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Drug Safety

Meta-analysis

Risk of lower limb amputation in diabetic patients using SGLT2 inhibitors *versus* DPP4 inhibitors or GLP-1 agonists: a meta-analysis of 2 million patients

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Abstract

Background: The objective of this review was to assess the risk of lower limb amputation (LLA) in type 2 diabetic patients based on the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) *versus* dipeptidyl peptidase 4 inhibitors (DPP4i) or glucagon-like peptide-1 receptor agonists (GLP1a).

Methods: PubMed, CENTRAL, Scopus, Web of Science, and Embase were referenced for articles published up to 5 February 2023. All types of studies comparing the drugs for LLA risk and reporting hazard ratios (HR) were included.

Results: Thirteen studies with 2,095,033 patients were included. Meta-analysis of eight studies comparing SGLT2i with Dipeptidyl peptidase inhibitors (DPPi) showed that there was no difference in the risk of LLA between the two drug groups (HR: 0.98 95% CI: 0.73, 1.31 $I^2 = 89\%$). The outcomes were unchanged on sensitivity analysis. Another pooled analysis of six studies found no significant difference in the risk of LLA between SGLT2i and GLP1a users (HR: 1.26; 95% CI: 0.99, 1.60; $I^2 = 69\%$). The exclusion of a single study showed an increased risk of LLA with SGLT2i (HR: 1.35; 95% CI: 1.14, 1.60; $I^2 = 14\%$).

Conclusion: The current updated meta-analysis found no significant difference in the risk of LLA between SGLT2i and DPP4i users. A tendency of increased risk of LLA was noted with SGLT2i as compared to GLP1a. Further studies shall increase the robustness of current findings.

Plain language summary

Risk of lower limb amputation with SGLT2 inhibitors in comparison with DPP4 inhibitors or GLP-1 agonists among diabetic patients

Diabetic foot leading to lower limb amputation (LLA) is a common complication of diabetes mellitus (DM). We compared the risk of LLA in DM patients taking either sodium-glucose cotransporter 2 inhibitors (SGLT2i) or dipeptidyl peptidase 4 inhibitors (DPP4i) / glucagon-like peptide-1 receptor agonists (GLP1a). We searched the available literature for published studies comparing the risk of LLA with SGLT2i *versus* DPP4i or GLP1a. Individual study data were combined to generate a comprehensive result. We could find 13 studies with data from approximately 2 million patients. After combining the data, we noted no difference in the risk of LLA between patients using SGLT2i *versus* DPPi or GLP1a. Nevertheless, when data from a single study was removed from the combined analysis, we noted an increased risk of LLA with SGLT2i in comparison with GLP1a users. To conclude, our study, which is a comprehensive literature review, found that there is no difference in the risk of LLA between SGLT2i and DPP4i users. A tendency of increased risk of LLA was seen with SGLT2i as compared to GLP1a, which requires further research.

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Introduction

Diabetes mellitus (DM) is an exceedingly prevalent metabolic ailment affecting 415 million patients worldwide, with an estimated 193 million undiagnosed of the condition.[1] More than 90% of cases are of type II DM with consequent macrovascular and microvascular complications, which have a profound physical and emotional impact on the patient and caregivers, notwithstanding the tremendous financial burden on the healthcare system.[2] Lifestyle changes and oral hypoglycemic agents are the cornerstone of DM management which can promote glycemic control and help lower complication rates. While the initial therapy for most patients is metformin-based, treatment failure calls for the use of newer agents like sodium-glucose cotransporter 2 inhibitors (SGLT2i), dipeptidyl peptidase 4 inhibitors (DPP4i), and glucagon-like peptide-1 receptor agonists (GLP1a).[3]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), namely canagliflozin, dapagliflozin, and empagliflozin, are a class of oral hypoglycemic drugs that were approved for clinical application in 2013. These drugs act on the kidneys to reduce glucose reabsorption and increase glucose excretion, thereby controlling blood glucose levels.[4] Working independently of insulin production, SGLT2i have cardioprotective and renoprotective effects and also lead to weight loss, all of which have substantially increased the clinical use of these drugs.[5] Nevertheless, there have been concerns over the increased risk of lower limb amputation (LLA) with the use of these agents following the landmark CANVAS (CANagliflozin cardioVascular Assessment Study) program results.[6] The elevated risk demonstrated in this study led to the issuance of black box warnings with canagliflozin and prompted intense clinical research and debate on the actual risk of LLA with these agents. While randomized controlled trials (RCTs) conducted post the CANVAS program did not find an elevated risk of amputation,[7] real-world observational data have thrown up conflicting results on the risk of LLA with SGLT2i vis-à-vis other second-line agents like DPP4i and GLP1a. On one hand, studies are showing an increased risk of LLA with SGLT2i *versus* DPP4i,[8,9] while others have reported completely contrasting results.[10,11] Similarly, results have not been congruent for the comparison of SGLT2i *versus* GLP1a, with one showing an increased risk of LLA[12] with SGLT2i and the other noting no such effect.[10] Meta-analysis studies[13–15] comparing these classes of drugs for LLA have not been reliable due to the inclusion of studies with duplicate and overlapping data, erroneous inclusion of studies, and not being up to date. Given the complexity of the problem, variations in individual studies, and unreliable meta-analyses in previous studies, the current updated meta-analysis was conducted to provide accurate evidence on the risk of LLA in DM patients with the use of SGLT2i *versus* DPP4i and GLP1a.

