pagepress

GLOBAL CARDIOLOGY
Global Cardiology 2023; **1**: 55-60
Published online 27 November 2023 | **DOI**: 10.4081/cardio.2023.2

ARTICLE

SGLT2 inhibitors and risk reduction for mortality in high-risk patients: a meta-analysis of randomized controlled trials

Tariq Jamal Siddiqi,[1] Javed Butler,[1,2] Andrew J.S. Coats,[3] Subodh Verma,[4] Tim Friede,[5,6] Gerasimos Filippatos,[7,8] Stefan D. Anker[9,10]

[1]Department of Medicine, University of Mississippi, Jackson, MS, USA; [2]Baylor Scott and White Research Institute, Dallas, TX, USA; [3]University of Warwick, UK; [4]Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Ontario, Canada; [5]Department of Medical Statistics, University Medical Center Göttingen, Germany; [6]DZHK - German Center for Cardiovascular Research, Göttingen, Germany; [7]National and Kapodistrian University of Athens, School of Medicine, Athens University, Greece; [8]Hospital Attikon, Athens, Greece; [9]Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany; [10]Department of Cardiology and Pneumology, University Medical Center Goettingen, Georg-August University, Goettingen, Germany

Abstract

Background: The aim of this paper is to assess the impact of sodium-glucose cotransporters-2 (SGLT2) inhibitors on all-cause and cardiovascular (CV) death in high-risk patients and compare the efficacy of empagliflozin and dapagliflozin.
Methods: PubMed was queried from inception to the last week of September 2023 for randomized controlled trials that compared SGLT2 inhibitors' empagliflozin or dapagliflozin with placebo and included patients with heart failure (HF), type 2 diabetes mellitus (T2DM), or chronic kidney disease (CKD). The outcome of interest was CV death or all-cause death. Hazard ratios (HR) with 95% confidence intervals (CI) were pooled using a random effect model, and forest plots were created to analyze the results visually. A chi-square test was performed to assess subgroup differences between empagliflozin and dapagliflozin.
Results: Eight trials (N=55,818) were included in our analysis, namely EMPA-REG, EMPEROR-Reduced, EMPEROR-Preserved, EMPA-KIDNEY, DECLARE-TIMI, DAPA-HF, DELIVER and DAPA-CKD. Pooled analysis demonstrated that compared to placebo, SGLT2 inhibition reduced the risk of CV death (SGLT2i arm = 1405 events, 29,089 total patients; placebo arm = 1515 events, 26,729 total patients; HR: 0.85; 95%CI: 0.79-0.93, p<0.001) and all-cause death (SGLT2i arm = 2,491 events, 29,062 total patients; placebo arm= 2,625 events, 26,729 total patients; HR: 0.86; 95% CI 0.79-0.95, p=0.002) in high-risk patients identified as having either T2DM, HF, or CKD. No differences were observed in the effect of empagliflozin and dapagliflozin on CV death ($HR_{empagliflozin}$: 0.81; 95% CI 0.68-0.97, $HR_{dapagliflozin}$: 0.88; 0.82-0.95, p=0.39) and all-cause death ($HR_{empagliflozin}$: 0.86; 95% CI 0.73-1.02, $HR_{dapagliflozin}$: 0.87; 0.78-0.97, p=0.94).
Conclusions: SGLT2 inhibitors reduce the risk of all-cause and CV death in high-risk patients. Notably, there were no discernible differences in the benefits of empagliflozin and dapagliflozin on these outcomes.

Key words SGLT2 inhibitors, mortality, cardiovascular death, high-risk patients.

Received: 29 October 2023; Accepted: 2 November 2023.
**Correspondence to: Stefan D. Anker, Department of Cardiology, Charité, Campus Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin, Germany.*
Tel: +49.30.450553407. E-mail: s.anker@cachexia.de

Introduction

The sodium-glucose cotransporters-2 (SGLT2) inhibitors, empagliflozin, and dapagliflozin, have been studied in 8 large trials that enrolled a vast array of individuals at high risk for adverse events. In brief, the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - Removing Excess Glucose) trial enrolled patients with type 2 diabetes mellitus (T2DM) and showed that empagliflozin reduces the risk of hospitalization of heart failure (HF) (HHF) by 35%.[1] This benefit was confirmed in the DECLARE-TIMI (Dapagliflozin Effect on Cardiovascular

