BMJ Open Diabetes Research & Care

Recent trends in GLP-1 RA and SGLT2i use among people with type 2 diabetes and atherosclerotic cardiovascular disease in the USA

Aaron King,[1] Xi Tan,[2] Neil Dhopeshwarkar,[3] Rhonda Bohn,[4] Katherine Dea,[5] Charles E Leonard ,[6] Adam de Havenon [7]

To cite: King A, Tan X, Dhopeshwarkar N, *et al*. Recent trends in GLP-1 RA and SGLT2i use among people with type 2 diabetes and atherosclerotic cardiovascular disease in the USA. *BMJ Open Diab Res Care* 2024;**12**:e004431. doi:10.1136/bmjdrc-2024-004431

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjdrc-2024-004431).

Received 27 June 2024
Accepted 11 September 2024

For numbered affiliations see end of article.

Correspondence to
Dr Adam de Havenon; adam.dehavenon@yale.edu

ABSTRACT

Introduction This study aimed to assess recent trends in the US use of glucagon-like peptide-1 receptor agonist (GLP-1 RA) and sodium-glucose cotransporter 2 inhibitor (SGLT2i) in people with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD), including incident use following newly diagnosed ASCVD.

Research design and methods This real-world, retrospective observational study used de-identified data from the TriNetX Dataworks–USA network. A longitudinal analysis of cross-sectional data (interval: January 01, 2018 to December 31, 2022) assessed the yearly prevalent use of GLP-1 RA and SGLT2i. A nested cohort study (January 01, 2017 to January 31, 2023) assessed the proportions of patients with T2D newly prescribed GLP-1 RAs and SGLT2is after incident ASCVD diagnosis.

Results Prevalent use of GLP-1 RA and/or SGLT2i increased from 9.2% of patients in 2018 to 27.1% in 2022, with eligible annual patient numbers ranging from 279,474 to 348,997. GLP-1 RA-alone use rose from 5.2% to 9.9% and SGLT2i-alone use rose from 2.8% to 12.2% over this interval. Incident use of GLP-1 RA and/or SGLT2i within the year following ASCVD diagnosis increased from 5.9% to 17.0% (2018–2022). For GLP-1 RA alone, this increase was from 3.6% to 7.8%, while for SGLT2i alone, it was from 1.8% to 7.0%.

Conclusions Use of GLP-1 RAs/SGLT2is in patients with T2D and ASCVD has increased in recent years in the USA, but remains suboptimal given the prevalence of ASCVD and its high morbidity and mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Data from several cardiovascular (CV) outcome trials have demonstrated a reduction in the risk of major adverse CV events with glucagon-like peptide-1 receptor agonist (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy compared with standard of care in people with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD). As a result, both therapies are now recommended for CV risk reduction in such patients by widely used T2D management guidelines. Despite this, there are limited data on the use of these treatments in recent years in the USA.

WHAT THIS STUDY ADDS

⇒ This real-world, retrospective, observational study demonstrated that the prevalent use of GLP-1 RAs and/or SGLT2is in patients with T2D and ASCVD in US clinical practice has increased from 9.2% in 2018 to 27.1% in 2022, and incident use of these two drug classes has increased from 5.9% in 2018 to 17.0% in 2022.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The use of these two drug classes recommended for CV risk reduction remains suboptimal, implying that further research is needed to understand the barriers to guideline adherence.

INTRODUCTION

The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and/or sodium-glucose cotransporter-2 inhibitors (SGLT2is) in people with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD) is suboptimal in the USA and worldwide.[1–4] In the USA, the proportion of adults with T2D who also have ASCVD is in the range of 45–51%,[3 5] and while the prescription rate of these glucose-lowering therapies has increased over time, many eligible patients are still not receiving them.[3 4]

Data from cardiovascular (CV) outcome trials (CVOTs) have demonstrated an overall reduction in the risk of major adverse cardiovascular events (MACE) associated with GLP-1 RA and SGLT2i therapy compared with standard of care in people with T2D and ASCVD.[6 7] As a result, professional society guidelines recommend treatment with these medications as an essential option in T2D therapy when there is concurrent ASCVD or high CV risk.[8]

Important developments in recent years have further strengthened the case for

using these drug classes as CV risk-mitigating agents in T2D. These include the arrival of new-generation GLP-1 RAs, such as dulaglutide and semaglutide, both of which reduced MACE in CVOTs,[9 10] and a growing evidence base for the CV, renal and other benefits of GLP-1 RAs and SGLT2is from outcomes studies and meta-analyses.[6 7 10] A combined analysis of the SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) and PIONEER 6 (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) clinical trials, for example, concluded that the GLP-1 RA semaglutide provides a consistent CV benefit, primarily driven by a reduction in the risk of non-fatal stroke.[11] Meanwhile, evidence has accumulated that SGLT2is can reduce hospitalization due to heart failure (HF), and progression of chronic kidney disease.[6 7]

A study using data from 2015 to 2019 for US adults (aged ≥50 years) with T2D and established ASCVD/HF, or at high risk thereof, however, showed a disappointing rate of uptake of these agents. The use of any glucose-lowering agent in people with established CV disease (CVD) and T2D was 60.9–69.9% (varying by year) in those aged ≥65 years, and 71.8–77.1% in those aged 50–64 years.[4] The reported use of SGLT2is in 2019 was just 3.4%, while for GLP-1 RAs it was just 4%. The findings for patients without established CVD/HF, but at high risk thereof, were similar. The authors therefore called for a greater awareness among healthcare professionals (HCPs) about T2D therapy recommendations, especially given the cardioprotective benefits of GLP-1 RAs and SGLT2is.

More recent data on prescription trends for GLP-1 RAs and SGLT2is in the USA are limited, so it is not known how recent CVOT data may have impacted the use of these agents in the 2020s and adherence to updated clinical practice guidelines. Furthermore, reports during the COVID-19 pandemic highlight substantial deficiencies in routine diabetes care and rationing of diabetes therapies that may have impacted prescription trends for GLP-1 RAs and SGLT2is.[12] Data from other countries indicate a continued increase in prescriptions in recent years. In Australia, for example, a numerical increase in prevalent and new users of GLP-1 RAs and SGLT2is was reported across the period 2014–2022, with a sharp increase in both prevalent and new users of GLP-1 RAs observed between 2021 and 2022.[2] Interestingly, while most users of GLP-1 RAs and SGLT2is in this study had both T2D and a CVD, a large increase in the new use of these drug classes was observed after 2021 among patients recorded as having CVD, but not T2D (accounting for 19.5% of SGLT2i new use, and 8.0% of GLP-1 RA new use). The Australian study did not, however, assess the use of these drugs among all patients with a potential indication.

In this real-world, retrospective observational study, we attempted to address this knowledge gap by assessing the use of GLP-1 RAs and SGLT2is in recent years among people in the USA with T2D and ASCVD. We aimed to evaluate recent trends in the prevalent use of these agents as well as their incident use in patients with T2D newly diagnosed with ASCVD.

METHODS

Data source

This analysis was conducted using the TriNetX Dataworks–USA network, a de-identified, longitudinal electronic health record (EHR)-derived dataset that includes outpatient and inpatient electronic medical records from 57 healthcare organizations across the USA. Network members include academic medical centers, integrated delivery networks, specialty hospitals, and large specialty physician practices.

Collected data included demographics, diagnoses recorded, medications and procedures administered, and prescriptions written for each medical encounter. All patient database data are harmonized to standard terminologies. Demographics were defined by Health Level 7 V.3, diagnoses were defined by International Classification of Diseases, 10th Revision, Clinical Modification, procedures were defined by Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS), and medications ordered were defined by RxNorm ingredient, CPT, HCPCS, and ICD-10-PCS.

Race and ethnicity data were reported by the patient or the HCP. Race was categorized as White, Black, other, or unknown. Other races included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, or other races. Ethnicity was categorized as Hispanic, not Hispanic, or unknown.