Materials and methods

Search and eligibility

The protocol registration was done on PROSPERO before commencing the literature search (CRD42023396355). The PRISMA statement reporting guidelines were a part of the reviewing process.[16] An intensive literature search was conducted by two independent reviewers and supervised by the medical librarian for the databases of PubMed, CENTRAL, Scopus, Web of Science, and Embase. It encompassed all articles published between 1 January 2000 and 5 February 2023. All studies were considered without any limitation on the date of publication and language.

The inclusion criteria were defined beforehand and consisted of all types of studies conducted on type II DM patients (*Population*). The *Intervention* was new users of SGLT2i *Compared* with new users of DPP4i or GLP1a. *The Outcome* of interest was LLA. Studies were to report adjusted data for the risk of LLA with SGLT2i *versus* DPP4i or GLP1a.

Exclusion criteria were: (1) Studies not reporting adjusted data. (2) Studies not reporting separate

data on DPP4i or GLP1a. (3) Studies with duplicate/overlapping data. If two or more articles used the same dataset from the same period, the study with the highest number of patients was included. Abstracts, review articles, and editorials were not considered for inclusion.

A mix of free-text and MeSH search terms with Boolean operators (AND/OR) were used in the literature search. The search terms included 'SGLT2 inhibitors', 'DPP4 inhibitors', 'GLP1 agonist', 'sodium-glucose cotransporter 2 inhibitor', 'dipeptidyl peptidase 4 inhibitors', 'glucagon-like peptide-1 receptor agonists', 'oral hypoglycemic agents', 'amputation', 'diabetic foot', and 'diabetes'. The PubMed search strategy is presented in detail in Supplemental Table 1. Identical search strings were used for the remaining databases. The search results were deduplicated and scrutinized based on the eligibility criteria by two reviewers separately, first at the title/abstract level and then at the full-text level. Articles completing all eligibility criteria were finally included. Any disagreements were solved by consensus. The references list of eligible articles and previous reviews were hand searched for other missed articles.

Data management and study quality

Data on the author's last name, publication time, study database, location, study type, use of baseline matching, type of SGLT2i, comparison drug, exposure definition, sample size, age, gender, outcome ratio, and follow-up were extracted by two reviewers independent of each other.

Two authors judged the study's quality based on Newcastle Ottawa Scale (NOS).[17] The NOS has three domains: representativeness of the study cohort, comparability, and measurement of outcomes. Points are given based on the preformatted queries. The final points of a study can range from 0 to 9.

Statistical analysis

Statistical analysis was done using 'Review Manager' (RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration), Copenhagen, Denmark; 2014). Hazard ratio (HR) was extracted from individual studies and pooled to calculate the total effect size with 95% confidence intervals (CI) in a random-effects model. Publication bias was examined using funnel plots. The I^2 statistic was the tool to determine interstudy heterogeneity. $I^2 < 50\%$ meant low and $>50\%$ meant substantial heterogeneity. A leave-one-out analysis was executed to scrutinize for any alteration in the outcomes on the exclusion of any study. Different analyses were conducted depending upon the comparator group.

