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Review

Lower-limb amputations in patients treated with SGLT2 inhibitors versus DPP-4 inhibitors: A meta-analysis of observational studies

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SUMMARY

Background: An increased risk of lower limb amputations (LLA) has been suspected with the use of sodium-glucose cotransporter type 2 inhibitors (SGLT2is) in the CANVAS programme with canagliflozin and in pharmacovigilance reports with all SGLT2is. Even if reassuring observations were reported in several large prospective placebo-controlled cardiovascular outcome trials, real-life conditions in more frailty patients might be associated with a higher risk.

Methods: This work analyses the incidence of LLA events in retrospective observational studies that compared SGLT2i users with patients treated with dipeptidyl peptidase-4 inhibitors (DPP-4is), a pharmacological class with an excellent safety profile. A meta-analysis of 12 comparative cohort studies (9 of them using a propensity score matching) worldwide has been performed.

Results: The relative risk of LLA tended to be slightly lower in SGLT2i users (1228 LLA events/711159 patients) versus DPP-4i users: 2167 LLA events/1121914 patients, with a hazard ratio 0.91, 95% CI 0.85-0.98, p=0.01). However, a high between-study heterogeneity was observed (I^2 = 79%, P<0.00001), which could not be explained by differences across countries, between studies with/without propensity score matching, between cohorts treated with/without canagliflozin or between patients with/without peripheral artery disease. The incidence rate expressed as a number of LLA events per 1000 patient.years was almost similar among SGLT2i users and DPP-4i users (2.48±1.45 versus 2.67±3.09, p=0.849).

Conclusion: Physicians should not fear an increased risk of LLA with SGLT2is compared with DPP-4is in daily clinical practice, even if caution may be advised in some patients exposed to special conditions.

Introduction

Dipeptidyl peptidase-4 inhibitors (DPP-4is) and sodium-glucose cotransporter type 2 inhibitors (SGLT2is) are the most recent oral glucose-lowering drugs available for the management of type 2 diabetes (T2D). Both pharmacological classes exert almost a similar glucose-lowering activity, yet a slightly greater reduction in glycated haemoglobin (HbA1c) has been reported with SGLT2is in patients with higher baseline HbA1c and normal renal function [1]. Other criteria beyond HbA1c lowering effect should be considered to help in the selection of one or the other class in patients with T2D after metformin failure. Whereas DPP-4is showed only safety but no superiority versus placebo in patients with high cardiovascular risk, SGLT2is have proven their efficacy in reducing the incidence of major cardiovascular events, hospitalisation for heart failure and progression of renal disease [2, 3]. Therefore, SGLT2is currently occupy a priviledged place in the management of T2D patients with or at high risk for such comorbidites [4].

Besides efficacy, safety is obviously a crucial element that may guide the clinician in choosing between two medications. The overall tolerance/safety profile appears to be better with DPP-4is [5] than with SGLT2is [6]. Results of the CANVAS ("CANagliflozin cardioVascular Assessment Study") programme unexpectedly reported a significant increase in the incidence of lower-limb amputations (LLA) in patients with T2D and high cardiovascular risk treated with canagliflozin compared to those treated with placebo [7, 8]. Since then, a special focus has been placed on this specific complication in the international literature dealing with SGLT2is. Several LLA cases were reported via the US Food and Drug Administration (FDA) Adverse Event Reporting System [9], so that the FDA published a warning about an increased risk of leg and foot amputations with canagliflozin in 2016-2017 [10]. A disproportionality analysis using the World Health Organization (WHO) global database of individual case safety reports (VigiBase®) revealed a LLA positive disproportionality signal for canagliflozin, but also for empagliflozin, and, for toe amputations

