

ORIGINAL ARTICLE

Healthcare costs and hospitalizations in US patients with type 2 diabetes and cardiovascular disease: A retrospective database study (OFFSET)

Marc Evans MD¹  | Abhishek Shankar Chandramouli BTech² | Mads Faurby MSc³ | Kasper Sommer Matthiessen MSc³ | Phillip Bredahl Mogensen MSc⁴ | Subodh Verma MD⁵

¹University Hospital Llandough, Penarth, Cardiff, UK

²Novo Nordisk Service Centre India Pvt Ltd, Bangalore, India

³Novo Nordisk A/S, Søborg, Denmark

⁴JP Statistics ApS, Copenhagen, Denmark

⁵Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Toronto, Canada

Correspondence

Marc Evans, MD, Department of Diabetes and Endocrinology, University Hospital, Llandough, Penarth, Cardiff, Wales, UK.
Email: marclyndon1@hotmail.com

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Abstract

Aim: To investigate the budget implications of treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) versus other glucose-lowering treatment (here termed 'standard of care' [SoC]) during 2012-2019.

Materials and Methods: GLP-1 RA-naïve adults with type 2 diabetes (T2D) in the IBM MarketScan database with at least one glucose-lowering medication claim within 6 months after their first cardiovascular disease (CVD) hospitalization were included (index date was the date of first claim for a GLP-1 RA for the GLP-1 RA group, and the date of the first claim, independent of medication type, for the SoC group). Monthly healthcare costs and hospitalization risk over 12 months postindex date were compared for those who initiated a GLP-1 RA posthospitalization versus those with a claim for any other glucose-lowering medication.

Results: Postindex date, mean observed total costs were lower for patients receiving a GLP-1 RA compared with SoC (\$3853 vs. \$4288). In adjusted analysis, both groups had similar total healthcare costs ($P = .56$). This was driven by significantly lower inpatient and outpatient costs and higher drug costs in the GLP-1 RA group compared with SoC ($P < .001$). Risks of all-cause (adjusted hazard ratio: 0.85) and CVD-related hospitalization (0.76) were significantly lower in the GLP-1 RA group compared with SoC ($P < .001$). Similar results were observed in a subgroup with atherosclerotic CVD.

Conclusions: These findings suggest that, in US patients with T2D and a CVD-related hospitalization, the added medical cost of treatment with GLP-1 RAs is offset by lower inpatient and outpatient care costs, resulting in budget neutrality against SoC.

KEYWORDS

analogue, antidiabetic drug, cardiovascular disease, diabetes complications, GLP-1, health economics, type 2 diabetes

1 | INTRODUCTION

Approximately one-third of patients with type 2 diabetes (T2D) worldwide also have cardiovascular disease (CVD).¹ CVD is a major contributor to morbidity and mortality in these patients: in a US epidemiological study of people with diabetes, covering the period 2010-2015, CVD was estimated to account for more than one-third of deaths.² All major forms of CVD have also been shown to have a negative impact on quality of life in patients with T2D.^{3,4} Furthermore, treatment for cardiovascular (CV) conditions, which includes drugs, hospitalizations and outpatient visits, is a significant contributor to costs in T2D.^{5,6} Therefore, treatment strategies to limit the number and severity of CV events in patients with T2D could be expected to improve their life expectancy and health-related quality of life (HRQoL), and to reduce the impact of the disease on healthcare systems.⁷

Following 2008 guidance from the US Food and Drug Administration (FDA), numerous CV outcomes trials (CVOTs) were carried out to assess rates of CVD in patients receiving novel classes of glucose-lowering treatments, and to determine that these medications are not associated with an increase in CV risk.⁸ Various CVOTs have shown CV benefit or non-inferiority for glucose-lowering medications against comparators. Among these, the results of eight pivotal trials examining glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been published since 2016, of which three (ELIXA, EXSCAL and PIONEER 6) showed no significant effect in reducing major adverse cardiovascular events (MACE), and five (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND and AMPLITUDE-O) showed significant reductions in composite CV outcome rates for a GLP-1 RA against placebo.^{9,10}

Based on the results from CVOTs, updates to the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines were published in 2019,¹¹ and updated European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention in clinical practice were published in 2021.¹² The updated guidelines state that either a GLP-1 RA or a sodium-glucose co-transporter-2 inhibitor (SGLT-2i) can be used as an add-on to metformin, or as first-line glucose-lowering treatment in case of intolerance or contraindication to metformin, for patients with T2D and established atherosclerotic CVD or high CVD risk. Thus, under the updated guidelines, glucose-lowering treatments with proven CV benefit can be prescribed earlier in the T2D treatment pathway than according to previous routine practice.

The budget implications of this potential expansion in the patient population eligible for GLP-1 RA treatment should be evaluated in the context of costs, clinical events and resource use. For example, hospital costs are a key cost driver in T2D,⁵ and treatment strategies that reduce hospitalizations are probable to provide both clinical and economic benefits, which must be weighed against the costs of prescribing drugs with CV benefit.

In the present study, we compared short-term total direct healthcare costs and rates of hospitalization between patients with T2D who received a GLP-1 RA after their first inpatient admission for CVD and those who received other glucose-lowering treatment

(hereafter referred to as standard of care [SoC]) in the same time period, using US administrative claims data.