Results

Six hundred forty articles were searched in all of the databases. On deduplication, 258 were screened by titles and abstracts and 34 were selected for full-text analysis. Of these, 13 studies fulfilled the inclusion criteria[8–12,18–25] (Figure 1).

The included studies were recently published between 2018 and 2022 and were based in the USA, the UK, Canada, Sweden, Denmark, Norway, Germany, Hungary, Slovenia, and Taiwan (Table 1). It was ensured that studies from the same database and the same study period were not included. All studies were retrospective, using data from national or insurance databases. Importantly, all studies matched the study groups for baseline variables. Prescription records were used to identify new users of SGLT2i and DPP4i or GLP1a. The studies differed in the minimum number of prescriptions needed to identify users of the particular class of drugs. Seven and five studies each compared SGLT2i with DPP4i and GLP1a, respectively, while one study had both comparative groups. Two studies had multiple cohorts in a single study. Fralick *et al.*[20] provided separate data for patients aged >65 years or <65 years and those with and without cardiovascular disease. Rodionov *et al.*[18] segregated data based on the prescription of SGLT2i before and after the European Medicines Agency (EMA) warning and the presence and absence of peripheral artery disease. The data of these separate cohorts were combined into one using the meta-analysis software in a random-effects model. The total sample size of all studies included in the review was 2,095,033. The follow-up duration of the studies varied from 7 to 62 months. The NOS score of the studies was either 7 or 8.

Meta-analysis of eight studies comparing SGLT2i with DPPi showed that there was no

