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Effect of glucagon-like peptide-1 receptor agonists on vascular risk factors among adults with type 2 diabetes and established atherosclerotic cardiovascular disease

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ABSTRACT

Introduction: Limited data exist on the cardiovascular effectiveness of once-weekly (OW) glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in real-world practice.

Methods: We assessed the OW GLP-1 RA effects on vascular risk factors in adults with type 2 diabetes and atherosclerotic cardiovascular disease using data from a large-scale US electronic health record database (index date = first prescription of OW GLP-1 RA). Exploratory analyses were performed on patients newly initiating OW GLP-1 RAs with semaglutide, OW GLP-1 RAs without semaglutide, and semaglutide. Changes in vascular risk factors were evaluated by comparing mean measures between the 12-month pre- and post-index periods. Analyses were conducted for all three cohorts and subpopulations including stratified by tercile of baseline vascular risk factor value.

Results: In the final cohorts ([1] OW GLP-1 RA including semaglutide: $n = 20{,}084$; [2] OW GLP-1 RA excluding semaglutide: $n = 16{,}894$; [3] semaglutide: $n = 3{,}435$), significant mean reductions ($P < 0.001$) were observed from baseline to post-index in hemoglobin A1c (%, [1] -1.1; [2] -1.1; [3] -1.2), low-density lipoprotein cholesterol (mg/dL, [1] -6.4; [2] -6.4; [3] -6.9), total cholesterol (mg/dL, [1] -11.0; [2] -11.1; [3] -10.7), triglycerides (mg/dL, [1] -31.8; [2] -31.4; [3] -33.1), systolic blood pressure (mmHg, [1] -1.5; [2] -1.2; [3] -3.1), body weight (kg, [1] -2.7; [2] -2.4; [3] -4.3) and body mass index (kg/m^2; [1] -0.9; [2] -0.8; [3] -1.4). Largest reductions were observed in the top tercile.

Conclusion: Our data suggest GLP-1 RAs are associated with significant reductions in key vascular risk factors in real-world practice.

Abbreviations: ACC, American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; EHR, electronic health record; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; OW, once-weekly; QRISK3, QRESEARCH risk estimator version 3; SD, standard deviation; SBP, systolic blood pressure; TT, top tercile; T2D, type 2 diabetes; VLDL-C, very-low-density lipoprotein cholesterol.

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1. Introduction

Patients with type 2 diabetes (T2D) are at high risk of developing cardiovascular disease (CVD), a major cause of mortality among this population [1]. Atherosclerotic cardiovascular disease (ASCVD) accounts for the majority of CVD diagnoses in patients with T2D, and it is estimated that around half of those with T2D in the US also have ASCVD [2,3].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce the risk of major adverse cardiovascular events (MACE) in patients with T2D [4]. There are several suggested mechanisms of cardiovascular protection by GLP-1 RAs through targeted modulation of mediators of macro- and microvascular pathophysiology and hemodynamics [5]. Importantly, GLP-1 RAs are associated with improvements in cardiovascular (CV) risk factors [6] including blood pressure (BP) [7], lipid profiles, e.g., triglycerides and cholesterol [8], and body weight [9–12], in addition to their glucose-lowering effects [13]. However, there may be considerable heterogeneity within the GLP-1 RA drug class with regard to CV benefits, with some research suggesting that older generations of daily GLP-1 RAs may be less efficacious in reducing CV events [14–16]. Additionally, newer once-weekly (OW) GLP-1 RAs are associated with superior adherence and persistence versus daily injectable GLP-1 RAs [17], and represent the majority of prescriptions for this class of medication in the US [18]. Therefore, analyses focused on newer OW GLP-1 RAs are important to examine a more clinically relevant effect on CV outcomes [14].

OW semaglutide (Ozempic®; Novo Nordisk, Bagsværd, Denmark), hereafter referred to as 'semaglutide', is a new-generation GLP-1 RA indicated, as an adjunct to diet and exercise, for the improvement of glycemic control in patients with T2D [19] and has been demonstrated to provide greater glycemic and weight-lowering efficacy than other GLP-1 RAs [20]. Semaglutide significantly reduces the risk of CVD in patients with T2D [21]; in a combined analysis of the SUSTAIN and PIONEER 6 trials, semaglutide reduced the risk of MACE vs placebo (hazard ratio 0.76; 95% confidence interval [CI] 0.62, 0.92). [22]

Despite their prevalent use, new-generation GLP-1 RAs have been underrepresented in real-world analyses of the CV effectiveness of GLP-1 RAs [23,24]. The aim of this exploratory analysis was to comprehensively investigate and compare the associations between OW GLP-1 RAs and changes in vascular risk factors in adults with T2D and established ASCVD, using a large-scale electronic health record (EHR) database in the US.

2. Materials and methods

2.1. Study design and data source

This was a retrospective observational cohort study utilizing the TriNetX Dataworks-USA network from January 01, 2017 to January 31, 2023. The TriNetX Dataworks-USA network is a de-identified, longitudinal EHR-derived dataset that includes outpatient and inpatient EHRs for >90 million patients from 57 healthcare organizations across the US. Network members include academic medical centers, integrated delivery networks, specialty hospitals, and large specialty physician practices. This retrospective study is exempt from informed consent. The data reviewed are a secondary analysis of existing de-identified data, do not involve intervention or interaction with human subjects, and are de-identified per the de-identification standard defined in Section §164.514 (a) of the HIPAA Privacy Rule.

Exploratory analyses were carried out on three cohorts: 1) patients newly initiating OW GLP-1 RAs (semaglutide, dulaglutide, or exenatide), 2) patients newly initiating OW GLP-1 RAs excluding semaglutide (dulaglutide or exenatide only), and 3) patients newly initiating semaglutide (see **Supplemental Figure S1)**. The OW GLP-1 RA cohorts are referred to from here on as OW GLP-1 RA (including semaglutide) and OW GLP-1 RA (excluding semaglutide). Mean changes in vascular risk factors were evaluated by comparing measures during the 12-month follow-up period relative to the 12-month baseline period. The baseline period was defined as the 12 months preceding (but not including) the index date (date of the first prescription of OW GLP-1 RA), and the 12-month follow-up period began on the index date.

