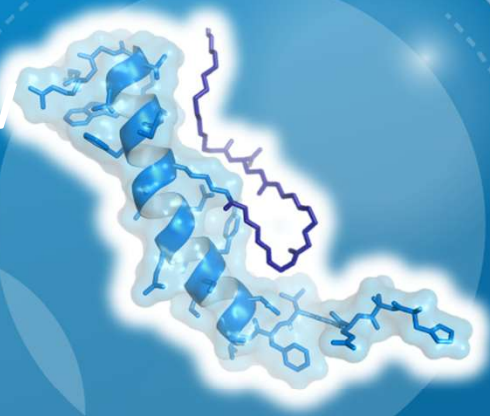
GLP1-RA Therapy through a new lense

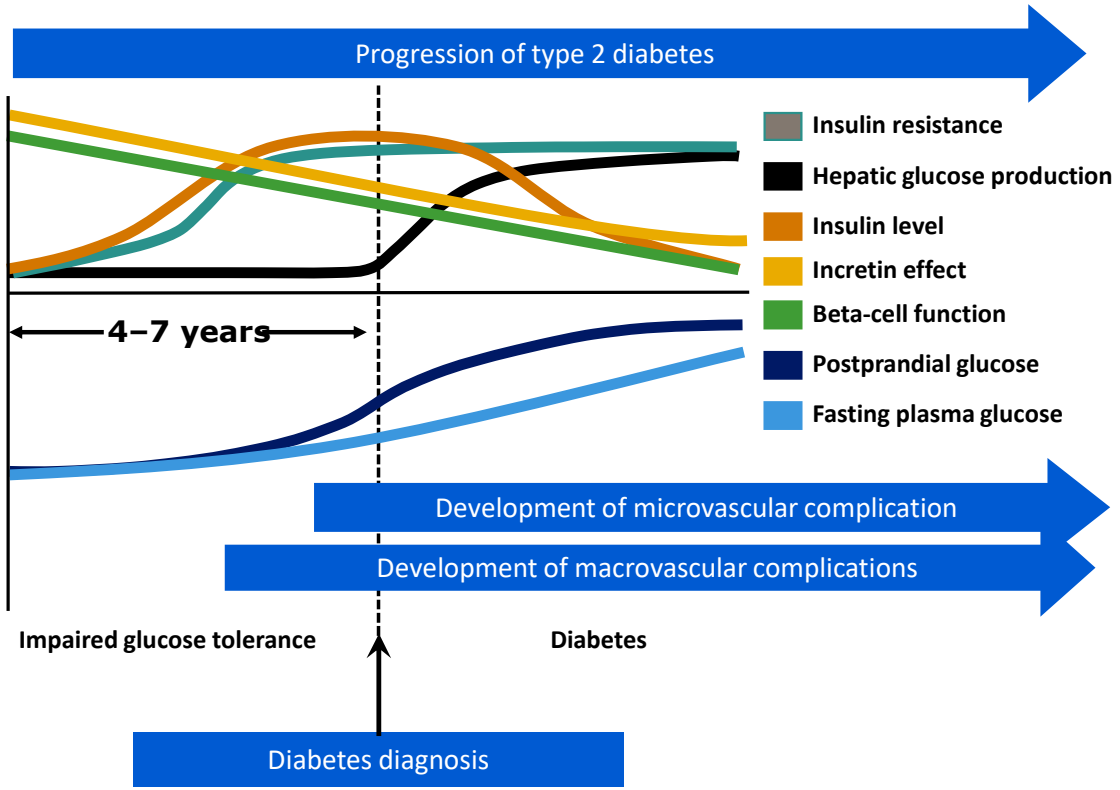
GLP1-RA therapy in 2025



Michelle Nel

Regional Medical Advisor Cardio-Metabolic and Kidney disease

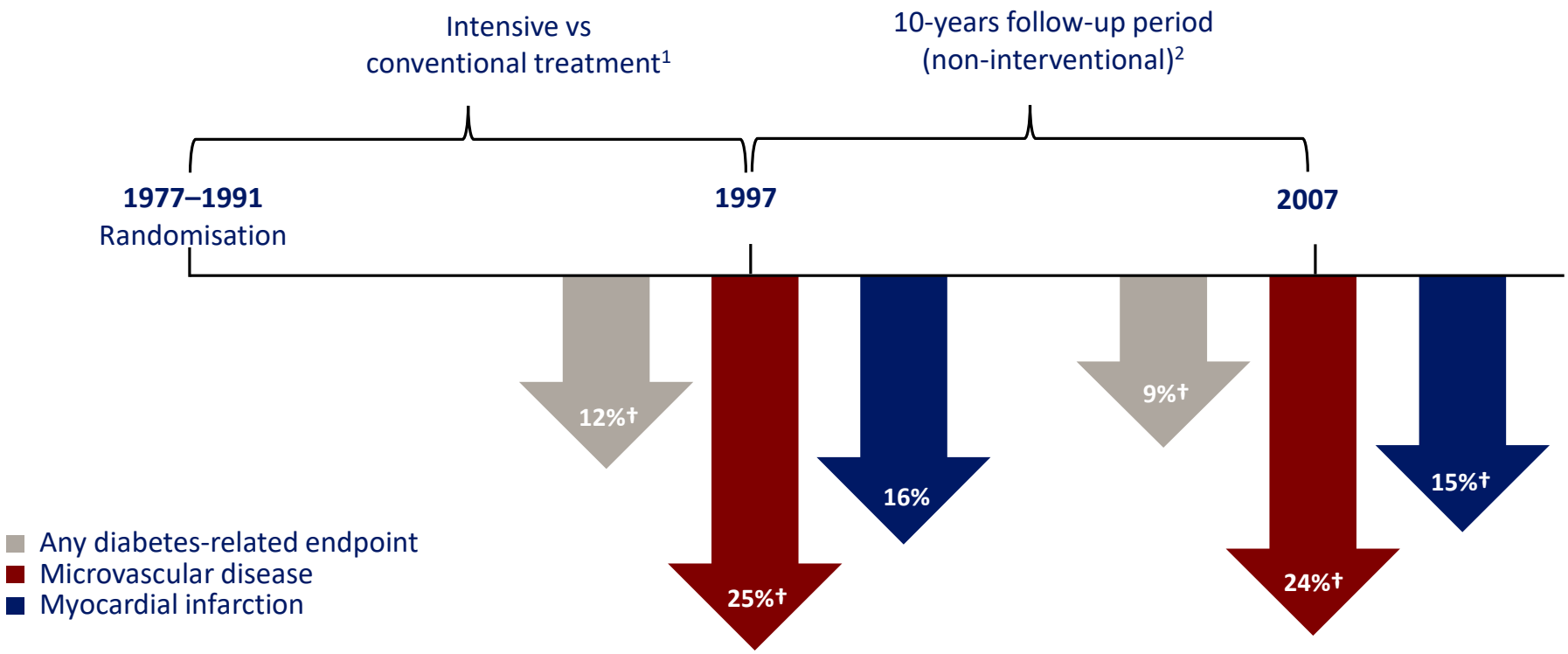
Progression of type 2 diabetes



Adapted from Kendall DM et al. *Am J Med* 2009:122(6 Suppl):S37–S50

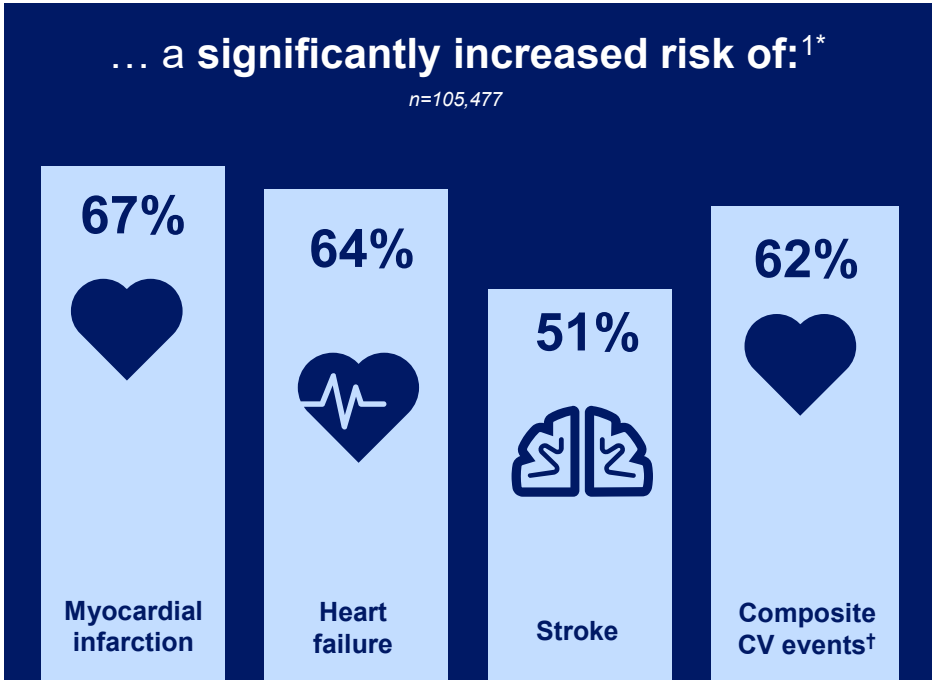
The benefits of early tight control: UKPDS 10-year post-trial follow-up

