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Comparative effectiveness of SGLT2i versus GLP1-RA on cardiovascular outcomes in routine clinical practice

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ABSTRACT

Background: To investigate the comparative effectiveness of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1-RA) on cardiovascular outcomes in routine clinical practice, which have never been directly compared in head-to-head outcome trials.

Methods: We compared outcomes of adults who newly started SGLT2i or GLP1-RA therapy in Stockholm, Sweden, during 2013–2019. The primary outcome was major adverse cardiovascular events (MACE), a composite of cardiovascular (CV) death, myocardial infarction and stroke. Secondary outcomes included the individual MACE components and hospitalization for heart failure. Cox regression with propensity score overlap weighting was used to estimate hazard ratios (HRs) with 95% confidence intervals and adjust for 57 covariates.

Results: We included 12,375 individuals, of which 5489 initiated SGLT2i and 6886 GLP1-RA therapy, followed for median 1.6 years. Mean age was 61 years and 37.6% were women. Compared with GLP1-RA, SGLT2i new users had similar risk of MACE risk (adjusted HR 1.04; 95% CI 0.83–1.31). The adjusted HRs (95% CI) for SGLT2i vs. GLP1-RA were 0.80 (0.59–1.09) for heart failure hospitalization, 0.95 (0.58–1.55) for cardiovascular death, 0.91 (0.67–1.24) for myocardial infarction and 1.71 (1.14–2.59) for ischemic stroke (5-year absolute risk difference for stroke 1.9% [95% CI 0.8–3.0]).

Conclusions: In a largely primary-prevention population of people undergoing routine care, no differences were observed in MACE risk among initiators of SGLT2i and GLP1-RA. However, compared with GLP1RA, the use of SGLT2i was associated with an increased risk of ischemic stroke that was small in absolute magnitude.

1. Introduction

Type 2 diabetes mellitus (T2DM) affects more than 400 million individuals worldwide [1]. Cardiovascular disease is a major complication and remains the leading cause of morbidity and mortality in this population [2,3]. Preventing fatal and non-fatal cardiovascular events is therefore a major aim in the management of patients with T2DM.

Recently, large cardiovascular outcome trials and their systematic reviews and meta-analyses have shown that both glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce the risk of major adverse cardiovascular events (MACE) in patients with T2DM [4–12]. Consequently, clinical practice guidelines now recommend these two classes of drugs in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) or at high cardiovascular risk [13–19].

Although randomized controlled trials found that both drug classes are efficacious compared with placebo, their relative effectiveness remains uncertain. To date, no trial has performed a head-to-head comparison of both drug classes. Comparing results between existing SGLT2i and GLP1-RA trials is challenging since they included different populations, with different methodologies, assessment and adjudication practices. However, the mechanisms by which these two medication

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classes exert their benefits appear to be distinct based on the purported mechanisms of action and the different time course over which benefits are observed [10–12,20,21].

In the absence of head-to-head randomized comparisons from large, adequately-powered trials, routinely collected healthcare data can provide valuable evidence on the comparative effectiveness of these agents to guide decision making. In this study we compared cardiovascular outcomes between individuals initiating SGLT2i versus GLP1-RA in the health system of Stockholm, Sweden.

2. Methods

2.1. Data sources

We used data from the Stockholm CREAtinine Measurements (SCREAM) project, a healthcare utilization cohort including all adult residents in Stockholm between 2006 and 2019 [22]. The region of Stockholm had a population of 2.3 million citizens in 2019 and provides universal healthcare with a single unified health-system. Administrative databases with complete information on demographic data, healthcare use, diagnoses and therapeutic/surgical procedures, and vital status were enriched with performed laboratory tests, dispensed prescriptions at Swedish pharmacies and validated kidney replacement therapy endpoints. Registries were linked and de-identified by the Swedish National Board of Welfare and are considered to have no or minimal loss to follow-up. Because the study utilized de-identified data, it was deemed not to require informed consent and was approved by the regional ethical review boards and the Swedish National Board of Welfare.

