Diabetes Epidemiology and Management 13 (2024) 100179

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Review

Similar incidence of stroke with SGLT2 inhibitors and GLP-1 receptor agonists in real-world cohort studies among patients with type 2 diabetes

André J. Scheen[a,b]

[a] Division of Clinical Pharmacology, Centre for Interdisciplinary Research on Medicines (CIRM), Liège University, Liège, Belgium
[b] Division of Diabetes, Nutrition and Metabolic Disorders, CHU Liège, Liège, Belgium

ARTICLE INFO

Article History:
Received 17 August 2023
Accepted 11 September 2023
Available online 21 September 2023

Keywords:
GLP-1 receptor agonist
Observational cohort study
Meta-analysis
Real-world evidence
SGLT2 inhibitor
Stroke

ABSTRACT

Background: Stroke represents a major burden in patients with type 2 diabetes. Yet, this cerebrovascular complication has been less well studied than coronary artery disease and heart failure. Some cardiovascular outcome data suggested that sodium-glucose cotransporter 2 inhibitors (SGLT2is) exert a less pronounced protection against stroke compared with glucagon peptide-1 receptor agonists (GLP-1RAs) despite similar efficacy regarding major cardiovascular events (MACE-3 points). However, this conclusion was derived from indirect comparisons of placebo- controlled trials (RCTs).
Methods: The present comprehensive review analyses the effects of SGLT2is versus GLP-1RAs on nonfatal and fatal/nonfatal strokes in real-life studies carried out worldwide.
Results: A large majority of retrospective observational cohort studies (19 out of 21) failed to find any significant difference in the risk of stroke between the two pharmacological classes, independently of the presence of established cardiovascular disease. Available, yet limited, findings suggested that SGLT2is could be more efficacious against haemorrhagic than ischaemic strokes, in patients at risk for atrial fibrillation or with chronic kidney disease.
Conclusion: In contrast to what was reported in RCTs, most observational studies showed similar incidence of stroke in SGLT2i users versus GLP-1RA users. Because both indirect comparisons of RCTs and retrospective cohort studies have limitations, a head-to-head RCT comparing the effects on stroke of an SGLT2i versus a GLP-1RA is needed to draw any definite conclusion.

Introduction

People with type 2 diabetes mellitus (T2DM) have an almost two-fold higher risk of stroke compared with people without diabetes [1]. Moreover, individuals with T2DM have poorer post-stroke outcomes and higher risk of stroke recurrence than those without diabetes [2]. Overall, stroke is a major cause of long-term disability and premature death among patients with T2DM [1–4]. The increase in the frequency of stroke is due to an increase in cerebral infarction, mainly lacunar infarcts, with the incidence of cerebral hemorrhage being less frequent [4]. In a meta-analysis of 27 studies, diabetes is an independent risk factor for stroke recurrence among patients with ischaemic stroke (pooled hazard ratio around 1.5 versus individuals without diabetes [2]. Another meta-analysis of 39 studies estimated the prevalence of diabetes to be 28 % among people with stroke, with a higher rate in ischaemic (33 %) compared with haemorrhagic strokes (26 %) [5].

Stroke prevention requires a global approach targeting all risk factors, i.e. hypertension, arrythmias (especially atrial fibrillation), dyslipidaemia, smoking, obesity and hyperglycaemia [6]. Of potential interest, some antidiabetic drugs have shown a protective effect against stroke, independently of glucose control, especially pioglitazone, a thiazolidinedione [7,8], and glucagon-like peptide 1 receptor agonists (GLP-1RAs) [9].

Evidence derived from randomised controlled trials (RCTs), especially cardiovascular outcome trials (CVOTs), suggested a superiority of GLP-1RAs over sodium-glucose cotransporter 2 inhibitors (SGLT2is) in reducing ischaemic stroke [1,10-12]. This specific difference regarding stroke contrasted with the equivalence between the two pharmacological classes for the reduction in the composite cardiovascular outcome MACE-3 points (major cardiovascular adverse events, i.e. cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke) and the clear-cut superiority of SGLT2is over GLP-1RAs in reducing hospitalization for heart failure [13,14]. Of note, however, there are no head-to-head CVOTs that compared SGLT2is versus GLP-1RAs and the conclusion of a better protection against stroke with GLP-1RAs compared with SGLT2is

E-mail address: andre.scheen@chu.ulg.ac.be

https://doi.org/10.1016/j.deman.2023.100179

emerged from indirect comparisons of the results of placebo-controlled CVOTs with each pharmacological class [15].

Despite the results of several meta-analyses of RCTs that showed neutral effects of SGLT2is versus placebo contrasting with the significant reduction in stroke events with GLP-1RAs (see recent review in [16]), whether SGLT2is play a role in preventing stroke and cerebrovascular disease is still a matter of debate [17]. Indeed, observational cohort studies reported more favourable results with SGLT2i therapy, which was associated with a significant reduction in the risk of stroke compared with dipeptidyl peptidase-4 inhibitors (DPP-4is) and other glucose-lowering agents [18–20]. Furthermore, no significant differences between SGLT2is and GLP-1RAs were reported in meta-analyses of studies carried out in real-life conditions regarding the protection against fatal/nonfatal strokes, yet only a limited number of retrospective cohorts was considered [21–24]. Nevertheless, a clinical practice guideline concluded that high certainty evidence demonstrated potentially important benefits of GLP-1RAs over SGLT2is on non-fatal stroke [25] and neurologists prioritized the use of GLP-1RAs [26].

The present comprehensive review compares the effects of SGLT2is and GLP-1RAs on the occurrence of stroke (fatal, nonfatal and both) in patients with T2DM using results from a larger number of worldwide retrospective observational cohort studies. The main objective is to verify whether the lower protection against stroke observed with SGLT2is versus GLP-1RAs derived from indirect comparison in placebo-controlled RCTs translates in real-life conditions.

Methods

Literature search

We searched PubMed, EMBASE and the Cochrane Database of Systematic Reviews to identify English-language studies published between 1 January 2015 and up 15 August 2023. The search was limited to studies evaluating the efficacy of GLP-1RAs or SGLT2is on cardiovascular outcomes in adult patients with or without T2DM in observational cohort studies. The terms used for the research were “GLP-1 receptor agonists” (including each individual compound of this pharmacological family) OR “SGLT2 inhibitors” (including each individual compound of this family), combined with “major cardiovascular adverse event” (“MACE”) OR “stroke” and also combined with “observational study” OR “real-life cohort”. The search was filtered to include observational cohort studies with data on stroke in patients with T2DM treated with SGLT2is versus GLP-1RAs, with studies restricted to at least 500 patients per arm to guarantee enough statistical power. The reference lists of previously published systematic reviews and meta-analyses were also scrutinized to identify any further reports of potential interest, especially meta-analyses that compared the incidence of stroke with SGLT2is compared with any other glucose-lowering drug in real-life practice.

