Original research

Shorter-acting glucagon-like peptide-1 receptor agonists are associated with increased development of gastro-oesophageal reflux disease and its complications in patients with type 2 diabetes mellitus: a population-level retrospective matched cohort study

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ABSTRACT

Background Shorter half-life glucagon-like peptide-1 receptor agonists (GLP-1 RAs) delay gastric emptying (DGE) more than GLP-1 RAs with longer half-lives. DGE is a known risk factor for gastro-oesophageal reflux disease (GERD) and its complications.

Aim To determine whether short-acting or long-acting GLP-1 RAs are associated with an increased risk of new GERD or GERD-related complications

Design We used the TriNetX global database to identify adult patients with type 2 diabetes mellitus and generated two cohorts totalling 1 543 351 patients on (1) GLP-1 RA or (2) other second-line diabetes medication. Using propensity-score matching, Kaplan-Meier Analysis and Cox-proportional hazards ratio (HR), we analysed outcomes and separately examined outcomes in patients starting short-acting (≤1 day) and long-acting (≥5 days) GLP-1 RAs.

Results 177 666 patients were in each propensity-matched cohort. GLP-1 RA exposure was associated with an increased risk (HR 1.15; 95% CI 1.09 to 1.22) of erosive reflux disease (ERD). However, this was solely due to short-acting (HR 1.215; 95% CI 1.111 to 1.328), but not long-acting (HR 0.994; 95% CI 0.924 to 1.069) GLP-1 RA exposure. Short-acting GLP-1 RAs were also associated with increased risk of oesophageal stricture (HR 1.284; 95% CI 1.135 to 1.453), Barrett's without dysplasia (HR 1.372; 95% CI 1.217 to 1.546) and Barrett's with dysplasia (HR 1.505; 95% CI 1.164 to 1.946) whereas long-acting GLP-1 RAs were not. This association persisted in sensitivity analyses, and when individually examining the short-acting GLP-1 RAs liraglutide, lixisenatide and exenatide.

Conclusion Starting shorter-acting GLP-1 RAs is associated with increased risks of GERD and its complications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Longer-acting glucagon-like peptide-1 receptor agonists appear to have less effect on gastric emptying than shorter-acting glucagon-like peptide-1 receptor agonists. Delayed gastric emptying is a known risk factor for gastro-oesophageal reflux disease (GERD) and its complications.

WHAT THIS STUDY ADDS

⇒ Patients with type 2 diabetes mellitus (T2DM) starting shorter-acting glucagon-like peptide-1 receptor agonists, particularly liraglutide, had significantly increased odds of a new diagnosis of GERD, erosive oesophagitis, oesophageal stricture and Barrett's with or without dysplasia compared with those starting longer-acting glucagon-like peptide-1 receptor agonists.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ To minimise the risk of GERD or its complications, clinicians should consider prescribing long-acting instead of short-acting glucagon-like peptide-1 receptor agonists for patients with T2DM.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are relatively new and effective medications approved for the treatment of type 2 diabetes (T2DM) and obesity. Since their approval in 2005, GLP-1 RAs have been increasingly prescribed for the treatment of T2DM due to their effective glycaemic control, weight loss, cardiovascular protection and low risk of hypoglycaemia.[1] Unfortunately, some of the same mechanisms resulting in weight loss and postprandial glucose control cause common gastrointestinal side effects.[2] These include nausea, vomiting, diarrhoea and delayed gastric emptying.[3] Evidence of delayed gastric emptying due to GLP-1 RAs has resulted in guidelines suggesting that GLP-1 RAs be held before gastric emptying studies to prevent inappropriate management of medication-induced gastroparesis.[4] Gastroparesis is

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associated with and may lead to refractory gastro-oesophageal reflux disease (GERD).[5] GERD is associated with high economic burden and, if untreated, can lead to severe complications such as erosive oesophagitis, oesophageal stricture, Barrett's oesophagus and even oesophageal adenocarcinoma.[6]

Despite the popularity of GLP-1 RAs, there have been minimal investigations into any relationship between GLP-1 RAs and GERD or its complications. Nevertheless, Ishihara *et al* reported one case of possible liraglutide-induced GERD resulting in erosive oesophagitis, and Moss *et al* suggested that GLP-1 RA-induced motility impairment resulted in a case of acute oesophageal necrosis.[7 8] GLP-1 RAs were also noted to have a higher incidence of GERD-like symptoms than dipeptidyl peptidase-4 inhibitors in one 2018 study of the Japanese adverse drug event reporting database.[9] This study noted that the association with GERD only occurred in GLP-1 RAs with half-lives of less than a day, administered daily. Dulaglutide, which has a half-life of 5 days, was not significantly associated with GERD-like symptoms.[10–13]

The primary aim of this study was to determine whether initiation of GLP-1 RAs is associated with increased odds of developing new GERD or GERD-related complications (including oesophageal stricture and Barrett's oesophagus) in adult patients with T2DM. Our secondary aim was to determine if these outcomes were more pronounced in patients taking GLP-1 RAs with shorter half-lives and more frequent administration than those with longer half-lives.