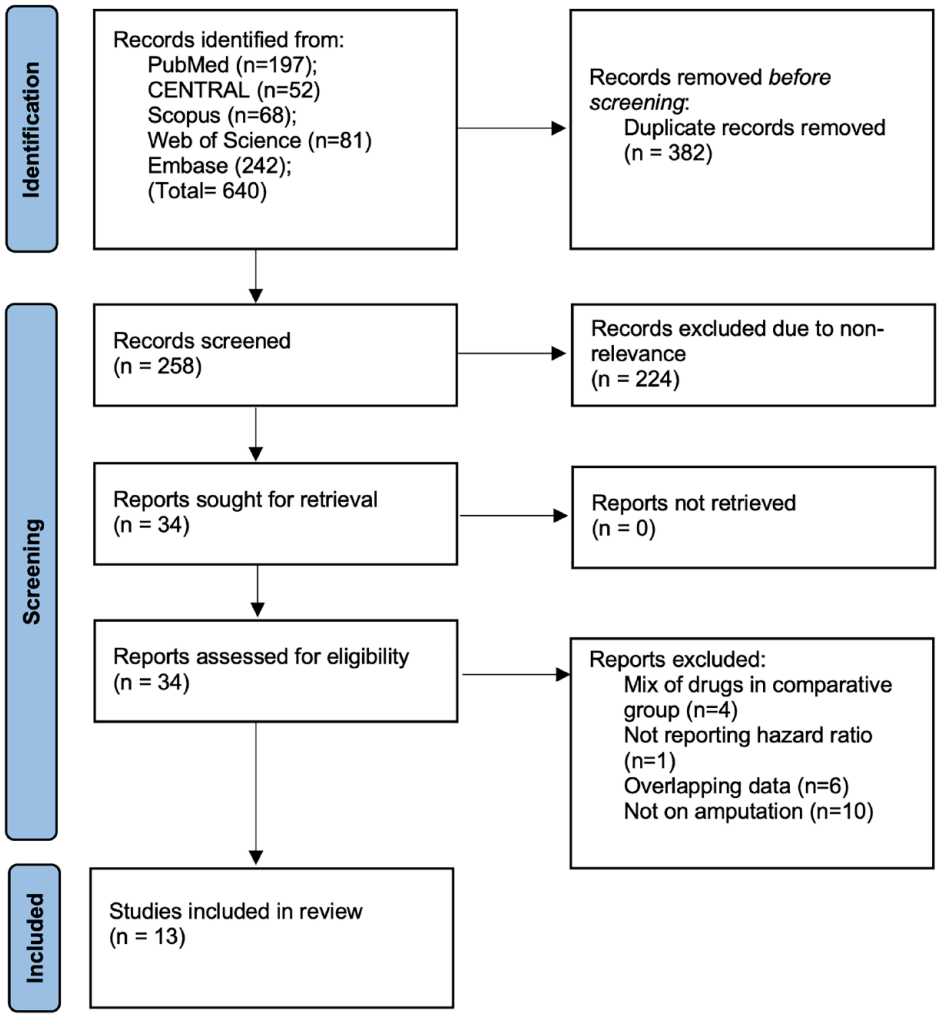

Figure 1. Study flowchart.

difference in the risk of LLA between the two drug groups (HR: 0.98 95% CI: 0.73, 1.31 $I^2 = 89\%$) (Figure 2). The outcome was unchanged on the sequential removal of studies. There was no publication bias on the funnel plot (Figure 3).

In the second pooled analysis of six studies, this review found no significant difference in the risk of LLA between SGLT2i and GLP1a users (HR: 1.26 95% CI: 0.99, 1.60 $I^2 = 69\%$) (Figure 4). There was one outliner study by Paul *et al.*,[10] the exclusion of which showed an increased risk of LLA with SGLT2i (HR: 1.35 95% CI: 1.14, 1.60 $I^2 = 14\%$). The funnel plot did not demonstrate publication bias (Figure 5).

Discussion

To summarize, after a detailed and comprehensive literature search, this review found 11 studies with data from around 2 million DM patients comparing the risk of LLA between SGLT2i and DPP4i or GLP1a users. Meta-analysis demonstrates no significant difference in the risk of LLA between SGLT2i and DPP4i or GLP1a users. However, with the exclusion of one outliner study, there was an increased risk of LLA with SGLT2i users *versus* GLP1a users.

The heightened risk of LLA with SGLT2i was initially demonstrated by the results of the CANVAS program[6] which integrated the results of two trials involving 10,142 participants, who

Table 1. Details of included studies.

Study	Location	Database	Study type	Matching	Type of SGLT2	Exposure definition	Groups	Sample size	Mean age (years)	Female (%)	HR	Follow-up (months)	NOS score
Ueda *et al.*[12]	Sweden/ Denmark	Nationwide health and administrative registers	R	Yes	Canagliflozin; dapagliflozin; empagliflozin	Patients were considered exposed to the study drug if prescriptions were refilled before the estimated end date of the most recent prescription	SGLT2 GLP1a	17213 17213	61 61	61 61	2.32 (1.37, 3.91)	9	7
Dawwas *et al.*[19]	USA	Truven Health	R	Yes	Canagliflozin; dapagliflozin	12 months of continuous enrollment in medical and pharmacy benefits prior to the index date and at least one prescription of an antidiabetic medication of interest	SGLT2 DPP4i	66633 66633	55 54	46.1 46.2	0.88 (0.65, 1.15)	12	8
Pasternak *et al.*[22]	Sweden/ Denmark/ Norway	Nationwide health and administrative registers	R	Yes	Canagliflozin; dapagliflozin; empagliflozin	Patients were considered exposed to the study drug if prescriptions were refilled before the estimated end date of the most recent prescription	SGLT2 DPP4i	20983 20983	61 61	40 40	1.26 (0.88, 1.81)	17	8
Fralick *et al.*[20]	USA	Optum Clinformatics Data Mart Database, Marketscan & Medicare	R	Yes	Canagliflozin	New users of study drugs were defined as those without a previous prescription for an SGLT2 inhibitor or GLP1a in the preceding 180 days	SGLT2 GLP1a SGLT2 GLP1a SGLT2 GLP1a SGLT2 GLP1a	80640 80640 10763 10763 44522 44522 19495 19495	51.9 51.9 55.9 55.8 71.1 71.1 72.6 72.6	49.4 49.5 35.2 35 55.3 55.3 42.5 42.7	1.09 (0.83, 1.43) 1.18 (0.86, 1.62) 1.30 (0.52, 3.26) 1.73 (1.30, 2.29)	9	7
Paul *et al.*[10]	USA	General Electric Centricity Electronic Medical Records	R	Yes	Canagliflozin; dapagliflozin; empagliflozin	Prescription of an antidiabetic medication of interest	SGLT2 DPP4i GLP1a	167739 448225 149826	57.5 62.8 56.8	47 50 60	DPP4i: 0.57 (0.50, 0.77) GLP1a: 0.88 (0.73, 1.06)	62	8
Yu *et al.*[25]	Canada, UK	Seven Canadian provinces & UK Clinical Practice Research Datalink	R	Yes	Canagliflozin; dapagliflozin; empagliflozin	Defined using an as-treated approach whereby exposure was time-fixed and defined by the cohort entry drug	SGLT2 DPP4i	207817 207817	63.8 64	41.6 41.9	0.88 (0.71, 1.09)	11	7
Rodionov *et al.*[18]	Germany	BARMER insurance database	R	Yes	Dapagliflozin; empagliflozin	Prescription of an antidiabetic medication of interest	SGLT2 GLP1a SGLT2 GLP1a SGLT2 GLP1a SGLT2 GLP1a	6032 2074 26677 9419 9299 2453 36222 8893	67.9 67.9 62.7 62.6 70.1 69.9 64.6 64.4	57.7 58.4 49.8 50.1 39 38 47.2 46.5	1.31 (0.89, 1.87) 1.79 (1.03, 3.02) 1.24 (0.84, 1.77) 0.89 (0.57, 1.33)	23 20 24 26	8