Outcomes

This review is focusing on the effects of either SGLT2is or GLP-1RAs on the incidence of strokes. A minority of studies reported data on both fatal and nonfatal strokes (“all strokes”) and very few made the distinction between ischaemic (including transient ischaemic attack [TIA]) and haemorrhagic strokes.

Statistical analysis

Results are presented as hazard ratio (HR) or odds ratio (OR) with 95 % confidence interval (CI) comparing the incidence of stroke in patients with T2DM treated with either an SGLT2i or a GLP-1RA in selected meta-analyses of cohort studies and a collection of individual retrospective observational studies. To mitigate possible selection bias, most observational studies compared the two treatment cohorts using either propensity score matching or inverse probability of treatment weighting approaches.

Results

Table 1 summarizes results from previous meta-analyses of observational studies that compared the efficacy of SGLT2is versus other glucose-lowering drugs, DPP4-is and GLP-1RAs. SGLT2is showed a significant reduction in the incidence of strokes compared with other glucose-lowering drugs (−13 % to −25 %) [18-20,27] and DPP-4is (−11 % to −16 %) [18,20]. In contrast, no significant differences were reported when comparing the incidence of stroke among SGLT2i-users and GLP-1 RA users (−1 to + 14 %) [20–22], except in one meta-analysis of eleven observational studies that reported a borderline significant increase in the risk of stroke among SGLT2i users versus GLP-1RA users (+ 10 %, $P = 0.04$) [23].

After a careful screening of the international literature, 21 retrospective observational cohort studies were identified, which reported detailed data about the risk of stroke in patients treated with either an SGLT2i or a GLP-1RA in real life conditions [28–49] (Table 2). They were performed in different countries, in United States of America, Europe and Asia. The average follow-up ranged between 0.4 and 4.3 years. All studies compared any type of SGLT2is versus any type of GLP-1RAs, except two studies that compared more specifically canagliflozin versus GLP-1RAs [29] or empagliflozin versus liraglutide

Table 1
Effects of SGLT2is compared to a variety of antihyperglycaemic medications on the risk of stroke in previously published meta-analyses of observational studies.

References	Number of cohorts	Type of Stroke	N SGLT2i/others	Odds ratio (95 % CI)	P value
SGLT2 inhibitors versus other glucose-lowering drugs					
Mascolo et al. 2021 [18]	5	Nonfatal	383,676/450,482	0.83 (0.77–0.91)	NA
Li et al. 2021 [27]	10	All	Total 1039,500	0.75 (0.72–0.78) (*)	< 0.001
Zhang et al. 2022 [20]	11	All	478,968/578,594	0.87 (0.80–0.95)	< 0.001
SGLT2 inhibitors versus DPP-4 inhibitors					
Mascolo et al. 2021 [18]	6	Nonfatal	267,398/311,073	0.89 (0.82–0.96)	NA
Zhang et al. 2022 [20]	11	All	631,475/675,150	0.84 (0.79–0.89)	NA
SGLT2 inhibitors versus GLP-1 receptor agonists					
Qiu et al. 2021 [22]	7	All	93,710/94,935	1.02 (0.94–1.11)	0.65
Caruso et al. 2022 [21]	5	All	211,088/206,269	0.99 (0.91–1.08)	0.84
Du et al. 2022 [23]	14	All	420,389/382,883	1.10 (1.01–1.19)	0.04
Zhang et al. 2022 [20]	3	All	36,934/34,521	1.14 (0.87–1.51)	NA

(*) With cardiovascular disease : odds ratio : 0.76 (0.73–0.80); without cardiovascular disease : odds ratio : 0.68 (0.62–0.75)
CI : confidence interval. NA : not available.

Table 2
Comparison of stroke outcomes in people with T2DM treated with an SGLT2i versus a GLP-1RA in observational studies. Results are expressed as hazard ratio (95 % confidence interval) with all SGLT2is versus all GLP-1RAs except otherwise mentioned.

Reference	Country	Follow-up (years)	Stroke outcome	Cohort adjustment	N SGLT2i/GLP-1RA	Hazard ratio (95% CI)
O'Brien et al. 2018 [28]	US	1.3	Hospitalization for strokes	Adjustment for covariates	5677/11,351	0.86 (NA) [a]
Patorno et al. 2018 [29]	US (canagliflozin versus all GLP-1RAs)	0.6	Hospitalization for ischaemic strokes	1:1 PSM	20,539/20,539	1.01 (0.77–1.32)
Longato et al. 2020 [30]	Italy	1.1	First occurrence of any stroke	1:1 PSM	4298/4298	0.90 (0.57–1.41) [b]
Pineda et al. 2020 [31]	US	0.8/07	Hospitalization for strokes	1:1 PSM	947/947	0.87 (0.38–1.97)
Deremer et al. 2021 [32]	US	0.7/0.5	First occurrence of strokes	Adjusment for covariates	7082/4829	1.08 (0.67–1.75)
Lugner et al. 2021 [33]	Sweden	1.1/1.7	First hospitalization for fatal/nonfatal strokes	PSM	12,097/9684	1.44 (0.99–2.08)
Patorno et al. 2021 [34]	US	0.6	Hospitalization for ischaemic or hemorrhagic strokes	1:1 PSM	186,040/186,040	0.98 (0.88–1.09) [c]
Patorno et al. 2021 [35]	US	8.5	Hospitalization for ischaemic or hemorrhagic strokes	1:1 PSM	45,047/45,047	1.04 (0.86–1.27) [d]
Hsiao et al. 2021 [36]	Taiwan	1.4	Ischaemic strokes	IPTW	19,101/3087	1.37 (1.10–1.70)
Poonawalla et al. 2021 [37]	US	1.0	All strokes	1:1 PSM	5507/5507	NA [e]
Ueda et al. 2022 [38]	Scandinavia	1.6/2.2	All strokes	IPTW	87,525/63,921	1.16 (0.97–1.37)
Norgaard et al. 2022 [39]	Denmark	4.3	Nonfatal strokes	Adjustment for covariates	5275/8913	NA [f]
Baviera et al. 2022 [40]	Italy	2.8	Hospitalization for strokes	1:1 PSM	20,762/20,762	NA [g]
Htoo et al. 2022 [41]	US (empagliflozin versus liraglutide)	0.4	Ischaemic or haemorrhagic strokes	1:1 PSM	22,894/22,894	1.08 (0.84–1.39) [d]
Dong et al. 2022 [42]	Taiwan	0.6	Total strokes	PSM	26,032/26,032	1.11 (0.85–1.45) [h]
Lin et al. 2022 [43]	Taiwan	1.8/1.9	Non-fatal ischaemic strokes	4:1 PSM	81,152/ 20,288	1.08 (0.93–1.23)
Fu et al. 2022 [44]	Sweden	1.6	Ischaemic strokes	Propensity score overlap weighting	5489/6886	1.71 (1.14–2.59)
Lyu et al. 2022 [45]	US	1.3	Hospitalization for strokes	IPTW	2492/1982	1.37 (0.63–2.95)
Wright et al. 2022 [46]	England/Wales	3.3–4.0	Hospitalization for ischaemic (including tia) or haemorrhagic strokes	Adjustment for covariates	13,100/8971	0.94 (NA) [i]
Rathmann & Kostev 2022 [47]	Germany	4.9	Nonfatal strokes/TIA	Adjustment for covariates	35,338/ 21,282	NA [j]
Lui et al. 2023 [48]	Hong-Kong	1.4	All strokes	1:1 PSM	2920/2920	1.46 (0.99–2.17) [k]
Xie et al. 2023 [49]	US	3.8	All strokes	Overlap weighting approach	46,516/26,038	0.91 (0.82- 1.01) [l]