METHODS

We conducted a retrospective cohort study using the TriNetX platform. TriNetX is an anonymised multicentre patient database that provides deidentified aggregate healthcare data for over 123 million patients from 100 participating healthcare organisations spanning 14 countries at the time of the search. TriNetX has built-in analytical functions that allow patient-level analyses while reporting only population-level data to maintain anonymity. TriNetX treats all counts between one and ten to be equivalent.[14] The results reported here follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.[15]

Formulation definition

Our study defines 'short-acting' GLP-1 RAs as versions with half-lives of around 24 hours or less administered at least once daily. 'Long-acting' GLP-1 RAs will include versions administered once weekly with a half-life of 5 days or greater. This is because GLP-1 RAs with lower half-lives appear to have a greater effect on gastric emptying than those with longer half-lives.[13]

Patient selection

We identified all non-deceased patients with active records on the TriNetX platform (12 May 2003 – 12 May 2023) with an associated diagnosis of T2DM and an age ≥18 (figure 1). An index event was identified based on the timing of the prescription of the diabetic drug defining each cohort. For the GLP-1 RA cohort, this was the first prescription of a GLP-1 RA, whereas the control cohort's index event was the prescription of other second-line diabetes medications, including sodium-glucose cotransporter-2 inhibitors (SGLT2i), thiazolidinediones (TZD) or a sulfonylurea. Query search criteria were based on standard diagnostic, procedural or medication codes (online supplemental table 1). SGLT2i, TZD or sulfonylurea initiation was chosen as the comparator index event as they are used in a very similar patient population[1] and are not associated with GERD when accounting for its antidiabetic effects. DPP-4 inhibitors were excluded because they have a biologically similar mechanism of effect to GLP-1 RAs. We constructed cohorts with clinical equipoise in mind. GLP-1 RAs were first available on the market in 2005.[16] Thus, patients could not be included if their test or control exposure occurred prior to this date. For formulation-specific GLP-1 RA sensitivity analyses, time periods were restricted to the years in which both options were available, starting the year after food and drug administration approval to allow time for market availability.

Patients in both cohorts were excluded if they ever had a history of scleroderma, lupus erythematosus, Sjogren syndrome, radiation therapy or oesophageal dysmotility. Patients were also excluded if they ever had major gastric or oesophageal surgery, except if the surgery could be for GERD or GERD-complications, such as Nissen fundoplication or oesophageal dilation or Roux-en-Y gastric bypass.[17] Patients could not have a GERD-related surgery or a diagnosis of gastroparesis until the day after the index event. Both cohorts were independent of each other. Thus, the GLP-1 RA cohort could never have been on any control medications and vice versa. Some patients had previously been diagnosed with an outcome and therefore could not have a 'first-time' diagnosis and were thus automatically excluded by TriNetX for pertinent outcome specific analyses.

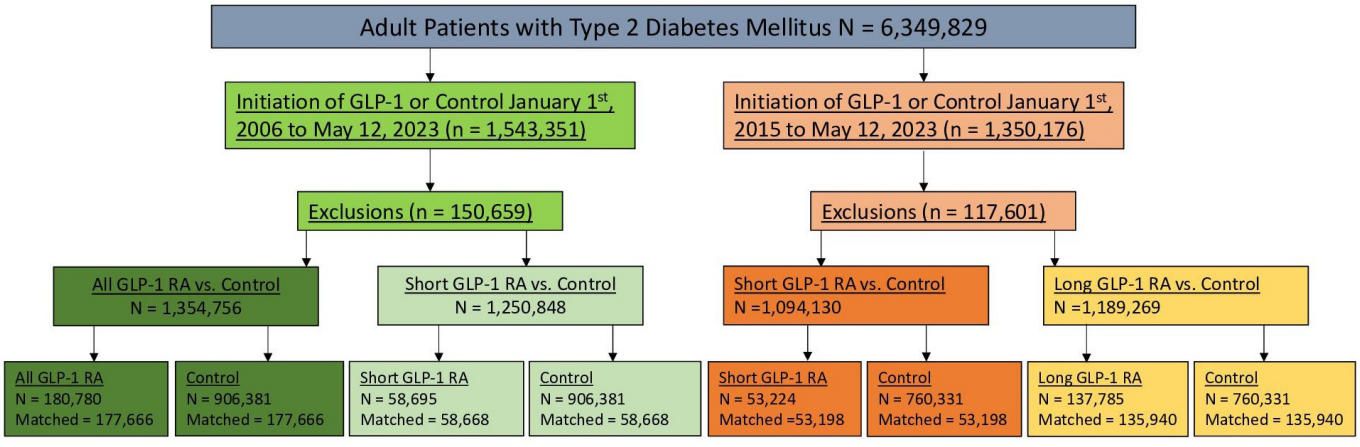

Figure 1 Flow chart of participant selection. GLP-1 RA, glucagon-like peptide-1 receptor agonists.

