FLOW: The Effects of Semaglutide on Chronic Kidney Disease in Patients with T2DM

SUMMARY

- In patients with **T2DM and CKD** (**eGFR** ≥25mL/min/1.73² AND **urine ACR** >10) on max tolerated ACEi/ARB, semaglutide 1mg subcut weekly vs placebo:
  - ↓ **major kidney disease events**: 18.7% vs 23.2% **NNT≈23**/3.4 year, driven by **≥50% reduction from baseline in eGFR NNT≈36**/3.4 year & **CV death NNT≈39**/3.4yr.
  - ↓ **all-cause mortality**: 12.8% vs 15.8% **NNT≈34**/3.4 year.
- SAE were lower with semaglutide. Discontinuation rates due to AEs were similar between groups; however, real-world data suggest **~40% stop by 12 months**.
- **Bottom Line**: semaglutide subcut 1mg/wk ☎▼ is an option for those with T2DM & CKD. Patient coverage & ability to tolerate GI AEs may limit use.

BACKGROUND

- GLP1 agonists (GLP1a) initially came to market to reduce blood glucose but have since demonstrated cardiovascular benefit in those with T2DM or obesity.[SUSTAIN-6, SELECT]
- **Secondary outcomes and/or post-hoc analyses** of **GLP1 agonist T2DM** landmark trials have shown a decrease in composite kidney outcomes.[SUSTAIN-6, LEADER, REWIND]
- Cochrane meta-analysis (42 RCTs, ~48,000 patients) with **T2DM & CKD** (~1/3 RCTs stage 3-5, most eGFR ≥60) found **GLP1 agonist vs placebo** reduced **all-cause mortality RR 0.85 (95% CI 0.74-0.98)** & **major adverse cardiovascular events RR 0.84 (95% CI 0.73-0.98)** but did not reduce kidney failure (dialysis, transplant) RR 0.86 (95% CI 0.66-1.13) or kidney composite outcomes RR 0.89 (95% CI 0.78-1.02); however, wide confidence intervals lead to an uncertain estimate of effect.[Natale'25 (FLOW results not included)]
- **Semaglutide** has shown the following related to kidney outcomes vs placebo (hypothesis generating, non-CKD RCTs):

Semaglutide subcut **OZEMPIC** ☎▼	**SUSTAIN-6**, N=3297 **with TD2M** (~85% CVD ± CKD, eGFR <60 ~28.5%)	**2º Renal composite** (renal death, CRRT initiation, doubling of SCr and CrCl <45mL/min, urine ACR >33.9mg/mmol): **3.8% (62/1648) vs 6.1% (100/1649) HR 0.64 (0.46 to 0.88)**
Semaglutide subcut **WEGOVY** ✗ ⊗ RxFiles Trial Summary	**SELECT**, N=17,604 **without diabetes**, BMI ≥27 (100% CVD, eGFR ~93, UACR 0.84mg/mmol)	**2º Renal composite** (renal death, CRRT initiation, eGFR <15mL/min, 50% reduction in eGFR, urine ACR >33.9mg/mmol): **1.8% (155/8803) vs 2.2% (198/8801) HR 0.33 (0.3 to 0.36)**
Semaglutide oral **RYBELSUS** ✗ ✆	**SOUL**, N=9650 **with T2DM** (~56% CVD, ~13% CKD eGFR <60, ~27% CVD/CKD)	**2º Renal composite** (renal death, CV death, dialysis/transplant, eGFR reduction ≥50%, eGFR<15): **2.1% vs 2.3% HR 0.91 (0.8-1.05)**

