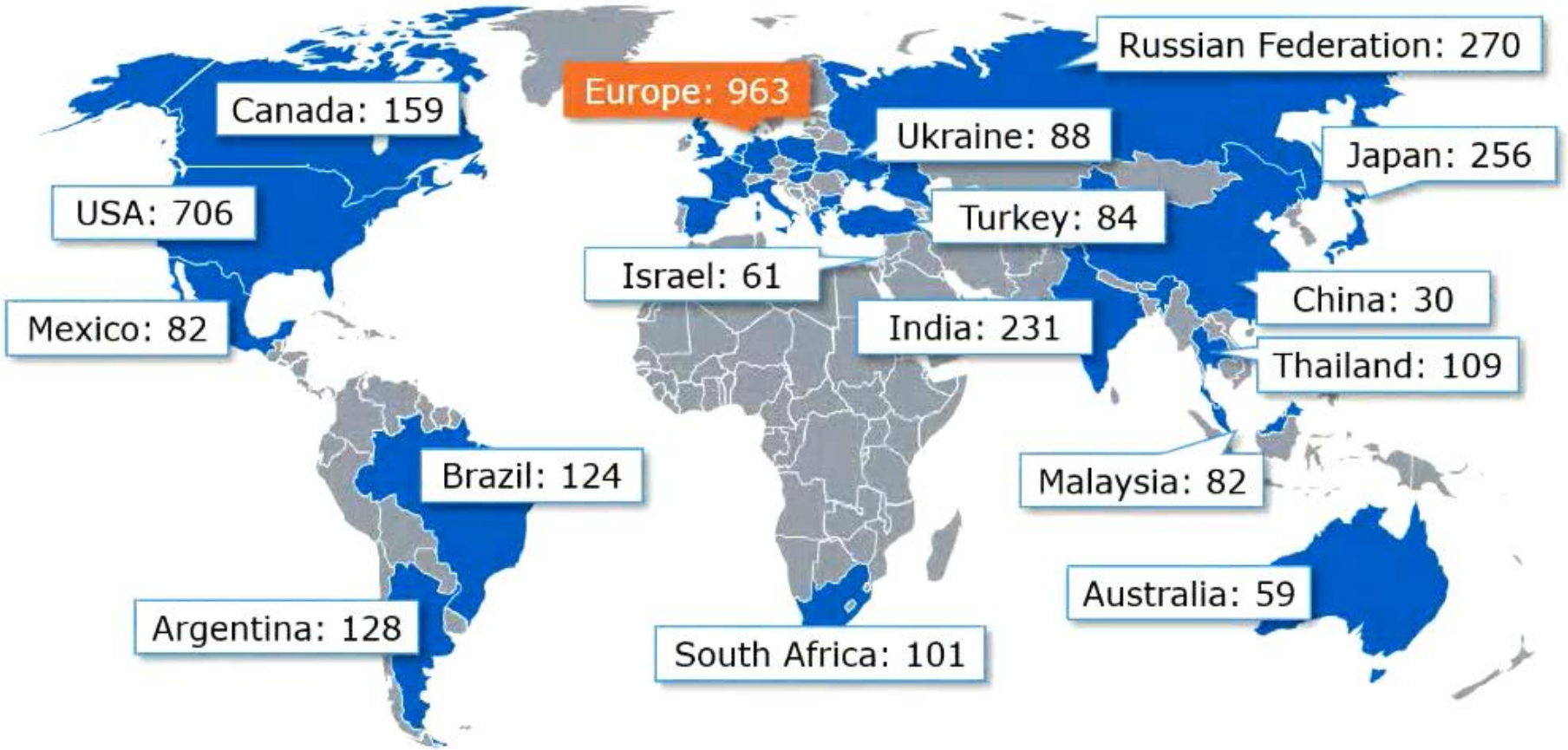
FLOW: A global kidney outcomes trial

RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, MULTINATIONAL, PHASE 3B TRIAL



3.4 years' median follow-up

28 countries

387 sites

3533 participants

Numbers in diagram represent number of participants.
Perkovic V et al. *N Engl J Med* 2024;391:109–121.