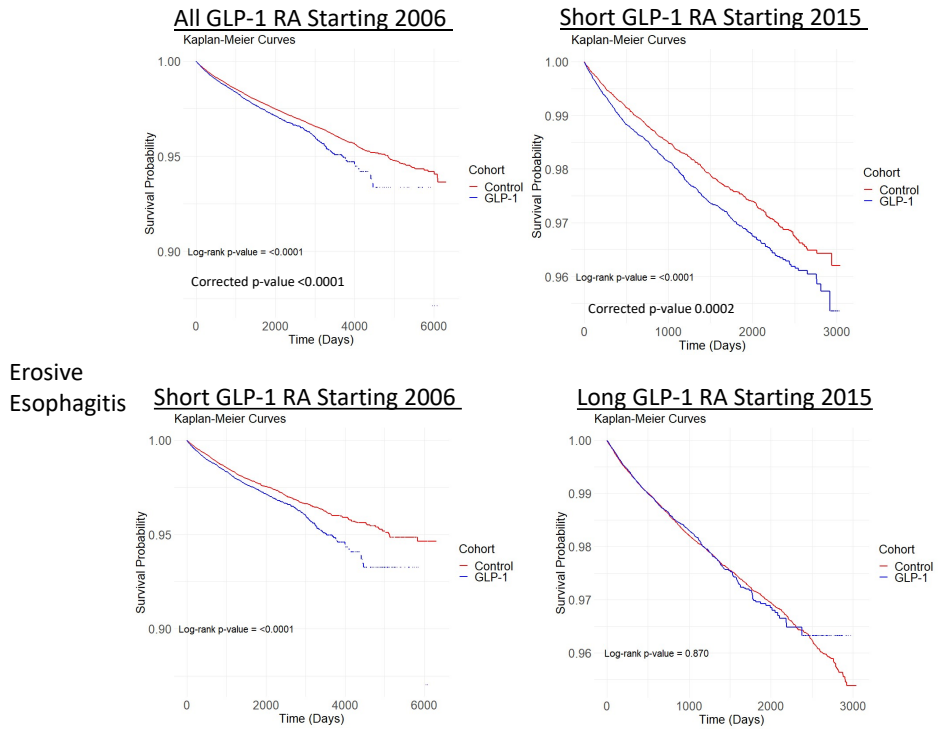

Figure 2 Kaplan-Meier curves of erosive oesophagitis following glucagon-like peptide-1 receptor agonist (GLP-1 RA) initiation in patient cohorts defined by type of GLP-1 RA initiation with sensitivity analyses in comparison to other second-line diabetes therapies. 2015, Index Event Starting in Year 2015; 2006, Index Event Starting in Year 2006; GLP-1 RA, glucagon-like peptide-1 receptor agonists; Long, GLP-1 RAs with Half-Lives of 5 days or Less; Short, GLP-1 RAs with Half-Lives of 1 day or less.

Covariates

We used the American Diabetes Association's 2022 T2DM management guidelines[1] to identify confounding factors affecting the choice of GLP-1 RA versus control initiation (online supplemental table 2) as documented by diagnostic codes (online supplemental table 1). We also identified confounding factors that could predict the odds of GERD or GERD-related outcomes, including initial A1c, initial body mass index, nicotine dependence, use of non-steroidal anti-inflammatory drugs, doxycycline, ferrous sulfate, alcohol use disorder, use of hormone replacement therapy[18] or use of systemic hormonal contraceptives.[19] One-to-one propensity score matching was performed between the test and control cohort based on the aforementioned factors, as well as age at index event, sex, ethnicity and race.[2] To avoid overadjustment bias, prior history of GERD and related complications were not matched for however were satisfactorily similar after matching for other variables (online supplemental table 2).[20] We applied this same propensity-matching strategy to all subanalyses.

Study outcomes

Primary study outcomes included the HR of 'first-time' diagnosis of GERD with (ERD) erosive oesophagitis starting the day after the index (figure 1). Primary study outcomes also included 'first-time' diagnosis of oesophageal stricture and Barrett's with (BWD) or without dysplasia (BWOD).[14] Secondary outcomes include 'first-time' diagnosis of non-erosive reflux disease (NERD), which is defined as GERD without erosive oesophagitis, 'first-time' undergoing EGD and 'first-time' usage of proton pump inhibitors (PPIs).

As a secondary analysis, we limited the test cohort to either short or long-acting GLP-1 RAs based on the half-life, as documented by the Anatomical Therapeutic Chemical Classification System (online supplemental figure 1). Short-acting GLP-1 RAs included lixisenatide, exenatide and liraglutide. Long-acting GLP-1 RAs included dulaglutide and semaglutide.[2 12 21] Once weekly and twice daily exenatides, were combined as they only differed by drug vehicle.[16] Although liraglutide is referred to as long acting in the literature, we felt its half-life appropriately suited our 'short-acting' category given the hypothesised mechanism; liraglutide is administered daily and has a half-life of only 13 hours.[10] We included the oral formulation of semaglutide in 'long acting' as the half-life is not different from the more commonly used injectable version.[22] Albiglutide was omitted. As a subanalysis, we examined the relationship between each specific medication formulation and GERD outcomes compared with the control cohort. In addition, we examined the effect of GLP-1 RAs on only patients that already had GERD at the index event. We performed three additional sensitivity analyses. The first was to run the same search on a USA only network to determine if prescribing differences between countries could affect the results. The second was to run short-acting and long-acting GLP-1 RAs on the same index event day to determine if clinical equipoise affected the results. Finally, we examined patients who had exposure to both control and GLP-1 RA medications compared with control alone.

Statistical analysis

All statistical analyses were conducted on the TriNetX platform or in R.[14] Outcomes were described using means, SD

