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THE ASSOCIATION OF SODIUM-GLUCOSE CO-TRANSPORTERS INHIBITORS AND LOWER LIMB AMPUTATION- A REVIEW OF LITERATURE

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Abstract:

In 2015, the global prevalence of diabetes mellitus (DM) has risen to 8.8% [1] and this high incidence of DM is associated with the increasing numbers of individuals with diabetic foot disease. Up to 75% of these patients is going for lower extremity amputations (LEAs) as part of treatment[2]. LEAs reduce the quality of life and increase mortality as well as medical costs[3,4]. Even though an overall reduction in amputations were observed, the incidence of LEAs in diabetic patient is high and it is estimated, one amputation every seven min in subjects ≥ years could be attributed to diabetes mellitus [5].In a review on the incidence of LEA in diabetic patients Narres et al[6] observed a significant decrease in incidence of LEA and this reduction in LEAs is attributed to the improvement in diabetic foot care. Three studies were on empagliflozin, two used dapagliflozin, four on canagliflozin, and eight were on all the three drugs. Three retrospective studies, the CANVAS and CANVAS-R trials, pooled data from fifteen trials, one review, one meta-analysis, a population-based cohort, Data from 4 large US administrative claims databases, A propensity-matched cohort, and 8 293 886 reports analysis. The authors names, year of publication, country, the study design, the numbers of patients included, the duration of follow-up, the final results, and limitations were recorded. SGLT2 inhibitors, a relatively new class of diabetic medication have been shown it effectiveness in glycemic control among type 2 diabetes patients and also showed its potential to improve body mass index, blood pressure, and diabetes-related end-organ complications. Apart from these therapeutic effect, there are some clinical reports that these agents are associated with increased risk for LEA in diabetic patients. Based on findings of this narrative review, as a class of drugs, the SGLT2 inhibitors are not associated with increased risk for lower extremity amputation in type 2 diabetes mellitus patients, when compared oral hypoglycemic agents such as sulphonylureas and placebo. However, some of systematic reviews showed the possibility for the association of canagliflozin with a higher risk of amputation in this patient cohort. Based on these observations, we suggest further systematic evaluation of canagliflozin for its association with increased risk of LEAs in type 2 diabetes mellitus patients.

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INTRODUCTION:

In 2015, the global prevalence of diabetes mellitus (DM) has risen to 8.8% [1] and this high incidence of DM is associated with the increasing numbers of individuals with diabetic foot disease. Up to 75% of these patients is going for lower extremity amputations (LEAs) as part of treatment[2]. LEAs reduce the quality of life and increase mortality as well as medical costs[3,4]. Even though an overall reduction in amputations were observed, the incidence of LEAs in diabetic patient is high and it is estimated, one amputation every seven min in subjects ≥ years could be attributed to diabetes mellitus [5].In a review on the incidence of LEA in diabetic patients Narres et al[6] observed a significant decrease in incidence of LEA and this reduction in LEAs is attributed to the improvement in diabetic foot care.