(Continued)

Table 1. (Continued)

Study	Location	Database	Study type	Matching	Type of SGLT2	Exposure definition	Groups	Sample size	Mean age (years)	Female (%)	HR	Follow-up (months)	NOS score
Suto *et al.*[9]	Hungary	National Institute of Health Insurance Fund database	R	Yes	NR	New users of study drugs were defined as those without a previous prescription in the preceding 1 year	SGLT2 DPP4i	18583 18583	NR	NR	1.35 (1.03, 1.77)	21	8
Lee *et al.*[24]	Taiwan	Taiwan's National Health Insurance Research Database	R	Yes	Dapagliflozin; empagliflozin	New users of study drugs were defined as those without a previous prescription for an SGLT2 inhibitor or GLP1a in the preceding 2 years	SGLT2 GLP1a	13378 13378	53.7 54	50.5 50.8	1.27 (0.63, 2.55)	7	7
Lin *et al.*[23]	Taiwan	Taiwan's National Health Insurance Research Database	R	Yes	NR	At least two prescription of an antidiabetic medication of interest	SGLT2 GLP1a	81152 20288	56.9 56.4	48.5 48.4	1.28 (0.84, 1.96)	22	8
Patorno *et al.*[21]	USA	Optum Clinformatics Data Mart Database, Marketscan & Medicare	R	Yes	Empagliflozin	New users of study drugs were defined as those without a previous prescription for an SGLT2 inhibitor or DPP4i in the preceding 1 year	SGLT2 DPP4i	39072 39072	60.2 60.2	45.4 45.5	1.12 (0.75, 1.67)	6	7
Yang *et al.*[11]	Taiwan	Taiwan's National Health Insurance Research Database	R	Yes	NR	At least three sequential refills of SGLT2is or DPP4is after treatment initiation and a prescription gap between any two consecutive refills of fewer than 30 days	SGLT2 DPP4i	21329 21329	57.9 58.6	43.3 43	0.64 (0.42, 0.98)	18	8
Zerovnik *et al.*[8]	Slovenia	Outpatient Prescription Medicines Database, National Hospital Health Care Statistics Database, and Causes of Death Registry	R	Yes	Dapagliflozin; empagliflozin	At least two prescription of an antidiabetic medication of interest	SGLT2 DPP4i	2939 2939	64 64	40.8 39.5	1.86 (1.10, 3.14)	24	8

DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1a, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; NOS, Newcastle Ottawa Scale; R, retrospective; SGLT2, Sodium-glucose cotransporter type-2 inhibitors.