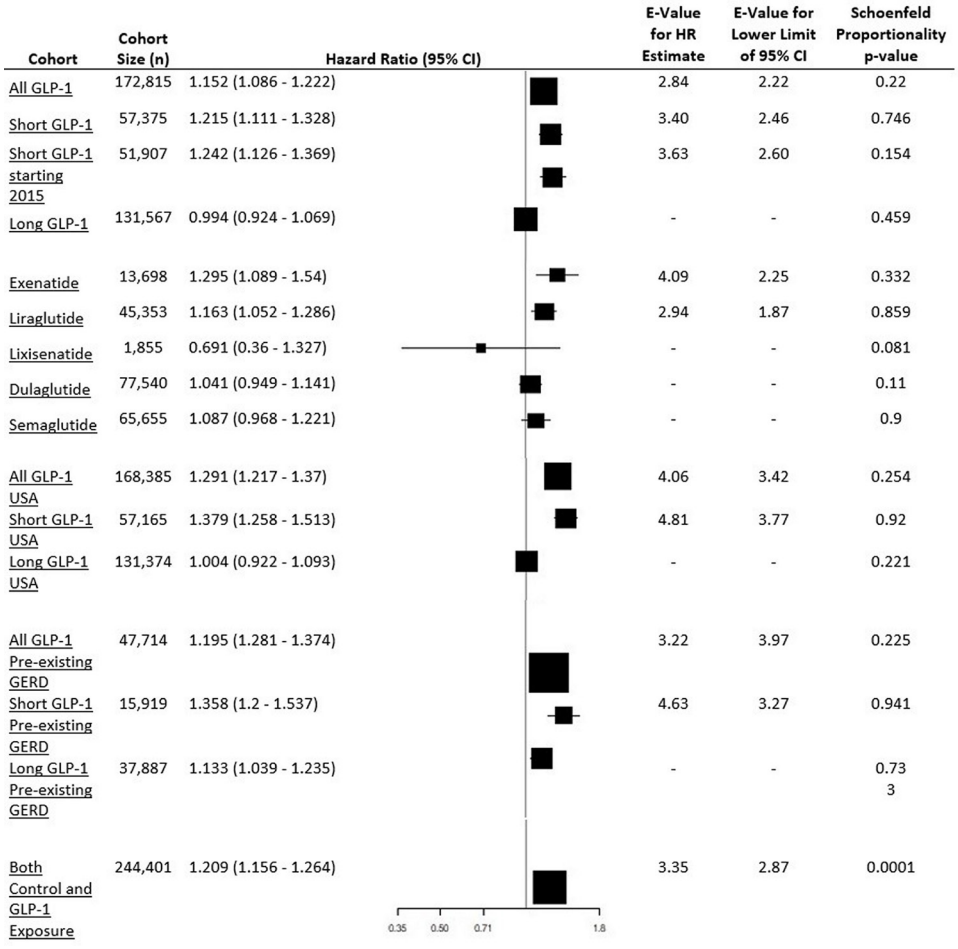

Figure 3 Cox-proportional HRs, E-values and Schoenfeld proportionalities of erosive oesophagitis following glucagon-like peptide-1 receptor agonist (GLP-1 RA) initiation in patient cohorts defined by type of GLP-1 RA initiation with sensitivity analyses. GERD, gastro-oesophageal reflux disease.

and proportions as appropriate. Propensity score matching for the study was performed within the TriNetX platform using one-to-one matching based on relevant covariates using greedy nearest neighbour algorithms with a calliper width of 0.1 pooled SDs. Characteristics with a standardised mean difference between cohorts lower than 0.1 were considered well matched.[23] Kaplan-Meier analysis was performed on the TriNetX platform on propensity matched groups as described by Austin.[24] Patients were followed until outcome or were censored after their last data point on record and when deceased. Log-rank testing was performed on the TriNetX platform to assess for statistical differences in time to event for each cohort. HRs were calculated using a univariate Cox-proportional HRs model on the TriNetX platform. The Cox proportional hazards model assumes that the chance of each hazard remains similar over time. TriNetX validates the use of this model with scaled Schoenfeld residual wherein a non-random association between these and time is evidence of a violation of the proportional hazards assumption.[25] Outcomes that invalidated the proportional hazards assumption were identified, and landmark analyses were performed at 6 months, 3 years and 5 years postindex event for key outcomes (online supplemental table 3) Potential confounding variables were investigated by E-value sensitivity analysis.[26] P values were corrected for multiple testing using the Benjamini and Hochberg method, which controls the false discovery rate and is appropriate for scenarios where outcome variables may be dependent on each other.[27] Statistical significance was determined at the 0.05 level after correction. Figures were generated in Microsoft Excel (Redmond, Washington, USA) V.2208, R 4.30 (Vienna, Austria) and RStudio V.2023.3.0.386 (Boston, Massachusetts, USA).

RESULTS

Overall cohorts

From a source population of 127 482 963 patients,[14] we identified 6 349 829 adult patients with T2DM. Among these, 1 543 351 patients had started either a GLP-1 RA or control between 1 January 2006 and 12 May 2023 and 1 350 176 had started a GLP-1 RA or control between 1 January 2015 and 12 May 2023 (figure 1). After applying the exclusion criteria, the exclusive 2006 GLP-1 RA cohort had 180, 780 patients and the exclusive 2006 control cohort had 906 381 patients. After one-to-one propensity matching, our matched cohorts comprised 177 666 patients each. Additional details for other cohorts were summarised in figure 1. The main demographic features and comorbidities are summarised in online supplemental table 2. All comparisons and baseline characteristics, including baseline GERD and its complications, were well matched after propensity score matching.[23]

Primary outcome

Patients starting a GLP-1 RA in the 2006 cohort were more likely to be diagnosed with ERD following medication initiation by the

