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ORIGINAL RESEARCH

Risk of Stroke in Real-World US Individuals with Type 2 Diabetes Receiving Semaglutide or a Dipeptidyl Peptidase 4 Inhibitor

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ABSTRACT

Introduction: People with type 2 diabetes (T2D) have a higher risk of stroke and worse outcomes than those without T2D. Pooled data from randomized controlled trials indicate that the glucagon-like peptide 1 receptor agonist semaglutide is associated with stroke risk reduction in people with T2D at high cardiovascular risk. We compared real-world stroke risk in people with T2D or T2D plus atherosclerotic cardiovascular disease (ASCVD) initiating either semaglutide or a dipeptidyl peptidase 4 inhibitor (DPP4i).

Methods: Adults (≥ 18 years old) in a US claims database with a claim indicating initiation of either semaglutide or a DPP4i (index date) during the index period (1 January 2018–30 September 2020), a diagnosis code for T2D on or before the index date and at least 12 months' continuous enrolment in the database pre-index were included and propensity score matched 1:1 on baseline demographic and clinical characteristics. The primary outcome was time to first stroke event during follow-up. Healthcare resource utilization was also compared between groups.

Prior Presentation: Data from these analyses have been presented at the European Society of Cardiology Congress 2022, 26–29 August 2022, Barcelona, Spain; the 58th European Association for the Study of Diabetes Annual Meeting, 19–23 September 2022, Stockholm, Sweden; and the virtual Cardiovascular Outcome Trial (CVOT) Summit 2022, 10–11 November 2022.

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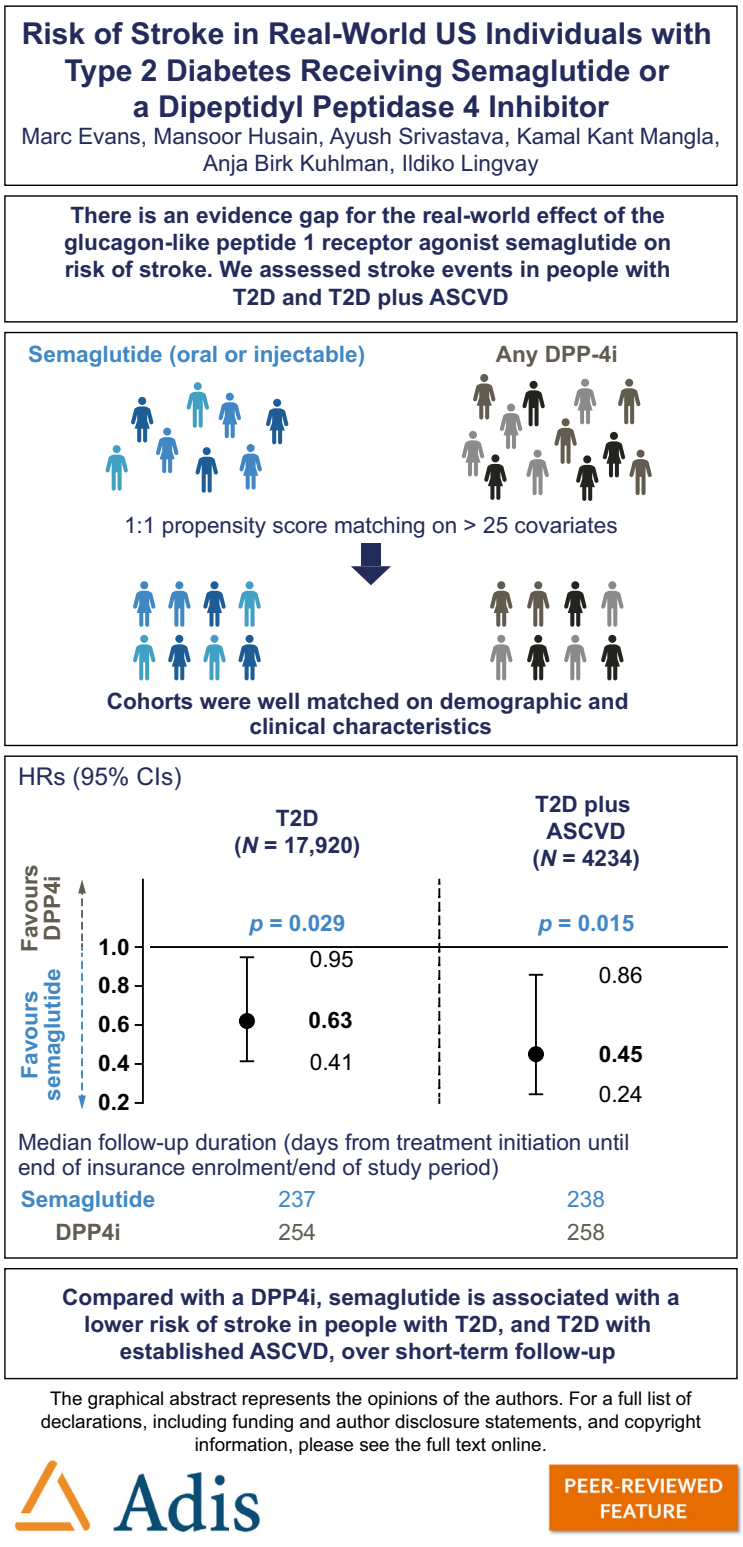
Results: The analysis included 17,920 matched pairs with T2D and 4234 matched pairs with T2D and ASCVD. The groups were well matched on baseline characteristics. People initiating semaglutide had a lower risk of stroke over short-term follow-up than those initiating a DPP4i (T2D: hazard ratio 0.63 [95% confidence interval 0.41–0.95], $p = 0.029$; T2D plus ASCVD: 0.45 [0.24–0.86], $p = 0.015$). Semaglutide was also associated with a lower rate of inpatient, outpatient and emergency room visits compared with a DPP4i.