2.2. Study population

For all cohorts, eligible patients were adults (aged ≥18 years at index) with a diagnosis of T2D during the baseline period and a diagnosis of ASCVD (based on the ICD codes listed in **Supplemental Table S1**) any time prior to index. Patients in the OW GLP-1 RA cohort (including semaglutide) had ≥2 prescriptions for either OW semaglutide, dulaglutide, or exenatide, patients in the OW GLP-1 RA cohort (excluding semaglutide) had ≥2 prescriptions for either dulaglutide or exenatide, and patients in the OW semaglutide cohort had ≥2 prescriptions for OW semaglutide during the patient selection period (01 January 2018–31 January 2022). In all cohorts, patients were required to have had at least one encounter once every 6 months during, and one encounter prior to, the baseline period, and at least one encounter once every 6 months during, and one encounter following, the 12-month follow-up period. A medical encounter in the inpatient and outpatient setting included demographics, diagnoses recorded, medications administered, prescriptions written, laboratory test results, vital signs, and procedures for each medical encounter and day of a hospital stay. Patients were also required to have at least one record of the vascular risk factor being evaluated in both baseline and follow-up periods.

For patients in the newly initiating OW GLP-1 RA cohorts (either including or excluding semaglutide), prescription of GLP-1 RAs during the baseline period or prescription of ≥2 types of OW GLP-1 RA on index date was not permitted. For patients in the newly initiating semaglutide cohort, ≥1 prescription for another GLP-1 RA during the baseline period or on index date was not permitted.

When evaluating changes in weight/body mass index (BMI) as a vascular risk factor, additional exclusions were having ≥1 prescription during the baseline period for an anti-obesity medication.

2.3. Variable measurement

2.3.1. Outcomes

Vascular risk factors assessed were HbA_{1c}, cholesterol (low-density lipoprotein cholesterol [LDL-C], very-low-density lipoprotein cholesterol [VLDL-C], high-density lipoprotein cholesterol [HDL-C] and total cholesterol), triglycerides, systolic and diastolic BP (SBP and DBP), body weight, and BMI.

As a data-cleaning rule, we only included values within the valid range of clinically possible measurement values of these risk factors in the analyses (see **Supplemental Table S2**). Valid ranges were determined by subject matter experts' recommendations, the data provider's reference ranges, and the range of the values in the dataset. Definitions of the vascular risk factors that we evaluated can be found in **Supplemental Table S2.**

During the follow-up period, a biologically plausible period of 90 days after the index date was used to allow the medications to have effect before recording changes in the vascular risk factors; therefore, only data for vascular risk factors measured during the follow-up period between 91 days and 12 months were used. From these, the measurement furthest from the index date and closest to the end of the follow-up period was used under the assumption that this would capture the maximum drug effect.

2.3.2. Covariates

Covariates were included for confounding adjustment in multivariable regression analyses (see Statistical Analysis below for details). These included patient demographics (age, sex, race, ethnicity, geographic region, year of index), comorbid and clinical measures

Table 1
Baseline demographics and clinical characteristics of patients with T2D and ASCVD newly prescribed OW GLP-1 RAs or semaglutide.

	OW GLP-1 RAs		Semaglutide ($N = 3435$)
	OW GLP-1 RAs (with semaglutide) ($N = 20,084$)	OW GLP-1 RAs (without semaglutide) ($N = 16,984$)	
Age (years), mean (SD)	63.5 (10.3)	63.7 (10.3)	62.8 (10.1)
Age (years), n (%)			
18–24	11 (0.1)	9 (0.1)	2 (0.1)
25–34	108 (0.5)	85 (0.5)	25 (0.7)
35–44	705 (3.5)	589 (3.5)	127 (3.7)
45–64	9532 (47.5)	7937 (47.0)	1721 (50.1)
≥65	9728 (48.4)	8274 (49.0)	1560 (45.4)
Sex, n (%)			
Male	10,597 (52.8)	8848 (52.4)	1868 (54.4)
Female	9486 (47.2)	8046 (47.6)	1566 (45.6)
Missing	1 (0.0)	0 (0.0)	1 (0.0)
Race, n (%)			
White	12,969 (64.6)	10,720 (63.5)	2413 (70.2)
Black	4043 (20.1)	3597 (21.3)	486 (14.1)
Other	531 (2.6)	460 (2.7)	75 (2.2)
Unknown	2541 (12.7)	2117 (12.5)	461 (13.4)
Ethnicity, n (%)			
Hispanic	1592 (7.9)	1394 (8.3)	218 (6.3)
Not Hispanic	14,541 (72.4)	12,104 (71.6)	2620 (76.3)
Unknown	3951 (19.7)	3396 (20.1)	597 (17.4)
US geographic region, n (%)			
Midwest	3799 (18.9)	3058 (18.1)	769 (22.4)
Northeast	7488 (37.3)	6224 (36.8)	1388 (40.4)
South	6541 (32.6)	5653 (33.5)	960 (27.9)
West	2176 (10.8)	1888 (11.2)	309 (9.0)
Unknown	80 (0.4)	71 (0.4)	9 (0.3)
Year of index, n (%)			
2018	3216 (16.0)	3046 (18.0)	170 (4.9)
2019	4418 (22.0)	3888 (23.0)	556 (16.2)
2020	4938 (24.6)	4025 (23.8)	987 (28.7)
2021	7162 (35.7)	5665 (33.5)	1631 (47.5)
2022	350 (1.7)	270 (1.6)	91 (2.6)
Type of OW index drug, n (%)			
Dulaglutide	16,276 (81.0)	16,328 (96.6)	N/A
Exenatide	565 (2.8)	566 (3.4)	N/A
Semaglutide	3243 (16.1)	N/A	N/A
DCSI score, n (%)			
0	2689 (13.4)	2221 (13.1)	509 (14.8)
1	3433 (17.1)	2873 (17.0)	596 (17.4)
2	4051 (20.2)	3431 (20.3)	664 (19.3)
3	2821 (14.0)	2356 (13.9)	502 (14.6)
4	2664 (13.3)	2225 (13.2)	473 (13.8)
5+	4426 (22.0)	3788 (22.4)	691 (20.1)
CCI, median (IQR)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)
Years since first T2D diagnosis, median (IQR)	5.7 (5.9)	5.7 (5.9)	6.0 (5.8)
Number of ADMs, median (IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)
Number of antidiabetic drug classes, n (%)			
0	1930 (9.6)	1655 (9.8)	297 (8.6)
1	4284 (21.3)	3601 (21.3)	724 (21.1)
2	6872 (34.2)	5799 (34.3)	1156 (33.7)
≥3	6998 (34.8)	5839 (34.6)	1258 (36.6)
Type of antidiabetic drug classes, n (%)			
Alpha-glucosidase inhibitors	49 (0.2)	42 (0.2)	7 (0.2)
Basal insulin	9344 (46.5)	7870 (46.6)	1618 (47.1)
Biguanides	11,768 (58.6)	9819 (58.1)	2080 (60.6)
Meglitinides	225 (1.1)	189 (1.1)	37 (1.1)
Other insulin	9593 (47.8)	8016 (47.4)	1695 (49.3)
SGLT2i	3390 (16.9)	2817 (16.7)	641 (18.7)
Sulfonylureas	6010 (29.9)	5097 (30.2)	974 (28.4)
Thiazolidinediones	884 (4.4)	744 (4.4)	155 (4.5)
Years since first ASCVD diagnosis, median (IQR)	4.0 (5.0)	3.5 (4.7)	4.0 (5.0)
Type of ASCVD, n (%)			
Transient ischemic attack	2512 (12.5)	2053 (12.2)	491 (14.3)
Other CHD	13,703 (68.2)	11,533 (68.3)	2337 (68.0)
Myocardial infarction	3639 (18.1)	3036 (18.0)	663 (19.3)
Ischemic stroke	4151 (20.7)	3440 (20.4)	758 (22.1)
Other atherosclerotic cerebrovascular disease	4278 (21.3)	3680 (21.8)	638 (18.6)
PAD	8301 (41.3)	7037 (41.7)	1375 (40.0)
ASCVD related procedures	2891 (14.4)	2422 (14.3)	515 (15.0)
Number of types of ASCVD, n (%)			
1	10,233 (51.0)	8603 (50.9)	1750 (50.9)
2	5428 (27.0)	4573 (27.1)	921 (26.8)
≥3	4335 (21.6)	3646 (21.6)	745 (21.7)
Number of ASCVD-related medications, median (IQR)	3.0 (2.0)	3.0 (2.0)	3.0 (2.0)
Type of ASCVD-related medication, n (%)			
Antihypertensive agents	17,143 (85.4)	14,357 (85.0)	2986 (86.9)
Antiplatelets	8908 (44.4)	7511 (44.5)	1491 (43.4)
Antihyperlipidemic agents	15,466 (77.0)	12,987 (76.9)	2668 (77.7)
Anticoagulants	6312 (31.4)	5288 (31.3)	1093 (31.8)
Other anti-anginal agents*	3677 (18.3)	3088 (18.3)	626 (18.2)
Comorbidities associated with T2D, n (%)			
Retinopathy	3848 (19.2)	3147 (18.6)	614 (17.9)
Neuropathy	7695 (38.3)	6607 (39.1)	1199 (34.9)
Nephropathy	7026 (35.0)	5924 (35.1)	1181 (34.4)
Cerebrovascular disease	3360 (16.7)	2884 (17.1)	506 (14.7)
CVD	12,504 (62.3)	10,434 (61.8)	2114 (61.5)
Peripheral vascular disease	5595 (27.9)	4744 (28.1)	931 (27.1)
Metabolic disease	7020 (35.0)	5926 (35.1)	1176 (34.2)
Hypertension	17,981 (89.5)	15,129 (89.6)	3065 (89.2)
Dyslipidemia	16,314 (81.2)	13,693 (81.1)	2823 (82.2)
Heart failure	4080 (20.3)	3425 (20.3)	697 (20.3)
NASH/NAFLD	1628 (8.1)	1342 (7.9)	305 (8.9)
Depression	5277 (26.3)	4484 (26.5)	856 (24.9)
Anxiety	4313 (21.5)	3573 (21.1)	791 (23.0)
Cancer	2658 (13.2)	2180 (12.9)	505 (14.7)