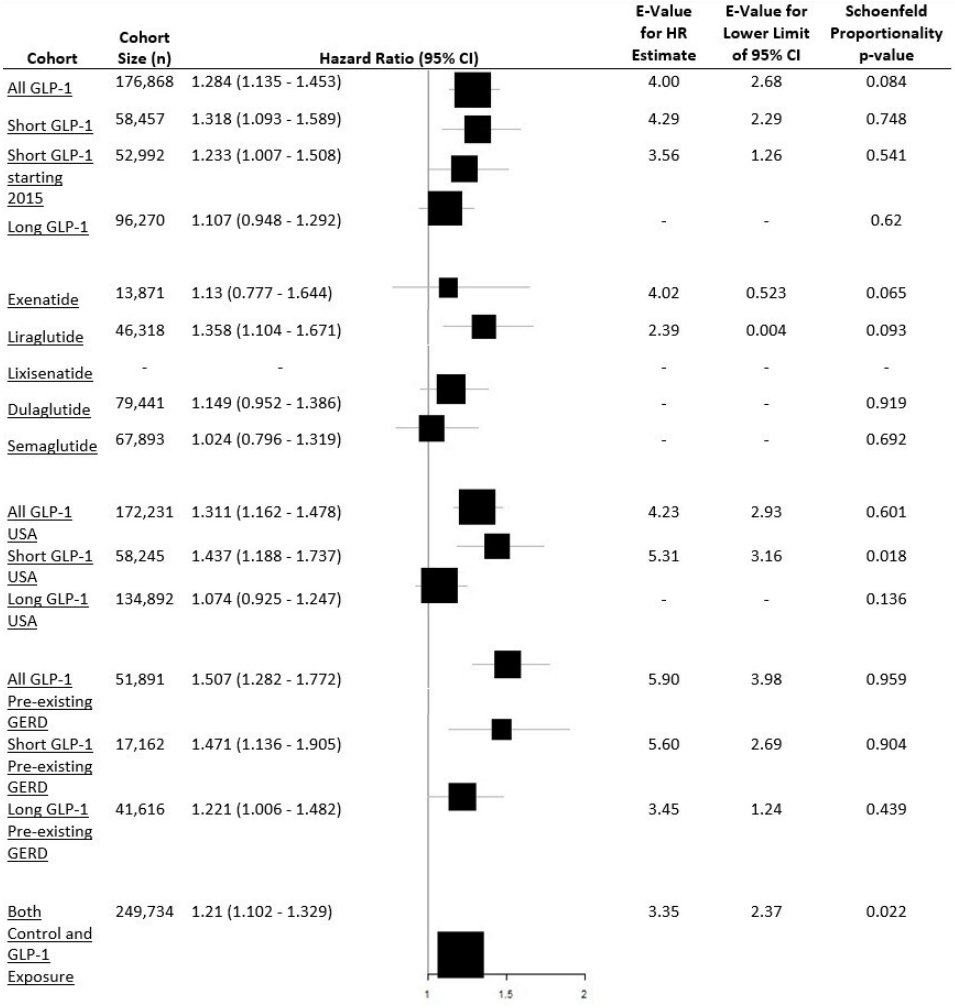

Figure 4 Cox-proportional HRs, E-values and Schoenfeld proportionalities of oesophageal stricture following glucagon-like peptide-1 receptor agonist (GLP-1 RA) initiation in patient cohorts defined by type of GLP-1 RA initiation with sensitivity analyses. GERD, gastro-oesophageal reflux disease.

end of the time period when compared with controls (12.87% vs 6.38%). Kaplan-Meier analysis showed that the cumulative incidence of ERD was higher among GLP-1 RA users compared with those starting control medications, with a statistically significant rapid and sustained divergence of curves after treatment initiation (figure 2). Propensity matched comparisons revealed that using any GLP-1 RA was associated with an increased risk of ERD compared with control (HR 1.15; 95% CI 1.09 to 1.22). E-value analysis suggested that an unobserved confounding variable would have to have a risk ratio of 2.84 or higher to negate the observed association.[26]

Primary outcome subanalyses and sensitivity analyses

When examining short-acting or long-acting GLP-1 RA only cohorts, patients were more likely to develop ERD (HR 1.215; 95% CI 1.111 to 1.328) when starting short GLP-1 RAs whereas patients starting long-acting GLP-1 RAs were not more likely to develop ERD (HR 0.994; 95% CI 0.924 to 1.069). Short-acting GLP-1 RAs had a greater risk when examining only patients receiving their care in the USA with a 38% risk of developing ERD (HR 1.379; 95% CI 1.258 to 1.513) whereas the lack of association remained with long-acting GLP-1 RAs (HR 1.004; 95% CI 0.922 to 1.093).

We performed a sensitivity analysis comparing patients starting short-acting GLP-1 RAs in 2015 to controls starting second-line diabetes medications in 2015 which showed that the association remained (HR 1.242; 95% CI 1.126 to 1.369). Those with pre-existing GERD on day of index event had a 36% increased risk of ERD (HR 1.358; 95% CI 1.2 to 1.537) when starting short-acting GLP-1 RAs, with a slightly increased risk also observed in those starting long-acting GLP-1 RAs (HR 1.133; 95% CI 1.039 to 1.235). Finally, when examining by medication subtype, patients starting short-acting GLP-1 RAs (n=45 353, patients with events=811) liraglutide (HR 1.163; 95% CI 1.052 to 1.286) and (n=13 698, patients with events=310) exenatide (HR 1.295; 95% CI 1.089 to 1.54) had increased risks of ERD. Lixisenatide, a short-acting GLP-1 RA, did not show an elevated risk of ERD (HR 0.691; 95% CI 0.36 to 1.327). However, the sample size was notably small with a total of 1855 patients, among which only 15 experienced events (figure 3). Long-acting GLP-1 RAs (n=77 540, patients with events=795), Dulaglutide (HR 1.041; 95% CI 0.949 to 1.141) and (n=65 655, patients with events=483) and semaglutide (1.087; 95% CI 0.968 to 1.221) did not have an association with ERD.

