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CADTH Reference List

Sodium-Glucose Cotransporter-2 Inhibitors for Heart Failure

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Summary of Abstracts

CADTH

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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.

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Key Message

We found 9 systematic reviews and 23 randomized controlled trials describing the potential clinical benefits and harms of sodium-glucose cotransporter-2 (SGLT2) inhibitors in adults with heart failure.

Research Question

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

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, 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 heart failure. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons. The search was completed on August 25, 2022, and limited to English-language documents published since January 1, 2017. An additional search was run for SGLT2 inhibitors and heart failure, and CADTH-developed search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. This search was limited to English-language documents published since January 1, 2022. If possible, retrieval was limited to the human population. Internet links were provided, if available.

Selection Criteria and Summary Methods

One reviewer screened the 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 section was based on information available in the abstracts of selected publications. If the abstract did not mention the mean age of the population, or if it was unclear whether adult or pediatric patients were included in the study, the citation was included in the results. Studies with unspecified population ages were identified by a footnote in the Summary of Findings tables.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients (≥ 18 years of age) with chronic heart failure including: • heart failure with reduced ejection fraction • heart failure with preserved ejection fraction
Intervention	SGLT2 inhibitors (i.e., empagliflozin, canagliflozin, dapagliflozin)
Comparator	Placebo Alternate SGLT2 inhibitor (i.e., empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) ACE inhibitor (e.g., ramipril, lisinopril, perindopril, enalapril, captopril, trandolapril) Beta blocker (e.g., bisoprolol, carvedilol, metoprolol) ARB (e.g., valsartan, candesartan, losartan) ARNI (i.e., sacubitril-valsartan)
Type of information	Descriptions of potential clinical benefits (e.g., all-cause mortality, blood pressure, cardiovascular outcomes, quality of life) and harms (e.g., hypoglycemia, hypotension, diabetic ketoacidosis)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; SGLT2 = sodium-glucose cotransporter-2.

Results

Nine systematic reviews[1-9] and 23 randomized controlled trials[10-32] describing the potential clinical benefits and harms of SGLT2 inhibitors in adults with heart failure were identified. No health technology assessments were identified.

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

Overall Summary of Findings

Nine systematic reviews with meta-analyses[1-9] describing the potential clinical benefits and harms of SGLT2 inhibitors in adults with heart failure were identified. Of these, 8 studied dapagliflozin,[1-6,8,9] 7 studied empagliflozin,[1-4,6-8] and 2 studied canagliflozin.[3,8] The comparator was most often placebo[1-3,5-7,9] or an alternative SGLT2 inhibitor.[2,3,8] However, 1 study compared dapagliflozin and empagliflozin with sacubitril-valsartan.[4] The included studies investigated the impact of SGLT2 inhibitors on the following outcomes: heart failure hospitalization,[1-9] cardiovascular mortality,[1-6,8,9] the composite of cardiovascular mortality and heart failure hospitalization,[1-5,7,8] all-cause mortality,[1-3,6,8,9] body weight,[6-9] blood pressure,[6,8,9] Kansas City Cardiomyopathy Questionnaire scores,[6,7] major adverse cardiac events,[8,9] hemoglobin A1C,[8,9] worsening heart failure,[2] the composite of worsening renal function and cardiovascular mortality,[3] emergency department visits due to heart failure,[6] hematocrit,[6] and 6-minute walk

test score.[7] Some studies reported on the harms of treatment, including hypoglycemia,[2,5,9] renal function,[3,8,9] volume depletion,[5,9] urinary tract infection,[5] serious adverse events,[6] creatinine,[6] and adverse events.[9] A detailed summary of the included systematic reviews can be found in Table 2.