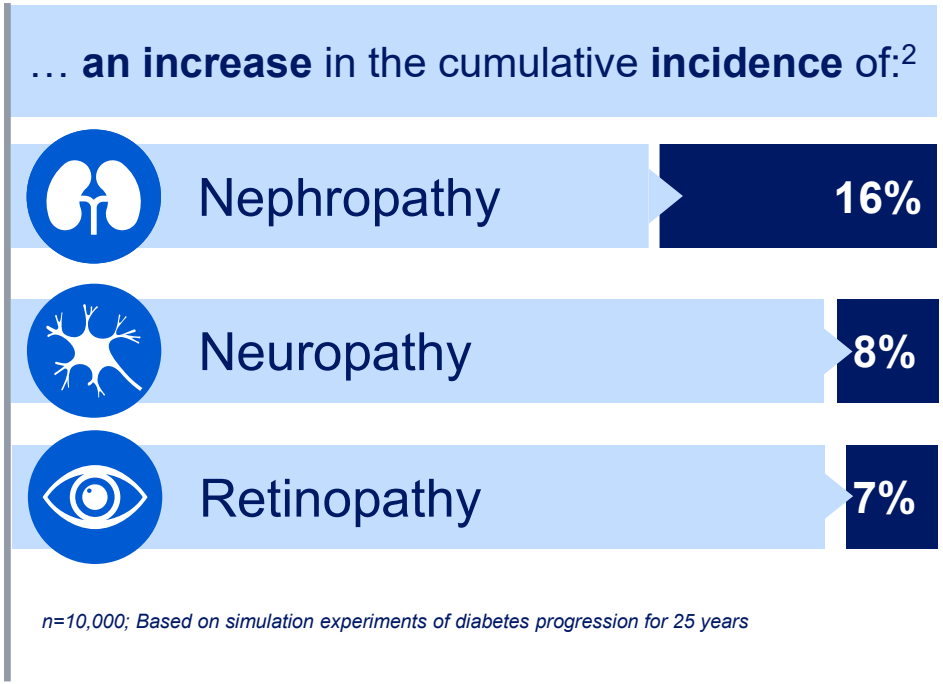
Reduction in endpoints on intensive treatment versus conventional treatment*



*Data from the sulphonylurea-insulin group. †p<0.05; intensive vs conventional treatment.
UKPDS, United Kingdom Prospective Diabetes Study
UK Prospective Diabetes Study Group. Lancet 1998;352:837–53; Holman RR, et al. N Eng J Med 2008;359:1577–89

One Year of poor glycaemic control in people with T2D can result in …





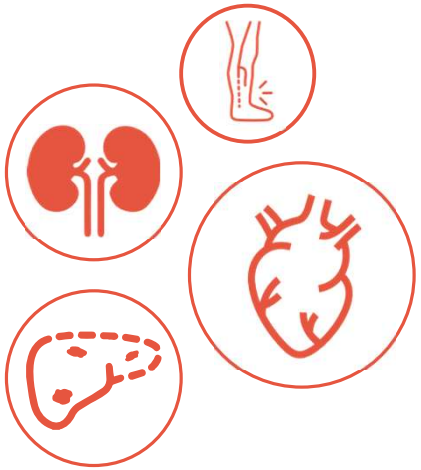
*Compared with patients with HbA_{1c} <7%; †The composite CV events was based on the occurrence of either MI, HF or stroke
CV, cardiovascular; HbA_{1c}, glycated haemoglobin; HF, heart failure; MI, myocardial infarction; T2D, type 2 diabetes
1. Paul SK, et al. Cardiovasc Diabetol. 2015;14:100–10. 2. Correa MF, et al. J Gen Intern Med. 2019;34:372–78

INTRODUCTION

Chronic CKM diseases are a consequence of complex and interlinked pathophysiological processes

Each condition can increase the risk of another[2,3]

These are all important risk factors for end-organ damage[4-7]



Weight gain, **adiposity** and **inflammation** are conditions that can initiate a **decline in metabolic health**[1,2]

Adiposity and **insulin resistance** can promote **hypertension**, and are associated with **dyslipidaemia** and **T2D** as well as **inflammation**[4-7]

The **association** of **T2D** and **obesity** with CKM diseases such as **CKD, CVD, PAD** and **MASH** has been well-documented[1,8]

CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; MASH, metabolic dysfunction-associated steatohepatitis; T2D, type 2 diabetes; PAD,peripheral artery disease

1. Lingvay I, et al. Lancet. *2022;399;394-405. 2. Li M, et al.* Sig Transduct Target Ther. *2022;7:216. 3. Schönknecht YB, et al.* Eur J Nutr. *2022; doi: 10.1007/s00394-022-02870-7. 4. Tasic I, et al.* Front. Biosci. *2018, 10(1), 166–174. 5. Musunuru K.* Lipids. *2010;45(10):907–14. 6. Mendrick DL, et al.* Toxicol Sci. *2018;162(1):36–42. 7. Sorriento D, et al.* Int J Mol Sci. *2019 Aug 9;20(16):3879. 8. Ndumele CE, et al. Circulation.2023;* https://doi.org/10.1161/CIR.0000000000001184

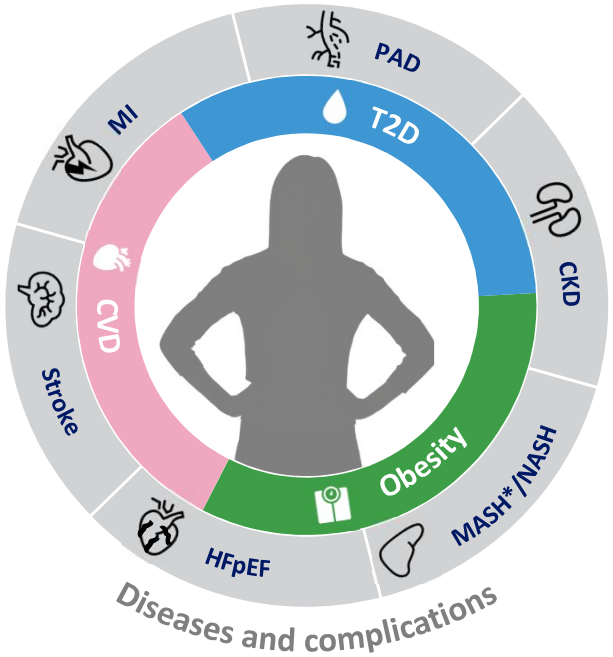
Chronic cardiometabolic diseases rarely occur in isolation

Chronic cardiometabolic diseases **share underlying risk factors**

RISK FACTORS

- Hypertension[1]
- Hyperglycaemia[1]
- Pro-inflammatory state[1,2]
- Dyslipidaemia[1,3]
- Abdominal adiposity[1]

These risk factors can **increase multimorbidity** over time, leading to **severe outcomes**[4–6]



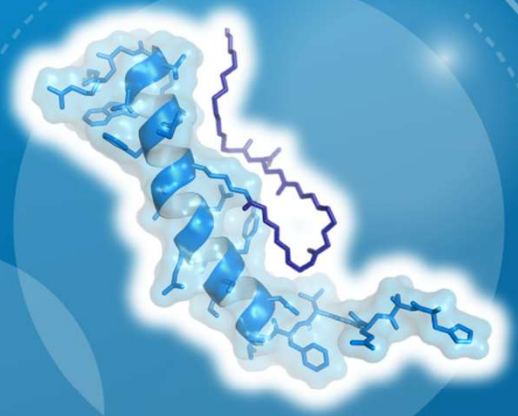
Management of people with cardiometabolic diseases requires a **holistic, multifactorial, person-centric** approach[7]

**MASH formerly known as NASH. CKD, chronic kidney disease; CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; MASH, metabolic dysfunction-associated steatohepatitis; MI, myocardial infarction; NASH, non-alcoholic steatohepatitis; PAD, peripheral artery disease.*

1. Mendrick DL et al. Toxicol Sci 2018;162:36–42; 2. Musunuru K. Lipids 2010;45:907–14; 3. Schönknecht YB et al. Eur J Nutr 2022;61:3077–83; 4. Kadowaki T et al. Diabetes Obes Metab 2022;24:2283–96; 5. Targher G et al. Lancet Gastroenterol Hepatol 2021;6:578–88; 6. Lingvay I et al. Lancet 2022;399:394–405; 7. Davies MJ et al. Diabetes Care 2022;45:2753–86.

What’s NEW with GLP1-RA

The Semaglutide Story



TYPE 2 DIABETES

Semaglutide is a simple-to-use treatment option with a well-established efficacy and tolerability profile, with proven CV and kidney benefits

Semaglutide efficacy and tolerability have been extensively demonstrated in PwT2D[1-17]

In clinical trials		In RWE
>30 RCTs		**>8** RWE studies
>26,000 patients		**>8,500** patients

Totalling over **22 million** patient-years of experience for all semaglutide across indications[17]

Semaglutide vs placebo reduced

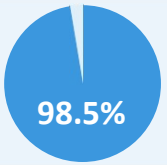
Injectable OW 1.0 mg

Risk of **MACE by 26%** in PwT2D and high CV risk[18‡]

Risk of **CKD progression by 24%** in PwT2D and CKD[19]

Oral

Risk of **MACE by 14%** in PwT2D and established CVD and/or CKD[20]

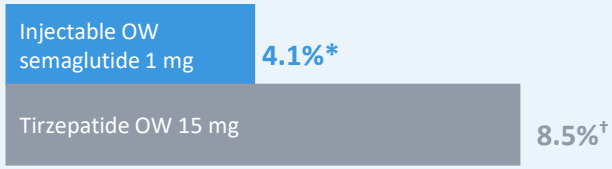


of patients find the pen easy to use[21]

Tolerability

in adults living with T2D

Fewer patients **discontinued** treatment due to AEs with semaglutide versus tirzepatide[22]