2 | MATERIALS AND METHODS

2.1 | Data source

The OFFSET study used data from IBM MarketScan, a large US administrative claims database containing anonymized claims data from more than 273 million patients across all US states.¹³

2.2 | Study design and population

This was a retrospective, observational cohort study, using data available from 1 September 2012 onwards; the database lock was 30 September 2019. Figure 1 illustrates the study design.

For inclusion, patients were required to have an International Classification of Diseases (ICD; ninth or 10th revision) diagnosis code for T2D in the baseline period (Table S1), an inpatient admission for CVD as the primary diagnosis (index CVD hospitalization) and at least one claim for a glucose-lowering treatment (index date) during the 6 months following the index CVD hospitalization. For patients with more than one claim in the 6 months posthospitalization, the index date was the date of first claim for a GLP-1 RA for the GLP-1 RA group, and the date of the first claim, independent of medication type, for the SoC group. A grace period of up to 6 months was allowed between the date of the index CVD hospitalization and the index date (Figure 1). Patients required 6 months' continuous enrolment in the database prehospitalization and up to 12 months' continuous enrolment following the index date, including during the grace period (Figure 2). Patients were excluded if they were younger than 18 years on the index date, if there was evidence that they had received a GLP-1 RA at any time preindex or if they had a diagnosis code for type 1 diabetes or gestational diabetes (Table S1).

Patients who met the inclusion criteria were grouped based on their first medication claim in the 6 months following index CVD hospitalization: patients who had a claim for any GLP-1 RA were allocated to the GLP-1 RA group, and those who had a claim for any other glucose-lowering treatment made up the SoC group. Glucose-lowering treatment classes in the SoC group comprised one or more of the following categories: alpha glucosidase inhibitors, amylin analogues, biguanides, dipeptidyl peptidase-4 inhibitors (DPP-4is), insulin, insulin-sensitizing agents, meglitinide analogues, SGLT-2is, sulphonylureas, antidiabetic drug combinations and antidiabetic drugs (other).

2.3 | Outcomes

The primary outcome was mean total direct healthcare costs over the 12 months postindex date. Because of the grace period between index hospitalization and index date (claim for glucose-lowering treatment), this did not include costs for the index CVD hospitalization.

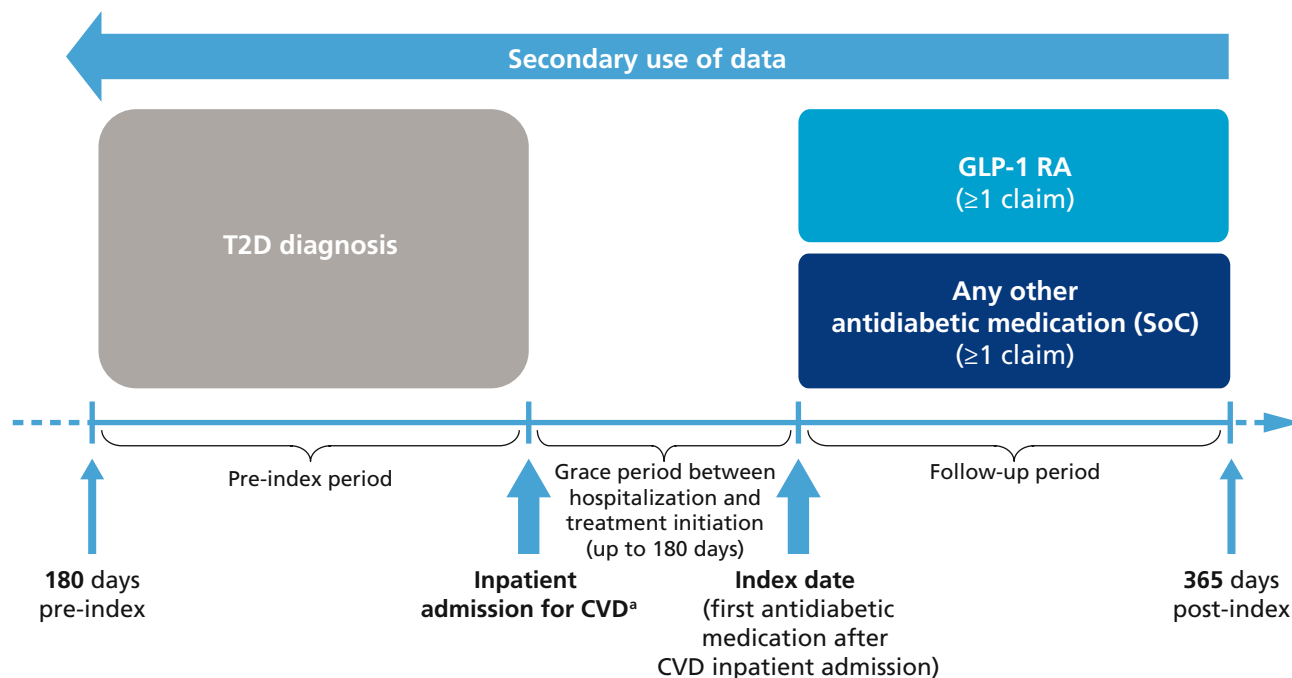


FIGURE 1 Study design. ^aDefined by International Classification of Diseases, ninth/10th revision codes 390–459/I00–I99. CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes

Constituent costs were drug costs, inpatient costs and outpatient costs. Drug costs included all medications, including glucose-lowering medications. All costs were expressed in US dollars per patient per month, adjusted for inflation to the year 2019.

