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ORIGINAL RESEARCH

Real-World Comparisons Between Glucagon-Like Peptide-1 Receptor Agonists and Other Glucose-Lowering Agents in Type 2 Diabetes: Retrospective Analyses of Cardiovascular and Economic Outcomes in England

Derek Connolly · Edward Collins · Hongye Ren · Simon Wan Yau Ming · Jennifer Davidson · Steve Bain

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ABSTRACT

Introduction: Clinical trials have demonstrated that glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce the risk of major adverse cardiovascular events (MACE) in adults with type 2 diabetes (T2D) who have established cardiovascular disease (CVD) or a high risk of CVD. Nevertheless, GLP-1RAs remain underutilized. This real-world, retrospective study compared cardiovascular and economic outcomes between individuals treated with GLP-1RAs and other glucose-lowering agents in England.

Methods: Clinical Practice Research Datalink-registered people indexed on GLP-1RAs, dipeptidyl peptidase-4 (DPP4) inhibitors, or basal insulin between January 1, 2014 and December 31, 2018 for their fourth line of T2D treatment were stratified into six cohorts based on their: (1) cardiovascular risk (high or very high risk) and (2) indexed therapy. Cox proportional hazards regression was used to compare the risk of MACE and all-cause death between GLP-1RA and other treatment cohorts. Generalized linear regression was used to quantify differences in healthcare resource use (HCRU) and costs between groups.

Results: Of 63,237 subjects, 10,607 were at high cardiovascular risk (GLP-1RA: 2709; DPP4 inhibitor: 2673; basal insulin: 5225) and 52,630 at very high cardiovascular risk (GLP-1RA: 14,692; DPP4 inhibitor: 18,461; basal insulin:

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D. Connolly (✉)
Birmingham City and Sandwell Hospitals, Birmingham, UK
e-mail: d.l.connolly@bham.ac.uk

D. Connolly
Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

D. Connolly
Aston Medical School, Aston University, Birmingham, UK

D. Connolly
Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK

D. Connolly
Clinical Research Facility, Lyndon, West Bromwich B71 4HJ, UK

E. Collins
Novo Nordisk, Gatwick, UK

H. Ren
Novo Nordisk A/S, Bagsværd, Denmark

S. Wan Yau Ming · J. Davidson
CorEvitas, Altrincham, UK

S. Bain
Diabetes Research Unit, Swansea University Medical School, Swansea, UK

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19,477). The crude incidence of all outcomes was lower in the GLP-1RA versus other treatment cohorts, regardless of cardiovascular risk. Among very-high-risk individuals treated with GLP-1RA, the adjusted risk of MACE was 33% (24–40%) and 23% (13–23%) lower versus DPP4 inhibitor and basal insulin cohorts, respectively. The adjusted total cardiovascular-related cost among very-high-risk individuals was £208.14 (£155.81–£260.47) and £151.74 (£110.69–£192.79) lower in the GLP-1RA versus DPP4 inhibitor or basal insulin cohorts, respectively.
***Conclusions*:** In a real-world setting, GLP-1RAs may be associated with a lower risk of MACE and reduced HCRU and costs than DPP4 inhibitors or basal insulin in individuals with T2D, particularly among those at very high cardiovascular risk.

Keywords: Cardiovascular; Cost; Diabetes; GLP-1RA; HCRU; MACE; T2D; DPP4 inhibitor; Basal insulin

Key Summary Points

Why carry out this study?

Cardiovascular disease (CVD) is highly prevalent in people with type 2 diabetes (T2D) and increases morbidity, mortality, healthcare resource utilization (HCRU), and costs in this population.

Although clinical trials have demonstrated that glucagon-like peptide-1 receptor agonists (GLP 1RAs) reduce the risk of major adverse cardiovascular events (MACE), these glucose-lowering agents remain underutilized in clinical practice.

This study aimed to evaluate whether GLP-1RAs are associated with a lower clinical and economic burden than other glucose-lowering agents for the treatment of T2D in England.

What was learned from this study?

People treated with GLP-1RAs had a lower risk of MACE and lower HCRU than those who received other glucose-lowering agents as part of their fourth line of T2D treatment in England; analyses were typically statistically significant in very-high-risk individuals.

The results of this study suggest that among individuals with T2D and existing CVD, as well as those at high risk of future CVD, GLP-1RAs may confer clinical and economic benefits over other glucose-lowering agents; people and healthcare systems may benefit from wider use of GLP 1RAs.

INTRODUCTION

Type 2 diabetes (T2D) continues to impart a substantial burden on people and healthcare systems globally [1]. In 2021, the estimated worldwide prevalence of diabetes was 9.8% (537 million individuals) and is expected to increase to 12.2% by 2040. Moreover, direct costs associated with diabetes account for 11.5% of global health expenditure, highlighting the high economic burden that this condition confers. Cardiovascular disease (CVD) is a major complication in people with T2D [1] and affects approximately 32% of these individuals [2]. CVD is a key driver of mortality, healthcare resource utilization (HCRU), and associated costs in those with T2D; results from a 2018 meta-analysis suggest that the presence of CVD increases healthcare costs associated with T2D by 47–196% [3].

Due to the high cardiovascular (CV) risk among people with diabetes, the Food and Drug Administration issued guidance in 2008 establishing the need to evaluate the safety of new glucose-lowering therapies in CV outcome trials (CVOTs) and demonstrate that these medicines do not increase CV risk [4]. In response, several rigorous CVOTs were conducted to assess the CV risk of three new

classes of glucose-lowering agents: glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors [5]. Promisingly, these CVOTs largely evidenced the CV safety of these agents and demonstrated that some GLP-1RAs and SGLT-2 inhibitors can reduce the risk of major adverse CV events (MACE) in people with T2D and existing CVD or high CV risk [5]. In particular, the LEADER (NCT01179048; liraglutide), SUSTAIN-6 (NCT01720446; semaglutide), Harmony Outcomes (NCT02465515; albiglutide), REWIND (NCT01394952; dulaglutide), and AMPLITUDE-O (NCT03496298; efpeglenatide) trials demonstrated that the occurrence of MACE was significantly lower in those who received GLP-1RAs versus placebo [6–10]. Additionally, MACE rates were lower in people treated with SGLT-2 inhibitors versus placebo in the EMPA-REG OUTCOME (NCT01131676; empagliflozin), CANVAS (NCT01032629, NCT01989754; canagliflozin), and SCORED (NCT03315143; sotagliflozin) trials [11–13].

Based on this evidence, the 2022 consensus report from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommended treatment with either GLP-1RAs or SGLT-2 inhibitors for people with T2D and established or subclinical atherosclerotic CVD to reduce their CV risk [14]. Moreover, the 2024 ADA guidelines recommend including GLP-1RAs or SGLT-2 inhibitors in the T2D treatment plan for adults with established, or a high risk of, atherosclerotic CVD, heart failure, and/or chronic kidney disease [15]. The guidelines also noted that GLP-1RAs are preferred over insulin for the treatment of adults with T2D. In contrast, the 2022 guidelines from the National Institute of Health and Care Excellence (NICE) recommended SGLT-2 inhibitors, but not GLP-1RAs, for first-line treatment of people with T2D and established CVD, a high risk of CVD, or chronic heart failure [16]. GLP-1RAs were not recommended, primarily due to the limited evidence demonstrating cost-effectiveness of these agents in people with established CVD or a high risk of developing CVD. Instead, the NICE guidelines recommend that clinicians prescribe GLP-1RAs as part of a triple treatment regimen in the fourth line of therapy (LoT) for T2D, if third-line treatment with metformin and two other antidiabetics is contraindicated, not tolerated, or does not sufficiently control T2D (Figure S1) [16, 17]. The fourth LoT generally involves combined treatment with oral antidiabetic and injectable therapies. GLP-1RAs and basal insulin are commonly prescribed as injectable therapies in this LoT, while DPP4 inhibitors are among the oral therapies used in combination with injectables [16]. Interestingly, the NICE guidelines do not recommend use of GLP-1RAs in the fourth LoT for all people with T2D; treatment with basal insulin is generally preferred at this stage. The NICE guidelines only recommend fourth-line treatment with GLP-1RAs in individuals who have a body mass index (BMI) of ≥ 35 kg/m^2 and additional obesity-related complications, those with a lower BMI who would benefit from weight loss for other comorbidities, or individuals for whom insulin-based therapy would have significant occupational implications.