Twenty-three randomized controlled trials[10-32] describing the potential clinical benefits and harms of SGLT2 inhibitors in adults with heart failure were identified. These studies or sub-studies from 7 major trials compared empagliflozin with placebo (EMPEROR-Preserved,[11,13,14,23-25] EMPEROR-Reduced,[21,22,31,32] EMPIRE HF,[27] EMPATROPISM[29]), dapagliflozin with placebo (DAPA-HF,[10,12,15-20,26] DAPA-VO_2[28]), and canagliflozin with placebo (CHIEF-HF[30]). The included studies investigated the impact of SGLT2 inhibitors on the following outcomes: composite of cardiovascular mortality and heart failure hospitalizations,[11,13,14,18,21-25,31] the composite of cardiovascular mortality and worsening heart failure,[10-12,15-20,26] heart failure hospitalizations,[13-15,20-25,31] cardiovascular mortality,[11,15,17,19-21,25,26] all-cause mortality,[15,17,19-21,26,32] Kansas City Cardiomyopathy Questionnaire scores,[13-15,17,18,29,30] worsening heart failure,[17,19,26,31] anemia or iron deficiency,[22,26] renal outcomes,[22] hyperuricemia,[26] stressed blood volume,[27] peak oxygen consumption,[28] 6-minute walk test score,[28] and Minnesota Living with Heart Failure Questionnaire score.[28] Harms studied were renal function,[10,11,13,24,25,32] study drug discontinuation,[16,18] serious adverse events,[16,18] hyperkalemia,[23,31] adverse events,[13] atrial fibrillation,[17] hypoglycemia,[24] and hypotension.[31] A brief overview of the major trials identified, as described by the abstracts of the included studies and post hoc analyses, can be found in Table 3.

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

Study citation	Included studies	Population	Intervention	Comparator	Outcomes measured	Harms measured
Ahmad et al. (2022)[1]	4 RCTs	People with HF[a] N = 15,684	Dapagliflozin Empagliflozin Sotagliflozin	Placebo	HF hospitalization CV mortality CV mortality or HF hospitalization All-cause mortality	NA
Shi et al. (2022)[2]	11 RCTs	People with HF[a] N = NR	Dapagliflozin Empagliflozin	Placebo Dapagliflozin Empagliflozin	HF hospitalization CV mortality CV mortality or HF hospitalization All-cause mortality Worsening HF	Hypoglycemia
Tager et al. (2022)[3]	22 RCTs	People with HF[a] N = 18,265	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin Sotagliflozin	Placebo Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin Sotagliflozin	HF hospitalization CV mortality CV mortality or HF hospitalization All-cause mortality Worsening renal function or CV mortality	Worsening renal function

Study citation	Included studies	Population	Intervention	Comparator	Outcomes measured	Harms measured
Aimo et al. (2021)[4]	6 RCTs	People with HFrEF[a] N = NR	Dapagliflozin Empagliflozin	Sacubitril-valsartan Vericiguat Standard of care	HF hospitalization CV mortality CV mortality or HF hospitalization	NA
Cai et al. (2021)[5]	9 RCTs	People with chronic HF[a] N = NR	Dapagliflozin	Placebo	HF hospitalization CV mortality CV mortality or HF hospitalization	Hypoglycemia Volume depletion UTI
Chambergo-Michilot et al. (2021)[6]	9 RCTs	People with HF[a] N = NR	Dapagliflozin Empagliflozin	Placebo	HF hospitalization CV mortality All-cause mortality Body weight BP KCCQ Emergency department visits due to HF Hematocrit Composite outcome (unspecified)	Serious adverse events Creatinine
Pan et al. (2021)[7]	7 RCTs	People with HF[a] N = 5,150	Empagliflozin	Placebo	HF hospitalization CV mortality or HF hospitalization Body weight KCCQ 6MWT	NA
Teo et al. (2021)[8]	10 RCTs	People with HF[a] N = 15,373	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	HF hospitalization CV mortality CV mortality or HF hospitalization All-cause mortality Body weight SPB MACE Hemoglobin A1C	Worsening renal function

Study citation	Included studies	Population	Intervention	Comparator	Outcomes measured	Harms measured
Zheng et al. (2021)[9]	4 RCTs	People with HF[a] N = 6,738	Dapagliflozin	Placebo	HF hospitalization CV mortality All-cause mortality Body weight SPB MACE Hemoglobin A1C	Hypoglycemia Renal impairment Volume depletion Adverse events

6MWT = 6-Minute Walk Test; BP = blood pressure; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; MACE = major adverse cardiovascular events; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SPB = systolic blood pressure; UTI = urinary tract infection.