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semaglutide

Objective: To evaluate the safety and efficacy of semaglutide in slowing kidney function decline and reducing major adverse kidney events in patients with type 2 diabetes.

Inclusion Criteria

- Adult patients
- Type 2 diabetes (HbA1c ≤10%)
- Stable maximum tolerated dose of a RAS inhibitor
- High risk CKD defined as:
  eGFR ≥50 to ≤75 ml/min/1.73 m2 & UACR >300 to <5000 mg/g
  /OR/
  eGFR ≥25 to <50 ml/min/1.73 m2 & UACR >100 to <5000 mg/g

Exclusion Criteria

@brian_rifkin

- Congenital or hereditary kidney disease
- Current NYHA Class IV heart failure
- History of malignancy within 5 years
- Pregnancy or breastfeeding
- MI, stroke, hospitalization for unstable angina or TIA within 60 days
- Use of any GLP1-RA (within 30 days) or combination RASi
- Planned coronary, carotid or peripheral artery revascularization
- Current dialysis (within 90 days)
- Uncontrolled proliferative diabetic retinopathy
- Transplant or awaiting transplant

A global kidney outcomes trial

Randomized controlled clinical trial

Semaglutide group (n = 1767) VS. **Placebo group (n = 1766)**

Demographics

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	Semaglutide (n=1767)	Placebo (n=1766)
Age, mean (SD), years	66.6 (9.0)	66.7 (9.0)
Sex, n (%)		
Female	519 (29.4)	550 (31.1)
Region, n (%)		
Asia	478 (27.1)	434 (24.6)
Europe	472 (26.7)	491 (27.8)
North America	423 (23.9)	442 (25.0)
Other	394 (22.3)	399 (22.6)

	Semaglutide (n=1767)	Placebo (n=1766)
Race, n (%)		
White	1155 (65.4)	1168 (66.1)
Asian	439 (24.8)	407 (23.0)
Black or African American	78 (4.4)	82 (4.6)
Other†	95 (5.4)	109 (6.2)
Ethnicity, n (%)		
Hispanic or Latino	273 (15.4)	283 (16.0)
Not Hispanic or Latino	1421 (80.4)	1411 (79.9)
Not reported	73 (4.1)	72 (4.1)

†Includes participants whose race was reported as 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander', or 'Not reported'.
SD, standard deviation.
Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Baseline characteristics