Events) trial and raised interest in SGLT2 inhibition as a potential therapy in HF.[2] The subsequent DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trials demonstrated that SGLT2 inhibitors improve major HF outcomes in patients with HF with reduced ejection fraction (HFrEF).[3,4] The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trials confirmed this benefit in patients with HF with preserved ejection fraction (HFpEF).[5,6] The subsequent DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) and EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) trials demonstrated the benefit of dapagliflozin and empagliflozin in patients with chronic kidney disease (CKD), respectively.[7,8]

Across these trials, the impact of SGLT2 inhibitors on all-cause or cardiovascular (CV) death was inconsistent. Taking the results of these trials together may represent an opportunity to define the effect of SGLT2 inhibition on all-cause and CV death in a high-risk population where adverse outcomes are of particular concern. Additionally, it remains to be seen whether empagliflozin and dapagliflozin offer similar effects. This knowledge gap could lead to under-prescription of these life-saving medications when either drug is unavailable in specific clinical settings.

Materials and Methods

This systematic review and meta-analysis are reported in conformity with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines.[9] Approval from the institutional review board was not required as publicly available aggregate data was used.

Objectives, eligibility criteria, and outcomes

Randomized controlled trials were considered eligible for inclusion if they: i) compared SGLT2 inhibitors' empagliflozin or dapagliflozin with placebo; ii) included patients with HF, T2DM, or/and CKD; and iii) reported CV or all-cause death. Only reports of trials with >1000 participants were considered to ensure the inclusion of well-conducted studies with outcome adjudication and sufficient treatment duration. To reduce heterogeneity, we used outcomes with empagliflozin in HFpEF using DELIVER-like endpoint definitions.[10]

Data sources and search

PubMed was queried from inception to the last week of September 2023. No language restrictions were placed. We also searched clinicaltrials.gov and scrutinized the reference list of eligible review papers to assess for relevant articles. The articles obtained from the systematic search were exported to EndNote Reference Library software for duplicate screening and removal. Two independent reviewers (JB and TJS) carefully evaluated the remaining articles and selected trials that met the predefined criteria. Initially, trials were short-listed based on their title and abstract, and then the full texts were reviewed to confirm relevance. Discrepancies were resolved by discussion until consensus.

Data extraction and risk of bias assessment

Trial characteristics, baseline demographics, and outcomes were extracted onto a predesigned Excel spreadsheet. T.J.S and J.B. conducted the quality assessment using the Cochrane Risk of Bias tool (version 1.0) to assess the risk of bias in the included trials.

Statistical analysis

RevMan (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all statistical analyses. The trial results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and pooled using a random effects model. Forest plots were created to assess visually the results of pooling. A chi-square test was performed to evaluate for differences between the subgroups. Heterogeneity among the studies was assessed using Higgins I^2.[11] Begg's test was performed to evaluate publication bias. A significance level of less than 0.05 was used in all cases.

Results

Study and participant characteristics

Results from the literature search and study selection process are summarized in Figure 1. We included eight RCTs enrolling 55,818 participants with a mean age of 65.7 years, with a median follow-up of 2.25 years (interquartile range: 1.75-2.75), Table 1. All included studies achieved a "high" quality rating, as shown in *Supplementary Figure 1*.

Results of meta-analysis

Cardiovascular death

Eight studies reported data on CV death (SGLT2 inhibitors, 29,089 patients; placebo, 26,729 patients). The pooled analysis demonstrates that SGLT2 inhibitors significantly reduce the risk for CV death compared with placebo (HR: 0.85; 95% CI 0.79-0.93), Figure 2A. The difference between the em-

pagliflozin (HR: 0.81; 95% CI 0.68-0.97) and dapagliflozin (HR: 0.88; 0.82-0.95) groups was statistically non-significant (p=0.39).

All-cause death

All studies reported the effects of SGLT2 inhibitors on all-cause death (SGLT2 inhibitors, 29,062 patients; placebo, 26,729 patients). SGLT2 inhibition was associated with significantly reducing the risk of all-cause death compared to placebo (HR: 0.86; 95% CI 0.79-0.95), Figure 2B. The difference between the empagliflozin (HR: 0.86; 95% CI 0.73-1.02) and dapagliflozin (HR: 0.87; 0.78-0.97) groups was statistically non-significant (p=0.94).