2.2. Study design

This observational cohort study consisted of all adult (>18 years old) community-dwelling individuals with type 2 diabetes from Stockholm who newly initiated therapy with SGLT2i or GLP1-RA between January 1, 2013 and December 31, 2019. New initiation was defined as a first dispensation for SGLT2i or GLP1-RA, with no previous dispensation of either drug in their records. The date of initiation was defined as the cohort entry date and start of follow-up (T_0). Patients were followed from index date to the first occurrence of a study outcome, death, emigration or end of follow-up (December 31, 2019). An overview of the longitudinal study design is presented in Supplemental Fig. S1. Patients were excluded if they had a diagnosis of type 1 or gestational diabetes, had a history of dialysis or kidney transplantation, had no specialist care contact or prescription drug dispensation in the last year, had a hospitalization in the 30 days before cohort entry for acute myocardial infarction, unstable angina, ischemic or hemorrhagic stroke, transient ischemic attack or heart failure, or if they had end stage illness (i.e. coma, malnutrition, dementia), drug misuse or severe pancreatic disorder (Supplemental Table S1).

2.3. Exposures and covariates

The study exposure was initiation or SGLT2i or GLP1-RA. Baseline covariates included sociodemographic characteristics, laboratory measurements, comorbidities, diabetes drugs, other medications and healthcare utilization in the preceding year (definitions in Supplemental Table S2). Comorbidities identified in this study used established algorithms with an 85–95% sensitivity or positive predictive value [23]. We only used laboratory measurements from the ambulatory setting. Estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI equation without correction for race using routine plasma creatinine measurements, all of which were performed by enzymatic or corrected Jaffe methods traceable to isotope dilution mass spectroscopy standards.

2.4. Outcomes

The primary outcome was MACE, which was defined as a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal ischemic stroke. Secondary outcomes included hospitalization for heart failure and the individual components of MACE. Supplemental Table S3 shows the ICD-10 codes used to define these outcomes.

2.5. Statistical analyses

Continuous variables are presented as mean with standard deviation or median with interquartile range (IQR), depending on the distribution, and categorical variables as percentages. Given that individuals prescribed SGLT2i or GLP1-RA have different characteristics, propensity score overlap weighting was used to address confounding [24]. In this method, each individual's weight is the probability of that individual being assigned to the opposite medication group [25]. This not only minimizes the influence of extreme propensity scores, but also gives the largest weight to individuals who are at clinical equipoise to receive both drugs, thereby mimicking the attributes of a pragmatic clinical trial that is highly inclusive [26]. By definition, overlap weighting leads to exact balance on the mean of every measured confounder (i.e., a standardized mean difference of 0). We estimated the probability of receiving SGLT2i versus GLP1-RA as a function of 57 baseline covariates (all variables reported in Table 1) including sociodemographic characteristics, laboratory measurements, comorbidities, diabetes drugs, other medications and healthcare utilization, using a multivariable logistic regression model.

For all outcomes, we calculated the number of events and incidence rates before weighting. To account for the fact that propensity score weighting was used, which reweights the original study population, we used robust variance estimation to calculate the confidence intervals [27]. Weighted Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals between SGLT2i versus GLP1-RA initiation and outcomes, with time since cohort entry as the time scale. In addition, weighted Kaplan-Meier plots of cumulative incidence were estimated to show absolute risks. Individuals were analyzed according to their initially assigned treatment group irrespective of discontinuation or treatment switch (intention-to-treat approach). Multiple imputation by chained equations was used to impute missing data for education (2.0%), eGFR (12.3%), glycated hemoglobin (HbA1c; 15.5%) and albumin-to-creatinine ratio (28.5%) [28,29]. The imputation model included the treatment variable, confounding variables, the censoring indicator of the composite primary outcome, the Nelson-Aalen estimate of the cumulative hazard, and interaction terms between treatment and confounders, producing 20 imputed datasets. Multiple imputation was combined with inverse probability treatment weighting using the *within* method. In the within method, effect estimates are obtained separately in each imputation using the propensity score, which are then combined to an overall estimate.

For the primary outcome, we performed subgroup analyses according to a priori defined strata: age (≥70 vs <70 years), sex, eGFR (≥60 vs <60 mL/min/1.73m^2), HbA1c (≥53 vs <53 mmol/mol), cardiovascular disease (defined as composite of acute coronary syndrome, ischemic heart disease, stroke, other cerebrovascular disease, heart failure and peripheral vascular disease), heart failure, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) use and metformin use. Subgroups according to insulin use and lipid-lowering therapy were added after reviewer request. To calculate the subgroup HRs, we separately estimated the propensity score model and Cox model for each subgroup. Multiplicative interaction was tested by including interaction terms between treatment and the variable of interest to the Cox model.