Proportion of patients discontinuing treatment due to AEs

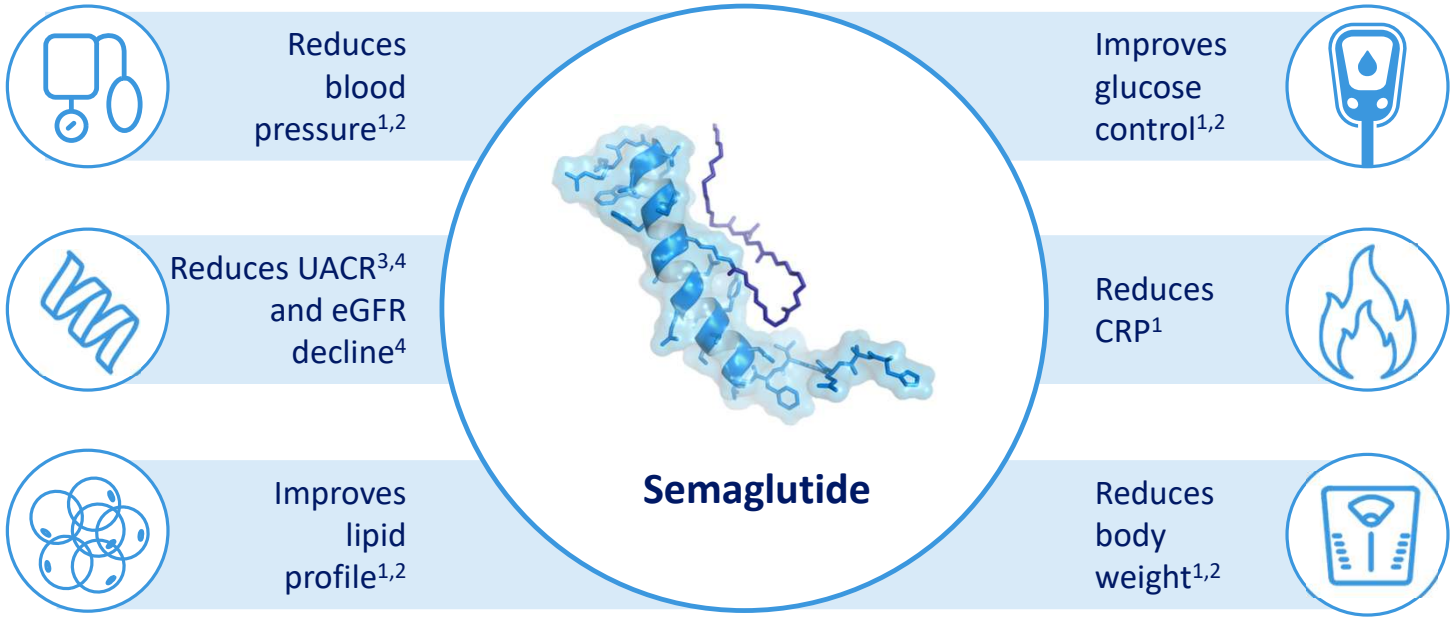
*n=469; †n=470; ‡HR: 0.74; 95% CI, 0.58-0.95.

AE, adverse event; CKD, chronic kidney disease; CV, cardiovascular; MACE, major adverse cardiovascular event; OW, once-weekly; PwT2D, people with type 2 diabetes; RCT, randomised controlled trial; RWE, real-world evidence; T2D, type 2 diabetes.

1. Yale JF, et al. Diabetes Obes Metab. *2021;23(10):2269-78. 2. Rajamand Ekberg N, et al.* Prim Care Diabetes. *2021;S1751-9918(21)00112-1. 3. Rudofsky G, et al.* Diabetes Res Clin Pract. *2021;178:108931. 4. Holmes P, et al.* Diabetes Ther. *2021;12:2891-905. 5. Jain AB, et al.* Diabetes Ther. *2021;12:527-36. 6. Wolffenbuttel BHR, et al.* Adv Ther. *2022;21:1-14. 7. Menzen M, et al.* Exp Clin Endocrinol Diabetes. *2023. doi: 10.1055/a-2007-2061. 8. Bellido V, et al.* J Clin Med. *2022;11:4938. 9. Crabtree TSJ, et al.* Diabetes Obes Metab. *2022;24:1398-401. 10. Catrina, SB. et al. PIONEER REAL Sweden. Diabetes Ther 15, 2079–2095 (2024); 11. Jain AB et al.. PIONEER REAL Canada. Diabetes Obes Metab. 2024 May;26(5):1799-1807. 12. van Houtum W et al. PIONEER REAL Netherlands. Diabetes Ther. 2024 Aug;15(8):1749-1768. 13. Kick A et al.. The PIONEER REAL Switzerland Multicentre, Prospective, Observational Study. Diabetes Ther. 2024 Mar;15(3):623-637; 14. Yabe D et al. PIONEER REAL Japan. J Diabetes Investig. 2024 Aug 22. doi: 10.1111/jdi.14291; 15. Saravanan P et al. PIONEER REAL UK. 16. Aroda VR et al. The IGNITE study. Diabetes Obes Metab. 2021 Sep;23(9):2177-2182. 17. Novo Nordisk data on file. 18. Marso S, et al.* N Engl J Med. *2016;375:1834-44. 19. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347.* 20. *SOUL Company announcement. 21. Philis-Tsimikas A, et al.* Adv Ther. *2013;30(6):607-22. 22. Frias, et al.* N Engl J Med. *2021;385(6):503-15.*

TYPE 2 DIABETES

Semaglutide may help prevent CVD through early management of modifiable CV risk factors

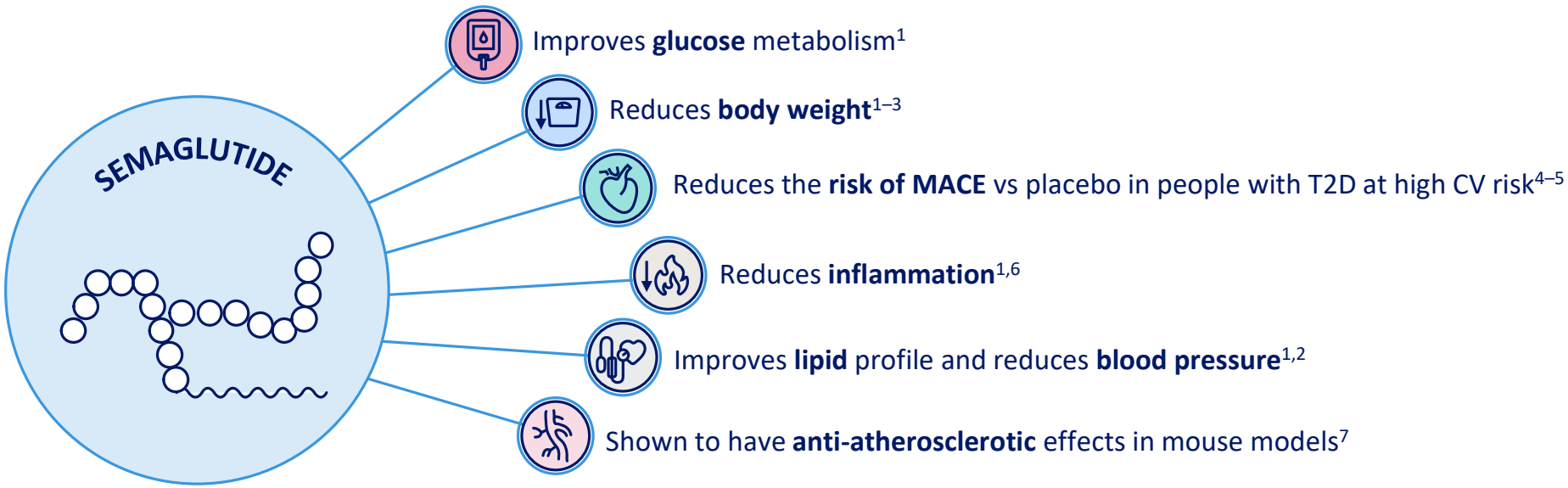


Global guidelines recommend **early use of T2D medication** to **address CV risk factors**[5,6]

CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio

1. Wilding JPH, et al. N Engl J Med. *2021;384:989-1002. 2. Yanai H, et al.* Cardiol Res. *2022;13:303-8. 3. Mann JFE, et al.* Lancet Diabetes Endocrinol. *2020;8:880-93. 4. Novo Nordisk. Company Announcement: Semaglutide 1.0 mg demonstrates 24% reduction in the risk of kidney disease-related events in people with type 2 diabetes and chronic kidney disease in the FLOW trial. 05 March 2024. Available at: https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=167028 5. Cosentino F, et al.* Eur Heart J. *2020;41:255-323. 6. Das SR, et al.* J Am Coll Cardiol. *2020;76(9):1117-1145.*

Semaglutide has a beneficial effect on CV risk factors



CV, cardiovascular; MACE, major adverse cardiovascular events.

1. Wilding JPH et al. N Engl J Med 2021;384:989–1002; 2. Aroda VR et al. Diabetes Metab 2019;45:409–18; 3. Marso SP et al. N Engl J Med 2016;375:1834–44; 4. Husain M et al. N Engl J Med 2019;381:841–51; 5. Husain M et al. Diabetes Obes Metab 2020;22:442–51; 6. Knudsen LB, Lau J. Front Endocrinol (Lausanne) 2019;10:155; 7. Rakipovski G et al. JACC Basic Transl Sci 2018;3:844–57.