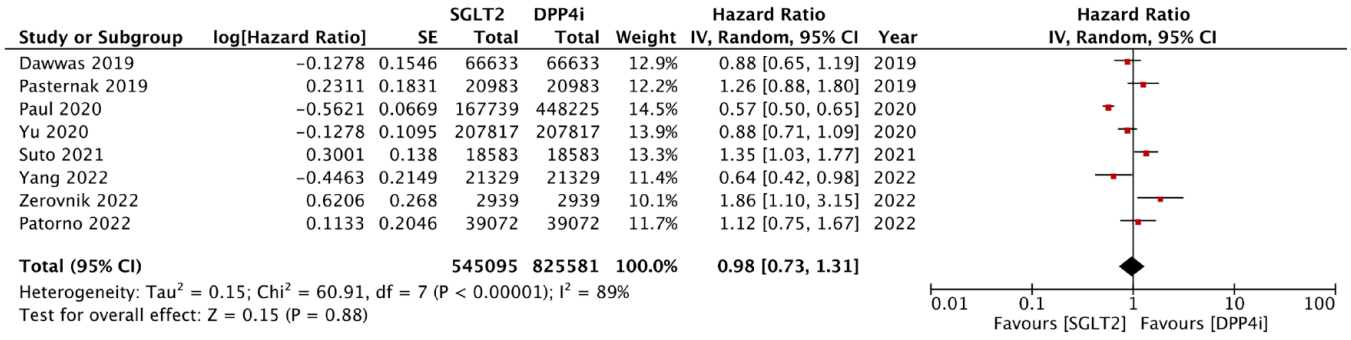

Figure 2. Meta-analysis of LLA risk between SGLT2i and DPPi.
LLA, lower limb amputation; SGLT2i, sodium-glucose cotransporter 2 inhibitors

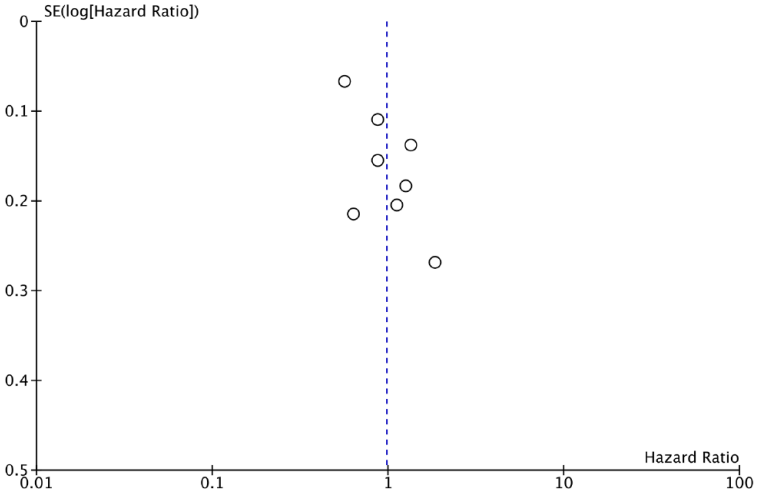

Figure 3. Funnel plot for the meta-analysis of LLA risk between SGLT2i and DPPi.
LLA, lower limb amputation; SGLT2i, sodium-glucose cotransporter 2 inhibitors

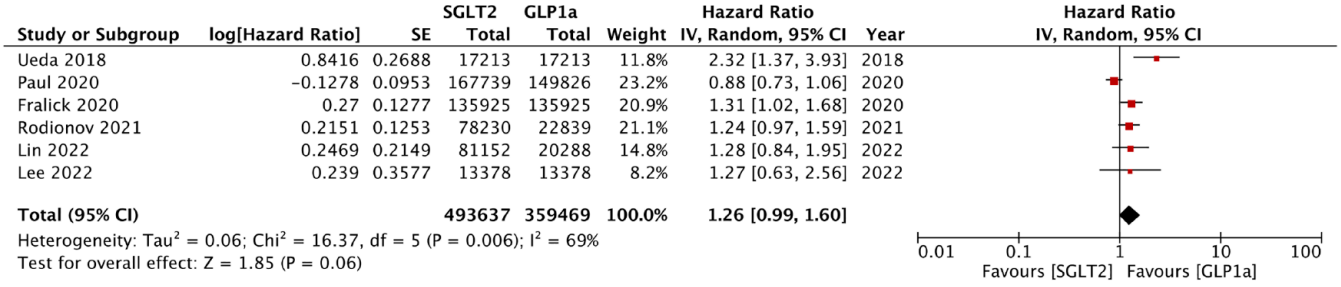

Figure 4. Meta-analysis of LLA risk between SGLT2i and GLP1a.
GLP1a, glucagon-like peptide-1 receptor agonists; LLA, lower limb amputation; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