While randomized controlled trials are often considered the gold standard of research, real-world data analyses provide additional evidence that reflects the clinical practice and allows indirect comparisons of both clinical and economic outcomes between drug classes. Results from a 2022 meta-analysis of real-world studies suggest that GLP-1RAs may be more effective at reducing the risk of MACE compared with other glucose-lowering drugs; however, data on cost-effectiveness were not reported [18]. The current study aimed to evaluate whether GLP-1RAs are associated with a reduced risk of MACE, associated HCRU, and costs than DPP4 inhibitors or basal insulin in a real-world setting, among people with T2D and existing CVD or a high risk of developing CVD who received these agents as part of their fourth LoT in England.

METHODS

Study Design and Datasets

In this retrospective cohort study, primary care data from the Clinical Practice Research Datalink (CPRD) Aurum database and routinely linked secondary care data from the Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death registrations were used.

CPRD Aurum collects de-identified coded data on diagnoses, issued prescriptions, basic demographics, test results, such as blood tests, and lifestyle factors, such as smoking status, from National Health Service (NHS) primary care general practices. Approximately 1330 practices in England submit data to the CPRD Aurum database [19]. HES provides information on NHS inpatient admissions, outpatient appointments, and accident and emergency attendances. The ONS death registry records the date and cause of death. Linkage between CPRD Aurum and HES data records is conducted by NHS Digital, a trusted third party; see the Supplementary Material for additional information.

The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Ethics committee approval was not required for this study; access to the dataset was approved by the CPRD Research Data Governance body (protocol number: 23_002661). The CPRD has ethics approval from the Health Research Authority to support research using anonymized patient data.

Study Population

CPRD-registered individuals aged ≥ 18 years who were diagnosed with T2D and at high or very high CV risk were included; the definitions of CV risk used in this study were adapted from the 2019 European Society of Cardiology Guidelines (Figure S2) [20]. In short, very-high-risk individuals had established CVD or three pre-specified CV risk factors (e.g., hypertension, dyslipidemia, obesity) or one pre-specified end-organ damage (e.g., end-stage renal disease). High-risk individuals did not have established CVD, but instead had 1–2 pre-specified CV risk factors or received their T2D diagnosis ≥ 10 years prior. Subjects also had to be initiated on at least two subsequent prescriptions of GLP-1RAs (injectable semaglutide, dulaglutide, or liraglutide), DPP4 inhibitors, or basal insulin between January 1, 2014 and December 31, 2018, following their T2D and CV risk diagnoses. Subjects were only eligible for inclusion if they were deemed to have been prescribed these therapies within their fourth LoT, as described by NICE guidance [17]. To our understanding, NICE guidance is typically strictly followed in the UK. As such, we focused on the fourth LoT to ensure suitable comparisons were made between treatment groups. Individuals who received GLP-1RAs that had not demonstrated a CV benefit in a CVOT were not considered for inclusion. No restrictions were placed on the type of DPP4 inhibitor or basal insulin individuals were prescribed.

Individuals were excluded from the study if they were pregnant at prescription of relevant therapy or had type 1 diabetes. Subjects were deemed to have type 1 diabetes if they received a type 1 diabetes diagnosis at any time before prescription of relevant therapy, or an unspecified diabetes diagnosis before they were 25 years old. Medical codes used to select individuals for inclusion in this study are available from authors on request.

Included subjects were stratified into six cohorts based on the therapy they were indexed on for their fourth LoT (GLP-1RAs, DPP4 inhibitors, or basal insulin) and their CV risk (high or very high risk, Figure S2) at that index date. Any use of a GLP-1RA was considered to represent initiation of the fourth LoT; these individuals were included in the GLP-1RA cohorts. Individuals who received combined treatment with DPP4 inhibitors and basal insulin were included in the DPP4 inhibitor cohorts, as DPP4 inhibitors are typically only prescribed in combination with basal insulin for fourth-line treatment of T2D (based on the assumption that most healthcare practitioners are following NICE guidelines). Finally, individuals who were prescribed basal insulin in combination with oral antidiabetic therapies other than GLP-1RAs or DPP4 inhibitors were included in the basal insulin cohorts. Therapies were considered to constitute part of a

combined treatment regimen if the second therapy was prescribed within 90 days of the first.

Subjects were followed up for 2 years (730 days) from the date of index prescription, or until the earliest of the following: pregnancy, death, transfer out of practice, last data collection from practice, or December 31, 2019. The study concluded in 2019 to avoid inclusion of data during the COVID-19 pandemic, as this would have impacted the incidence of MACE unrelated to drug class.

Outcomes and Statistical Analyses

The clinical outcomes investigated in this study were composite MACE (non-fatal myocardial infarction [MI], non-fatal stroke, CV-related death), its individual components, and all-cause death. Incidence rates of the clinical outcomes were calculated for each cohort per 100,000 person-years. Separate Cox proportional hazards regression models for each cohort (very high risk and high risk were used and were then used to compare the crude and adjusted risk of the clinical outcomes in subjects indexed for treatment with GLP-1RAs versus DPP4 inhibitors or basal insulin. The covariates considered and selected for adjustment included potential confounders such as demographic and clinical characteristics. The final list of covariates in the adjusted models were selected and weighted using the least absolute shrinkage selection operator (LASSO) automatic feature selection tool. Several pre-specified variables were forced into the model, regardless of LASSO selection (age, gender, prior MACE, time since diabetes diagnosis, SGLT-2 inhibitor use, BMI, and prior DPP4 inhibitor treatment). The covariates considered for adjustment are listed in Table S1.

The economic outcomes investigated in this study were CV-related and all-cause HCRU and costs in secondary care. Further details on how care costs were attributed are outlined in the Supplementary Material. Reported outcomes included the proportion of individuals in each cohort who experienced hospitalizations or outpatient appointments during follow-up, the number of bed days per person per year (PPPY) for hospitalizations, and inpatient and outpatient care costs PPPY. Although the number of CV-related and all-cause hospitalizations, all-cause outpatient appointments, and outpatient cardiology appointments PPPY were also calculated, the results are not reported here; the occurrence of these outcomes were typically very low in each cohort and PPPY results did not enable meaningful comparisons between the treatment exposures. As such, the proportion of individuals who experienced these events were reported to improve the comparability and relevance of the results. Generalized linear regression models were then used to compare the number and duration of CV-related and all-cause hospitalizations, number of outpatient cardiology appointments, number of all-cause outpatient appointments, and total CV-related costs between the GLP-1RA and DPP4 inhibitors or basal insulin cohorts. Crude and adjusted analyses were performed. The approach used to select and weight confounders for the adjusted models (LASSO automatic feature selection) was the same as that used for the clinical outcomes analyses, with the following pre-specified variables pre-selected for inclusion in the adjusted models: age, gender, follow-up duration, time since diabetes diagnosis, SGLT-2 inhibitor use, BMI, and prior DPP4 inhibitor treatment. The covariates considered for adjustment are listed in Table S2.

Separate comparisons were conducted for the high- and very-high-risk cohorts across all outcomes and analyses. The datasets were processed using PostgreSQL hosted in DB Visualiser 10.0.22 and data analysis was performed using R for Windows 4.0.3. Medical codes used to identify outcomes are available from authors upon request.