Study designs and populations

This retrospective, observational study covered the period from January 01, 2017, to January 31, 2023. The study population comprised patients with a diagnosis of T2D and ASCVD. The objectives were evaluated using two study designs outlined below.

Design 1: cross-sectional study assessing the annual prevalent use of GLP-1 RAs or SGLT2is among patients with T2D and ASCVD

This longitudinal assessment of cross-sectional yearly data spanned the interval from January 01, 2018, to December 31, 2022 (figure 1A). Patients were classified as being prescribed a GLP-1 RA (liraglutide, lixisenatide, exenatide, dulaglutide, and semaglutide) or SGLT2i (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) if they had at least one prescription order or procedure code record for any of these medications at any point during the year of evaluation. Fixed-dose combination drugs containing GLP-1 RA or SGLT2i were also included. Patients who had treatment orders for medications in both the GLP-1 RA and SGLT2i drug classes during the calendar year of evaluation were counted in each drug class. Patients were required to be ≥18 years of age at the

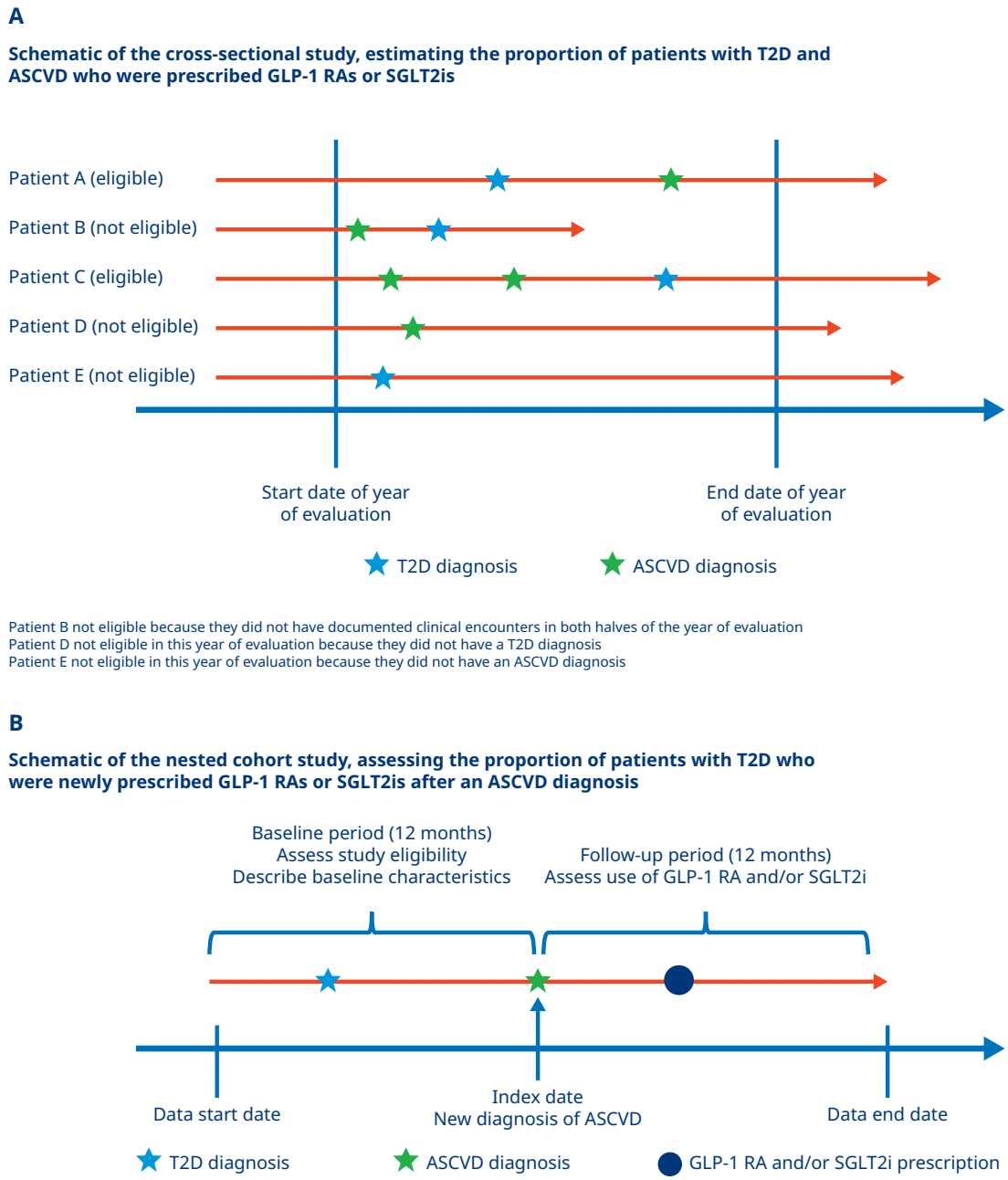


Figure 1 (A) Schematic of the cross-sectional study, estimating the proportion of patients with T2D and ASCVD who were prescribed GLP-1 RAs or SGLT2is. (B) Schematic of the nested cohort study, assessing the proportion of patients with T2D who were newly prescribed GLP-1 RAs or SGLT2is after an ASCVD diagnosis. ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

beginning of the year of evaluation, have a diagnosis of T2D and ASCVD during the year of evaluation, and have at least one documented clinical encounter once every 6 months.

Design 2: nested cohort study assessing the proportion of patients with T2D who were newly prescribed GLP-1 RAs or SGLT2is after an incident ASCVD diagnosis

This retrospective nested cohort study used a study period spanning January 01, 2017, to January 31, 2023 (figure 1B). The study period included a baseline period (of 12 months preceding the index date), a patient selection period, and a follow-up period (of 12 months following the index date). The patient selection period (during which patients meeting eligibility criteria were included in the assessment) was from January 01, 2018, to January 31, 2022, to allow data collection for the 12-month baseline and follow-up periods. The index date was the date the patient fulfilled the criteria of a new ASCVD diagnosis (online supplemental material: supplementary information). The prescription of a GLP-1 RA or SGLT2i was evaluated during the 12-month follow-up period. Patients who had prescription orders

for medications in both the GLP-1 RA and SGLT2i drug classes during the 12 months of follow-up were counted in each drug class. Patients were required to be ≥18 years of age at index, and to have a T2D diagnosis and, subsequently, a new ASCVD diagnosis during the patient selection period. They were also required to have at least one documented clinical encounter once every 6 months during the baseline period and follow-up period, at least one documented encounter prior to the baseline period, and at least one documented encounter after the 12-month follow-up period. Patients with prescription records for GLP-1 RA or SGLT2i use prior to the index date were excluded, along with patients with a diagnosis of ASCVD prior to T2D diagnosis.

Statistical analysis

Baseline characteristics were described using means and standard deviations (SDs), medians and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. Baseline characteristics were compared among patient groups who were prescribed GLP-1 RAs and/or SGLT2is using absolute standardized differences (ASDs). Patients not prescribed GLP-1 RAs and/or SGLT2is during the follow-up period served as the reference group. ASDs were calculated as the weighted mean difference between the two groups divided by the weighted pooled SD. An ASD threshold of ≥10% was considered a meaningful difference.[13]

RESULTS

Cross-sectional study

The identification of patients eligible for the analysis by year is shown in online supplemental figure S1. The number of eligible patients ranged from 279,474 to 348,997 between 2018 and 2022.

The percentage of the prevalent use of a GLP-1 RA and/or SGLT2i prescription increased almost threefold from 9.2% in 2018 to 27.1% in 2022 (figure 2). The proportion of patients with a prescription for a GLP-1 RA alone rose 1.9-fold from 5.2% in 2018 to 9.9% in 2022. For SGLT2i alone, the proportion rose 4.4-fold from 2.8% in 2018 to 12.2% in 2022. The proportion of patients with a prescription for both a GLP-1 RA and an SGLT2i increased from 1.2% in 2018 to 5.0% in 2022.