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only, for dapagliflozin [11]. Thus a question arose: does LLA concern all SGLT2is [12] ? Fortunately, reassuring findings were published from several randomised controlled trials (RCTs) as no such increased risk of LLA was detected in other cardiovascular and renal outcome trials with empagliflozin, dapagliflozin and ertugliflozin, including canagliflozin in CREDENCE ("Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy") [13] as summarized in several meta-analyses [14–17]. In the particular conditions of these RCTs, a neutral effect of SGLT2is was also consistent across different levels of subgroups, including subgroups with or without established peripheral artery disease (PAD) [18, 19]. Nevertheless, one cannot exclude that more fragile patients (i.e. elderly persons, exposed to dehydration, other comorbidities or comedications, among which diuretics) [20] might be exposed to an increased risk of LLA when treated with SGLT2is in real-life conditions. The aim of this comprehensive review is to summarize the effects of SGLT2is on the risk of LLA in large retrospective observational studies that compared SGLT2i users versus DPP-4i users.

Methods

Data sources and search strategy

Electronic searches were performed in Pubmed from January 2010 to December 2021 using the following search terms: sodium-glucose cotransporter type 2 inhibitor (SGLT2 inhibitor) OR dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) combined with the terms "amputation" ("lower limb amputation", "lower extremity amputation"). In a complementary approach, the same search was performed for each SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) OR for each DPP-4i (sitagliptin, saxagliptin, vildagliptin, linagliptin) commercialized worldwide. The reference lists of systematic reviews and meta-analyses dedicated to SGLT2is or DPP-4is and of eligible related articles were manually examined to identify any additional publication relevant to the present study. Abstracts presented in 2021 at the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) annual congresses have also been looked for. Search for duplicates was done manually and using Endnote. Two independent researchers (A.S. and M.M.) screened literature, analysed the selected studies and summarized the search results, using the same inclusion and exclusion criteria. Any resulting discrepancies were resolved by mutual discussion.

Inclusion/exclusion criteria and data extraction

Inclusion criteria were as follows: (a) observational study that compared SGLT2i users versus DPP-4i users in patients with T2D; (b) detailed information about the incidence of LLA in the two treated subgroups should be available. Exclusion criteria were as follows: (a) RCTs; (b) case reports and review articles.

The following data were extracted from all studies: (a) reference (first author, publication year); (b) country where the study was performed; (c) median duration of the follow-up; (d) mean age of the population; (e) type of SGLT2i; (f) definition of LLA; (g) use of propensity score matching; (h) number of patients in each subgroup; (i) number of LLA events in each group; (j) incidence rates expressed as events per 1000 patient.years; (k) hazard rate (HR) with 95% confidence interval (CI); (l) presence of PAD.

The definition of LLA may vary across studies, yet most of them used ICD ("International Classification of Diseases": ICD-9 and/or ICD-10) scores. Patients with antecedents of LLA at baseline were excluded in most studies.

Data synthesis and statistical analysis

Results are expressed as means with 95 % CI or as means (± standard deviation). Meta-analysis used fixed effects, a method that is appropriate when the number of studies is low. The amount of heterogeneity across observational studies is assessed using the I^2, a classical measure of the amount of variation in clinical outcomes due to variance in true effect sizes. Statistical differences in incidence rates between the two treatment groups were estimated using paired t tests. Calculations and forest plots were made using the review manager 5.3 programme.

Results

We identified twelve retrospective studies that compared the risk of LLA in patients with T2D treated with SGLT2is compared with those treated with DPP-4is (Table 1) [21–32]. One recent study from Taiwan reported only one LLA event in SGLT2i users (6507 patient.years; mean age 53.5 ± 8.5 years) versus 84 LLA events in DPP-4i users (178 188 patient.years) [33]. Because such a low number of events among SGLT2is, this study was not included in the meta-analysis. Published studies were carried out in different countries, in North America, Europe and Asia. Nine of these twelve studies used the propensity-score matching approach to compare the two subgroups in order to minimize possible biases. The numbers of patients included in each treated group ranged from 2939 to 207,817 across studies with propensity score matching. The median follow-up was rather short (< 1 year) in most studies, except in two of them that proposed a follow-up between 1.8 and 3.3 years. Mean age ranged from 52.5 to 64.0 years. Most studies included patients treated with any SGLT2i, but two studies recruited SGLT2i-treated patients excluding canagliflozin [27, 29], four studies enrolled ≥ 70% of canagliflozin-treated persons [21-23, 25] and two studies recruited patients only treated with empagliflozin [30, 31] (Table 1).