We performed two sensitivity analyses. First, we used inverse probability of treatment weighting instead of overlap weighting and repeated our analyses [30,31]. Second, after observing the results of our analyses,

Table 1
Baseline characteristics of patients initiating SGLT2i or GLP1-RA treatment between January 2013 and December 2019 in Stockholm before and after weighting.

	Before overlap weighting			After overlap weighting		
	SGLT2i	GLP1-RA	SMD[§‡]	SGLT2i	GLP1-RA	SMD[§]
Number of individuals	5489	6886		5489	6886	
Age, mean (SD), y	63 (11)	59 (13)	0.29	61 (12)	61 (12)	0.0
Age group, %						
<50 years	12.2	21.3	0.25	15.8	15.8	0.0
50–59	25.5	28.2	0.06	27.7	27.7	0.0
60–69	33.2	28.3	0.11	31.5	31.5	0.0
70–79	24.4	19.4	0.12	21.5	21.5	0.0
≥80	4.7	2.9	0.09	3.5	3.5	0.0
Women, %	33.8	42.6	0.18	37.6	37.6	0.0
eGFR, median (IQR), ml/min/1.73 m^2 *	90 [78, 100]	91 [75, 102]	0.04	91 [77, 101]	91 [77, 101]	0.0
eGFR category, %						
G1	49.6	52.4	0.06	52.3	52.3	0.0
G2	44.0	35.2	0.18	39.4	39.4	0.0
G3a	5.3	7.8	0.10	6.3	6.3	0.0
G3b	1.0	4.0	0.19	1.9	1.9	0.0
G4–5	0.1	0.6	0.08	0.1	0.1	0.0
HbA1c, median (IQR), mmol/mol*	59 [52, 69]	61 [53, 72]	0.11	60 [52, 69]	60 [52, 69]	0.0
ACR, median (IQR), mg/mmol	1.2 [0.6, 3.3]	1.4 [0.7, 3.9]	0.08	1.3 [0.6, 3.4]	1.3 [0.6, 3.4]	0.0
ACR category, %						
A1 (<3 mg/mmol)	72.4	68.9	0.08	71.5	71.5	0.0
A2 (3–30)	24.1	25.6	0.03	24.5	24.5	0.0
A3 (>30)	3.5	5.5	0.10	4.0	4.0	0.0
Medical history, %						
Cardiovascular disease[†]	26.7	19.3	0.18	22.1	22.1	0.0
Acute coronary syndrome	13.7	7.6	0.20	9.9	9.9	0.0
Other ischemic heart disease	21.3	13.9	0.20	16.7	16.7	0.0
Hypertension	69.4	69.1	0.01	69.3	69.3	0.0
Diabetic complications	41.9	42.6	0.01	41.5	41.5	0.0
Heart failure	9.3	7.6	0.06	7.9	7.9	0.0
Valve disorders	2.0	1.8	0.02	1.8	1.8	0.0
Stroke	5.8	4.7	0.05	5.0	5.0	0.0
Other cerebrovascular disease	5.9	4.7	0.05	5.0	5.0	0.0
Atrial fibrillation	9.3	7.8	0.05	8.5	8.5	0.0
Other arrhythmia	7.6	5.8	0.07	6.6	6.6	0.0
Peripheral vascular disease	4.1	2.9	0.06	3.3	3.3	0.0
Coronary revascularization	13.6	7.5	0.20	9.8	9.8	0.0
Chronic obstructive pulmonary disease	6.0	6.5	0.02	6.3	6.3	0.0
Other lung disease	14.9	18.3	0.09	16.4	16.4	0.0
Venous thromboembolism	4.6	5.3	0.03	4.9	4.9	0.0