Conclusion: This proof-of-concept analysis indicates that semaglutide has the potential to reduce the risk of stroke in people with T2D when prescribed in clinical practice.

Graphical Abstract:



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PEER-REVIEWED FEATURE

Keywords: Diabetes mellitus - Type 2; Glucagon-like peptide 1; Hospitalization; Stroke

Key Summary Points

Why carry out this study?

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are recommended for the treatment of type 2 diabetes (T2D) in people with atherosclerotic cardiovascular disease (ASCVD) or high cardiovascular risk.

Clinical trial data have shown that the GLP-1 RA semaglutide is associated with risk reductions for stroke; however, evidence is lacking for its effect in clinical practice.

Real-world patients with T2D or T2D and ASCVD, receiving either semaglutide or a dipeptidyl peptidase 4 inhibitor (DPP4i), were propensity score matched and compared.

What was learned from the study?

Semaglutide was associated with lower risk of stroke and lower healthcare resource utilization than DPP4is over short-term follow-up.

This proof-of-concept analysis provides some of the first real-world evidence on stroke outcomes with semaglutide, and can be used as a basis for subsequent studies on stroke management in T2D.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24610002.

INTRODUCTION

Type 2 diabetes (T2D) is a major modifiable risk factor for stroke. The likelihood of stroke occurrence is up to twofold higher in people with T2D compared with those without T2D [1, 2]; furthermore, T2D is widely recognized as being linked to earlier stroke events, more deleterious clinical outcomes [3, 4] and higher risk of stroke recurrence [5]. Worse glycaemic control in T2D is also associated with stroke-related mortality [6]. The occurrence of stroke in T2D results in high costs and healthcare resource utilization (HCRU) compared with T2D alone and compared with various other cardiovascular (CV) events or conditions [7, 8]. Overall, stroke in T2D represents a key area of unmet need for both patients and healthcare systems.

CV risk is an important consideration in treatment decision-making for T2D. People who do not achieve a reduction in blood glucose to a target threshold, despite diet and lifestyle modifications and use of metformin, require treatment intensification with an additional glucose-lowering medication. For people with T2D and atherosclerotic cardiovascular disease (ASCVD) or high CV risk, clinical guidelines developed by the American Diabetes Association and the European Association for the Study of Diabetes specifically recommend the use of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) or sodium–glucose cotransporter 2 inhibitors (SGLT2is) [9, 10], irrespective of baseline blood glucose levels or metformin use. These recommendations are also included in guidelines from the European Society for Cardiology [11] and the American Heart Association/American Stroke Association [12].

Meta-analyses using data from randomized, controlled CV outcomes trials showed that GLP-1 RAs were associated with a significant reduction in the risk of three-component major adverse CV events (CV death, non-fatal myocardial infarction and non-fatal stroke), and a significant reduction in the risk of fatal or non-fatal stroke, versus placebo in addition to standard-of-care (SoC) treatment [13, 14]. There was an overall stroke risk reduction of 17% with GLP-1 RAs across the trials ($p = 0.0002$) [13],

with significant reductions in the risk of both stroke overall and ischaemic stroke (both 17%) [14].

The GLP-1 RA semaglutide has proven efficacy in improving both glycaemic control and weight loss [9]. An analysis of pooled data from the SUSTAIN 6 and PIONEER 6 CV outcomes trials has also indicated that injectable or orally administered semaglutide is associated with a lower risk of stroke versus placebo in people with T2D and high CV risk, regardless of whether they had previously experienced stroke [15]. Analyses of real-world data are needed to assess whether semaglutide reduces stroke risk in clinical practice and to compare the effectiveness of glucose-lowering medications. An analysis of US claims data has indicated that GLP-1 RAs are budget-neutral compared with SoC in people with T2D with a pre-existing CV event; however, additional real-world data are needed to assess fully the cost impact of prescribing GLP-1 RAs according to CV risk guidelines [16].

The present study was a proof-of-concept analysis using real-world US claims data to assess the burden of stroke in patients with T2D and T2D plus ASCVD who initiated semaglutide. People who received a dipeptidyl peptidase 4 inhibitor (DPP4i), which was considered to represent SoC in T2D, were included as a comparator group.

METHODS

Data Source, Study Design and Eligibility Criteria

This was a retrospective observational study (Fig. 1) conducted using US claims data from the Merative™ MarketScan® Commercial and Medicare Databases.

Individuals were included if they were at least 18 years old and had a claim indicating initiation of either semaglutide (injectable or orally administered) for T2D or a DPP4i during the index period (1 January 2018–30 September 2020). The index date was the date of treatment initiation. Eligible individuals required a diagnosis code for T2D on or at any time before the index date and at least 12 months' continuous enrolment in the database pre-index (baseline period). For inclusion in the group with T2D and a history of ASCVD, individuals also required a diagnosis of ASCVD at any time pre-index, broadly defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes (online Supplementary Table S1). Individuals were followed from index date until the first stroke event (for the primary outcome analysis), end of enrolment in their insurance plan or the end of the study period (30 September 2020), whichever was earliest.

Individuals were excluded if they had a claim for orally administered or injectable semaglutide, any other GLP-1 RA, any DPP4i, an amylin analogue or insulin during the 12-month baseline period. Use of these medications on the index date was also an exclusion criterion, with the exception of treatment initiation with semaglutide or DPP4i on the index date in the corresponding study groups. Individuals with a diagnosis code for type 1 or secondary diabetes during the baseline period or on the index date or a claim associated with pregnancy or gestational diabetes at any time during the study period were also excluded.