CARDIOVASCULAR DISEASE

Semaglutide is a recommended first-line GLP-1 RA with proven CVD benefits in PwT2D at high risk of ASCVD[3]

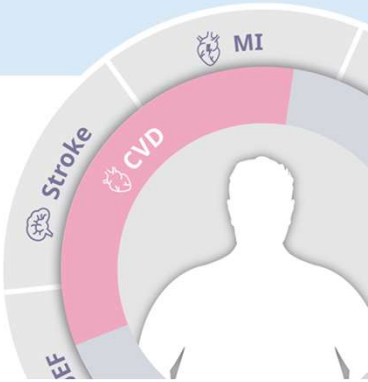
Semaglutide reduces the risk of MACE in PwT2D at high CV risk[1,2]

Injectable semaglutide 1.0 mg significantly reduced the risk of **MACE*** by **26%** in PwT2D[ǂ] versus placebo[1]

Oral semaglutide significantly reduced the risk of **MACE*** by **14%** in PwT2D[ǂ] versus placebo on top of standard of care (incl. up to 49% receiving a SGLT2i at some point during the trial) [2]

Semaglutide improves **maximum walking distance**[‡] by **13%** (median **26 meters**, mean **40 meters**) in PwT2D and PAD[4]

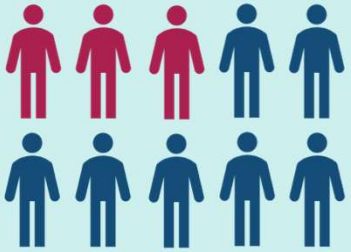
The on-going **ASCEND PLUS trial** will further investigate CV outcomes with **oral semaglutide** in **PwT2D** with **no previous MI/stroke**[5]



** Time from randomisation to first occurence of CV death;, non-fatal myocardial infarction or non-fatal stroke. ǂ The SUSTAIN 6 trial (Injectable semaglutide 1.0 mg) included patients with established CVD (Previous MI, stroke, PAD or HF) and/or established CKD or high risk of CV. The SOUL trial (oral semaglutide) included patients with established CVD (previous MI, stroke or PAD). ‡Change in maximum walking distance on a constant load treadmill test (at constant speed and incline (3.2 km/h, 12%) at week 52.*
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2i, sodium-glucose co-transporter 2 inhibitor; PwT2D, people with type 2 diabetes; PAD, peripheral artery disease
1. Marso S, et al. N Engl J Med. *2016;375:1834-44. 2. SOUL company announcement 3. Davies M, et al.* Diabetes Care. *2022;45:2753-86. 4. Novo Nordisk, data on file. 5. Study Details | A Study of Cardiovascular Events iN Diabetes Plus | ClinicalTrials.gov*

The prevalence of PAD is higher in people with T2D than in those without

The prevalence of concomitant PAD in people with T2D are **13-29%**, and people with diabetes are **twice as likely to develop PAD** compared to those without diabetes[1-2]



Glucose intolerance is associated with a >20% prevalence of an abnormal ankle brachial index* relative to 7% in those with normal glucose tolerance[2]

>20%

Approximately 50–70% of people with chronic limb-threatening ischaemia have diabetes[3]

50–70%

**Ankle brachial index is a diagnostic tool for PAD where a lower value indicates a more severe disease state.*
CV, cardiovascular; PAD, peripheral arterial disease.
1. Verma S et al. Diabetes therapy 2024; 15: 1893-1961; 2. Hirsch AT et al. JAMA. 2001;286:1317-1324; 3. Marx N et al. Eur Heart J 2023:44:4043–140.

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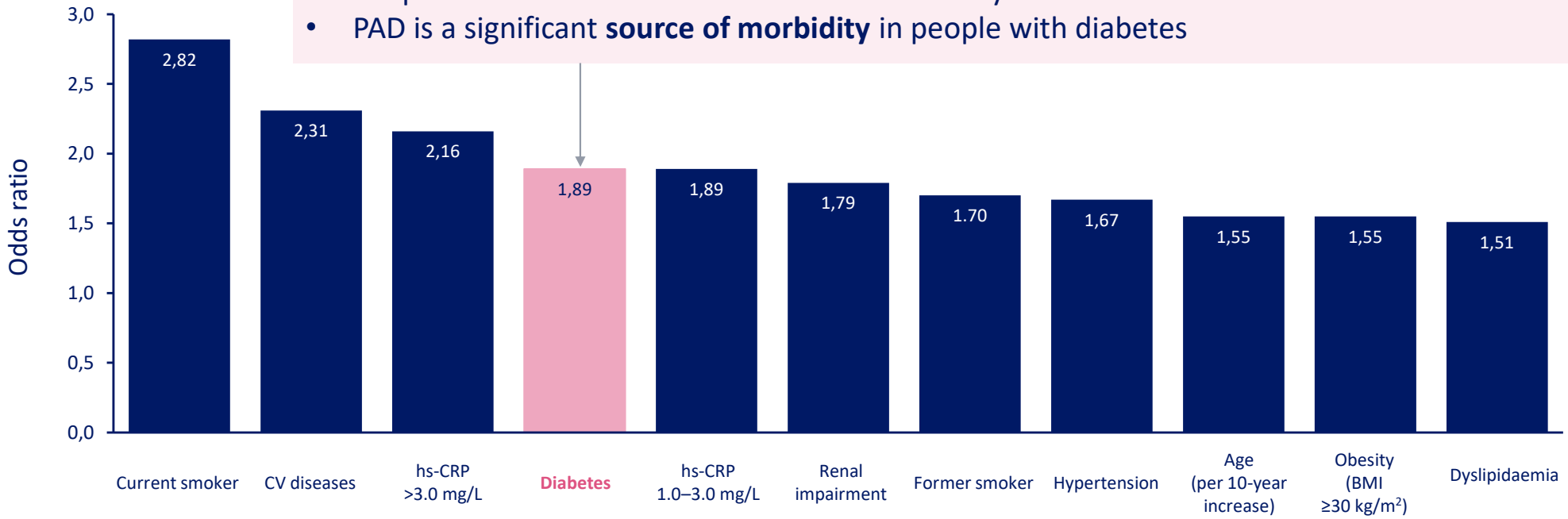
Diabetes is one of the main risk factors of PAD

Worldwide estimates from a meta-analysis of **118 studies from low- and high-income countries**

- People with diabetes were **1.89 times more** likely to have PAD than those without
- PAD is a significant **source of morbidity** in people with diabetes



BMI, body mass index; CV, cardiovascular; hs-CRP, high-sensitivity C-reactive protein; PAD, peripheral arterial disease.
Song P et al. Lancet Glob Health 2019;7:e1020–30.

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People with diabetes at high risk of PAD should be screened using ABI

Recommendations from the ADA 2025 Standards of Care

Screening for PAD is recommended in **asymptomatic** people with diabetes

- ≥ 65 years of age
- Microvascular disease
- Foot complications from diabetes
- Any end-organ damage from diabetes

Screening for PAD should be considered in people with:

- Diabetes duration ≥10 years
- High cardiovascular risk

ABI, ankle brachial index; ADA, American diabetes Association; PAD, peripheral arterial disease.

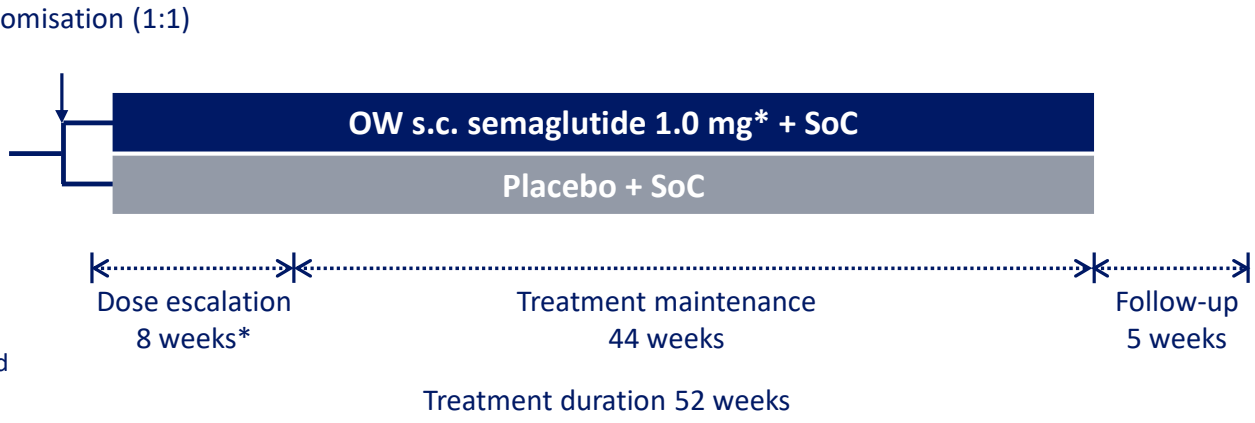
American Diabetes Association Professional Practice Committee; 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S207–S238. https://doi.org/10.2337/dc25-S010

STRIDE: trial design

Functional outcomes in people with PAD and T2D

792 people with T2D

- Age ≥18 years
- T2D diagnosis ≥180 days prior to screening
- HbA_{1c} ≤10%
- PAD with intermittent claudication (Fontaine stage IIa) ≥3 months and:
  - Pain-free walking distance >200 m on a flat treadmill test
  - Maximum walking distance ≤600 m on a constant load treadmill test
  - ABI ≤0.90 or TBI ≤0.70



Trial information

- **Trial objective:** to compare the effect of OW s.c. semaglutide on functional capacity in terms of maximum walking distance in people with PAD and T2D, vs placebo
- Randomised, phase 3b, double-blind, parallel-group trial

Primary endpoint

- Change from baseline in maximum walking distance on a constant load treadmill test† at week 52

**OW s.c. semaglutide dose escalation from starting dose of 0.25 mg; doubled every 4 weeks until trial maintenance dose achieved. †Treadmill at constant speed and incline (3.2 km/h, 12%).*
ABI, ankle brachial index; OW, once-weekly; PAD, peripheral arterial disease; s.c., subcutaneous; SoC, standard of care; TBI, toe brachial index; VascuQol-6, Vascular Quality of Life Questionnaire-6.
https://clinicaltrials.gov/ct2/show/NCT04560998. Bonaca MP et al, Eur Heart J - Cardiovascular Pharmacotherapy, 2024; pvae071, https://doi.org/10.1093/ehjcvp/pvae071

STRIDE: study endpoints

PRIMARY ENDPOINT

Change in **maximum walking distance** on a constant load treadmill from baseline to week 52