ADM, antidiabetic medication; ASCVD, atherosclerotic cardiovascular disease; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; CVD, cardiovascular disease; DCSI, Diabetes Complication Severity Index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; N/A, not applicable; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OW, once-weekly; PAD, peripheral artery disease; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SD, standard deviation; T2D, type 2 diabetes.

* Other anti-anginal agents include nitrates [including nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate] and ranolazine. Calcium channel blockers and beta blockers are included in antihypertensive agents.

(Diabetes Complication Severity Index [25], Charlson Comorbidity Index, years since first ASCVD diagnosis, years since first T2D diagnosis), type of antidiabetic drug classes, number of antidiabetic medications, type of ASCVD-related medications, type of ASCVD, T2D complications, and other related comorbidities.

2.4. Statistical analysis

Risk factors were described using means and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. Changes in risk factors were estimated by comparing mean values between the baseline and follow-up periods. For univariable analyses, comparisons were made between the baseline and follow-up periods using paired *t*-tests and Wilcoxon signed-rank test for continuous variables, and McNemar's test for categorical variables. A multivariable linear regression was used for patients prescribed OW GLP-1

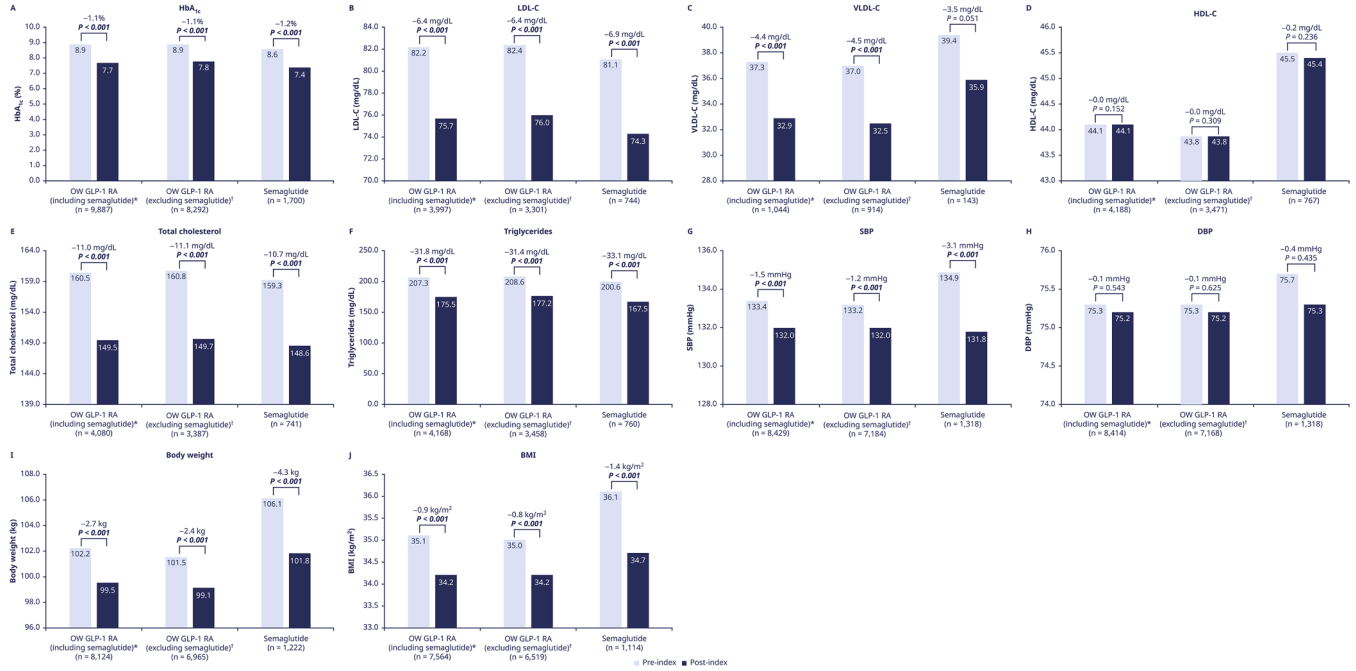


Fig. 1. Change from baseline to 12 months' follow-up in vascular risk factors in the cohorts of patients newly prescribed either OW GLP-1 RAs (including or excluding semaglutide) or semaglutide. *Semaglutide, dulaglutide or exenatide. †Dulaglutide or exenatide. Significant P-values are denoted in bold. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OW, once-weekly; VLDL-C, very-low-density lipoprotein cholesterol.