Discussion

We present several noteworthy findings in this pooled analysis involving over 55,000 high-risk patients identified as having either T2DM, HFrEF, HFpEF, or CKD. SGLT2 inhibitors reduced the risk of CV and all-cause death by 15% and 14%, respectively. Moreover, our analysis found no discernible difference in the benefits of empagliflozin and dapagliflozin on these outcomes.

Differences in the impact of SGLT2 inhibitors on CV and overall mortality across the individual trials may be due to variations in the baseline characteristics of the enrolled participants or inclusion criteria. In DECLARE-TIME, no effect was observed for dapagliflozin on CV or all-cause death. In con-

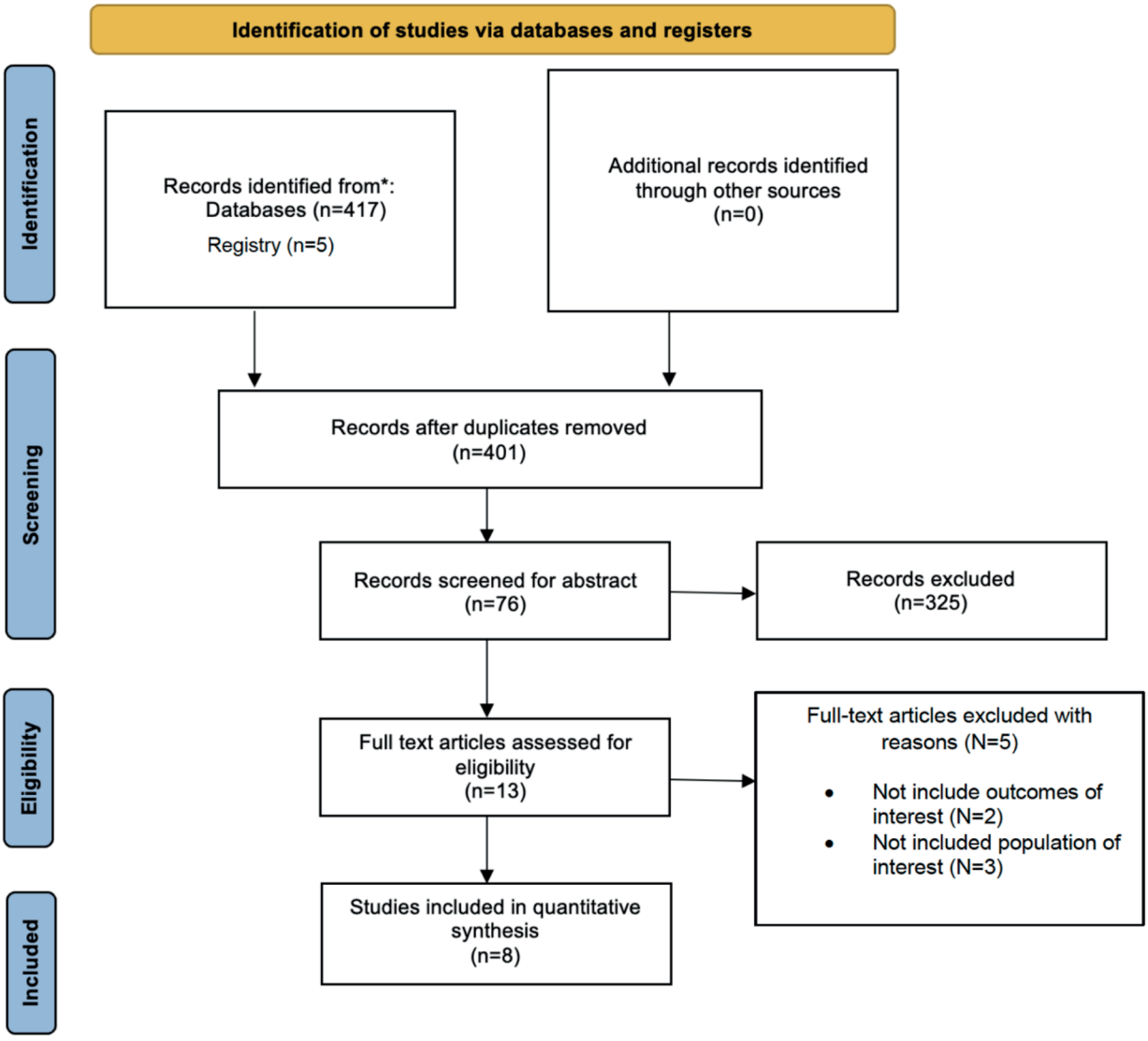

Figure 1. PRISMA flowchart summarizing the study selection process.