SECONDARY CONFIRMATORY ENDPOINTS

Change in **maximum walking distance** on a constant load treadmill from baseline to **week 57**

Change in **Vascular QoL Questionnaire-6** from baseline to week 52

Change in **pain-free walking distance** on constant load treadmill from baseline to week 52

SUPPORTIVE SECONDARY ENDPOINTS

Change from baseline to end of follow-up (week 57):

Pain-free walking distance on a constant load treadmill test

Change from baseline to week 52 in:

HbA_{1c}

SBP

Body weight

Blood lipids*

Change from screening (week –2) to week 52 in:

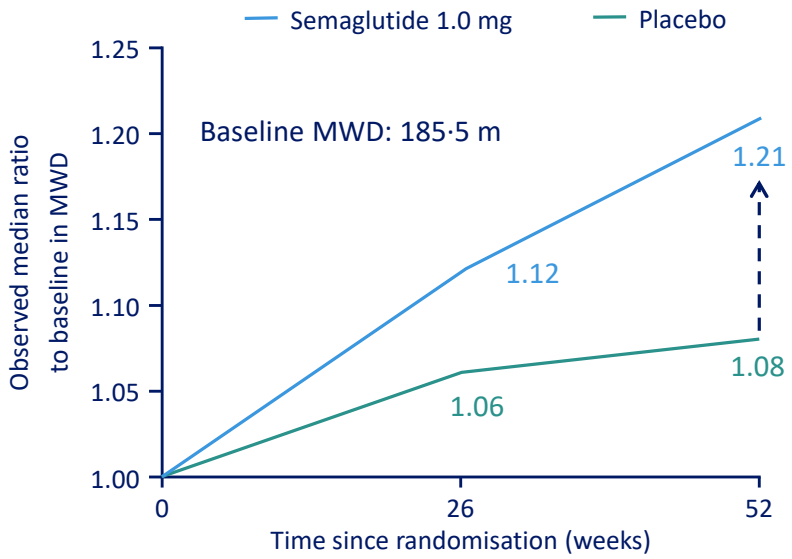
ABI and TBI

Change from baseline to week 52 in:

WIQ global score and SF-36 physical functioning domain

**Total cholesterol, low-density lipoprotein-cholesterol; high-density lipoprotein-cholesterol and triglycerides.*
ABI, ankle brachial index; QoL, quality of life; SBP, systolic blood pressure; SF-36, Short Form 36; TBI, toe brachial index; WIQ, Walking Impairment Questionnaire.
https://clinicaltrials.gov/ct2/show/NCT04560998. Bonaca MP et al, Eur Heart J - Cardiovascular Pharmacotherapy, 2024; pvae071, https://doi.org/10.1093/ehjcvp/pvae071

Maximum walking distance: ratio to baseline at week 52



Baseline median (IQR) MWD — metres

- Semaglutide 1.0 mg (N=395): 184.5 (126.5–274.0147.5)
- Placebo (N=396): 185.8 (133.8–262.0128.3)

OW Semaglutide demonstrated a **13% MWD improvement** compared with placebo on top of SoC [ETR **1.13** (95% CI, 1.06–1.21; p<0.001)]

Median improvement* **26.4 m (HL)** (95% CI, 11.8–40.9)

Mean improvement* **39.9 m (ETD)** (95% CI, 13.9–66.0)

**Represents an exploratory analysis based on patients who adhered to treatment*
The number of participants included in this analysis was 338 in the semaglutide group and 345 in the placebo group
CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; HL, Hodges–Lehmann estimate for location shift; IQR, interquartile range; MWD, maximum walking distance; SoC, standard of care
Bonaca MP et. al. Lancet 2025: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)00509-4/fulltext.

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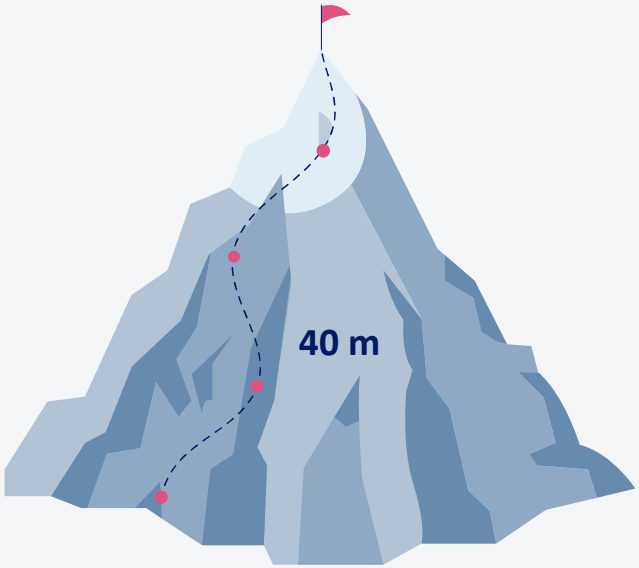
What are the clinical implications of the STRIDE results?

A 40-metre increase in MWD translates to:



Walking about **half a football field up a fairly steep hill**

An improvement in functional capacity improves patients' ability to:

- Walk to the mailbox
- Get groceries
- Walk the dog
- Do daily activities

With fewer pauses due to pain or discomfort

STRIDE
semaglutide | study in peripheral artery disease

CHRONIC KIDNEY DISEASE

Semaglutide is the only GLP-1 RA with proven kidney benefits in people with T2D and CKD, confirmed in a dedicated kidney outcomes trial

Semaglutide is the only GLP-1 RA with proven kidney benefits in people with T2D and CKD, confirmed in the FLOW trial[1]

Semaglutide lowered the risk of kidney disease progression

24%

risk reduction in **people with T2D and CKD** with OW injectable semaglutide 1.0 mg versus placebo in addition to SoC[1]

Semaglutide lowered the risk of kidney outcomes

36%

Risk reduction* in **PwT2D and high CV risk** with OW injectable semaglutide 1.0 mg versus placebo[2†]

This risk reduction was driven by a **reduction in albuminuria[2]**

22%

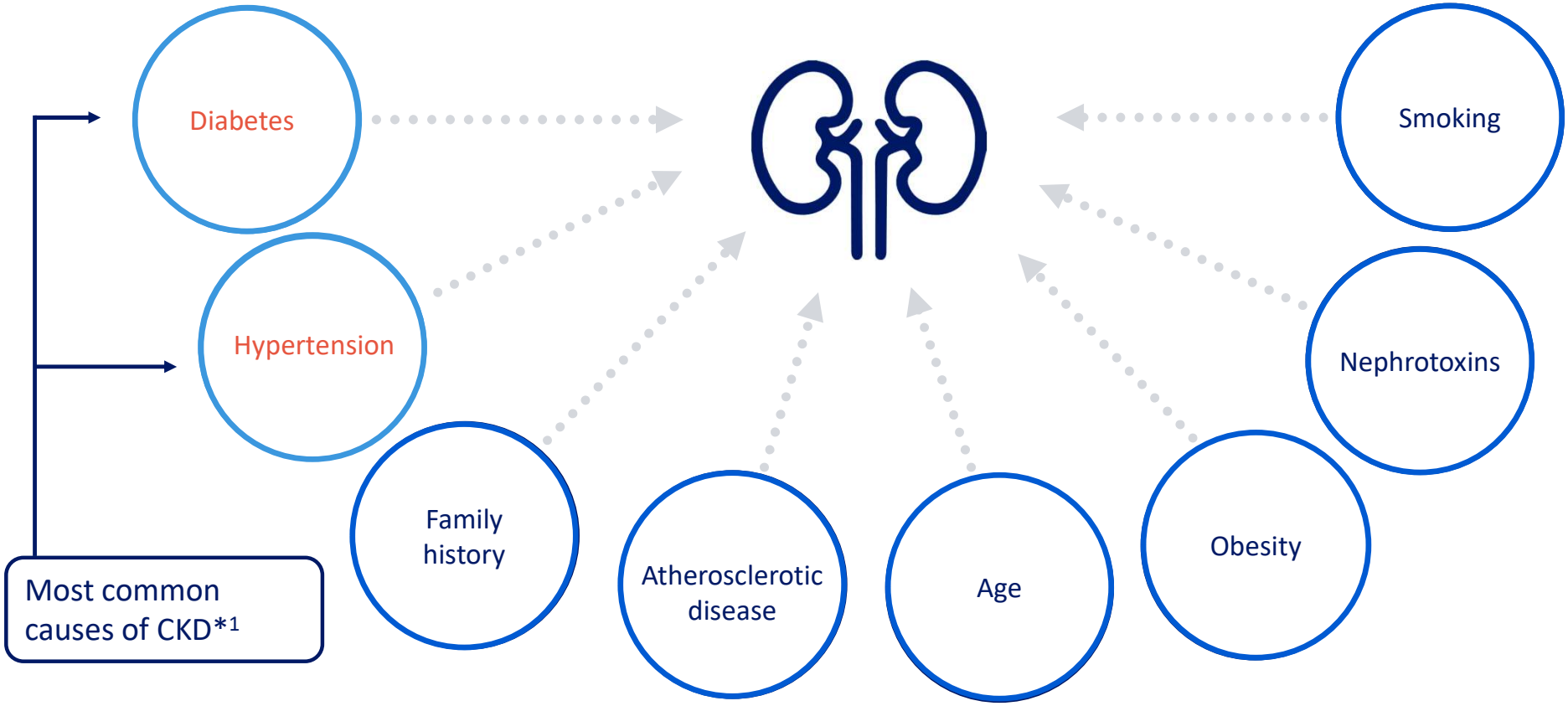
Risk reduction‡ in **PwO with established CVD** with OW semaglutide 2.4 mg versus placebo [3§]

Post hoc analysis suggests semaglutide (oral or injectable) slowed the rate of eGFR decline in PwT2D[4]