RAs to compare changes in vascular risk factors between individual index drugs while adjusting for baseline characteristics, with dulaglutide as the reference group. The dependent variable of the model was absolute change from baseline for each risk factor and was calculated as the post-period value minus the pre-period value. The model's independent variables included type of index drug, age, sex, race/ethnicity, baseline value of the vascular risk factor, Diabetes Complications Severity Index, Charlson Comorbidity Index, years since first ASCVD diagnosis, years since first T2D diagnosis, antidiabetic medications, ASCVD-related medications, type of ASCVD, and comorbidities associated with T2D.

2.5. Subgroup and stratified analyses

Change in select vascular risk factors from baseline to follow-up was assessed in the overall study population and in subpopulations of patients with a baseline HbA_{1c} ≥7% (pre-specified) or stratified by age (<65 years and ≥65 years; pre-specified) or by tercile of baseline vascular risk factor value (post hoc).

3. Results

3.1. Patient demographics

The study cohorts included 20,084 patients newly prescribed OW GLP-1 RAs (including semaglutide), 16,894 patients newly prescribed OW GLP-1 RAs (excluding semaglutide), and 3435 newly prescribed semaglutide (see **Supplemental Figure S2**). Demographics and clinical characteristics for the three cohorts are displayed in Table 1. In the OW GLP-1 RA cohort (including semaglutide), 81.0% of patients had received treatment with dulaglutide, 16.1% had received semaglutide, and 2.8% had received exenatide, and the mean (SD) age was 63.5 (10.3) years. In the OW GLP-1 RA cohort (excluding semaglutide), 96.6% of patients had received treatment with dulaglutide and 3.4% had received exenatide, and the mean (SD) age was 63.7 (10.3) years. In the semaglutide cohort, the mean (SD) age was 62.8 (10.1) years. The sex distribution was similar between cohorts with 52.8% being male in the OW GLP-1 RA cohort (including semaglutide), 52.4% male in the OW GLP-1 RA cohort (excluding semaglutide), and 54.4% male in the semaglutide cohort. In terms of race, 64.6% and 63.5% of the OW GLP-1 RA cohort (including and excluding semaglutide, respectively) were White, while in the semaglutide cohort 70.2% were White. The median (interquartile range, IQR) time since T2D diagnosis was 5.7 (5.9) years and median (IQR) time since ASCVD diagnosis was 4.0 (5.0) years in the OW GLP-1 RA cohort (including semaglutide). In the OW GLP-1 RA cohort (excluding semaglutide), median (IQR) times since T2D diagnosis and ASCVD diagnosis were 5.7 (5.9) years, and 3.5 (4.7) years, respectively. In the semaglutide cohort, median (IQR) times since T2D diagnosis and ASCVD diagnosis were 6.0 (5.8) years, and 4.0 (5.0) years, respectively.

3.2. Analysis of overall study population

Univariable analyses of the change in vascular risk factors in the cohorts of patients newly initiating OW GLP-1 RAs and semaglutide are shown in Fig. 1. Multivariable analyses of the cohort newly initiating OW GLP-1 RAs are presented in Table 2.

3.2.1. HbA_{1c}

A significant ($P < 0.001$) reduction in mean HbA_{1c} was observed in the cohort newly prescribed OW GLP-1 RAs (including semaglutide: −1.1%; excluding semaglutide: −1.1%) after 12 months of follow-up (Fig. 1). After adjusting for confounding in the multivariable analysis, semaglutide was associated with a significantly greater reduction in mean HbA_{1c} (−0.28%; 95% CI= [−0.35,−0.20]; $P < 0.001$) compared with dulaglutide, while exenatide was associated with a non-significant increase (0.17%; 95% CI = [−0.01, 0.36]; $P = 0.058$) (Table 2). Similarly, a significant reduction in mean HbA_{1c} (−1.2%, $P < 0.001$) was observed in the cohort prescribed semaglutide (Fig. 1).

Table 2
Multivariable linear regression analysis estimating the change in vascular risk factors (pre- and post-GLP-1 RA initiation) in patients newly initiating OW GLP-1 RAs.

Vascular Risk Factor	Coefficient (95% CI)	*P*-value
HbA_{1c}, % ($n = 9887$)		
Semaglutide	−0.28 (−0.35, −0.20)	**< 0.001**
Exenatide	0.17 (−0.01, 0.36)	0.058
LDL-C, mg/dL ($n = 3997$)		
Semaglutide	−1.02 (−3.30, 1.26)	0.382
Exenatide	4.22 (−1.49, 9.93)	0.147
VLDL-C, mg/dL ($n = 1044$)		
Semaglutide	2.18 (−0.57, 4.92)	0.120
Exenatide	3.78 (−3.19, 10.74)	0.288
HDL-C, mg/dL ($n = 4188$)		
Semaglutide	0.41 (−0.47. 1.29)	0.362
Exenatide	1.62 (−0.67, 3.91)	0.166
Triglycerides, mg/dL ($n = 4168$)		
Semaglutide	−5.18 (−13.5, 3.09)	0.219
Exenatide	30.20 (9.05, 51.36)	**0.005**
Total cholesterol, mg/dL ($n = 4080$)		
Semaglutide	−0.24 (−3.03, 2.54)	0.863
Exenatide	5.90 (−1.18, 12.98)	0.102
SBP, mmHg ($n = 8429$)		
Semaglutide	−0.58 (−1.65, 0.49)	0.287
Exenatide	−0.21 (−2.65, 2.24)	0.869
DBP, mmHg ($n = 8414$)		
Semaglutide	−0.13 (−0.74, 0.48)	0.673
Exenatide	−1.67 (−3.07, −0.27)	**0.019**
Body weight, kg ($n = 8124$)		
Semaglutide	−1.68 (−2.15, −1.21)	**< 0.001**
Exenatide	0.65 (−0.36, 1.66)	0.205

The reference group is dulaglutide. Significant *P*-values denoted in bold.
The models adjusted for age, sex, race/ethnicity, baseline value of the vascular risk factor, Diabetes Complications Severity Index, Charlson Comorbidity Index, years since first ASCVD diagnosis, years since first T2D diagnosis, antidiabetic medications, ASCVD-related medications, type of ASCVD, and comorbidities associated with T2D.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; DBP, diastolic blood pressure; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; OW, once-weekly; VLDL-C, very-low-density lipoprotein cholesterol.