Nested cohort study

The attrition of patients identified for inclusion in the nested cohort study (evaluating the proportion of patients with T2D with a new diagnosis of ASCVD who were newly prescribed a GLP-1 RA or SGLT2i) is presented in online supplemental figure S2. The study cohort comprised a total of 203,115 patients, for whom demographic and clinical characteristics are summarized in online supplemental table S1. The mean (SD) age of this cohort was 64.7 (13.0) years; 53.4% were women, and a majority (67.8%) were White in race. The most represented US region was the South (44.4%) followed by the Northeast (29.2%), Midwest (15.6%), and the West (9.7%).

Data concerning the morbidities and medications of the cohort are also summarized in online supplemental table S1. The most common comorbidities included hypertension (70.6%), dyslipidemia (56.9%), and nephropathy (25.2%). The most common types of ASCVD diagnoses at the index included other coronary heart disease (45.8%), peripheral artery disease (29.7%), and ischemic stroke (15.5%). The most frequently used other antidiabetic medications at baseline were an insulin regimen, including basal and other insulin (41.5%), biguanides (29.9%) and sulfonylureas (12.0%).

Across the entire study period, 16,635 patients (8.2%) were newly prescribed a GLP-1 RA and/or SGLT2i in the year following a diagnosis of ASCVD (figure 3). However, the percentage of incident use of these agents

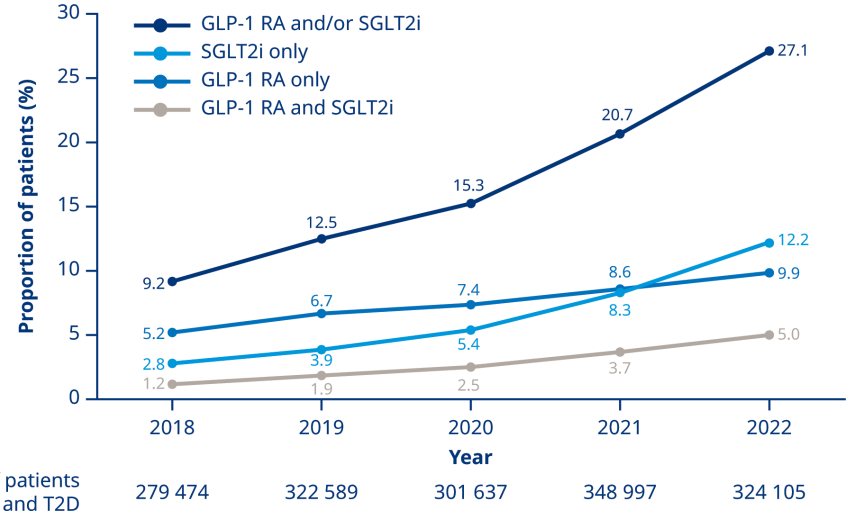


Figure 2 Cross-sectional study outcomes. Proportion of patients with T2D and ASCVD who were prescribed GLP-1 RAs or SGLT2is by year. ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

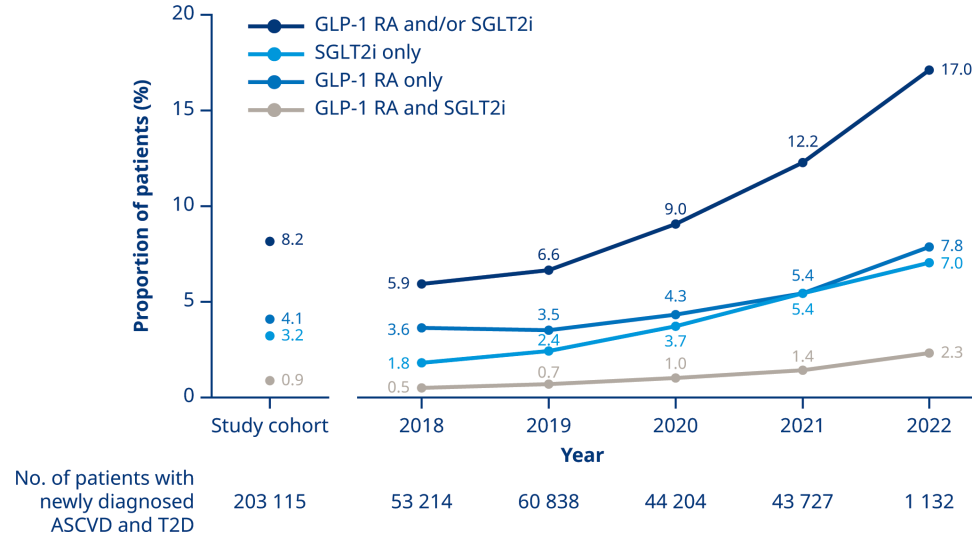


Figure 3 Nested cohort outcomes. Proportion of patients with T2D and newly diagnosed ASCVD who were newly prescribed GLP-1 RAs or SGLT2is, overall and by year. ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

(GLP-1 RA and/or SGLT2i) increased almost threefold between 2018 and 2022, from 5.9% to 17.0%.

Considering each class separately, GLP-1 RAs only and SGLT2is only were prescribed to 8,388 (4.1%) and 6,481 (3.2%) patients, respectively, across the study period (figure 3). In 2018, the proportion of patients given a GLP-1 RA prescription was 3.6%, compared with 1.8% of patients given an SGLT2i prescription. In 2022, these proportions had increased by 2.2-fold to 7.8%, and 3.9-fold to 7.0%, respectively. The number of patients given both a GLP-1 RA and SGLT2i across the study period was 1,766 (0.9%). This proportion also increased each year, from 0.5% in 2018 to 2.3% in 2022.

Some demographic differences were observed when comparing the 8.2% of the study cohort who were newly prescribed a GLP-1 RA and/or SGLT2i with the 91.8% who were not (online supplemental table S1). Patients with a prescription for a GLP-1 RA and/or SGLT2i were generally younger than patients without (mean age 62.2 years for GLP-1 RA and/or SGLT2i (ASD 22.5%), 61.0 years for GLP-1 RA only (ASD 32.0%), 64.3 years for SGLT2i only (ASD 5.6%), 60.3 years for both GLP-1 RA and SGLT2i (ASD 38.7%), compared with 65.0 years for no GLP-1 RA and/or SGLT2i prescription). This was likely driven by the greater proportion of patients aged ≥65 years in the group without a prescription for a GLP-1 RA and/or SGLT2i than those with a prescription (57.9% vs 45.2%, ASD 25.5%; online supplemental table S1).

In the Midwest region of the USA, a lower proportion of people had a prescription for a GLP-1 RA and/or SGLT2i agent compared with those who did not (12.3% vs 15.9%, ASD 10.4%). Conversely, in the Northeast region, a greater proportion of people had a prescription for a GLP-1 RA and/or SGLT2i agent compared with those who did not (34.6% vs 28.7%, ASD 12.8%). No meaningful differences were observed in the South or West regions of the USA (online supplemental table S1).

Patients with a prescription for a GLP-1 RA and/or SGLT2i were also observed to be receiving a higher mean number of antidiabetic medications at baseline (1.5 for GLP-1 RA and/or SGLT2i (ASD 48.5%), 1.5 for GLP-1 RA only (ASD 53.7%), 1.4 for SGLT2i only (ASD 42.8%), 1.4 for both GLP-1 RA and SGLT2i (ASD 44.7%) compared with 0.9 for no GLP-1 RA and/or SGLT2i prescription; online supplemental table S1). A greater proportion of patients with a prescription for a GLP-1 RA alone were also prescribed basal/other insulin, biguanides, sulfonylureas, thiazolidinediones, and DPP4is when compared with patients without a prescription for a GLP-1 RA or SGLT2i (online supplemental table S1). Similar observations were made for patients with a prescription for an SGLT2i alone, except for "other insulins", of which the proportion was similar to patients not prescribed with a GLP-1 RA or SGLT2i.