This reduction in eGFR decline was **regardless of baseline eGFR, HbA_{1c} or blood pressure[4,5]**

**New or worsening nephropathy including persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of <45 ml/min/1.73 m² of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy; † HR, 0.64; 95% CI, 0.46-0.88; p=0.005; ‡ 5-component composite nephropathy endpoint consisting of onset of persistent macroalbuminuria, persistent 50% reduction in eGFR compared with baseline (randomisation), onset of persistent eGFR <15 ml/min/1.73 m², initiation of chronic renal replacement therapy (dialysis or transplantation), or renal death; § HR, 0.78; 95% CI, 0.63-0.96.*
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, haemoglobin A_{1c}; HR, hazard ratio; OW, once-weekly; PwO, people with obesity; PwT2D, people with type 2 diabetes; SoC, standard of care; T2D, type 2 diabetes
1. Novo Nordisk. Company Announcement: Semaglutide 1.0 mg demonstrates 24% reduction in the risk of kidney disease-related events in people with type 2 diabetes and chronic kidney disease in the FLOW trial. 05 March 2024. Available at: https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=167028 2. Marso SP, et al. N Engl J Med. *2016;375:1834-44. 3. Lincoff AM et al.* N Engl J Med. *2023;DOI:10.1056/NEJMoa2307563. 4. Tuttle, KR, et al.* Kidney Int. *2023;103:772-781. 5. Cherney D, et al.* SA-PO265 J Am Soc Nephrol. *2022;33:675.*

CKD risk factors and causes



*CKD, chronic kidney disease; *~38% of adults with diabetes and ~ 26% with hypertension are diagnosed with CKD. 1. NIDDK. Available from: Causes of Chronic Kidney Disease | NIDDK (nih.gov) accessed May 2021; 2. Kazancioğlu R. Kidney Int Suppl (2011) 2013; 3(4):368–371; 3. Woolfson R. Postgrad Med J 2001; 77(904):68–74; 4. Hall ME et al. Int J Nephrol Renovasc Dis 2014; 7:75–88; 5. Orr SE et al. Int J Mol Sci 2017; 18:pii: E1039*

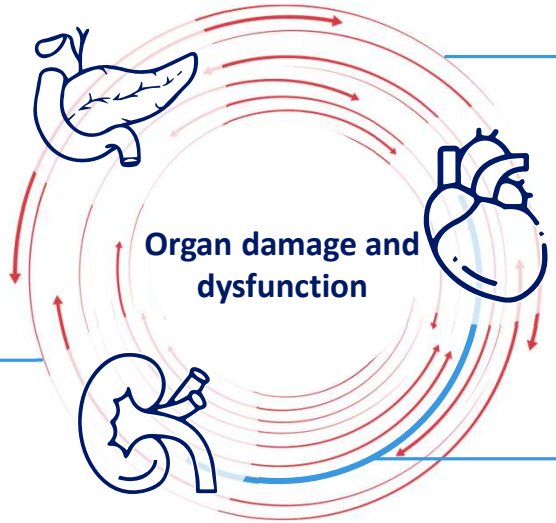
FLOW semaglutide | renal outcomes trial

Cardiovascular, kidney and metabolic conditions are intimately interconnected

Conditions of the cardio-kidney-metabolic systems affect more than 1 billion people worldwide[3,4]

~37% of adults with diabetes have been diagnosed with CKD*[1]

Diabetes and/or hypertension is the primary cause of **~75% of ESKD** prevalent cases in the US[2]



~One-third of patients with T2D have CV disease[3,4]

CV disease is the **leading cause of mortality** in patients with T2D[5,6]

CV mortality accounts for **40-50% of deaths in patients with advanced CKD or ESKD** (compared to 26% in controls with normal kidney function)[7]

**As per NHANES 2011–2012 data.*

CKD, chronic kidney disease; CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure; NHANES, National Health and Nutrition Examination Survey; T2D, type 2 diabetes

1. Murphy D et al. Ann Intern Med 2016; 165(7):473-481; 2. Saran R et al. Am J Kidney Dis 2019; S0272-6386(19)31008-X; 3. Einarson TR et al. Cardiovasc Diabetol 2018; 17(1):83; 4. International Diabetes Federation. IDF Diabetes Atlas. 9th edn. 2019. https://www.diabetesatlas.org/ (accessed August 2020); 5. Morrish NJ et al. Diabetologia 2001; 44(Suppl. 2):S14; 6. American Diabetes Association. Diabetes Care 2020; 43(S1):S1-S212; 7. Jankowski J et al. Circulation. 2021; 143:1157-1172

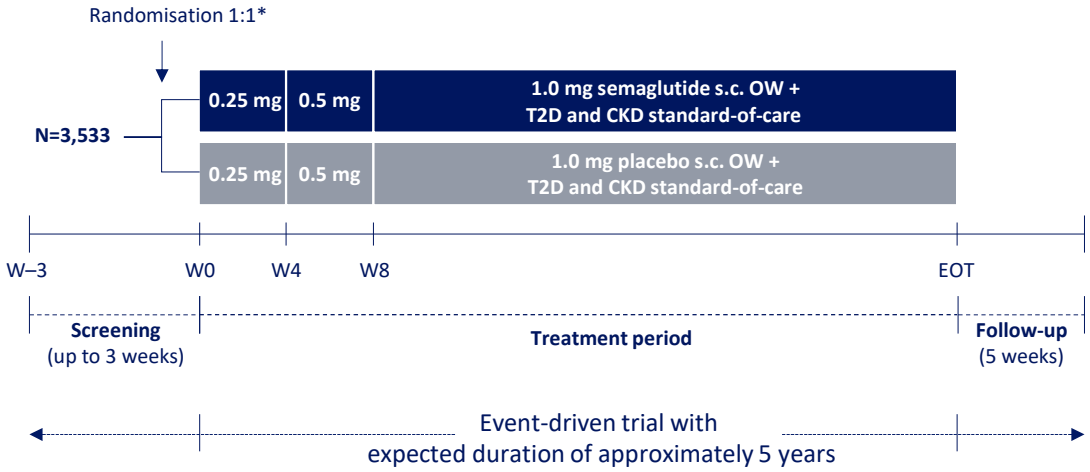
FLOW semaglutide | renal outcomes trial

FLOW trial design

Adults with CKD and T2D

- Age ≥18 years†
- HbA_{1c} ≤10% (≤86 mmol/mol)
- eGFR ≥50 to ≤75 mL/min/1.73 m^2 and UACR >300 to <5,000 mg/g

  OR
- eGFR ≥25 to <50 mL/min/1.73 m^2 and UACR >100 to <5,000 mg/g
- On background RAAS blockade



Trial information

- Randomised, double-blind, parallel-group, multinational phase 3b trial
- Eligibility criteria designed to select broad population with CKD and T2D and at risk for progression of CKD
- Number of participants with eGFR ≥60 mL/min/1.73 m^2 at randomisation was capped at 20% to ensure predominance of participants with moderate-to-severe CKD

*†≥20 years in Japan; *Stratified by sodium-glucose cotransporter-2 inhibitor use (yes/no).*
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EOT, end of treatment; N, number of participants; OW, once-weekly; RAAS, renin-angiotensin-aldosterone system; s.c., subcutaneous; UACR, urine albumin-to-creatinine ratio; W, week. Rossing P et al. Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051; Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

FLOW semaglutide | renal outcomes trial

Primary and secondary end points

Primary composite endpoint

Time to first occurrence of composite endpoint consisting of:

- Onset of persistent ≥50% reduction in eGFR (CKD-EPI)
- Persistent* eGFR <15 mL/min/1.73 m^2
- Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)
- Death from kidney failure
- CV death

Confirmatory secondary endpoints

- Annual rate of change in eGFR (CKD-EPI)
- Time to first occurrence of composite CV MACE (Non-fatal MI, non-fatal stroke, CV death)
- Time to occurrence of all-cause death

Supportive secondary endpoints#:

- Time to occurrence of each individual components of primary and secondary composite endpoints
- Time to first occurrence of MALE (acute or chronic limb ischaemia hospitalisation)
- Annual rate of change in eGFR (CKD-EPI) (chronic eGFR slope)
- Change in eGFR (CKD-EPI and cystatin C CKD-EPI)

Supportive secondary endpoints (continued):

- Relative change in UACR
- Change in body weight, HbA_{1c}, SBP, DBP
- Number of severe hypoglycaemic episodes

Exploratory endpoints:

- Change in EQ-5D-5L index score
- Change in EQ-5D-5L visual analogue scale score

