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Semaglutide and Kidney Outcomes in Type 2 Diabetes Patients at Low to Moderate Kidney Risk: A Retrospective Active-Comparator Cohort Study

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Abstract

Background

Semaglutide has demonstrated kidney benefits in advanced chronic kidney disease (CKD), but evidence in adults with type 2 diabetes at low-to-moderate kidney risk remains limited. We compared kidney outcomes after semaglutide or dipeptidyl peptidase-4 inhibitor (DPP4i) initiation in this population.

Methods

This retrospective active-comparator, new-user cohort study used data from August 1, 2019 to February 28, 2025 from Maccabi Healthcare Services (MHS), Israel. Adults with type 2 diabetes and low-to-moderate risk according to Kidney Disease: Improving Global Outcomes (KDIGO) who initiated semaglutide (oral or subcutaneous) or DPP4i were propensity score-matched 1:1 and stratified by baseline sodium–glucose cotransporter-2 inhibitor (SGLT2i) use. The primary endpoint was the first occurrence of a composite of confirmed ≥ 30% decline in the estimated glomerular filtration rate (eGFR), new-onset or worsening albuminuria, end-stage kidney disease, or all-cause death. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated via Cox proportional hazards regression.

Results

The final matched cohort comprised 6,705 participants per group. Among the matched semaglutide initiators, 6,230 (92.9%) received subcutaneous semaglutide and 475 (7.1%) received oral semaglutide. Over 36 months, the primary composite outcome occurred in 581 (8.7%) semaglutide- and 844 (12.6%) DPP4i-treated participants (HR 0.69; 95% CI 0.60–0.78; $p < 0.001$). Rates were lower with semaglutide for ≥ 30% eGFR decline [125 (1.9%) vs 191 (2.8%); $p = 0.004$], albuminuria progression [399 (6.0%) vs 545 (8.1%); $p < 0.001$], and all-cause death [61 (0.9%) vs 114 (1.7%); $p < 0.001$]; kidney failure was rare in both groups. The composite was driven mainly by albuminuria and, to a lesser extent, by eGFR decline and all-cause death. Associations were consistent across KDIGO risk categories and regardless of baseline SGLT2i use.

Conclusions

Among adults with type 2 diabetes at low-to-moderate KDIGO risk, semaglutide initiation was associated with a lower risk of adverse kidney outcomes than DPP4i initiation was, extending evidence regarding semaglutide and kidney outcomes beyond advanced CKD.

Research insights

What is currently known about this topic?	In the FLOW trial, semaglutide reduced kidney risk in established diabetic kidney disease. Kidney risk in type 2 diabetes extends to people with preserved kidney function. Evidence on kidney outcomes with semaglutide in this population remains limited.
What is the key research question?	Is semaglutide use associated with a lower risk of adverse kidney outcomes in people with type 2 diabetes at low-to-moderate KDIGO risk?
What is new?	Semaglutide was associated with a lower risk of adverse kidney outcomes than DPP-4 inhibitors. The association was consistent across KDIGO risk categories and SGLT2 inhibitor use strata. Semaglutide was associated with fewer shifts to higher KDIGO risk and more shifts to lower risk.
How might this study influence clinical practice?	This study may bring kidney risk into treatment considerations earlier in type 2 diabetes.

Background

Type 2 diabetes (T2D) is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease globally, with CKD affecting 20–40% of individuals with type 2 diabetes [1], some estimates suggest a prevalence of up to 50% depending on population characteristics [2]. The coexistence of CKD and type 2 diabetes markedly increases cardiovascular risk and mortality, while even a modest decrease in estimated glomerular filtration (eGFR) is associated with increased subsequent all-cause and cardiovascular mortality across baseline kidney-function levels [3, 4]. Current guidelines recommend glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter-2 inhibitors (SGLT2is) as cornerstone therapies for type 2 diabetes because of their cardiorenal protective effects beyond glycemic control [1, 5]. The landmark FLOW trial demonstrated that once-weekly semaglutide reduced the risk of the composite of kidney failure, cardiovascular or kidney death, and persistent ≥ 50% eGFR reduction by 24% in a population with diabetic kidney disease that was predominantly at high or very high risk according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria [6]. However, evidence regarding semaglutide and kidney outcomes among individuals with low to moderate kidney risk remains limited. This represents an important knowledge gap, as a substantial proportion of patients with type 2 diabetes in routine clinical practice have preserved or mildly reduced kidney function yet remain at risk of kidney disease progression [7]. This population includes patients with early kidney involvement (mild albuminuria or eGFR 60–90 mL/min/1.73 m²) and those with currently normal kidney function who carry elevated lifetime CKD risk. Even with a preserved eGFR and normoalbuminuria at baseline, the 4-year incidence of CKD can exceed 30% in patients with T2D [8]. The 2025 KDIGO Controversies Conference on CKD Prevention emphasized that kidney disease prevention remains

underaddressed, calling for studies of GLP-1 RAs and SGLT2i in broader at-risk populations before advanced CKD develops [9]. In this retrospective cohort study using Maccabi Healthcare Services (MHS) database, we aimed to evaluate kidney outcomes associated with semaglutide initiation in adults with T2D at low-to-moderate KDIGO risk, a population underrepresented in clinical trials, using dipeptidyl peptidase-4 inhibitors (DPP4is) as an active comparator.

Methods

Study design and data sources

This retrospective comparative effectiveness cohort study used deidentified data from Maccabi Healthcare Services (MHS), the second-largest health provider in Israel, covering 2.8 million members. The MHS database provides longitudinal data on demographics, diagnoses, laboratory results, and complete medication dispensation records. The study was approved by the MHS Institutional Review Board with a waiver of informed consent.

Study population

Eligible participants were adults (≥ 18 years) recorded in the MHS type 2 diabetes registry before initiating semaglutide (subcutaneous or oral) or a DPP4i (sitagliptin, linagliptin, vildagliptin, or saxagliptin) between August 1, 2019, and August 31, 2024. Eligibility also required at least one eGFR measurement and one urine albumin—creatinine ratio (UACR) measurement within the 365 days preceding treatment initiation, and at least one measurement of each within the 365 days following initiation, and low or moderate kidney risk according to KDIGO: eGFR ≥ 60 mL/min/1.73 m² with UACR < 300 mg/g (< 33.9 mg/mmol), or eGFR 45–<60 mL/min/1.73 m² with UACR < 30 mg/g (< 3.4 mg/mmol). Participants were excluded if they had a history of type 1 diabetes, kidney transplantation or dialysis, confirmed by International Classification of Diseases (ICD-9) and Current Procedural Terminology (CPT) procedures codes recorded by MHS; used any DPP4i or GLP-1 RA (other than semaglutide) in the semaglutide group; or any GLP-1 RA in the DPP4i group within 90 days preceding treatment initiation. Participants were also excluded if they died or were transferred to another health maintenance organization within 120 days after treatment initiation in alignment with the outcome ascertainment period as detailed in the next section.

A detailed rationale for active comparator selection is provided in Supplementary Methods S1.