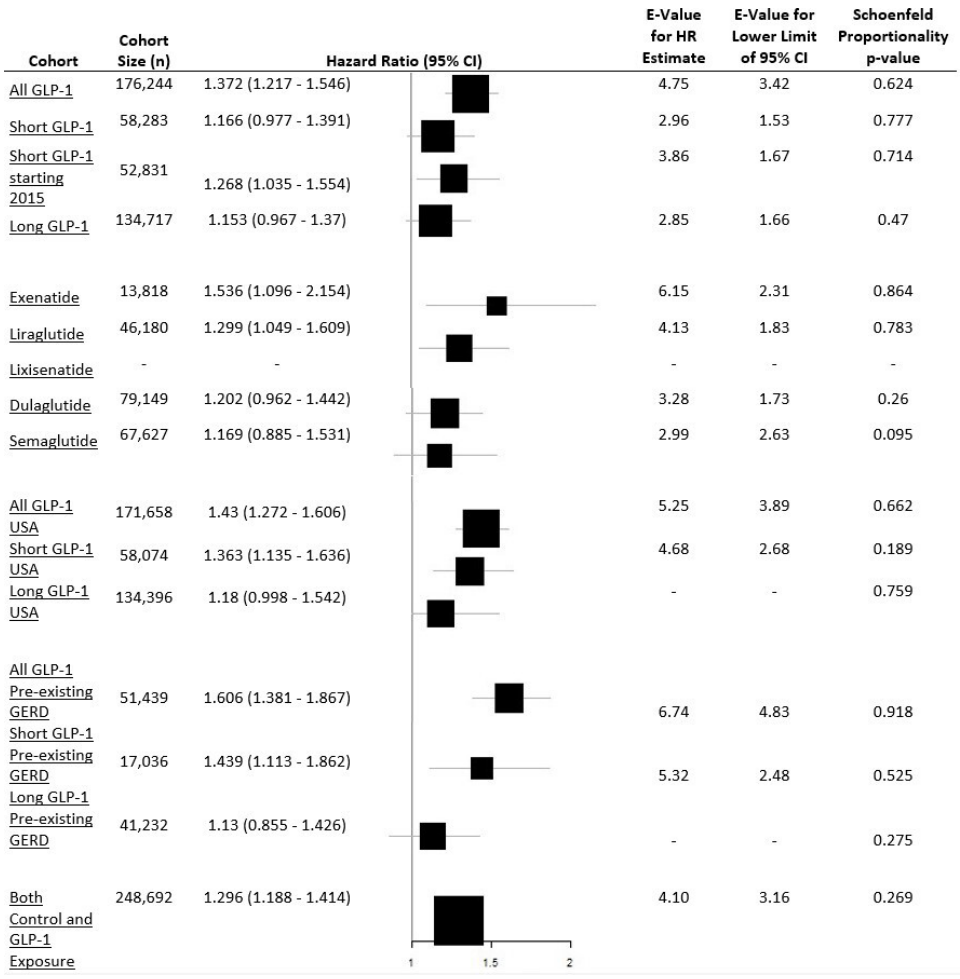

Figure 5 Cox-proportional HRs, E-values and Schoenfeld proportionalities Barrett's without dysplasia following glucagon-like peptide-1 receptor agonist (GLP-1 RA) initiation in patient cohorts defined by Type of GLP-1 RA initiation with sensitivity analyses. GERD, gastro-oesophageal reflux disease.

Secondary outcomes: long-term oesophageal complications

When examining other oesophageal complications, patients starting any GLP-1 RA had an increased risk of oesophageal stricture (HR 1.284; 95% CI 1.135 to 1.453), BWOD (HR 1.372; 95% CI 1.217 to 1.546) and BWD (HR 1.505; 95% CI 1.164 to 1.946) (figures 4–6). Proportional hazards were rejected for the BWD analysis because the risk for developing BWD increased at 3 and 5 years after GLP-1 RA initiation and was not increased at 6 months (online supplemental table 3).

Secondary outcome sensitivity analyses: long-term oesophageal complications

Patients who started short-acting GLP-1 RAs had a 32% increased risk of oesophageal stricture (HR 1.318; 95% CI 1.093 to 1.589) and an 85% increased risk of BWD (HR 1.851; 95% CI 1.234 to 2.778) supported by landmark analysis (online supplemental table 3). Interestingly, we noticed regional differences in BWOD as it did not have an elevated risk in the short-acting GLP-1 RA global analysis (HR 1.166; 95% CI 0.977 to 1.391) but was in the USA-only short-acting GLP-1 RA analysis (HR 1.363; 95% CI 1.125 to 1.636). When restricting short GLP-1 RAs to starting in 2015 (HR 1.268; 95% CI 1.035 to 1.391) and if patients had a pre-existing GERD diagnoses (HR 1.439; 95% CI 1.113 to 1.862), these trends persisted in medication-specific subanalysis (figure 5). Exceptions were lixisenatide, due to insufficient patient numbers (n<10) hampering analysis while ensuring anonymity on the TriNetX platform, and BWD in the exenatide cohort (HR 1.479; 95% CI 0.793 to 2.759). Patients starting long-acting GLP-1 RAs without a prior GERD diagnoses never had an association with oesophageal stricture, BWOD or BWD, even when restricted to USA-only and in medication specific analyses (figures 3–6). Patients starting long-acting GLP-1 RAs with pre-existing GERD did have an association with (figure 4) oesophageal stricture (HR 1.221; 95% CI 1.006 to 1.482) but not BWOD (HR 1.13; 95% CI 0.855 to 1.426) or BWD (HR 1.346; 95% CI 0.947 to 1.914).