Table 1. Study and baseline characteristics of included studies.

	EMPA - REG		EMPEROR - Reduced		EMPEROR - Preserved		EMPA - KIDNEY		DAPA - HF		DECLARE - TIMI		DAPA - CKD		DELIVER	
	Empagliflozin (n=4687)	Placebo (n=2333)	Empagliflozin (n=1863)	Placebo (n=1867)	Empagliflozin (n=2997)	Placebo (n=2991)	Empagliflozin (n=3304)	Placebo (n=3305)	Dapagliflozin (n=2373)	Placebo (n=2371)	Dapagliflozin (n=8582)	Placebo (n=8578)	Dapagliflozin (n=2152)	Placebo (n=2152)	Dapagliflozin (n=3131)	Placebo (n=3132)
Follow-up, yrs	3.1	1.3	2.2	2.0	1.5	4.2	2.4	2.3								
Age, years	63.1±8.6	63.2±8.8	67.2±10.8	66.5±11.2	71.8±9.3	71.9±9.6	63.9±13.9	63.8±13.9	66.2±11.0	66.5±10.8	63.9±6.8	64.0±6.8	61.8±12.1	61.9±12.1	71.8±9.6	71.5±9.5
Female (%)	1351 (28.9)	653 (30)	437 (23.5)	456 (24.4)	1338 (44.6)	1338 (44.7)	1097 (33.2)	1095 (33.1)	564 (23.8)	545 (23.0)	3171 (36.9)	3251 (37.9)	709 (32.9)	716 (33.3)	1364 (43.6)	1383 (44.2)
HTN, n (%)	NA	NA	1349 (72.4)	1349 (72.3)	2721 (90.8)	2703 (90.4)	NA	NA	NA	NA	NA	NA	NA	NA	2755 (88.0)	2798 (89.3)
AF, n (%)	NA	NA	664 (35.6)	705 (37.8)	1543 (51.5)	1514 (50.6)	NA	NA	916 (38.6)	902 (38.0)	NA	NA	NA	NA	1758 (56.1)	1794 (57.3)
DM, n (%)	4687 (100)	2333 (100)	927 (49.8)	929 (49.8)	1466 (48.9)	1472 (49.2)	1525 (46.2)	1515 (45.8)	993 (41.8)	990 (41.8)	8582 (100)	8578 (100)	1455 (67.6)	1451 (67.4)	1401 (44.7)	1405 (44.9)
CAD, n (%)	3545 (75.6)	1763 (75.6)	NA	NA	NA	NA	NA	NA	NA	NA	2824 (32.9)	2834 (33.0)	NA	NA	NA	NA
HF, n (%)	462 (9.9)	244 (10.5)	1863 (100)	!867 (100)	2997 (100)	2991 (100)	NA	NA	2373 (100)	2371 (100)	852 (9.9)	872 (10.2)	235 (10.9)	233 (10.8)	3131 (100)	3132 (100)
ACEi, n (%)	3798 (81.0)	1868 (80.1)	1314 (70.5)	1286 (68.9)	2428 (81.0)	2404 (80.4)	NA	NA	1332 (56.1)	1329 (56.1)	6977 (81.3)	6973 (81.3)	673 (31.3)	681 (31.6)	1144 (36.5)	1151 (36.7)
ARNi, n (%)	NA	NA	340 (18.3)	387 (20.7)	65 (2.2)	69 (2.3)	NA	NA	250 (10.5)	258 (10.9)	NA	NA	NA	NA	165 (5.3)	136 (4.3)
Diuretic, n (%)	2047 (43.7)	988 (42.3)	NA	NA	NA	NA	1362 (41.2)	1453 (44.0)	2216 (93.4)	2217 (93.5)	3488 (40.6)	3479 (40.6)	928 (43.1)	1399 (65.0)	2403 (76.7)	2408 (76.9)
BB, n (%)	3056 (65.2)	1498 (64.2)	1765 (94.7)	1768 (94.7)	2598 (86.7)	2569 (85.9)	NA	NA	2278 (96.0)	2280 (96.2)	4498 (52.4)	4532 (52.8)	NA	NA	2592 (82.8)	2585 (82.5)
MRA, n (%)	305 (6.5)	136 (5.8)	1306 (70.1)	1355 (72.6)	1119 (37.3)	1125 (37.6)	NA	NA	1696 (71.5)	1674 (70.6)	NA	NA	NA	NA	1340 (42.8)	1327 (42.4)