Study periods

The identification period (the period through which participants could have initiated the treatment) spanned from August 1, 2019, to August 31, 2024. The index date was defined as the date of the first confirmed dispensation of the study medication (semaglutide or DPP4i). The participants were followed

up until the earliest of death, transfer to another health maintenance organization, or February 28, 2025. To account for the dose escalation period and potential transient hemodynamic effects on the eGFR in the semaglutide group, which do not necessarily reflect true kidney injury [10], outcome ascertainment began 120 days after the index date.

Follow-up was administratively censored at 36 months to reduce the influence of sparse, calendar-selected risk sets at longer follow-up, given differences in treatment initiation over time. A sensitivity analysis included all available follow-up data through February 28, 2025 (up to approximately five years).

Primary endpoint

The primary endpoint was the time to first occurrence of a composite kidney outcome: (1) confirmed eGFR decline ≥ 30% from baseline; (2) confirmed new-onset or worsening of albuminuria; (3) end-stage kidney disease (dialysis, transplantation, or eGFR < 15 mL/min/1.73 m²); or (4) all-cause death. The primary comparison was semaglutide versus DPP4i. Baseline eGFR and UACR values were the most recent measurements taken within 365 days before treatment initiation. eGFR- and UACR-related outcomes require confirmation in two consecutive measurements to reduce misclassification from laboratory variability and transient changes. The eGFR was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation [11].

For baseline UACR < 30 mg/g (< 3.4 mg/mmol), new-onset or worsening albuminuria was defined as an increase to ≥ 30 mg/g (≥ 3.4 mg/mmol) and an absolute increase of at least 10 mg/g (1.13 mg/mmol). For baseline UACRs ≥ 30 mg/g (≥ 3.4 mg/mmol), worsening required a ≥ 30% relative increase. A detailed rationale for primary endpoint selection is provided in *Supplementary Methods S2*.

Secondary endpoints

The secondary endpoints included the following: (1) modified composite outcomes substituting the ≥ 30% eGFR decline component with ≥ 40% or ≥ 50% thresholds; (2) the composite outcome excluding the all-cause death component; (3) subgroup analyses examining the composite outcome by baseline KDIGO risk category and baseline SGLT2i use; (4) subgroup analysis with treatment-by-subgroup interaction testing by the following baseline subgroups: KDIGO risk category (low vs moderate), SGLT2i use (yes vs no), renin–angiotensin system inhibitors (RASI) use (yes vs no), age (< 75 vs ≥ 75 years), glycated hemoglobin (HbA1c) of (< 7% vs ≥ 7%; equivalent cutoff 53 mmol/mol), body mass index (BMI) of (< 30 vs ≥ 30 kg/m²), eGFR (< 60 vs 60–<90 vs ≥ 90 mL/min/1.73 m²), UACR (< 30 vs ≥ 30 mg/g; equivalent cutoff 3.4 mg/mmol), and diabetes duration (< 5, 5–<10, 10–<15, ≥ 15 years); and (5) time to transition across KDIGO categories, including deterioration or regression to low risk. Detailed definitions of the outcomes for this analysis are reported in *Supplementary Methods S3*.

Statistical analysis

Statistical power estimation

Detailed statistical power estimates for the primary end point analysis are provided in *Supplementary Methods S4*.

Baseline variables

Baseline continuous variables with a distribution close to normality are described as the mean and standard deviation (SD), and those with a skewed distribution are described as the median and interquartile range (IQR). Categorical variables are described as proportions.

Propensity score matching

Participants were matched 1:1 by nearest-neighbor propensity score matching without replacement, within strata of baseline SGLT2i use, with a maximum absolute difference of 0.1 between estimated propensity scores. The propensity score model included demographics, clinical parameters, baseline medications, and comorbidities. The variables included in the propensity score model were entered categorically, as specified in *Supplementary Table S1*; variable definitions are specified in *Supplementary Table S2*. For the matching process, missing values were classified into a missing category. A standardized mean difference was used to assess the baseline differences between the semaglutide and DPP4i groups, with < 0.10 indicating adequate balance. As a post hoc assessment, laboratory testing frequency was compared between treatment groups. Baseline testing frequency was examined as an additional indicator of balance in healthcare monitoring not included in the propensity score model, whereas follow-up testing frequency was assessed for potential differential outcome ascertainment.

Primary endpoint analysis

The primary analysis followed an intention-to-treat principle; all matched participants were analyzed according to their initial treatment assignment regardless of treatment discontinuation or switching. Time—to-event analyses were performed via the Kaplan—Meier (KM) method, and the results were compared via the log rank test. Hazard ratios (HRs), 95% confidence intervals (CIs), and p values were estimated via Cox proportional hazards regression models. Both unadjusted and adjusted Cox models were fitted. The proportional hazards assumption was assessed via Schoenfeld residuals. The adjusted models included propensity score matching variables as well as additional baseline covariates. Variables entered categorically in the propensity score model were adjusted in the models according to their original scale when appropriate to account for residual confounding after matching and to improve the precision of the association estimates. An E value was calculated for the adjusted hazard ratio of the primary composite outcome to evaluate the potential impact of unmeasured confounding.

The full covariate list is provided in *Supplementary Table S3*, covariate definitions are specified in *Supplementary Table S2*.

On-treatment analysis

The primary endpoint was evaluated after censoring participants at the earliest of treatment discontinuation, defined as no medication purchases for six consecutive months; initiation of semaglutide or another GLP-1 RA in the DPP4i group; or initiation of DPP4i or switching to another GLP-1 RA in the semaglutide group.

Secondary outcome analyses

Analyses of the composite outcome were repeated after the ≥ 30% eGFR decline component was replaced with thresholds of ≥ 40% and ≥ 50%. The kidney-specific composite outcome was analyzed via Cox proportional hazards and Fine–Gray competing-risks models, with death treated as a competing event in the latter. Within each baseline KDIGO risk category and SGLT2i-use stratum, adjusted treatment HRs were estimated from Cox models fitted separately within that stratum. Treatment-effect heterogeneity across nine prespecified baseline subgroups was assessed via adjusted Cox models containing treatment, subgroup, and treatment-by-subgroup interaction terms; cardiovascular disease status was evaluated as an additional exploratory subgroup. Kaplan–Meier curves were generated for each subgroup. No adjustment was made for multiple comparisons. An exploratory joint analysis of baseline HbA1c and diabetes duration is described in *Supplementary Methods S3*. For KDIGO risk-category transitions, the follow-up category was determined from the last available paired eGFR and UACR measurements, and the time to transition was the first date on which that category was reached. Transitions were analyzed via Cox models, with death included in deterioration outcomes *(Supplementary Methods S3)*.

Handling of missing data

As a sensitivity analysis, the primary analysis was repeated after missing baseline covariate data were handled via multiple imputation by chained equations (MICEs). Twenty imputed datasets were generated via five iterative cycles of the imputation algorithm and analyzed via prespecified statistical models. Estimates were pooled across imputations via Rubin's rules.

Statistical software

Statistical analyses were performed via R statistical software version 4.5.0; RStudio version 2025.9.1.401 (R Foundation for Statistical Computing, Vienna, Austria). The full specifications of the R packages used for the analysis can be found in *Supplementary Methods S5*.