RESULTS

Demographics and Clinical Characteristics

A total of 63,237 individuals were identified for inclusion (Fig. 1), of whom 10,607 were at high CV risk and 52,630 were at very high CV risk. In total, 17,401 subjects were indexed for treatment with GLP-1RAs, 21,134 for DPP4 inhibitors

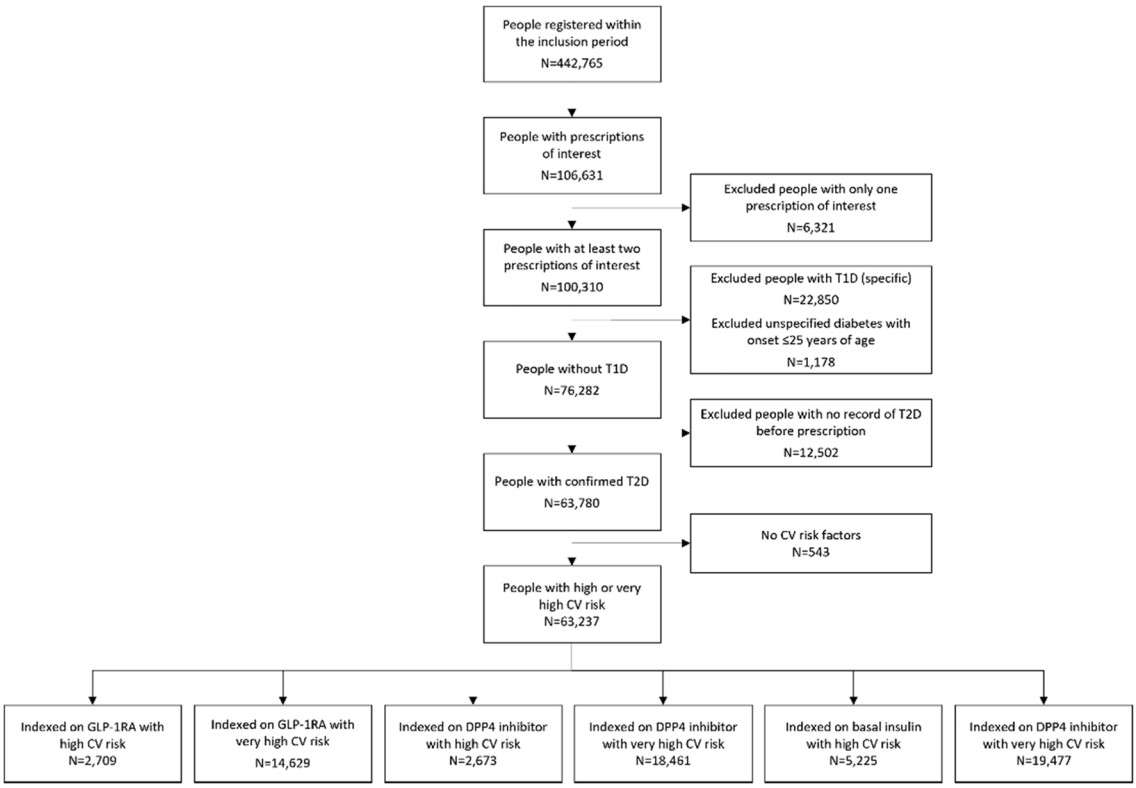


Fig. 1 Study flow diagram. Definitions for high and very high CV risk are provided in Figure S1, *CV* cardiovascular, *DPP4* dipeptidyl peptidase-4, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *T1D* type 1 diabetes, *T2D* type 2 diabetes

and 24,702 for basal insulin. Median follow-up duration was 24.3 months across all treatment exposures (Table 1).

Male-to-female ratios were relatively consistent between the cohorts (Table 1). Those at high or very high CV risk indexed for treatment with a GLP-1RA were younger (mean age 52.1 and 58.8 years, respectively) than those in the DPP4 inhibitor (60.4 and 68.7 years, respectively) or basal insulin cohorts (56.6 and 65.1 years, respectively). Additionally, a higher proportion of subjects indexed for treatment with a GLP-1RA were living with obesity compared with those in the other treatment cohorts. Across all treatment exposures, metformin and sulfonylureas were the most commonly prescribed additional oral glucose-lowering therapies in the fourth LoT (Table 2). SGLT-2 inhibitors were more frequently co-prescribed in the GLP-1RA cohorts compared with the DPP4 inhibitor and basal insulin cohorts, in both high- (22% vs. 9% and 9%, respectively) and very-high-risk (21% vs. 6% and 10%, respectively) individuals. Full baseline and clinical characteristics are summarized in Tables 1 and 2, respectively.

Treatment with GLP-1RAs was Typically Associated with Lower Risk of MACE Compared with DPP4 Inhibitor or Basal Insulin Treatment

Overall, the incidence of composite MACE, non-fatal MI, non-fatal stroke, CV-related death, and all-cause death were lower in individuals treated with GLP-1RAs compared with those indexed on DPP4 inhibitors or basal insulin, regardless of CV risk status (Fig. 2). Age-stratified incidence rates are provided in Table S3.

In the Cox proportional hazards regression for individuals at very high CV risk, the crude

Table 1 Summary of demographics across treatment cohorts

	GLP-1RA		DPP4 inhibitor		Basal insulin	
	High CV risk	Very high CV risk	High CV risk	Very high CV risk	High CV risk	Very high CV risk
Subjects, *n*	2709	14,692	2673	18,461	5225	19,477
Age, years, mean (SD)	52.1 (10.4)	58.8 (10.3)	60.4 (13.4)	68.7 (12.4)	56.6 (13.7)	65.1 (13.2)
Sex, male, *n* (%)	1441 (53.2)	6794 (46.2)	1253 (46.9)	8290 (44.9)	2298 (44.0)	8606 (44.2)
Ethnicity, *n* (%)						
White	2100 (77.5)	12,229 (83.2)	1853 (69.3)	13,761 (74.5)	3675 (70.3)	15,793 (81.1)
Black	124 (4.6)	635 (4.3)	200 (7.5)	1321 (7.2)	484 (9.3)	1168 (6.0)
Multiracial/other[a]	93 (3.4)	334 (2.3)	103 (3.9)	560 (3.0)	232 (4.4)	499 (2.6)
South Asian	288 (10.6)	1210 (8.2)	433 (16.2)	2608 (14.1)	625 (12.0)	1723 (8.8)
Unknown	104 (3.8)	284 (1.9)	84 (3.1)	211 (1.1)	209 (4.0)	294 (1.5)
Smoking status, *n* (%)						
Current smoker	132 (4.9)	1403 (9.5)	194 (7.3)	1494 (8.1)	481 (9.2)	2064 (10.6)
Ex-smoker	870 (32.1)	4877 (33.2)	749 (28.0)	5999 (32.5)	1278 (24.5)	6242 (32.0)
Non-smoker	1344 (49.6)	6581 (44.8)	1375 (51.4)	8724 (47.3)	2617 (50.1)	8348 (42.9)
Unconfirmed or unknown	363 (13.4)	1831 (12.5)	355 (13.3)	2244 (12.2)	849 (16.2)	2823 (14.5)
Alcohol consumption, *n* (%)						
Heavy	93 (3.4)	464 (3.2)	99 (3.7)	587 (3.2)	295 (5.6)	857 (4.4)
Non-heavy	2459 (90.8)	13,854 (94.3)	2399 (89.7)	17,104 (92.6)	4265 (81.6)	17,034 (87.5)
Unknown	201 (7.4)	578 (3.9)	228 (8.5)	1028 (5.6)	747 (14.3)	1861 (9.6)
Weight, kg, mean (SD)	108.5 (29.0)	106.8 (24.6)	79.4 (18.9)	86.6 (58.0)	81.3 (22.0)	88.8 (24.3)
BMI category, *n* (%)						
Underweight (< 18.5 kg/m^2)	S	S	47 (1.8)	163 (0.9)	143 (2.7)	229 (1.2)
Normal (18.5–24.9 kg/m^2)	46 (1.7)	138 (0.9)	642 (24.0)	2695 (14.6)	1364 (26.1)	2859 (14.7)
Overweight (25.0–29.9 kg/m^2)	448 (16.5)	1285 (8.7)	1295 (48.4)	5755 (31.2)	2032 (38.9)	4990 (25.6)

Table 1 continued

	GLP-1RA		DPP4 inhibitor		Basal insulin	
	High CV risk	Very high CV risk	High CV risk	Very high CV risk	High CV risk	Very high CV risk
Obese (30.0–39.9 kg/m^2)	1290 (47.6)	8777 (59.7)	474 (17.7)	7927 (42.9)	1019 (19.5)	8342 (42.8)
Severely obese (≥ 40.0 kg/m^2)	529 (19.5)	3815 (26.0)	78 (2.9)	1388 (7.5)	199 (3.8)	1851 (9.5)
Unknown	S	S	137 (5.1)	533 (2.9)	468 (9.0)	1206 (6.2)

Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors

[a]Anything that does not follow any of the other defined classifications

BMI, body mass index; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; S, suppressed ($n < 5$); SD, standard deviation

risk of all clinical outcomes was statistically significantly lower in the GLP-1RA cohort compared with the DPP4 inhibitor or basal insulin cohorts (Table S4). After adjusting for confounders, the risk of all outcomes, other than CV-related death, remained statistically significantly lower in very-high-risk people treated with GLP-1RAs (Fig. 3, Table S4). Overall, the adjusted risk of composite MACE in very-high-risk subjects treated with GLP-1RAs was 33% (95% CI [confidence interval]): 24–40%) lower than those indexed on DPP4 inhibitors and 23% (95% CI: 13–23%) lower than those indexed on basal insulin.