A greater proportion of patients with a prescription for a GLP-1 RA and/or SGLT2i had metabolic disease at baseline, including hyperosmolarity, ketoacidosis, and hypoglycemia with/without coma (22.8% vs 16.8%, ASD 15.0%) and neuropathy (25.4% vs 20.9%, ASD 10.6%) when compared with patients without a prescription. This discrepancy was greatest between patients prescribed a GLP-1 RA alone and patients without a prescription for either drug class (online supplemental table S1). Conversely, patients who were prescribed a GLP-1 RA only and both a GLP-1 RA and SGLT2i had lower proportions of baseline CVD (19.6% vs 24.0% (ASD 10.8%) and 17.6% vs 24.0% (ASD 16.0%), respectively) and baseline cancer (11.9% vs 16.4% (ASD 12.9%), and 10.0% vs 16.4% (ASD 16.4%), respectively) compared with patients who were not prescribed GLP-1 RAs and/or SGLT2is. Patients who were prescribed SGLT2is

only and both a GLP-1 RA and SGLT2i had lower proportions of baseline nephropathy (21.0% vs 25.4% (ASD 10.4%), and 20.2% vs 25.4% (ASD 12.4%), respectively) and baseline anxiety (14.5% vs 20.8% (ASD 16.7%), and 16.4% vs 20.8% (ASD 11.5%), respectively) compared with patients who were not prescribed GLP-1 RAs and/or SGLT2is. Another observation considered as a meaningful difference was the greater proportion of patients with HF (13.5% vs 9.8%, ASD 11.3%) and smaller proportion of patients with depression (15.0% vs 20.0%, ASD 13.1%) among those prescribed an SGLT2i when compared with patients without a prescription for GLP-1 RA/SGLT2i (9.8%). People prescribed SGLT2is-only or both GLP-1 RA and SGLT2i had a lower burden of comorbidities as evidenced by a lower baseline Charlson Comorbidity Index score compared with people without a prescription for GLP-1 RA/SGLT2i. People prescribed GLP-1 RA or SGLT2i or GLP-1 RAs-only had the greatest differences in baseline antidiabetic drug and ASCVD-related drug burden compared with those without GLP-1 RA/SGLT2i (online supplemental table S1).

Higher percentages of baseline myocardial infarction, ischemic stroke, other coronary heart disease, or peripheral artery disease were found between those prescribed SGLT2is only and those without a prescription for GLP-1 RA or SGLT2i. Additionally, greater proportions of myocardial infarction and other coronary heart disease at baseline were observed in those prescribed both GLP-1 RA and SGLT2i compared with those without a prescription for GLP-1 RA or SGLT2i (online supplemental table S1).

DISCUSSION

This study provides updated information on the use of GLP-1 RAs and SGLT2is in patients with T2D and ASCVD in clinical practice in the USA. The TriNetX Dataworks–USA network includes a vast number of patients throughout different regions of the USA. Consequently, the recent longitudinal EHR de-identified data from this network have enabled a large-scale assessment of prescribing patterns that may reflect the current usage of these drugs in the USA. Our findings demonstrate that the proportion of patients prescribed a GLP-1 RA and/or an SGLT2i has increased over time, with similar increases observed when evaluating both prevalent and incident use of GLP-1 RAs and/or SGLT2is. Despite the observed increases, the use of these agents was low—even in 2022. In our study, the most recent prevalent and incident use rates of a GLP-1 RA or SGLT2i in patients with T2D and ASCVD were only 27.1% and 17.0%, respectively. These data are comparable to previous studies, in which trends in the use of GLP-1 RA and SGLT2i were estimated for earlier years. For example, Arnold *et al*, using data from more than a million US people from an outpatient diabetes registry, reported an increase in the percentage prescribed a GLP-1 RA or SGLT2i from 7.3% in 2013 to 28.8% in 2019.[3] Interestingly, this study also found greater prevalent use of these agents in patients without established CV or renal disease (25.5%) than in those with these comorbidities (18.3%). Meanwhile, a study of 1,590 patients with diabetes (95.7% having T2D) enrolled in the prospective US-based observational study (who were recruited in 2016–2018 and followed up over 2 years, reported a small increase in the proportion prescribed an SGLT2i or GLP-1 RA during this time, from 15.0% to 17.4%.[14] Another study by Nanna *et al* using EHR data from >320,000 patients with T2D and ASCVD in US community practice reported an increase in the proportion using SGLT2is from 5.8% to 12.9% between January 2018 and early 2021.[15] The use of GLP-1 RAs increased during this interval from 6.9% to 13.8%, and use of either agent increased from 11.4% to 23.2%.

Prevalent and incident rates for the combined use of GLP-1 RA and SGLT2i also increased over the studied time periods of our analysis. Recent evidence indeed supports the combination, and therefore increased use, of SGLT2i and GLP-1 RAs, which may have additive benefits in people with T2D. In people with inadequately controlled T2D (SUSTAIN 9 trial), subcutaneous semaglutide once weekly (OW, 1 mg) added to SGLT2i resulted in a 1.5% glycated hemoglobin (HbA1c) reduction as well as a greater proportion of people achieving ≥5% and ≥10% weight loss compared with add-on placebo (49.9% vs 8.2% and 15.1% versus 1.4%, respectively) after 30 weeks of treatment.[16] Additionally, a UK observational database analysis found that GLP-1 RA and SGLT2i combination in people with T2D was significantly associated with a 30% risk reduction for MACE and a 57% risk reduction for HF compared with regimens that did not involve SGLT2i or GLP-1 RA agents.[17]

The patient populations with and without a prescription for a GLP-1 RA/SGLT2i in our study were broadly similar. However, consistent with the observations of Arnold *et al*,[3] we found that patients without a prescription tended to be older and possibly less well managed as evidenced by the number of existing antidiabetic medications. The reasons for such discrepancies are unclear. It may be that patients without a prescription are more likely to be following lifestyle/dietary, rather than pharmacological management strategies. Concerns over polypharmacy, institutional and/or geographical variations, or higher out-of-pocket costs may also contribute to the observed discrepancies. There is clearly a need to further investigate the reasons why prescriptions for GLP-1 RAs/SGLT2is are or are not given to patients with T2D and comorbidities for which these agents are indicated.

While differences in designs, dates, and the composition of cohorts in these various studies all likely contribute to the variation observed in the proportions of patients prescribed GLP-1 RA or SGLT2i, it is clear from all of these investigations and our large-scale study that there are significant proportions of treatment-eligible patients who are not prescribed either agent. Several reasons have been suggested to account for the relatively

limited use of GLP-1 RA and SGLT2i compared with the high prevalence of concurrent T2D and ASCVD. These include clinical inertia and a lack of practical knowledge on the use of these agents, and concerns about potential adverse effects, patient fear of injections (most GLP-1 RAs are given subcutaneously), and the challenges of polypharmacy in elderly patients.[1 3 4] Furthermore, the studies reported by Arnold *et al*[14] and Nanna *et al*[15] found evidence of socioeconomic factors impacting the likelihood of a patient with T2D and ASCVD receiving a GLP-1 RA or SGLT2i.