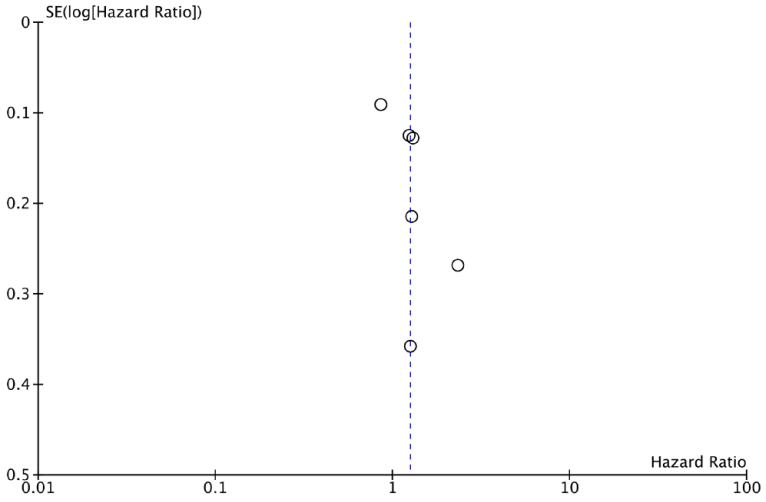

Figure 5. Funnel plot for the meta-analysis of LLA risk between SGLT2i and GLP1a.
GLP1a, glucagon-like peptide-1 receptor agonists; LLA, lower limb amputation; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

were randomized to either canagliflozin or placebo. Besides the known adverse reactions of canagliflozin, the study reported an increased risk of amputation at the level of the toe or metatarsal among users of the SGLT2i (HR: 1.97 95% CI, 1.41, 2.75). These results not only raised significant concerns among regulatory agencies in the USA and Europe but also gave impetus to studies to examine such association in real-world use.[12,18,25] The CANVAS results were compounded by additional pharmacovigilance reports suggesting that the increased risk is not limited to canagliflozin but is also seen with dapagliflozin and empagliflozin when compared with other oral hypoglycemic agents.[26] Furthermore, one study from Scandinavia reported a two-times increased risk of LLA with SGLT2is as opposed to those using GLP1a.[12] Considering such results, the USA Food and Drug Administration[27] in May 2017 issued an official warning concerning canagliflozin while the EMA[28] in the same year warned regarding the use of an entire class of SGLT2i. The EMA warning stated that patients should be reminded to regularly check their feet and stop SGLT2is in the presence of events preceding amputation. Since then, there has been an intense debate on the safety of SGLT2i *versus* other agents and if SGLT2i should be routinely prescribed, given the availability of newer agents like DPP4i and GLP1a. DPP4i are commonly prescribed in individuals failing metformin treatment due to their negligible risk of hypoglycemia, weight gain, and cardiovascular disease.[29] Also, GLP1a are protective against major adverse cardiac events in diabetics due to their anti-atherogenic effect and have widespread use in clinical practice.[30]

Indeed, previous meta-analysis studies have compared SGLT2i with DPP4i and GLP1a for risk of LLA, however, with serious errors. Du *et al.*[15] in 2022 published a pooled analysis of eight studies comparing LLA risk between SGLT2i with DPP4i/GLP1a but without segregating the results of DPP4i and GLP1a. The inclusion of several studies from the USA using the same databases from the same period led to an erroneous increase in the number of studies in the review. Also, one[31] of the included studies included all oral hypoglycemic drugs in the comparator group and were not exclusively focused on DPP4i/GLP1a. Two meta-analyses studies by Scheen *et al.*[13,14] separately compared SGLT2i with DPP4i and GLP1a but with a similar error of including overlapping studies. Repeated inclusion of the same population in a meta-analysis can tilt the result in favor of the overlapping data leading to invalid results. Given that most of the studies in the literature use similar national and insurance databases, it is critical that repeated inclusions of the same database are avoided while including studies in the review. Secondly, their reviews[13,14] did not pool adjusted HR but only crude event rates of LLA in their meta-analysis. It is important that the adjusted

HR generated by the study is pooled to avoid the influence of confounders. Given these shortcomings from the prior reviews and with the inclusion of newer studies[23,24] in our updated analysis, the current review provides the most updated and reliable evidence on the risk of LLA between users of SGLT2i and DPP4i or GLP1a.