The average monthly costs of treatment incurred before the index CVD hospitalization were also calculated, based on all available cost data in the patients' records prehospitalization, for all patients with at least 6 months' cost data prehospitalization. The average duration of the pre-index hospitalization period for calculation of costs was similar in the GLP-1 RA (mean: 730 days) and SoC groups (mean: 694 days).

Secondary outcomes included CVD-related inpatient and outpatient costs, the proportion of patients with all-cause or CVD-related hospitalization in the 12 months postindex date, time to first all-cause or CVD-related hospitalization, and, in patients who were rehospitalized, the total duration of hospital stays and the mean duration per hospital stay in the 12 months postindex date. All-cause hospitalization was defined as any inpatient admission during the 12 months following the index date. CVD-related hospitalization was defined as any inpatient admission during the 12 months following the index date where the primary diagnosis was for a CVD (as defined by ICD codes 390–459/I00–I99). Costs were considered CVD-related if the associated primary diagnosis was a CVD, as defined by ICD codes 390–459/I00–I99.

2.4 | Subgroup analysis: patients with atherosclerotic CVD

Total healthcare costs over the 12 months postindex date, as well as inpatient, outpatient and drug costs, were examined in patients with

atherosclerotic CVD as the cause of index CVD hospitalization (cerebrovascular disease, ischaemic heart disease or peripheral vascular disease [Table S1]).

2.5 | Statistical analyses

Both observed, and adjusted, mean monthly inpatient, outpatient, drug and total healthcare costs are presented. Statistical testing of differences between GLP-1 RAs and SoC are denoted by *P* values derived from analyses using mean costs from a generalized linear model adjusted for potential confounders. To derive adjusted means, costs were regressed onto the following set of covariates: age at index date, sex (male/female), glucose-lowering treatment at index (GLP-1 RA/other), Charlson co-morbidity index, insurance plan (commercial/Medicare), previous glucose-lowering treatment, previous CV medication and baseline costs, using a generalized linear model with a log link and gamma-distributed residuals. This is a common choice for modelling of costs, because these data are often heavily right-skewed.¹⁴ Baseline costs adjusted for in the model were the costs per patient per month before the index CVD hospitalization (calculated as average monthly costs per patient based on all available cost data in the patients' records prehospitalization). Previous glucose-lowering and CV medication use were recorded as yes/no for previous receipt of each of the constituent medication classes, based on all claims available in the patient records before the index CVD hospitalization. The CV medication classes included were antihypertensive drugs, angiotensin-converting enzyme inhibitors, alpha/beta blockers, antiarrhythmic agents, beta blockers, calcium channel blockers, cardiac

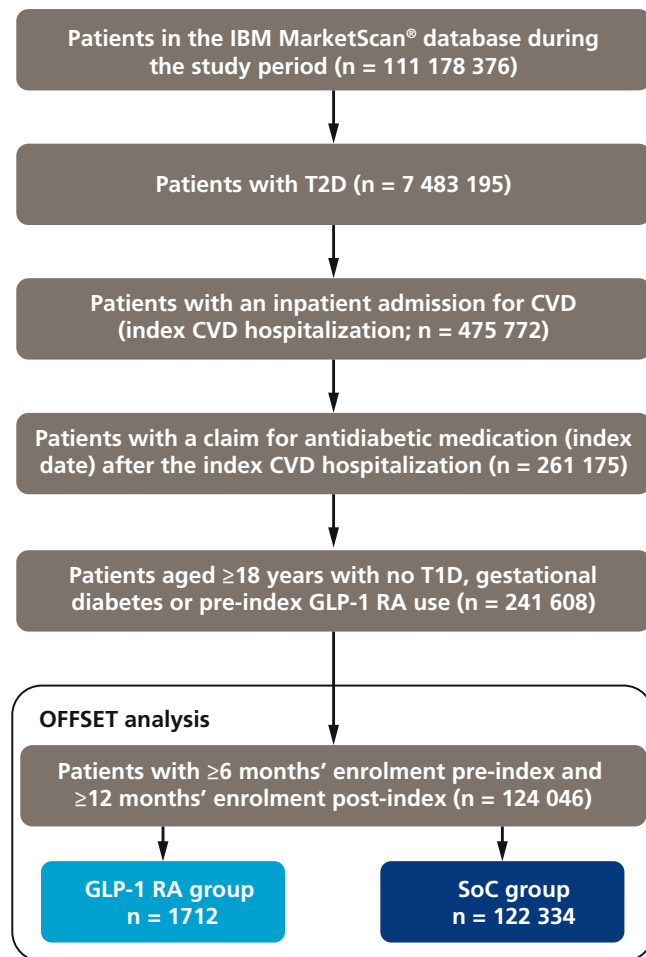


FIGURE 2 Study attrition. CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide receptor agonist; SoC, standard of care; T1D, type 1 diabetes; T2D, type 2 diabetes

glycosides, hypotensive agents, kallikrein inhibitors, natriuretic peptides, phosphodiesterase inhibitors, sclerosing agents and vasodilating agents.

For inpatient costs, a similar model was employed, using a Tweedie distribution.¹⁵ This was chosen because many patients had zero inpatient costs, and the Tweedie distribution allows for a point mass at zero.¹⁵

Time to first all-cause or CVD-related hospitalization was assessed using Kaplan–Meier survival analysis and risk of hospitalization was assessed using a multivariate Cox proportional hazard model adjusted for age, sex, glucose-lowering treatment at index, Charlson co-morbidity index, insurance plan, previous glucose-lowering treatment, previous CVD medication and baseline costs.