CI : confidence interval.
IPTW : inverse probability of treatment weighting.
NA : not available.
PSM : propensity score matching.
TIA : transient ischaemic attack.
[a] DPP-4is as reference : HR 0.56 (0.26–1.12) with SGLT2is versus HR 0.65 (0.44–0.97) with GLP-1RAs.
[b] Without CVD : HR 1.01 (0.54–1.90); with CVD : HR 0.79 (0.37–1.69).
[c] Without CVD : HR 0.96 (0.82–1.13); with CVD : HR 1.00 (0.87–1.15).
[d] Patients with T2DM older than 65 years.
[e] 16.1 % vs 15.6 %.
[f] Δ 0.1 % (−0.5 to 0.6).
[g] 0.6 % vs 0.6 % : without CVD : 1.01 (0.74–1.37); with CVD : HR 1.12 (0.75–1.67).
[h] Ischaemic stroke : 1.16 (0.88–1.54), haemorrhagic stroke : 1.14 (0.80–1.59).
[i] Estimated HR 0.94. Pooled data of three nested case-control studies : All strokes : HR 0.84 (0.72–0.98) with SGLT2is versus HR 0.89 (0.74–1.07) with GLP-1RAs.
[j] Using Cox regression, adjusted HR for stroke/transient ischaemic attack (per 1 year of treatment): 0.59 (0.54–0.64) for SGLT2is and 0.79 (0.74–0.85) for GLP-1RAs.
[k] Ischaemic stroke : 1.53 (1.01–2.33), haemorrhagic stroke : 1.29 (0.53–3.14).
[l] Pragmatic trial.

[41]. The range of evaluated patients was very broad and varied between 2492 and 186,040 in the SGLT2i cohort and between 1982 and 186,040 in the GLP-1RA cohort (except one study that recruited only 947 in both groups after propensity score matching) [31]. HR values when comparing the risk of all strokes with SGLT2is versus GLP-1RAs were around one in all studies (none of them showing statistically significant between-class differences), except in two cohort studies (one in Taiwan and one in Sweden) that focused on ischaemic strokes only [36,44]. Two other studies reported separated findings for ischaemic strokes versus haemorrhagic strokes in addition to all-type strokes : one reported non-significant difference between the two pharmacological classes whatever the type of stroke [42] whereas the other reported a borderline significant higher risk for ischaemic stroke but not for haemorrhagic strokes [46] when comparing SGLT2is versus GLP-1RAs. Four cohort studies reported separated data in patients with established cardiovascular disease (CVD) versus those without CVD and none of them showed significant differences regarding the risk of strokes between SGLT2is and GLP-1RAs whatever the subgroup considered (Table 3) [30,32,34,40]. Finally, two studies focused on older patients with T2DM (≥ 65 years) and found similar results in stroke incidence with SGLT2is versus GLP-1RAs (Table 2) [35,41].

Discussion

Different pieces of information collected in the present review suggested that when patients with T2DM were studied in real-life conditions SGLT2is were associated with a significant reduction in stroke events when compared with other glucose-lowering drugs, including DPP-4is, and with an almost similar risk of stroke events when compared with GLP-1RAs.

Table 3
Comparison of stroke outcomes with an SGLT2i versus a GLP-1RA in observational studies among patients with or without cardiovascular disease.Results are expressed as hazard ratio (95 % confidence interval).

Reference	Country	Follow-up (years)	Stroke outcome	N SGLT2i/GLP-1RA	Category	HR SGLT2is versus GLP-1RAs
Longato et al. 2020 [30]	Italy	1.1	First occurrence of any stroke	4298/4298	All patients	0.90 (0.57−1.41)
				786/759	With CVD	0.79 (0.37−1.69)
				3512/3539	Without CVD	1.01 (0.54−1.90)
Patorno et al. 2021 [34]	US	0.6	Hospitalization for ischaemic or haemorrhagic stroke	186,040/186,040	All patients	0.98 (0.88−1.09)
				52,901/52,901	With CVD	1.00 (0.87−1.15)
				133,139/133,139	Without CVD	0.96 (0.82−1.13)
Deremer et al. 2021 [32]	US	0.7/0.5	Any stroke	7706/5300	All patients with CVD	NA
				624/471		0.85 (0.50−1.70)
				7082/4829	Without CVD	1.08 (0.67−1.75)
Baviera et al. 2022 [40]	Italy	2.8	Hospitalization for stroke	20,762/20,762	All patients	1.04 (0.83−1.33)
				2660/2659	With CVD	1.12 (0.75−1.67)
				18,102/18,103	Without CVD	1.01 (0.74−1.37)

CVD : cardiovascular disease. NA : not available.