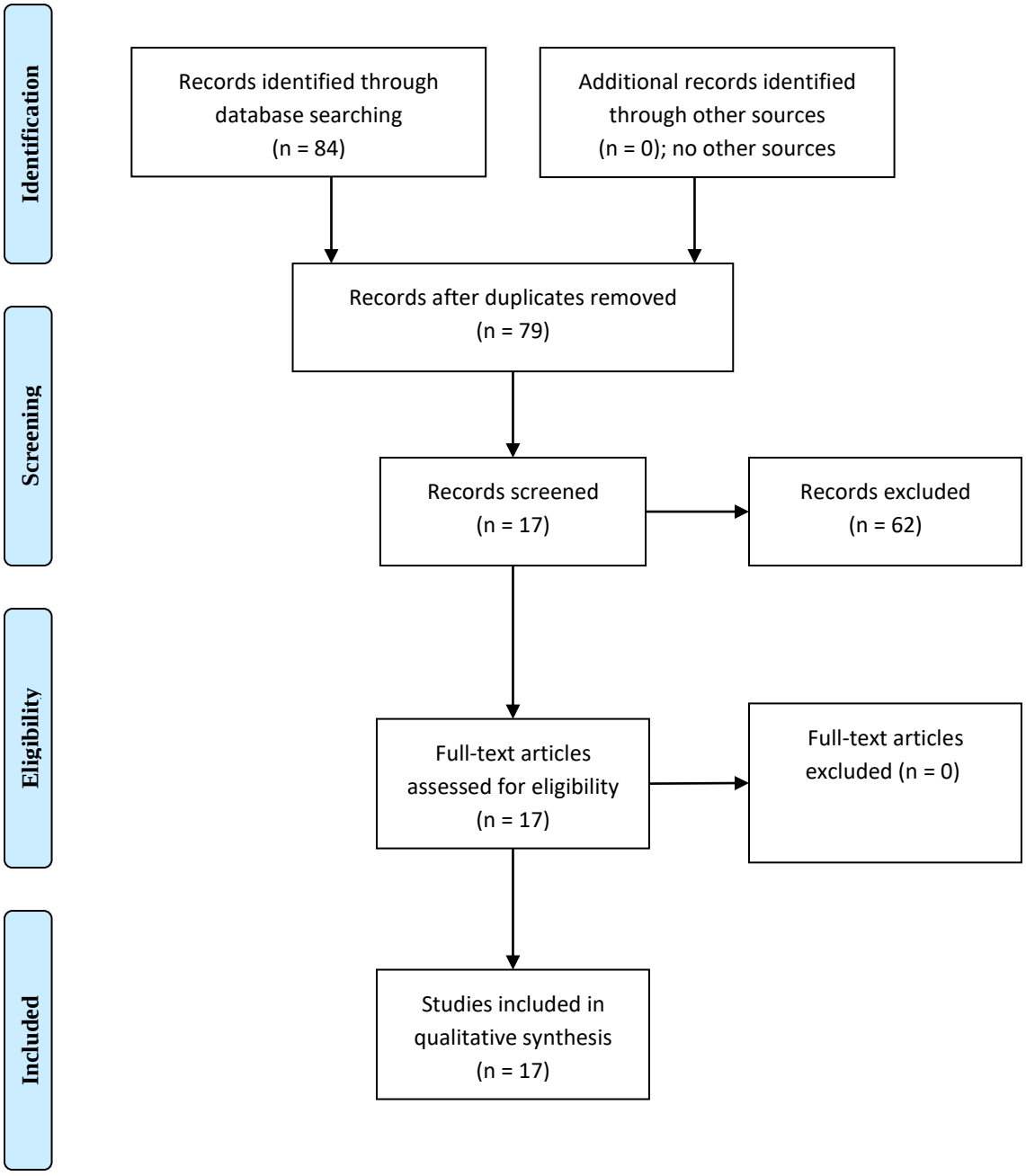
A good number of innovative pharmaceutical agents are introduced for the treatment of DM recently. Sodium-glucose co-transporter (SGLT2) inhibitors are new members of a group of medication, that have been shown not only to improve glycemic control among patients with diabetes but also reduce body mass index, blood pressure, and diabetes-related end-organ complications [7].However, there are some observational report on a SGLT2 inhibitors, that these agents are associated with increased risk for LEA in diabetic patients[8]. This observation is also supported by the clinical trials results suggest that canagliflozin, a member of SGLT 2 inhibitors used for the treatment of diabetes mellitus may be associated with lower limb amputation [9]. Since the SGLT-2 inhibitors are a promising option in the management of patients with type 2 diabetes mellitus and cardiovascular risk, the observed association with amputation is of great concern because amputation has a great negative impact on patients clinical course and quality of life (10,11). However, there are some study report contradicting the role of SGLT 2 inhibitors in increased role of LEA in diabetic patients. In a retrospective cohort study, Yuan Z et al observed no evidence for the association of canagliflozin with high causation of below knee amputation in type 2 DM patients[12]. In this context, since the available data shows conflict information on this complication of SGLT 2 inhibitors, we conducted this review with primary objective to assess the risk of lower amputation among SGLT-2 inhibitors.

METHODOLOGY:

We conducted an extensive manual and electronic literature search in data bases Pub Med and Google scholar using the following search criteria: the full human trail articles published in English language during the period from 2013 to 2018, using the key words of 'canagliflozin', 'dapagliflozin', 'empagliflozin', 'limb amputation', 'peripheral arterial disease', and 'SGLT-2 inhibitors'. Two researchers independently reviewed the collected articles for its relevance and to avoid duplication. The details of the process is shown in fig:1. A total of eighty four articles, (forty four randomized control trials and related articles published in PubMed, and forty Google scholar articles) were identified. After search for relevance and duplication based on search criteria, identified seventeen full articles for final analysis.