Use of Large Language Models (LLMs)

During manuscript preparation, ChatGPT (GPT-5.6 Pro; OpenAI) was used for language editing and formatting support. It was also used to generate selected schematic and descriptive figures that were not derived from statistical model outputs. For figures presenting analytic results, artificial intelligence (AI) assistance was strictly limited to visual refinement, including titles, fonts, sizing, and layout. All AI-assisted content was verified against the source data and reviewed and approved by the authors, who

take full responsibility for the final manuscript. Large language models were additionally used as programming aids in developing the analytic code. These included Google Gemini models (Gemini 2.5 Flash, Gemini 3 Flash, Gemini 3.5 Flash, Gemini 2.5 Pro, Gemini 3 Pro, and Gemini 3.1 Pro) and Anthropic Claude models (Claude Sonnet 4.6, Claude Sonnet 5, Claude Opus 4.7, Claude Opus 4.8, and Claude Opus 5). Their use included generating, refactoring, and reviewing R code, always under human direction and oversight.

Results

Participant selection and baseline characteristics

The initial study cohort included adults with type 2 diabetes who initiated semaglutide or DPP4i therapy between August 1, 2019 and August 31, 2024, with at least one eGFR and UACR measurement before and one measurement after treatment initiation and without a history of type 1 diabetes. This cohort, which was extracted and provided by the MHS, included 25,915 semaglutide initiators and 10,841 DPP4i initiators. After applying the inclusion and exclusion criteria, 21,955 semaglutide initiators and 8,388 DPP4i initiators were eligible for matching. Following 1:1 propensity score matching stratified by baseline SGLT2i use, the final matched cohort comprised 6,705 participants per group (Fig. 1).

MHS, Maccabi Healthcare Services; T2D, type 2 diabetes; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; eGFR, estimated glomerular filtration rate; UACR, urine albumin—creatinine ratio; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2i, sodium—glucose cotransporter-2 inhibitor.

Among the 6,705 matched semaglutide initiators, 6230 (92.9%) received subcutaneous semaglutide and 475 (7.1%) received oral semaglutide.

Before matching, the semaglutide group had a higher BMI, greater SGLT2i and insulin use, and a greater cardiovascular burden, whereas the DPP4i group was older and had higher HbA1c *(Supplementary Table S4)*. After matching, the baseline characteristics were well balanced between the groups (Table 1). The standardized mean differences (SMDs) were < 0.10 for all the matched variables except BMI (SMD 0.11), indicating only a minor residual imbalance; BMI was additionally included in the adjusted outcome models. Most participants (73.8%) were in the low-KDIGO risk category, and baseline SGLT2i use was 17.5% in both groups.

Table 1
Baseline characteristics after matching

Characteristics	DPP4i N = 6705	Semaglutide N = 6705	SMD
Sex			< 0.01
Male	3487 (52.0%)	3480 (51.9%)	
Female	3218 (48.0%)	3225 (48.1%)	
Age, years			
Mean (SD)	62.4 (11.3)	61.5 (11.0)	0.08
Socioeconomic status category			0.02
1–3 (low)	751 (11.2%)	779 (11.6%)	
4–5 (medium-low)	1890 (28.2%)	1909 (28.5%)	
6–7 (medium-high)	2259 (33.7%)	2243 (33.5%)	
8–10 (high)	1793 (26.7%)	1760 (26.2%)	
Missing	12 (0.2%)	14 (0.2%)	
Diabetes duration, years			
Median (IQR)	6.4 (2.4–11.3)	6.7 (2.6–11.6)	0.05
HbA1c, %			
Mean (SD)	7.6 (1.6)	7.5 (1.5)	0.08
Missing N (%)	37 (0.6%)	32 (0.5%)	
HbA1c, mmol/mol			
Mean (SD)	59.6 (17.5)	58.5 (16.4)	0.08
eGFR, mL/min/1.73 m²			
Mean (SD)	87.4 (16.6)	87.5 (16.5)	0.01
eGFR category, mL/min/1.73 m²	0.02		
45-<60	392 (5.8%)	380 (5.7%)	
60-<90	3038 (45.3%)	2985 (44.5%)	
≥ 90	3275 (48.8%)	3340 (49.8%)	
Missing N (%)	0 (0.0%)	0 (0.0%)	
UACR, mg/g			
Median (IQR)	6.4 (0.0-23.4)	7.0 (0.0–24.0)	0.03

Characteristics	DPP4i N = 6705	Semaglutide N = 6705	SMD
UACR, mg/mmol			
Median (IQR)	0.72 (0.00–2.65)	0.79 (0.00–2.71)	0.03
UACR category	0.02		
< 30 mg/g (< 3.4 mg/mmol)	5361 (80.0%)	5313 (79.2%)	
30–<300 mg/g (3.4–<33.9 mg/mmol)	1344 (20.0%)	1392 (20.8%)	
Missing N (%)	0 (0.0%)	0 (0.0%)	
Kidney risk category (KDIGO classification)	0.01		
Low	4969 (74.1%)	4933 (73.6%)	
Moderate	1736 (25.9%)	1772 (26.4%)	
BMI, kg/m^2			
Mean (SD)	31.4 (5.3)	32.0 (5.4)	0.11
Missing N (%)	1135 (16.9%)	1122 (16.7%)	
Systolic blood pressure, mm Hg			
Mean (SD)	132.9 (15.3)	133.0 (15.7)	0.01
Missing N (%)	455 (6.8%)	476 (7.1%)	
Diastolic blood pressure, mm Hg			
Mean (SD)	78.6 (9.4)	78.8 (9.4)	0.02
Missing N (%)	455 (6.8%)	476 (7.1%)	
HDL cholesterol, mmol/L			
Mean (SD)	1.20 (0.29)	1.20 (0.29)	0.01
Missing N (%)	74 (1.1%)	79 (1.2%)	
LDL cholesterol, mmol/L			
Mean (SD)	2.46 (0.94)	2.44 (0.94)	0.02
Missing N (%)	141 (2.1%)	124 (1.8%)	
Triglycerides, mmol/L			
Median (IQR)	1.77 (1.29–2.45)	1.74 (1.29–2.43)	0.02
Missing N (%)	67 (1.0%)	75 (1.1%)	

Characteristics	DPP4i N = 6705	Semaglutide N = 6705	SMD
Medications			
Metformin	4708 (70.2%)	4624 (69.0%)	0.03
Insulin	553 (8.2%)	619 (9.2%)	0.03
SGLT2 inhibitor	1171 (17.5%)	1171 (17.5%)	< 0.01
Renin-angiotensin system inhibitor	3334 (49.7%)	3373 (50.3%)	0.01
Mineralocorticoid receptor antagonist	169 (2.5%)	174 (2.6%)	<0.01
Diuretic	1057 (15.8%)	1019 (15.2%)	0.02
Lipid modifying agent	4264 (63.6%)	4135 (61.7%)	0.04
Antithrombotic agent	2253 (33.6%)	2280 (34.0%)	0.01
Comorbidities			
Ischemic heart disease	739 (11.0%)	755 (11.3%)	0.01
Stroke	153 (2.3%)	139 (2.1%)	0.01
Peripheral vascular disease	152 (2.3%)	163 (2.4%)	0.01
Heart failure	78 (1.2%)	83 (1.2%)	0.01
Atrial fibrillation	317 (4.7%)	345 (5.1%)	0.02
Retinopathy	137 (2.0%)	145 (2.2%)	0.01

Data are presented as n (%) for categorical variables, means (SDs) for normally distributed continuous variables, and medians (IQRs) for nonnormally distributed continuous variables. Balance was assessed via standardized mean differences; SMD < 0.10 indicated adequate balance. BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; LDL, low-density lipoprotein; SD, standard deviation; SGLT2i, sodium—glucose cotransporter-2 inhibitor; UACR, urine albumin—creatinine ratio. SMD, standardized mean difference. For variables presented as medians (interquartile ranges), the SMD was calculated using the group means and standard deviations. SMDs are reported as absolute values.

Follow-up duration

In the primary analysis population, the median follow-up was 31.7 months (IQR 20.4–36.0) in the semaglutide group and 36.0 months (IQR 23.7–36.0) in the DPP4i group. This difference reflects temporal enrollment patterns: DPP4i use peaked from 2020–2021 and declined thereafter, whereas semaglutide enrollment increased progressively, with peak enrollment occurring in 2022 (*Supplementary Figure S1)*.

In the on-treatment population, the median follow-up was 16.8 months (IQR 6.0–32.6) in the semaglutide group and 15.2 months (IQR 6.9–29.7) in the DPP4i group.

Laboratory testing frequency

The reporting frequency of parameters essential for outcome ascertainment (eGFR and UACR) was broadly comparable between the treatment groups during both the baseline and follow-up periods *(Supplementary Table S5)*.

Primary composite outcome

In the primary analysis, the composite outcome occurred in 581 participants (8.7%) in the semaglutide group and 844 (12.6%) in the DPP4i group during 36 months of follow-up ($p < 0.001$). Individual components were also less common with semaglutide than with DPP4i: confirmed ≥ 30% eGFR decline, 125 (1.9%) versus 191 (2.8%; $p = 0.004$); new-onset or worsening albuminuria, 399 (6.0%) versus 545 (8.1%; $p < 0.001$); and all-cause death, 61 (0.9%) versus 114 (1.7%; $p < 0.001$). End-stage kidney disease events were rare: 3 versus 2 events, respectively ($p = 0.6$) *(Supplementary Table S6)*.

All hazard ratios reported hereafter are adjusted unless otherwise specified; Kaplan—Meier curves show unadjusted comparisons. According to the time-to-event analysis, semaglutide was associated with a 31% lower risk of the primary composite outcome than DPP4i was (HR 0.69; 95% CI 0.60–0.78; $p < 0.001$) (Fig. 2A). The assessment of Schoenfeld residuals revealed no evidence of a violation of the proportional hazards assumption for the treatment variable. The Kaplan–Meier curves were separated after approximately 6–9 months of follow-up.

On-treatment analysis

In the on-treatment analysis, follow-up was censored at treatment discontinuation or comparator class initiation. Discontinuation of index treatment without comparator class initiation was broadly similar between the groups, occurring in 1,414 (21.1%) of the DPP4i initiators and 1,335 (19.9%) of the semaglutide initiators. In contrast, comparator-class treatment initiation was asymmetric: 2,590 (38.6%) participants in the DPP4i group initiated GLP-1 RA treatment, whereas 363 (5.4%) participants in the semaglutide group initiated DPP4i. Semaglutide was associated with a 54% lower risk of the primary composite outcome (HR 0.46; 95% CI 0.39–0.54; $p < 0.001$) (Fig. 2B).

Sensitivity analyses of the primary outcome

Among the 13,410 participants, 2,876 (21.4%) had missing baseline covariate data. In the sensitivity analysis using multiple imputation (20 imputed datasets pooled via Rubin's rules), the estimated adjusted HR was 0.71; 95% CI 0.63–0.80; $p < 0.001$, which was consistent with the primary analysis.

A sensitivity analysis using fully available follow-up data, with a maximum of approximately 5 years, revealed similar results: HR 0.69; 95% CI 0.61–0.79; $p < 0.001$ *(Supplementary Figure S2)*.

To assess robustness to unmeasured confounding, we calculated an E value of 2.26 for the primary composite outcome, indicating that an unmeasured confounder would need to be associated with both treatment and outcome by a risk ratio of at least 2.26-fold each to fully explain the observed association.

Secondary analyses

Modified composite outcomes with alternative eGFR decline thresholds

Secondary analyses using more stringent eGFR decline thresholds as components of the primary composite outcome yielded consistent results, with an HR of 0.72 (95% CI 0.64–0.82; p < 0.001) for an eGFR decline ≥ 40% and 0.72 (95% CI 0.63–0.82; p < 0.001) for an eGFR decline ≥ 50% (*Supplementary Figures S3, S4).*

Kidney -specific composite outcome

When all-cause death was excluded, the kidney-specific composite outcome comprised confirmed ≥ 30% eGFR decline from baseline, confirmed new-onset or worsening albuminuria, or end-stage kidney disease. Compared with DPP4i, semaglutide initiation was associated with a lower risk of kidney-specific composite outcomes: adjusted HR 0.71; 95% CI 0.61–0.81; p < 0.001 (*Supplementary Figure S5).* To account for death as a competing risk, we additionally performed a Fine—Gray competing-risk analysis, which showed similar results: adjusted subdistribution hazard ratio (sHR) 0.71; 95% CI 0.62–0.80; p < 0.001 *(Supplementary Figure S6).*

Composite outcomes stratified by baseline KDIGO risk category and SGLT2i use

Associations between semaglutide and a lower risk of the primary composite outcome were consistent across baseline KDIGO risk categories and regardless of baseline SGLT2i use. Among participants with low baseline KDIGO risk (N = 9,902), semaglutide was associated with a lower risk of the primary composite outcome than DPP4i was (HR 0.71; 95% CI 0.60–0.83; p < 0.001), with similar findings observed among those with moderate KDIGO risk: N = 3,508; HR 0.68; 95% CI 0.57–0.81; p < 0.001 (Fig. 2C–D). Similarly, semaglutide was associated with a lower risk of the primary composite outcome both among participants receiving SGLT2i at baseline (N = 2,342; HR 0.69; 95% CI 0.53–0.91; p = 0.01) and among those not receiving SGLT2i (N = 11,068; HR 0.69; 95% CI 0.61–0.79; p < 0.001) (Fig. 2E–F).

Kaplan—Meier curves for the primary composite outcome comparing semaglutide with DPP4i in the primary analysis (A), on-treatment analysis (B), low-KDIGO-risk subgroup (C), moderate-KDIGO-risk subgroup (D), participants with baseline SGLT2i use (E), and participants without baseline SGLT2i use (F). The primary composite outcome comprised confirmed ≥ 30% eGFR decline, new-onset or worsening albuminuria, ESKD, or all-cause death. Curves and displayed HRs are unadjusted; adjusted HRs are reported in the text. CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated

glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

The similarity of associations across KDIGO risk and SGLT2i use strata was consistent with the formal treatment-by-subgroup interaction analyses presented in Fig. 3.

Subgroup analyses

Nine prespecified subgroup analyses were conducted. The association between semaglutide and a lower risk of the primary composite outcome was consistent across most subgroups (Fig. 3), including baseline SGLT2i and RASI use, eGFR and UACR categories and baseline KDIGO risk category, as well as age and BMI categories (all p values for interaction > 0.2).

Two subgroup interactions reached nominal statistical significance. The association with lower primary composite outcome risk was stronger in the baseline HbA1c < 7% (< 53 mmol/mol) subgroup than in the HbA1c ≥ 7% (≥ 53 mmol/mol) subgroup (HR 0.54; 95% CI 0.45–0.66 vs HR 0.81; 95% CI 0.69–0.94; p for interaction = 0.001). The association also varied by diabetes duration (p for interaction = 0.014), with HRs of 0.57 (95% CI 0.46–0.70) for durations < 5 years, 0.65 (95% CI 0.52–0.82) for durations 5–10 years, 0.73 (95% CI 0.55–0.97) for durations 10–15 years, and 0.95 (95% CI 0.75–1.21) for durations ≥ 15 years. The results of an exploratory joint analysis of baseline HbA1c and diabetes duration are shown in *Supplementary Figure S7.*

Adjusted HRs and 95% CIs for the primary composite outcome across baseline subgroups. All subgroup analyses except those for cardiovascular disease were prespecified. Stratum-specific HRs and interaction p values were estimated from adjusted Cox models including treatment, subgroup, and treatment-by-subgroup interaction terms; no adjustments were made for multiple comparisons. SI equivalents: HbA1c 7% = 53 mmol/mol; UACR 30 mg/g = 3.4 mg/mmol. BMI, body mass index; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; RASI, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter-2 inhibitor; UACR, urine albumin–creatinine ratio.

KDIGO risk category transitions

Among participants with baseline low KDIGO risk, deterioration (progression to moderate, high, or very high risk, or death) occurred in 13.0% (638/4,906) of semaglutide-treated participants versus 16.4% (811/4,945) in the DPP4i group (HR 0.82; 95% CI 0.72–0.94; p = 0.003). Among participants with baseline moderate KDIGO risk, deterioration (progression to high or very high risk, or death) occurred in 15.4% (271/1,765) of semaglutide-treated participants versus 19.9% (344/1,728) in the DPP4i group (HR 0.78; 95% CI 0.64–0.96; p = 0.018). More semaglutide-treated participants experienced regression to low risk: 36.1% (637/1,765) versus 32.5% (562/1,728) in the DPP4i group: HR 1.23; 95% CI 1.07–1.43; p = 0.005 (*Supplementary Figure S8).*

Discussion

In this large, real-world propensity score–matched cohort study of adults with type 2 diabetes at low to moderate KDIGO risk, the initiation of semaglutide, compared with the initiation of DPP4i, was associated with a 31% lower risk of the composite kidney outcome during 36 months of follow-up. The primary composite outcome was driven mainly by new-onset or worsening albuminuria, alongside confirmed eGFR decline and all-cause death, whereas end-stage kidney disease (ESKD) events were rare. This outcome composition differs from that of FLOW, where eGFR decline and kidney failure are more prominent [6], and reflects the expected natural history in this population with preserved kidney function, where albuminuria is often the earliest detectable marker of kidney damage [12] and independently predicts kidney failure, cardiovascular events, and mortality even in patients with eGFRs > 60 mL/min/1.73 m² [13, 14, 15]. The findings were consistent in secondary analyses using more stringent eGFR decline thresholds (≥ 40% and ≥ 50%) after all-cause death was excluded from the composite and across baseline KDIGO risk and SGLT2i use strata. The primary analysis (HR 0.69) and on-treatment analysis (HR 0.46) were directionally consistent, providing complementary evidence under different treatment-exposure assumptions. The similar estimates after excluding death from the composite and treating death as a competing event suggest that the primary association was not attributable solely to differences in all-cause mortality. Because the vast majority of semaglutide initiators received subcutaneous semaglutide, the findings predominantly reflect subcutaneous semaglutide use.

The earlier-risk context is clinically important, as kidney injury may precede conventional CKD thresholds and provide an opportunity for preventive intervention [9]. Notably, 4,969 (74.1%) participants in the DPP4i group and 4,933 (73.6%) in the semaglutide group were at low KDIGO risk and did not formally qualify for an established CKD diagnosis. While these participants do not fulfill the definition of CKD, the prognostic significance of even minimal albuminuria is well established: even among individuals with preserved eGFRs, a higher UACR within the normoalbuminuric range is associated with greater subsequent risks of adverse kidney and cardiovascular outcomes [16, 17]. This substantial subgroup supports further evaluation of semaglutide's role in prevention-oriented kidney risk management.

The KDIGO risk transition analysis provides additional clinical context beyond conventional time-to-event outcomes. In both baseline-risk groups, semaglutide initiators had a lower adjusted hazard of deterioration—defined as progression to a higher KDIGO risk category or death—than DPP4i initiators. Among participants with moderate baseline risk, semaglutide initiators also had a higher adjusted hazard of regression to the low-risk category. Because the KDIGO categories integrate both kidney function and albuminuria [5] and are widely used for risk stratification and therapeutic decision-making, these findings are consistent with a more favorable overall kidney-risk trajectory among semaglutide initiators rather than only isolated differences in kidney function measures.

An association between semaglutide and reduced kidney risk was observed both among participants receiving and not receiving SGLT2i at baseline. This finding is particularly relevant given the increasing use of combination therapy in contemporary diabetes care. In the FLOW trial, only a minority of

participants were receiving SGLT2i, limiting the ability to draw definitive conclusions regarding combination therapy [6]. In the present study, the associations between semaglutide and lower kidney risk were similar regardless of baseline SGLT2i use. These findings are consistent with the concept that kidney risk reductions associated with GLP-1 receptor agonists and SGLT2i may be complementary rather than redundant, providing real-world support for current guideline recommendations favoring the combined use of these therapies in appropriate patients [1, 5].

Nine prespecified subgroup analyses were conducted without adjustment for multiple comparisons; interaction findings should therefore be interpreted as exploratory. The association between semaglutide initiation and a lower risk of the primary composite outcome appeared to be strongest among participants with HbA1c < 7% (< 53 mmol/mol) and among those with a shorter diabetes duration. Exploratory joint stratification revealed a similar diabetes duration pattern within both HbA1c strata (< 7% and ≥ 7%), suggesting that the duration finding was not solely explained by baseline glycemic control. Together, these observations lead to the hypothesis that semaglutide-associated kidney benefits may be more apparent earlier in the disease course and may involve mechanisms beyond glucose lowering, which is consistent with the findings of studies by LEADER and SUSTAIN-6 suggesting that changes in glycemic control explain only a modest proportion of GLP-1 receptor agonist–associated kidney benefits [18].

An important consideration for interpretation is the population represented by the matched comparison. Approximately 70% of eligible semaglutide initiators were not included in the matched analysis, resulting in a matched semaglutide cohort that was somewhat older and had a lower BMI, cardiovascular disease burden, and SGLT2i use than did the broader eligible semaglutide cohort. The baseline profile of the matched semaglutide cohort—mean age 61.5 years, HbA1c 7.5% (58.5 mmol/mol), BMI 32.0 kg/m², predominantly preserved kidney function, and modest cardiovascular burden—reflects a type 2 diabetes population in which both semaglutide and DPP4i may have been considered in routine care, particularly during the study period (2019–2024). As treatment paradigms increasingly emphasize weight management and cardiorenal risk reduction beyond glycemic control alone, this population remains clinically relevant for evaluating whether semaglutide initiation is associated with more favorable kidney outcomes than DPP4i initiation is. Compared with the high cardiovascular risk population studied in SUSTAIN-6 [19] and the high kidney risk population studied in FLOW [6], our matched semaglutide cohort had lower baseline cardiovascular and kidney risk, thereby extending rather than duplicating evidence to a population not directly studied in either trial *(Supplementary Figure S9)*.

Strengths

Several strengths of this study deserve mention. These include the large sample size, with more than 1,400 primary composite outcome events, a nationwide real-world setting, and the availability of longitudinal laboratory data, including eGFRs and UACRs. The active-comparator, new-user design, which compares incident semaglutide initiators with incident DPP4i initiators, reduces the potential for healthy-user and prevalent-user bias that can arise in comparison with nonusers or prevalent users. Additional

strengths include comprehensive propensity score matching and the evaluation of clinically relevant secondary and subgroup analyses. Sensitivity analyses using alternative eGFR thresholds, exclusion of death, competing-risk modeling, and extended follow-up provided supportive evidence for the primary association.

Limitations

Several limitations should be acknowledged. As with all observational studies, residual confounding cannot be excluded despite extensive matching and adjustment, including confounding by indication; the E value of 2.26 indicates that an unmeasured confounder would need to be associated with both treatment and outcome by a risk ratio of at least 2.26-fold each to fully explain the observed association. Treatment selection may have operated in both directions: semaglutide may have been preferentially prescribed to more engaged patients suitable for injectable therapy and to higher-risk patients requiring intensive cardiometabolic management, whereas DPP4i may have been favored in stable patients with mild hyperglycemia and in older, frailer individuals. Residual confounding could therefore bias the association in either direction rather than uniformly favoring one treatment. The matched cohort, although not capturing the full spectrum of real-world semaglutide initiators, represents a clinically relevant earlier-risk population underrepresented in randomized trials. Semaglutide-associated body composition changes could theoretically influence creatinine-based eGFR estimates, since cystatin C was unavailable; however, cystatin C– and creatinine-based eGFR declines were nearly identical in the FLOW trial [6], which is reassuring. Finally, the 36-month administrative censoring point was not prespecified and was chosen on the basis of calendar-time enrollment patterns and late risk-set composition rather than observed outcome differences; the similar estimate using the fully available follow-up (HR 0.70; 95% CI 0.62–0.79) supports robustness to this choice.

Conclusions

Among adults with type 2 diabetes at low to moderate risk for adverse kidney outcomes, semaglutide initiation was associated with a 31% lower risk of the composite kidney outcome than DPP4i therapy during 36 months of follow-up. This association was consistent in secondary analyses using alternative eGFR thresholds and after excluding all-cause death and across baseline KDIGO risk categories and SGLT2i use strata. These findings suggest that semaglutide may be associated with favorable kidney outcomes at earlier stages of kidney risk in individuals with type 2 diabetes, including patients without established CKD, supporting its potential role in prevention-oriented kidney risk management in individuals with type 2 diabetes.

Abbreviations

AI
artificial intelligence
ATC

Anatomical Therapeutic Chemical
BMI
body mass index
HF
heart failure
CI
confidence interval
CKD
chronic kidney disease
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration
CPT
Current Procedural Terminology (CPT)
DPP4i
dipeptidyl peptidase-4 inhibitor
eGFR
estimated glomerular filtration rate
EMA
European Medicines Agency
ESKD
end-stage kidney disease
FDA
US Food and Drug Administration
GLP-1 RA
glucagon-like peptide-1 receptor agonist
HbA1c
glycated hemoglobin
HDL
high-density lipoprotein
HR
hazard ratio
ICD
International Classification of Diseases
IHD
ischemic heart disease
IQR
interquartile range
KDIGO
Kidney Disease: Improving Global Outcomes
KM

Kaplan–Meier
LDL
low-density lipoprotein
MHS
Maccabi Healthcare Services
MICE
multiple imputation by chained equations
PVD
peripheral vascular disease
RASI
renin–angiotensin system inhibitor
RWE
real-world evidence
SD
standard deviation
SGLT2i
sodium–glucose cotransporter-2 inhibitor
sHR
subdistribution hazard ratio
SMD
standardized mean difference
T2D
type 2 diabetes
UACR
urine albumin–creatinine ratio.

Declarations

Ethics approval and consent to participate

The study was approved by the Maccabi Healthcare Services Institutional Review Board (MHS-0001-25) on 15 March 2025. The requirement for informed consent was waived because the study used deidentified retrospective data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to Israeli Ministry of Health regulations. Specific requests for remote access to deidentified, community-level data may be referred to the Kahn-Sagol-Maccabi Research and Innovation Center, Maccabi Healthcare Services, Tel Aviv, Israel.

Competing interests

GAH reported consultancy fees from Novo Nordisk; participation on advisory boards for Sanofi and Eli Lilly, serving as principal investigator on several clinical trials sponsored by Novo Nordisk, Eli Lilly, Sanofi, AstraZeneca and Bayer including the CONFIDENCE study, through Hadassah Medical Center; travel support from Novo Nordisk and Medtronic through Hadassah Medical Center and AstraZeneca through Sheba Medical Center; and participation in speakers' bureaus for AstraZeneca, Novo Nordisk, Eli Lilly and Sanofi.

JFEM reported grants from Novo Nordisk and McMaster University (Hamilton, Canada); consulting fees from Novo Nordisk, AstraZeneca, and Bayer; honoraria from Novo Nordisk, AstraZeneca, Bayer, UpToDate and Hexal; participation on data safety monitoring boards or advisory boards for Axio, Cytel, IQVIA, Parexel, WCG, AstraZeneca and Sanofi; and a leadership role within the KDIGO group.

AA is an employee of Novo Nordisk.

AHR were independent statistical consultants and received compensation from Novo Nordisk for the statistical analysis related to this manuscript. They report no equity, employment, or other financial interest in Novo Nordisk beyond consulting fees. Both authors are affiliated with the Department of Endocrinology and Metabolism, Hadassah Medical Center (Hebrew University of Jerusalem), where they participate in an ongoing research program evaluating the outcomes of glucose-lowering therapies (GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors); this program has previously received funding from AstraZeneca for unrelated trials (DECLARE-TIMI 58, SAVOR-TIMI 53). Both authors also provide independent statistical consulting to the diabetes research program at Sheba Medical Center and to other biopharmaceutical companies with diabetes/obesity development programs.

AD was an independent consultant and received compensation from Novo Nordisk for data management and statistical analysis related to this manuscript. AD reports no equity, employment, or other financial interest in Novo Nordisk beyond this consulting fee.

EL is an employee of the KSM Research Institute, Maccabi Healthcare Services

SG was an employee of the KSM Research Institute, Maccabi Healthcare Services during the conduct of the study.

OM was an independent consultant and received compensation from Novo Nordisk for data management services related to this manuscript. OM reports no equity, employment, or other financial

interest in Novo Nordisk beyond this consulting fee.

GC reported consultancy fees from Novo Nordisk; honoraria form Novo Nordisk, AstraZeneca, Bayer, Boehringer Ingelheim and travel support from Novo Nordisk.

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Authors' contributions

GAH contributed to conceptualization, methodology, investigation and writing–review and editing.

JFEM contributed to the methodology, investigation and writing–review and editing.

AA contributed to conceptualization, methodology, investigation, writing–original draft, writing–review and editing, project administration and funding acquisition.

AHR contributed to conceptualization, methodology, investigation, formal analysis and writing–review and editing.

IY contributed to conceptualization, methodology, investigation, formal analysis and writing–review and editing.

AD contributed to the methodology, software, validation, formal analysis, data curation and management, and visualization.

EL contributed to resources, data curation and writing–review.

SG contributed to the methodology and writing–review and editing.

OM contributed to software, data curation and writing–review and editing.

GC contributed to the methodology, investigation and writing–review and editing.

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Figures

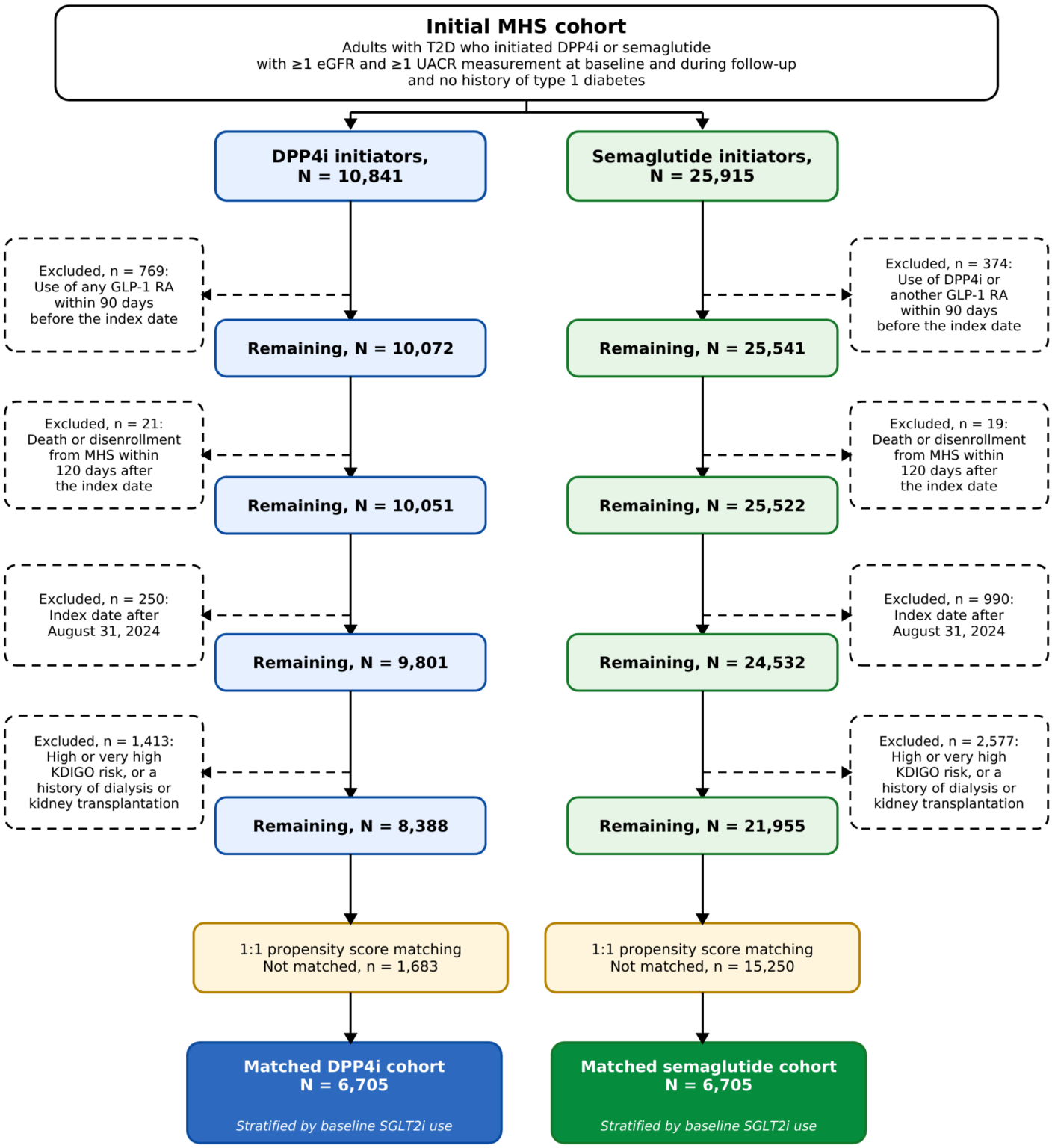


Figure 1

Cohort selection and propensity score matching

MHS, Maccabi Healthcare Services; T2D, type 2 diabetes; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; eGFR, estimated glomerular filtration rate; UACR, urine

albumin–creatinine ratio; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

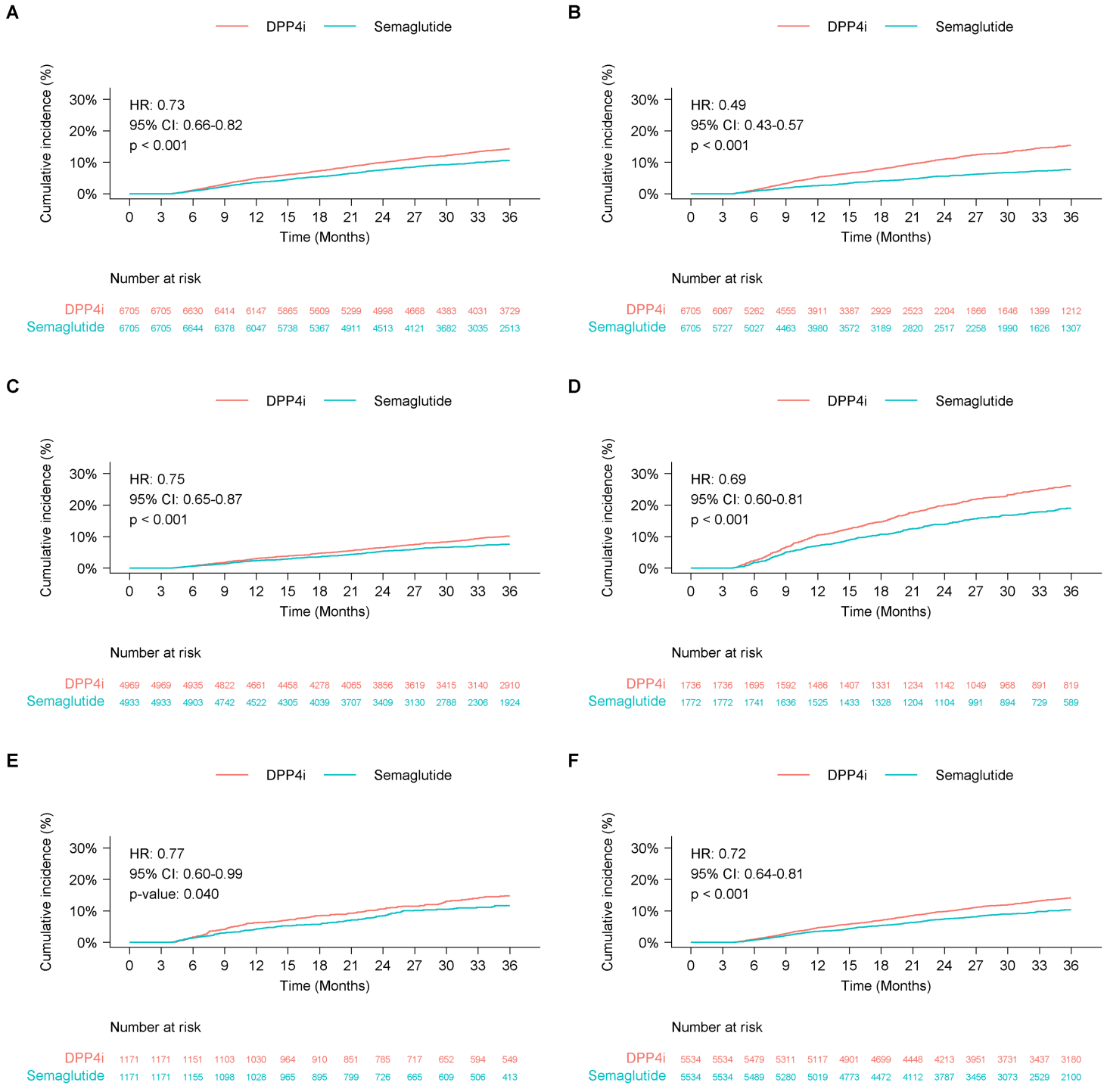


Figure 2

Primary composite outcome across analyses and subgroups

Kaplan–Meier curves for the primary composite outcome comparing semaglutide with DPP4i in the primary analysis (A), on-treatment analysis (B), low-KDIGO-risk subgroup (C), moderate-KDIGO-risk

subgroup (D), participants with baseline SGLT2i use (E), and participants without baseline SGLT2i use (F). The primary composite outcome comprised confirmed ≥30% eGFR decline, new-onset or worsening albuminuria, ESKD, or all-cause death. Curves and displayed HRs are unadjusted; adjusted HRs are reported in the text. CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT2i, sodium—glucose cotransporter-2 inhibitor.

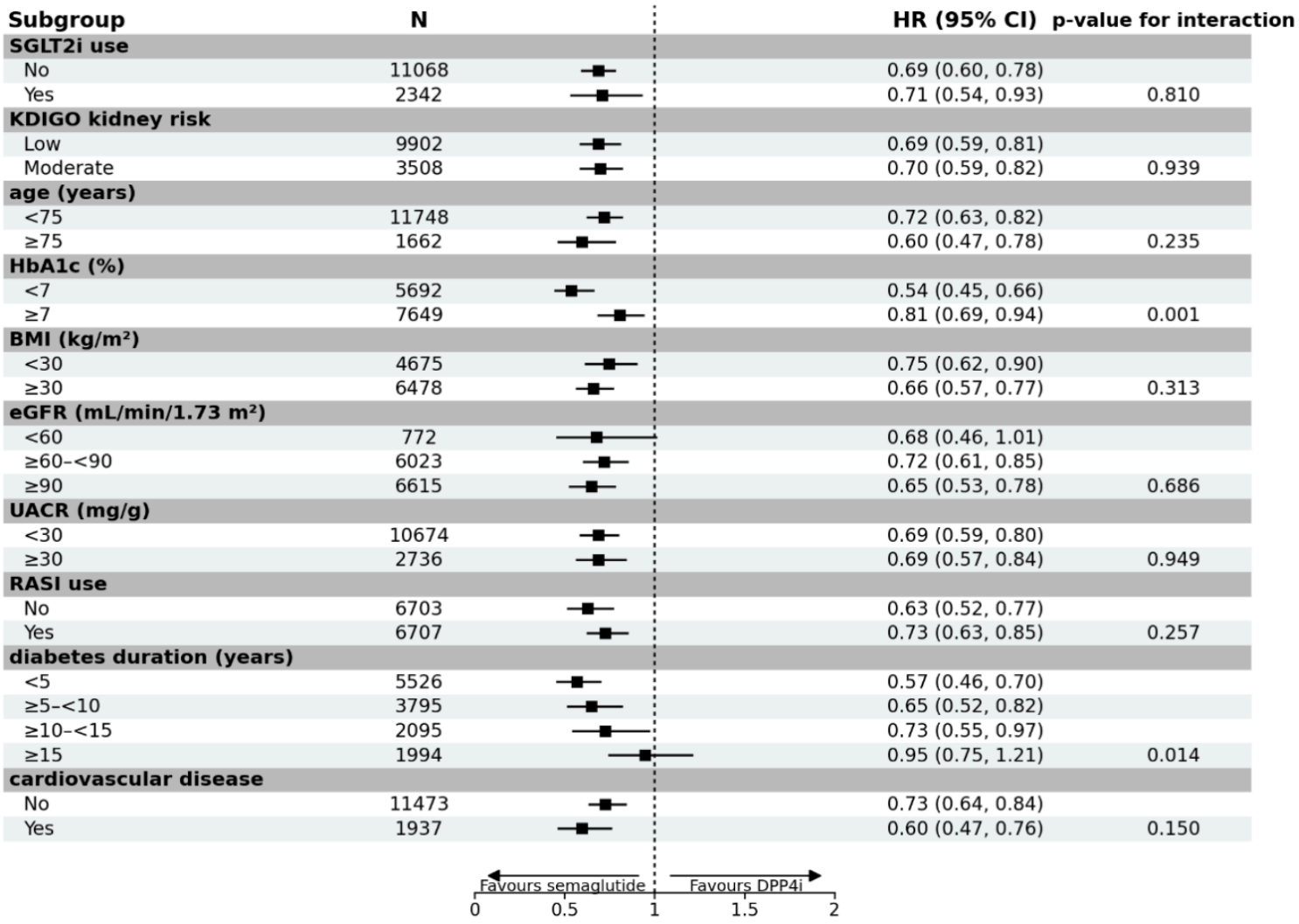


Figure 3

Subgroup analysis

Adjusted HRs and 95% CIs for the primary composite outcome across baseline subgroups. All subgroup analyses except those for cardiovascular disease were prespecified. Stratum-specific HRs and interaction p values were estimated from adjusted Cox models including treatment, subgroup, and treatment-by-subgroup interaction terms; no adjustments were made for multiple comparisons. SI equivalents: HbA1c 7% = 53 mmol/mol; UACR 30 mg/g = 3.4 mg/mmol. BMI, body mass index; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes;

RASI, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter-2 inhibitor; UACR, urine albumin–creatinine ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.docx
- floatimage1.png