Other secondary outcomes and subanalyses

Most analyses revealed that patients had an increased risk of undergoing an EGD for the first time, regardless of GLP-1 RA type, following medication initiation (online supplemental figure 1). Across all GLP-1 RAs, patients also had increased risks of the short-term outcome: new NERD diagnoses, except when starting lixisenatide, which trended towards an increased risk (due to a limited sample size=130), and were more likely to be diagnosed with GERD (online supplemental figures 2 and 3). Patients were also equally unlikely to be initiated on PPI following GLP-1 RA initiation of any type compared with control except if they had prior diagnoses of GERD or were receiving care in the USA(online supplemental figure 4). Patients

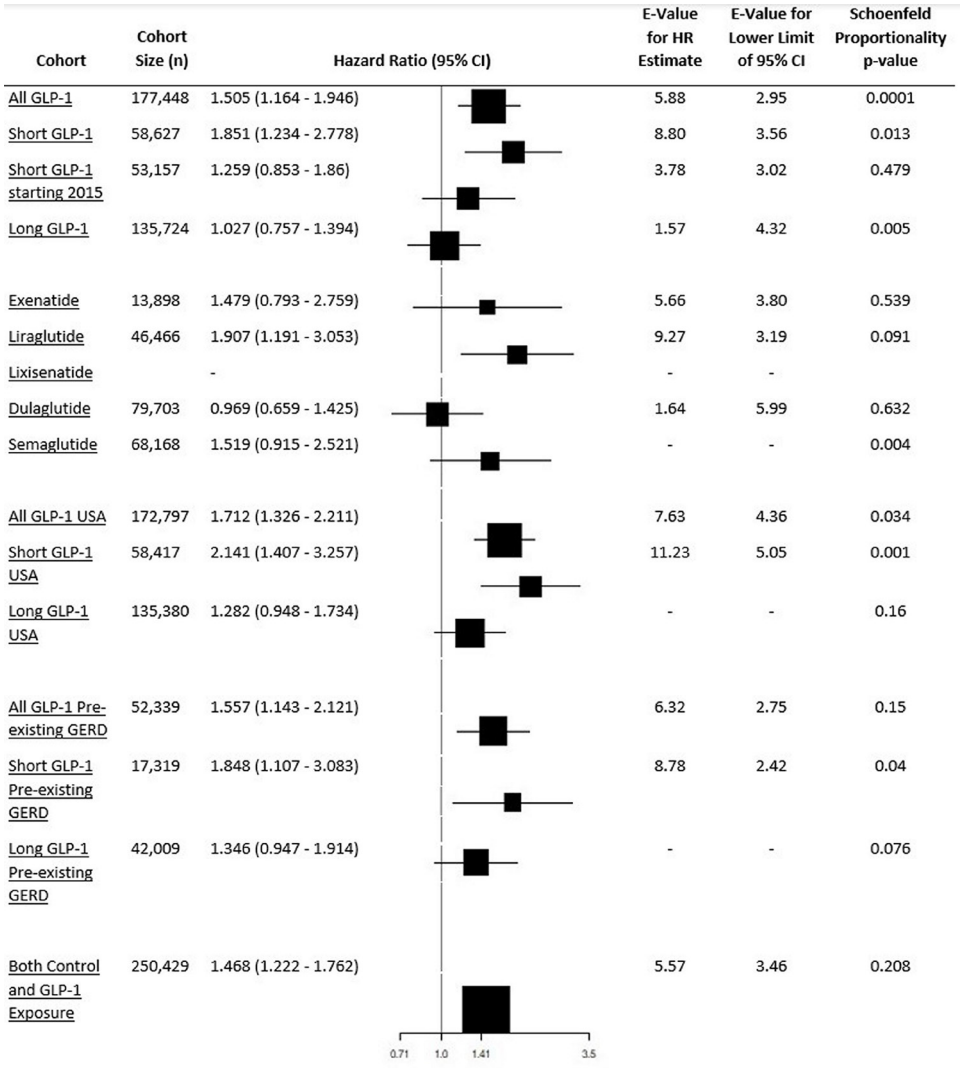

Figure 6 Cox-proportional HRs, E-values and Schoenfeld proportionalities Barrett's with dysplasia following glucagon-like peptide-1 receptor agonist (GLP-1 RA) initiation in patient cohorts defined by type of GLP-1 RA initiation with sensitivity analyses. GERD, gastro-oesophageal reflux disease.

who were exposed to any GLP-1 RA and any control medication did not have any significant differences from patients exposed to any GLP-1 RA only (figures 3–6) suggesting that any effect would be due to the GLP-1 RA alone. E-value analyses for all short-acting GLP-1 RAs ranged between 2.96 and 8.8 for all primary outcomes, suggesting a robust relationship that requires an unmeasured confounder with a very high magnitude, and one that has not been addressed in propensity-score matching (figures 3–6).