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

Table 3: Summary of Included Randomized Controlled Trials

Trial name and relevant citations	Trial design	Main study population	Intervention	Comparator	Outcomes measured[a]	Harms measured
CHIEF-HF **Spertus et al. (2022)**[30]	Remote, patient-centred, double-blind, randomized trial	People with HF[b] N = 476	Canagliflozin	Placebo	**KCCQ**	NA
DAPA-HF[c] **Post hoc: Adamson et al. (2022);**[10] **Berg et al. (2022);**[12] **Butt et al. (2022);**[15] **Butt et al. (2022);**[16] **Butt et all (2022);**[17] **Docherty et al. (2022);**[18] **Docherty et al. (2022;)**[19] **Docherty et al. (2022);**[20] **McDowell et al. (2022)**[26]	Phase III, multi-national, double-blind, placebo-controlled, randomized trial	Adults with NYHA class II to IV symptoms and HFrEF (≤ 40%)[b] N = 4,744	Dapagliflozin	Placebo	**Worsening HF or CV mortality** CV mortality or HF hospitalization HF hospitalization CV mortality All-cause mortality KCCQ Worsening HF Iron deficiency Hyperuricemia	eGFR decline Study drug discontinuation Serious adverse events New-onset AF
DAPA-VO_2 **Palau et al. (2022)**[28]	Multi-centre, double-blind, randomized trial	Adults with HFrEF N = 90	Dapagliflozin	Placebo	**Peak oxygen consumption** 6MWT MLHFQ	NA

Trial name and relevant citations	Trial design	Main study population	Intervention	Comparator	Outcomes measured[a]	Harms measured
EMPATROPISM **Post hoc: Requena-Ibanez et al. (2022)**[29]	NR	People with HFrEF[b] N = NR	Empagliflozin	Placebo	KCCQ	NA
EMPEROR-Preserved[c] **Post hoc: Anker et al. (2022);**[11] **Bohm et al. (2022);**[13] **Butler et al. (2022);**[14] **Ferreira et al. (2022);**[23] **Filippatos et al. (2022);**[24] **Januzzi et al. (2022)**[25]	Double-blind	Adults with class II to IV HFpEF (> 40%) N = 5,988	Empagliflozin	Placebo	**CV mortality or HF hospitalization** Worsening HF/CV mortality HF hospitalization CV mortality KCCQ	eGFR decline or renal death eGFR decline Adverse events Hypoglycemia Hyperkalemia
EMPEROR-Reduced[c] **Post hoc: Doehner et al. (2022)**[21]**; Ferreira et al. (2022)**[22]**; Verma et al. (2022)**[31]**; Zannad et al. (2022)**[32]	Multi-national, double-blind, parallel-group, randomized trial	Adults with NYHA class II to IV HFrEF (≤ 40%) N = 3,730	Empagliflozin	Placebo	**CV mortality or HF hospitalization** HF hospitalization CV mortality All-cause mortality Kidney composite outcome (not specified) Anemia In- and outpatient HF events Hyperuricemia	Hypotension Hyperkalemia eGFR decline Kidney safety events
EMPIRE HF **Post hoc: Omar et al. (2022)**[27]	Investigator-initiated, double-blind, placebo-controlled, randomized trial	Adults with HFrEF N = 70	Empagliflozin	Placebo	Stressed blood volume	NA

6MWT = 6-minute walk test; AF = atrial fibrillation; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NA = not applicable; NR = not reported; NYHA = New York Heart Association.

[a]Primary outcomes are bolded.

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

[c]Outcomes listed are not necessarily evaluated by each associated substudy.

References

Health Technology Assessments

No literature identified.