Another potential barrier to use concerns the locus of care. GLP-1 RAs and SGLT2is are now familiar to and widely used by diabetologists, but patients with T2D and incident or chronic ASCVD may be receiving more regular contact with cardiology departments. While our study could not establish the specialty of the prescribers, previous studies demonstrated that GLP-1 RAs[18] and SGLT2is[19] were relatively infrequently prescribed by cardiologists. Indeed, the assessment of patients with diabetes and ASCVD in a previous study found that those treated by cardiologists (when compared with treatment by primary care and other specialists) were notably less likely to be on SGLT2is and GLP-1 RAs (OR, 0.65 [0.42–1.000].[14] This may be due in part to cardiologists' relative lack of experience or confidence with these medications, and the fact that they are considered to be "diabetes drugs".[2 3 14] Furthermore, there may be unclear interdisciplinary boundaries in the care of T2D with comorbid CVD, hence optimum care might follow the establishment of a multidisciplinary team-based approach to cardiometabolic risk management.[3 14] Nevertheless, there have been recent increases in the use of SGLT2is, especially, by cardiologists, likely driven by the expansion of the indications for these agents to include use in HF,[2] and recommendations for using SGLT2is to prevent HF hospitalization and other CV endpoints in patients with and without T2D have been made in recent cardiac societies' guidelines.[20] Awareness of the CV benefits of GLP-1 RAs and the combination of GLP-1 RAs with SGLT2is may still need to be improved.

Our analysis benefits from several strengths including a large, longitudinal, observational dataset offered by the TriNetX Dataworks–USA network database, which provides key clinical patient information and a real-world indication of prescription behaviors over the last 5 years in the USA. Further, our analysis provided a dual study design approach to ensure both prevalent and incident use of GLP-1 RA and SGLT2is were captured. Importantly, our analysis builds on previous studies and provides a necessary update, representative of the last 5 years, regarding the use of therapeutic agents that remain key in T2D and ASCVD management guidelines.

Limitations

There are some limitations that need to be accounted for in the interpretation of the data. While the database included data indicating patients' medication orders, it did not include information on whether the patient filled the prescription, insurance type, or on the actual use of medication. Furthermore, information was not available for prescriber type or socioeconomic status, so we could not carry out potentially informative analyses with data stratified by the specialty of the prescribers or socioeconomic determinants of health. Other factors that may be associated with the use of GLP-1 RA and/or SGLT2i such as HbA1c levels or ASCVD severity were not evaluated in our analysis, but indeed warrant further investigation. For the cross-sectional analysis, baseline demographic and clinical characteristics of patients were not described because of the lack of a well-defined index date and baseline period. The study population was derived from a limited network of healthcare organizations with a variable distribution across the USA, therefore caution is needed when the results are generalized to the entire US population.

In conclusion, the prescription of GLP-1 RAs/SGLT2is among people with T2D and ASCVD has increased in the USA since 2018, yet the use is still suboptimal in this population. Although these medications are recommended for CV risk reduction in such patients by widely used T2D management guidelines, the new use of GLP-1 RA or SGLT2i in this population was only 17.0% in 2022, which implies that an immediate call for action is required. Further research is warranted to better understand the barriers to guideline adherence.

Author affiliations
[1]MedFirst Primary Care - Quarry, Baptist Health System Physicians Network, San Antonio, Texas, USA
[2]Novo Nordisk Inc, Plainsboro, New Jersey, USA
[3]TriNetX LLC, Cambridge, Massachusetts, USA
[4]Bohn Epidemiology LLC, Boston, Massachusetts, USA
[5]Statlog Econometrics, Montreal, Quebec, Canada
[6]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[7]Department of Neurology, Yale University, New Haven, Connecticut, USA

Acknowledgements Larisa Yedigarova contributed clinical input to the study design. Jeffrey S Brown provided strategic leadership and expertize on the TriNetX dataset. The authors acknowledge the medical writing and editorial assistance of Ashfield MedComms, an Inizio company, funded by Novo Nordisk.

Contributors All authors conceived and designed the analysis. ND and KD performed the analysis. All authors participated in interpretation of the data. All authors critically reviewed and contributed to the writing of the manuscript. XT and KD are the guarantors who take full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decison to publish.

Funding The study was funded by Novo Nordisk.

Competing interests AK: Paid speaker and clinical advisor for Astellas Pharma, Abbott, Dexcom, Eli Lilly, MannKind and Novo Nordisk. XT: Employee of Novo Nordisk. ND: Employee of TriNetX LLC. RB: No conflicts of interest. KD: Consultant of TriNetX LLC. CEL: CEL reports NIH funding. CEL is a special government employee of the US Food and Drug Administration. CEL recently received honoraria from the American College of Clinical Pharmacy Foundation and the Consortium for Medical Marijuana Clinical Outcomes Research. CEL consults for Novo Nordisk and TriNetX, LLC. CEL's spouse is employed by Merck; neither she nor he own stock in the company. AdH: AdH reports NIH funding, consultant fees from Novo Nordisk, royalty fees from UpToDate, and has equity in Titin KM and Certus.

Patient consent for publication Not applicable.

Ethics approval This retrospective study is exempt from informed consent. The data reviewed is a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is de-identified per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert refreshed on December 2020.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The datasets generated and/or analyzed for the current study are not publicly available because TriNetX Dataworks, USA, is commercially available and restrictions apply to the availability of these data, which were used under license of this study.

ORCID iDs
Charles E Leonard http://orcid.org/0000-0002-5092-9657
Adam de Havenon http://orcid.org/0000-0001-8178-8597

REFERENCES

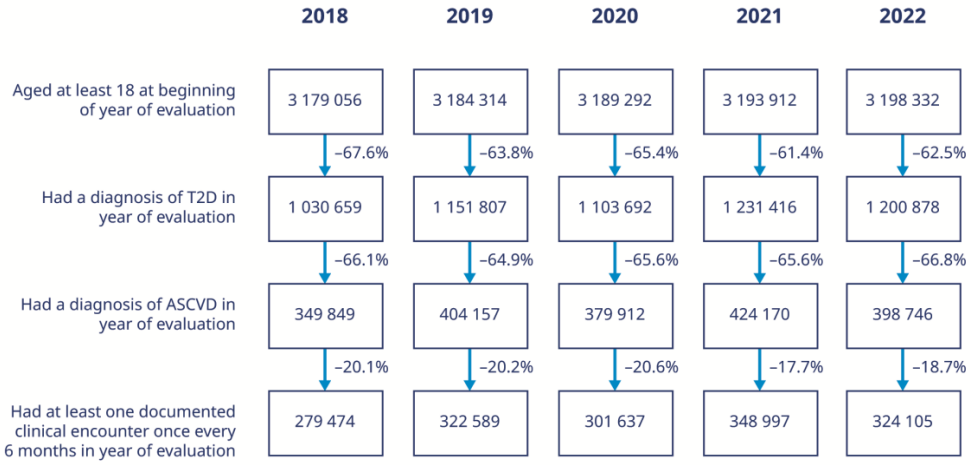
1 Romera I, Rubio-de Santos M, Artola S, *et al*. GLP-1 RAs in Spain: a short narrative review of their use in real clinical practice. *Adv Ther* 2023;40:1418–29.
2 Lin J, Pearson S-A, Greenfield JR, *et al*. Trends in use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) in Australia in the era of increased evidence of their cardiovascular benefits (2014-2022). *Eur J Clin Pharmacol* 2023;79:1239–48.
3 Arnold SV, Gosch K, Kosiborod M, *et al*. Contemporary use of cardiovascular risk reduction strategies in type 2 diabetes. Insights from the diabetes collaborative registry. *Am Heart J* 2023;263:104–11.
4 Nair R, Mody R, Yu M, *et al*. Real-world treatment patterns of glucose-lowering agents among patients with type 2 diabetes mellitus and cardiovascular disease or at risk for cardiovascular disease: an observational, cross-sectional, retrospective study. *Diabetes Ther* 2022;13:1921–32.
5 Weng W, Tian Y, Kong SX, *et al*. The prevalence of cardiovascular disease and antidiabetes treatment characteristics among a large type 2 diabetes population in the United States. *Endocrinol Diabetes Metab* 2019;2:e00076.
6 Palmer SC, Tendal B, Mustafa RA, *et al*. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021;372:m4573.
7 Zelniker TA, Wiviott SD, Raz I, *et al*. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation* 2019;139:2022–31.
8 Introduction: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019;42:S1–2.
9 Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121–30.
10 Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016;375:1834–44.
11 Husain M, Bain SC, Jeppesen OK, *et al*. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. *Diabetes Obes Metab* 2020;22:442–51.
12 Khunti K, Aroda VR, Aschner P, *et al*. The impact of the COVID-19 pandemic on diabetes services: planning for a global recovery. *Lancet Diabetes Endocrinol* 2022;10:890–900.
13 Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;38:1228–34.
14 Arnold SV, de Lemos JA, Zheng L, *et al*. Use of optimal medical therapy in patients with diabetes and atherosclerotic cardiovascular disease: insights from a prospective longitudinal cohort study. *Diabetes Obes Metab* 2023;25:1750–7.
15 Nanna MG, Kolkailah AA, Page C, *et al*. Use of sodium-glucose cotransporter 2 inhibitors and glucagonlike peptide-1 receptor agonists in patients with diabetes and cardiovascular disease in community practice. *JAMA Cardiol* 2023;8:89–95.
16 Zinman B, Bhosekar V, Busch R, *et al*. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019;7:356–67.
17 Wright AK, Carr MJ, Kontopantelis E, *et al*. Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes. *Diabetes Care* 2022;45:909–18.
18 Vaduganathan M, Patel RB, Singh A, *et al*. Prescription of glucagon-like peptide-1 receptor agonists by cardiologists. *J Am Coll Cardiol* 2019;73:1596–8.
19 Vaduganathan M, Sathiyakumar V, Singh A, *et al*. Prescriber patterns of SGLT2i after expansions of U.S. Food and Drug Administration labeling. *J Am Coll Cardiol* 2018;72:3370–2.
20 Seferović PM, Fragasso G, Petrie M, *et al*. Heart Failure Association of the European Society of Cardiology update on sodium-glucose co-transporter 2 inhibitors in heart failure. *Eur J Heart Fail* 2020;22:1984–6.