DISCUSSION

This is the first large-scale population database study examining associations between GLP-1 RAs and GERD, its complications, and the incidence of its associated diagnostic procedures. In this study of more than 127 million patients,[14] we found that in adult patients with T2DM, starting a GLP-1 RA was associated with an increased risk of 'first-time-ever' diagnosis of GERD, NERD, ERD, oesophageal stricture, BWOD and BWD. The increase in ERD and long-term GERD complications appears to be primarily driven by the short-acting GLP-1 RA group and was confirmed when examining formulation-specific propensity-matched outcomes. Long-acting GLP-1 RAs largely did not appear to increase the risk of long-term GERD-related outcomes, except when patients already had an established diagnosis of GERD, whereby it mildly increased risk of ERD and oesophageal stricture but not BWOD or BWD. These trends remained within our sensitivity analyses, and analyses within only USA had more pronounced relationships between short GLP-1 RAs and primary adverse outcomes.

While possible symptoms of GERD are reported in manuscripts on clinical trials, the outcome of GERD itself is not reported and only intermittently in the clinical trials database.[21 28–32] GERD is a clinically impactful disease with high morbidity and can lead to serious adverse outcomes.[6] A review of the clinical trials database does show a relative risk of 2.05 (95% CI 1.27 to 3.3) and a statistically significant absolute risk difference (χ^2 analysis p=0.05) of 3.23% in the rate of GERD between semaglutide 2.4 mg and placebo in the STEP 1 trial.[21] Similar results are found between semaglutide 2.4 mg or liraglutide 3.0 mg vs placebo in the STEP 8 trial or liraglutide 3.0 mg compared with placebo in the SCALE trial.[31 32] These are consistent with our findings suggesting increased risk of GERD after starting a GLP-1 RA. None of these trials reported stricture as an outcome, and SCALE reported Barrett's only in placebo. Our

results report, for the first time, that GLP-1 RAs may be associated with increased odds of developing ERD, oesophageal stricture, BWOD and BWD. These differences may be due to sample size, under-reporting or length of follow-up.

GLP-1 RAs with shorter half-lives are known to delay gastric emptying more than long-acting GLP-1 RAs.[13] Quast *et al* stated that there was no difference in 'long-acting' versus short-acting GLP-1 RAs in terms of oesophageal reflux which is contrary to our findings. However, it is notable that they used liraglutide as their long-acting GLP-1 RA while we have not; liraglutide is administered daily and has a half-life of 13 hours[10] whereas semaglutide is administered weekly and has a half-life of 1 week.[22] Using our definition, we found that short-acting GLP-1 RAs had a more pronounced rate of GERD development and other GERD-related outcomes, most of which were statistically and clinically significant when compared with the control cohort or the long-acting GLP-1 RA cohort. Quast *et al* noted that starting liraglutide trended towards an increase in reflux events but was not significant.[13] In the context of our findings, the number of subjects likely limited the assessment of this outcome.

While Quast *et al* noted a greater delay in gastric emptying with exenatide compared with liraglutide, they did not report a difference in oesophageal motility.[13] While the mechanism of delayed gastric emptying causing GERD is not established, it is well known that it is a risk factor for GERD.[5] We, therefore, believe that impaired gastric emptying is the primary mechanism for new GERD development due to GLP-1 RAs.[33 34] Our study accounted for baseline gastroparesis during propensity matching, and the tachyphylaxis of longer-acting GLP-1 RAs on gastric emptying likely explains why patients might develop new NERD and undergo an EGD, but not experience GERD complications which would likely take longer exposure to occur.[2 3] Those with pre-existing GERD, however, did have a mild increase in ERD or oesophageal stricture suggesting that long-acting GLP-1 RAs may exacerbate existing GERD to the point where longer-term complications may arise. However, the effect sizes were very small, suggesting that this may not be clinically relevant or potentially due to chance.

Our analysis benefits from large cohort sizes of over 170 000 patients each and the ability to follow patients for long durations of time. However, there are several limitations to our study. First, there are differences in medication duration on the market which may affect the average expected follow-up for each patient. To address this, we excluded albiglutide and conducted time-to-event analyses. Furthermore, we performed a sensitivity analysis whereby short-acting GLP-1 RAs were compared with long-acting GLP-1 RAs starting the day both were available and found similar results. Second, due to limitations in the TriNetX platform, we are not able to identify patients that switched from GLP-1 RAs to control or vice versa for censoring purposes. However, we addressed this by performing a sensitivity analyses where we examined patients with exposure to both medications during the time period. We noted that the outcomes were not statistically different from those that had begun a GLP-1 alone, thus suggesting that though these biases existed, there does not appear to be an additive or different effect. Lastly, medication dosages are heterogeneous between groups and were not reported in this study due to limitations in how dosages are recorded in TriNetX. Future studies should consider using accurate dosing data to establish whether a dose-dependent association is also present between GLP-1 RA and GERD.

In conclusion, this is the first study to demonstrate that shorter-acting GLP-1 RAs are significantly associated with increased risk of developing NERD, ERD, oesophageal stricture, BWD and BWOD in patients with T2DM. While the delayed gastric emptying effect and subsequent blunting of postprandial glucose spikes is one of the reasons why GLP-1 RAs have a beneficial impact on T2DM management,[35] our research suggests that clinicians should be aware of the risks of new GERD or GERD complications when prescribing GLP-1 RAs. It may be prudent to prescribe long-acting over short-acting GLP-1s for patients at risk of GERD or its complications, especially with semaglutide showing superior weight loss and A1c control compared with liraglutide in population studies and randomised controlled trials.[32 36–38] Clinicians should counsel and monitor patients starting GLP-1 RAs for the development of GERD or GERD-like symptoms and strongly consider PPI initiation to prevent adverse outcomes. Future prospective trials are needed to confirm and characterise this relationship further.

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