Systematic Reviews

1. Ahmad Y, Madhavan MV, Stone GW, et al. Sodium-glucose cotransporter 2 inhibitors in patients with heart failure: a systematic review and meta-analysis of randomized trials. *Eur Heart J Qual Care Clin Outcomes*. 2022; 8(4): 383-390. PubMed
2. Shi Z, Gao F, Liu W, He X. Comparative Efficacy of Dapagliflozin and Empagliflozin of a Fixed Dose in Heart Failure: A Network Meta-Analysis. *Front Cardiovasc Med*. 2022; 9: 869272. PubMed
3. Tager T, Frankenstein L, Atar D, et al. Influence of receptor selectivity on benefits from SGLT2 inhibitors in patients with heart failure: a systematic review and head-to-head comparative efficacy network meta-analysis. *Clin Res Cardiol*. 2022; 111(4): 428-439. PubMed
4. Aimo A, Pateras K, Stamatelopoulos K, et al. Relative Efficacy of Sacubitril-Valsartan, Vericiguat, and SGLT2 Inhibitors in Heart Failure with Reduced Ejection Fraction: a Systematic Review and Network Meta-Analysis. *Cardiovasc Drugs Ther*. 2021; 35(5): 1067-1076. PubMed
5. Cai RP, Xu YL, Su Q. Dapagliflozin in Patients with Chronic Heart Failure: A Systematic Review and Meta-Analysis. *Cardiol Res Pract*. 2021; 2021: 6657380. PubMed
6. Chambergo-Michilot D, Tauma-Arrue A, Loli-Guevara S. Effects and safety of SGLT2 inhibitors compared to placebo in patients with heart failure: A systematic review and meta-analysis. *Int J Cardiol Heart Vasc*. 2021; 32: 100690. PubMed
7. Pan D, Xu L, Chen P, Jiang H, Shi D, Guo M. Empagliflozin in Patients With Heart Failure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front Cardiovasc Med*. 2021; 8: 683281. PubMed
8. Teo YH, Yoong CSY, Syn NL, et al. Comparing the clinical outcomes across different sodium/glucose cotransporter 2 (SGLT2) inhibitors in heart failure patients: a systematic review and network meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol*. 2021; 77(10): 1453-1464. PubMed
9. Zheng XD, Qu Q, Jiang XY, Wang ZY, Tang C, Sun JY. Effects of Dapagliflozin on Cardiovascular Events, Death, and Safety Outcomes in Patients with Heart Failure: A Meta-Analysis. *Am J Cardiovasc Drugs*. 2021; 21(3): 321-330. PubMed

Randomized Controlled Trials

10. Adamson C, Docherty KF, Heerspink HJL, et al. Initial Decline (Dip) in Estimated Glomerular Filtration Rate After Initiation of Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction: Insights From DAPA-HF. *Circulation*. 2022; 146(6): 438-449. PubMed
11. Anker SD, Siddiqi TJ, Filippatos G, et al. Outcomes with empagliflozin in heart failure with preserved ejection fraction using DELIVER-like endpoint definitions. *Eur J Heart Fail*. 2022; 24(8): 1400-1405. PubMed
12. Berg DD, Docherty KF, Sattar N, et al. Serial Assessment of High-Sensitivity Cardiac Troponin and the Effect of Dapagliflozin in Patients With Heart Failure With Reduced Ejection Fraction: An Analysis of the DAPA-HF Trial. *Circulation*. 2022; 145(3): 158-169. PubMed
13. Bohm M, Butler J, Filippatos G, et al. Empagliflozin Improves Outcomes in Patients With Heart Failure and Preserved Ejection Fraction Irrespective of Age. *J Am Coll Cardiol*. 2022; 80(1): 1-18. PubMed
14. Butler J, Filippatos G, Jamal Siddiqi T, et al. Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. *Circulation*. 2022; 145(3): 184-193. PubMed
15. Butt JH, Dewan P, DeFilippis EM, et al. Effects of Dapagliflozin According to the Heart Failure Collaboratory Medical Therapy Score: Insights From DAPA-HF. *JACC Heart Fail*. 2022; 10(8): 543-555. PubMed
16. Butt JH, Dewan P, Merkely B, et al. Efficacy and Safety of Dapagliflozin According to Frailty in Heart Failure With Reduced Ejection Fraction: A Post Hoc Analysis of the DAPA-HF Trial. *Ann Intern Med*. 2022; 175(6): 820-830. PubMed
17. Butt JH, Docherty KF, Jhund PS, et al. Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. *Eur J Heart Fail*. 2022; 24(3): 513-525. PubMed
18. Docherty KF, Ogunniyi MO, Anand IS, et al. Efficacy of Dapagliflozin in Black Versus White Patients With Heart Failure and Reduced Ejection Fraction. *JACC Heart Fail*. 2022; 10(1): 52-64. PubMed
19. Docherty KF, Simpson J, Jhund PS, et al. Effect of Dapagliflozin, Compared With Placebo, According to Baseline Risk in DAPA-HF. *JACC Heart Fail*. 2022; 10(2): 104-118. PubMed
20. Docherty KF, Welsh P, Verma S, et al. Iron Deficiency in Heart Failure and Effect of Dapagliflozin: Findings From DAPA-HF. *Circulation*. 2022 Aug 16: 101161CIRCULATIONAHA122060511. PubMed
21. Doehner W, Anker SD, Butler J, et al. Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial. *Eur Heart J*. 2022; 05: 05. PubMed