In a meta-analysis of these 12 observational studies, the relative risk of LLA was slightly lower in SGLT2i users (1228 LLA events/711 159 patients) compared to DPP-4i users: 2167 LLA events/1 121 914 patients, with a HR 0.91, 95% CI 0.85-0.98, p=0.01. However, a high between-study heterogeneity should be pointed out (I^2 = 79%, P<0.00001), and the statistical significance was mainly driven by the recent data reported by Paul et al [32]. Of note, the more positive results in favour of SGLT2is were obtained in the three studies that tested the largest cohorts (relative weight > 10%) [23, 25, 32] (Figure 1).

Because of the median follow-up may be different between the two treated groups in several studies (small differences in most studies, except that by Paul et al [32]: 1.8 years for SGLT2i users versus 3.3 years for DPP-4i users), it is important to standardize the results by calculating the incidence rate expressed as a number of LLA events per 1000 patient.years. No notable difference could be found between SGLT2i users and DPP-4i users (2.48 ± 1.45 versus 2.67 ± 3.09, p=0.849). Of note, one study from Taiwan exclusively recruited patients with PAD and as expected it reported higher incidence rates of LLA events, interestingly much more marked in patients with DPP-4is than in those treated with SGLT2is (12.3 versus 5.4 events per 1000 patient.years) [27]. When excluding this particular study from the overall comparison, no difference in the incidence rate was noticed between SGLT2i users and DPP-4i users (2.21 ± 1.18 versus 1.79 ± 0.62, p=0.308). In another Taiwanese study not included in the meta-analysis, the incidence rates were much lower in both groups, and lower in SGLT2i users than in DPP-4i users (0.15 versus 0.46 LLA events per 1000 patient.years) [33].

Comparison of studies that used propensity score matching with those that didn't give almost similar results. Similarly, no apparent difference could be detected between the 6 studies performed in the United States versus the 6 studies carried out outside the US, in

Table 1
Summary of observational studies that compared the risk of lower-limb amputations in SGLT2i users versus DPP-4i users.