3.2.2. Lipids

In the cohort of patients newly prescribed OW GLP-1 RAs, significant reductions were observed in mean LDL-C (including semaglutide: −6.4 mg/dL; excluding semaglutide: −6.4 mg/dL), VLDL-C (including semaglutide: −4.4 mg/dL; excluding semaglutide: −4.5 mg/dL), total cholesterol (including semaglutide: −11.0 mg/dL; excluding semaglutide: −11.1 mg/dL), and triglycerides (including semaglutide: −31.8 mg/dL; excluding semaglutide: −31.4 mg/dL) (all $P < 0.001$) (Fig. 1). No significant change was observed in mean HDL-C. After adjusting for confounding in the multivariable analysis, semaglutide was not associated with significant changes in lipids compared with dulaglutide (Table 2). In the cohort of patients newly prescribed semaglutide, significant reductions were also observed in mean LDL-C (−6.9 mg/dL), total cholesterol (−10.7 mg/dL), and triglycerides (−33.1 mg/dL) (all $P < 0.001$) (Fig. 1). There was no significant change observed in mean VLDL-C (−3.5 mg/dL; $P = 0.051$) and HDL-C (−0.2 mg/dL; $P = 0.236$).

3.2.3. BP

In the cohort of patients newly prescribed OW GLP-1 RAs, a significant reduction was observed in mean SBP (including semaglutide: −1.5 mmHg; excluding semaglutide: −1.2 mmHg; both $P < 0.001$), but not DBP (including semaglutide: −0.1 mmHg, $P = 0.543$; excluding semaglutide: −0.1 mmHg, $P = 0.625$) (Fig. 1). After adjusting for confounding in the multivariable analysis, semaglutide was not associated with significant changes in blood pressure compared with dulaglutide (Table 2). In the cohort of patients prescribed semaglutide, there was also a significant reduction in mean SBP (−3.1 mmHg; $P < 0.001$), but not DBP (−0.4 mmHg; $P = 0.435$) (Fig. 1).

3.2.4. Body weight and BMI

In the cohort of patients newly prescribed OW GLP-1 RAs (including semaglutide), a significant reduction in mean body weight was observed (-2.7 kg, $P < 0.001$). For patients newly prescribed OW GLP-1 RAs (excluding semaglutide), a significant reduction in mean body weight of was observed (-2.4 kg, $P < 0.001$). After adjusting for confounding in the multivariable analysis, semaglutide was associated with a significantly greater reduction in mean body weight (−1.68 kg; 95% CI= [−2.15, −1.21]; $P < 0.001$) compared with dulaglutide, while exenatide was associated with a non-significant increase (0.65 kg; 95% CI= [−0.36, 1.66]; $P = 0.205$) (Table 2). In the cohort prescribed semaglutide, the change in mean body weight was −4.3 kg ($P < 0.001$) (Fig. 1).

In the cohort of patients newly prescribed OW GLP-1 RAs, mean BMI also decreased significantly by −0.9 kg/m^2 ($P < 0.001$) including semaglutide, and by −0.8 kg/m^2 ($P < 0.001$) excluding semaglutide, and in the semaglutide cohort, mean BMI decreased by −1.4 kg/m^2 ($P < 0.001$) (Fig. 1).

With the exception of BMI category <18.5 kg/m^2, significant changes in the proportions of patients in each BMI category were observed post-index, reflecting patients moving from higher to lower BMI categories. Thus, in the cohort of patients newly prescribed OW GLP-1 RAs (including semaglutide), the changes observed were: 18.5–25 kg/m^2: +2.4% ($P < 0.001$); 25–29.9 kg/m^2: +2.6% ($P < 0.001$); 30–39.9 kg/m^2: −1.4% ($P = 0.005$); ≥40 kg/m^2: −3.8% ($P < 0.001$). For OW GLP-1 RAs (excluding semaglutide), the changes observed were: 18.5–25 kg/m^2: +2.2% ($P < 0.001$); 25–29.9 kg/m^2: +2.7% ($P < 0.001$); 30–39.9 kg/m^2: −1.7% ($P = 0.001$); ≥40 kg/m^2: −3.3% ($P < 0.001$). The significant respective changes observed post-index in BMI