22. Ferreira JP, Anker SD, Butler J, et al. Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced. *Eur J Heart Fail*. 2022; 24(4): 708-715. PubMed

23. Ferreira JP, Butler J, Zannad F, et al. Mineralocorticoid Receptor Antagonists and Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol*. 2022; 79(12): 1129-1137. PubMed

24. Filippatos G, Butler J, Farmakis D, et al. Empagliflozin for Heart Failure With Preserved Left Ventricular Ejection Fraction With and Without Diabetes. *Circulation*. 2022 Aug 30: 101161CIRCULATIONAHA122059785. PubMed

25. Januzzi JL, Jr., Butler J, Zannad F, et al. Prognostic Implications of N-Terminal Pro-B-Type Natriuretic Peptide and High-Sensitivity Cardiac Troponin T in EMPEROR-Preserved. *JACC Heart Fail*. 2022; 10(7): 512-524. PubMed

26. McDowell K, Welsh P, Docherty KF, et al. Dapagliflozin reduces uric acid concentration, an independent predictor of adverse outcomes in DAPA-HF. *Eur J Heart Fail*. 2022; 24(6): 1066-1076. PubMed

27. Omar M, Jensen J, Burkhoff D, et al. Effect of Empagliflozin on Blood Volume Redistribution in Patients With Chronic Heart Failure and Reduced Ejection Fraction: An Analysis From the Empire HF Randomized Clinical Trial. *Circ Heart Fail*. 2022; 15(3): e009156. PubMed

28. Palau P, Amiguet M, Dominguez E, et al. Short-term effects of dapagliflozin on maximal functional capacity in heart failure with reduced ejection fraction (DAPA-VO2): a randomized clinical trial. *Eur J Heart Fail*. 2022 May 23. PubMed

29. Requena-Ibanez JA, Santos-Gallego CG, Rodriguez-Cordero A, Vargas-Delgado AP, Badimon JJ. Empagliflozin improves quality of life in nondiabetic HFrEF patients. Sub-analysis of the EMPATROPISM trial. *Diabetes Metab Syndr*. 2022; 16(2): 102417. PubMed

30. Spertus JA, Birmingham MC, Nassif M, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. *Nat Med*. 2022; 28(4): 809-813. PubMed

31. Verma S, Dhingra NK, Butler J, et al. Empagliflozin in the treatment of heart failure with reduced ejection fraction in addition to background therapies and therapeutic combinations (EMPEROR-Reduced): a post-hoc analysis of a randomised, double-blind trial. *Lancet Diabetes Endocrinol*. 2022; 10(1): 35-45. PubMed

32. Zannad F, Ferreira JP, Gregson J, et al. Early changes in estimated glomerular filtration rate post-initiation of empagliflozin in EMPEROR-Reduced. *Eur J Heart Fail*. 2022 Jun 16. PubMed

Appendix 1: References of Potential Interest

Previous CADTH Reports

Dapagliflozin Reimbursement Review. Ottawa (ON): CADTH. 2021. https://www.cadth.ca/dapagliflozin-1. Accessed 30 Aug 2022.