- FDA **expanded subcut semaglutide OZEMPIC indication to ↓ the risk of sustained eGFR decline, ESKD, and CV death in adults with T2DM & CKD** January 2025.[FDA]
- At the time of publication (July 2025), **no GLP1a, including subcut semaglutide OZEMPIC, is indicated by Health Canada to ↓ kidney event risk**.[Product Monograph, Canada]
- The **American Diabetes Association 2025 guideline has incorporated results from FLOW into their recommendations**; whereas other guidelines (Diabetes Canada 2024, KDIGO 2024) were published before results of the **FLOW** RCT were known. Guidelines recommend:
  - **American Diabetes Association, 2025**: *T2DM + CKD (eGFR <60 OR ACR ≥3mg/mmol) on max tolerated ACEi/ARB, an SGLT2 inhibitor or GLP1 agonist with demonstrated benefit should be used for both blood glucose (irrespective of A1c) and for slowing progression of CKD and reduction in cardiovascular events (A).*
  - **Diabetes Canada, 2024**: *consider GP1 agonists in those with T2DM & CKD with an A1c in target or above (ungraded); also use metformin & SGLT2 inhibitor.*
  - **KDIGO, 2024**: *recommend long-acting GLP1 agonist in those with T2DM & CKD who have NOT achieved A1c target with metformin & SGLT2 inhibitor (1B).*
- Potential GLP1a renal MOA: vasoconstriction of afferent arteriole; ↑: natriuresis, tubuloglomerular feedback; ↓: plasma renin activity, renal oxidative stress.[Greco'19]

TRIAL BACKGROUND

DESIGN: randomized, double blind (participants, clinicians, outcome assessors), placebo-controlled, multicentre (37 sites, 28 countries [including Canada]) trial. Primary efficacy and safety analysis was conducted in the intention to treat population (all participants randomized were analyzed). If superiority for the primary outcome was confirmed, then testing of the confirmatory secondary outcomes was performed in a prespecified hierarchical order. Enrollment: June 2019 to May 2021. Trial sponsor: Novo Nordisk (semaglutide **OZEMPIC** manufacturer).

INTERVENTION: **semaglutide OZEMPIC** 1mg vs **placebo** (matched) subcutaneous weekly (average semaglutide dose obtained not published)

- 8-week dose escalation regimen (extended or paused based on tolerability): 0.25mg/week x 4 weeks, then 0.5mg/week x 4 weeks, then 1mg/week

INCLUSION: ≥18 years + T2DM + maximum tolerated/max dose ACEi/ARB x ≥4 weeks + CKD as defined (eGFR calculation - CKD-EPI 2009):

- **eGFR** ≥50 & ≤75mL/min/1.73² AND **urine ACR** >30 & <50mg/mmol (>300 & <5000mg/g)
- **eGFR** ≥25 & <50mL/min/1.73² AND **urine ACR** >10 & <50mg/mmol (>100 & <5000mg/g)

EXCLUSION: A1c >10%, dialysis, congenital/hereditary kidney diseases, personal or first-degree relative history of multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid carcinoma, MI/unstable angina/stroke/TIA within 60 days, New York Heart Association class IV heart failure.

POPULATION n=3533 randomized & at baseline:

- ♂ 70%; age ~67yr (<55yr ~10%, ≥55 to 65yr ~27%, ≥65 to <75 ~45%, ≥75 to <85yr ~18%, ≥85yr ~1%), White ~66%, Europe ~27%, Asia ~26%, North America ~25%.
- **mean eGFR** (randomization & screening) 47mL/min/1.73²; **eGFR distribution**: **≥60 ~20%, ≥45 to <60 ~30%, ≥30 to <45 ~38%**, <30 ~11%; ~6% eGFR ≥75
- **median urine ACR** ~57mg/mmol; **albuminuria category**: A1 (normoalbuminuria) ~3%, A2 (microalbuminuria (~28%), A3 (macroalbuminuria) ~69%.
- A1c ~7.8%, T2DM ≥15 years ~57%, BMI 32, ~90kg, systolic BP ~140, diastolic BP ~76, heart failure 19%, previous MI/stroke ~23%, never smoked ~40%.
- ACEi/ARB ~95%, diuretic ~50%, lipid lowering agent ~80%, insulin ~61%, SGLT2 inhibitor ~16%.