Cancer in previous year	3.3	3.2	0.01	3.2	3.2	0.0
Liver disease	4.6	5.3	0.03	5.0	5.0	0.0
Fracture in previous year	1.9	2.1	0.01	2.0	2.0	0.0
Hospital admissions in previous year, %						
Cardiovascular causes	6.0	4.0	0.09	4.7	4.7	0.0
Type-2-diabetes-related causes	0.6	1.9	0.11	0.9	0.9	0.0
Non-cardiovascular/type 2 diabetes related causes	63.9	68.1	0.09	65.4	65.4	0.0
Outpatient contacts in previous year, %						
Cardiovascular causes	12.8	10.1	0.08	11.0	11.0	0.0
Type 2 diabetes related causes	14.7	21.3	0.17	16.6	16.6	0.0
Other causes	98.3	98.5	0.02	98.3	98.3	0.0
Drugs for diabetes in previous 6 months, %						
None	10.5	15.6	0.15	12.6	12.6	0.0
Metformin	77.8	69.6	0.19	74.9	74.9	0.0
Sulfonylureas	24.0	19.5	0.11	22.1	22.1	0.0
Dipeptidyl peptidase-4 inhibitor	19.3	14.8	0.12	17.2	17.2	0.0
Insulin	17.6	36.7	0.44	24.6	24.6	0.0
Other drugs for diabetes (glitazones, glinides, acarbose)	3.0	3.1	0.01	3.1	3.1	0.0
Time since first-ever diabetes drug, %						
<1 year	15.2	19.9	0.12	17.1	17.1	0.0
1–3 years	13.4	14.4	0.03	14.4	14.4	0.0
>3–5 years	13.1	13.2	0.00	13.7	13.7	0.0
>5–7 years	14.0	12.1	0.06	13.3	13.3	0.0
>7 years	44.3	40.3	0.08	41.6	41.6	0.0
Concomitant medications, %						
Beta blocker	38.7	35.3	0.07	36.4	36.4	0.0
Calcium channel blocker	30.8	31.2	0.01	31.2	31.2	0.0
Diuretic	16.9	20.4	0.09	17.9	17.9	0.0
ACEi/ARB	64.4	63.5	0.02	64.1	64.1	0.0
Lipid-lowering drug	63.2	55.9	0.15	59.8	59.8	0.0
Digoxin	1.9	1.5	0.03	1.6	1.6	0.0
Nitrate	7.8	5.7	0.09	6.4	6.4	0.0
Antiplatelet	29.2	22.2	0.16	24.9	24.9	0.0
Anticoagulant	8.9	7.6	0.05	8.1	8.1	0.0
β-2 agonist inhalant	6.9	8.3	0.05	7.5	7.5	0.0
Anticholinergic inhalant	2.6	3.2	0.04	2.9	2.9	0.0
Glucocorticoid inhalant	8.3	10.1	0.06	9.4	9.4	0.0
Oral glucocorticoid	5.5	6.2	0.03	5.7	5.7	0.0
NSAID	14.2	16.7	0.07	15.6	15.6	0.0
Opioid	10.3	13.7	0.11	11.5	11.5	0.0
No of prescription drugs in previous year, %						
0–5	14.7	12.9	0.05	14.2	14.2	0.0
6–10	41.3	36.3	0.10	39.3	39.3	0.0
11–15	25.3	28.3	0.07	26.7	26.7	0.0
>15	18.8	22.5	0.09	19.9	19.9	0.0
Calendar year, %						
2013	1.1	4.0	0.18	1.8	1.8	0.0
2014	3.2	5.9	0.13	4.1	4.1	0.0
2015	5.9	9.7	0.14	7.4	7.4	0.0
2016	10.0	11.7	0.05	11.0	11.0	0.0
2017	14.8	16.1	0.04	15.7	15.7	0.0
2018	28.8	23.3	0.13	26.4	26.4	0.0

(continued on next page)

Table 1 (*continued*)

	Before overlap weighting			After overlap weighting		
	SGLT2i	GLP1-RA	SMD[§‡]	SGLT2i	GLP1-RA	SMD[§]
2019	36.1	29.5	0.14	33.6	33.6	0.0
Education,* %						
Compulsory school	25.2	22.1	0.07	23.5	23.5	0.0
Secondary school	43.8	45.5	0.03	44.8	44.8	0.0
University	31.0	32.4	0.03	31.7	31.7	0.0

SMD = standardized mean difference; SD = standard deviation; y = year; eGFR = estimated glomerular filtration rate; IQR = interquartile range; ACEi = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; NSAID = nonsteroidal anti-inflammatory drug; ACR = albumin-to-creatinine ratio.

* eGFR, HbA1c, education and ACR were missing in 12.3%, 15.5%, 2.0%, and 28.5% respectively. Inverse probability weighting was performed after imputation. Baseline characteristics are shown after imputation and weighting.

† Cardiovascular disease was defined as a composite of acute coronary syndrome, ischemic heart disease, stroke, other cerebrovascular disease, heart failure, and peripheral vascular disease.

§ A standardized difference > 0.1 indicates meaningful imbalance between groups.

‡ Standardized difference for the mean was calculated for age, eGFR, HbA1c and ACR.

we calculated an *E*-value for the outcome ischemic stroke to explore the magnitude of confounding needed to fully explain away the observed treatment-outcome association [32].

2.6. Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study.

3. Results

3.1. Baseline characteristics

In total, we included 12,375 individuals who fulfilled all eligibility criteria, of which 5489 initiated an SGLT2i and 6886 a GLP1-RA (Supplemental Fig. S2). Baseline characteristics before and after weighting are reported in Table 1. After propensity score overlap weighting, the two groups were balanced on all measured covariates. Mean (SD) age in the weighted population was 61 [12] years and 38% were women (Table 1). Median (IQR) eGFR was 91 (77–101) ml/min/1.73m^2, median (IQR) HbA1c was 60 (52–69) mmol/mol and median (IQR) ACR was 1.3 (0.6–3.4) mg/mmol. Furthermore, 69% of individuals had a diagnosis of hypertension and 22% had a history of cardiovascular disease. The most commonly used concomitant medications were metformin (75%), ACEi/ARB (64%), lipid-lowering drugs (60%) and β-blockers (36%).

The majority of individuals in the SGLT2i arm initiated empagliflozin (66.8%) and dapagliflozin (32.6%). In the GLP1-RA arm, the majority initiated liraglutide (85.8%), whereas the use of dulaglutide (7.3%) and semaglutide (4.3%) was low.

3.2. Comparative effectiveness of SGLT2i vs. GLP1-RA initiation on cardiovascular outcomes

The propensity score distributions stratified by treatment initiation before and after overlap weighting are shown in Supplemental Fig. S3, which illustrates that individuals for whom there was clinical equipoise received the most weight. During a median (IQR) follow-up time of 1.6 (0.7–2.9) years, the primary outcome of MACE occurred in 155 individuals of the SGLT2i arm and 211 individuals of the GLP1-RA arm, corresponding with incidence rates (95% CI) of 16.4 (13.9–19.2) and 14.1 (12.3–16.1) events per 1000 person years, respectively (Table 2). The adjusted HR (95% CI) for the primary outcome was 1.04 (0.83–1.31) for SGLT2i vs. GLP1-RA. The weighted cumulative incidence curve is depicted in Fig. 1A. At 5 years, the absolute risk was 8.0% (95% CI; 5.4%–10.5%) for the SGLT2i arm and 7.4% (95% CI; 4.8%–10.0%) for the GLP1-RA arm, corresponding to a risk difference of 0.6% (95% CI; −1.3% to 2.4%).

The adjusted HRs (95% CI) were 0.80 (0.59–1.09) for heart failure hospitalization, 0.95 (0.58–1.55) for cardiovascular death and 0.91 (0.67–1.24) for myocardial infarction for SGLT2i vs. GLP1-RA. An increased risk of ischemic stroke was observed for SGLT2i compared with GLP1-RA, with an adjusted HR of 1.71 (1.14–2.59) (Table 2; Fig. 1B). Absolute risks and risk differences for all secondary outcomes are reported in Supplemental Table S4 and weighted Kaplan Meier curves in Supplemental Fig. S4.

3.3. Subgroup and sensitivity analyses

No significant interactions were observed across subgroups of age, sex, eGFR, HbA1c, heart failure, use of ACEi/ARB, use of insulin or lipid-lowering therapy. There was neither suggestion of heterogeneity across presence/absence of prior cardiovascular disease, with an adjusted HR of 1.11 (0.81–1.51) for SGLT2i versus GLP1-RA in patients without and 1.08 (0.77–1.51) in patients with cardiovascular disease (*p*-value for interaction 0.9). There was a trend towards increased MACE risk for SGLT2i compared with GLP1-RA in individuals who did not use metformin (adjusted HR 1.52; 95% CI 0.98–2.35) (Supplemental Table S5). When using inverse probability of treatment weighting to adjust for confounding, we obtained results consistent with our primary analysis of no difference in MACE risk (adjusted HR 1.08; 95% CI 0.85–1.38) but a higher ischemic stroke risk (adjusted HR 1.85; 95% CI 1.20–2.85) among new users of SGLT2i versus GLP1-RA (Supplemental Table S6). The *E*-value for ischemic stroke was 2.81 for the point estimate and 1.54 for the lower limit of the confidence interval, meaning that an unmeasured confounder would need to be associated with both the SGLT2i initiation and ischemic stroke by a risk ratio of 2.81 to bring the point estimate to 1.0, and a risk ratio of 1.54 to bring the lower confidence limit to 1.0.

4. Discussion

In this cohort study of individuals from routine clinical practice, we observed no differences in MACE risk between new users of SGLT2i and GLP1-RA. This was consistent across subgroups, including patients with or without cardiovascular disease. There was a non-significant tendency towards lower risk of heart failure hospitalization for SGLT2i users, and no difference in risk for cardiovascular death or myocardial infarction. We observed a significantly higher risk for ischemic stroke in the SGLT2i group compared with GLP1-RA. However, the absolute risk difference for stroke was small.

Although no randomized controlled trials have performed a head-to-head comparison of these two medication classes, our observations do agree with indirect evidence. In meta-analyses of GLP1-RA versus placebo [10] and SGLT2i versus placebo [11,12], similar reductions in MACE risk were found, with a pooled HR of 0.88 (95% CI 0.82–0.94) for GLP1-RA and 0.89 (95% CI 0.83–0.96) for SGLT2i. Although cardiovascular death and myocardial infarction were lowered to the same magnitude for both medication classes [10–12], a reduction of stroke was observed for only GLP1-RA [10–12]. Conversely, the effect on heart failure was greater in trials of SGLT2i than in trials of GLP1-RA [10–12]. A recently published network meta-analysis of 764 randomized trials found that there were no differences for SGLT2i versus GLP1-RA for cardiovascular death or nonfatal myocardial infarction. However, odds ratios were higher for nonfatal stroke (OR 1.20; 95% CI 1.03–1.41), and lower for heart failure hospitalization (OR 0.74; 95% CI 0.65–0.85)

Table 2
Number of events, incidence rates and adjusted hazard ratios for the association between SGLT2i vs. GLP1-RA initiation and cardiovascular outcomes.

	SGLT2 inhibitors		GLP1-RA		
Outcome	Events*	Events per 1000 person years*	Events*	Events per 1000 person years*	Adjusted Hazard Ratio (95% CI)†
Primary outcome					
MACE	155	16.4 (13.9–19.2)	211	14.1 (12.3–16.1)	1.04 (0.83–1.31)
Secondary outcomes					
HF hospitalization	74	7.7 (6.1–9.7)	143	9.5 (8–11.2)	0.80 (0.59–1.09)
Cardiovascular death	31	3.2 (2.2–4.6)	51	3.4 (2.5–4.4)	0.95 (0.58–1.55)
Myocardial infarction	81	8.5 (6.7–10.6)	119	7.9 (6.6–9.5)	0.91 (0.67–1.24)
Ischemic stroke	61	6.4 (4.9–8.2)	49	3.2 (2.4–4.3)	1.71 (1.14–2.59)

CI = confidence interval; MACE = major adverse cardiovascular events (composite cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke); CV = cardiovascular; HF = heart failure; SGLT2i = sodium glucose cotransporter 2 inhibitor; GLP1-RA = glucagon-like peptide receptor agonist.
* Number of events, person years and incidence rates were calculated in the original, unweighted population.
† Analyses were adjusted for all variables mentioned in Table 1.

[33]. This was graded with high certainty evidence for patients at low (i.e., T2DM with cardiovascular risk factors) to very high risk (T2DM with established cardiovascular disease or chronic kidney disease) [33].

Our study provides a direct head-to-head comparison of two efficacious medication classes in a heterogeneous population not well represented in the pivotal trials: the proportion of individuals in our study with established cardiovascular disease at baseline was 22%, which is lower than in any of the cardiovascular outcome trials, where it varied between 41 and 100% for SGLT2i trials [6,7,34,35] and 31–83% for GLP1-RA trials [4,5,8]. As such, the incidence rate for MACE was 16.4 per 1000 person years in the SGLT2i arm of our study compared with 22.6–39.0 in the SGLT2i trials [6,7,34,35], and 14.1 per 1000 person years in the GLP1-RA arm of our study compared with 23.5–34 in the GLP1-RA trials [4,5,8]. Interestingly, the benefits of both medication classes on MACE have been observed in trials among patients with established cardiovascular disease [10–12]. The null effect on MACE between SGLT2i and GLP1-RA in our study is compatible with both drugs having effects of similar magnitude, but also with the hypothesis that neither drug had an effect on MACE risk in this largely primary prevention sample. Although we found a relative increased ischemic stroke risk of 71%, we note that the absolute 5-year risk difference was only 1.9%, in part explained by the outcome being rare and the population included of predominantly low-risk.

A few observational studies have compared the effects of SGLT2i and GLP1-RA [36–39], with somewhat varying findings. An analysis of the Swedish Diabetes registry found a similar risk of MACE, cardiovascular death and myocardial infarction, but an increased risk of stroke for SGLT2i versus GLP1-RA [37], which aligns with our analysis. An Italian claims study, however, reported a significantly lower risk of MACE for SGLT2i compared with GLP1-RA, primarily due to a reduction in myocardial infarction, with no differences in stroke [38]. A recent US claims study among older adults found a similar MACE risk and reduced risk of hospitalization for heart failure for SGLT2i versus GLP1-RA over a median follow-up of 6 months [39], with no difference in ischemic or hemorrhagic stroke. Another study by the same authors in a larger population found similar results, with no differences in MACE between SGLT2i and GLP1-RA initiation. Furthermore, they observed consistent reductions in heart failure and no large differences in risk for myocardial infarction or stroke regardless of presence or absence of cardiovascular disease [40]. Finally, a Danish registry-based study found no differences between empagliflozin and liraglutide with respect to expanded MACE, heart failure hospitalization or all-cause mortality [41]. While there are multiple differences between the studies including those of population and health setting, the variation in results generates hypotheses on potential differences in the effects of the individual agents. It is important to note that the US study predominantly compared individuals initiating canagliflozin (77%) versus liraglutide (59%). In our study, the majority of individuals in the SGLT2i arm (99%) initiated empagliflozin and dapagliflozin, and the majority in the GLP1-RA arm initiated liraglutide (86%), with smaller proportions initiating dulaglutide and semaglutide (together 11%). Future studies should clarify whether the discrepancies observed for stroke risk between these studies could be related to differences in individual agents studied, differences in confounding adjustment, duration of follow-up or a chance finding.

Strengths of our study include wide adjustment for confounders, including laboratory values such as eGFR, glycated hemoglobin levels and albuminuria, which were not available in previous studies using purely administrative databases [38]. In addition, we applied overlap weighting to emphasize the population at clinical equipoise who could have received both medications. Our study also has limitations. Since our study had a relatively small sample size and the population was at low risk of cardiovascular outcomes, the number of events were low, and our results were imprecise with wide confidence intervals, and, for heart failure the conventional threshold of statistical significance ($p < 0.05$) was not reached. We were therefore not able to separately assess the comparative effectiveness of both agents on nonfatal or fatal myocardial infarction and stroke separately. However, our results are very much in line with findings from previous trials. Finally, there was not enough diversity to investigate potential differences in individual agents between classes and the duration of follow-up was relatively short, neither did our study investigate the comparative safety of both agents.

In conclusion, our study of individuals undergoing routine clinical care at low risk for cardiovascular events, showed similar effectiveness between users of SGLT2i and GLP1-RA for various cardiovascular outcomes, including MACE, myocardial infarction and cardiovascular death. However, use of SGLT2i was associated with higher ischemic stroke risk compared to GLP1-RA.

Authors' contributions

ELF, MJJ and JJC initiated the study. ELF and JJC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ELF drafted the manuscript and performed the statistical analysis. All authors contributed to the design of the study; the acquisition, analysis and interpretation of data; and to the critical revision of the manuscript for important intellectual content. ELF and JJC are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CRediT authorship contribution statement

Edouard L. Fu: Conceptualization, Methodology, Software, Formal

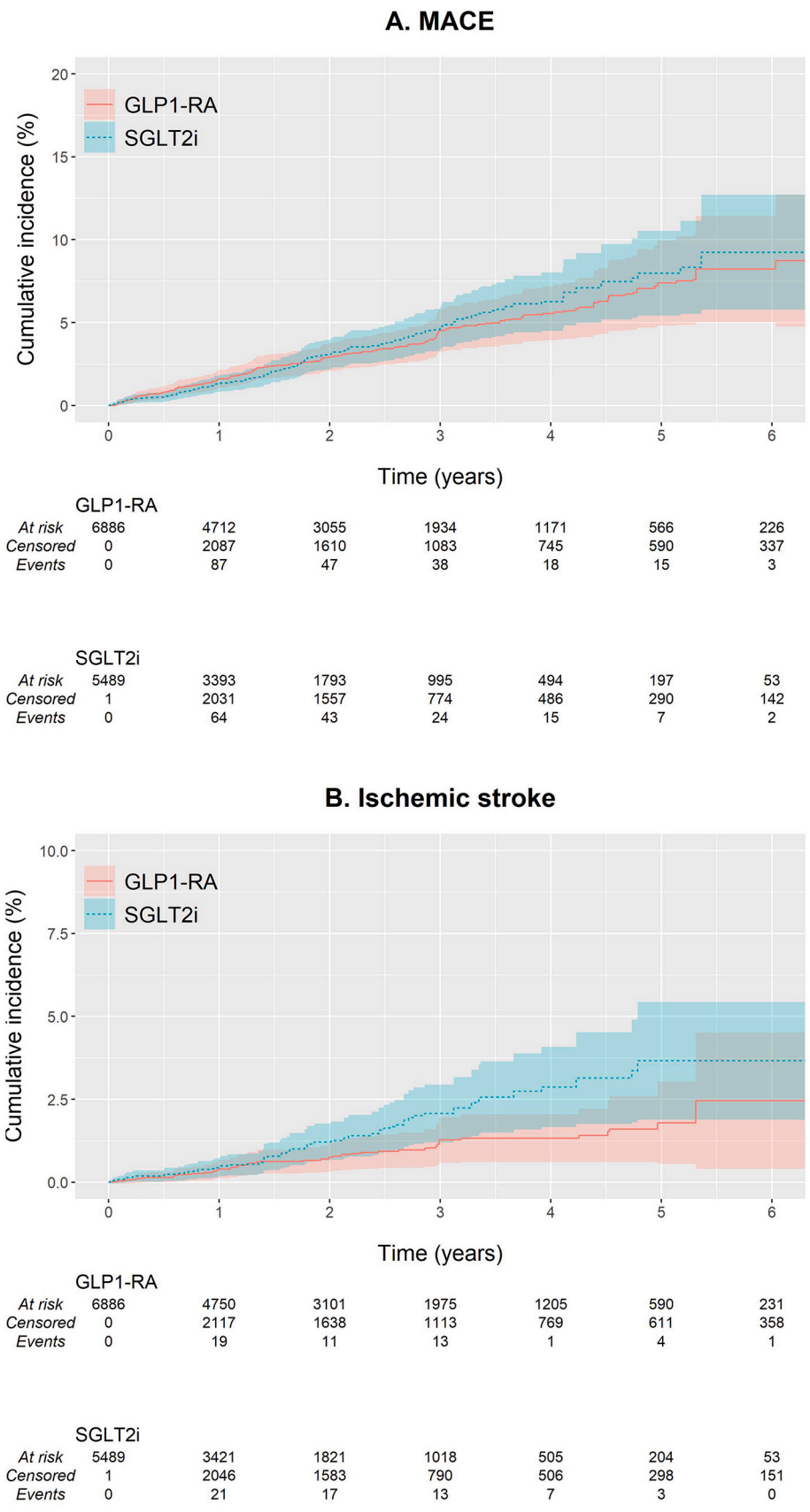

Fig. 1. Weighted cumulative incidence curves for MACE (A) and ischemic stroke (B) stratified by SGLT2i or GLP1-RA initiation.
MACE = major adverse cardiovascular events (composite cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke); SGLT2i = sodium glucose cotransporter 2 inhibitor; GLP1-RA = glucagon-like peptide receptor agonist.

analysis, Investigation, Writing – original draft. **Catherine M. Clase:** Investigation, Writing – review & editing. **Roemer J. Janse:** Investigation, Writing – review & editing. **Bengt Lindholm:** Investigation, Writing – review & editing. **Friedo W. Dekker:** Investigation, Writing – review & editing. **Meg J. Jardine:** Investigation, Conceptualization, Writing – review & editing. **Juan-Jesus Carrero:** Conceptualization, Resources, Investigation, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.01.042.

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