Systematic Reviews

Unclear Methodology — Systematic Search of Literature Not Specified

Qiu M, Ding LL, Zhang M, Zhou HR. Safety of four SGLT2 inhibitors in three chronic diseases: A meta-analysis of large randomized trials of SGLT2 inhibitors. *Diab Vasc Dis Res*. 2021; 18(2): 14791641211011016. PubMed

Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. 2020; 396(10254): 819-829. PubMed

Mixed Population

Shi FH, Li H, Shen L, et al. Beneficial Effect of Sodium-Glucose Co-transporter 2 Inhibitors on Left Ventricular Function. *J Clin Endocrinol Metab*. 2022; 107(4): 1191-1203. PubMed

Wang M, Zhang Y, Wang Z, Liu D, Mao S, Liang B. The effectiveness of SGLT2 inhibitor in the incidence of atrial fibrillation/atrial flutter in patients with type 2 diabetes mellitus/heart failure: a systematic review and meta-analysis. *J Thorac Dis*. 2022; 14(5): 1620-1637. PubMed

Zhao LM, Huang JN, Qiu M, Ding LL, Zhan ZL, Ning J. Gliflozins for the prevention of stroke in diabetes and cardiorenal diseases: A meta-analysis of cardiovascular outcome trials. *Medicine (Baltimore)*. 2021; 100(39): e27362. PubMed

Mixed Intervention — Dapagliflozin-Empagliflozin and Sotagliflozin

Pandey AK, Dhingra NK, Hibino M, Gupta V, Verma S. Sodium-glucose cotransporter 2 inhibitors in heart failure with reduced or preserved ejection fraction: a meta-analysis. *ESC Heart Fail*. 2022; 9(2): 942-946. PubMed

Norre T, Grimm D, Simonsen U. Sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat for congestive heart failure therapy. *Basic Clin Pharmacol Toxicol*. 2022; 130(4): 425-438. PubMed

Unclear Intervention — Not Specific to Empagliflozin, Canagliflozin, or Dapagliflozin

Cao Y, Li P, Li Y, Han Y. Sodium-glucose cotransporter-2 inhibitors in heart failure: an updated meta-analysis. *ESC Heart Fail*. 2022; 9(3): 1942-1953. PubMed

Chieng JHL, Sia TK, Teo YH, et al. Evaluating the Initiation of Sodium/Glucose Cotransporter 2 Inhibitors within 2 Weeks of an Acute Hospital Admission: A Systematic Review and Meta-Analysis of Nine Clinical Trials. *Med Princ Pract*. 2022; 31(3): 215-223. PubMed

Giri Ravindran S, Kakarla M, Ausaja Gambo M, Yousri Salama M, Haidar Ismail N, Tavalla P, Uppal P, Mohammed SA, Rajashekar S, Hamid P. The Effects of Sodium-Glucose Cotransporter-2 Inhibitors (SLGT-2i) on Cardiovascular and Renal Outcomes in Non-diabetic Patients: A Systematic Review. *Cureus*. 2022; 14(5): e25476. PubMed

Li M, Yi T, Fan F, et al. Effect of sodium-glucose cotransporter-2 inhibitors on blood pressure in patients with heart failure: a systematic review and meta-analysis. *Cardiovasc*. 2022; 21(1): 139. PubMed

Luo L, Yang X, Tang K, et al. Efficacy of three novel drugs in the treatment of heart failure: A network meta-analysis. *Medicine (Baltimore)*. 2022; 101(29): e29415. PubMed

Pagnesi M, Baldetti L, Aimo A, et al. Prognostic Benefit of New Drugs for HFrEF: A Systematic Review and Network Meta-Analysis. *J Clin Med*. 2022; 11(2): 348. PubMed

Razuk V, Chiarito M, Cao D, et al. SGLT-2 inhibitors and cardiovascular outcomes in patients with and without a history of heart failure: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2022; 8(6): 557-567. PubMed

Teo YN, Teo YH, Syn NL, et al. Comparing Sacubitril/Valsartan Against Sodium-Glucose Cotransporter 2 Inhibitors in Heart Failure: A Systematic Review and Network Meta-analysis. *Clin Drug Invest*. 2022; 42(1): 1-16. PubMed

Vukadinovic D, Abdin A, Anker SD, et al. Side effects and treatment initiation barriers of sodium-glucose cotransporter 2 inhibitors in heart failure: a systematic review and meta-analysis. *Eur J Heart Fail*. 2022 Jun 22. PubMed

Yin Z, Zheng H, Guo Z. Effect of Sodium-Glucose Co-transporter Protein 2 Inhibitors on Arrhythmia in Heart Failure Patients With or Without Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Front Cardiovasc Med*. 2022; 9: 902-923. PubMed

Younes AM, Salem M, Maraey A, et al. Safety outcomes of SGLT2i in the heart failure trials: A systematic review and Meta-analysis. *Int J Cardiol*. 2022; 366: 51-56. PubMed

Zhao L, Guo W, Huang W, Wang L, Huang S. Benefit of sodium-glucose cotransporter-2 inhibitors on survival outcome is related to the type of heart failure: A meta-analysis. *Diabetes Res Clin Pract*. 2022; 187: 109871. PubMed

Zhou H, Peng W, Li F, et al. Effect of Sodium-Glucose Cotransporter 2 Inhibitors for Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Front Cardiovasc Med*. 2022; 9: 875327. PubMed

Zou X, Shi Q, Vandvik PO, et al. Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Heart Failure: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2022; 175(6): 851-861. PubMed

Bazoukis G, Papadatos SS, Thomopoulos C, et al. Impact of SGLT2 inhibitors on major clinical events and safety outcomes in heart failure patients: a meta-analysis of randomized clinical trials. *J Geriatr Cardiol*. O2021; 18(10): 783-795. PubMed

Camilli M, Lombardi M, Chiabrando JG, et al. Sodium-Glucose Cotransporter Inhibitors Reduce Mortality and Morbidity in Patients With Heart Failure: Evidence From a Meta-Analysis of Randomized Trials. *Am J Ther*. 2021; 29(2): e199-e204. PubMed

Cardoso R, Graffunder FP, Ternes CMP, et al. SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis. *EClinicalMedicine*. 2021; 36: 100933. PubMed

Chen C, Peng H, Li M, et al. Patients With Type 2 Diabetes Mellitus and Heart Failure Benefit More From Sodium-Glucose Cotransporter 2 Inhibitor: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)*. 2021; 12: 664533. PubMed

Gager GM, Gelbenegger G, Jilma B, et al. Cardiovascular Outcome in Patients Treated With SGLT2 Inhibitors for Heart Failure: A Meta-Analysis. *Front Cardiovasc Med*. 2021; 8: 691907. PubMed

He Z, Yang L, Nie Y, et al. Effects of SGLT-2 inhibitors on health-related quality of life and exercise capacity in heart failure patients with reduced ejection fraction: A systematic review and meta-analysis. *Int J Cardiol*. 2021; 345: 83-88. PubMed

Li HL, Lip GYH, Feng Q, et al. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and cardiac arrhythmias: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2021; 20(1): 100. PubMed

Li X, Zhang Q, Zhu L, et al. Effects of SGLT2 inhibitors on cardiovascular, renal, and major safety outcomes in heart failure: A meta-analysis of randomized controlled trials. *Int J Cardiol*. 2021; 332: 119-126. PubMed

Lu Y, Li F, Fan Y, Yang Y, Chen M, Xi J. Effect of SGLT-2 inhibitors on cardiovascular outcomes in heart failure patients: A meta-analysis of randomized controlled trials. *Eur J Intern Med*. 2021; 87: 20-28. 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

Shoar S, Shah AA, Ikram W, et al. Cardiovascular benefits of SGLT2 inhibitors in patients with heart failure: a meta-analysis of small and large randomized controlled trials. *Am J Cardiovasc Dis*. 2021; 11(3): 262-272. PubMed

Shrestha DB, Budhathoki P, Sedhai YR, et al. Sodium-glucose cotransporter-2 Inhibitors in Heart Failure: An Updated Systematic Review and Meta-analysis of 13 Randomized Clinical Trials Including 14,618 Patients With Heart Failure. *J Cardiovasc Pharmacol*. 2021; 78(4): 501-514. PubMed

Singh AK, Singh R. Cardiovascular Outcomes with SGLT-2 inhibitors in patients with heart failure with or without type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Syndr*. 2021; 15(1): 351-359. PubMed

Teo YH, Teo YN, Syn NL, et al. Effects of Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors on Cardiovascular and Metabolic Outcomes in Patients Without Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials. *J Am Heart Assoc*. 2021; 10(5): e019463. PubMed

Tsampasian V, Baral R, Chattopadhyay R, et al. The Role of SGLT2 Inhibitors in Heart Failure: A Systematic Review and Meta-Analysis. *Cardiol Res Pract*. 2021; 2021: 9927533. PubMed

Turgeon RD, Barry AR, Hawkins NM, Ellis UM. Pharmacotherapy for heart failure with reduced ejection fraction and health-related quality of life: a systematic review and meta-analysis. *Eur J Heart Fail*. 2021; 23(4): 578-589. PubMed

Yan Y, Liu B, Du J, et al. SGLT2i versus ARNI in heart failure with reduced ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail*. 2021; 8(3): 2210-2219. PubMed

Yin D, Qiu M, Wei X, Duan X. Meta-analyzing the factors affecting the efficacy of gliflozins in patients with heart failure based on heart failure trials. *Medicine (Baltimore)*. 2021; 100(28): e26561. PubMed

Arnott C, Li Q, Kang A, et al. Sodium-Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2020; 9(3): e014908. PubMed

Butler J, Usman MS, Khan MS, et al. Efficacy and safety of SGLT2 inhibitors in heart failure: systematic review and meta-analysis. *ESC Heart Fail*. 2020; 7(6): 3298-3309. PubMed

Kumar K, Kheiri B, Simpson TF, Osman M, Rahmouni H. Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure: A Meta-Analysis of Randomized Clinical Trials. *Am J Med*. 2020; 133(11): e625-e630. PubMed

Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019; 393(10166): 31-39. PubMed

Alternative Comparator — Combined SGLT2i and ARNI Therapy

Lin Y, Zhang H, Zhao S, et al. The Efficacy and Safety of the Combined Therapy of Sodium-Glucose Co-Transporter-2 Inhibitors and Angiotensin Receptor-Neprilysin Inhibitor in Patients With Heart Failure With Reduced Ejection Fraction: A Meta-Analysis of the EMPEROR-Reduced and DAPA-HF Sub-Analysis. *Front Cardiovasc Med*. 2022; 9: 882089. PubMed

Randomized Controlled Trials

Unclear Comparator — Heart Failure Medication

Reis J, Teixeira AR, Goncalves AV, et al. Dapagliflozin Impact on the Exercise Capacity of Non-Diabetic Heart Failure with Reduced Ejection Fraction Patients. *J Clin Med*. 2022; 11(10): 23. PubMed

Alternative Outcome

Jensen J, Omar M, Ali M, et al. The effect of empagliflozin on contractile reserve in heart failure: Prespecified sub-study of a randomized, double-blind, and placebo-controlled trial. *Am Heart J.* 2022; 250: 57-65. PubMed

Omar M, Jensen J, Kistorp C, et al. The effect of empagliflozin on growth differentiation factor 15 in patients with heart failure: a randomized controlled trial (Empire HF Biomarker). *Cardiovasc*. 2022; 21(1): 34. PubMed

Protocol

Zeng J, Zhu Y, Zhao W, et al. Rationale and Design of the ADIDAS Study: Association Between Dapagliflozin-Induced Improvement and Anemia in Heart Failure Patients. *Cardiovasc Drugs Ther*. 2022; 36(3): 505-509. PubMed

Review Articles

Pooled Analysis

Butler J, Packer M, Filippatos G, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J.* 2022; 43(5): 416-426. PubMed

Ferreira JP, Zannad F, Butler J, et al. Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled. *Eur Heart J.* 2022; 43(31): 2984-2993. PubMed

Kosiborod M, Gause-Nilsson I, Xu J, Sonesson C, Johnsson E. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and concomitant heart failure. *J Diabetes Complications*. 2017; 31(7): 1215-1221. PubMed