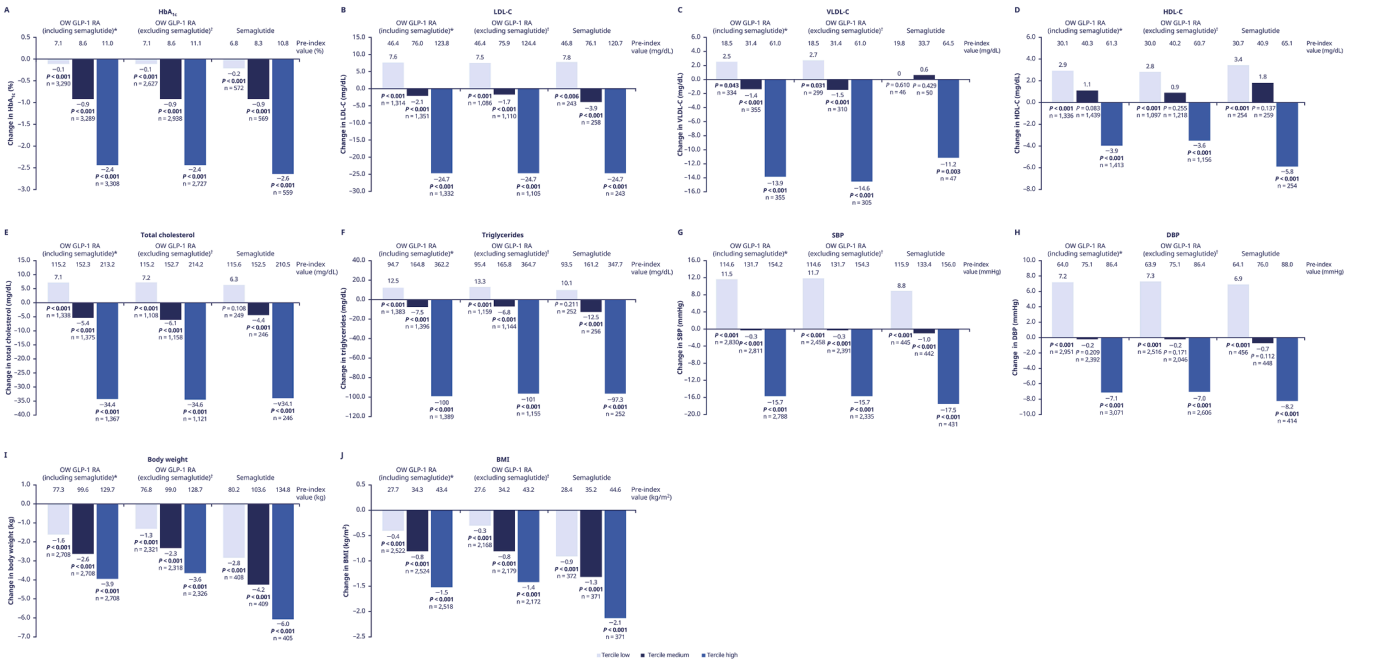


Fig. 2. Change from baseline to 12 months' follow-up in vascular risk factors in the cohorts of patients newly prescribed either OW GLP-1 RAs (including or excluding semaglutide) or semaglutide, stratified by tercile (low, medium, or high) of baseline vascular risk factor value. *Semaglutide, dulaglutide or exenatide. †Dulaglutide or exenatide. Significant P-values denoted in bold. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; GLP-1 RA, glucagon-like receptor agonist.

categories of the cohort prescribed semaglutide were: 18.5–25 kg/m^2: +3.6% ($P < 0.001$); 25–29.9 kg/m^2: +2.3% ($P = 0.037$), and ≥40 kg/m^2: −6.4% ($P < 0.001$).

3.3. Stratification by tercile of baseline vascular risk factor value

Changes from baseline to the 12-month follow-up for each cohort stratified by tercile of baseline vascular risk factor value are shown in Fig. 2, and those within the top tercile in **Supplemental Figure S3**.

3.3.1. HbA_{1c}

In all cohorts, the reduction in mean HbA_{1c} was statistically significant in each tercile, but the extent of reduction increased with each tercile (Fig. 2). In the highest tercile, for patients newly prescribed OW GLP-1 RAs (including semaglutide: pre-index mean HbA_{1c} 11.0%; excluding semaglutide: pre-index mean HbA_{1c} 11.1%), a change in mean HbA_{1c} of −2.4% ($P < 0.001$) for both groups was observed, and for those newly prescribed semaglutide (pre-index mean HbA_{1c} 10.8%), the change was −2.6% ($P < 0.001$; **Supplemental Figure S3**).

3.3.2. Lipids

Significant reductions were observed for all mean lipid measures in the highest terciles for both cohorts. For those newly prescribed GLP-1 RAs (including and excluding semaglutide) and semaglutide, respectively, these were: LDL-C: −24.7 mg/dL, −24.7 mg/dL and −24.7 mg/dL; VLD-C: −13.9 mg/dL, −14.6 mg/dL and −11.2 mg/dL; HDL-C: −3.9 mg/dL, −3.6 mg/dL and −5.8 mg/dL; total cholesterol: −34.4 mg/dL, −34.6 mg/dL and −34.1 mg/dL; and triglycerides: −100 mg/dL, −101 mg/dL and −97.3 mg/dL (**Supplemental Figure S3**). In the low and medium terciles, several increases were observed in mean LDL-C, VLDL-C, HDL-C, total cholesterol and triglycerides (Fig. 2).

3.3.3. BP

Significant increases in mean SBP and DBP were observed for both cohorts in the lowest tercile, while significant decreases were observed in the highest tercile (Fig. 2). For patients newly prescribed OW GLP-1 RAs (including semaglutide), in the highest tercile, (pre-index mean SBP 154.2 mmHg, pre-index mean DBP 86.4 mmHg), reductions of 15.7 mmHg and 7.1 mmHg were observed for mean SBP and DBP, respectively (both $P < 0.001$). Similarly for patients newly prescribed OW GLP-1 RAs (excluding semaglutide), in the highest tercile, (pre-index mean SBP 154.3 mmHg, pre-index mean DBP 86.4 mmHg), reductions of 15.7 mmHg and 7.0 mmHg were observed for mean SBP and DBP, respectively (both $P < 0.001$). In the cohort newly prescribed semaglutide, in the highest tercile, (pre-index mean SBP 156.0 mmHg, pre-index mean DBP 88.0 mmHg), reductions of 17.5 mmHg and 8.2 mmHg were observed for mean SBP and DBP, respectively (both $P < 0.001$) (**Supplemental Figure S3**).

3.3.4. Body weight and BMI

The reduction in mean body weight increased with each tercile in both cohorts (Fig. 2). In the highest tercile, for patients newly prescribed OW GLP-1 RAs (including semaglutide: pre-index mean body weight 129.7 kg), a weight change of −3.9 kg ($P < 0.001$) was observed. A weight change of −3.6 kg ($P < 0.001$) was observed in patients newly prescribed OW GLP-1 RAs, excluding semaglutide (pre-index mean body weight 128.7 kg). For the cohort newly prescribed semaglutide (pre-index mean body weight 134.8 kg), the change was −6.0 kg ($P < 0.001$) (**Supplemental Figure S3**).

With respect to mean BMI, there were significant reductions in each tercile of baseline value in both cohorts, with the extent of the reduction increasing with tercile (Fig. 2). In the highest tercile, BMI reductions of 1.5 kg/m^2, 1.4 kg/m^2, and 2.1 kg/m^2 were observed in the cohorts newly prescribed GLP-1 RAs including semaglutide (pre-index mean

BMI: 43.4 kg/m^2), GLP-1 RAs excluding semaglutide (pre-index mean BMI: 43.2 kg/m^2), and semaglutide (pre-index mean BMI: 44.6 kg/m^2), respectively (**Supplemental Figure S3**).

3.4. Subgroup analysis of patients with baseline HbA_{1c} ≥7%

Full results of the subgroup analysis are provided in **Supplemental Tables S3, S4, and S5**. Results in this subgroup for patients newly prescribed OW GLP-1 RAs were generally similar to those of the full population, but a larger reduction in mean HbA_{1c} was observed (−1.3% vs −1.1%), regardless of including semaglutide. Similarly, for patients newly prescribed semaglutide, the results were comparable to those of the full population, but again a larger reduction in mean HbA_{1c} was observed (−1.5% vs −1.2%).