SUPPLEMENTAL MATERIAL for:

Recent trends in GLP-1 RA and SGLT-2i use among people with type 2 diabetes and atherosclerotic cardiovascular disease in the USA

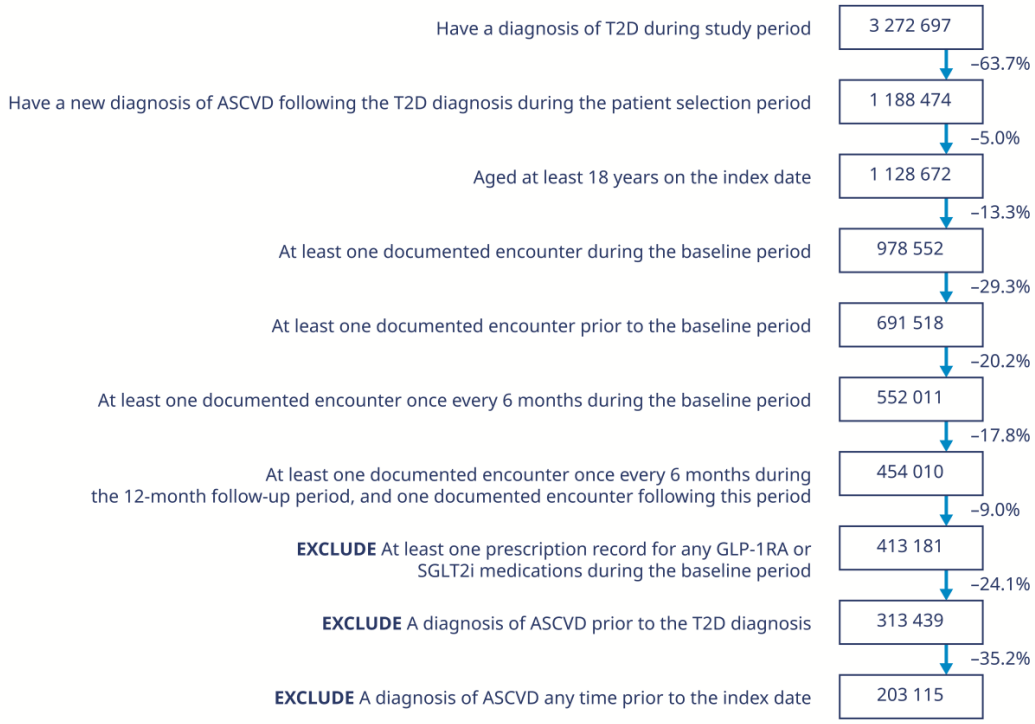
Aaron King, Xi Tan, Neil Dhopeshwarkar, Rhonda Bohn, Katherine Dea, Charles E. Leonard, Adam de Havenon

Supplementary figure S1. Cross-sectional attrition, showing patient numbers by year meeting each inclusion criterion



ASCVD, atherosclerotic cardiovascular disease; T2D, type 2 diabetes

Supplementary figure S2. Nested cohort attrition (patient number and % reduction after applying each inclusion criterion)



%, percentage; ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

Supplementary table S1. Baseline demographics and clinical characteristics of nested cohort study

	Study cohort (n=203 115)	Patients with a GLP-1 RA and/or SGLT2i prescription (n=16 635)		Patients with GLP-1 RA prescriptions only (n=8388)		Patients with SGLT2i prescriptions only (n=6481)		Patients with both GLP-1 RA and SGLT2i prescriptions (n=1766)		Patients without a GLP-1 RA and/or SGLT2i prescription (n=186 480)
	n (%)	n (%)	ASD (%)†	n (%)	ASD (%)†	n (%)	ASD (%)†	n (%)	ASD (%)†	n (%)
Demographic variables at index										
Mean age, years (SD)	64.7 (13.0)	62.2 (11.3)	**22.5***	61.0 (11.5)	**32.0***	64.3 (10.9)	5.6	60.3 (11.0)	**38.7***	65.0 (13.2)
Age										
18–24	1965 (1.0)	47 (0.3)	9.3	35 (0.4)	7.2	8 (0.1)	**12.0***	4 (0.2)	**10.2***	1918 (1.0)
25–34	4564 (2.2)	230 (1.4)	6.9	157 (1.9)	3.2	49 (0.8)	**12.5***	24 (1.4)	7.2	4334 (2.3)
35–44	9111 (4.5)	911 (5.5)	5.0	527 (6.3)	8.4	252 (3.9)	2.6	132 (7.5)	**13.0***	8200 (4.4)
45–54	22 826 (11.2)	2674 (16.1)	**15.4***	1507 (18.0)	**20.4***	839 (12.9)	6.6	328 (18.6)	**22.1***	20 152 (10.8)
55–64	49 183 (24.2)	5249 (31.6)	**17.9***	2736 (32.6)	**20.2***	1906 (29.4)	**13.3***	607 (34.4)	**24.1***	43 934 (23.6)
65+	115 466 (56.8)	7524 (45.2)	**25.5***	3426 (40.8)	**34.6***	3427 (52.9)	**10.1***	671 (38.0)	**40.6***	107 942 (57.9)
Sex										
Missing	10 (0.0)	2 (0.0)	-	1 (0.0)	-	-	**-**	1 (0.1)	-	8 (0.0)
Female	108 479 (53.4)	8357 (50.2)	6.9	4751 (56.6)	5.9	2745 (42.4)	**22.8***	861 (48.8)	9.9	100 122 (53.7)
Male	94 626 (46.6)	8276 (49.8)	6.9	3636 (43.3)	5.9	3736 (57.6)	**22.8***	904 (51.2)	9.8	86 350 (46.3)
Race										
Black	37 946 (18.7)	3134 (18.8)	0.4	1641 (19.6)	2.3	1187 (18.3)	0.9	306 (17.3)	3.5	34 812 (18.7)
Other	6128 (3.0)	489 (2.9)	0.5	211 (2.5)	3.1	222 (3.4)	2.3	56 (3.2)	0.8	5639 (3.0)
Unknown	21 229 (10.5)	1810 (10.9)	1.5	863 (10.3)	0.4	738 (11.4)	3.1	209 (11.8)	4.5	19 419 (10.4)
White	137 812 (67.8)	11 202 (67.3)	1.2	5673 (67.6)	0.6	4334 (66.9)	2.2	1195 (67.7)	0.5	126 610 (67.9)
Ethnicity										
Hispanic	17 182 (8.5)	1495 (9.0)	2.0	735 (8.8)	1.3	599 (9.2)	2.9	161 (9.1)	2.5	15 687 (8.4)
Not Hispanic	149 592 (73.6)	12 085 (72.6)	2.5	6164 (73.5)	0.6	4684 (72.3)	3.3	1237 (70.0)	8.2	137 507 (73.7)
Unknown	36 341 (17.9)	3055 (18.4)	1.3	1489 (17.8)	0.3	1198 (18.5)	1.6	368 (20.8)	7.6	33 286 (17.8)