HTN, hypertension; AF, atrial fibrillation; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; ACEi, angiotensin converting enzyme inhibitors; ARNI, angiotensin-neprilysin inhibitors; BB, beta blockers.

trast, in EMPA-REG, empagliflozin reduced the risk of CV and all-cause death by 38% and 32% in patients with T2DM, respectively. This was true despite EMPA-REG enrolling sicker patients having a higher frequency of comorbidities such as a history of coronary artery disease (75% *vs*. 32%), stroke (23% *vs*. 8%), peripheral artery disease (21% *vs*. 6%) and worse renal functions (eGFR 74 *vs*. 85 ml/min/1.73 m^2). In DELIVER, dapagliflozin reduced the risk of CV death by 12% in patients with HFpEF. A similar benefit was observed for empagliflozin in EMPEROR-Preserved. These two trials differed in their inclusion criteria concerning N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Indeed, in the EMPEROR-Reduced trial, the NT-proBNP criteria for patients with LVEF ≥31-40% were unusually high compared to those patients with LVEF ≤30%. Of note, variation in treatment response according to baseline NT-proBNP has been well reported.[12,13] In DAPA-CKD, dapagliflozin reduced the risk of all-cause death by 31% in patients with CKD. EMPA-CKD showed a similar, but non-significant, effect of empagliflozin on all-cause death. In EMPA-CKD, patients were generally healthier with a lower frequency of comorbidities such as cardiovascular disease (27% *vs*. 37%) and T2DM (44% *vs*. 67%), due to which there may have been lesser room for improvement observed with empagliflozin.

Perhaps the most important key message of our analysis was that despite there being a moderate difference between dapagliflozin and empagliflozin by their SGLT2i selectivity, the clinical outcome and benefit seem identical and homogenous. These findings are consistent with real-world experiences. Data from the Korean National Insurance Service database that included >100,00 patients with T2DM showed that the risk of all-cause mortality was similar between the dapagliflozin and empagliflozin users.[14] Similarly, a propensity-score matching analysis of 921 patients treated with dapagliflozin and an equal number of patients treated with empagliflozin showed no significant difference in reduction of risk of cardiovascular death between dapagliflozin and empagliflozin cohorts.[15] A recent analysis also demonstrated that empagliflozin and dapagliflozin have comparable value in improving outcomes in patients with HFrEF.[16]

Conclusions

The findings from the present analyses should be interpreted considering some limitations. This was a study-level analysis, as individual patient data was not available. There were some variations in the definition of the endpoint across the included studies.