3.5. Age-stratified subgroup analysis

Full results of the age-stratified subgroup analysis are given in **Supplemental Tables S6, S7, and S8**. Larger reductions were observed in the younger subgroup of patients newly prescribed OW GLP-1 RAs (including semaglutide) in mean HbA_{1c} (<65 years: −1.3%; ≥65 years: −1.0%) and triglycerides (<65 years: −40.9 mg/dL; ≥65 years: −22.6 mg/dL). In patients newly prescribed OW GLP-1 RAs (excluding semaglutide), larger reductions were observed in the younger subgroup in mean HbA_{1c} (<65 years: −1.2%; ≥65 years: −1.0%) and triglycerides (<65 years: −40.8 mg/dL; ≥65 years: −22.2 mg/dL). A similar pattern was observed in patients newly prescribed semaglutide, with the younger subgroup being associated with larger reductions in mean HbA_{1c} (<65 years: −1.3%; ≥65 years: −1.1%) and triglycerides (<65 years: −41.4 mg/dL; ≥65 years: −23.9 mg/dL).

4. Discussion

This exploratory analysis provided a comprehensive assessment of the relationship between OW GLP-1 RA use and vascular risk factors in a real-world setting, making use of a large US EHR database, the TriNetX Dataworks-USA network, which seeks to establish a network of de-identified clinical data as representative of various US patient populations as possible [26]. This study also provides more recent real-world data on the influence of semaglutide, in particular, on vascular risk factors than have been previously published. This exploratory analysis demonstrated statistically significant reductions in several vascular risk factors in patients who newly initiated OW GLP-1 RAs, including semaglutide, particularly in the top tercile of patients by baseline vascular risk factor value.

In the present analysis of patients with T2D, mean reductions in HbA_{1c} of 1.1%, 1.1%, and 1.2% with OW GLP-1 RAs (including and excluding semaglutide) and semaglutide, respectively, were observed. These findings are largely consistent with those observed in other real-world analyses, in which reductions of between 1.00–1.55% with several OW GLP-1 RAs, including semaglutide, have been reported [27]. The results of the multivariable linear regression were comparable to those of the SUSTAIN 7 study, which also demonstrated superiority for semaglutide vs dulaglutide for HbA_{1c} reduction (estimated treatment difference at highest dose: −0.41%; 95% CI = [−0.57, −0.25]; $P <$ 0.0001 for non-inferiority and superiority) [28]. Subgroup analyses of HbA_{1c} indicated that the glucose-lowering effect in all cohorts was slightly greater in patients aged <65 years, and in patients with a baseline HbA_{1c} ≥7%.

There was a significant improvement in all cohorts in almost all lipids apart from HDL-C. For VLDL-C, significant improvements were observed in the OW GLP-1 RA cohort (both including and excluding semaglutide), and improvements approaching statistical significance were observed in the semaglutide cohort ($P = 0.051$). Similarly to HbA_{1c} this observation is consistent with previous studies. Modest reductions in LDL-C, total cholesterol, and triglycerides have been reported previously with GLP-1 RAs [8]. With respect to HDL-C, the effect of GLP-1 RAs is more variable, with some studies showing significant increases, and others showing no effect [8,29]. In our study, the reductions in total, LDL- and VLDL-C, and triglycerides were substantial in the terciles of highest baseline value (**Supplemental Figure S3**), suggesting a potentially clinically meaningful benefit for patients with an adverse lipid profile. For example, in the American College of Cardiology (ACC) Risk Estimator+ and QRESEARCH risk estimator version 3 (QRISK3) risk calculators, such findings translate into a 10-year ASCVD risk reduction [30–32].

In this study, significant reductions in SBP were observed in all cohorts, although the semaglutide cohort appeared to benefit from a greater effect (−3.1 vs −1.5 mmHg [OW GLP-1 RA cohort including semaglutide] and −1.2 mmHg [OW GLP-1 RA cohort excluding semaglutide]). This observed reduction is clinically meaningful; one large-scale meta-analysis demonstrated that a 5 mmHg reduction of SBP reduced the risk of major CV events by 10% [33].

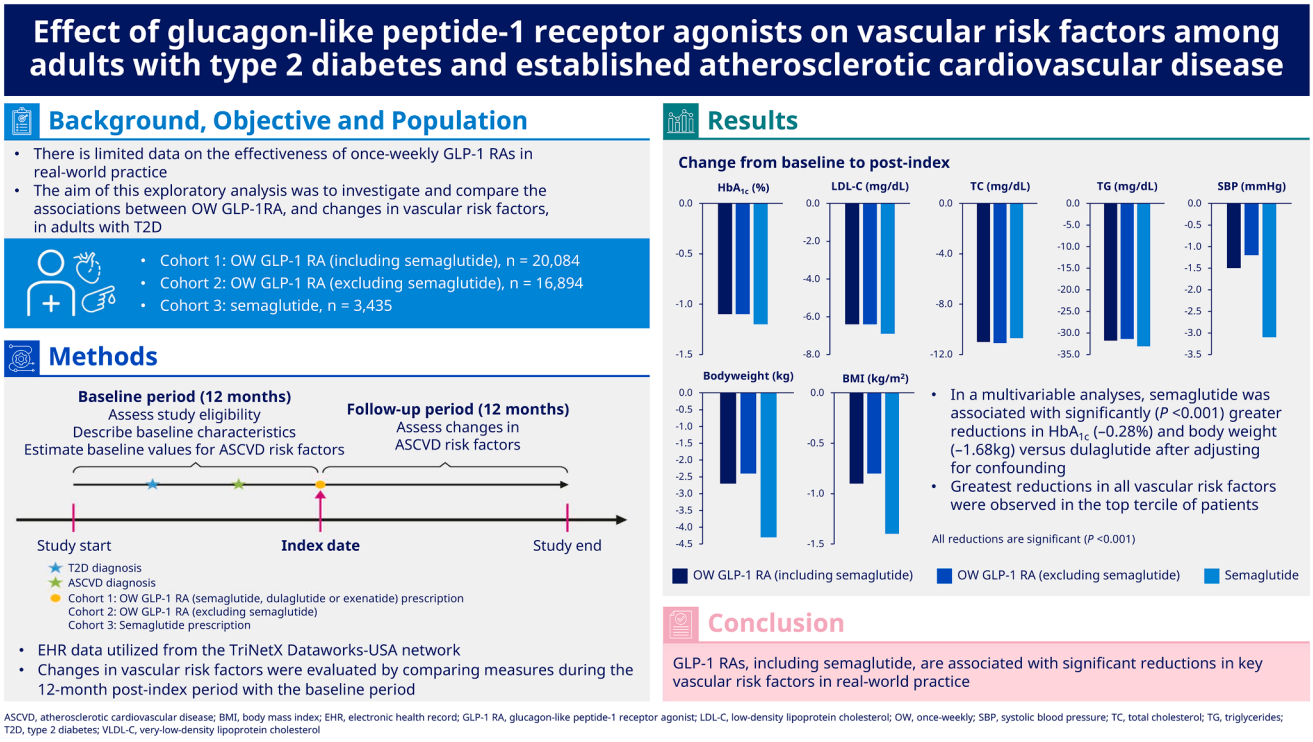
Weight reduction in patients with T2D following GLP-1 RA treatment has been shown in a previous study to be positively associated with reductions in SBP and DBP ($\beta = 0.821$ and $\beta = 0.287$, respectively; both $P < 0.001$) [34]. GLP-1 RAs have been consistently observed to reduce body weight and BMI in patients with overweight or obesity and T2D, with semaglutide often shown to have superior efficacy over other GLP-1 RAs in trials [35]. The results of this study are aligned with those seen in previous studies. While both the OW GLP-1 RA (both including and excluding semaglutide) and semaglutide cohorts had significant weight loss and a reduction in BMI, semaglutide was associated with significantly greater weight loss than dulaglutide in the multivariable analysis. This is also reflective of the SUSTAIN 7 study, in which semaglutide was found to be superior to dulaglutide for weight loss (estimated treatment difference at highest dose: −3.55 kg; 95% CI= [−4.32, −2.78]; $P <$ 0.0001) [28].