RESULTS

follow-up: 3.4 years

EFFICACY ENDPOINTS	Semaglutide OZEMPIC N=1767	Placebo N=1766	Hazard Ratio (95% Confidence Interval)	ARR¥	NNT¥ / ~3.4 years
PRIMARY OUTCOME – Composite (kidney failure, ≥50% reduction from baseline in eGFR, death from kidney or CV causes)					
Major kidney disease events	331 (18.7%)	410 (23.2%)	**0.76 (0.66 to 0.88)**	**~4.5%**	**~23**
***Primary Outcome Composite Components**					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3%)	213 (12.1%)	0.73 (0.59 to 0.89)	**~2.8%**	**~36**
Persistent eGFR <15	92 (5.2%)	110 (6.2%)	0.8 (0.61 to 1.06)	-	-
Initiation of kidney-replacement therapy	87 (4.9%)	100 (5.7%)	0.84 (0.63 to 1.12)	-	-
Kidney-related death	5 (0.3%)	5 (0.3%)	0.97 (0.27 to 3.49)	-	-
CV death	123 (7%)	169 (9.6%)	0.71 (0.56 to 0.89)	**~2.6%**	**~39**
SECONDARY OUTCOMES					
Annual rate of eGFR change	-2.19	-3.36	1.16 (0.86 to 1.47)#	P<0.001	
MACE composite*	212 (12%)	254 (14.4%)	**0.82 (0.68 to 0.98)**	**~2.4%**	**~42**
*CV death	123 (7%)	169 (9.6%)	0.71 (0.56 to 0.89)	**~2.6%**	**~39**
*Nonfatal MI	52 (2.9%)	64 (3.6%)	0.8 (0.55 to 0.1.15)	-	-
*Nonfatal stroke	63 (3.6%)	51 (2.9%)	1.22 (0.84 to 1.77)	-	-
All-cause mortality	227 (12.8%)	279 (15.8%)	**0.8 (0.67 to 0.95)**	**~3%**	**~34**
Death (non-CV, non-kidney)	99 (0.%)	105 (0.%)	0.93 (0.7 to 1.22)#	-	-
uACR wk 104 to baseline ratio	0.6	0.88	0.68 (0.62 to 0.75)#	-	-
A1c baseline to week 104	-0.87%	-0.06%	-0.81% (-0.9% to -0.72%)#	-	-
Weight, baseline to week 104	-5.55kg	-1.45kg	-4.1kg (-4.56 to -3.65)#	-	-

- Primary composite results driven by ≥50% eGFR reduction from baseline & CV death.
- Initial drop in eGFR ~2mL/min/1.73m² during first 12 weeks of therapy.
- Subgroup analysis of primary composite outcome showed consistent benefit for semaglutide vs placebo based on the point estimate (note, CIs did cross HR 1).
- North American subgroup was neutral and imprecise HR 0.98 (95% CI 0.74-1.13) which is consistent with other GLP1a RCTs. [SUSTAIN-6, REWIND, LEADER] Possible GLP1a benefit may not be realized in North American patients given subgroup data? see RxFiles: Q&A.
- **FLOW** is the only semaglutide subcut RCT to show ↓in all-cause mortality (result was NS in **SUSTAIN-6**). Others: liraglutide **NNT≈72**/3.8 years, semaglutide oral had a non-significant primary outcome but showed a ↓all-cause mortality.

A1c=glycosylated hemoglobin **ARR**=absolute risk reduction **CI**=confidence interval **CV**=cardiovascular **eGFR**=estimated glomerular filtration rate **HR**=hazard ratio **MACE**=major adverse cardiovascular events **MI**=myocardial infarction **N**=population **NNT**=number needed to treat **NS**=non-signifigant **UACR**=urine albumin to creatinine ratio. **¥** calculated by RxFiles.