Data analysis was conducted using the SAS statistical software package (version 9.4). All tests were two-tailed, and *P* less than .05 was considered statistically significant. In the two analyses where multiple tests were performed, a Bonferroni correction was applied to the significance level to control the familywise error rate, meaning that *P* less than .0125 was considered statistically significant.

2.6 | Sensitivity analyses

To determine whether the follow-up period for cost data had any impact on the results, sensitivity analyses were conducted to compare the costs of care between treatment groups for both shorter (6 months) and longer (18 months) periods postindex date. To account for costs incurred after hospitalization but before the subsequent glucose-lowering treatment prescription, a sensitivity analysis that considered index date as the date of CVD hospitalization was also carried out.

To maximize the size of the study population, the beginning of the study period in the main analysis was set several years before GLP-1 RAs were recommended specifically for CV benefit. However, in a fourth sensitivity analysis, the beginning of the study period was defined as August 2017, when the first GLP-1 RA had an FDA label update, approving its use to reduce the risk of MACE in adults with T2D and established CVD.¹⁶

3 | RESULTS

3.1 | Study population and baseline characteristics

Approximately 111 million patients had records in the database during the study period. In total, 7 483 195 patients had a T2D diagnosis from 1 September 2012 to 30 September 2019, of whom 124 046 patients met the eligibility criteria: 1712 patients (1.4%) in the GLP-1 RA group, and 122 334 patients (98.6%) in the SoC group (Figure 2).

Table 1 summarizes the patient characteristics at baseline. Similar proportions of patients in each group were women (GLP-1 RA: 40.1% vs. SoC: 39.2%). Patients in the SoC group were older on average than those in the GLP-1 RA group and had more comorbidities (mean [SD] Charlson co-morbidity index score: 1.87 [1.93] vs. 1.33 [1.67]). Fewer patients in the SoC group (48.0%) had commercial health insurance than in the GLP-1 RA group (77.2%). Similar proportions of patients in the groups had received insulin (31.5%–33.3%) or a DPP-4i (8.1%–8.8%) prior to hospitalization. Slightly more patients in the SoC group had received metformin than in the GLP-1 RA group (38.1% vs. 33.1%), but fewer had received an SGLT-2i (1.5% vs. 5.6%). In both groups, the index CVD hospitalization event was most frequently a result of acute myocardial infarction or coronary atherosclerosis, followed by heart failure and arrhythmias. The index GLP-1 RAs were liraglutide (46% of patients), dulaglutide (23%), exenatide once weekly (17%), exenatide twice daily (6%), other GLP-1 RA monotherapy (5%) or GLP-1 RA combination therapy (3%). The index treatments received by the SoC group were metformin (33% of patients), insulin (30%), DPP-4i (6%), SGLT-2i (1%), other monotherapy (17%), dual therapy (12%) and triple therapy (1%; Table S2). The average duration of the grace period (time from index CVD hospitalization to index date) ranged from 32 to 92 days across the different treatment groups (Table S2).

TABLE 1 Baseline characteristics of the study population

	GLP-1 RA (n = 1712) ^a	SoC (n = 122 334) ^a
Women, n (%)	687 (40.1)	47 943 (39.2)
Age (y), mean (SD)	58.4 (10.6)	66.5 (12.5)
CCI score, mean (SD)	1.33 (1.67)	1.87 (1.93)
Insurance type, n (%)		
Commercial	1322 (77.2)	58 705 (48.0)
Medicare	390 (22.8)	63 629 (52.0)
Region, n (%)		
Northeast	317 (18.5)	24 646 (20.2)
North central	398 (23.2)	38 599 (31.6)
South	826 (48.2)	47 486 (38.8)
West	158 (9.2)	11 103 (9.1)
Unknown	13 (0.8)	500 (0.4)
Last treatment before index CVD hospitalization, n (%) ^b		
DPP-4i ^c	121 (8.8)	8313 (8.1)
Insulin ^c	456 (33.3)	32 154 (31.5)
Metformin ^c	453 (33.1)	38 957 (38.1)
SGLT-2i ^c	77 (5.6)	1547 (1.5)
Other monotherapy	195 (14.3)	17 074 (16.7)
Dual therapy	57 (4.2)	3744 (3.7)
Triple therapy	9 (0.7)	423 (0.4)
Index CVD event, n (%)		
Acute myocardial infarction	334 (19.5)	20 338 (16.6)
Coronary atherosclerosis and other heart disease	325 (19.0)	18 467 (15.1)
Heart failure	191 (11.2)	17 219 (14.1)
Cardiac dysrhythmias	221 (12.9)	14 852 (12.1)
Cerebral infarction	191 (11.2)	13 880 (11.3)
Other CVD	450 (26.3)	37 578 (31.7)

Abbreviations: CCI, Charlson co-morbidity index; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SoC, standard of care.

^aUnless otherwise noted.

^bAmong patients with an available claim for glucose-lowering medication (n = 1368 in the GLP-1 RA group, and n = 102 212 in the SoC group).

^cAs monotherapy.

3.2 | Healthcare costs before CVD hospitalization and postindex date

Monthly total healthcare costs per patient before the index CVD hospitalization were similar in the two groups (GLP-1 RA: \$2011 vs. SoC: \$1934). Drug costs (\$265 vs. \$251), inpatient costs (\$1176 vs. \$1093) and outpatient costs (\$570 vs. \$590) were also similar in the two groups (Figure 3A). When the preindex period for calculation of costs was limited to 6 months, mean total healthcare costs and all types of constituent costs were also similar in the two groups.

In the 12 months after index date, observed total costs were lower in the GLP-1 RA group than in the SoC group (\$3853 vs. \$4288). In the GLP-1 RA and SoC groups, inpatient costs were \$1147 and \$1458, respectively, outpatient costs were \$1660 and \$2155, and drug costs were \$1046 and \$675 (Figure 3B). CVD-related inpatient costs in the GLP-1 RA group were \$537, compared with \$746 in the SoC group. CV-related outpatient costs were \$510 for the GLP-1 RA group and \$549 for the SoC group. In adjusted analyses, drug costs were significantly higher for the GLP-1 RA group (\$1201) compared with the SoC group (\$705), but inpatient (\$1070 vs. \$1374) and outpatient (\$1712 vs. \$1970) costs were significantly lower (all $P < .001$). Total healthcare costs were not significantly different between the two groups (\$3584 vs. \$3638; $P = .56$; Figure 3B).

3.3 | Healthcare costs for patients with atherosclerotic CVD

Approximately one-third of the full cohort had atherosclerotic CVD as the cause of their index CVD hospitalization: 652 patients in the GLP-1 RA group and 44 594 patients in the SoC group. Similar results to those in the main analysis were observed in this subgroup of individuals: observed total healthcare costs (\$3170 vs. \$3481) were numerically lower in the GLP-1 RA group compared with the SoC group ($P = .87$ in adjusted analyses; Figure 4).

3.4 | All-cause and CVD-related hospitalization

Fewer patients in the GLP-1 RA group were hospitalized for any cause during the 12 months postindex date than in the SoC group (28% vs. 35%; Figure 5A). Patients in the GLP-1 RA group had a significantly lower risk of all-cause hospitalization than patients in the SoC group after adjustment for potential confounders (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.78-0.93; $P < .001$).

Patients in the SoC group who were hospitalized for any cause had a 21.1% longer average total hospital stay over the 12 months postindex date (11.5 vs. 9.5 days) and a 17.3% longer average hospital stay per admission (6.1 vs. 5.2 days), compared with the GLP-1 RA group.

The rate of CVD-related hospitalization in the first year postindex date was also lower in the GLP-1 RA group (11.7%) than in the SoC group (16.3%; Figure 5B). The risk of CVD hospitalization was 24% lower in the GLP-1 RA group than in the SoC group (HR: 0.76; 95% CI: 0.61-0.91; $P < .001$). Mean observed costs associated with CVD-related hospitalization in the first year postindex date were \$537 in the GLP-1 RA group and \$746 in the SoC group.

3.5 | Costs of care over 6 and 18 months' follow-up

In the sensitivity analysis with a shorter index period, the results were similar to those in the main analysis. Observed monthly total costs

FIGURE 3 Healthcare costs in the GLP-1 RA and SoC groups after CVD hospitalization and glucose-lowering treatment initiation. Data are mean monthly costs per patient, A, Before the index CVD hospitalization (data from all available patient records prior to hospitalization), and B, During the 12 months following the index date (date of treatment initiation after the index CVD hospitalization), and not including costs for the index CVD hospitalization. Adjusted costs are means and 95% confidence intervals, using a model adjusted for age, sex, glucose-lowering treatment at index, CCI score, insurance plan, previous glucose-lowering treatment, previous CVD medication and baseline costs. CCI, Charlson co-morbidity index; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPPM, per patient per month; SoC, standard of care

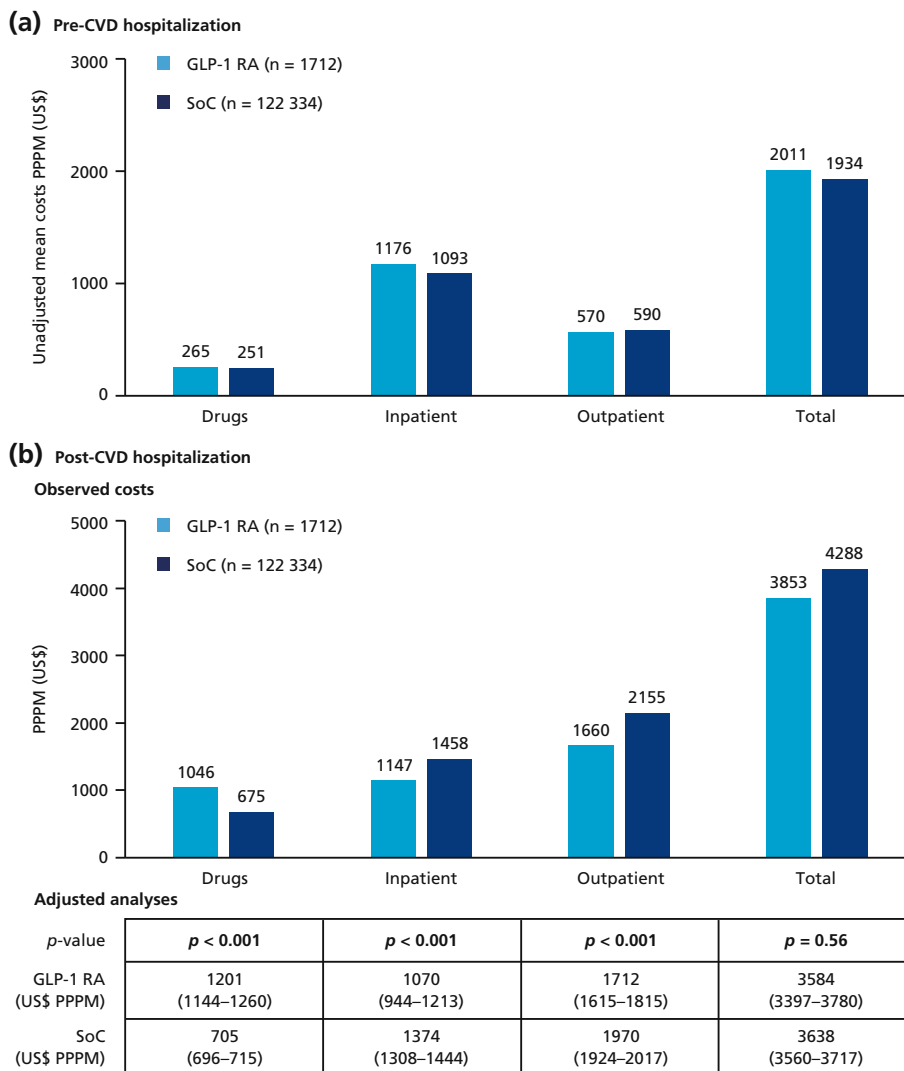
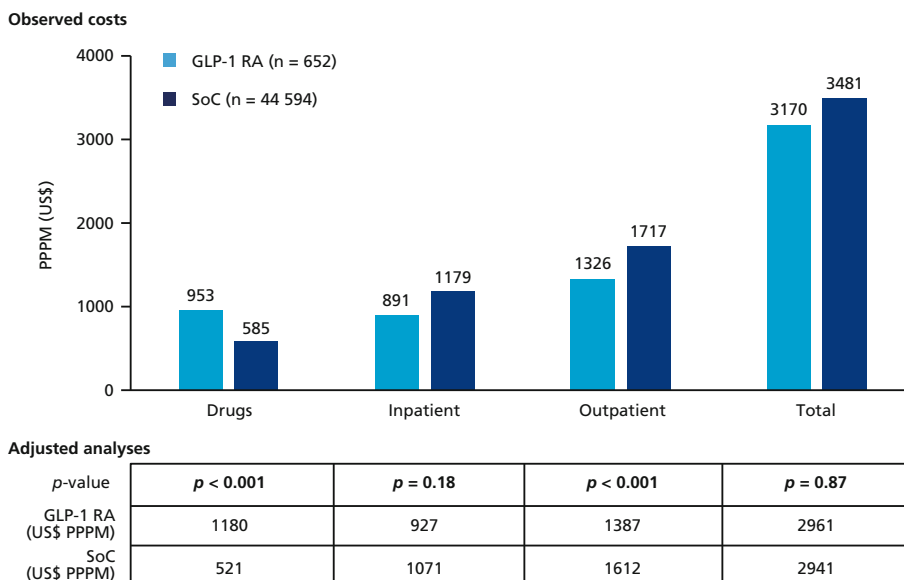


FIGURE 4 Healthcare costs in the subgroup with atherosclerotic CVD as the cause for the index CVD hospitalization. Data are mean monthly costs per patient during the 12 months following the index date (date of treatment initiation after the index CVD hospitalization), and not including costs for the index CVD hospitalization. CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPPM, per patient per month; SoC, standard of care



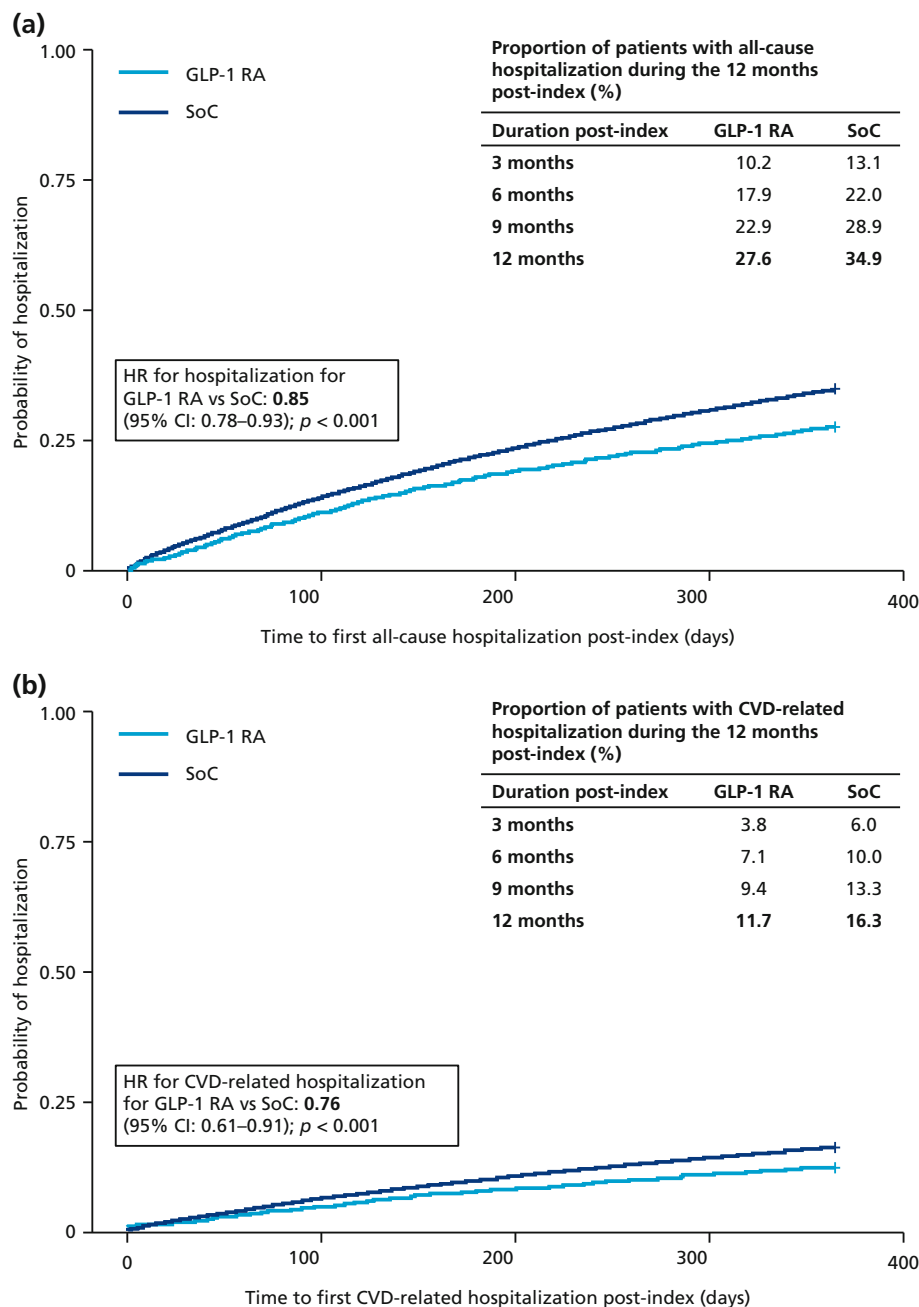


FIGURE 5 Kaplan–Meier curve for time to A, First all-cause hospitalization, and B, First CVD-related hospitalization postindex date in the GLP-1 RA and SoC groups. The HRs shown are adjusted for age, sex, glucose-lowering treatment at index, Charlson co-morbidity index, insurance plan, previous glucose-lowering treatment, previous CVD medication and total direct healthcare costs at baseline. CI, confidence interval; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SoC, standard of care

were \$4206 in the GLP-1 RA group and \$4597 in the SoC group. In adjusted analyses, there was no significant difference in average total monthly costs of care between groups (\$3944 vs. \$4419; $P = .13$), inpatient and outpatient costs were significantly lower in the GLP-1 RA group than in the SoC group, and drug costs were significantly higher (Table S3).

The results were similar when an 18-month index period was used. Observed monthly total costs were \$2163 for the GLP-1 RA group and \$2344 for the SoC group. There was no significant difference in total costs between groups in adjusted analyses (\$2005 vs. \$2058; $P = .39$), inpatient and outpatient costs were significantly

lower in the GLP-1 RA group than in the SoC group, and drug costs were significantly higher (Table S3).

3.6 | Costs of care post-CVD hospitalization

In the sensitivity analysis that used first CVD hospitalization as the index date, observed total monthly costs of care were similar in the GLP-1 RA and SoC groups (\$3474 vs. \$3577), and adjusted analyses showed no significant difference (\$3446 vs. \$3420; $P = .73$). Drug costs were significantly higher for the GLP-1 RA group, and inpatient

costs were significantly lower; however, outpatient costs were similar for the two groups (Table S3).

3.7 | Restriction of study period to CV indication for GLP-1 RAs

In total, 12 909 patients met the inclusion criteria in the period from August 2017 onwards and were eligible for inclusion in the sensitivity analysis; 353 patients were in the GLP-1 RA group (21% of the cohort in the main analyses) and 12 556 patients were in the SoC group (10% of the cohort in the main analyses). Total monthly observed costs were lower for the GLP-1 RA group than for the SoC group (\$3538 vs. \$4654), and there was no significant difference between the groups in adjusted analyses (\$4742 vs. \$4640; $P = .74$). Inpatient costs were significantly lower for the GLP-1 RA group, drug costs were significantly higher, and there was no significant difference in outpatient costs between the two groups (Table S3).

4 | DISCUSSION

The cost of managing T2D and its complications represents a growing challenge for healthcare systems worldwide. Following the 2019 ADA/EASD and 2021 ESC guideline updates recommending earlier use of GLP-1 RAs in patients with CVD,^{11,12} an investigation of the potential impact on healthcare budgets is warranted. In the present study of more than 120 000 US individuals with T2D and a recent CVD hospitalization, higher drug costs associated with GLP-1 RAs against SoC were offset by significantly lower inpatient and outpatient care costs within 1 year of treatment initiation, resulting in budget neutrality against SoC. Patients receiving GLP-1 RAs were also at lower risk of all-cause and CVD-related hospitalization than patients receiving SoC. Overall, these data suggest that the health benefits offered by GLP-1 RAs may offset their cost burden in the short term, and that implementation of the ADA/EASD guidelines is probable to improve patient outcomes, without significantly increasing healthcare expenditure.

We observed that monthly total direct healthcare costs approximately doubled after CVD hospitalization, and the sensitivity analysis showed that average monthly costs in the first 6 months postindex date were approximately double the monthly costs over the first 18 months, suggesting that healthcare costs are highest in the first few months following a CVD hospitalization. Our findings are in line with published estimates: in a recent large analysis of data from Taiwan, a diagnosis of ischaemic heart disease or arrhythmia resulted in a 2- to 2.5-times increase in T2D healthcare costs in the following year.¹⁷ The economic impact of CVD in patients with T2D has been estimated in several studies. In a UK study, 44% of the costs of treating T2D complications were associated with CVD,¹⁸ and a systematic review of 24 studies found that treatment for CVD was responsible for 20%-49% of the total direct costs of T2D.¹⁹ The ADA estimates that inpatient costs constitute 84% of the total cost of

treating CVD in T2D.²⁰ In a recent, large real-world study, patients with T2D and atherosclerotic CVD had more than double the healthcare costs of patients without atherosclerotic CVD, an increase that was driven more by inpatient and outpatient costs than by drug costs.²¹ This is consistent with our observation that the inpatient and outpatient costs were the main cost drivers in both the total population and the subgroup with atherosclerotic CVD. Furthermore, the subgroup with atherosclerotic CVD had numerically lower total healthcare costs when treated with GLP-1 RAs rather than with SoC. Therefore, although the costs associated with GLP-1 RAs may partly underlie clinical inertia in prescribing these drugs to eligible patients,²² our results indicate that this budget impact is probable to be mitigated by significant reductions in one of the major cost drivers in patient populations with CVD and T2D.

Use of medications with CV benefit as part of the integrated management of T2D is probable to improve both clinical and economic outcomes. The cardioprotective properties of GLP-1 RAs may be partly linked to improved glycaemic control, weight loss and reductions in blood pressure,²³ and HbA1c is a major predictor of risk of CVD and CV mortality.²⁴ The precise factors contributing to the lower rates of all-cause and CVD-related hospitalization in the GLP-1 RA group in the present study are not known, but may be the result of better glycaemic control in the GLP-1 RA group than in the SoC group. This has been observed previously in a real-world study comparing dulaglutide and basal insulin²⁵; however, a similar comparison could not be made in the present study because HbA1c data were not available. The reduction in risk of CVD-related hospitalization in the GLP-1 RA group relative to the SoC group is probable to be linked to the cardioprotective action of GLP-1 RAs.²⁶

The present study only reports direct healthcare costs, and does not take indirect costs, clinical benefits or HRQoL into account. However, the lower hospitalization rates and shorter hospital stays in the GLP-1 RA group compared with the SoC group suggest that these patients may experience fewer absences from work and a lower risk of co-morbidities, with an overall reduction in indirect costs. A recent large study in Sweden estimated that the costs of absence from work attributable to diabetes complications were nearly double those of the hospital-based care costs.⁵ Therefore, the results of our study probably represent an underestimate of the true economic benefit associated with GLP-1 RAs.

This is one of the largest real-world studies to date evaluating the costs of GLP-1 RAs compared with SoC. Each of the sensitivity analyses supported the main findings, and the results were similar to those of previous studies examining GLP-1 RAs. Further, a study of patients at high CVD risk with up to 5 years' follow-up found that liraglutide users had similar total healthcare costs to basal insulin users, despite having higher drug costs.²⁷ Some disparities between the treatment groups at baseline were observed in the present study; furthermore, other differences between patients that influenced both treatment choice and costs incurred may not have been captured in the data source. The analyses were adjusted for relevant confounding factors, to limit the risk that observed differences in cost were related to reasons other than treatment choice, but residual confounding

factors, such as possible differences in overall quality of healthcare between the two groups, cannot be excluded. Patients were also required to have continuous database enrolment throughout the study, which led to the exclusion of patients who died during the year after their first CVD hospitalization and may have influenced cost estimates, introducing potential bias. The grace period between the index CVD hospitalization and index date varied across groups, but the sensitivity analysis that considered the index CVD hospitalization to be the index date, and therefore did not include a variable grace period, confirmed the findings of the main analysis. Mortality data were not available for all patients, and therefore a comparison of mortality rates between treatment groups was not possible.

To maximize the available data, we conducted an analysis including all eligible patients, with adjustment for potential confounders. However, the size of the GLP-1 RA group was small relative to the SoC group; therefore, further studies evaluating healthcare costs in patients receiving GLP-RAs are needed to confirm our findings. Our study period spanned 2012–2019, and therefore the newest generation of GLP-1 RAs are probable to be under-represented. Based on the results of recent CVOTs, it is expected that the trend observed in the present study will be maintained and strengthened in later studies that include patients receiving these newer treatment options.

In conclusion, in this large study of adult patients with T2D, initiation of GLP-1 RA treatment after CVD hospitalization was budget-neutral against SoC, and was associated with comparatively lower rates and shorter duration of hospitalization. As updated guidelines continue to be applied in clinical practice, and glucose-lowering treatments with CV benefit are used earlier in the T2D treatment pathway, further studies should be designed to assess the impact that this has on clinical outcomes, costs and healthcare resource use.

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CONFLICT OF INTEREST

ME has received honoraria from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. MF, KSM and ASC are employees of Novo Nordisk. PBM is employed as a consultant by Novo Nordisk A/S. SV holds a Tier 1 Canada Research Chair in Cardiovascular Surgery, and has received research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, PhaseBio, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group. He is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization.

AUTHOR CONTRIBUTIONS

ASC, MF, KSM and PBM contributed to the design and conceptualization of the study. ASC conducted analyses. All authors contributed to the interpretation of data and critical review of the manuscript, and approved the final version for submission.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14703>.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are under licence from IBM. Aggregate datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

ORCID

Marc Evans  <https://orcid.org/0000-0003-0671-0778>

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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