The favourable effects of SGLT2is on the incidence of strokes reported in meta-analyses that compared SGLT2is with other glucose-lowering drugs [18-20,27] or with DPP-4is [18,20] (Table 1) were confirmed in two large multinational observational studies, one that compared SGLT2is with other glucose-lowering drugs (CVD REAL, 13 countries across three continents, 440,599 in both treatment groups after propensity-score matching: HR 0.78, 95 % CI 0.72−0.85) [50] and one that compared the SGLT2i empagliflozin with DPP-4is (EMPRISE, "EMPagliflozin compaRative effectIveness and SafEty", 11 countries in Europe and Asia, 83,946 in both treatment groups after propensity-score matching: HR 0.83, 95 % CI 0.73−0.95) [51]. Of note, in a real-world study performed in Korea, the risk of stroke was similar in T2DM patients treated with SGLT2is compared with those on pioglitazone (HR 1.054, 95 % CI 0.904−1.229) [52], a thiazolidinedione that previously showed a significant protection against stroke in high-risk patients [7,8].

In contrast to what was reported in placebo-controlled RCTs and CVOTs [16], our series of 21 retrospective observational cohort studies shows no significant differences in the risk of fatal and fatal/non-fatal strokes when comparing patients with T2DM treated with either an SGLT2i or a GLP-1RA (Table 2). Thus, our work confirms and extends the findings of previous meta-analyses performed in a lower number of observational cohort studies [20−23] (Table 1). Only one meta-analysis that specifically focused on the risk of stroke with SGLT2is versus other glucose-lowering agents (not specifically GLP-1RAs) compared results obtained in both RCTs and observational studies [20]. SGLT2is showed no significant effects on risk of stroke in eight RCTs versus placebo in patients with T2DM (HR 0.98, 95 % CI 0.88−1.09: P = 0.272). In contrast, in real-life conditions, SGLT2is alone significantly reduced the risk of stroke compared with other glucose-lowering drugs (HR 0.87, 95 % CI 0.80−0.95, $P < 0.001$), yet with a rather high between-study heterogeneity (I^2 = 72.2 %). Of special interest, in observational studies that compared SGLT2is to GLP-1RAs, SGLT2is did not significantly affect the risk of stroke as only a numerically trend for a higher risk was observed (HR 1.14, 95 % CI 0.87−1.51) [20] (Table 1). Meta-regression analyses reported that age, gender, and follow-up time were not responsible for heterogeneity between observational studies [20]. An umbrella review of evidence from RCTs versus real-world observational studies also revealed a significant discrepancy between the two types of studies regarding the effects on the risk of stroke of SGLT2is versus other glucose-lowering drugs: risk ratio [RR] 0.99, 95 % CI 0.76−1.29; I^2 = 93.4 % for RCTs versus OR 0.75, 95 % CI 0.72−0.78; I^2 = 23.0 % for observational studies [19].

Thus, when considering the results of observational cohort studies, it does not appear that SGLT2is exert a significantly lower protection against stroke compared with GLP-1RAs. Thus, the gap between the two pharmacological classes suggested by data in RCTs seems to be leveling off for this cerebrovascular protective effect as it was already discussed for other outcomes [53].

Very few findings regarding stroke events differentiated ischaemic and haemorrhagic strokes in observational studies. Furthermore, regarding ischaemic strokes, no distinction could be made between events secondary to thrombosis or arterial embolism and scarce or no information was available concerning the rate of transient ischaemic attacks (TIA). In the series of 21 retrospective observational studies summarized in Table 2, only one study from Sweden showed a statistically significant higher risk of stroke with SGLT2is compared with GLP-1RAs (HR 1.71, 95 % CI 1.14−2.59) [44]. Of note, this study restricted the analysis to ischaemic strokes. In another study from Hong-Kong that showed no significant differences in all strokes between SGLT2is and GLP-1RAs, a borderline significant increased risk was noticed for ischaemic strokes but not for haemorrhagic strokes [48] (Table 2). However, such a difference between the two types of stroke was not confirmed in another cohort study from Taiwan, which reported a numerically slight and similar increase in both ischaemic (+ 16 %) and haemorrhagic stokes (+ 14 %) with SGLT2is versus GLP-1RAs [42]. Results from a Japanese Pharmacovigilance Study showed that the reporting odds ratios for stroke following SGLT2i use versus non-use differ greatly depending on the stroke subtypes : whereas SGLT2is were associated with significantly higher reporting for all ischaemic stroke (thrombosis, lacunar infarction and embolism), no significantly higher reporting was identified for haemorrhagic stroke [54]. Thus, the respective effects on ischaemic strokes of the two pharmacological classes remains an open question that certainly deserves more comparative studies focusing specifically on these cerebrovascular events.

As previously discussed [16], four special populations deserve attention because they are exposed to a higher risk of stroke: patients with atrial fibrillation, heart failure, CVD and/or chronic kidney disease (CKD). In a large observational study using TriNetX, a global health research real-world network, SGLT2is significantly reduced the risk of cerebrovascular events in an analysis that focused on individuals with T2DM and atrial fibrillation. At 3-year follow-up, the risk of ischaemic stroke/TIA was higher in patients not receiving SGLT2is compared with SGLT2i users (HR 1.12, 95 % CI 1.01−1.24), a difference even larger for intracranial hemorrhage (HR 1.57, 95 % CI 1.25−1.99) [55]. Similarly, in a historical cohort from the National Taiwan University of patients with T2DM and atrial fibrillation, SGLT2i users had a 20 % reduction in stroke (HR 0.80, 95 % CI, 0.64−0.99; P = 0.043) compared with SGLT2i non-users, after adjustment for the risk of arterial embolism using the CHA(2)DS(2)-VASc score [56].

The most impressive positive effect of SGLT2is concerns the reduction in hospitalization for heart failure [57], a complication known to be associated with an increased risk of stroke

independently of the presence of atrial fibrillation [58]. In a meta-analysis of 18 observational studies that compared SGLT2is with GLP-1RAs, SGLT2is were associated with a borderline significant 10 % increase in risk of stroke (HR 1.10, 95 % CI 1.01−1.19; P for effect size = 0.04) despite a 21 % highly significant reduction in the risk of hospitalization for heart failure (HR 0.79, 95 % CI 0.71−0.88; P for effect size < 0.01) [23]. A recent large observational study using US Medicare fee-for-service data compared the effects of SGLT2is versus GLP-1RAs in two cohorts of patients with heart failure with reduced (HFrEF) or preserved (HFpEF) ejection fraction and reported concordant results in both cohorts : initiation of SGLT2is versus GLP-1RAs was associated with significantly lower risk of hospitalization for heart failure, without any difference for stroke [59]. Thus, the remarkable effect of SGLT2is on heart failure appears to be dissociated from the less marked effect on stroke.