Propensity Score Matching and Baseline Characteristics

Individuals were propensity score matched 1:1 using nearest neighbour matching without replacement, with a narrow width of calliper (0.1 rather than 0.2) to minimize the difference between matched pairs. For matching, iterations were performed by selecting multiple combinations of characteristics to obtain a balanced cohort. The final matching used 27 characteristics for the T2D groups and 26 characteristics for the T2D plus ASCVD groups (see online Supplementary Methods). Baseline demographic characteristics used in the matching (age, sex and region) were assessed at the index date. Baseline CV comorbidities were assessed using data from any time before the index date, whereas non-CV comorbidities, medication use and disease severity scores (Quan–Charlson Comorbidity Index and

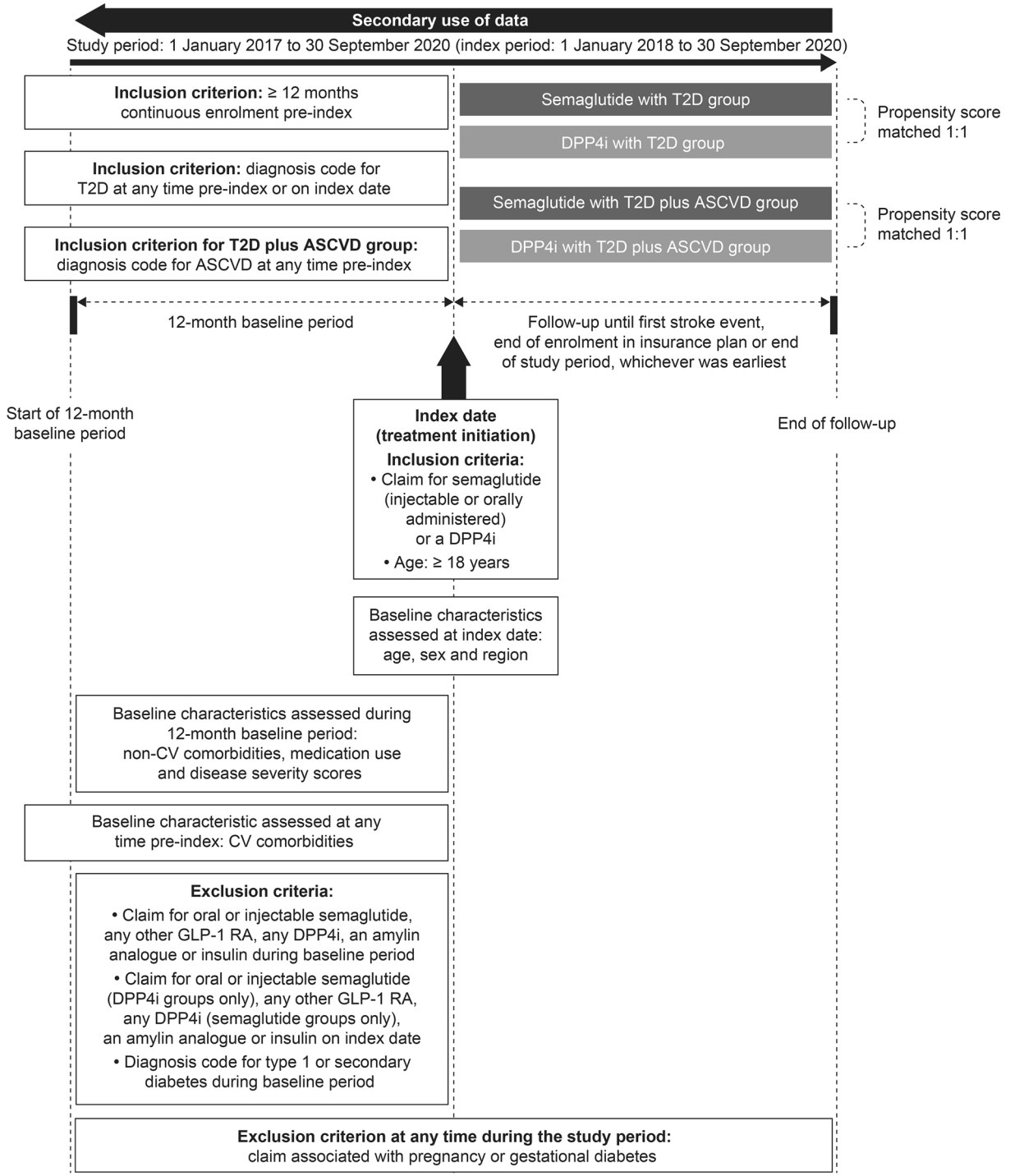

Fig. 1 Study design. *ASCVD* atherosclerotic cardiovascular disease, *CV* cardiovascular, *DPP4i* dipeptidyl peptidase 4 inhibitor, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *T2D* type 2 diabetes

adapted Diabetes Complications Severity Index [aDCSI]) were assessed in the 12-month baseline period. The aDCSI has been shown to be a robust predictor of factors including hospitalizations, mortality and inpatient and prescription costs in claims data sets using ICD-9-CM

[17] and ICD-10-CM [18] codes. After matching, the groups were considered to be well matched if the standardized mean difference was 10% or less.

Outcomes

The primary outcome was the time to first stroke event during follow-up, which was defined as a medical claim with stroke as the primary diagnosis (ICD-10-CM diagnosis codes I61 [nontraumatic intracerebral haemorrhage] and I63 [cerebral infarction]; online Supplementary Table S2) during an inpatient or emergency room visit; this could be either a primary or secondary stroke event. Individuals with no stroke event during follow-up were censored at the end of enrolment or the end of the study period, whichever was earliest.

HCRU during follow-up was included as a secondary outcome. The numbers of inpatient admissions, emergency room visits and outpatient appointments related to stroke were compared between the semaglutide and DPP4i groups. Numbers of visits are shown as per person per year (PPPY) $\times$ 1000. Two HCRU analyses were conducted: in the first, stroke was required to be present as the primary diagnosis; in the second, stroke could be either the primary or a secondary diagnosis.