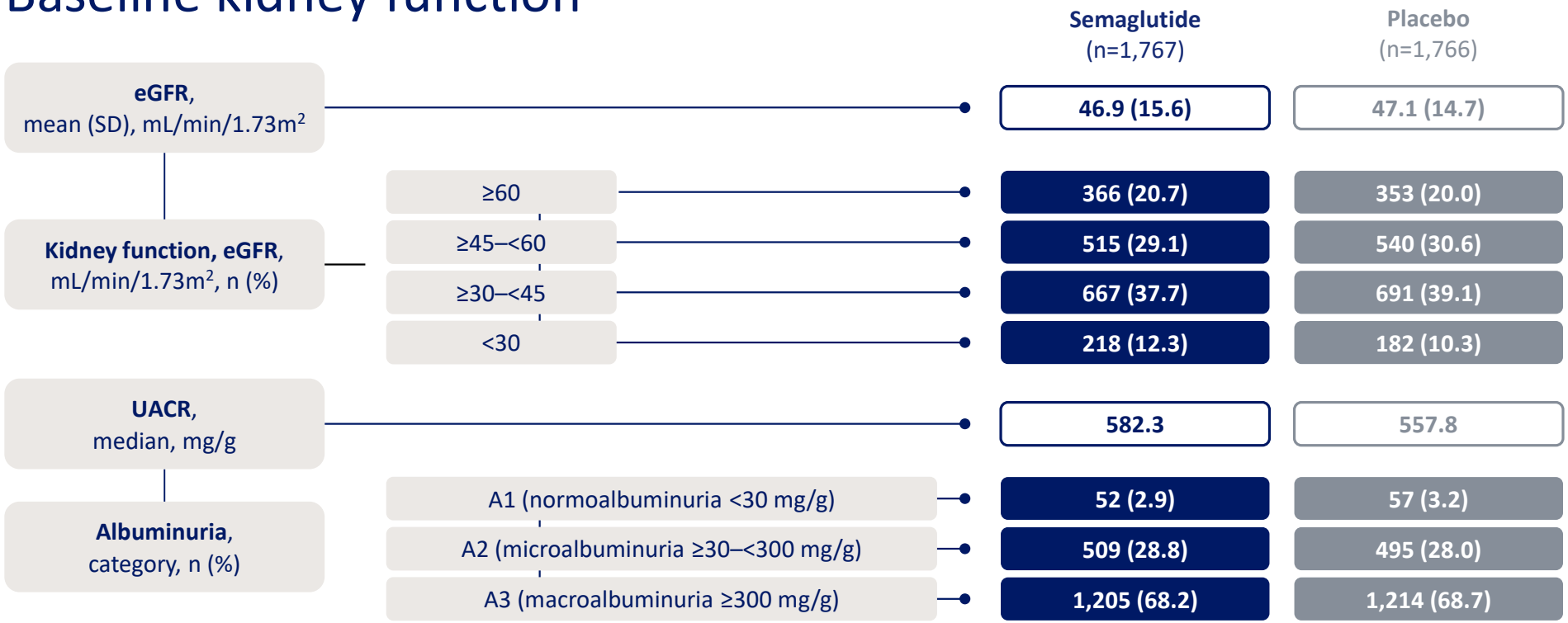
Adapted from Table 2.

*Randomisation = week 0; End-of-trial = a period expected to be 61 months or more for the individual participant; *Persistent = two consecutive central laboratory assessments that meet criteria, at least 4 weeks apart. # The supportive secondary endpoint change in eGFR /CKD EPI is observed from randomization to week 12. All other changes are from randomization to week 156/week104 incl change in cystatin C (CKD EPI). Events including deaths, those leading to kidney replacement therapy, acute coronary syndrome, stroke or transient ischaemic attack, and MALE is reviewed by an independent external event adjudication committee (EAC) in a blinded manner. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EOT, end of trial; EQ-5D-5L, five-level version of the EuroQol five-dimensional questionnaire; MACE, major adverse cardiovascular event; MALE, major adverse limb events; MI, myocardial infarction; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio. Rossing P et al. Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051; Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347.*

FLOW semaglutide | renal outcomes trial

Novo Nordisk®

Baseline kidney function



FLOW participants had a significant CKD burden: 93% at high/very high risk for CKD progression
mean eGFR: 46.9 mL/min/1.73m^2, mean UACR: 582 mg/g

For eGFR, baseline assessment was defined as the mean of the two assessments from the randomisation visit and the screening visit. Albuminuria categories are based on UACR, and baseline assessment was defined as the mean of the two assessments from the randomisation visit. If only one of the assessments for either UACR or eGFR is available, this is used as the baseline assessment. The renal function categories are based on the eGFR as per CKD-EPI.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urinary albumin:creatinine ratio. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

FLOW semaglutide | renal outcomes trial

Novo Nordisk®

93% of the participants were at high or very high risk for CKD progression

According to KDIGO guideline categorisation, 68.2% were at very high risk for CKD progression

KDIGO risk categories among FLOW participants, n (%)

eGFR categories (mL/min/1.73 m²)	UACR categories (mg/g)		
	<30	≥30–<300	≥300
≥90	1 (<0.1)	7 (0.2)	23 (0.6)
≥60–<90	24 (0.7)	173 (4.9)	491 (13.9)
≥45–<60	37 (1.0)	324 (9.2)	694 (19.6)
≥30–<45	40 (1.1)	414 (11.7)	905 (25.6)
≥15–<30	7 (0.2)	87 (2.5)	306 (8.6)
<15	NA	NA	NA

FLOW population

Low risk n=25 (0.7%) | Moderate risk n=217 (6.1%) | High risk n=878 (24.8%) | Very high risk n=2,413 (68.2%)

Adapted from KDIGO Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease; Kidney International (2022) 102 (Suppl 5S), S1–S127.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-creatinine ratio. Rossing P et al. Nephrol Dial Transplant 2023;38:2041–2051; Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

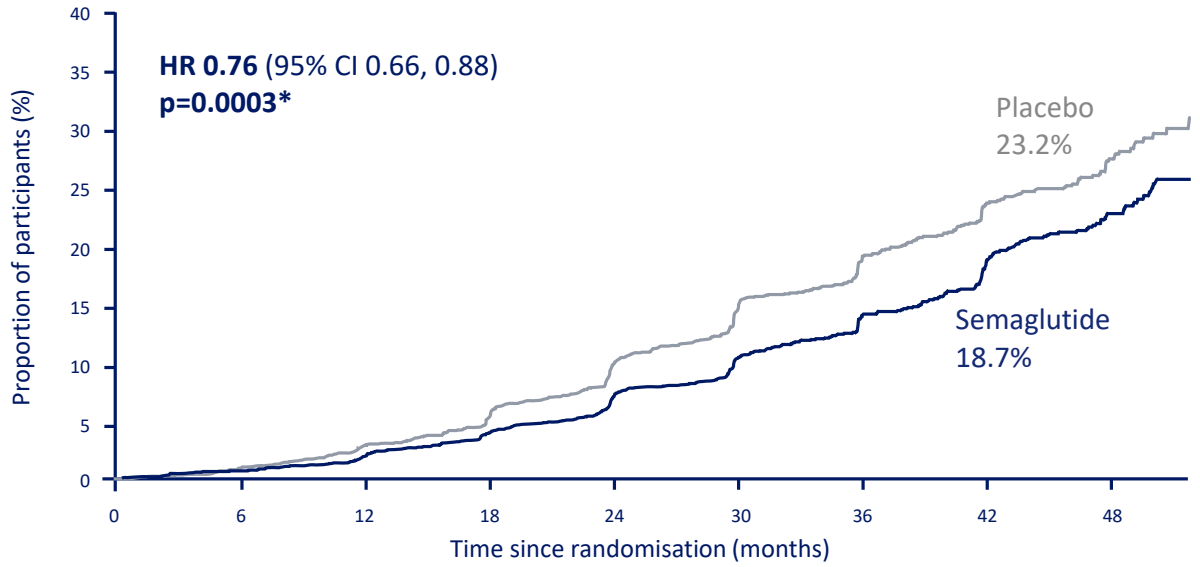
FLOW semaglutide | renal outcomes trial

OW semaglutide s.c. 1.0 mg demonstrated a 24% risk reduction of a composite outcome, incl. kidney disease progression, CV and kidney death in people with CKD and T2D

Time to first occurrence of a composite endpoint consisting of:

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

First composite kidney event: Primary outcome



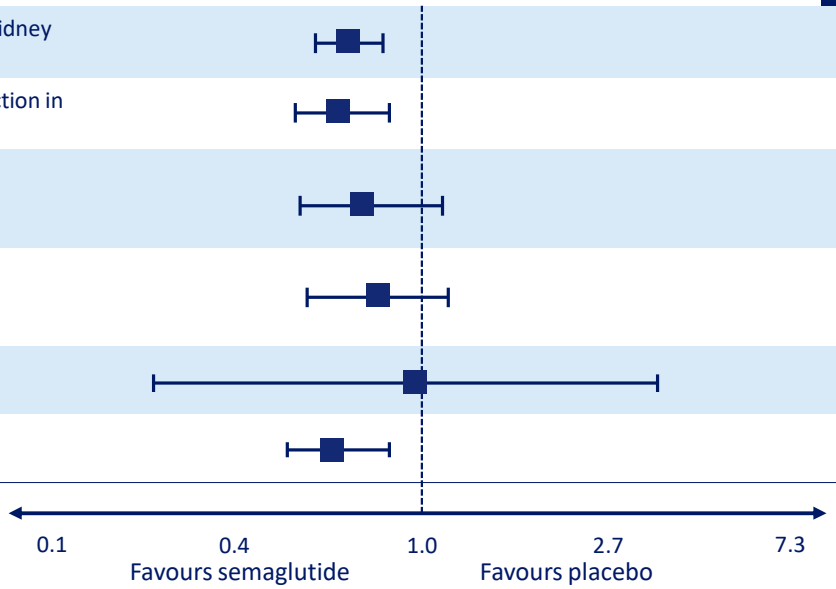
Semaglutide	1,767	1,738	1,693	1,640	1,572	1,489	1,131	742	392
Placebo	1,766	1,736	1,682	1,605	1,516	1,408	1,048	660	354

*Full analysis set. Data from the in-trial period. * Superiority if p value <0.0322*
Numbers shown in the lower panels represent the number of participants at risk. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

FLOW semaglutide | renal outcomes trial

Novo Nordisk®

Consistent risk reduction across the components of the primary composite endpoint



	HR (95% CI)	Semaglutide (n/N)	Placebo (n/N)
Primary endpoint: Composite kidney outcome	**0.76** (0.66, 0.88)	331/1,767	410/1,766
Onset of persistent ≥50% reduction in eGFR	**0.73** (0.59, 0.89)	165/1,767	213/1,766
Onset of persistent eGFR <15 mL/min/1.73 m^2	**0.80** (0.61, 1.06)	92/1,767	110/1,766
Initiation of chronic kidney replacement therapy	**0.84** (0.63, 1.12)	87/1,767	100/1,766
Kidney death	**0.97** (0.27, 3.49)	5/1,767	5/1,766
CV death	**0.71** (0.56, 0.89)	123/1,767	169/1,766