Mean age: 66.6 years
Male: 69.7%
Caucasians: 65.7%

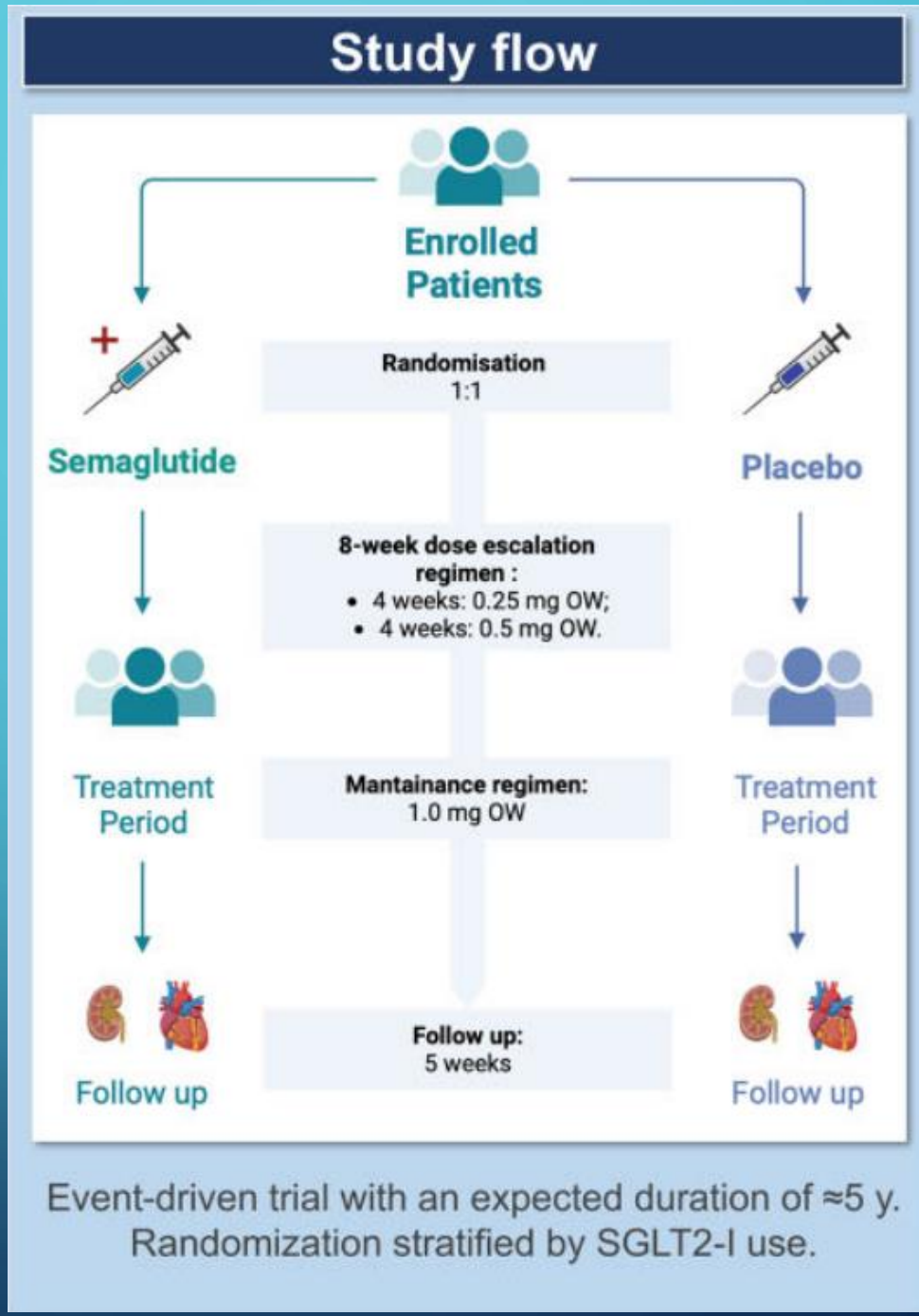
Diabetes
Mean baseline HbA_{1c}: 7.8%
Mean T2DM duration: 17.4 y
Mean BMI: 32.0 kg/m^2

Chronic kidney disease
Mean baseline eGFR: 47.0 ml/min/1.73 m^2
Median UACR: 568 mg/g
68.2% of patients at very high risk for CKD progression (according to KDIGO).

Medications
15.5% on SGLT2-I
95.3% on RAAS inhibitors

Experimental arm		Control arm
Semaglutide (1.0 mg s.c. OW) + T2DM and CKD standard of care	vs	Placebo (1.0 mg s.c. OW) + T2DM and CKD standard of care

*OW-Once weekly



Primary outcome

Time to first occurrence of major kidney outcomes consisting of:

- Onset of persistent ≥50% reduction in eGFR compared with baseline
- Kidney failure:
  - Onset of persistent eGFR <15 mL/min/1.73 m^2
  - Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)
- Kidney death
- CV death

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

Other supportive secondary outcomes

- Time to occurrence of each of the individual components of the primary composite outcome, and of the confirmatory secondary MACE outcome
- Time to first occurrence of composite of acute limb ischaemia hospitalization or chronic limb ischaemia hospitalization
- Change in eGFR, UACR, body weight, HbA_{1c}, BP

Primary and secondary outcomes other than eGFR assessments derived from the central laboratory were adjudicated in a blinded fashion by an Event Adjudication Committee

eGFR was calculated using the CKD-EPI formula. CV death includes undetermined cause of death.
BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; UACR, urine albumin:creatinine ratio.
Perkovic V et al. *N Engl J Med* 2024;391:109–121.