The use of glucose-lowering medications during baseline compared with use during follow-up was also assessed. Individuals were considered to be using a glucose-lowering medication if they had at least one claim for the medication during the entire follow-up period (index date until end of enrolment in insurance or end of the study period, whichever was earliest). This analysis was intended to indicate how semaglutide or DPP4i initiation might affect receipt of other glucose-lowering medications, and to provide a broader context for the stroke events analysis by examining concomitant medication use.

Statistical Analyses

Baseline characteristics and medication use are reported using descriptive statistics. Numbers of stroke events, incidence rates (IRs) per 100 person-years and incidence rate ratios (IRRs) for semaglutide compared with DPP4i are reported.

Hazard ratios (HRs), 95% confidence intervals (CIs) and p values for stroke were calculated using a Cox proportional hazards model, with DPP4i as the reference group. Estimates were adjusted for baseline covariates (see online Supplementary Methods) to address any residual confounding. Adjusted mean rate ratios, 95% CIs and p values for HCRU were obtained via generalized linear models using a Tweedie distribution and log link function with number of visits as the dependent variable and treatment arm as a covariate. The estimates were adjusted for baseline characteristics. Variable follow-up time was adjusted for as an offset in the model. Unadjusted estimates for both analyses are also reported. $p < 0.05$ was the threshold for statistical significance.

Sensitivity Analyses

Three sensitivity analyses were conducted. In sensitivity analysis 1, only people who had not received an SGLT2i during the baseline period were included. In sensitivity analysis 2, to remove the possible confounding factor of recent stroke events, only people who had not had a stroke event (defined as in the main analysis) in the 90 days before the index date were included. In sensitivity analysis 3, individuals were censored upon discontinuation of semaglutide or DPP4i. Discontinuation was defined as a medication gap of at least 90 days, starting from the last day of treatment with the index drug. This date was estimated on the basis of the number of days' supply on the last claim for index treatment. For the DPP4i groups, individuals were allowed to switch to a DPP4i other than the DPP4i received on the index date, and therefore a gap in the use of any DPP4i was considered as meeting this criterion.

Compliance with Ethics Guidelines

This study was performed in accordance with the Declaration of Helsinki (1964). Ethical approval and informed consent were not

required, because these were fully anonymized data. The data analysed during the study were licensed under an agreement between Novo Nordisk and Merative.

RESULTS

Study Attrition and Baseline Characteristics

In total, 18,856 eligible individuals initiating semaglutide and 45,442 eligible individuals initiating a DPP4i were included in the propensity score matching. After matching, the cohorts included 17,920 pairs of individuals with T2D and 4234 pairs of individuals with T2D plus ASCVD (Online Supplementary Fig. S1). For both T2D and T2D plus ASCVD, the semaglutide and DPP4i groups were well matched on baseline demographic characteristics, comorbidities, and use of glucose-lowering and CV disease medications (Table 1).

In the groups with T2D, the mean age was 52 years and approximately 50% of people were women (semaglutide: 53.0%; DPP4i: 51.9%). People in the groups with T2D plus ASCVD were slightly older and more likely to be male (semaglutide: mean age 56.4 years, 47.5% women; DPP4i: mean age 56.6 years, 47.0% women).

Across all groups, approximately 75% of people received metformin in the baseline period. Approximately 25% received a sulfonylurea and a similar proportion received an SGLT2i. Most people who initiated semaglutide received the injectable form (T2D: 87.5%; T2D plus ASCVD: 88.6%).

Most people had previous hypertension (T2D groups: 80%; T2D plus ASCVD groups: 93–94%) and dyslipidaemia (T2D groups: 68–69%; T2D plus ASCVD groups: 79–81%), and approximately 50% had obesity. Overall, 2% of people in the T2D groups, but 10% in the T2D plus ASCVD groups, had experienced a previous stroke.

Stroke Incidence and Risk of Stroke

Figure 2a shows cumulative stroke events over follow-up in the groups with T2D. There were 34 stroke events in the semaglutide group (IR per 100 person-years: 0.24) over a median follow-up of 237 days (interquartile range: 107–427) and 60 events in the DPP4i group (IR per 100 person-years: 0.39) over a median follow-up of 254 days (120–468). The IRR was 0.62 (95% CI: 0.40–0.95), and adjusted analyses indicated that people receiving semaglutide were significantly less likely to experience a stroke event than those receiving a DPP4i (HR: 0.63 [0.41–0.95]; $p = 0.029$; Table 2).

A similar trend was observed in the groups with T2D plus ASCVD (Fig. 2b). There were 13 stroke events in the semaglutide group (IR per 100 person-years: 0.39; median follow-up: 238 days [107–426]) and 32 events in the DPP4i group (IR per 100 person-years: 0.89; median follow-up: 258 days [120–465]). The IRR was 0.44 (0.23–0.85) and the adjusted HR was 0.45 (95% CI: 0.24–0.86; $p = 0.015$; Table 2). In both analyses, unadjusted HRs were similar to adjusted HRs (Table 2).

Healthcare Resource Utilization

Overall, few people in any group experienced inpatient admissions, emergency room visits or outpatient appointments during follow-up (Table 3). Compared with those receiving a DPP4i, people receiving semaglutide had significantly fewer inpatient admissions (adjusted mean rate ratio: 0.52 [95% CI 0.30–0.89]; $p = 0.018$) or emergency room visits (0.54 [0.35–0.85]; $p = 0.007$) with stroke as the primary diagnosis during follow-up. A stronger trend in favour of semaglutide was observed for outpatient appointments (0.34 [0.23–0.48]; $p < 0.0001$). Similar results were observed in the treatment groups with T2D plus ASCVD (inpatient: 0.30 [0.12–0.74]; $p = 0.0089$; emergency room: 0.48 [0.24–0.94]; $p = 0.031$; outpatient: 0.24 [0.15–0.38]; $p < 0.0001$).