SAFETY ENDPOINTS	Semaglutide OZEMPIC N=1767	Placebo N=1766	P value¥	ARR/ ARI¥	NNT/ NNH ~3.4 years¥	COMMENTS
Serious adverse event	877 (49.6%)	950 (53.8%)	P=0.015	4.2%	~24	- ITT analysis used which likely minimizes AE rates (per protocol preferred for safety). - Serious adverse events were higher in placebo arm which is consistent with other trials GLP1 agonist trials e.g. dulaglutide,[REWIND] semaglutide.[SUSTAIN-6] - Ongoing post-marketing surveillance to assess safety signals e.g. ileus added to monograph based on reports in 2023.[FDA] - Hypoglycemia definition: severe cognitive impairment requiring external assistance.
Serious adverse event, **GI**	95 (5.4%)	94 (5.3%)	P=0.997	-	-	
Serious adverse event, **eye**	53 (3%)	30 (1.7%)	P=o.0015	-	-	
Discontinuation due to adverse event*	233 (13.2%)	211 (11.9%)	P=0.661	-	-	
Diabetic retinopathy	402 (22.8%)	398 (22.5%)	P=0.911	-	-	
Acute kidney failure	172 (9.7%)	182 (10.3%)	P=0.61	-	-	
Malignant tumor	120 (6.8%)	104 (5.9%)	P=0.545	-	-	
Acute gallbladder disease	32 (1.8%)	39 (2.2%)	P=0.47	-	-	
Acute pancreatitis	10 (0.6%)	7 (0.4%)	P=0.628	-	-	
Severe hypoglycemia episodes	47	46	HR 1.02 (95%CI 0.62 to 1.67)			

ARI=absolute risk increase **ARR**=absolute risk reduction **GI**=gastrointestinal **N**=population **NNH**=number needed to harm **NNT**=number needed to treat. **¥** calculated by RxFiles.
*Driven by discontinuation due to GI disorders (semaglutide 4.5% vs placebo 1.1%)

STRENGTHS, LIMITATIONS, & UNCERTAINTIES [6-11]

STRENGTHS:

- Addressed an important question – does semaglutide benefit patients with T2DM & CKD – following positive secondary outcome exploratory results.[SUSTAIN-6, SELECT]
- Risk of confounding was limited by: randomization with allocation concealment, similar baseline characteristics between study groups, & ITT analysis conducted.
  - Minority of participants did not complete trial, semaglutide: 43 (2.4%) & placebo 58 (3.3%); unknown vital status, semaglutide: 8 (0.5%) & placebo: 14 (0.8%).
- While multiple outcomes tested, type 1 error (positive result due to chance) was limited via adjustment for multiplicity & prespecified hierarchical testing order.

LIMITATIONS:

- Inclusion criteria were limiting e.g. of N=5,581 individuals screened N=3,533 randomized, indicating 63% of eligible patients were included in the study. Reasons why patients failed screening were not reported. **Many patients have an A1c >10% who would have been excluded from this trial**.
- Limited high-risk kidney populations included e.g. <1% American Indian or Alaska Native.
- Multiple opportunities for patient, clinician, or outcome assessor unblinding due to differences in active drug vs placebo e.g. **GI adverse events** (incidence and potential impact on dose escalation), **weight loss (~4kg difference), A1c lowering (~0.8% difference)**.
- Median dose of semaglutide achieved by patients was not reported. GI adverse events can limit whether patients are able to achieve 1mg subcut weekly.
- Primary efficacy composite outcome included both patient-important e.g. kidney-related death & non-patient important (surrogate, e.g. persistent ≥50% eGFR reduction from baseline). Results were driven by **persistent ≥50% eGFR reduction** from baseline and **CV death** while other patient-important kidney outcomes (i.e. persistent eGFR <15, initiation of kidney-replacement therapy, kidney-related death) were **not significant**.
- **FLOW** was stopped early for benefit based on prespecified stopping criteria (~67% of planned events had accrued when the trial was stopped; published results were based on 3 additional months of follow-up and 87% of planned events).[Kaul'24] Trials that stop early for benefit tend to overestimate benefit by up to ~30% depending on the number of events accrued.[Bassler'10, Wang'16] They may also underestimate the rate of infrequent events.[Kaul'24]
  - Landmark trials assessing CKD have also been stopped early for benefit i.e. canagliflozin **CREDENCE**, dapagliflozin **DAPA-KIDNEY**, empagliflozin **EMPA-KIDNEY**.