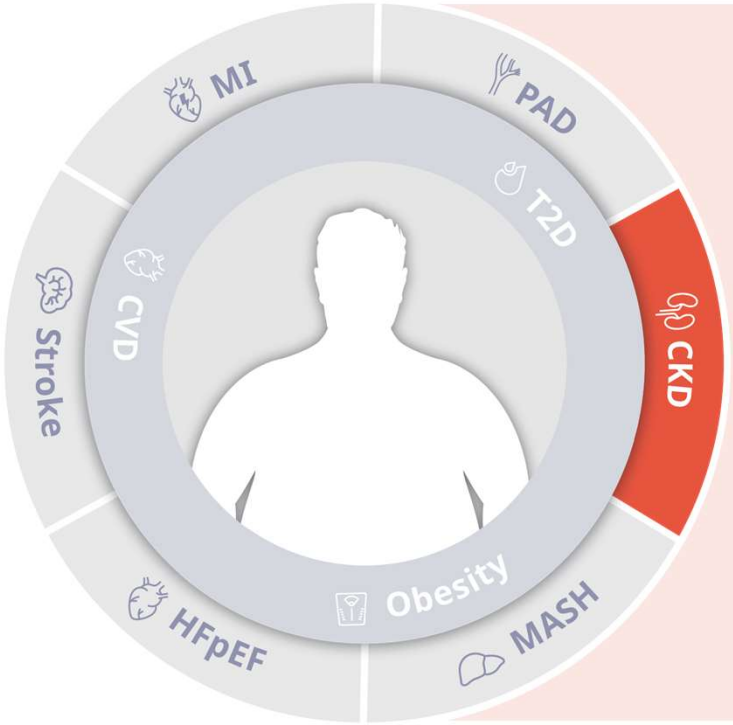
1) Both kidney and cardiovascular components of the primary composite endpoint contributed to the risk reduction.
2) Consistent risk reductions for kidney disease components of the primary composite endpoint.

Full analysis set. Data from the in-trial period.
**Data on file. End-stage kidney disease was a 3-component composite endpoint consisting of initiation of chronic replacement therapy (dialysis or kidney transplantation), onset of persistent eGFR, <15 mL/min/1.73 m^2, and kidney death.CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347*

FLOW semaglutide | renal outcomes trial

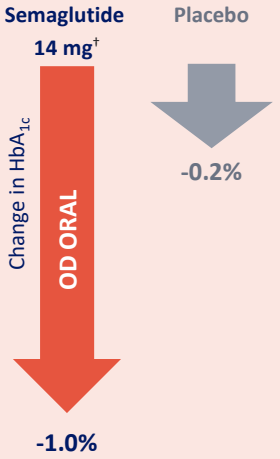
CHRONIC KIDNEY DISEASE

Glycaemic efficacy of semaglutide is sustained in people with moderately to severely decreased kidney function



Semaglutide's glycaemic effect remains prominent in PwT2D and moderately to severely decreased eGFR*[1]

Oral semaglutide **significantly decreased HbA_{1c}** versus placebo in PwT2D and renal impairment[1]



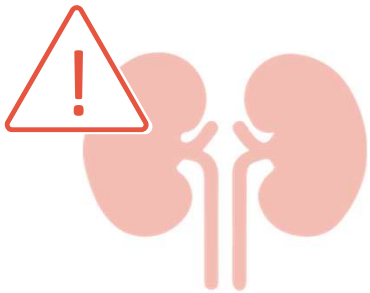
No dose adjustment of OD semaglutide‡ is required in PwT2D with eGFR <45 ml/min per 1.73 m^2 while most SGLT-2 inhibitors require dose adjustment or are not recommended[2-6]

*eGFR <60 ml/min per 1.73 m²; †ETD, -0.8%; 95% CI, -1.0 to -0.6; p<0.0001; ‡Semaglutide is not recommended in patients with end-stage renal disease.
eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; HbA_{1c}, haemoglobin A_{1c}; PwT2D, people with type 2 diabetes; OD, once daily; SGLT-2, sodium-glucose co-transporter-2

1. Mosenzon O, et al. Lancet Diabetes Endocrinol. 2019;7:515-27. 2. Semaglutide (Rybelsus®) Summary of Product Characteristics, last revised October 2023. 3. Canagliflozin (Invokana®) Summary of Product Characteristics, last revised July 2023. 4. Empagliflozin (Jardiance®) Summary of Product Characteristics, last revised August 2023. 5. Dapagliflozin (Forxiga®) Summary of Product Characteristics, last revised May 2023. 6. Ertugliflozin (Steglatro®) Summary of Product Characteristics, last revised December 2022.

CHRONIC KIDNEY DISEASE

Semaglutide has a proven safety profile in people with T2D and CKD



Semaglutide exposure is similar in people with **severe kidney impairment** (creatinine clearance ≤30 ml/min) compared to those with normal renal function[1]

In **FLOW**, semaglutide 1.0 mg was **well tolerated** with a safety profile consistent with previous semaglutide 1.0 mg experience[2]

A **real-world study** of PwT2D and CKD found injectable semaglutide 1.0 mg to be **safe and well-tolerated**[3]

CKD, chronic kidney disease; PwT2D, people with type 2 diabetes; T2D, type 2 diabetes.

1. Marbury TC, et al. Clin Pharmacokinet. *2017;56(11):1381-1390. 2. Novo Nordisk. Company Announcement: Semaglutide 1.0 mg demonstrates 24% reduction in the risk of kidney disease-related events in people with type 2 diabetes and chronic kidney disease in the FLOW trial. 05 March 2024. Available at: https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=167028 3. Bueno BA, et al.* Clin Kidney J. *2022;15(8):1593-1600.*

INTRODUCTION

Multiple studies are ongoing to further examine the effects of semaglutide in patients with CKM diseases

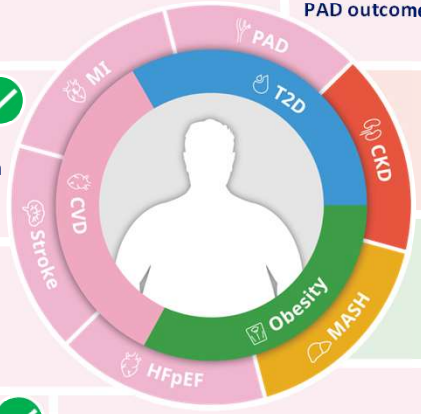
SOUL[17] ✓
(oral 14 mg)
CV outcomes in PwT2D with CVD or CKD

STRIDE[18] ✓
(injectable 1.0 mg)
PAD outcomes in PwT2D

SUSTAIN OPTIMIZE[1]
(injectable 2.0 mg add-on to dose-reduced insulin glargine)
HbA_{1c} reduction in PwT2D

PIONEER PLUS[2] ✓
(oral 14 mg, 25 mg or 50 mg)
HbA_{1c} reduction in PwT2D

CV MOA[16] ✓
(injectable 1.0 mg)
Effect on atherosclerosis in PwT2D and CVD



FLOW[3] ✓
(injectable 1.0 mg)
Kidney outcomes in PwT2D and CKD

ReMoDEL[4]
(injectable 1.0 mg)
Mechanistic trial on the kidneys in PwT2D and CKD

FOCUS[5]
(injectable 2.0 mg)
Microvascular endpoints (diabetic retinopathy) in PwT2D

ASCEND PLUS[15]
(oral 14 mg)
Time to first MACE in PwT2D

STEP UP[6]
(injectable 7.2 mg)
Weight management in PwO

STEP UP T2D[7]
(injectable 7.2 mg)
Weight management in PwO and T2D

STEP 10[8] ✓
(injectable 2.4 mg)
Weight management in PwO and prediabetes

OASIS 1[9] ✓
(oral 50 mg)
Weight management in PwO

SELECT[14] ✓
(injectable 2.4 mg)
CV outcomes in PwO with CVD

STEP-HFpEF[12] ✓
(injectable 2.4 mg)
HF symptoms and physical limitations, and weight loss in people with the obesity phenotype of HFpEF

ESSENCE[11]
(injectable 2.4 mg)
Hepatic outcomes in people living with MASH with and without T2D

OASIS 4[10]
(oral 25 mg)
Weight management in PwO

STEP-HFpEF-DM[13] ✓
(injectable 2.4 mg)
HF symptoms and physical limitations, and weight loss in people with the obesity phenotype of HFpEF and T2D

✓ **Completed**

CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HbA_{1c}, haemoglobin A_{1c}; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular event; MI, myocardial infarction; MASH, metabolic dysfunction-associated steatohepatitis; PAD, peripheral artery disease; PwT2D, people with type 2 diabetes; PwO, people with obesity; T2D, type 2 diabetes.

1. ClinicalTrials.gov. NCT05514535. 2. ClinicalTrials.gov. NCT04707469. 3. ClinicalTrials.gov. NCT03819153. 4. ClinicalTrials.gov. NCT04865770. 5. ClinicalTrials.gov. NCT03811561. 6. ClinicalTrials.gov. NCT05646706. 7. ClinicalTrials.gov. NCT05649137. 8. ClinicalTrials.gov. NCT05040971. 9. ClinicalTrials.gov. NCT05035095. 10. ClinicalTrials.gov. NCT05564117. 11. ClinicalTrials.gov. NCT04822181. 12. ClinicalTrials.gov. NCT04788511. 13. ClinicalTrials.gov. NCT04916470. 14. Ryan DH, et al. Am Heart J. *2020;229:61-69. 15. ClinicalTrials.gov. NCT05441267. 16. ClinicalTrials.gov. NCT04032197. 17. ClinicalTrials.gov. NCT03914326. 18. ClinicalTrials.gov. NCT04560998.*

Thank you

GLP1 though a new lense - The Semaglutide narrative