In the analysis with stroke as either a primary or a secondary diagnosis, the reductions in HCRU for semaglutide compared with DPP4i were generally similar to those in the analysis with stroke as primary diagnosis only (Table 3). In all analyses, unadjusted ratios were generally similar to adjusted ratios.

Table 1 Baseline demographic and clinical characteristics

	T2D			T2D plus ASCVD		
	Semaglutide (*n* = 17,920)	**DPP4i (*n* = 17,920)**	**SMD (%)**	**Semaglutide (*n* = 4234)**	**DPP4i (*n* = 4234)**	**SMD (%)**
Age, years, mean (SD)	52.2 (9.1)	52.4 (9.0)	2.9	56.4 (7.8)	56.6 (7.6)	2.6
Women, *n* (%)	9501 (53.0)	9306 (51.9)	2.2	2011 (47.5)	1990 (47.0)	1.0
Region, *n* (%)						
Northeast	1810 (10.1)	1850 (10.3)	0.7	579 (13.7)	600 (14.2)	1.4
North central	3001 (16.7)	2996 (16.7)	0.1	642 (15.2)	637 (15.0)	0.3
South	11,566 (64.5)	11,523 (64.3)	0.5	2734 (64.6)	2737 (64.6)	0.1
West	1509 (8.4)	1513 (8.4)	0.1	273 (6.4)	254 (6.0)	1.9
Glucose-lowering medications use, *n* (%) (12-month baseline period)						
Metformin	13,875 (77.4)	13,856 (77.3)	0.3	3214 (75.9)	3201 (75.6)	0.7
Sulfonylurea	4289 (23.9)	4295 (24.0)	0.1	1112 (26.3)	1090 (25.7)	1.2
SGLT2i	4378 (24.4)	3861 (21.5)	6.9	1161 (27.4)	983 (23.2)	9.7
TZD	1042 (5.8)	946 (5.3)	2.3	273 (6.4)	209 (4.9)	6.5
Comorbidities, *n* (%) (12-month baseline period)						
Anxiety	2721 (15.2)	2391 (13.3)	5.3	695 (16.4)	697 (16.5)	0.1
Dyslipidaemia	12,347 (68.9)	12,240 (68.3)	1.3	3443 (81.3)	3344 (79.0)	5.9
Obesity	9030 (50.4)	8711 (48.6)	3.6	2246 (53.0)	2192 (51.8)	2.6
Renal disease	742 (4.1)	729 (4.1)	0.4	313 (7.4)	337 (8.0)	2.1
Diabetic nephropathy	1100 (6.1)	1024 (5.7)	1.8	364 (8.6)	348 (8.2)	1.4
Diabetic retinopathy	672 (3.8)	679 (3.8)	0.2	218 (5.1)	213 (5.0)	0.5
Diabetic neuropathy	1616 (9.0)	1401 (7.8)	4.3	618 (14.6)	552 (13.0)	4.5
Severity score, mean (SD)						
aDCSI	0.63 (1.1)	0.62 (1.1)	1.2	1.48 (1.5)	1.50 (1.5)	1.4
QCI	0.74 (1.2)	0.72 (1.3)	0.9	1.19 (1.5)	1.18 (1.6)	0.3
CV comorbidities, *n* (%) (any time pre-index)						
Hypertension	14,356 (80.1)	14,389 (80.3)	0.5	3957 (93.5)	3953 (93.4)	0.4
ASCVD	4177 (23.3)	4040 (22.5)	1.8	4234 (100)	4234 (100)	0.0
Cerebrovascular	1477 (8.2)	1452 (8.1)	0.5	1485 (35.1)	1492 (35.2)	0.3
Stroke[a]	421 (2.3)	416 (2.3)	0.2	418 (9.9)	418 (9.9)	0.0
Ischaemic heart disease	2854 (15.9)	2810 (15.7)	0.7	2850 (67.3)	2836 (67.0)	0.7
Myocardial infarction	428 (2.4)	422 (2.4)	0.2	437 (10.3)	434 (10.3)	0.2
Peripheral artery disease	946 (5.3)	922 (5.1)	0.6	959 (22.6)	953 (22.5)	0.3

Table 1 continued

	T2D			T2D plus ASCVD		
	Semaglutide (*n* = 17,920)	**DPP4i (*n* = 17,920)**	**SMD (%)**	**Semaglutide (*n* = 4234)**	**DPP4i (*n* = 4234)**	**SMD (%)**
Heart failure	848 (4.7)	841 (4.7)	0.2	621 (14.7)	621 (14.7)	0.0
CV-related medication use, *n* (%) (12-month baseline period)						
ACE inhibitors	6045 (33.7)	6457 (36.0)	4.8	1487 (35.1)	1630 (38.5)	7.0
Dual α- and β-blockers	65 (0.4)	80 (0.4)	1.3	23 (0.5)	33 (0.8)	2.9
Antiarrhythmic agents	119 (0.7)	129 (0.7)	0.7	74 (1.7)	93 (2.2)	3.2
β-blockers	4089 (22.8)	4136 (23.1)	0.6	1814 (42.8)	1858 (43.9)	2.1
Calcium channel blockers	3383 (18.9)	3571 (19.9)	2.7	1079 (25.5)	1194 (28.2)	6.1
Cardiac glycosides	31 (0.2)	48 (0.3)	2.0	22 (0.5)	41 (1.0)	5.2
Cardiac drugs, NEC	4983 (27.8)	4592 (25.6)	4.9	1498 (35.4)	1324 (31.3)	8.7
Anti-hyperlipidaemic drugs, NEC	10,947 (61.1)	10,914 (60.9)	0.4	3163 (74.7)	3090 (73.0)	3.9
Hypotensive agents, NEC	540 (3.0)	568 (3.2)	0.9	211 (5.0)	256 (6.0)	4.7
Vasodilating agents, NEC	365 (2.0)	372 (2.1)	0.3	329 (7.8)	326 (7.7)	0.3