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Superiority of semaglutide versus placebo was confirmed for kidney, CV and mortality outcomes

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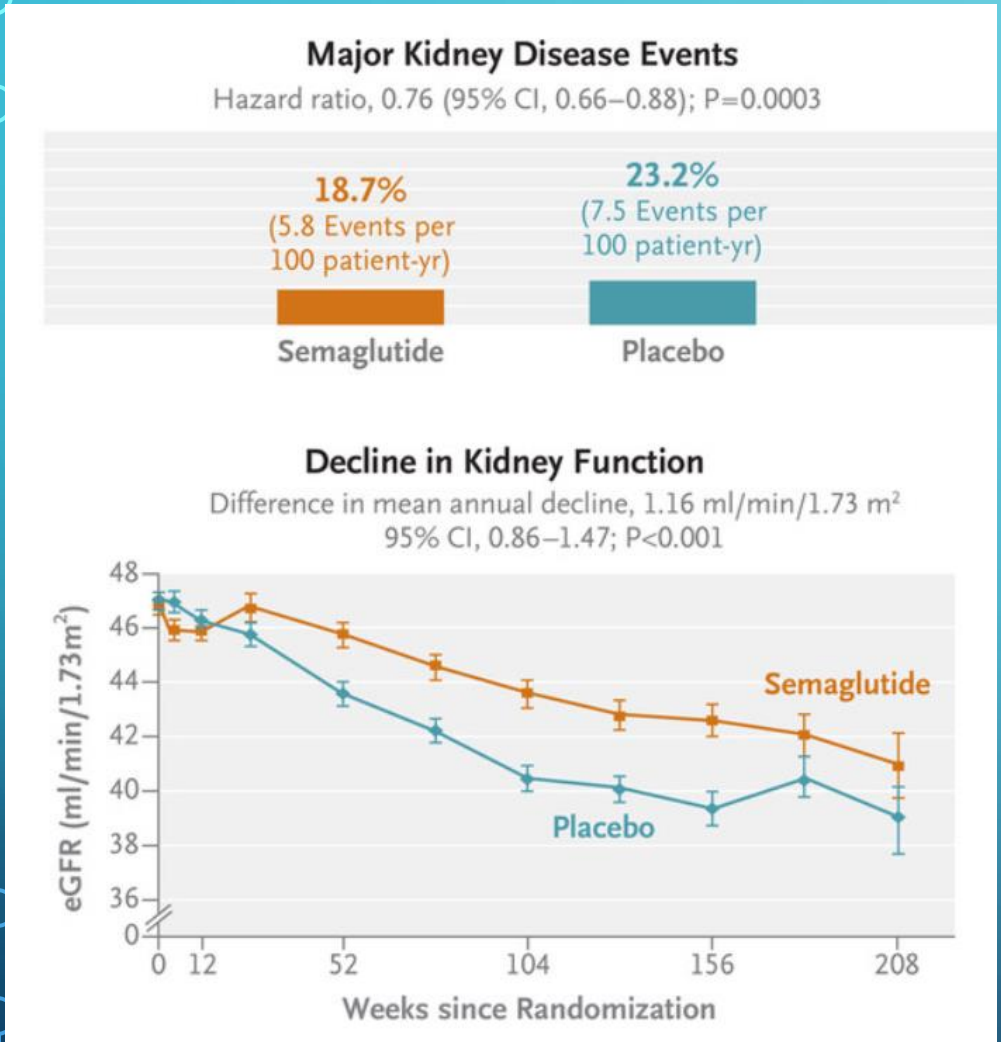
Composite primary endpoint[1] HR 0.76 [0.66, 0.88]$_{95\%\ CI}$	✓	24% RRR
Annual rate of change in eGFR (total slope)[1] ETD 1.16 [0.86, 1.47]$_{95\%\ CI}$	✓	ETD 1.16 mL/min/1.73 m^2/year
MACE[1] HR 0.82 [0.68, 0.98]$_{95\%\ CI}$	✓	18% RRR
All-cause death[1] HR 0.80 [0.67, 0.95]$_{95\%\ CI}$	✓	20% RRR

Additional benefit for HF:

HF event or CV death[2] HR 0.73 [0.62, 0.87]$_{95\%\ CI}$	BENEFIT	27% RRR

eGFR was calculated using the CKD-EPI formula.
CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; RRR, relative risk reduction.
1. Perkovic V, et al. *N Engl J Med.* 2024;391:109–121; 2. Pratley R, et al. *JACC* 2024. DOI: 10.1016/j.jacc.2024.08.004.



CONCLUSIONS

In adults with type 2 diabetes and chronic kidney disease, semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes.