

Supplementary Material

Comparative Effectiveness of Once-Weekly Semaglutide versus Sulfonylureas, DPP4 Inhibitors, and Thiazolidinediones in Patients with Type 2 Diabetes and Chronic Kidney Disease

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* At the time of study

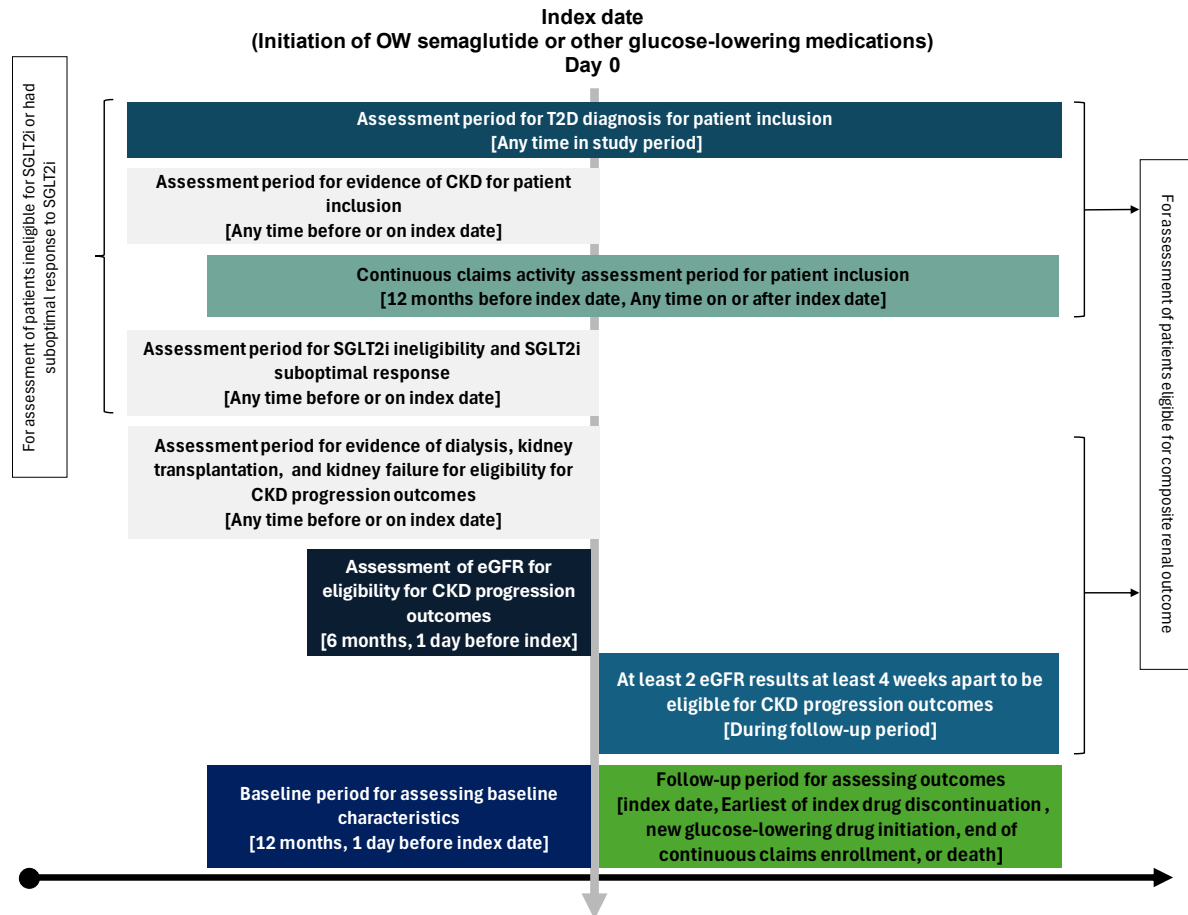
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Supplementary Figure 1: Study design

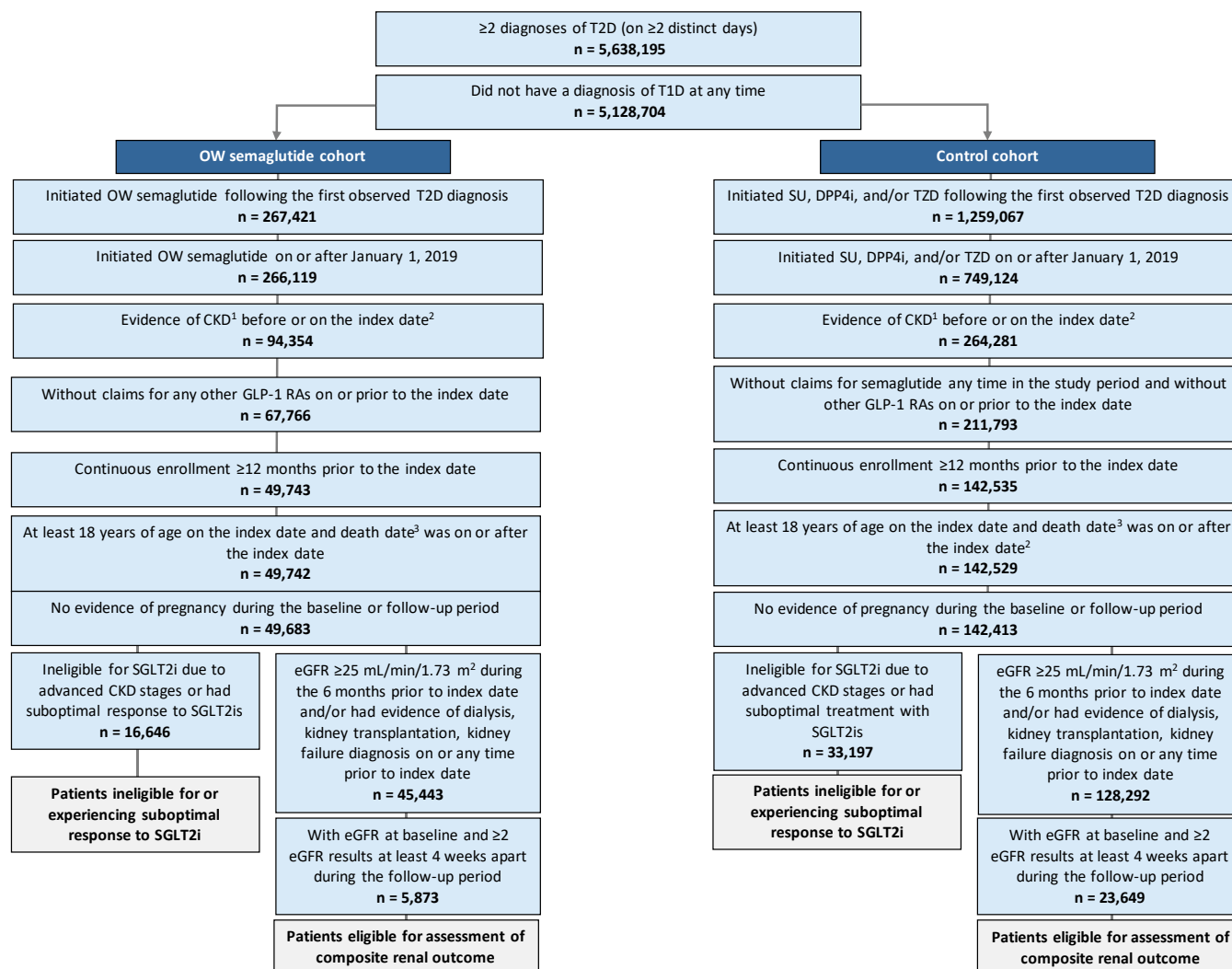


Abbreviations: OW, once-weekly; T2D, type 2 diabetes; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2i, Sodium-glucose co-transporter-2 inhibitors; ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification; UACR: Urine albumin-to-creatinine ratio

Notes:

1. T2D was defined as having at least two diagnoses of T2D (ICD-10-CM, E11) on distinctive days.
2. Evidence of CKD was identified based on one of the following criteria: 1) at least one diagnosis of CKD based on ICD-10-CM codes, 2) at least two eGFR readings <90 mL/min/1.73 m² measured 90 to 365 days apart, or 3) at least two impaired UACRs (≥ 30 mg/g) measured 90 to 365 days apart.

Supplementary Figure 2: Sample selection



Abbreviations: T2D, type 2 diabetes; T1D, type 1 diabetes; OW, once-weekly; SU, sulphonylureas; DPP-4i, dipeptidyl peptidase-4 inhibitors; TZD, thiazolidinediones; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

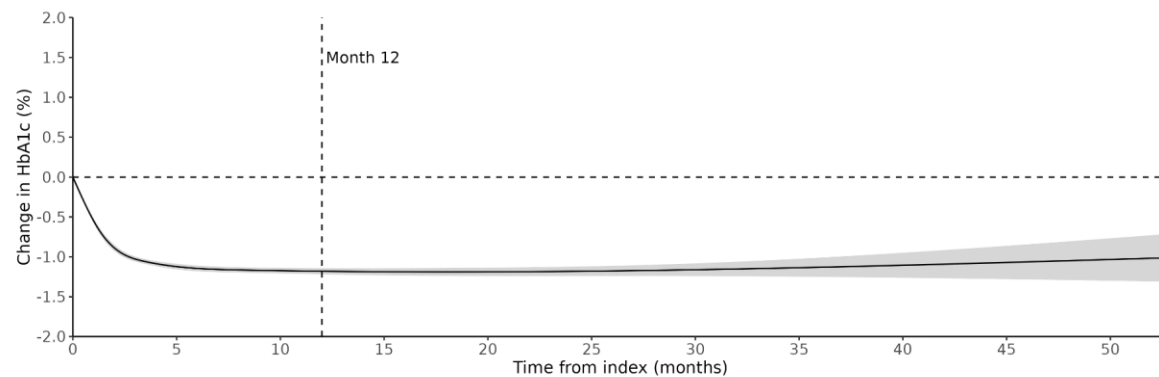
Notes:

1. CKD was identified based on one of the following criteria before or on the index date: (a) ≥ 1 diagnosis code for CKD, or (b) ≥ 2 reduced eGFR (< 90 mL/min/1.73 m²) measured 90 days to 365 days apart, or (c) ≥ 2 impaired UACR (≥ 30 mg/g) measured 90 days to 365 days apart.
2. Index date was defined as the date of the first pharmacy claim for the index drug. The index drug for the OW semaglutide cohort was the first OW semaglutide meeting the selection criteria. The index drug for the control cohort was randomly selected if multiple drugs in the SU, DPP4i or T2D classes met the selection criteria.
3. Death date was imputed as the 15th of the documented month of death.

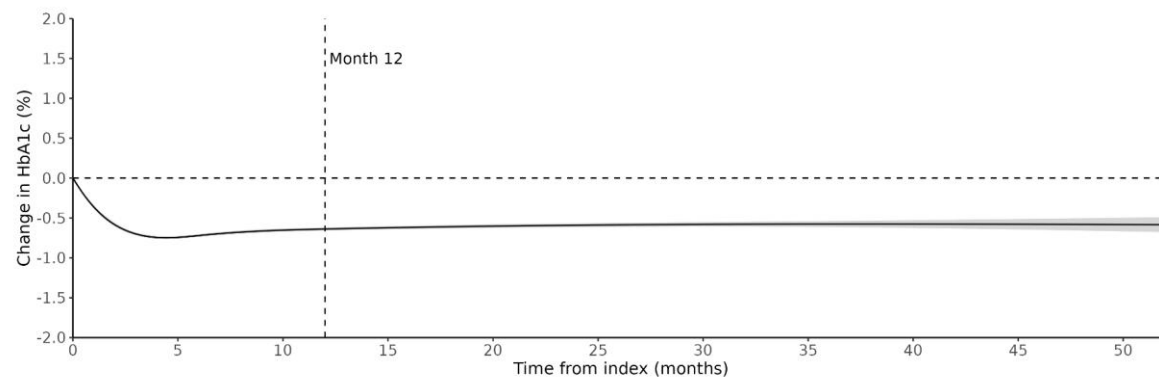
Supplementary Figure 3A: Unadjusted Pre-post changes in clinical outcomes¹ among patients ineligible for or experiencing suboptimal response to SGLT2i

i. HbA1c

OW semaglutide

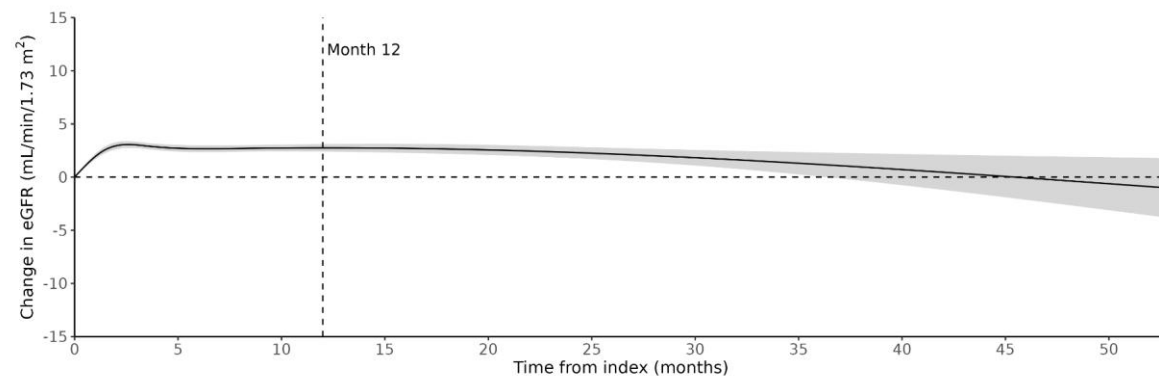


Control

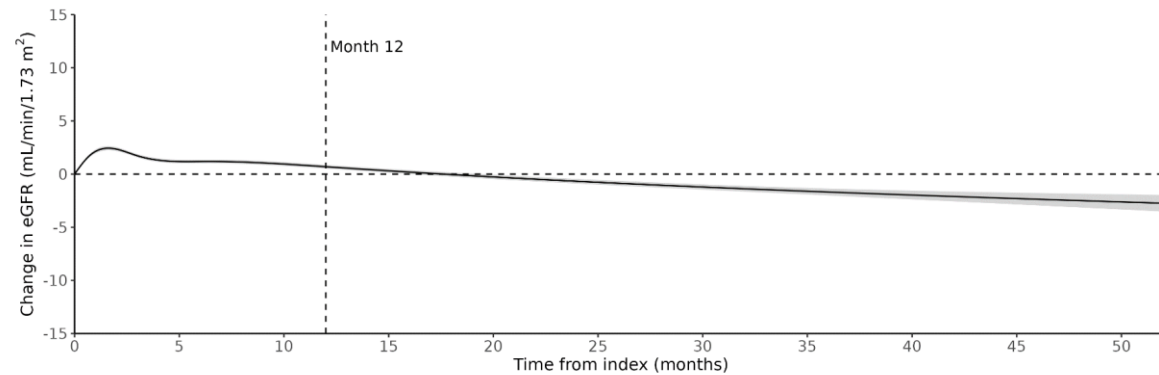


ii. eGFR

OW semaglutide

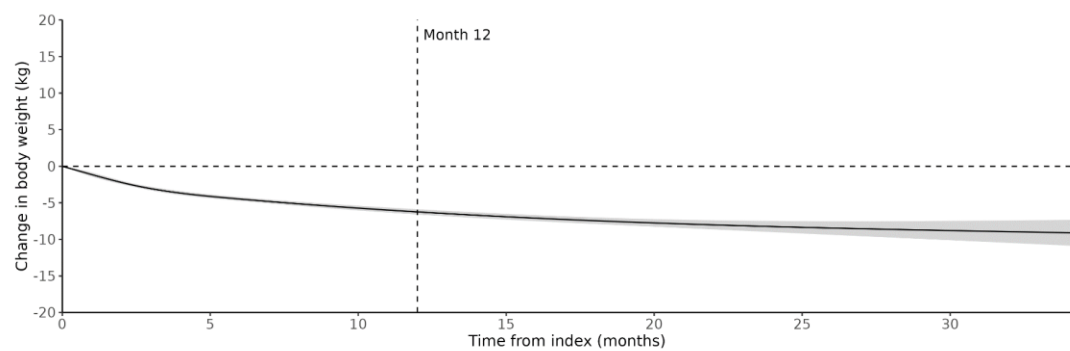


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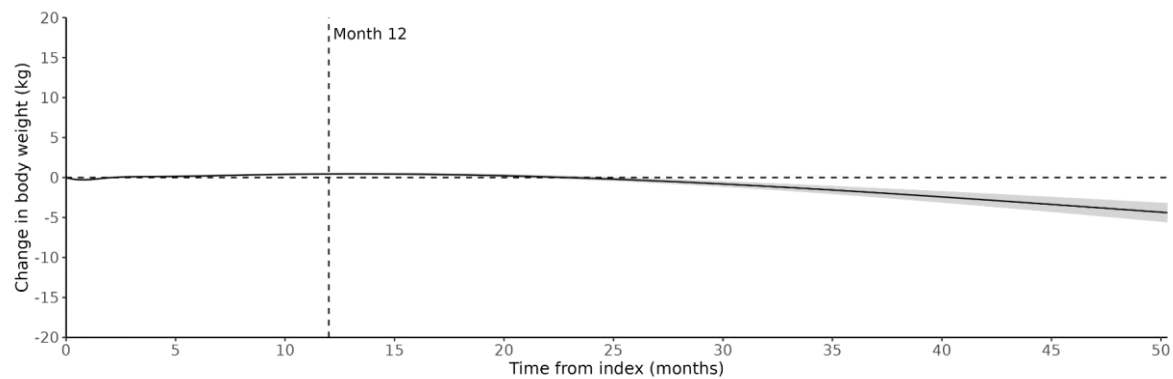


iii. Body weight

OW semaglutide

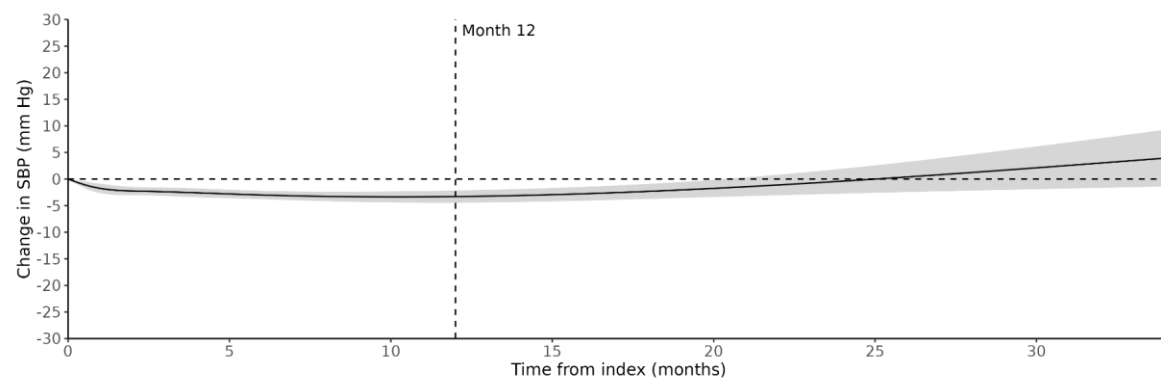


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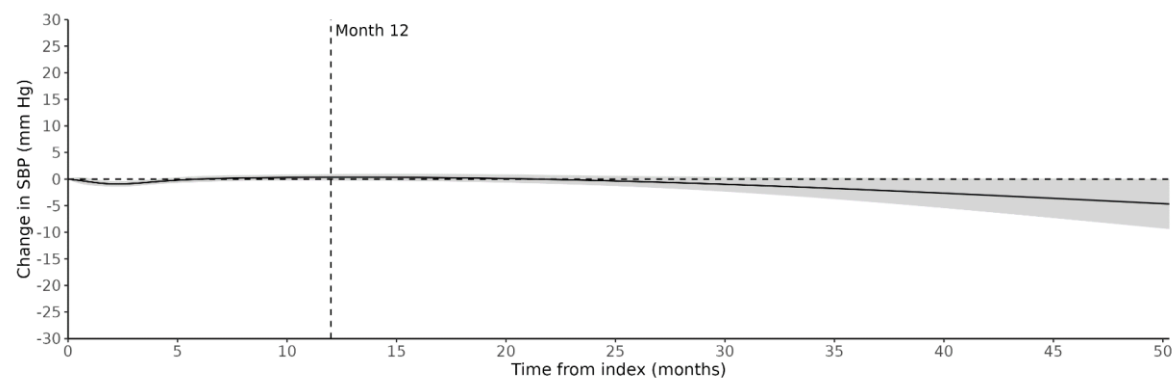


iv. SBP

OW semaglutide



Control



Abbreviations: OW, once-weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitors; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

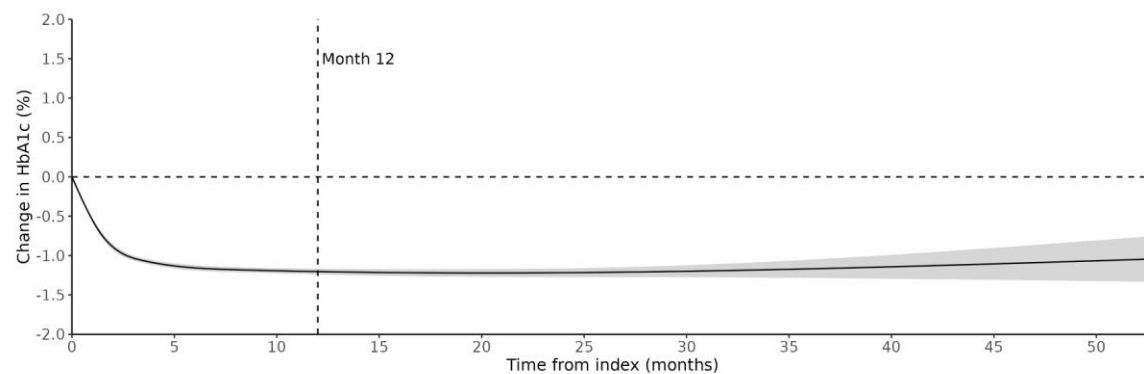
Notes:

1. Four clinical outcomes were evaluated: HbA1c, eGFR, body weight, and SBP. In the control cohort, data for all four outcomes extended beyond 50 weeks after the index date. While the same data duration applied for HbA1c and eGFR in the OW semaglutide cohort, data for body weight and SBP were only available up to 35 months after the index date in this cohort.

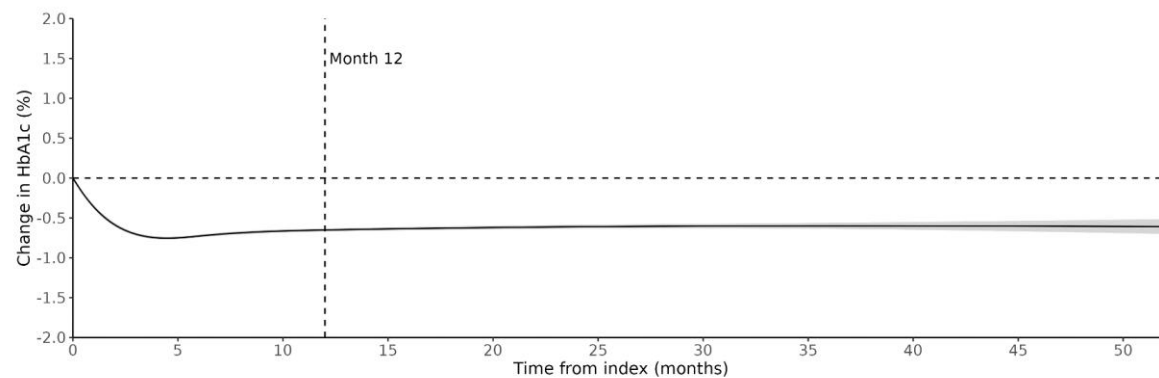
Supplementary Figure 3B: Adjusted¹ Pre-post changes in clinical outcomes² among patients ineligible for or experiencing suboptimal response to SGLT2i

i. HbA1c

OW semaglutide

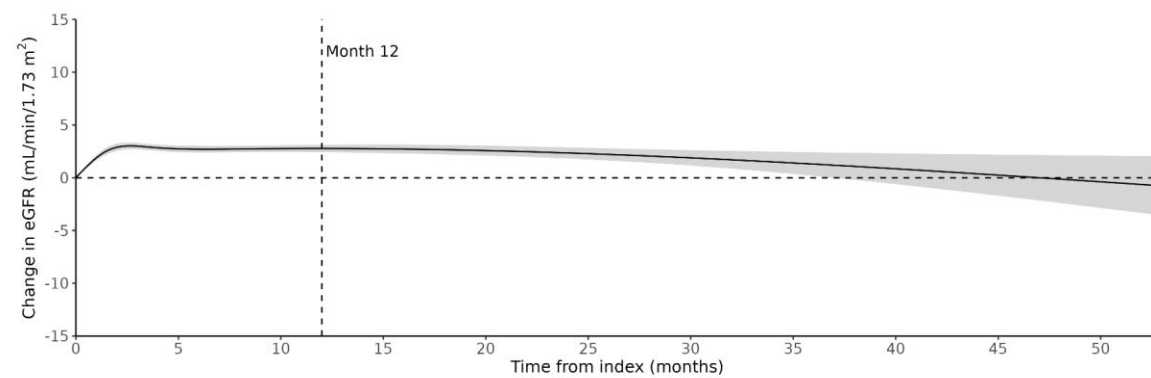


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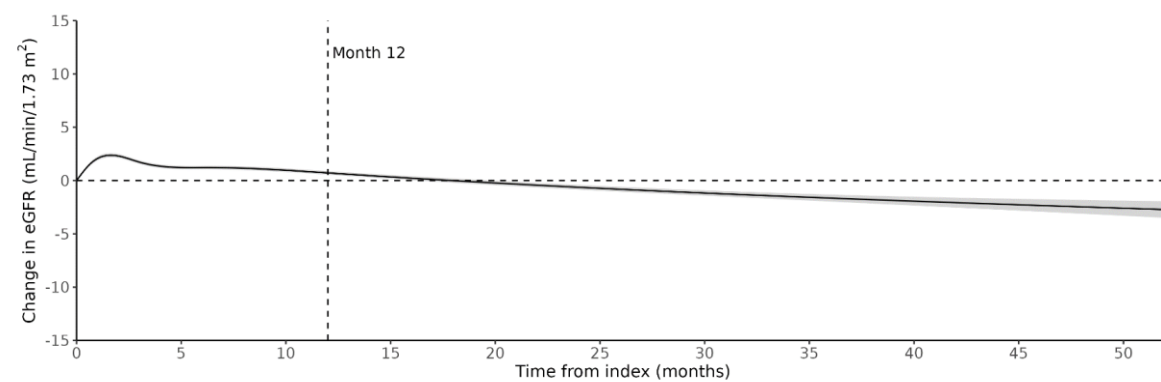