Although the same pattern was observed in the high-risk cohorts, comparisons for CV-related death could not be modeled as the overall occurrence of these events was very low in each treatment cohort (Table S4). Moreover, the overall occurrence of MACE was low across the cohorts and several other comparisons did not achieve statistical significance. Where Cox proportional hazards regression could be performed, the GLP-1RA cohort had a lower adjusted risk of all clinical outcomes compared with the DPP4 inhibitor or basal insulin cohorts. Overall, the adjusted risk of composite MACE in high-risk individuals treated with GLP-1RAs was 55% (95% CI: 0–80%) lower than those indexed on DPP4 inhibitors and 67% (95% CI: 32–84%) lower than those indexed on basal insulin. Additionally, the adjusted risk of non-fatal MI was 72% (95% CI: 13–91%) and 58% (95% CI: − 25–86%) lower in the high-risk GLP-1RA cohort than the high-risk DPP4 inhibitor and basal insulin cohorts, respectively, and 26% (95% CI: − 146–78%) and 64% (95% CI: 7–86%) lower for non-fatal stroke, respectively.

Treatment with GLP-1RAs was Typically Associated with Lower CV-Related HCRU in Secondary Care than DPP4 Inhibitor or Basal Insulin Treatment

The proportions of individuals in the GLP-1RA cohorts who experienced CV-related hospitalizations and outpatient cardiology appointments were lower compared with their respective risk groups in the DPP4 inhibitor and basal insulin cohorts (Fig. 4). The mean number of bed days for CV-related hospitalizations PPPY were also lower in the GLP-1RA cohorts compared with the other treatment cohorts (Table 3). Furthermore, adjusted multivariable linear regression analyses demonstrated that, among individuals

Table 2 Summary of clinical characteristics across treatment cohorts

	GLP-1RA		DPP4 inhibitor		Basal insulin	
	High CV risk	Very high CV risk	High CV risk	Very high CV risk	High CV risk	Very high CV risk
Subjects, *n*	2709	14,692	2673	18,461	5225	19,477
Follow-up period per person, months, median (IQR)	24.3 (19.6, 24.4)	24.3 (20.0, 24.4)	24.3 (21.3, 24.4)	24.3 (19.8, 24.4)	24.3 (20.3, 24.4)	24.3 (20.2, 24.4)
Time since diabetes diagnosis, months, median (IQR)	45.3 (20.3, 90.1)	85.2 (40.2, 141.8)	58.8 (23.4, 115.5)	117.6 (57.4, 172.7)	28.3 (3.0, 82.0)	82.5 (28.4, 143.1)
HbA1c measurement, %, mean (SD)	9.29 (1.72)	9.34 (1.64)	9.76 (2.04)	9.44 (1.88)	10.40 (2.50)	10.10 (2.30)
Other oral antidiabetics in LoT 4, *n* (%)						
Metformin	2374 (87.6)	12,760 (86.8)	2220 (83.1)	13,005 (70.4)	3459 (66.2)	13,036 (66.9)
SGLT-2 inhibitor	586 (21.6)	3132 (21.3)	246 (9.2)	1130 (6.1)	487 (9.3)	1896 (9.7)
Sulfonylurea	1113 (41.1)	7353 (50.0)	1782 (66.7)	11,502 (62.3)	2463 (47.1)	11,334 (58.2)
Pioglitazone	136 (5.0)	873 (5.9)	98 (3.7)	709 (3.8)	227 (4.3)	1187 (6.1)
Other medications, *n* (%)						
Long-term steroids[a]	522 (27.4)	3447 (31.0)	443 (25.1)	4991 (35.1)	789 (25.8)	5055 (35.7)
Cardioprotective medication, *n* (%)						
ACE inhibitors	822 (30.3)	10,717 (72.9)	1100 (41.2)	14,044 (76.1)	1493 (28.6)	12,772 (65.6)
Antiplatelet drugs	498 (18.4)	7209 (49.1)	721 (27.0)	12,071 (65.4)	932 (17.8)	10,434 (53.6)
Angiotensin II receptor antagonist	255 (9.4)	3851 (26.2)	359 (13.4)	5714 (31.0)	459 (8.8)	4613 (23.7)
Beta-blockers	435 (16.1)	5872 (40.0)	502 (18.8)	9194 (49.8)	898 (17.2)	8326 (42.7)

Table 2 continued

	GLP-1RA		DPP4 inhibitor		Basal insulin	
	High CV risk	Very high CV risk	High CV risk	Very high CV risk	High CV risk	Very high CV risk
Statins	1972 (72.8)	13,029 (88.7)	2108 (78.9)	16,878 (91.4)	2914 (55.8)	15,696 (80.6)
Comorbidities, *n* (%)						
Hypertension	498 (18.4)	11,584 (78.8)	1027 (38.4)	15,375 (83.3)	1689 (32.3)	15,556 (79.9)
Ischemic heart disease	S	3168 (21.6)	S	6403 (34.7)	S	6306 (32.4)
Atrial fibrillation	59 (2.2)	1083 (7.4)	97 (3.6)	2995 (16.2)	198 (3.8)	3001 (15.4)
Stroke	S	554 (3.8)	S	1627 (8.8)	S	1860 (9.5)
Peripheral vascular disease	S	729 (5.0)	8 (0.3)	2104 (11.4)	9 (0.2)	2136 (11.0)
CKD 3/4	47 (1.7)	1707 (11.6)	246 (9.2)	6721 (36.4)	262 (5.0)	4767 (24.5)
End-stage renal failure	S	24 (0.2)	S	218 (1.2)	S	219 (1.1)
Chronic liver disease	102 (3.8)	698 (4.8)	90 (3.4)	950 (5.1)	398 (7.6)	1647 (8.5)
COPD	135 (5.0)	1326 (9.0)	166 (6.2)	2555 (13.8)	282 (5.4)	2669 (13.7)
Rheumatoid arthritis/SLE	122 (4.5)	874 (5.9)	135 (5.1)	1145 (6.2)	199 (3.8)	1217 (6.2)
Cancer	234 (8.6)	1612 (11.0)	342 (12.8)	3645 (19.7)	748 (14.3)	3644 (18.7)
Depression	1012 (37.4)	5662 (38.5)	775 (29.0)	5615 (30.4)	1415 (27.1)	6348 (32.6)

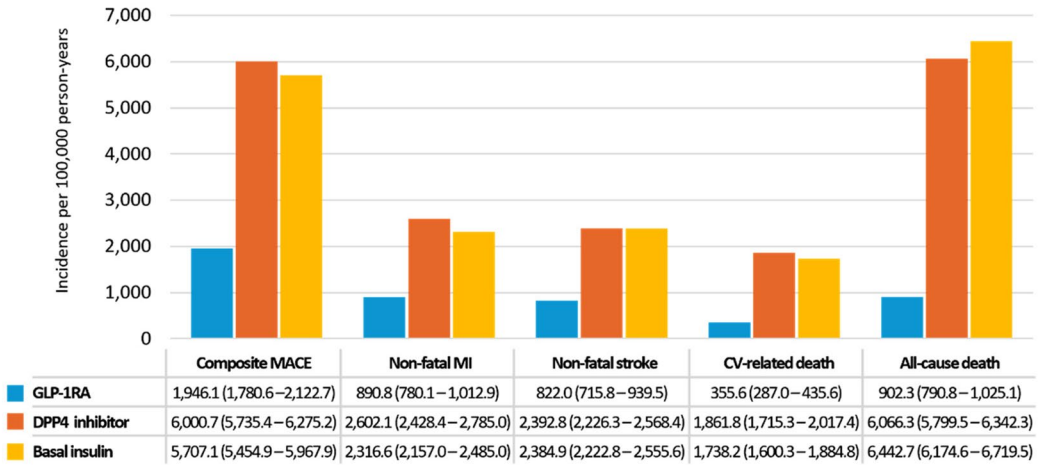
Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors

[a]Long-term steroids are defined as prednisolone prescribed daily covering 100 days in the prior year

ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1C; IQR, interquartile range; LoT 4, line of treatment 4; S, suppressed ($n < 5$); SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2; SLE, systemic lupus erythematosus

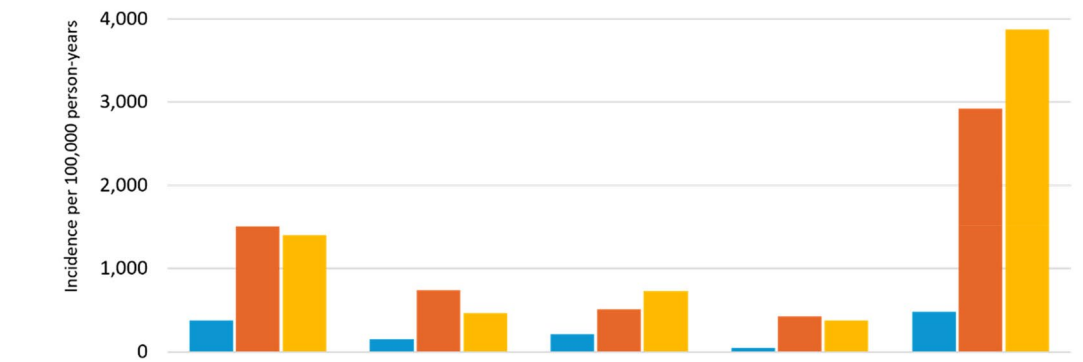
at very high CV risk, the number of CV-related hospitalizations and outpatient cardiology appointments, as well as number of bed days for CV-related hospitalizations, were statistically significantly lower in those treated with GLP-1RAs compared with DPP4 inhibitors or basal insulin over the study period (Table 4). Among individuals at high CV risk, differences between the treatment cohorts were less pronounced and not all analyses achieved statistical significance.

i) Individuals with high CV risk



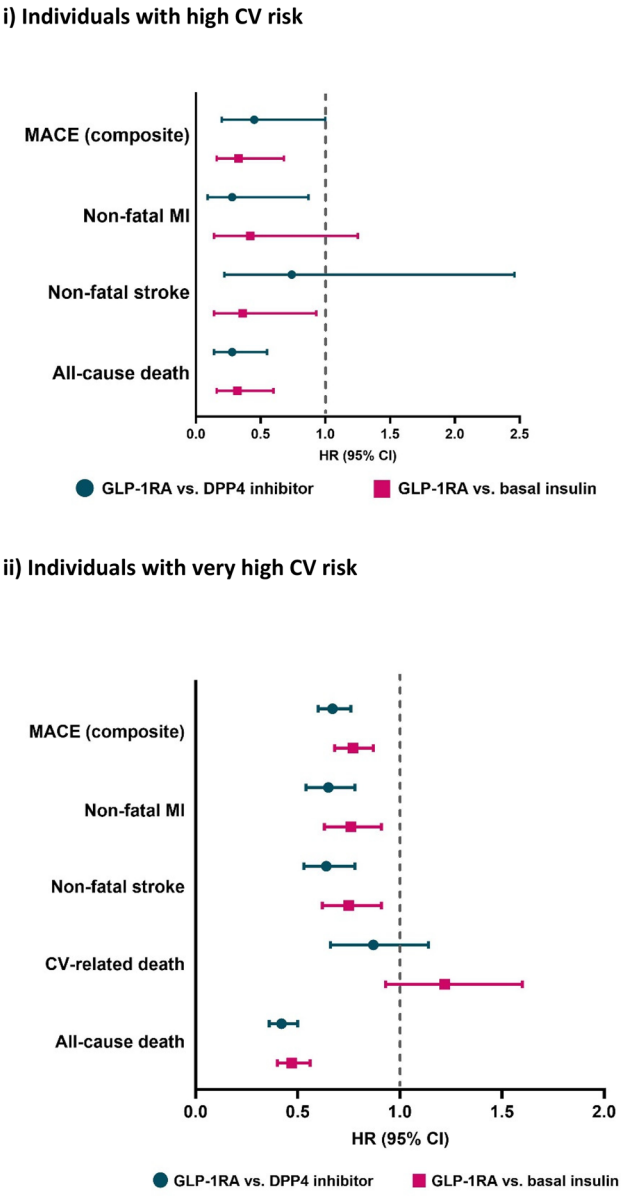
	Composite MACE	Non-fatal MI	Non-fatal stroke	CV-related death	All-cause death
GLP-1RA	1,946.1 (1,780.6–2,122.7)	890.8 (780.1–1,012.9)	822.0 (715.8–939.5)	355.6 (287.0–435.6)	902.3 (790.8–1,025.1)
DPP4 inhibitor	6,000.7 (5,735.4–6,275.2)	2,602.1 (2,428.4–2,785.0)	2,392.8 (2,226.3–2,568.4)	1,861.8 (1,715.3–2,017.4)	6,066.3 (5,799.5–6,342.3)
Basal insulin	5,707.1 (5,454.9–5,967.9)	2,316.6 (2,157.0–2,485.0)	2,384.9 (2,222.8–2,555.6)	1,738.2 (1,600.3–1,884.8)	6,442.7 (6,174.6–6,719.5)

ii) Individuals with very high CV risk



	Composite MACE	Non-fatal MI	Non-fatal stroke	CV-related death	All-cause death
GLP-1RA	377.1 (223.5–595.9)	146.6 (59.0–302.1)	209.5 (100.5–385.2)	41.9 (5.1–151.3)	481.8 (305.4–723.0)
DPP4 inhibitor	1,503.0 (1,173.9–1,895.9)	740.9 (516.1–1,030.5)	508.1 (325.5–756.0)	423.4 (258.6–653.9)	2,921.4 (2,454.3–3,451.5)
Basal insulin	1,396.9 (1,164.5–1,662.1)	462.0 (332.9–624.5)	726.0 (561.5–923.6)	374.0 (259.0–522.6)	3,871.8 (3,477.8–4,298.1)

Fig. 2 Incidence of first MACE[a] and all-cause death among individuals with T2D at (i) high or (ii) very high CV risk, indexed on GLP-1RA, DPP4 inhibitor, or basal insulin treatment. Values are reported as incidence per 100,000 person-years (95% CI). Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors. Population numbers in the high-risk cohorts are as follows: GLP-1RA, 2709; DPP4 inhibitor, 2673; basal insulin, 5225. Population numbers in the very-high-risk cohorts are as follows: GLP-1RA, 14,692; DPP4 inhibitor, 18,461; basal insulin, 19,477. [a]Composite MACE (non-fatal MI, non-fatal stroke, or CV-related death) and its individual components. *CI* confidence interval, *CV* cardiovascular, *DPP4* dipeptidyl peptidase-4, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *MACE* major adverse cardiac event, *MI* myocardial infarction, *T2D* type 2 diabetes



Nevertheless, the number of outpatient cardiology appointments was statistically significantly lower in the GLP-1RA group compared with the DPP4 inhibitor and basal insulin groups, and the number and length of CV-related hospitalizations were statistically significantly lower in the GLP-1RA group versus the DPP4 inhibitor group.