Pooling data of around 2 million patients, we noted no increased risk of LLA between users of SGLT2i and DPP4i or GLP1a. These results are similar to clinical trials which have recently shown no increased risk of LLA with SGLT2i. Patoulias *et al.*[7] have combined data from eight large cardiovascular and renal outcome clinical trials comparing SGLT2i with placebo to find a nonsignificant increased risk of LLA with SGLT2i [RR (risk ratio): 1.21 95% CI: 0.97–1.51, $I^2 = 59\%$]. On the exclusion of the CANVAS trial from the meta-analysis, the interstudy heterogeneity was reduced to 0% with no change in their results (RR: 1.09 95% CI: 0.94–1.26, $I^2 = 0\%$). An indirect comparison meta-analysis by Palmer *et al.*[32] has shown similar results. Seven hundred sixty-four RCTs comparing SGLT-2i or GLP1a with placebo, standard care, or other glucose-lowering treatments were pooled in a network meta-analysis to show no increased risk of LLA with SGLT-2i. In another network, a meta-analysis of RCTs and observational studies comparing SGLT2i *versus* non-SGLT2i drugs, Qiu *et al*[33] noted no increased risk of LLA with SGLT2i *versus* placebo, but an increased risk was noted when compared to GLP1a users. In this review also, a tendency of increased risk of LLA with SGLT2i *versus* GLP1a was seen given the CI (0.99, 1.60). Further, the exclusion of Paul *et al.*[10] indicated a 35% increased risk of LLA with SGLT2i and reduced the interstudy heterogeneity to 14%. Given the outcomes of SGLT2i *versus* placebo, it is plausible that the higher risk of LLA compared with GLP1a could be due to the protective effect of the latter rather than the harmful effect of SGLT2i. The post hoc analysis of the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial has shown that DM patients managed with liraglutide had a significantly lower risk of LLA due to foot ulcers when compared with placebo.[34] It has been suggested that GLP1a decreases the proliferation of vascular smooth muscle cells and endothelial cells, lower oxidative stress, and elevates nitric oxide production, leading to increased blood flow at the microvascular level, which could contribute to a protective effect against LLA in DM patients.[35] Animal studies have demonstrated better nerve repair and regeneration with GLP1a in diabetic models.[36] Since patients with diabetic neuropathy have a higher risk of LLA, such a neuroprotective effect could reduce the risk of LLA.[23]

Our meta-analysis is not without limitations. Foremost is that most data was from retrospective observational studies with inherent errors and selection bias. Patients were identified from prescription patterns that may not reflect regular use of the drugs. Errors in data entry and prescriptions could have skewed the outcomes. While all studies used baseline matching, several unknown confounders could have been missed, which may have affected the risk of LLA. Also, outcomes in our review could not be segregated based on risk factors like peripheral artery disease, which could have better reflected the risk of these drugs on LLA. Additionally, separate analysis for individual SGLT2i could not be done due to the want of data. Several studies had less than a year of follow-up, which may be inadequate to register adverse events like LLA. Lastly, most studies were from limited countries with available national databases which record adverse events. Despite the large sample size of the review, the results may not be generalizable worldwide till further data from other regions are made available.

Conclusions

The currently updated meta-analysis taking into account the limitations of prior reviews has shown no significant difference in the risk of LLA between SGLT2i and DPP4i users. However, a tendency of increased risk of LLA was noted with SGLT2i as compared to GLP1a, which may be due to the protective effect of GLP1a rather than the harmful effect of the former. Further studies shall increase the robustness of current findings.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Yang Lu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Visualization; Writing – original draft.

Caiyun Guo: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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