US region										
Midwest	31 784 (15.6)	2048 (12.3)	**10.4***	1148 (13.7)	6.4	736 (11.4)	**13.4***	164 (9.3)	**20.2***	29 736 (15.9)
Northeast	59 273 (29.2)	5764 (34.6)	**12.8***	2906 (34.6)	**12.8***	2215 (34.2)	**11.8***	643 (36.4)	**16.5***	53 509 (28.7)
South	90 171 (44.4)	6916 (41.6)	6.2	3476 (41.4)	6.5	2696 (41.6)	6.2	744 (42.1)	5.1	83 255 (44.6)
West	19 622 (9.7)	1857 (11.2)	5.4	833 (9.9)	1.4	814 (12.6)	9.7	210 (11.9)	7.7	17 765 (9.5)
Unknown	2265 (1.1)	50 (0.3)	**10.3***	25 (0.3)	**10.4***	20 (0.3)	**10.2***	5 (0.3)	**10.6***	2215 (1.2)
Year of index										
2018	53 214 (26.2)	3148 (18.9)	**18.9***	1923 (22.9)	9.1	963 (14.9)	**29.8***	262 (14.8)	**29.9***	50 066 (26.8)
2019	60 838 (30.0)	4006 (24.1)	**14.4***	2134 (25.4)	**11.2***	1456 (22.5)	**18.2***	416 (23.6)	**15.6***	56 832 (30.5)
2020	44 204 (21.8)	3965 (23.8)	5.4	1890 (22.5)	2.3	1631 (25.2)	8.5	444 (25.1)	8.4	40 239 (21.6)
2021	43 727 (21.5)	5323 (32.0)	**26.1***	2353 (28.1)	**17.4***	2352 (36.3)	**35.3***	618 (35.0)	**32.6***	38 404 (20.6)
2022	1132 (0.6)	193 (1.2)	7.2	88 (1.0)	6.2	79 (1.2)	7.7	26 (1.5)	9.8	939 (0.5)
Comorbid and clinical measures										
DCSI										
0	94 067 (46.3)	7712 (46.4)	0.1	3705 (44.2)	4.3	3119 (48.1)	3.6	888 (50.3)	8.0	86 355 (46.3)
1	23 548 (11.6)	2447 (14.7)	**10.1***	1303 (15.5)	**12.4***	854 (13.2)	5.7	290 (16.4)	**14.8***	21 101 (11.3)
2	44 313 (21.8)	3106 (18.7)	8.5	1504 (17.9)	**10.4***	1308 (20.2)	4.7	294 (16.6)	**13.8***	41 207 (22.1)
3	14 786 (7.3)	1359 (8.2)	3.6	757 (9.0)	6.7	474 (7.3)	0.4	128 (7.2)	0.2	13 427 (7.2)
4	14 651 (7.2)	1053 (6.3)	3.8	558 (6.7)	2.5	406 (6.3)	4.1	89 (5.0)	9.4	13 598 (7.3)
≥5	11 750 (5.8)	958 (5.8)	0.1	561 (6.7)	3.7	320 (4.9)	3.8	77 (4.4)	6.5	10 792 (5.8)
Mean Charlson Comorbidity Index, n (SD)	1.9 (1.6)	1.8 (1.4)	6.6	1.9 (1.5)	0.4	1.7 (1.3)	**14.1***	1.7 (1.4)	**13.6***	1.9 (1.6)
Mean number of antidiabetic medications, n (SD)	0.9 (1.1)	1.5 (1.3)	**48.5***	1.5 (1.3)	**53.7***	1.4 (1.3)	**42.8***	1.4 (1.3)	**44.7***	0.9 (1.1)
Mean number of antidiabetic drug classes, n (SD)	0.9 (1.1)	1.4 (1.3)	**48.6***	1.5 (1.3)	**54.0***	1.4 (1.2)	**42.8***	1.4 (1.3)	**44.5***	0.9 (1.1)
Number of antidiabetic drug classes										
0	98 529 (48.5)	5051 (30.4)	**41.1***	2405 (28.7)	**45.0***	2034 (31.4)	**38.9***	612 (34.7)	**31.7***	93 478 (50.1)
1	47 931 (23.6)	3888 (23.4)	0.6	1896 (22.6)	2.4	1643 (25.4)	4.0	349 (19.8)	9.4	44 043 (23.6)
2	36 505 (18.0)	4109 (24.7)	**18.1***	2102 (25.1)	**18.9***	1588 (24.5)	**17.6***	419 (23.7)	**15.8***	32 396 (17.4)
≥3	20 150 (9.9)	3587 (21.6)	**35.9***	1985 (23.7)	**40.9***	1216 (18.8)	**28.9***	386 (21.9)	**36.6***	16 563 (8.9)
Antidiabetic drug classes										
AGIs	221 (0.1)	23 (0.1)	0.9	14 (0.2)	1.6	7 (0.1)	0.1	2 (0.1)	0.2	198 (0.1)
Basal insulin	33 238 (16.4)	4638 (27.9)	**30.8***	2738 (32.6)	**41.4***	1403 (21.6)	**16.3***	497 (28.1)	**31.4***	28 600 (15.3)
Other insulin	50 890 (25.1)	5310 (31.9)	**16.7***	3003 (35.8)	**25.0***	1747 (27.0)	5.8	560 (31.7)	**16.2***	45 580 (24.4)
Biguanides	60 653 (29.9)	7532 (45.3)	**35.3***	3739 (44.6)	**33.9***	3035 (46.8)	**38.6***	758 (42.9)	**30.5***	53 121 (28.5)
Meglitinides	953 (0.5)	117 (0.7)	3.4	51 (0.6)	2.2	51 (0.8)	4.3	15 (0.8)	5.0	836 (0.4)
SGLT2i	0 (0.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-	0 (0.0)
Sulfonylureas	24 317 (12.0)	3555 (21.4)	**28.0***	1721 (20.5)	**25.9***	1478 (22.8)	**31.5***	356 (20.2)	**25.0***	20 762 (11.1)
Thiazolidinediones	3889 (1.9)	606 (3.6)	**11.6***	293 (3.5)	**10.8***	254 (3.9)	**13.0***	59 (3.3)	10.0	3283 (1.8)
DPP4i	13 095 (6.4)	2236 (13.4)	**26.0***	1102 (13.1)	**25.2***	893 (13.8)	**27.0***	241 (13.6)	**26.6***	10 859 (5.8)