Efforts to understand the underlying mechanisms behind the cardioprotective effects of GLP-1 RAs on MACE (and other CV event risk reduction), established from clinical trials and real-world data [4,14,36], are ongoing. In clinical trials, GLP-1 RAs have been shown to result in modest reductions in SBP, LDL-C, total cholesterol, and triglycerides, all of which may contribute to CV risk reduction independent of glucose-lowering effects [37,38]. This exploratory analysis evaluating the changes in vascular risk factors with OW GLP-1 RAs in a real-world setting is in agreement with the data obtained from clinical studies and suggests a beneficial broad impact on cardiometabolic markers. As we assessed effects across OW GLP-1 RAs, future studies utilizing comparison groups may be useful to further elucidate these effects in clinical practice.

The utilization of CV risk factors for informing clinical decision making with respect to treatment benefit, intensification, and additional interventions to prevent ASCVD is becoming increasingly established. For example, the European Society of Cardiology introduced the SCORE2-Diabetes algorithm [39] in their latest guideline recommendations with the aim of individualizing treatment strategies [40]. Thus, evaluating the effects of GLP-1 RAs on vascular risk factors is important for our understanding of the clinical utility of such tools. One of the most important clinical lessons illustrated by this exploratory analysis is that clinicians should be considering prescribing GLP-1 RAs to patients with particularly poor ASCVD profiles. This is underlined by the stratified analysis, in which the reductions to the greatest extent (in all vascular risk factors, and all statistically significant) were observed in the highest tercile subgroups for ASCVD risk. Such patients should be explored as a potential target group for the cardioprotective effects of GLP-1 RA therapy.

Central Illustration

Effect of glucagon-like peptide-1 receptor agonists on vascular risk factors among adults with type 2 diabetes and established atherosclerotic cardiovascular disease



4.1. Limitations

Due to the nature of the observational study design, we were unable to make any conclusions around causality, including but not limited to limitations on temporal relationship and confounding bias. Also, as this was an exploratory analysis, we did not have a sufficiently large sample size for many of the vascular risk factors for which reductions were observed, to enable detection of significant differences. Furthermore, the number of exenatide users in the OW GLP-1 RA cohort was small, potentially limiting conclusions that could be drawn from the multivariable analyses. The data available within the constraints of the study design unfortunately did not provide enough tirzepatide users for analysis. However, we recognize that this is an important consideration for future research.

Some data may be missing and results may not be representative of the entire US population, as healthcare encounters, laboratory measures, and prescriptions that occurred outside the network of the database used were not captured. The fact that this was a non-interventional study reflecting routine clinical practice rather than mandatory assessments at prespecified time points, as would occur in clinical trials (e.g., laboratory measures), may also have had an impact on the amount of data and its interpretation.

There may also have been miscoding or underreporting of disorders. For example, all medication exposures in TriNetX Dataworks-USA network are coded using RxNorm medication ingredient-level codes. RxNorm ingredient codes do not contain information on brand, strength, or dosing. In an effort to minimize this issue, an algorithm was used to differentiate different brand name drugs by using the brand name drug specific information available in medication records as well as available National Drug Codes numbers in some records; however, there may still have been misclassification. Finally, while we accounted for other cardiovascular drug use in the multivariable analyses, we were unable to assess drug dosing and so cannot exclude that some of the observed changes in endpoints were influenced by intensification of concomitant medications, or indeed GLP-1 RA dose adjustment.

5. Conclusion

This exploratory analysis demonstrates that real-world use of GLP-1 RAs in T2D cohorts may be associated with significant reductions in key vascular risk factors, including HbA_{1c}, lipids, blood pressure, body weight, and BMI. Numerically larger reductions were typically observed in the cohort newly initiating semaglutide, as well as in patients in the highest terciles of baseline ASCVD risk. The trends and associations between GLP-1 RAs and vascular risk factors observed in this exploratory analysis warrant further research, both to confirm the exploratory results presented and to potentially elucidate underlying mechanisms for the cardioprotective effects of GLP-1 RAs. The observed associations may be important in guiding individualized treatment options for patients with T2D.

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Ethical review statement

This retrospective study is exempt from informed consent. The data reviewed are a secondary analysis of existing de-identified data, do not involve intervention or interaction with human subjects, and are de-identified per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule.

CRediT authorship contribution statement

Aaron King: Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Xi Tan:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Neil Dhopeshwarkar:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Rhonda Bohn:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Katherine Dea:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Charles E. Leonard:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Adam de Havenon:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

Aaron King: Paid speaker and clinical advisor for Astellas Pharma, Abbott, Dexcom, Eli Lilly, Mannkind and Novo Nordisk Inc.

Xi Tan: Employee of Novo Nordisk Inc.

Neil Dhopeshwarkar: Employee of TriNetX, LLC.

Rhonda Bohn: Nothing to declare.

Katherine Dea: Consultant of TriNetX, LLC.

Charles E. Leonard: Dr. Leonard is a Special Government Employee of the US Food and Drug Administration. Dr. Leonard reports NIH funding. Dr. Leonard recently received honoraria from the American College of Clinical Pharmacy Foundation, the Consortium for Medical Marijuana Clinical Outcomes Research, and Ancora Education. Dr. Leonard consults for Novo Nordisk and TriNetX, LLC. Dr. Leonard's spouse is employed by Merck; neither she nor he own stock in the company.

Adam de Havenon: Dr. de Havenon reports NIH funding, consultant fees from Novo Nordisk Inc., royalty fees from UpToDate, and has equity in TitinKM and Certus.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100922.

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