ii. eGFR

OW semaglutide

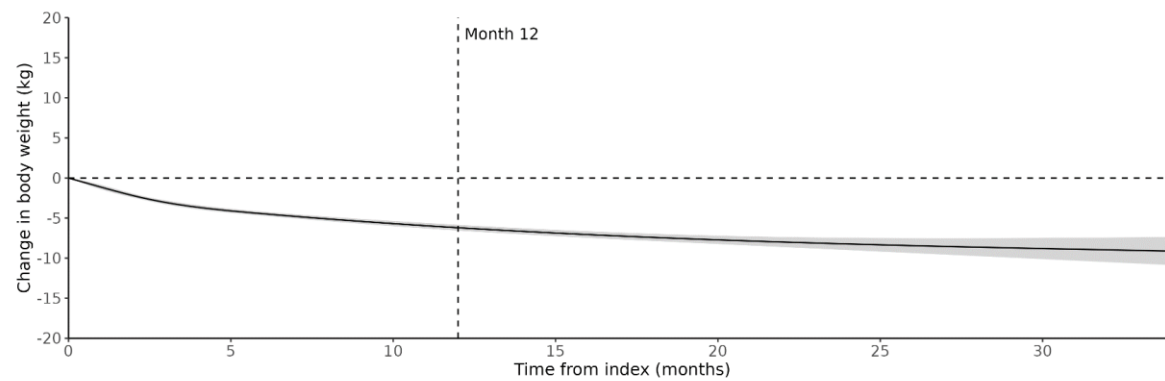


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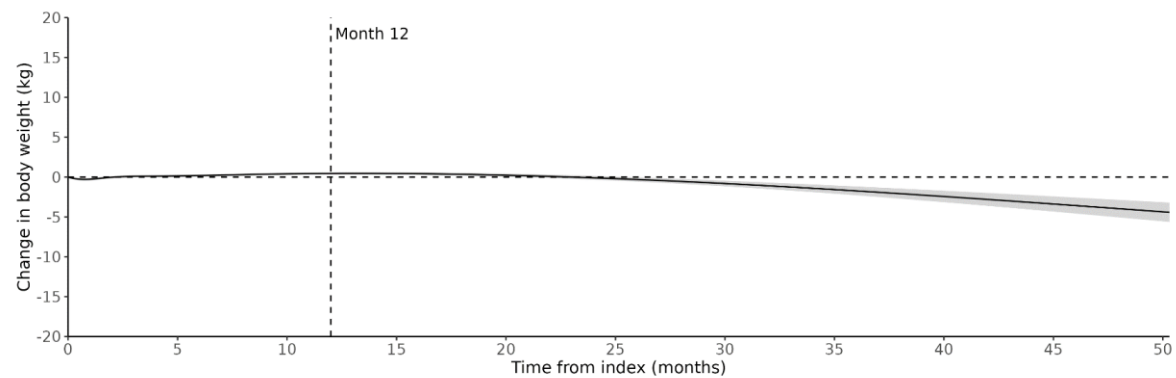


iii. Body weight

OW semaglutide

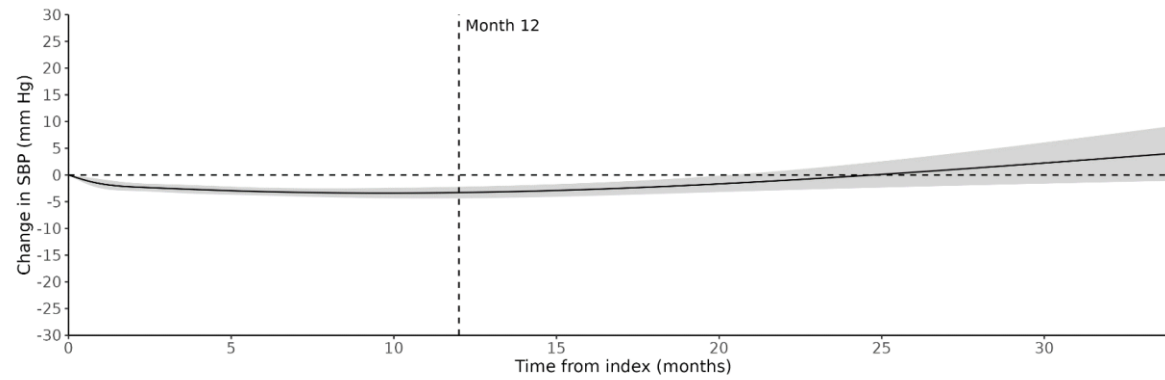


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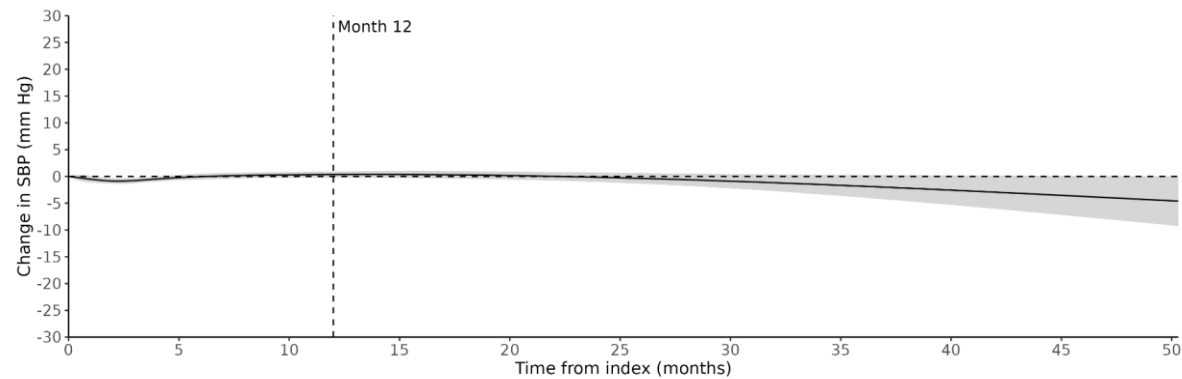


iv. SBP

OW semaglutide



Control



Abbreviations: OW, once-weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitors; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Notes:

2. Adjusted linear mixed-effects model was used to regress the pre-post change in each clinical measure against a spline term for time trend and baseline covariates, including patient demographics and clinical characteristics in each cohort. Random intercepts were included to account for within-patient correlations.
3. Four clinical outcomes were evaluated: HbA1c, eGFR, body weight, and SBP. In the control cohort, data for all four outcomes extended beyond 50 weeks after the index date. While the same data duration applied for HbA1c and eGFR in the OW semaglutide cohort, data for body weight and SBP were only available up to 35 months after the index date in this cohort.

Supplementary Table 1. Baseline characteristics of the OW semaglutide and control cohorts in the overall sample

Patient Characteristics	OW Semaglutide Cohort	Control Cohort
	N = 49,683	N = 142,413
Demographics		
Age groups on the index date (years), n (%)		
<65	16,120 (32.4)	20,826 (14.6)
65-74	22,489 (45.3)	55,811 (39.2)
75+	11,074 (22.3)	65,776 (46.2)
Sex, n (%)		
Male	21,528 (43.3)	72,099 (50.6)
Female	28,150 (56.7)	70,308 (49.4)
Unknown	5 (0.0)	6 (0.0)
Race/ethnicity, n (%)		
White	31,120 (62.6)	79,941 (56.1)
Black	8,043 (16.2)	21,686 (15.2)
Hispanic	6,067 (12.2)	23,615 (16.6)
Asian	1,187 (2.4)	7,329 (5.1)
Other/Unknown	3,266 (6.6)	9,842 (6.9)
Geographic region, n (%)		
South	29,255 (58.9)	76,643 (53.8)
West	8,526 (17.2)	31,104 (21.8)
Midwest	7,543 (15.2)	20,006 (14.0)
Northeast	4,337 (8.7)	14,589 (10.2)
Other/Unknown	22 (0.0)	71 (0.0)
Comorbidities on or before the index date		
CKD stage ¹		
Stage I	2,229 (4.5)	4,849 (3.4)
Stage II	21,415 (43.1)	52,679 (37.0)