Mean number of ASCVD-related medications, n (SD)	1.5 (1.2)	1.7 (1.2)	**10.2***	1.7 (1.2)	**11.1***	1.7 (1.2)	**13.2***	1.5 (1.2)	5.1	1.5 (1.2)
Number of ASCVD-related medications										
0	55 690 (27.4)	3747 (22.5)	**12.3***	1818 (21.7)	**14.4***	1424 (22.0)	**13.6***	505 (28.6)	1.6	51 943 (27.9)
1	42 842 (21.1)	3542 (21.3)	0.5	1834 (21.9)	1.9	1316 (20.3)	1.9	392 (22.2)	2.7	39 300 (21.1)
2	55 809 (27.5)	5101 (30.7)	7.7	2610 (31.1)	8.6	2001 (30.9)	8.1	490 (27.7)	1.2	50 708 (27.2)
≥3	48 774 (24.0)	4245 (25.5)	3.8	2126 (25.3)	3.4	1740 (26.8)	6.8	379 (21.5)	5.8	44 529 (23.9)
Type of ASCVD-related medications, n (%)										
Antihypertensive agents	127 421	11 313 (68.0)	**12.1***	5737 (68.4)	**12.9***	4484 (69.2)	**14.6***	1092 (61.8)	0.9	116 108
Antiplatelets	(62.7)	3997 (24.0)	0.8	2033 (24.2)	1.3	1607 (24.8)	2.6	357 (20.2)	8.4	(62.3)
Antihyperlipidemic agents	48 180 (23.7)	9050 (54.4)	**18.5***	4569 (54.5)	**18.6***	3626 (55.9)	**21.6***	855 (48.4)	6.4	44 183 (23.7)
Anticoagulants	93 348 (46.0)	3242 (19.5)	6.9	1669 (19.9)	5.9	1277 (19.7)	6.4	296 (16.8)	**14.0***	84 298 (45.2)
	44 840 (22.1)									41 598 (22.3)
Type of ASCVD at index date										
Ischemic stroke	31 412 (15.5)	2342 (14.1)	4.2	1310 (15.6)	0.1	743 (11.5)	**12.1***	289 (16.4)	2.1	29 070 (15.6)
Transient ischemic attack	13 419 (6.6)	1191 (7.2)	2.4	676 (8.1)	5.8	377 (5.8)	3.1	138 (7.8)	4.9	12 228 (6.6)
Other atherosclerotic CBVD	21 444 (10.6)	1405 (8.4)	7.8	686 (8.2)	8.8	571 (8.8)	6.5	148 (8.4)	8.0	20 039 (10.7)
Myocardial infarction	17 297 (8.5)	1673 (10.1)	5.8	696 (8.3)	0.3	756 (11.7)	**11.0***	221 (12.5)	**13.6***	15 624 (8.4)
Other coronary heart disease	93 012 (45.8)	8713 (52.4)	**14.4***	4063 (48.4)	6.5	3699 (57.1)	**23.9***	951 (53.9)	**17.4***	84 299 (45.2)
Peripheral artery disease	60 266 (29.7)	4493 (27.0)	6.4	2556 (30.5)	1.2	1447 (22.3)	**22.3***	490 (27.7)	4.8	55 773 (29.9)
ASCVD related procedures	3785 (1.9)	423 (2.5)	5.1	145 (1.7)	0.6	227 (3.5)	3.5	51 (2.9)	7.2	3362 (1.8)
Comorbidities associated with T2D										
Cardiovascular disease‡	48 259 (23.8)	3491 (21.0)	7.2	1641 (19.6)	**10.8***	1540 (23.8)	0.6	310 (17.6)	**16.0***	44 768 (24.0)
Cerebrovascular disease§	948 (0.5)	50 (0.3)	2.9	20 (0.2)	4.1	20 (0.3)	2.8	10 (0.6)	1.2	898 (0.5)
Metabolic diseasell	35 146 (17.3)	3787 (22.8)	**15.0***	2047 (24.4)	**18.8***	1343 (20.7)	10.0	397 (22.5)	**14.3***	31 359 (16.8)
Nephropathy	51 215 (25.2)	3848 (23.1)	5.3	2130 (25.4)	0.0	1361 (21.0)	**10.4***	357 (20.2)	**12.4***	47 367 (25.4)
Neuropathy	43 258 (21.3)	4223 (25.4)	**10.6***	2376 (28.3)	**17.2***	1408 (21.7)	1.9	439 (24.9)	9.4	39 035 (20.9)
Peripheral vascular disease¶	18 083 (8.9)	1720 (10.3)	5.3	984 (11.7)	9.8	574 (8.9)	0.3	162 (9.2)	1.4	16 363 (8.8)
Retinopathy	22 974 (11.3)	2051 (12.3)	3.4	1112 (13.3)	6.2	727 (11.2)	0.0	212 (12.0)	2.4	20 923 (11.2)
Anxiety	41 781 (20.6)	2932 (17.6)	8.1	1704 (20.3)	1.3	939 (14.5)	**16.7***	289 (16.4)	**11.5***	38 849 (20.8)
Cancer	32 578 (16.0)	2034 (12.2)	**11.9***	997 (11.9)	**12.9***	861 (13.3)	8.7	176 (10.0)	**19.0***	30 544 (16.4)
Depression	40 373 (19.9)	3091 (18.6)	3.6	1807 (21.5)	3.8	974 (15.0)	**13.1***	310 (17.6)	6.2	37 282 (20.0)
Dyslipidemia	115 530	10 136 (60.9)	9.0	5109 (60.9)	8.9	3976 (61.3)	9.8	1051 (59.5)	6.1	105 394
Heart failure	(56.9)	1786 (10.7)	3.0	754 (9.0)	2.9	872 (13.5)	**11.3***	160 (9.1)	2.6	(56.5)
Hypertension	20 107 (9.9)	11 890 (71.5)	2.0	6092 (72.6)	4.6	4574 (70.6)	0.1	1224 (69.3)	2.7	18 321 (9.8)
NASH/NAFLD	143 449	1051 (6.3)	8.4	554 (6.6)	9.5	380 (5.9)	6.5	117 (6.6)	9.6	131 559
	(70.6)									(70.5)
	9318 (4.6)									8267 (4.4)

Data are presented as n (%) unless otherwise stated. The baseline period was defined as the 12 months preceding (but not including) the index date (the date of the first code used to fulfill the ASCVD diagnosis criteria). Patients were defined as having a comorbidity if they have at least one record of the diagnosis code of the comorbidity of interest in any clinical setting during the baseline period.

**ASD ≥10% was considered a meaningful difference. †Standardized difference is the difference between the 'Patients with a GLP-1 RA and/or SGLT2i prescription' and 'Patients without a GLP-1 RA and/or SGLT2i prescription. ‡Cardiovascular disease includes certain diagnoses that are not included in the ASCVD definition: cardiac arrest, paroxysmal tachycardia, atrial fibrillation and flutter, other cardiac arrythmias, heart failure, aneurysm of heart, coronary artery aneurysm and dissection, aortic aneurysm and dissection. Cardiovascular disease excludes old myocardial infarction, which is included in the ASCVD definition. §Cerebrovascular disease includes certain diagnoses that are not included in the ASCVD definition: nontramautic intracerebral hemorrhage, cerebral infarction due to embolism of precerebral artery, cerebral infarction due to embolism of cerebral arteries, cerebral infarction due to cerebral venous thrombosis. ‖Metabolic disease includes metabolic complications of diabetes: hyperosmolarity, ketoacidosis, and hypoglycemia with/without coma. ¶ Peripheral vascular disease includes certain diagnoses that are not included in the ASCVD definition: diabetes (type 1/type 2/drug or chemical-induced/underlying condition/other) with circulatory complications, diabetes (type 1/type 2/drug or chemical-induced/underlying condition/other) with foot ulcer, aneurysm of artery of lower extremity, gangrene, non-pressure chronic ulcer of lower limb, open wound of foot.*

AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; ASD, absolute standardized difference; CBVD, cerebrovascular disease; DCSI, Diabetes Complications Severity Index; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SD, standard deviation; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes