CADTH

CADTH Reference List

Sodium-Glucose Cotransporter-2 Inhibitors for Type 2 Diabetes Mellitus

September 2022

Summary of Abstracts

CADTH

Authors: Weiyi Xie, Jennifer Horton

Cite As: *Sodium-Glucose Cotransporter-2 Inhibitors for Type 2 Diabetes Mellitus*. (CADTH reference list: summary of abstracts). Ottawa: CADTH; 2022 Sep.

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up to date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein do not necessarily reflect the views of Health Canada, Canada's provincial or territorial governments, other CADTH funders, or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **requests@cadth.ca**

Key Message

We found 7 systematic reviews about potential clinical benefits and harms of sodium-glucose cotransporter-2 inhibitors in adults with type 2 diabetes mellitus.

Research Question

What literature describes the potential clinical benefits and harms of sodium-glucose cotransporter-2 inhibitors in adults with type 2 diabetes mellitus?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, and the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were SGLT2 inhibitors and type 2 diabetes. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons. Where possible, retrieval was limited to the human population. The search was completed on September 12, 2022, and limited to English-language documents published since January 1, 2021. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information available in the abstracts of selected publications. If the abstract did not mention the mean age of the population, or it was unclear whether adult or pediatric patients were included in the study, the citation was included in the results and a footnote was used in the Summary of Findings table to identify studies with unspecified population ages.

Results

Seven systematic reviews with meta-analyses were identified regarding potential clinical benefits and harms of sodium-glucose cotransporter-2 (SGLT2) inhibitors in adults with type 2 diabetes mellitus (T2DM).[1-7] No relevant health technology assessments were identified.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients (≥ 18 years of age) with type 2 diabetes
Intervention	SGLT2 inhibitors (i.e., empagliflozin, canagliflozin, dapagliflozin)
Comparator	Alternate SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) Glucagon-like peptide-1 agonists (e.g., exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide) Dipeptidyl peptidase-4 inhibitors (e.g., sitagliptin, saxagliptin, linagliptin, alogliptin) Biguanide (i.e., metformin)
Outcomes	Descriptions of potential clinical benefits (e.g., glycemic control, blood pressure, weight loss, cardiovascular outcomes) and harms (e.g., hypoglycemia, hypotension, diabetic ketoacidosis)
Study designs	Health technology assessments, systematic reviews

SGLT2 = sodium-glucose cotransporter-2.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

Seven systematic reviews with meta-analyses regarding potential clinical benefits and harms of SGLT2 inhibitors in patients with T2DM were identified.[1-7] Five systematic reviews[1,2,5-7] studied empagliflozin, dapagliflozin, and canagliflozin. Two systematic reviews[3,4] compared the effect of canagliflozin to other SGLT2 inhibitors. Other studies compared SGLT2 inhibitors to ertugliflozin,[5-7] glucagon-like peptide-1 agonists,[6,7] biguanides,[6,7] thiazolidinediones,[6,7] and dipeptidyl peptidase-4 inhibitors.[7]

Two systematic reviews investigated the impact of SGLT2 inhibitors on cardiovascular outcomes, including all-cause mortality,[2,5] cardiovascular events,[2] cardiovascular mortality,[5] and worsening heart failure.[5] Other outcomes measured were serum uric acid levels,[1] glycemic control,[3] alanine aminotransferase levels,[4] high-density and low-density lipoprotein cholesterol levels,[4] triglyceride levels,[4] blood pressure,[6] and weight loss.[3,4,6] Potential harms evaluated were volume depletion[2] and fracture.[7] A detailed summary of the included systematic reviews and meta-analyses can be found in Table 2.

Table 2: Summary of Included Systematic Reviews and Meta-Analyses

Study citation	Included studies	Population	Intervention	Relevant comparators	Outcomes measured	Harms measured
Hu et al. (2022)[1]	19 RCTs	People with T2DM[a] N = 4,218	SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin, and canagliflozin)	SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin, and canagliflozin)	Serum uric acid levels	NA

Study citation	Included studies	Population	Intervention	Relevant comparators	Outcomes measured	Harms measured
Jiang et al. (2022)[2]	47 RCTs	People with T2DM[a] N = 70,574	SGLT2 inhibitors (i.e., empagliflozin, dapagliflozin, and canagliflozin) at varying doses	SGLT2 inhibitors (i.e., empagliflozin, dapagliflozin, and canagliflozin) at varying doses	All-cause mortality and cardiovascular events	Volume depletion
Pinto et al. (2022)[3]	18 RCTs	People with T2DM[a] N = 16,095	SGLT2 inhibitors (e.g., canagliflozin) at varying doses	SGLT2 inhibitors (e.g., canagliflozin) at varying doses	Body weight and hemoglobin A1C	NA
Chen et al. (2021)[4]	36 RCTs	People with T2DM[a]	SGLT2 inhibitors (e.g., canagliflozin)	SGLT2 inhibitors (e.g., canagliflozin)	Body weight, HDL and LDL cholesterol levels, triglyceride levels, and ALT levels	NA
Tager et al. (2021)[5]	64 RCTs	People with T2DM[a] N = 74,874	SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin, and canagliflozin)	SGLT2 inhibitors (i.e., empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin)	All-cause mortality, cardiovascular mortality, and worsening heart failure	NA
Tsapas et al. (2021)[6]	424 RCTs	Adults with T2DM N = 276,336	SGLT2 inhibitors (i.e., empagliflozin, dapagliflozin, and canagliflozin)	SGLT2 inhibitors (i.e., empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin); GLP1 agonists (i.e., semaglutide, exenatide, and liraglutide); biguanide (i.e., metformin); and thiazolidinedione (i.e., pioglitazone)	Blood pressure and body weight	NA
Zhang et al. (2021)[7]	117 RCTs	People with T2DM[a] N = 221,364	SGLT2 inhibitors (i.e., empagliflozin, dapagliflozin, and canagliflozin)	SGLT2 inhibitors (i.e., empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin); DPP-4 inhibitors (i.e., linagliptin, alogliptin, omarigliptin, trelagliptin, vildagliptin, sitagliptin, and saxagliptin); thiazolidinediones; GLP1 agonists (e.g., albiglutide, nateglinide, exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide); sulfonylureas; meglitinides; alpha-glucosidase inhibitors; and biguanides	NA	Fracture risk

ALT = alanine transaminase; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

[a]Age of the population was unclear or unreported in the abstract.

CADTH

References

Health Technology Assessments

No literature identified.

Systematic Reviews

1. Hu X, Yang Y, Hu X, et al. Effects of sodium-glucose cotransporter 2 inhibitors on serum uric acid in patients with type 2 diabetes mellitus: A systematic review and network meta-analysis. *Diabetes Obes Metab*. 2022;24(2):228-238. PubMed
2. Jiang Y, Yang P, Fu L, Sun L, Shen W, Wu Q. Comparative Cardiovascular Outcomes of SGLT2 Inhibitors in Type 2 Diabetes Mellitus: A Network Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne)*. 2022;13:802992. PubMed
3. Pinto LC, Rados DV, Remonti LR, Viana MV, Leitao CB, Gross JL. Dose-ranging effects of SGLT2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis. *Arch Endocrinol Metab*. 2022;66(1):68-76. PubMed
4. Chen MB, Wang H, Cui WY, Xu HL, Zheng QH. Effect of SGLT inhibitors on weight and lipid metabolism at 24 weeks of treatment in patients with diabetes mellitus: A systematic review and network meta-analysis. *Medicine (Baltimore)*. 2021;100(6):e24593. PubMed
5. Tager T, Atar D, Agewall S, et al. Comparative efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i) for cardiovascular outcomes in type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *Heart Fail Rev*. 2021;26(6):1421-1435. PubMed
6. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetes Obes Metab*. 2021;23(9):2116-2124. PubMed
7. Zhang YS, Zheng YD, Yuan Y, Chen SC, Xie BC. Effects of Anti-Diabetic Drugs on Fracture Risk: A Systematic Review and Network Meta-Analysis. *Front Endocrinol (Lausanne)*. 2021;12:735824. PubMed

CADTH

Appendix 1: References of Potential Interest

Note that this appendix has not been copy-edited.

Systematic Reviews

Unclear Intervention – Empagliflozin, Canagliflozin, and Dapagliflozin Not Specified

Chai S, Zhang R, Zhang Y, et al. Influence of dipeptidyl peptidase-4 inhibitors on glycemic variability in patients with type 2 diabetes: A meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2022;13:935039. PubMed

Chalmoukou K, Polyzos D, Manta E, et al. Renal outcomes associated with glucose-lowering agents: Systematic review and meta-analysis of randomized outcome trials. *Eur J Intern Med*. 2022;97:78-85. PubMed

He L, Wang J, Ping F, et al. Dipeptidyl peptidase-4 inhibitors and gallbladder or biliary disease in type 2 diabetes: systematic review and pairwise and network meta-analysis of randomised controlled trials. *BMJ*. 2022;377:e068882. PubMed

Kawai Y, Uneda K, Yamada T, et al. Comparison of effects of SGLT-2 inhibitors and GLP-1 receptor agonists on cardiovascular and renal outcomes in type 2 diabetes mellitus patients with/without albuminuria: A systematic review and network meta-analysis. *Diabetes Res Clin Pract*. 2022;183:109146. PubMed

Li W, Chen X, Xie X, et al. Comparison of Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-like Peptide Receptor Agonists for Atrial Fibrillation in Type 2 Diabetes Mellitus: Systematic Review With Network Meta-analysis of Randomized Controlled Trials. *J Cardiovasc Pharmacol*. 2022;79(3):281-288. PubMed

Oh S, Purja S, Shin H, Kim M, Kim E. Hypoglycemic agents and glycemic variability in individuals with type 2 diabetes: A systematic review and network meta-analysis. *Diab Vasc Dis Res*. 2022;19(3):14791641221106866. PubMed

Sim R, Chong CW, Loganadan NK, et al. Comparative effectiveness of cardiovascular, renal and safety outcomes of second-line antidiabetic drugs use in people with type 2 diabetes: A systematic review and network meta-analysis of randomised controlled trials. *Diabet Med*. 2022;39(3):e14780. PubMed

Wang S, Wu T, Zuo Z, Jin P, Luo X, Deng M. Comparison of cardiovascular outcomes and cardiometabolic risk factors between patients with type 2 diabetes treated with sodium-glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors: a meta-analysis. *Eur J Prev Cardiolog*. 2022;28(16):1840-1849. PubMed

Yang S, He W, Zhao L, Mi Y. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with kidney outcomes in patients with type 2 diabetes: A systematic review and network meta-analysis. *PLoS ONE*. 2022;17(4):e0267025. PubMed

Bae JH, Park EG, Kim S, Kim SG, Hahn S, Kim NH. Comparative Renal Effects of Dipeptidyl Peptidase-4 Inhibitors and Sodium-Glucose Cotransporter 2 Inhibitors on Individual Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis. *Endocrinol Metab (Seoul)*. 2021;36(2):388-400. PubMed

Escobar C, Barrios V, Cosin J, et al. SGLT2 inhibitors and GLP1 agonists administered without metformin compared to other glucose-lowering drugs in patients with type 2 diabetes mellitus to prevent cardiovascular events: A systematic review. *Diabet Med*. 2021;38(3):e14502. PubMed

Jia S, Wang Z, Han R, et al. Incretin mimetics and sodium-glucose co-transporter 2 inhibitors as monotherapy or add-on to metformin for treatment of type 2 diabetes: a systematic review and network meta-analysis. *Acta Diabetol*. 2021;58(1):5-18. PubMed

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(2):e0244689. PubMed

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. PubMed

Mishriky BM, Okunrintemi V, Jain S, Sewell KA, Powell JR, Cummings DM. Do GLP-1RAs and SGLT-2is reduce cardiovascular events in women with type 2 diabetes? A systematic review and meta-analysis. *Diabetes Metab*. 2021;47(1):101160. PubMed

Uneda K, Kawai Y, Yamada T, et al. Systematic review and meta-analysis for prevention of cardiovascular complications using GLP-1 receptor agonists and SGLT-2 inhibitors in obese diabetic patients. *Sci Rep*. 2021;11(1):10166. PubMed

Unclear Comparator

Alexander JT, Staab EM, Wan W, et al. Longer-term Benefits and Risks of Sodium-Glucose Cotransporter-2 Inhibitors in Type 2 Diabetes: a Systematic Review and Meta-analysis. *J Gen Intern Med*. 2022;37(2):439-448. PubMed

Banerjee M, Pal R, Mukhopadhyay S. Can SGLT2 inhibitors prevent incident gout? A systematic review and meta-analysis. *Acta Diabetol*. 2022;59(6):783-791. PubMed

Colacci M, Fralick J, Odutayo A, Fralick M. Sodium-Glucose Cotransporter-2 Inhibitors and Risk of Diabetic Ketoacidosis Among Adults With Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Can J Diabetes*. 2022;46(1):10-15.e12. PubMed

Ma Y, Lin C, Cai X, et al. The association between the use of sodium glucose cotransporter 2 inhibitor and the risk of diabetic retinopathy and other eye disorders: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol*. 2022;15(7):877-886. PubMed

Wei R, Wang W, Pan Q, Guo L. Effects of SGLT-2 Inhibitors on Vascular Endothelial Function and Arterial Stiffness in Subjects With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne)*. 2022;13:826604. PubMed

Alkabbani W, Pelletier R, Gamble JM. Sodium/Glucose Cotransporter 2 Inhibitors and the Risk of Diabetic Ketoacidosis: An Example of Complementary Evidence for Rare Adverse Events. *Am J Epidemiol*. 2021;190(8):1572-1581. PubMed

Augusto GA, Cassola N, Dualib PM, Saconato H, Melnik T. Sodium-glucose cotransporter-2 inhibitors for type 2 diabetes mellitus in adults: An overview of 46 systematic reviews. *Diabetes Obes Metab*. 2021;23(10):2289-2302. PubMed

Chen MB, Wang H, Zheng QH, Xu HL, Cui WY. Effect of sodium-dependent glucose transporter inhibitors on glycated hemoglobin A1c after 24 weeks in patients with diabetes mellitus: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2021;100(1):e24101. PubMed

Cintra RM, Nogueira AC, Bonilha I, et al. Glucose-lowering Drugs and Hospitalization for Heart Failure: A Systematic Review and Additive-effects Network Meta-analysis With More Than 500 000 Patient-years. *J Clin Endocrinol Metab*. 2021;106(10):3060-3067. PubMed

Masson W, Lavalle-Cobo A, Nogueira JP. Effect of SGLT2-Inhibitors on Epicardial Adipose Tissue: A Meta-Analysis. *Cells*. 2021;10(8):2150. PubMed

Alternative Comparator — Placebo

Li C, Zhou Z, Neuen BL, et al. Sodium-glucose co-transporter-2 inhibition and ocular outcomes in patients with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2021;23(1):252-257. PubMed

Salah HM, Al'Aref SJ, Khan MS, et al. Effect of sodium-glucose cotransporter 2 inhibitors on cardiovascular and kidney outcomes-Systematic review and meta-analysis of randomized placebo-controlled trials. *Am Heart J*. 2021;232:10-22. PubMed

Tsai WH, Chuang SM, Liu SC, et al. Effects of SGLT2 inhibitors on stroke and its subtypes in patients with type 2 diabetes: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):15364. PubMed

Alternative Outcome — Serum Electrolyte Levels

Zhang J, Huan Y, Leibensperger M, Seo B, Song Y. Comparative Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Serum Electrolyte Levels in Patients with Type 2 Diabetes: A Pairwise and Network Meta-Analysis of Randomized Controlled Trials. *Kidney360*. 2022;3(3):477-487. PubMed

Review Articles

Lee YM, Lee SH, Kim TH, Park EJ, Park YA, Jang JS. Cardiovascular outcomes with glucagon-like peptide 1 agonists and sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes: A meta-analysis. *Cardiol J*. 2022;29(3):499-508. PubMed

Scheen AJ. Lower limb amputations: protection with GLP-1 receptor agonists rather than increased risk with SGLT2 inhibitors? *Diabetes Metab*. 2022;48(2):101325. PubMed

Tian Q, Guo K, Deng J, Zhong Y, Yang L. Effects of SGLT2 inhibitors on haematocrit and haemoglobin levels and the associated cardiorenal benefits in T2DM patients: A meta-analysis. *J Cell Mol Med*. 2022;26(2):540-547. PubMed

Coelho FDS, Borges-Canha M, von Hafe M, et al. Effects of sodium-glucose co-transporter 2 inhibitors on liver parameters and steatosis: A meta-analysis of randomized clinical trials. *Diabetes Metab Res Rev*. 2021;37(6):e3413. PubMed

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 (Baltimore)*. 2021;100(30):e26431. PubMed

Hu J, Chen L. Comparison of glucagons like peptide-1 receptor agonists and dipeptidyl peptide-4 inhibitors regarding cardiovascular safety and mortality in type 2 diabetes mellitus: A network meta-analysis. *Prim Care Diabetes*. 2021;15(2):227-233. PubMed

Lazzaroni E, Ben Nasr M, Loretelli C, et al. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. *Pharmacol Res*. 2021;171:105782. PubMed

Wang M, Zhang X, Ni T, et al. Comparison of New Oral Hypoglycemic Agents on Risk of Urinary Tract and Genital Infections in Type 2 Diabetes: A Network Meta-analysis. *Adv Ther*. 2021;38(6):2840-2853. PubMed

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(2):208-211. PubMed