Stage III	17,587 (35.4)	57,054 (40.1)
Stage IV	2,406 (4.8)	8,865 (6.2)
Kidney failure	3,782 (7.6)	12,087 (8.5)
Unknown/unspecified	2,264 (4.5)	6,879 (4.9)
Albuminuria ² , n (%)	10,246 (20.6)	29,177 (20.5)
Obesity ³ , n (%)	39,900 (80.3)	76,293 (53.6)
Hypertension, n (%)	47,592 (95.8)	136,735 (96.0)
Deep vein thrombosis or pulmonary embolism, n (%)	7,888 (15.9)	23,713 (16.7)
CCI ⁴		
Mean ± SD	3.3 ± 2.3	3.5 ± 2.5
DCSI ⁵		
Mean ± SD	3.5 ± 2.4	3.8 ± 2.4
Individual Components, n (%)		
Retinopathy	15,461 (31.1)	45,802 (32.2)
Nephropathy	30,132 (60.6)	95,243 (66.9)
Neuropathy	25,227 (50.8)	68,885 (48.4)
Cerebrovascular	9,723 (19.6)	33,575 (23.6)
Cardiovascular	28,866 (58.1)	87,797 (61.6)
Peripheral vascular disease	17,609 (35.4)	55,674 (39.1)
Metabolic	4,793 (9.6)	13,244 (9.3)
CKD-related comorbidities ⁶ , n (%)		
Arrhythmia	23,529 (47.4)	68,166 (47.9)
Anemia	20,647 (41.6)	63,386 (44.5)
Cardiovascular disease	18,950 (38.1)	61,081 (42.9)
Hyperlipidemia	47,306 (95.2)	134,865 (94.7)
Heart failure	11,281 (22.7)	34,077 (23.9)
Sleep disorders	25,774 (51.9)	49,323 (34.6)
Electrolyte abnormalities	16,949 (34.1)	51,088 (35.9)
Procedure on or before the index date		

Dialysis	2,178 (4.4)	6,175 (4.3)
Kidney transplant	496 (1.0)	888 (0.6)
Treatment for T2D		
Number of glucose-lowering treatment classes at baseline ⁷		
Mean ± SD	1.7 ± 1.1	1.4 ± 1.0
Baseline glucose-lowering treatment, n (%)		
Insulin	14,654 (29.5)	18,907 (13.3)
TZD	4,052 (8.2)	8,322 (5.8)
SU	15,047 (30.3)	40,577 (28.5)
Biguanides	31,053 (62.5)	91,221 (64.1)
Meglitinides	495 (1.0)	1,552 (1.1)
Alpha-glucosidase inhibitors	184 (0.4)	632 (0.4)
SGLT2i	10,876 (21.9)	16,319 (11.5)
DPP4i	8,758 (17.6)	22,593 (15.9)
Lab measures during the baseline period		
HbA1c (%) ⁸		
Mean ± SD	7.9 ± 1.7	8.0 ± 1.6
eGFR (mL/min/1.73 m ²) ⁹		
Mean ± SD	66.2 ± 20.6	61.8 ± 21.1
Body weight (kg) ⁸		
Mean ± SD	100.6 ± 22.9	86.3 ± 20.6
SBP (mm Hg) ⁸		
Mean ± SD	132.8 ± 17.1	133.7 ± 18.2

Abbreviations: OW, once-weekly; SGLT2i, Sodium-glucose co-transporter-2 inhibitors; SD, standard deviation; CKD, chronic kidney disease; CCI, Charlson Comorbidity Index; DCSI, Diabetes Complications Severity Index; T2D, type 2 diabetes; TZD, thiazolidinediones; SU, sulphonylureas; DPP4i, dipeptidyl peptidase-4 inhibitors; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification; UACR, urine albumin-to-creatinine ratio.

Notes:

1. CKD stage was identified based on ICD-10-CM diagnosis codes, or eGFR values as specified in the KDIGO guidelines, and procedure codes as the following: Stage I: eGFR ≥90 mL/min/1.73 m²; Stage II: ≥2 eGFR 60 - <90 mL/min/1.73 m² measured 90 days to 365 days apart; Stage III: ≥2 eGFR 30 - <60 mL/min/1.73 m² measured 90

days to 365 days apart; Stage IV: ≥ 2 eGFR 15 - <30 mL/min/1.73 m² measured 90 days to 365 days apart; kidney failure: ≥ 2 eGFR <15 mL/min/1.73 m² measured 90 days to 365 days apart, or ≥ 1 procedure code for dialysis. For patients who met the criteria for >1 CKD stages, the most severe CKD stage was used. The “Unknown/unspecified” category included patients identified based on elevated UACR alone, without eligible eGFR labs or CKD diagnoses and patients with ≥ 2 eGFR <90 mL/min/1.73 m² measured 90 days to 365 days apart but without two eGFR tests indicating the same stage.

2. Albuminuria was identified based on ≥ 2 impaired UACR (≥ 30 mg/g) measured 90 days to 365 days apart, or based on diagnosis codes.
3. Obesity was identified based on documented or derived BMI ≥ 30 per lab results, or based on diagnosis codes.
4. CCI was calculated per the Quan et al. (2005) study [1].
5. DCSI was calculated per the Glasheen et al. (2017) study [2].
6. CKD-related and other baseline comorbidities were identified using ICD-10-CM diagnosis codes.
7. Glucose-lowering treatment classes included insulin, TZD, SU, biguanides, meglitinides, alpha-glucosidase inhibitors, SGLT2i, and DPP4i.
8. Lab measures for HbA1c, body weight, and SBP during baseline were evaluated on a date closest to the index date within a 6-month window before index.
9. Lab measure for eGFR during baseline was selected as the lowest value within a 6-month window before index.