Three studies were on empagliflozin, two used dapagliflozin, four on canagliflozin, and eight were on all the three drugs. Three retrospective studies, the CANVAS and CANVAS-R trials, pooled data from fifteen trials, one review, one meta-analysis, a population-based cohort, Data from 4 large US administrative claims databases, A propensity-matched cohort, and 8 293 886 reports analysis. The authors names, year of publication, country, the study design, the numbers of patients included, the duration of follow-up, the final results, and limitations were recorded.The results were shown in table 1, 2 &3. Some of the studies assessed two drugs (dapagliflozin and canagliflozin)

Diagram 1: The Process of Literature Search: Flow Chart



RESULTS AND DISCUSSION:

Empagliflozin:

The EMPA-REG OUTCOME trial with enrollment of 7020 type 2 diabetes mellitus, who were treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo in addition to standard of care and with a median follow up observation time of 3.1 years. In this trial 22% of patients with history of peripheral artery occlusive disease. During the interval of trial 131 patients underwent for LLAs with 88 patients in

empagliflozin group and 43 in placebo group. The incidence rate was 6.5 per 1000 patient-years in both groups. In data analysis for the time of first event, the risk for LLA was found similar in both groups of empagliflozin and placebo. There was no difference between empagliflozin 10 mg (HR 0.96 [95% CI 0.63, 1.47]) and empagliflozin 25 mg (HR 1.04 [95% CI 0.69, 1.58])[13].

Yabe De et al,[14] in 2018 conducted a pooled analysis of data from phase I-III clinical trial in East Asian patients with type 2 diabetes mellitus to establish the safety of empagliflozin. In this study, 709 patients received placebo, 724 patients received empagliflozin 10mg and 708 patients received empagliflozin 25mg with total exposure of 953, 1072 1nd 1033 patient-years respectively. The data from the analysis of results concludes with similar risk of LLAs in patients received empagliflozin and placebo for the treatment of type 2 diabetes mellitus in East Asian population.

Table 1. Data on empagliflozin

Author	year	Country	Study	Patients no	Duration	Results
Inzucchi Et al.	2018	USA	EMPA-REG trial	2070	3.1 years	Not associates
Yabe D et al.	2018	Japan	Pooled data from 15 phase 1-111 trials	709, 724		Amputation risk was similar to placebo
Frampton et al.	2018	Newzealand	Review			No association

DAPAGLIFLOZIN:

Ina systematic review analysis Jabbour et al. [15] pooled data from 13 placebo controlled trials up to 24 weeks duration, 21 trials of ≥ 208 weeks and 30 trials of ≥ 12 weeks with dapagliflozin in type 2 diabetes mellitus to find out safety and tolerability of the drug. In their analysis they found 0.1% (8 patients) and 0.2% (7 patients) lower limb amputations in patients receiving dapagliflozin and control, respectively in 30 trial pool and concluded that no association of dapagliflozin with LLAs in type 2 diabetes mellitus patients.

Table 2: Data on dapagliflozin

Author	year	Country	Study	Patients no	Duration	Results
Jabbour Et al.	2018	USA	Data from 33 trials &21 comprator control pool	27818	24 weeks	Not associates

CANAGLIFLOZIN:

Two multinational randomized placebo controlled trial(CANVAS and CANVAS-R trials)[16] with involvement of 10142 patients used cangliflozin to find out the safety of the drug in type 2 diabetes patients with cardiovascular disease or with the risk for cardiovascular disease. The mean duration of the trails was 188.2 weeks and they used canagliflozin 100mg and 300mg and placebo in 1:1:1 ratio randomized patients in CANVAS and cangliflozin 100mg with optional increase up to 300mg and placebo in 1:1 ration randomized patients. The study concluded that an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal in patients received canagliflozin.