Reference	Country	Follow-up (years)	Age (years) Mean ± SD	SGLT2i molecule	LLA definition	Propensity score matching	N patients SGLT2i vs DPP-4i	Events per 1000 patient. years SGLT2i vs DPP-4i	N LLA events SGT2i vs DPP-4i	Relative risk (*) (95% CI)
Adimadhyam et al 2018 [21]	USA	0.6	54.8 ± 9.9	70% cana NA dapa NA empa	ICD-9 or ICD-10	Yes	30216 vs 30216	1.62 vs 1.15	36 vs 24	1.38 (0.83-2.31)
Chang et al 2018 [22]	USA	0.32/0.35	53.5 ± 8.5	70% cana 22% dapa 8% empa	ICD-9	No	39869 vs 105023	1.05 vs 0.85	18 vs 41	1.50 (0.85-2.67)
Dawwas et al 2019 [23]	USA	≈ 1	55.0 ± 9.2	75% cana 25% dapa	ICD-9	Yes	65847 vs 65847	1.8 vs 1.9	120 vs 171	0.88 (0.65-1.15)
Pasternak et al 2019 [24]	Denmark, Sweden, Norway	1.4	61.0 ± 10.0	1% cana 83% dapa 16% empa	ICD-10	Yes	20983 vs 20983	3.1 vs 2.6	59 vs 64	1.26 (0.88-1.81)
Yang et al 2019 [25]	USA	0.64 vs 1.06	52.5 ± 8.2	70.3% cana 27.4% dapa 7.3% empa	ICD-9	No	49324 vs 116439	2.3 vs 1.6	70 vs 136	1.45 (1.08-1.93)
Yu et al 2020 [26]	Canada/UK	0.92	63.8 ± 9.5	42.3% cana 30.7% dapa 27.0% empa	BKLA	Yes	207,817 vs 207,817	1.3 vs 1.5	253 vs 281	0.88 (0.71-1.09)
Lee et al 2020 [27]	Taiwan	0.96 vs 0.66	64.7 ± 10.7	56% dapa 44% empa	ICD-9 or ICD-10	Yes	11431 vs 11431	5.4 vs 12.3 (**)	41 vs 96	0.43 (0.30-0.62)
Zerovnik et al 2021 [28]	Slovenia	3.3	64.0 ± 8.8	41% dapa 59% empa	Non-traumatic LLA (Australian codes)	Yes	2939 vs 2939	4.3 vs 2.3	37 vs 25	1.86 (1.10-3.14)
Suto et al 2021 [29]	Hungary	1.74 vs 1.80	60.5 ± 9.5	37% dapa 63% empa	ICPM codes	Yes	18583 vs 18583	NA vs NA	127 vs 88	1.35 (1.03-1.77)
Patorno et al 2021 [30]	USA	≈ 0.5	60.2 ± 9.0	100% empa	LLA requiring surgery	Yes	39072 vs 39072	2.78 vs 2.43	58 vs 44	1.12 (0.75-1.67)
Karasik et al 2021 [31]	Europe-Asia	NA	≈ 60	100% empa	LLA	Yes	55 339 vs 55339	0.86 vs 1.30	31 vs 51	0.68 (0.42-1.08)
Paul et al 2021 [32]	USA	1.8 vs 3.3	57.5 ± 10.8	46% cana 21% dapa 23% empa 10% multiple	ICD or SNOMED	No	169739 vs 448228	1.26 vs 1.42	378 vs 1146 (***)	0.65 (0.56- 0.75)
Chang et al 2021 [33] (****)	Taiwan	0.8 vs 1.0	56.2 ± 12.0	Not specified	ICD-9 or ICD-10	No	8285 vs 174422	0.15 vs 0.46	1 vs 82	NA

BKLA: below-knee lower extremity amputation. CI: confidence interval. DPP-4is: dipeptidyl peptidase-4 inhibitors. ICD: International Classification of Diseases. ICPM: International Classification of Procedures in Medicine. LLA: lower-limb amputation. NA: not available. PAD: peripheral artery disease. SD: standard deviation. SGLT2i: sodium-glucose cotransporter type 2 inhibitor. SNOMED: Systematized Nomenclature of Medicine Clinical Terms.

* Relative risk expressed by hazard ratio, odds ratio or risk ratio across studies.

** Higher incidence rate because all patients had peripheral artery disease

*** The number of LLA events among DPP-4i users was calculated from incidence rate (1.42/1000 patient.years) and adjusted for 448225 patients and a mean follow-up of 1.8 years (rather than 3.3 years, to consider the same duration as for SGLT2is)

**** Not included in the meta-analysis because of the very low number of LLA events among SGLT2i users (only one event !)

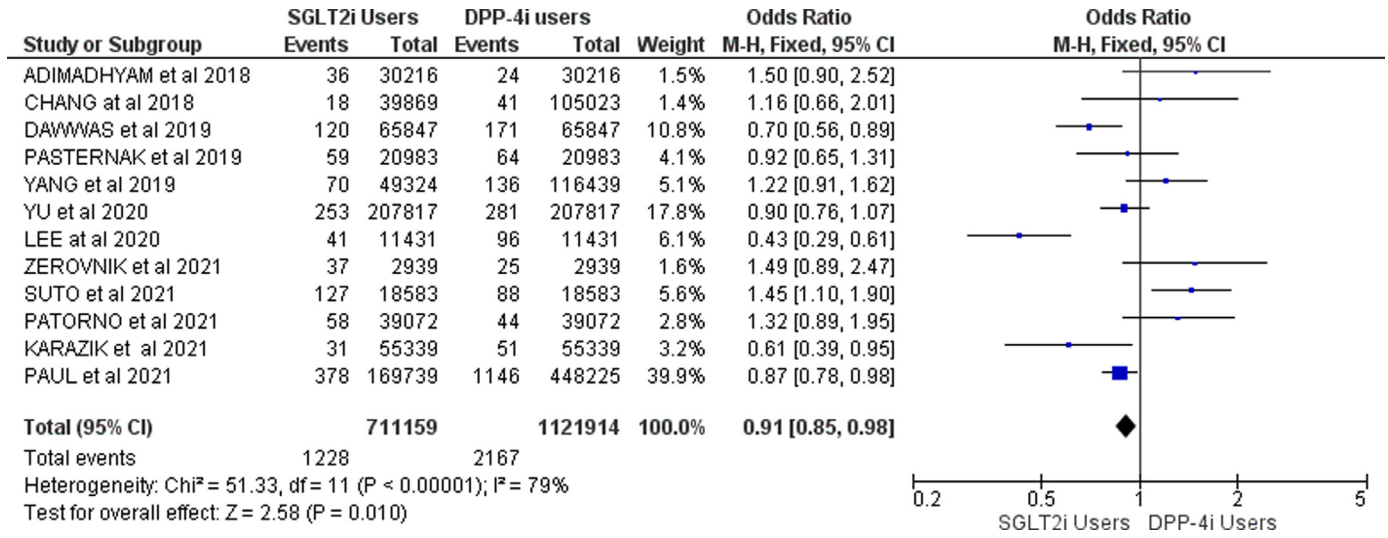

Fig. 1. Meta-analysis of observational studies that compared the risk of lower-limb amputations in SGLT2i users versus DPP-4i users.

For Paul et al (2021), the number of LLA events among DPP-4i users was calculated from incidence rate (1.42/1000 patient.years) and adjusted for 448225 patients and a mean follow-up of 1.8 years (rather than 3.3 years, to consider the same duration as for SGLT2is)

Europe and Asia. The results were also comparable in studies that included or excluded canagliflozin among SGLT2is. Thus, no obvious explanation could be proposed to elucidate the reasons for the high heterogeneity across studies.

Discussion

Our results derived from a large set of observational studies in real-life conditions demonstrate that SGLT2is are not associated with an increased risk of LLA compared with DPP-4is used as active comparators. Thus these reassuring real-world findings confirm results reported in seven large prospective RCTs that compared SGLT2is with placebo in T2D patients at high cardiovascular or renal risk which also showed no significant increased risk of LLA associated with SGLT2i therapy (RR = 1.21, 95% CI = 0.97-1.51, I^2 = 59%) and almost neutral effect after the exclusion of CANVAS with no more heterogeneity (RR = 1.09, 95% CI 0.94-1.26, I^2 = 0 %) [16]. The absence of a significant increase risk of LLA was also reported when considering a larger set of 12 RCTs that combined phase 3 trials and cardiovascular outcome trials [15]. Fixed effects analysis showed an increased risk of LLA associated with SGLT2is (RR 1.27, 95% CI 1.09-1.48), but again with a statistical heterogeneity (I^2 = 62%; p = 0.003); however, this difference failed to reach statistical significance when a random effects meta-analysis was performed (RR 1.28, 95% CI 0.93-1.76; I^2 = 62.0%; p=0.12). In a further meta-analysis that included not only cardiovascular outcome trials but also other trials (total of 15 RCTs), the risk of LLA in patients treated with SGLT2is compared with a placebo or other active comparators was significantly increased (OR 1.23, 95% CI 1.08-1.40, P=0.002, with a surprising low heterogeneity (I^2 = 2%) that contrasted with all other analyses including ours [17].

In a 2020 systematic review that considered both RCTs and observational studies comparing SGLT2i users with non-users (placebo or any active comparator), the conclusion was that the findings from observational studies were too heterogeneous to be pooled in a meta-analysis and draw meaningful conclusions [15]. Only one systematic review and meta-analysis that compared real-world data concluded that SGLT2is do not increase the risk of LLA [34]. In this meta-analysis of seven observational studies that reported LLA data among 1 718 247 patients, a significantly lower incidence of below-knee amputations was reported in patients treated with SGLT2is compared to those treated with other glucose-lowering drugs (including DPP-4is) (HR 0.83, 95% CI 0.71-0.98, p=0.02), but with a high heterogeneity (I^2 = 75%, p< 0.001) [34]. Of note, this paper mainly focused on cardiovascular outcomes with only a paucity of data regarding LLA events. Our meta-analysis, the only one that is specifically devoted to the LLA complications and restricts the comparison with DPP-4is, fully confirms and extends the safety profile of SGLT2is.