Supplementary Table 2. Differences in pre-post changes in clinical outcomes in the OW semaglutide and control cohorts among patients ineligible for or experiencing suboptimal response to SGLT2i

Clinical measure	OW Semaglutide Cohort Mean (95% CI)	Control Cohort Mean (95% CI)	Difference
Unadjusted estimates			
Change in HbA1c (%)			
Month 6	-1.15 (-1.18, -1.11)	-0.72 (-0.74, -0.70)	-0.42 (-0.46, -0.39)
Month 12	-1.18 (-1.22, -1.14)	-0.64 (-0.66, -0.62)	-0.54 (-0.58, -0.50)
Month 18	-1.19 (-1.24, -1.14)	-0.61 (-0.63, -0.59)	-0.58 (-0.63, -0.53)
Month 24	-1.18 (-1.24, -1.12)	-0.59 (-0.62, -0.57)	-0.59 (-0.65, -0.53)
Change in eGFR (mL/min/1.73 m²)			
Month 6	2.66 (2.35, 2.98)	1.18 (1.03, 1.33)	1.48 (1.13, 1.83)
Month 12	2.75 (2.40, 3.10)	0.69 (0.52, 0.85)	2.06 (1.67, 2.45)
Month 18	2.64 (2.19, 3.08)	-0.05 (-0.24, 0.14)	2.69 (2.20, 3.17)
Month 24	2.32 (1.79, 2.84)	-0.68 (-0.89, -0.46)	2.99 (2.42, 3.56)
Change in body weight (kg)			
Month 6	-4.49 (-4.73, -4.24)	0.19 (0.05, 0.33)	-4.67 (-4.95, -4.40)
Month 12	-6.24 (-6.60, -5.89)	0.45 (0.30, 0.59)	-6.69 (-7.07, -6.31)
Month 18	-7.45 (-7.89, -7.00)	0.34 (0.16, 0.52)	-7.79 (-8.27, -7.31)
Month 24	-8.25 (-9.01, -7.49)	-0.10 (-0.33, 0.13)	-8.15 (-8.94, -7.36)
Change in SBP (mm Hg)			
Month 6	-2.99 (-3.76, -2.22)	-0.01 (-0.56, 0.54)	-2.99 (-3.93, -2.04)
Month 12	-3.29 (-4.42, -2.16)	0.34 (-0.23, 0.91)	-3.63 (-4.89, -2.37)
Month 18	-2.30 (-3.71, -0.90)	0.22 (-0.50, 0.93)	-2.52 (-4.09, -0.95)
Month 24	-0.39 (-2.71, 1.94)	-0.25 (-1.14, 0.65)	-0.14 (-2.63, 2.35)
Adjusted estimates			
Change in HbA1c (%)			

Clinical measure	OW Semaglutide Cohort Mean (95% CI)	Control Cohort Mean (95% CI)	Difference
Month 6	-1.16 (-1.19, -1.12)	-0.73 (-0.74, -0.71)	-0.43 (-0.47, -0.39)
Month 12	-1.20 (-1.24, -1.17)	-0.65 (-0.67, -0.63)	-0.55 (-0.59, -0.51)
Month 18	-1.22 (-1.27, -1.17)	-0.63 (-0.65, -0.61)	-0.59 (-0.64, -0.54)
Month 24	-1.22 (-1.27, -1.16)	-0.61 (-0.63, -0.59)	-0.61 (-0.67, -0.55)
Change in eGFR (mL/min/1.73 m²)			
Month 6	2.70 (2.38, 3.01)	1.21 (1.06, 1.36)	1.49 (1.14, 1.84)
Month 12	2.77 (2.42, 3.11)	0.71 (0.55, 0.88)	2.05 (1.67, 2.44)
Month 18	2.65 (2.21, 3.09)	-0.01 (-0.20, 0.18)	2.66 (2.18, 3.15)
Month 24	2.35 (1.82, 2.87)	-0.64 (-0.85, -0.42)	2.98 (2.42, 3.55)
Change in body weight (kg)			
Month 6	-4.46 (-4.70, -4.22)	0.19 (0.05, 0.33)	-4.65 (-4.93, -4.37)
Month 12	-6.21 (-6.56, -5.85)	0.45 (0.31, 0.60)	-6.66 (-7.04, -6.27)
Month 18	-7.41 (-7.86, -6.97)	0.34 (0.16, 0.53)	-7.76 (-8.24, -7.28)
Month 24	-8.23 (-8.99, -7.47)	-0.10 (-0.33, 0.13)	-8.13 (-8.93, -7.34)
Change in SBP (mm Hg)			
Month 6	-3.11 (-3.85, -2.38)	-0.03 (-0.57, 0.50)	-3.08 (-3.99, -2.17)
Month 12	-3.29 (-4.36, -2.22)	0.36 (-0.19, 0.92)	-3.65 (-4.86, -2.45)
Month 18	-2.24 (-3.55, -0.92)	0.28 (-0.41, 0.97)	-2.51 (-4.00, -1.02)
Month 24	-0.28 (-2.50, 1.93)	-0.16 (-1.03, 0.71)	-0.12 (-2.50, 2.26)

Abbreviations: OW, once-weekly; SGLT2i, Sodium-glucose co-transporter-2 inhibitors; CI: confidence interval; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Notes:

1 Spline estimates are presented as least square means and 95% CIs.

References:

1. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005 Nov;43(11):1130-9.
2. Glasheen WP, Renda A, Dong Y. Diabetes Complications Severity Index (DCSI)-Update and ICD-10 translation. *J Diabetes Complications*. 2017 Jun;31(6):1007-13.