A few observational studies that compared the effects of SGLT2is versus GLP-1RAs on the incidence of stroke gave concordant results in patients without versus with established CVD [30,32,34,40] (Table 3). In a meta-analysis of 11 cohort studies, SGLT2is versus GLP-1RAs had similar stroke risk in T2DM patients with CVD (HR 1.01, 95 % CI 0.91−1.12) or without CVD (HR 1.13, 95 % CI 0.95−1.33), and the between-subgroup difference had no statistical significance (P = 0.26) [24].

Finally, in a nationwide retrospective cohort study using data from the Taiwan Health Insurance database in patients with T2DM and CKD, SGLT2i users exhibited significantly low rates of new-onset stroke compared with non-SGLT2i users after propensity score matching (HR 0.80, 95 % CI 0.76−0.84) [60]. These findings confirm those of a meta-analysis that specifically targeted patients with CKD and showed a significant reduction in the risk of stroke with SGLT2is but not with GLP-1RAs versus placebo [61], thus opposite results when compared to those reported in meta-analyses of RCTs among patients with T2DM and no CKD [16]. It has been speculated that the stroke prevention effects of SGLT2is may differ for different renal function levels in diabetic patients, being more pronounced in those with more advanced renal impairment and related to the positive effect of gliflozins on renal protection [62−64].

Thus, findings from real-world evidence (RWE) collected in retrospective cohort studies (Tables 1 and 2) showed discrepancies with those emerging from placebo-controlled RCTs when considering the effects of SGLT2is on fatal and fatal/nonfatal stroke in T2D patients, especially when compared with the results reported with GLP-1RAs [16,19]. Such a discordance has not been observed when considering heart failure issues as observational studies confirmed results from CVOTs with a clear-cut superiority of SGLT2is over GLP-1RAs [65]. A major difference between RCTs/CVOTs and real-life observational studies which might explain different results regarding stroke protection concerns the profile of the populations recruited in the two types of studies. Indeed, most RCTs were carried out in patients with T2D and established CVD or at high cardiovascular risk whereas observational studies recruited a majority of individuals at lower cardiovascular risk. A recent trial sequential analysis of RCTs showed that GLP-1RAs and SGLT2is reduce the incidence of MACEs to a similar extent in patients with and without CVD, but suggested that they may have a differential effect on the reduction of fatal or non-fatal strokes [66]. Nevertheless, the results were inconclusive because of a too low number of RCTs that gave detailed results on strokes in patients with versus without CVD so that the required sample size was not reached [66]. However, four observational studies that compared the results in patients with versus without CVD gave concordant results with no difference between patients treated with SGLT2is compared to patients treated with GLP-1RAs whatever the presence or not of CVD [24,30,34,40] (Table 3).

There are several limitations in this review that compares the effects on the risk of stroke of SGLT2is versus GLP-1RAs. Cohort studies have well-known limitations, especially when they have a retrospective design with post-hoc analyses [67,68]. Yet they bring complementary information to that provided by RCTs, especially in absence of head-to-head RCTs (a lack that obliges to use indirect comparison between placebo-controlled RCTs, as it was the case for the comparison SGLT2is versus GLPI-1RAs) [16] and when the aim is to compare the effectiveness of two medications in real-life conditions [69,70]. Most observational cohort studies collected in the present meta-analyses used propensity score matching or inverse probability of treatment weighting to limit the risk of biases (yet some hidden ones may still remain). Importantly they gave reproducible results whatever the country involved and the characteristics of populations recruited. Some other limitations may be pointed out : variability in the stroke definitions used and information reported across observational studies prohibit the comparison, replication, and aggregation of findings [71]; the lack of precise information about the type of stroke (ischaemic versus haemorrhagic) in most retrospective observational cohort studies as already discussed; the lack of information regarding secondary prevention of stroke as most available data from cohort studies (and from RCTs/CVOTs as well) concerned the occurrence of first event (primary stroke) [72]; possible heterogeneity between molecules within each class which has not been specifically addressed, an heterogeneity apparently more marked within the GLP-1RA family (lower efficacy of short-acting agents and exendin-4 derivatives) [73] than within the SGLT2i class [74−77].

Conclusion

Stroke is a major vascular complication among patients with T2DM. GLP-1RAs have proven their efficacy in reducing the risk of nonfatal stroke in many RCTs and CVOTs collected in meta-analyses in contrast to SGLT2is whose cerebrovascular protection raised concern. In contrast to what was suggested by indirect comparisons of placebo-controlled RCTs, worldwide findings from numerous observational cohort studies showed no significant difference between the risk of nonfatal and fatal/nonfatal strokes observed in SGLT2i users versus GLP-1RA users independent of the presence of established CVD. Some data suggested that SGLT2is may exert a better protection on haemorrhagic strokes than ischaemic stroke as well as on fatal/nonfatal strokes in a population with CKD and in patients with or at risk of atrial fibrillation. In absence of head-to-head RCTs comparing stroke outcomes in patients with T2DM treated with either an SGLT2i or a GLP-1RA, a definite conclusion should be taken with caution regarding the prioritization of GLP-1RAs over SGLT2is to prevent strokes in patients with T2DM.

Funding details

No sources of funding were used to assist in the preparation of this manuscript.

Declaration of Competing Interest

The author reports there are no competing interests to declare.

He has received lecturer/scientific advisor/clinical investigator fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, NovoNordisk and Sanofi. He worked as clinical investigator in PROactive, TECOS, EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58, LEADER and HARMONY Outcomes cardiovascular outcome trials.

References

[1] Mosenzon O, Cheng AY, Rabinstein AA, Sacco S. Diabetes and stroke: what are the connections? J Stroke 2023;25:26–38.