A recent meta-analysis by Li D et al, in 2018 (17) with an aim to evaluate the potential risk of SGLT2is to cause diabetic foot syndrome and amputation. The study evaluated fourteen Randomized Controlled

Trials with participation of 26,167 patients. Data analysis proved, as a class SGLT2is has no significant association with increased risk for amputation, however subclass analysis indicates an increased risk of amputation in patients using canagliflozin (OR 1.89, 95% CI: 1.37-2.60), on cross analysis with oral hypoglycemic drugs and placebo.

Very recently in 2018 July, Dawwas et al. (18) conducted a retrospective cohort study using Truven HealthMarketScan (Truven Health Analytics, Ann Arbor, MI, USA), with inclusion of type 2 diabetes mellitus patients. In the analysis after matching, a total of 125 534 patients were included in the SGLT2 inhibitors(dapagliflozin and canagliflozin) vs sulfonylureas cohort (n = 62 767 per exposure group) and a total of 133 266 patients in the SGLT2 inhibitors vs DPP-4 inhibitors cohort (n = 66 633 per exposure group). They considered the lower extremity amputation as secondary outcome in data evaluation and found lowering the risk for amputation in SGLT2i using patients than sulfonylureas cohort in subclass analysis which showed that dapagliflozin vs sulfonylureas (HR, 0.55; 95% CI, 0.43, 0.70) and canagliflozin vs sulfonylureas (HR, 0.61; 95% CI, 0.54, 0.69).

Table 3: Data on Canagliflozin

Author	year	Country	Study	Patients no	Duration (Mean)	Results
Neal Et al.	2017	Australia	Two trials, CANVAS and CANVAS-R	10,142	188.2 weeks	Increase amputation
Li et al.	2018	China	A Meta-analysis of Randomized Controlled Trials.	Fourteen RCTs involving 26,167 patients	1.6 years	Associated with amputation
Dawwas et al.	2018	USA	Retrospective	62767 on SGLT-2	12 months	Less amputation compared to DPP-4 inhibitors and sulphonylureas
Yuan et al.	2018	USA	Retrospective cohort	344641	40 months	No increased risk compared to non-SGLT-2

CANVAS: . Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.

Yuan Z et al [19] conducted a retrospective cohort study in 2018, to examine the incidence of lower extremity amputation in type 2 diabetic patients on SGLT2 inhibitors, especially with canagliflozin. The article analysed data of 118018 new users of SGLT2inhibitors, including 73024 patients with canagliflozin and 226623 new users of non-SGLT2inhibitors. This real world study observed no evidence for the increased risk of lower extremity amputation in the new users of canagliflozin than the patients on non-SGLT2 inhibitors. The incidence rates of amputation were 1.18 and 1.12 events per 1000 person-years with canagliflozin and non-SGLT2 inhibitor, respectively; with hazard ratio of 0.98 (95% confidence interval 0.68-1.41; P = .92, calibrated P = .95).

CONCLUSION:

In conclusion, SGLT2 inhibitors, a relatively new class of diabetic medication have been shown it effectiveness in glycemic control among type 2 diabetes patients and also showed its potential to improve body mass index, blood pressure, and diabetes-related end-organ complications. Apart from these therapeutic effect, there are some clinical reports that these agents are associated with increased risk for LEA in diabetic patients. Based on findings of this narrative review, as a class of drugs, the SGLT2 inhibitors are not associated with increased risk for lower extremity amputation in type 2 diabetes mellitus patients, when compared oral hypoglycemic agents such as sulphonylureas and placebo. However, some of systematic reviews showed the possibility

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REFERENCES:

1. International Diabetes Federation. IDF Diabetes Atlas—7th edition 2016. http://www.idf.org/diabetesatlas
2. Trautner C, Haastert B, Spraul M, Giani G, Berger M. Unchanged incidence of lower-limb amputations in a German City, 1990–1998. Diabetes Care. 2001;24(5):855–9.
3. Price P. The diabetic foot: quality of life. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2004;39 Suppl 2:S129–31. Epub 2004/08/13. doi: 10.1086/383274
4. Hoffstad O, Mitra N, Walsh J, Margolis DJ. Diabetes, lower-extremity amputation, and death. Diabetes Care. 2015;38(10):1852–7. Epub 2015/07/24. doi: 10.2337/dc15-0536 . [PubMed]
5. Carinci F, Massi Benedetti M, Klazinga NS, Uccioli L.Lower extremity amputation rates in people with diabetes as an indicator of health systems performance. A critical appraisal of the data collection 2000-2011 by the Organization for Economic Cooperation and Development (OECD). Acta Diabetol. 2016 Oct;53(5):825-32. doi: 10.1007/s00592-016-0879-4. Epub 2016 Jul 21
6. Maria Narres, Tatjana Kvitkina, Heiner Claessen, Sigrid Droste, Bjo¨rn Schuster , Stephan Morbach, Gerhard Ru¨menapf , Kristien Van Acker , Andrea Icks. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: A systematic review. PLOS ONE | https://doi.org/10.1371/journal.pone.0182081 August 28, 2017
7. d'Emden M, Amerena J, Deed G, Pollock C, Cooper ME. SGLT2 inhibitors with cardiovascular benefits: Transforming clinical care in Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2018 Feb;136:23-31. doi: 10.1016/j.diabres.2017.11.023. Epub 2017 Dec 2.
8. Sruthi A, Todd A L, Gregory SC, Daphne ESM, Brian T L, Glen TS. Risk of amputations associated with SGLT2 inhibitors compared to DPP-4 inhibitors: A propensity-matched cohort study. Diabetes Obes Metab.2018;20:2792–2799. DOI: 10.1111/dom.13459;
9. Chang HY, Singh S, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients With Type 2 Diabetes. JAMA Intern Med. 2018 Sep 1;178(9):1190-1198. doi: 10.1001/jamainternmed.2018.3034
10. Deeks ED, Scheen AJ. Canagliflozin: A Review in Type 2 Diabetes. Drugs. 2017 Sep;77(14):1577-1592. doi: 10.1007/s40265-017-0801-6.
11. Tanaka A, Node K. Increasedamputation risk with canagliflozin treat ment: behind the large cardiovascular benefit?. Cardiovasc Diabetol. 2017 Oct 12;16(1):129. doi: 10.1186/s12933-017-0611-x.
12. Yuan Z, Frank JDF, Patrik BR, Martijn JS, Paul ES, Jesse AB, Mehul D, Norm R. Risk of lower extremity amputation in peoples with type 2 diabetes mellitus treated with sodium-glucose co-transporter -2 inhibitors in the USA. A retrospective cohort study. Diabetes Obes Metab. 2018;20:582-589. DOI:10.1111/dom.13115
13. Inzucchi SE, Iliev H, Pfarr E Zinman B. Empagliflozin and Assessment of Lower-Limb Amputations in the EMPA-REG OUTCOME Trial. Diabetes Care. 2018 Jan;41(1):e4-e5. doi: 10.2337/dc17-1551. Epub 2017 Nov 13.
14. Yabe D, Yasui A, Ji L, Lee MK, Ma RCW, Chang TJ, Okamura T, Zeller C, Kaspers S, Lee J, Kohler S, Seino Y. Safety and tolerability of empagliflozin in East Asian patients type 2 diabetes: pooled analysis of Phase I-III clinical trials. J Diabetes Investig. 2018 Aug 12. doi: 10.1111/jdi.12910. [Epub ahead of print]
15. Jabbour S, Seufert J, Scheen A, Bailey CJ, Karup C, Langkilde AM. Dapagliflozin in patients with type 2 diabetes mellitus: A pooled analysis of safety data from phase IIb/I II clinical trials. Diabetes Obes Metab. 2018 Mar;20(3):620-628. doi: 10.1111/dom.13124. Epub 2017 Oct 26.
16. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12
17. Li D, Yang JY, Wang T, Shen S, Tang H. Risks of diabetic foot syndrome and amputation associated with sodium glucose

co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials. Diabetes Metab. 2018 Feb 13. pii: S1262-3636(18)30041-7. doi: 10.1016/j.diabet.2018.02.001. [Epub ahead of print]

18. Dawwas GK, Smith SM, Park H. Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes. Diabetes Obes Metab. 2018 Jul 23. doi: 10.1111/dom.13477. [Epub ahead of print]
19. Yuan Z, DeFalco FJ, Ryan PB, Schuemie MJ, Stang PE, Berlin JA, Desai M, Rosenthal N. Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: A retrospective cohort study. Diabetes Obes Metab. 2018 Mar;20(3):582-589. doi: 10.1111/dom.13115. Epub 2017 Oct 11.