Treatment with GLP-1RAs was Typically Associated with Lower CV-Related Costs in Secondary Care than DPP4 Inhibitor or Basal Insulin Treatment

Mean CV-related inpatient and outpatient costs PPPY were also lower in the GLP-1RA cohorts compared with the DPP4 inhibitor or basal insulin cohorts (Table 3). Adjusted multivariable linear regression analyses demonstrated that total CV-related costs for individuals at

◂**Fig. 3** Adjusted[a] Cox proportional hazards models of time-to-first MACE[b] and all-cause death in individuals with T2D at (i) high or (ii) very high CV risk. Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors. In the high-risk cohorts, full case data were available for 2045 individuals indexed on GLP-1RAs (75.5% of cohort), 2200 individuals indexed on DPP4 inhibitors (82.3% of cohort), and 3710 individuals indexed on basal insulin (71.0% of cohort). In the very-high-risk cohorts, full case data were available for 13,062 individuals indexed on GLP-1RAs (88.9% of cohort), 16,100 individuals indexed on DPP4 inhibitors (87.2% of cohort), and 15,553 individuals indexed on basal insulin (79.9% of cohort). CV-related death could not be modeled in the high-risk cohorts. [a]Covariates for adjustment were selected using the LASSO automatic feature selection tool. The following variables were forced into the model: age, gender, prior MACE, time since diabetes diagnosis, SGLT-2 inhibitor use, BMI, and prior treatment with DPP4 inhibitors; [b]Composite MACE (non-fatal MI, non-fatal stroke, or CV-related death) and its individual components. *BMI* body mass index, *CI* confidence interval, *CV* cardiovascular, *DPP4* dipeptidyl peptidase-4, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *HR* hazard ratio, *LASSO* least absolute shrinkage selection operator, *MACE* major adverse cardiovascular event, *MI* myocardial infarction, *SGLT-2* sodium-glucose cotransporter-2, *T2D* type 2 diabetes

very high CV risk were statistically significantly lower in the GLP-1RA cohort compared with the DPP4 inhibitor and basal insulin cohorts, with estimated mean cost-savings in the GLP-1RA cohort of approximately £208 (95% CI: £156–£261) and £152 (95% CI: £111–£193) compared to the DPP4 inhibitor and basal insulin cohorts, respectively (Table 4).

In the adjusted analyses for the high-risk cohorts, GLP-1RA treatment was not associated with statistically significant differences in total CV-related costs compared with DPP4 inhibitor (£19 [– £38 to £76]) or basal insulin (£15 [£8 to 38]) treatment.

Treatment with GLP-1RAs was Typically Associated with Lower All-Cause HCRU and Costs in Secondary Care than DPP4 Inhibitor or Basal Insulin Treatment

All-cause HCRU and costs were lower in the GLP-1RA cohorts than their respective risk groups in the DPP4 inhibitor and basal insulin cohorts (Table S5). In the adjusted analyses for individuals at very high CV risk, the number of hospitalizations, number of bed days for hospitalizations, number of outpatient appointments, and total costs were statistically significantly lower in those treated with GLP-1RAs compared with DPP4 inhibitors or basal insulin (Table S6). In high-risk individuals, adjusted HCRU and costs were also lower in the GLP-1RA cohort than the DPP4 inhibitor and basal insulin cohorts. These differences were statistically significant for outpatient appointments and total costs. For the number and length of hospitalizations, the differences were only statistically significantly different between the GLP-1RA and DPP4 inhibitor cohorts.

DISCUSSION

In this retrospective, real-world analysis, individuals with T2D at high or very high CV risk treated with GLP-1RAs had fewer MACE and less HCRU and costs than those indexed on DPP4 inhibitor or basal insulin treatment as part of their fourth LoT in England. After adjusting for confounding factors, these differences generally remained statistically significant among patients at very high CV risk. Although the comparisons typically did not achieve statistical significance in people at high CV risk, this may be attributed to the low event rates among high-risk individuals in this study; very few non-fatal MI, non-fatal stroke, or CV-related death events occurred in the high-risk GLP-1RA cohort throughout the study period.

The results from this real-world analysis are consistent with evidence from numerous studies that suggest GLP-1RAs confer greater reductions in MACE risk than DPP4 inhibitors or basal

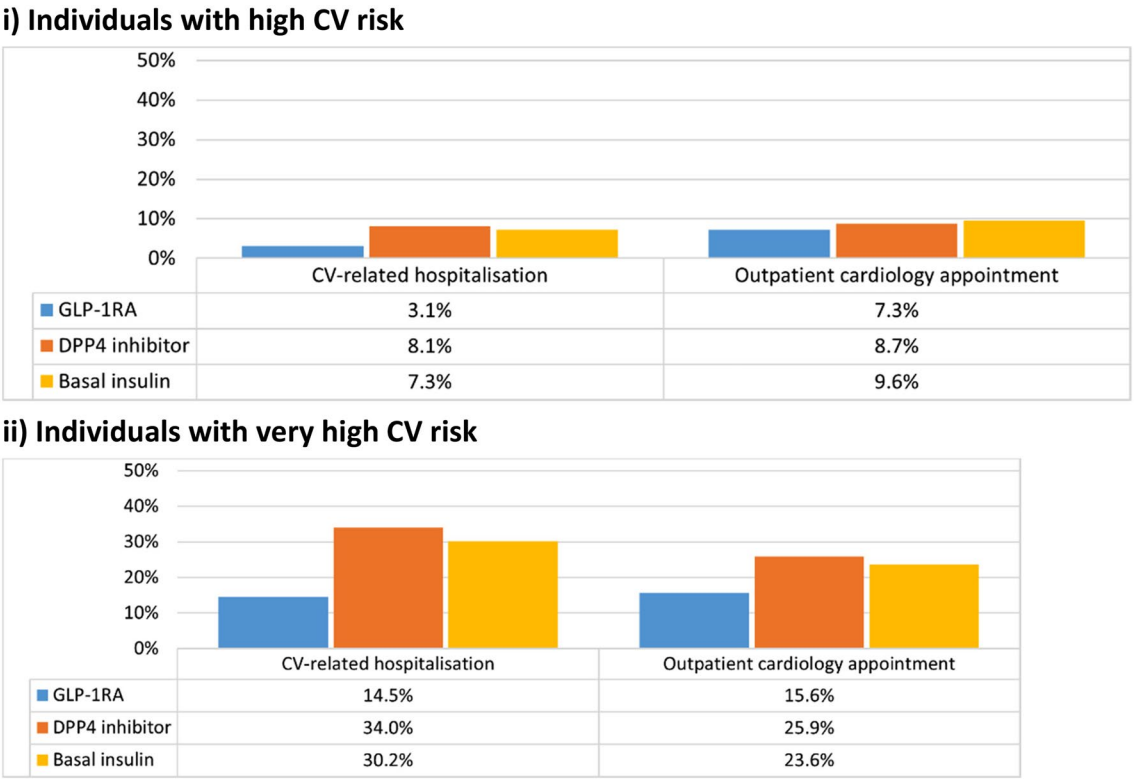


Fig. 4 Proportions of individuals with T2D indexed on GLP-1RA, DPP4 inhibitor, or basal insulin treatment who experienced CV-related hospitalizations and outpatient cardiology appointments in secondary care in the (i) high- or (ii) very-high-risk cohorts. Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors. Population numbers in the high-risk cohorts are as follows: GLP-1RA, 2709; DPP4 inhibitor, 2673; basal insulin, 5225. Population numbers in the very-high-risk cohorts are as follows: GLP-1RA, 14,692; DPP4 inhibitor, 18,461; basal insulin, 19,477. *CV* cardiovascular, *DPP4* dipeptidyl peptidase-4, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *T2D* type 2 diabetes

insulin. A 2023 meta-analysis of head-to-head real-world studies and clinical trials between GLP-1RAs and other glucose-lowering agents demonstrated that the risk of MI and stroke was 18% and 17% lower in people with T2D treated with GLP-1RAs compared with DPP4 inhibitors, and 30% and 50% lower in those treated with GLP-1RAs versus basal insulin, respectively [21]. Moreover, a 2022 meta-analysis of real-world studies demonstrated that GLP-1RAs reduced the risk of MACE by 30% compared with other glucose-lowering agents, including DPP4 inhibitors and insulin, across the included studies [18]. When compared solely to DPP4 inhibitors, GLP-1RAs reduced the risk of MACE by 10–45% in people with T2D. Interestingly, the studies included in this meta-analysis comprised of people with low CV risk, suggesting that GLP-1RA-mediated reductions in MACE risk may not be limited to those with existing CVD or at high risk of CVD. Additionally, the meta-analysis did not include people treated with injectable semaglutide, which has previously been associated with substantial MACE reduction in those at high CV risk [6].