[2] Zhang L, Li X, Wolfe CDA, O'Connell MDL, Wang Y. Diabetes as an independent risk factor for stroke recurrence in ischemic stroke patients: an updated meta-analysis. Neuroepidemiology 2021;55:427–35.
[3] Kernan WN, Forman R, Inzucchi SE. Caring for patients with diabetes in stroke neurology. Stroke 2023;54:894–904.
[4] Bell DSH, Goncalves E. Stroke in the patient with diabetes (part 1)—epidemiology, etiology, therapy and prognosis. Diabetes Res Clin Pract 2020;164:108193.
[5] Lau LH, Lew J, Borschmann K, Thijs V, Ekinci EI. Prevalence of diabetes and its effects on stroke outcomes: a meta-analysis and literature review. J Diabetes Investig 2019;10:780–92.
[6] Bell DSH, Goncalves E. Stroke in the patient with diabetes (Part 2) - Prevention and the effects of glucose lowering therapies. Diabetes Res Clin Pract 2020;164:108199.
[7] Lee M, Saver JL, Liao HW, Lin CH, Ovbiagele B. Pioglitazone for secondary stroke prevention: a systematic review and meta-analysis. Stroke 2017;48:388–93.
[8] Zhou Y, Huang Y, Ji X, Wang X, Shen L, Wang Y. Pioglitazone for the primary and secondary prevention of cardiovascular and renal outcomes in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis. J Clin Endocrinol Metab 2020;105:dgz252.
[9] Rahman A, Alqaisi S, Saith SE, Alzakhari R, Levy R. The impact of glucagon-like peptide-1 receptor agonist on the cardiovascular outcomes in patients with type 2 diabetes mellitus: a meta-analysis and systematic review. Cardiol Res 2023;14:250–60.
[10] Bonnet F, Scheen AJ. Impact of glucose-lowering therapies on risk of stroke in type 2 diabetes. Diabetes Metab 2017;43:299–313.
[11] Ahn CH, Lim S. Effects of thiazolidinedione and new antidiabetic agents on stroke. J Stroke 2019;21:139–50.
[12] Lim S, Oh TJ, Dawson J, Sattar N. Diabetes drugs and stroke risk: intensive versus conventional glucose-lowering strategies, and implications of recent cardiovascular outcome trials. Diabetes Obes Metab 2020;22:6–15.
[13] Du L, Zhang Y, Wang P, Li Z, Zhao Y. Substantially different findings concerning the cardiovascular and cerebrovascular effectiveness of GLP1RAs vs. SGLT2is. Front Cardiovasc Med 2022;9:1034095.
[14] Yanai H, Adachi H, Hakoshima M, Katsuyama H. Glucagon-like peptide 1 receptor agonists versus sodium-glucose cotransporter 2 inhibitors for atherosclerotic cardiovascular disease in patients with type 2 diabetes. Cardiol Res 2023;14:12–21.
[15] Scheen AJ. Cardiovascular outcome studies in type 2 diabetes : comparison between SGLT2 inhibitors and GLP-1 receptor agonists. Diabetes Res Clin Pract 2018;143:88–100.
[16] Scheen AJ. Do SGLT2 inhibitors and GLP-1 receptor agonists modulate differently the risk of stroke ? Discordance between randomized controlled trials and observational studies. Diabetes Metab 2023;49:101474.
[17] Al Hamed FA, Elewa H. Potential therapeutic effects of sodium glucose-linked cotransporter 2 inhibitors in stroke. Clin Ther 2020;42:e242–9.
[18] Mascolo A, Scavone C, Scisciola L, Chiodini P, Capuano A, Paolisso G. SGLT-2 inhibitors reduce the risk of cerebrovascular/cardiovascular outcomes and mortality: a systematic review and meta-analysis of retrospective cohort studies. Pharmacol Res 2021;172:105836.
[19] Seo B, Su J, Song Y. Exploring heterogeneities of cardiovascular efficacy and effectiveness of SGLT2 inhibitors in patients with type 2 diabetes: an umbrella review of evidence from randomized clinical trials versus real-world observational studies. Eur J Clin Pharmacol 2022;78:1205–16.
[20] Zhang C, Zhang X, Wang P, Zhu Q, Mei Y, Zhang Z, et al. Effect of SGLT2 inhibitors on risk of stroke in diabetes: a meta-analysis. Cerebrovasc Dis 2022;51:585–93.
[21] Caruso I, Cignarelli A, Sorice GP, Natalicchio A, Perrini S, Laviola L, et al. Cardiovascular and renal effectiveness of GLP-1 receptor agonists vs. other glucose-lowering drugs in type 2 diabetes: a systematic review and meta-analysis of real-world studies. Metabolites 2022;12:183.
[22] Qiu M, Wei XB, Wei W. SGLT2is vs. GLP1RAs reduce cardiovascular and all-cause mortality. Front Cardiovasc Med 2021;8:791311.
[23] Du L, Qin J, Wang D, Zhao Y, Xu N, Wu C. Commentary: SGLT2is vs. GLP1RAs reduce cardiovascular and all-cause mortality. Front Cardiovasc Med 2022;9:987025.
[24] Du L, Li Z, Lan P, Huang H, Cheng W. Effectiveness of SGLT2is vs. GLP-1RAs on cardiovascular and cerebrovascular outcomes in T2D patients according to CVD status. Front Cardiovasc Med 2022;9:1011535.
[25] Li S, Vandvik PO, Lytvyn L, Guyatt GH, Palmer SC, Rodriguez-Gutierrez R, et al. SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. BMJ 2021;373:n1091.
[26] Goldenberg RM, Cheng AYY, Fitzpatrick T, Gilbert JD, Verma S, Hopyan JJ. Benefits of GLP-1 (glucagon-like peptide 1) receptor agonists for stroke reduction in type 2 diabetes: a call to action for neurologists. Stroke 2022;53:1813–22.
[27] Li CX, Liang S, Gao L, Liu H. Cardiovascular outcomes associated with SGLT-2 inhibitors versus other glucose-lowering drugs in patients with type 2 diabetes: a real-world systematic review and meta-analysis. PLoS One 2021;16:e0244689.
[28] O'Brien MJ, Karam SL, Wallia A, Kang RH, Cooper AJ, Lancki N, et al. Association of second-line antidiabetic medications with cardiovascular events among insured adults with type 2 diabetes. JAMA Netw Open 2018;1:e186125.
[29] Patorno E, Goldfine AB, Schneeweiss S, Everett BM, Glynn RJ, Liu J, et al. Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study. BMJ 2018;360:k119.
[30] Longato E, Di Camillo B, Sparacino G, Gubian L, Avogaro A, Fadini GP. Cardiovascular outcomes of type 2 diabetic patients treated with SGLT-2 inhibitors versus GLP-1 receptor agonists in real-life. BMJ Open Diabetes Res Care 2020;8:e001451.