ACE angiotensin-converting enzyme, *aDCSI* adapted Diabetes Complications Severity Index, *ASCVD* atherosclerotic cardiovascular disease, *CV* cardiovascular, *DPP4i* dipeptidyl peptidase 4 inhibitor, *NEC* not elsewhere classified, *QCI* Quan–Charlson Comorbidity Index, *SD* standard deviation, *SGLT2i* sodium–glucose cotransporter 2 inhibitor, *SMD* standardized mean difference, *T2D* type 2 diabetes, *TZD* thiazolidinedione

[a]Stroke during the baseline period was identified on the basis of the presence of a stroke-related diagnosis (primary or secondary) during any type of visit (inpatient, outpatient, emergency room)

Use of Glucose-Lowering Medication

Table 4 shows receipt of glucose-lowering medications. Claims for metformin decreased from baseline to follow-up in all groups, with larger decreases in those receiving semaglutide (T2D: 17.5%; T2D plus ASCVD: 17.8%) than in those receiving a DPP4i (T2D: 5.2%; T2D plus ASCVD: 9.8%). For sulfonylureas, claims decreased from baseline to follow-up in the semaglutide groups (T2D: 29.6%; T2D plus ASCVD: 29.2%) but remained similar for the DPP4i groups (T2D: 3.9% increase; T2D plus ASCVD: 0.6% decrease).

In the T2D groups, 3.6% of those with semaglutide and 5.4% of those with DPP4i as index treatment initiated insulin during follow-up. This pattern was similar in the T2D plus ASCVD groups (semaglutide: 4.0%; DPP4i: 6.5%). In the DPP4i groups, 10% of people initiated a GLP-1 RA during follow-up, whereas in the semaglutide groups, 2% initiated a DPP4i during follow-up.

Sensitivity Analyses

Semaglutide was associated with a lower risk of stroke than a DPP4i in all sensitivity analyses; in each case, this effect was most pronounced in the

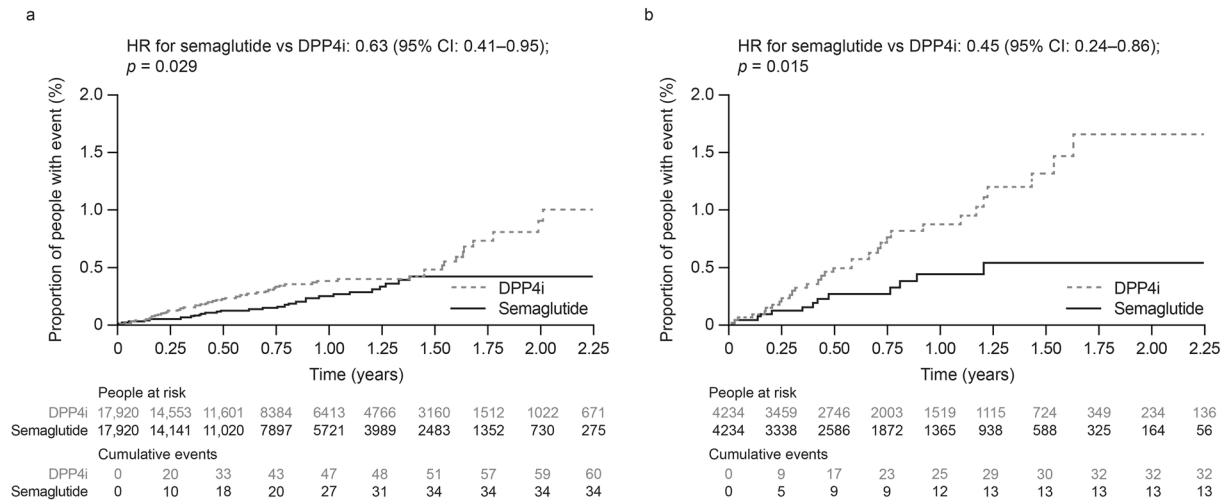

Fig. 2 Cumulative incidence of stroke in the groups with T2D (**a**) and T2D plus ASCVD (**b**). HRs, 95% CIs and *p* values for stroke were calculated using a Cox proportional hazards model, with DPP4i as the reference group. *ASCVD* atherosclerotic cardiovascular disease, *CI* confidence interval, *DPP4i* dipeptidyl peptidase 4 inhibitor, *HR* hazard ratio, *T2D* type 2 diabetes

Table 2 Stroke events in the main analysis

	T2D		T2D plus ASCVD	
	Semaglutide (*n* = 17,920)	**DPP4i (*n* = 17,920)**	**Semaglutide (*n* = 4234)**	**DPP4i (*n* = 4234)**
Follow-up duration, days, median (IQR)	237 (107–427)	254 (120–468)	238 (107–426)	258 (120–465)
Number of events, *n* (%)	34 (0.2)	60 (0.3)	13 (0.3)	32 (0.8)
IR per 100 person-years	0.24	0.39	0.39	0.89
IRR (95% CI)	0.62 (0.40–0.95)	Ref.	0.44 (0.23–0.85)	Ref.
Unadjusted HR (95% CI)	0.61 (0.40–0.93)	Ref.	0.43 (0.23–0.83)	Ref.
p value	0.022	Ref.	0.011	Ref.
Adjusted HR (95% CI)	0.63 (0.41–0.95)	Ref.	0.45 (0.24–0.86)	Ref.
p value	0.029	Ref.	0.015	Ref.

ASCVD atherosclerotic cardiovascular disease, *CI* confidence interval, *DPP4i* dipeptidyl peptidase 4 inhibitor, *HR* hazard ratio, *IQR* interquartile range, *IR* incidence rate, *IRR* incidence rate ratio, *Ref.* reference group, *T2D* type 2 diabetes

groups with T2D plus ASCVD, and unadjusted HRs were similar to adjusted HRs (online Supplementary Table S3). Online Supplementary Fig. S2 shows the cumulative incidence of stroke in sensitivity analysis 3.

Table 3 Healthcare resource utilization

	T2D						
	Semaglutide (n = 17,920)		DPP4i (n = 17,920)		Semaglutide vs DPP4i		
	Number of patients	Mean (SD), PPPY × 1000	Number of patients	Mean (SD), PPPY × 1000	Unadjusted mean ratio (95% CI)	Adjusted mean ratio (95% CI)	p value
Stroke as the primary diagnosis							
Inpatient	22	1.6 (43.9)	42	3.1 (66.3)	0.49 (0.29–0.86)	0.52 (0.30–0.89)	0.0182
Emergency room visit	34	2.6 (55.4)	59	5.0 (108.9)	0.51 (0.33–0.80)	0.54 (0.35–0.85)	0.0070
Outpatient	86	11.2 (192.9)	117	34.3 (861.3)	0.27 (0.18–0.41)	0.34 (0.23–0.48)	< 0.0001
Stroke as the primary or secondary diagnosis							
Inpatient	34	2.6 (59.5)	61	5.5 (101.0)	0.47 (0.30–0.74)	0.48 (0.31–0.76)	0.0016
Emergency room visit	39	2.9 (61.5)	67	5.7 (121.5)	0.51 (0.33–0.77)	0.53 (0.35–0.81)	0.0033
Outpatient	113	21.2 (417.3)	165	58.2 (1152.7)	0.33 (0.24–0.47)	0.34 (0.25–0.47)	< 0.0001
	T2D plus ASCVD						
	Semaglutide (n = 4234)		DPP4i (n = 4234)		Semaglutide vs DPP4i		
	Number of patients	Mean (SD), PPPY × 1000	Number of patients	Mean (SD), PPPY × 1000	Unadjusted mean ratio (95% CI)	Adjusted mean ratio (95% CI)	p value
Stroke as the primary diagnosis							
Inpatient	7	2.1 (57.2)	23	7.5 (106.8)	0.28 (0.11–0.69)	0.30 (0.12–0.74)	0.0089
Emergency room visit	13	4.2 (76.0)	31	9.4 (119.8)	0.44 (0.23–0.87)	0.48 (0.24–0.94)	0.0311
Outpatient	52	29.1 (341.9)	90	133.2 (1642.1)	0.20 (0.12–0.33)	0.24 (0.15–0.38)	< 0.0001
Stroke as the primary or secondary diagnosis							
Inpatient	15	4.8 (74.4)	36	14.7 (167.1)	0.32 (0.16–0.62)	0.34 (0.18–0.66)	0.0015
Emergency room visit	17	5.4 (83.4)	39	12.4 (152.6)	0.43 (0.24–0.77)	0.47 (0.26–0.84)	0.0114
Outpatient	75	66.7 (820.7)	124	196.8 (1996.8)	0.33 (0.22–0.50)	0.35 (0.24–0.50)	< 0.0001

ASCVD atherosclerotic cardiovascular disease, *CI* confidence interval, *DPP4i* dipeptidyl peptidase 4 inhibitor, *PPPY* × *1000* per 1000 patients per year, *SD* standard deviation, *T2D* type 2 diabetes

Table 4 Glucose-lowering medication use in the baseline period and during follow-up

	T2D						T2D plus ASCVD					
	Semaglutide (*n* = 17,920)			DPP4i (*n* = 17,920)			Semaglutide (*n* = 4234)			DPP4i (*n* = 4234)		
	Baseline	Follow-up	Change from baseline	Baseline	Follow-up	Change from baseline	Baseline	Follow-up	Change from baseline	Baseline	Follow-up	Change from baseline
Follow-up, days, median (IQR)	NA	237 (107–426)	NA	NA	253 (120–468)	NA	NA	237.5 (106–426)	NA	NA	254.5 (120–464)	NA
Glucose-lowering medication use, *n* (%)												
Biguanides (metformin)	13,875 (77.4)	11,440 (63.8)	↓	13,856 (77.3)	13,139 (73.3)	↓	3214 (75.9)	2641 (62.4)	↓	3201 (75.6)	2887 (68.2)	↓
DPP4i	0 (0.0)	335 (1.9)	↑	NA	NA	NA	0 (0.0)	76 (1.8)	↑	NA	NA	NA
GLP-1 RA	NA	NA	NA	0 (0.0)	1836 (10.2)	↑	NA	NA	NA	0 (0.0)	414 (9.8)	↑
Insulin	0 (0.0)	652 (3.6)	↑	0 (0.0)	973 (5.4)	↑	0 (0.0)	171 (4.0)	↑	0 (0.0)	274 (6.5)	↑
TZD	1042 (5.8)	840 (4.7)	↓	946 (5.3)	976 (5.4)	↑	273 (6.4)	204 (4.8)	↓	209 (4.9)	195 (4.6)	↓
SGLT2i	4378 (24.4)	4017 (22.4)	↓	3861 (21.5)	3756 (21.0)	↓	1161 (27.4)	1055 (24.9)	↓	983 (23.2)	940 (22.2)	↓
Sulfonylureas	4289 (23.9)	3019 (16.8)	↓	4295 (24.0)	4463 (24.9)	↑	1112 (26.3)	787 (18.6)	↓	1090 (25.7)	1084 (25.6)	↓

Light grey shading indicates instances in which the relevant group showed the larger (or only) numerical decrease from baseline; dark grey shading indicates instances in which the relevant group showed the larger (or only) numerical increase from baseline. *n* refers to the number of patients with at least one claim for the medication

ASCVD atherosclerotic cardiovascular disease, *DPP4i* dipeptidyl peptidase 4 inhibitor, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *IQR* interquartile range, *SGLT2i* sodium–glucose cotransporter 2 inhibitor, *T2D* type 2 diabetes, *TZD* thiazolidinedione

DISCUSSION

The results of this real-world observational study indicate that semaglutide has the potential to reduce the risk of stroke when prescribed in clinical practice. Over short-term follow-up, people with T2D receiving semaglutide had a significantly lower risk of stroke than those receiving DPP4is; this difference was greater in people with T2D and established ASCVD.