There is no obvious explanation for the high heterogeneity found across observational studies. No difference could be observed when comparing studies performed in the United States and those carried out in Europe or Asia. Similarly, results of studies that included canagliflozin among other SGLT2is [21-23, 25, 26] and those that excluded canagliflozin [27–31] resulted in comparable results. In a recent observational study from the US, the incidence rate (per 1000 patient.years) of LLA was not increased when comparing canagliflozin-treated patients (1.07, 95% CI 0.91-1.25) with those treated with dapagliflozin (1.29, 95% CI 1.03-1.62) or empagliflozin (1.52, 95% CI 1.21-1.91) [32]. These results are in line with the 2017 publication by the FDA that removed boxed warning about the risk of leg and foot amputations for canagliflozin [35]. Overall, after early concerns [11, 12], recent available observations are reassuring for all the class of SGLT2is regarding the potential risk of LLA [36].

The presence of PAD was associated with more than a four-fold increased risk of LLA (95% CI 3.6-6.0) in SGLT2i users as well as in non-users [32]. Of note, in a nationwide retrospective cohort study based on the Taiwan National Health Insurance Research Database, SGLT2i therapy was associated with lower risks (HR 0.43, 95% CI 0.30-0.62) of adverse lower limb events compared with DPP-4i therapy among patients with T2D and PAD in real-world practice [27].

In contrast with the numerous observational studies that investigated the incidence of LLA with SGLT2is, similar studies devoted to DPP-4is are scarce. A retrospective registry analysis using Taiwan's National Health Insurance Research Database was the first to demonstrate that treatment with DPP-4is is associated with lower risk of PAD occurrence and LLA in patients with T2D compared with DPP-4i nonusers (HR 0.65; 95% CI 0.54-0.79) [37]. By using the same source of data, a recent study showed that the use of glucagon-like petptide-1 receptor agonists was associated with significantly lower risk of major adverse limb events when compared with the use of DPP4is (LLA: HR 0.55, 95% CI 0.30-0.99] [38].

This meta-analysis is the first one that pooled all observational studies which compared the incidence of LLA in SGLT2i users versus DPP-4i users. Even if the results of a meta-analysis should be

interpreted with caution [39], our meta-analysis has the advantage of analysing a large set of homogeneous data from different countries so that generalisability of the results may be expected. Furthermore, most studies used a propensity score matching to minimize potential differences in the characteristics of the two groups. One first limitation is that all studies were retrospective and none of them were specifically designed to investigate LLA events, which were collected among other major adverse events. As a consequence, the definition of LLA may differ between studies even if most of them used the ICD-9/10 classification. A second limitation is the lack of detailed information about the level of amputation (below the knee or toes only ?) in most reports. A third limitation is inherent to retrospective observational studies, which may expose to confounding and selection bias that could distort the findings, even after propensity score matching [40, 41]. A fourth limitation is due to the rather short-term follow-up in all these studies, most of them having less than one-year duration. A fifth limitation results from the high heterogeneity across studies, a finding that requires caution before drawing definite conclusion, in the absence of any explanation to delineate this heterogeneity [39].

Conclusion

The reassuring data regarding the potential risk of LLA in patients with T2D treated with SGLT2is reported in large prospective placebo-controlled RCTs are confirmed in retrospective observational studies in real-life conditions worldwide. No increased risk of LLA is observed when comparing SGLT2i users with DPP-4i users in a large set of data, yet a high heterogeneity should be recognized across studies. Thus, health care providers should not fear an increased risk of LLA with SGLT2is, even if caution is still recommended in some patients and special conditions that may increase the risk.

Disclosure

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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