[31] Pineda ED, Liao IC, Godley PJ, Michel JB, Rascati KL. Cardiovascular outcomes among patients with type 2 diabetes newly initiated on sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and other antidiabetic medications. J Manag Care Spec Pharm 2020;26:610–8.
[32] DeRemer CE, Vouri SM, Guo J, Donahoo WT, Winterstein AG, Shao H. Comparing cardiovascular benefits between GLP-1 receptor agonists and SGLT2 inhibitors as an add-on to metformin among patients with type 2 diabetes: a retrospective cohort study. J Diabetes Complicat. 2021;35:107972.
[33] Lugner M, Sattar N, Miftaraj M, Ekelund J, Franzen S, Svensson AM, et al. Cardiorenal and other diabetes related outcomes with SGLT-2 inhibitors compared to GLP-1 receptor agonists in type 2 diabetes: nationwide observational study. Cardiovasc Diabetol 2021;20:67.
[34] Patorno E, Htoo PT, Glynn RJ, Schneeweiss S, Wexler DJ, Pawar A, et al. Sodium-glucose cotransporter-2 inhibitors versus glucagon-like peptide-1 receptor agonists and the risk for cardiovascular outcomes in routine care patients with diabetes across categories of cardiovascular disease. Ann Intern Med 2021;174:1528–41.
[35] Patorno E, Pawar A, Bessette LG, Kim DH, Dave C, Glynn RJ, et al. Comparative effectiveness and safety of sodium-glucose cotransporter 2 inhibitors versus glucagon-like peptide 1 receptor agonists in older adults. Diabetes Care 2021;44:826–35.
[36] Hsiao FC, Lin CP, Tung YC, Wu CT, Chu PH. Major adverse limb events in type 2 diabetes patients receiving glucagon-like peptide-1 receptor agonists versus sodium-glucose cotransporter 2 inhibitors: a retrospective multi-institutional study. Diabetes Res Clin Pract 2021;180:109076.
[37] Poonawalla IB, Bowe AT, Tindal MC, Meah YA, Schwab P. A real-world comparison of cardiovascular, medical and costs outcomes in new users of SGLT2 inhibitors versus GLP-1 agonists. Diabetes Res Clin Pract 2021;175:108800.
[38] Ueda P, Wintzell V, Dahlqwist E, Eliasson B, Svensson AM, Franzen S, et al. The comparative cardiovascular and renal effectiveness of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a Scandinavian cohort study. Diabetes Obes Metab 2022;24:473–85.
[39] Norgaard CH, Starkopf L, Gerds TA, Vestergaard P, Bonde AN, Fosbol E, et al. Cardiovascular outcomes with GLP-1 receptor agonists vs. SGLT-2 inhibitors in patients with type 2 diabetes. Eur Heart J Cardiovasc Pharmacother 2022;8:549–56.
[40] Baviera M, Foresta A, Colacioppo P, Macaluso G, Roncaglioni MC, Tettamanti M, et al. Effectiveness and safety of GLP-1 receptor agonists versus SGLT-2 inhibitors in type 2 diabetes: an Italian cohort study. Cardiovasc Diabetol 2022;21:162.
[41] Htoo PT, Tesfaye H, Schneeweiss S, Wexler DJ, Everett BM, Glynn RJ, et al. Comparative effectiveness of empagliflozin vs liraglutide or sitagliptin in older adults with diverse patient characteristics. JAMA Netw Open 2022;5:e2237606.
[42] Dong YH, Chang CH, Lin JW, Yang WS, Wu LC, Toh S. Comparative cardiovascular effectiveness of glucagon-like peptide-1 receptor agonists versus sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes: a population-based cohort study. Diabetes Obes Metab 2022;24:1623–37.
[43] Lin DS, Yu AL, Lo HY, Lien CW, Lee JK, Chen WJ. Major adverse cardiovascular and limb events in people with diabetes treated with GLP-1 receptor agonists vs SGLT2 inhibitors. Diabetologia 2022;65:2032–43.
[44] Fu EL, Clase CM, Janse RJ, Lindholm B, Dekker FW, Jardine MJ, et al. Comparative effectiveness of SGLT2i versus GLP1-RA on cardiovascular outcomes in routine clinical practice. Int J Cardiol 2022;352:172–9.
[45] Lyu B, Grams ME, Chang A, Inker LA, Coresh J, Shin JI. Sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors, and risk of hospitalization. Am J Cardiol 2022;165:124–30.
[46] Wright AK, Carr MJ, Kontopantelis E, Leelarathna L, Thabit H, Emsley R, et al. Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. Diabetes Care 2022;45:909–18.
[47] Rathmann W, Kostev K. Association of glucose-lowering drugs with incident stroke and transient ischaemic attacks in primary care patients with type 2 diabetes: disease analyzer database. Acta Diabetol 2022;59:1443–51.
[48] Lui DTW, Tang EHM, Wu T, Au ICH, Lee CH, Woo YC, et al. Risks of stroke, its subtypes and atrial fibrillation associated with glucagon-like peptide 1 receptor agonists versus sodium-glucose cotransporter 2 inhibitors: a real-world population-based cohort study in Hong Kong. Cardiovasc Diabetol 2023;22:40.
[49] Xie Y, Bowe B, Xian H, Loux T, McGill JB, Al-Aly Z. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised target trial using electronic health records. Lancet Diabetes Endocrinol 2023;11:644–56.
[50] Khunti K, Kosiborod M, Kim DJ, Kohsaka S, Lam CSP, Goh SY, et al. Cardiovascular outcomes with sodium-glucose cotransporter-2 inhibitors vs other glucose-lowering drugs in 13 countries across three continents: analysis of CVD-REAL data. Cardiovasc Diabetol 2021;20:159.
[51] Karasik A, Lanzinger S, Chia-Hui Tan E, Yabe D, Kim DJ, Sheu WH, et al. Empagliflozin cardiovascular and renal effectiveness and safety compared to dipeptidyl peptidase-4 inhibitors across 11 countries in Europe and Asia: results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. Diabetes Metab 2023;49:101418.
[52] Lee SE, Nam H, Choi HS, Kim H, Kyoung DS, Kim KA. Comparative effects of sodium-glucose cotransporter 2 inhibitor and thiazolidinedione treatment on risk of stroke among patients with type 2 diabetes mellitus. Diabetes Metab J 2022;46:567–77.
[53] Giugliano D, Scappaticcio L, Longo M, Bellastella G, Esposito K. GLP-1 receptor agonists vs. SGLT-2 inhibitors: the gap seems to be leveling off. Cardiovasc Diabetol 2021;20:205.