The additional analyses provided context for these results. Use of other glucose-lowering medications generally decreased slightly in the semaglutide groups from baseline to follow-up, but increased or remained the same in the DPP4i groups. This may reflect underlying differences in T2D severity or clinical management between the treatment groups. Importantly, the lower risk of stroke in people treated with semaglutide compared with DPP4i was observed despite the fact that 10% of people in the DPP4i groups initiated a GLP-1 RA during follow-up. The results of the sensitivity analyses supported the main findings.

People in the semaglutide groups had significantly lower stroke-related HCRU than those in the DPP4i groups, particularly in terms of a

reduced rate of outpatient appointments. Overall, more outpatient appointments than inpatient or emergency room visits were observed in all groups, which may be because some outpatient appointments related to stroke events that had occurred before the study period. In addition to improving clinical outcomes and reducing the economic impact of hospital admissions, treatments that limit the risk of CV events can also bring indirect benefits. For example, reductions in inpatient care can contribute to lowering the environmental impact of healthcare by saving energy and water and reducing the generation of waste [19]. It must be noted that the final 6–7 months of the study period overlapped with the beginning of the coronavirus disease 2019 (COVID-19) pandemic. In addition to the widespread disruption to routine healthcare appointments in the USA during the pandemic, including for the management of T2D [20], COVID-19 has been identified as a risk factor for acute ischaemic stroke [21]. Both of these factors may have affected the study findings.

The large sample size in our analysis permitted propensity score matching on multiple characteristics, including aDCSI score, a well-validated measure of diabetes severity [17, 18]. Matching limited the risk of bias, and subsequent adjustment for baseline characteristics was also carried out to reduce the chance of confounding. Concordance between unadjusted and adjusted HRs indicates that the cohorts were well balanced following matching, even before this additional adjustment. Our sensitivity analyses also addressed some potential limitations of the main analysis. For example, it was technically possible for an included individual to initiate treatment and experience a stroke event on the same day, but the sensitivity analysis in which no stroke event was permitted in the 90 days before treatment initiation, including on the index date, partly overcame this limitation. Overall, this intention-to-treat analysis represents an initial step in addressing an evidence gap for real-world stroke occurrence in people with T2D, indicating that differences between treatment groups can be detected even with relatively short follow-up time and small numbers of stroke events. Consequently, these analyses lay the foundations for studies with longer follow-up, which would allow assessment of additional outcomes and treatment comparisons.

The results of the analysis should be interpreted in the context of the study scope, real-world setting and data source. Using US claims data permits the inclusion of a large sample, but imposes limits on the generalizability and interpretation of the data. The southern USA was over-represented in this data set, and data on ethnicity, social deprivation and other factors that may underlie clinical outcomes and access to healthcare were not available in a structured form. Furthermore, the data set is representative only of people with health insurance. It was not possible to include all relevant clinical parameters in the analysis, notably HbA1c measurements at baseline and during follow-up. Although this meant that the analysis did not fully address the relationship between T2D severity and stroke risk, matching cohorts on aDCSI scores and other disease characteristics helped to limit the risk of bias.

Median follow-up for each treatment group was less than 12 months, meaning that most stroke events occurred early in the maximum follow-up period and the absolute numbers of stroke events were small. This is highlighted by the overlapping lines in the Kaplan–Meier plot in Fig. 2a. Analyses with longer follow-up will help to determine the broader clinical and economic impact of semaglutide on risk of stroke, and to examine factors that could not be assessed in this analysis, such as differentiation between primary and secondary stroke risk reduction and between fatal and non-fatal stroke. The inclusion of additional treatment comparators, such as SGLT2is, and clinical parameters including HbA1c, would also be of interest.

In our analyses, semaglutide was associated with a lower short-term risk of stroke and less HCRU compared with DPP4is in people with T2D and T2D with established ASCVD. This study provides some of the first real-world evidence on stroke outcomes with semaglutide, and acts as a proof-of-concept analysis to inform future studies addressing the unmet

need for real-world data on stroke risk reduction in T2D.

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Declarations

Conflict of Interest. Marc Evans has received fees from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. Mansoor Husain has received research grants from AstraZeneca, Merck and Novo Nordisk; consultancy fees for participation in advisory board meetings from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk and Roche; speaker fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck and Novo Nordisk; and payment for expert testimony from Novo Nordisk. He holds one patent relating to GLP-1 peptides and has one patent pending relating to methods for inhibiting platelet aggregation using GLP-1 peptides. Ayush Srivastava is an employee of Novo Nordisk Service Centre Pvt. Ltd. Kamal Kant Mangla and Anja Birk Kuhlman are employees of Novo Nordisk A/S. Ayush Srivastava, Kamal Kant Mangla and Anja Birk Kuhlman hold Novo Nordisk stocks. Ildiko Lingvay has received research funding (paid to institution) from Boehringer Ingelheim, Merck, Mylan, Novo Nordisk, Pfizer and Sanofi; and advisory/consulting fees and/or other support from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GI Dynamics, Intarcia Therapeutics, Intercept Pharmaceuticals, Janssen, MannKind, Merck, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, Target Pharma, Valeritas and Zealand Pharma.

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