UNCERTAINITIES:

- While majority were on a "maximally tolerated or max dose" of ACEi/ARB x ≥4 weeks at baseline (~95%), doses reached were not reported. In practise, how much should you push the ACEi/ARB dose prior to adding semaglutide?
- Mineralocorticoid receptor agonist (MRA) use was not reported and ~19% of patients had HF at baseline. Were patients on a steroidal MRA which impacted outcomes? The non-steroidal MRA, finerenone, was likely not used during this trial as FDA approval was July 2021 and trial enrollment ended May 2021.[Lexicomp]
- CKD was not considered a compelling indication for an SGLT2 inhibitor during the timeframe of the trial so few patients on baseline SGLT2 inhibitor (~16%). SGLT2i use for those with T2DM and CKD is now considered standard of care.
  - **FLOW** primary composite subgroup analysis found those using an SGLT2i (N=550, ~16%) had a HR 1.07 (95% CI 0.69-1.67) which is difficult to determine where the estimated benefit would lie given the wide confidence interval. Those not using an SGLT2i (N=2983, ~84%) had a HR 0.73 (95% CI 0.63- 0.85).[Mann'24]
- Primary efficacy composite outcome included both kidney outcomes and CV death. Are these appropriate to combine?
  - Previous semaglutide trials (**SUSTAIN-6**, **SELECT**) did not include CV death in composite renal outcome (secondary outcomes, exploratory).
  - Other trials (**SOUL**, **CREDENCE**, **DAPA-KIDNEY**, **EMPA-KIDNEY**) did include CV death in composite primary outcome.
- Semaglutide may be used in eGFR ≥15 and dialysis. **FLOW** enrolled eGFR ≥25 (~11% eGFR <30) & excluded those on dialysis. What is the role in these patients?
- **Adherence to semaglutide was ~89% – what would this be in the real world**? In those with T2DM, USA/Europe cohort data has found ~40% discontinue GLP1 agonist at 12 months.[Weiss'22, Do'24] In addition, ~26% of total participants in **FLOW** permanently discontinued semaglutide or placebo.
- T2DM is associated with many people experiencing "diabetes distress" (negative emotions and burden of self-management related to living with diabetes).[Diabetes Canada, Diabetes & Mental Health] What impact does adding yet another drug to their regimen have in those with T2DM + CKD? E.g. BP management + A1c/blood glucose management + ACEi/ARB + SGLT2 inhibitor + statin + metformin ± finerenone…
- **FLOW** was only conducted in those with T2DM. What impact would semaglutide have in those without T2DM and CKD e.g. obesity and CKD?

COST: semaglutide **OZEMPIC** subcut ☎ ▼x 3 months (0.25mg/wk $385; 0.5mg/wk $720; 1mg/wk $720; includes: acquisition cost + mark up + dispensing fee)
SK Drug Plan: ☎ **EDS** (possible online adjudication) – T2DM in combination with metformin & sulfonylurea, when diet/exercise do not achieve adequate glucose control.
NIHB: ▼ **open benefit** – therapeutic note – T2DM in combination with max tolerated metformin, when diet/exercise do not achieve adequate glucose control.

RxFILES RELATED LINKS

- GLP1 agonist Adverse Events Tool (health care professional facing): SGLT2 Inhibitors-GLP1-Adverse Effects-InfoGraphic.pdf
- RxFiles Chart: Perspectives on Diabetes and the Kidneys: Diabetes & The Kidneys | RxFiles
- RxFiles Chart: Diabetes Agents Colour Comparison: Anti-Hyperglycemic Agents Comparison | RxFiles