In the present analysis, the CV benefits of GLP-1RAs over DPP4 inhibitors or basal insulin were generally slightly more pronounced

Table 3 Average length of stay for CV-related hospitalizations and CV-related costs in secondary care among individuals with T2D at high or very high CV risk indexed on GLP-1RA, DPP4 inhibitor, or basal insulin treatment

	High CV risk			Very high CV risk		
	GLP-1RA ***n*** **= 2709**	**DPP4 inhibitor** ***n*** **= 2673**	**Basal insulin** ***n*** **= 5225**	**GLP-1RA** ***n*** **= 14,692**	**DPP4 inhibitor** ***n*** **= 18,461**	**Basal insulin** ***n*** **= 19,477**
CV-related length of stay, bed days per person per year						
Mean (SD)	0.2 (2.3)	0.9 (6.3)	1.2 (9.3)	0.9 (6.8)	6.3 (21.5)	4.7 (18.2)
Median (min–max)	0.0 (0.0–53.5)	0.0 (0.0–135.7)	0.0 (0.0–305.6)	0.0 (0.0–311.5)	0.0 (0.0–336.3)	0.0 (0.0–356.8)
CV-related cost per person per year, £						
Inpatient						
Mean (SD)	113 (1355)	378 (2262)	409 (2652)	536 (2496)	2,355 (6578)	1982 (6,319)
Median (min–max)	0 (0–59,096)	0 (0–62,897)	0 (0–84,448)	0 (0–90,993)	0 (0–167,349)	0 (0–249,056)
Outpatient						
Mean (SD)	19 (98)	24 (109)	27 (153)	46 (158)	92 (261)	85 (258)
Median (min–max)	0 (0–1517)	0 (0–1866)	0 (0–6526)	0 (0–3234)	0 (0–5730)	0 (0–6252)

Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors. Population numbers in the high-risk cohorts are as follows: GLP-1RA, 2709; DPP4 inhibitor, 2673; basal insulin, 5225. Population numbers in the very-high-risk cohorts are as follows: GLP-1RA, 14,692; DPP4 inhibitor, 18,461; basal insulin, 19,477

CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SD, standard deviation; T2D, type 2 diabetes

than in prior studies. The notable differences in MACE risk between the GLP-1RA and the other treatment cohorts in this analysis may have been influenced by the selection of GLP-1RAs that have demonstrated a CV benefit in CVOTs; the GLP-1RAs investigated in this study were associated with statistically significantly lower rates of MACE compared with placebo in the SUSTAIN-6 (semaglutide), REWIND (dulaglutide), and LEADER (liraglutide) CVOTs [6, 8, 10]. Moreover, results from the recent SELECT trial (NCT03574597) further highlight the association between semaglutide treatment and MACE reduction [22]. Although individuals enrolled into SELECT did not have T2D, semaglutide was superior to placebo ($p < 0.001$) for the reduction of MACE in people with CVD and a BMI ≥ 27 kg/m^2. Results from prior studies and meta-analyses may have been more prominent if they focused solely on GLP-1RAs that significantly reduced the risk of MACE compared with placebo in CVOTs. Of note, a network meta-analysis of CVOTs for GLP-1RAs, SGLT-2 inhibitors, and DPP4 inhibitors reported that GLP-1RAs and SGLT-2 inhibitors were associated with a similarly reduced risk of MACE than DPP4 inhibitors (risk ratio [RR]: 0.89, for both) across the included CVOTs, and concluded that the risk was not significantly different between these two classes (RR: 0.99) [23]. Although this meta-analysis highlights the impact of GLP-1RAs on reducing MACE risk, the evidence base for

Table 4 Generalized linear regression models for CV-related HCRU outcomes and costs in secondary care among individuals with T2D at high or very high CV risk

Outcome	Comparison	Mean[a]	Unadjusted difference		Adjusted[b]	
			Est (95% CI)	*p* value	Est (95% CI)	*p* value
High CV risk						
Number of CV-related hospitalizations	DPP4 inhibitor	0.2	ref	–	ref	–
	GLP-1RA	0.1	− 0.09 (− 0.13, − 0.05)	< 0.001	− 0.20 (− 0.33, − 0.07)	0.0031
	Basal insulin	0.2	ref	–	ref	–
	GLP-1RA	0.1	− 0.09 (− 0.12, − 0.06)	< 0.001	− 0.07 (− 0.14, 0.00)	0.0663
Length of CV-related hospitalizations, number of bed days	DPP4 inhibitor	1.2	ref	–	ref	–
	GLP-1RA	0.3	− 0.86 (− 1.42, − 0.50)	< 0.001	− 0.67 (− 1.16, − 0.18)	0.0069
	Basal insulin	1.3	ref	–	ref	–
	GLP-1RA	0.3	− 0.96 (− 1.36, − 0.66)	< 0.001	− 0.24 (− 0.49, 0.01)	0.0625
Number of outpatient cardiology appointments	DPP4 inhibitor	0.2	ref	–	ref	–
	GLP-1RA	0.2	− 0.03 (− 0.09, 0.02)	0.242	− 1.34 (− 2.05, − 0.62)	< 0.001
	Basal insulin	0.3	ref	–	ref	–
	GLP-1RA	0.2	− 0.07 (− 0.12, − 0.02)	0.0043	− 2.12 (− 2.95, − 1.28)	< 0.001
Total CV-related cost, £	DPP4 inhibitor	619	ref	–	ref	–
	GLP-1RA	322	− 297.48 (− 494.21, − 135.76)	< 0.001	− 18.88 (− 76.18, 38.42)	0.5184
	Basal insulin	610	ref	–	ref	–
	GLP-1RA	322	− 288.03 (− 421.09, − 161.34)	< 0.001	− 14.69 (− 37.58, 8.21)	0.2088
Very high CV risk						
Number of CV-related hospitalizations	DPP4 inhibitor	1.0	ref	–	ref	–
	GLP-1RA	0.3	− 0.70 (− 0.74, − 0.66)	< 0.001	− 0.76 (− 0.89, − 0.63)	< 0.001
	Basal insulin	0.9	ref	–	ref	–
	GLP-1RA	0.3	− 0.57 (− 0.61, − 0.53)	< 0.001	− 0.28 (− 0.36, − 0.20)	< 0.001
Length of CV-related hospitalizations, number of bed days	DPP4 inhibitor	7.2	ref	–	ref	–
	GLP-1RA	1.4	− 5.80 (− 6.28, − 5.36)	< 0.001	− 2.85 (− 3.23, − 2.48)	< 0.001
	Basal insulin	5.5	ref	–	ref	–
	GLP-1RA	1.4	− 4.15 (− 4.53, − 3.79)	< 0.001	− 1.33 (− 1.62, − 1.03)	< 0.001

Table 4 continued

Outcome	Comparison	Mean[a]	Unadjusted difference		Adjusted[b]	
			Est (95% CI)	*p* value	Est (95% CI)	*p* value
Number of outpatient cardiology appointments	DPP4 inhibitor	1.0	ref	–	ref	–
	GLP-1RA	0.5	− 0.50 (− 0.56, − 0.45)	< 0.001	− 2.68 (− 3.09, − 2.27)	< 0.001
	Basal insulin	0.9	ref	–	ref	–
	GLP-1RA	0.5	− 0.42 (− 0.47, − 0.37)	< 0.001	− 1.93 (− 2.31, − 1.56)	< 0.001
Total CV-related cost, £	DPP4 inhibitor	3300	ref	–	ref	–
	GLP-1RA	1100	− 2199.73 (− 2352.11, − 2053.86)	< 0.001	− 208.14 (− 260.47, − 155.81)	< 0.001
	Basal insulin	2747	ref	–	ref	–
	GLP-1RA	1100	− 1647.08 (− 1775.76, − 1523.08)	< 0.001	− 151.74 (− 192.79, − 110.69)	< 0.001

Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors. In the high-risk cohorts, full case data were available for 2,045 individuals indexed on GLP-1RAs (75.5% of cohort), 2,200 individuals indexed on DPP4 inhibitors (82.3% of cohort), and 3,710 individuals indexed on basal insulin (71.0% of cohort). In the very-high-risk cohorts, full case data were available for 13,062 individuals indexed on GLP-1RAs (88.9% of cohort), 16,100 individuals indexed on DPP4 inhibitors (87.2% of cohort), and 15,553 individuals indexed on basal insulin (79.9% of cohort)

[a]Per person mean during follow-up (not annualized); [b]Covariates for adjustment were selected using the LASSO automatic feature selection tool. The following variables were forced into the model: age, gender, follow-up duration, time since diabetes diagnosis, SGLT-2 inhibitor use, BMI, and prior treatment with DPP4 inhibitors

BMI body mass index; *CI* confidence interval; *CV* cardiovascular; *DPP4* dipeptidyl peptidase-4; *Est* estimated; *GLP-1RA*, glucagon-like peptide-1 receptor agonist; *HCRU* healthcare resource utilization; *LASSO* least absolute shrinkage selection operator; ref, reference; *SGLT-2* sodium-glucose cotransporter-2; *T2D* type 2 diabetes

this meta-analysis included CVOTs that investigated GLP-1RAs without a proven CV benefit, such as ELIXA (NCT01147250; lixisenatide); the results may have been more pronounced if the meta-analysis focused on injectable semaglutide, dulaglutide, and liraglutide. In the present study, it was noted that SGLT-2 inhibitors were more commonly co-prescribed in the GLP-1RA cohorts (Table 2); this may have contributed to the prominent differences in MACE rates between the treatment cohorts, with the greatest reduction in MACE seen in the GLP-1RA cohort. It is possible that clinicians who prescribe SGLT-2 inhibitors are more acutely aware of the heightened CV risk in people with T2D and, therefore, may select GLP-1RAs over DPP4 inhibitors or basal insulin in the fourth LoT. Nevertheless, SGLT-2 inhibitor use was preselected for inclusion in our adjusted analyses to reduce the impact of these imbalances on the hazard ratio calculations.

The results of the present study suggest that preferential use of GLP-1RAs over DPP4 inhibitors or basal insulin may reduce HCRU and costs for people with T2D at very high CV risk of CVD. While there are limited real-world data on the impact of GLP-1RAs on CV-related HCRU and costs among individuals with T2D, available evidence suggests that GLP-1RAs are not associated with a higher overall healthcare expenditure than other glucose-lowering agents. A US analysis that compared total healthcare

costs between people treated with GLP-1RAs and those who received other agents found that the high initial costs of GLP-1RAs were offset by significantly lower inpatient and outpatient care costs across 1 year of treatment [24]. These results suggest that the clinical benefits of GLP-1RAs may translate into a reduced long-term economic burden. In line with this, another US study reported that people who discontinued GLP-1RA treatment accumulated increasing HCRU and costs over the course of 1 year, driven largely by outpatient expenditures [25]. Moreover, two systematic reviews that included cost-effectiveness comparisons between GLP-1RAs and DPP4 inhibitors [26, 27] or insulin [27] concluded that GLP-1RAs were likely to be more cost-effective than these agents. The present study provides further evidence supporting the cost-effectiveness of GLP-1RAs versus DPP4 inhibitors and basal insulin, in the context of the healthcare system in England. It is acknowledged that the economic benefits of GLP-1RA treatment may be higher than estimated in this study since only direct costs associated with CV events were reported. Indirect costs, prescription costs, and health-related quality of life were not considered. While prescription costs associated with GLP-1RAs will be higher than the initial costs of DPP4 inhibitors and basal insulin, overall expenditure may be offset by long-term cost-savings, as demonstrated in the aforementioned US studies [24, 25].

Although the 2022 ADA/EASD consensus report and 2024 ADA guidelines recognize the benefit of GLP-1RA use in people with T2D and CVD, or a high risk of CVD [14, 15], GLP-1RAs continue to be positioned as a fourth-line treatment option in England, after failure to achieve glycemic control with triple oral therapy [16]. Nevertheless, the results of this study suggest that a wider uptake of GLP-1RA treatment may be beneficial, particularly in those with very high CV risk. Furthermore, recent results from the FLOW trial (NCT03819153) demonstrated that subcutaneous semaglutide was able to reduce the risk of MACE by 18% compared with placebo in patients with T2D and comorbid kidney disease [28]. The ongoing SOUL trial (NCT03914326) will further inform on the impact of oral semaglutide on CV outcomes in individuals at high CV risk [29], as will the ASCEND plus trial (NCT05441267) in lower-risk individuals [30].

Limitations

By nature, retrospective real-world studies have a high risk of residual bias attributed to unmeasured confounders. Furthermore, the risk of MACE depends upon factors such as treatment adherence, duration of diabetes, whether diabetes is controlled or uncontrolled (partly indicated by hemoglobin A1C levels), as well as a host of non-diabetes confounders such as genetic and environmental factors. Although treatment adherence was not measured in this study, other potential confounding factors were considered for adjustment. Key variables, such as duration of diabetes, were pre-selected for inclusion in the models. Additionally, key clinical and demographic characteristics that were imbalanced between the groups (age, BMI, SGLT-2 inhibitor use) were also pre-selected for adjustment in the models.

There was, unexpectedly, a high prevalence of patients receiving long-term steroids in our study. Although this suggests that people with steroid-induced diabetes may have been included in this study, subjects with steroid-induced diabetes codes in the CPRD were not eligible for inclusion. It is possible that the high level of steroid use in this study may have been attributed to steroid-induced hyperglycemia as opposed to steroid-induced diabetes; subjects may have had comorbidities requiring steroid treatment that were not considered for baseline characteristic collection, such as brittle asthma, temporal arteritis, and other autoimmune conditions. Nevertheless, subjects without type 1 diabetes (T1D)- or T2D-specific codes were assumed to have T2D, and it is possible that patients with steroid-induced diabetes may have been included.

Additionally, several assumptions were made to define the fourth LoT. It is possible that some of the individuals may not have received the therapies as part of their fourth-line treatment regimen for T2D. Moreover, only injectable semaglutide, dulaglutide, and liraglutide

were considered for these analyses. As such, the results cannot be extended to represent class effects of GLP-1RAs. Primary care HCRU and costs were also not reported; due to the nature of coding, it was not possible to assign events as such. Despite these limitations, the study used data from a large, nationally representative dataset.

CONCLUSIONS

In line with international treatment guidelines, the results of this real-world, retrospective study suggest that GLP-1RAs may confer a greater CV benefit than DPP4 inhibitors or basal insulin in people with T2D and established CVD or a high risk of CVD in England, which may translate into reduced HCRU and costs. GLP-1RAs may be a more suitable option than DPP4 inhibitors and basal insulin for fourth-line T2D treatment in England. Additionally, it may be beneficial to integrate GLP-1RAs into earlier lines of treatment, particularly in subjects with T2D at very high risk of CVD.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available. This study was conducted using data obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (MHRA) following study protocol approval by the Research Data Governance (RDG) process. Data from the Hospital Episode Statistics (HES) and death registrations from Office for National Statistics (ONS) dataset were linked to CPRD Aurum data by NHS England and reused with permission. Access to CPRD and linked datasets must be requested by application via the CPRD RDG.

Declarations

Conflict of Interest. Derek Connolly and Steve Bain have received consultancy fees from Novo Nordisk. Steve Bain is an Editorial Board member of *Diabetes Therapy*. Steve Bain was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Edward Collins and Hongye Ren are employees of Novo Nordisk. Simon Wan Yau Ming and Jennifer Davidson are employees of CorEvitas; CorEvitas received funding from Novo Nordisk to conduct the study.

Ethical Approval. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Ethics committee approval was not required for this study; access to the dataset was approved by the CPRD Research Data Governance body (protocol number: 23_002661). The CPRD has ethics approval

from the Health Research Authority to support research using anonymized patient data.

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