[54] Sato K, Mano T, Iwata A, Toda T. Subtype-dependent reporting of stroke with SGLT2 inhibitors: implications from a Japanese pharmacovigilance study. J Clin Pharmacol 2020;60:629–35.
[55] Proietti R, Rivera-Caravaca JM, Lopez-Galvez R, Harrison SL, Marin F, Underhill P, et al. Cerebrovascular, cognitive and cardiac benefits of SGLT2 inhibitors therapy in patients with atrial fibrillation and type 2 diabetes mellitus: results from a global federated health network analysis. J Clin Med 2023;12:2814.
[56] Chang SN, Chen JJ, Huang PS, Wu CK, Wang YC, Hwang JJ, et al. Sodium-glucose cotransporter-2 inhibitor prevents stroke in patients with diabetes and atrial fibrillation. J Am Heart Assoc 2023;12:e027764.
[57] Scheen AJ. Sodium-glucose co-transporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2020;16:556–77.
[58] Berger JS, Peterson E, Lalibert EF, Germain G, Lejeune D, Schein J, et al. Risk of ischemic stroke in patients newly diagnosed with heart failure: focus on patients without atrial fibrillation. J Card Fail 2019;25:436–47.
[59] Gonzalez J, Bates BA, Setoguchi S, Gerhard T, Dave CV. Cardiovascular outcomes with SGLT2 inhibitors versus DPP4 inhibitors and GLP-1 receptor agonists in patients with heart failure with reduced and preserved ejection fraction. Cardiovasc Diabetol 2023;22:54.
[60] Jong GP, Lin TK, Liao PL, Huang JY, Yang TY, Pan LF. Risk of new-onset stroke in patients with type 2 diabetes with chronic kidney disease on sodium-glucose co-transporter-2 inhibitor users. Transl Stroke Res 2023 Jul 140.1007/s12975-023-01174-0.
[61] Nguyen BN, Nguyen L, Mital S, Bugden S, Nguyen HV. Comparative efficacy of sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists in chronic kidney disease and type 2 diabetes: a systematic review and network meta-analysis. Diabtes Obes Metab 2023;25:1614–23.
[62] Hsieh CY, Sung SF. From kidney protection to stroke prevention: the potential role of sodium glucose cotransporter-2 inhibitors. Int J Mol Sci 2022;24:351.
[63] Lin DS, Yu AL, Lo HY, Lien CW, Lee JK, Chiang FT, et al. Differential effects of sodium-glucose cotransporter 2 inhibitors on cardiovascular and renal outcomes according to renal function: a dose-response meta-analysis involving 10 randomized clinical trials and 71 553 individuals. Eur J Endocrinol 2023;189:S17–25.
[64] Rahman H, Khan SU, Lone AN, Ghosh P, Kunduru M, Sharma S, et al. Sodium-glucose cotransporter-2 inhibitors and primary prevention of atherosclerotic cardiovascular disease: a meta-analysis of randomized trials and systematic review. J Am Heart Assoc 2023;12:e030578.
[65] Hinton W, Ansari AS, Whyte MB, McGovern AP, Feher MD, Munro N, et al. Sodium-glucose co-transporter-2 inhibitors in type 2 diabetes: are clinical trial benefits for heart failure reflected in real-world clinical practice? A systematic review and meta-analysis of observational studies. Diabetes Obes Metab 2023;25:501–15.
[66] Kilickap M, Kozluca V, Tan TS. Akbulut Koyuncu I.M GLP-1 receptor agonists and SGLT-2 inhibitors in patients with versus without cardiovascular disease: a systematic review, meta-analysis, and trial sequential analysis. Angiology 2023:33197231183229. doi: 10.1177/00033197231183229.
[67] Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. Lancet 2002;359:341–5.
[68] Suissa S. Lower risk of death with SGLT2 inhibitors in observational studies: real or bias? Diabetes Care 2018;41:6–10.
[69] Ho PM, Peterson PN, Masoudi FA. Evaluating the evidence: is there a rigid hierarchy? Circulation 2008;118:1675–84.
[70] Scheen AJ. Pragmatic trials, a step forward to assess cardiovascular efficacy of new glucose-lowering agents. Lancet Diabetes Endocrinol 2023 Jul 24;S2213-8587(23)00161-4..
[71] Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol 2021;21:241.
[72] Malhotra K, Katsanos AH, Lambadiari V, Goyal N, Palaiodimou L, Kosmidou M, et al. GLP-1 receptor agonists in diabetes for stroke prevention: a systematic review and meta-analysis. J Neurol 2020;267:2117–22.
[73] Scheen AJ. GLP-1 receptor agonists and cardiovascular protection. Class effect or not ? Diabetes Metab 2018;44:193–6.
[74] Qiu M, Ding LL, Wei XB, Liu SY, Zhou HR. Comparative efficacy of glucagon-like peptide 1 receptor agonists and sodium glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular events in type 2 diabetes: a network meta-analysis. J Cardiovasc Pharmacol 2021;77:34–7.
[75] Duan XY, Liu SY, Yin DG. Comparative efficacy of 5 sodium glucose cotransporter 2 inhibitor and 7 glucagon-like peptide 1 receptor agonists interventions on cardiorenal outcomes in type 2 diabetes patients: a network meta-analysis based on cardiovascular or renal outcome trials. Medicine 2021;100:e26431.
[76] Wei XB, Wei W, Ding LL, Liu SY. Comparison of the effects of 10 GLP-1 RA and SGLT2 inhibitor interventions on cardiovascular, mortality, and kidney outcomes in type 2 diabetes: a network meta-analysis of large randomized trials. Prim Care Diabetes 2021;15:208–11.
[77] Maskery MP, Holscher C, Jones SP, Price CI, Strain WD, Watkins CL, et al. Glucagon-like peptide-1 receptor agonists as neuroprotective agents for ischemic stroke: a systematic scoping review. J Cereb Blood Flow Metab 2021;41:14–30.