☎=Exception Drug Status (EDS) in SK ✗ =Non-formulary in SK ✆=prior approval for non-insured health benefits for First Nations ⊗=not covered by NIHB ▼=Covered by NIHB & ONLY for those drugs which have SK Formulary restrictions such as EDS or non-formulary status ♂=male **A1c**=glycosylated hemoglobin **ACR**=albumin to creatinine ratio **AE**=adverse event(s) **ARI**=absolute risk increase **ARR**=absolute risk reduction **BMI**=body mass index **BP**=blood pressure **CRRT**=continuous renal replacement therapy **CI**=confidence interval **CKD**=chronic kidney disease **CrCL**=creatinine clearance **CRRT**=continuous renal replacement therapy **CV**=cardiovascular **CVD**=cardiovascular disease **eGFR**=estimated glomerular filtration rate **ESKD**=end stage kidney disease **FDA**=US Food and Drug Administration **GI**=gastrointestinal **GLP1**=glucagon-like peptide-1 **HR**=hazard ratio **ITT**=intention to treat analysis **kg**=kilogram **MACE**=major adverse cardiovascular events **MI**=myocardial infarction **MOA**=mechanism of action **MRA**=mineralocorticoid receptor antagonist **N**=population **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-signifigant **RCT**=randomized controlled trial **RR**=relative risk **SAE**=serious adverse event **SCr**=serum creatinine **SGLT2i**=sodium-glucose cotransporter-2 inhibitor **subcut**=subcutaneous **T2DM**=type 2 diabetes mellitus **UACR**=urine albumin to creatinine ratio **yr**=year(s).

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Lexidrug: Finerenone. Finerenone (Lexi-Drugs) - UpToDate® Lexidrug™.

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Extras:

- **Subcutaneous (subcut) semaglutide OZEMPIC** ☎ ▼ has been on the Canadian market since 2018 for people with T2DM (USA: 2017). In the landmark RCT, **SUSTAIN-6**, n=3297 people with TD2M (~85% established CVD ± CKD, eGFR <60 ~28.5%). Semaglutide **OZEMPIC 0.5 to 1mg subcut** vs placebo over 2.1 years found:
  - Primary outcome (CV death, nonfatal MI, nonfatal CVA): HR 0.74 (0.58 to 0.95) **NNT≈44/2.1 years**
  - CV death: HR 0.98 (0.65 to 1.48), All-cause death 1.05 HR (0.74 to 1.5)
  - **Renal composite** (renal death, CRRT initiation, doubling of SCr and CrCl <45mL/min, UACR >33.9mg/mmol): **3.8% (62/1648) vs 6.1% (100/1649) HR 0.64 (0.46 to 0.88) *hypothesis-generating** as not adjusted for multiplicity
    - Renal composite drive by persistent microalbuminuria 2.7% (44/1648) vs 4.9% (81/1649) HR 0.54 (0.37 to 0.77)
- **Oral semaglutide RYBELSUS ✗** ✆ has been on the Canadian market since 2020 for people with T2DM (USA: 2019). In the landmark RCT, **PIONEER-6**, n=3183 people with TD2M (~85% established CVD or CKD, ~27% eGFR<60mL/min, ~33% microalbuminuria or proteinuria at baseline). Semaglutide **RYBELSUS 14mg po daily** vs placebo over 1.3 years found:
  - Primary outcome (CV death, nonfatal MI, nonfatal CVA): HR 0.79 (0.57 to 1.11) [NS]
  - CV death: HR 0.49 (0.27-0.92), All-cause death: HR 0.51 (0.31-0.84); *hypothesis-generating as primary outcome NS
  - **Renal outcomes: not studied**
- **Subcut semaglutide WEGOVY ✗** ⊗ has been on the Canadian market since 2025 for people with obesity (USA: 2021). In the landmark RCT, **SELECT** (RxFiles Trial Summary), n=17,604 people a BMI ≥27kg/m^2 without diabetes (100% established CVD, mean eGFR ~93mL/min, median UACR ~0.84mg/mmol at baseline) found semaglutide **WEGOVY 2.4mg subcut weekly** vs placebo over 3.3 years:
  - Primary outcome (CV death, nonfatal MI, nonfatal CVA): HR 0.8 (0.72 to 0.9) **NNT≈67/3.3 years**
  - CV death: HR 0.85 (0.71 to 1.01), All-cause death: HR 0.81 (0.71-0.93) *hypothesis-generating as CV death NS
  - **Renal composite** (renal death, CRRT initiation, eGFR <15mL/min, 50% reduction in eGFR, UACR >33.9mg/mmol): **1.8% (155/8803) vs 2.2% (198/8801) HR 0.33 (0.3 to 0.36) *hypothesis-generating** as CV death NS per statistical analysis
    - Renal composite was not broken down so unsure what drove outcome; however, overall event rate was low.