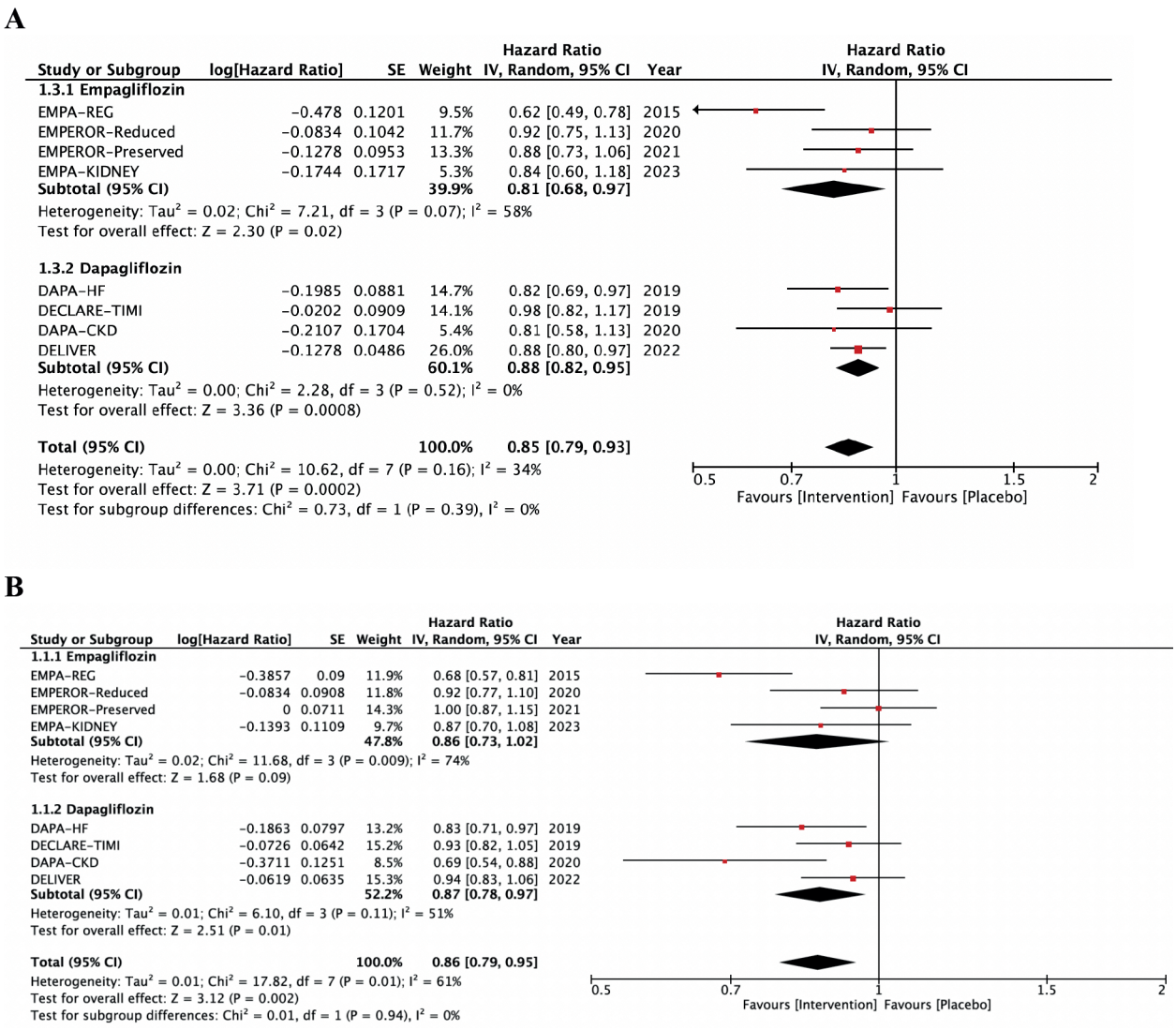

Figure 2. Forest plots showing effects of SGLT2 inhibitors, in comparison with placebo on cardiovascular death (A) and all-cause death (B).

In conclusion, SGLT2 inhibition was associated with a significant reduction in the risk of all-cause and cardiovascular death. Importantly, no differences were observed in the benefit of empagliflozin and dapagliflozin on these outcomes.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

TJS has nothing report. JB has served as a consultant to Abbott, Adrenomed, Arena Pharma, Array, Amgen, Applied Therapeutics, Astra Zeneca, Bayer, Boehringer Ingelheim, Cardior, CVRx, Eli Lilly, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Sequana Medical, V-Wave Limited, and Vifor. AJSC reported honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics, Respicardia, and Viatris. Dr Verma has received research and/or speaking honoraria from Amgen, Amarin, AstraZeneca, Bayer, CMS, Janssen, HLS, Sanofi, NovoNordisk, Novartis, Merck, and Phase Bio; has received personal fees from Boehringer Ingelheim; is president of the Canadian Medical and Surgical Knowledge Translation Research Group; and holds the Tier1 Canada Research Chair in Cardiovascular Surgery. TF reported consulting fees from Vifor Pharma,

Bayer, Biosense Webster, CSL Behring, Galapagos, Minoryx, Novartis, LivaNova, Janssen, Roche, and honoraria from Fresenius Kabi. GF reported honoraria from Bayer and Boehringer Ingelheim, committee membership for Medtronic, Vifor Pharma, Amgen, Servier, and Novartis, and grants from the European Commission. SDA reports consulting fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma.

Ethics approval and consent to participate

Our study did not require institutional board review as de-identified publicly available was used.

Funding

None.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
2. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.
3. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.
4. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-24.
5. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451-61.
6. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089-98.
7. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.
8. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388:117-27.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:71.
10. Anker SD, Siddiqi TJ, Filippatos G, Zannad F, Ferreira JP, Pocock SJ, et al. Outcomes with empagliflozin in heart failure with preserved ejection fraction using DELIVER-like endpoint definitions. Eur J Heart Fail 2022;24:1400-5.
11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
12. Ezekowitz JA, O'Connor CM, Troughton RW, Alemayehu WG, Westerhout CM, Voors AA, et al. N-terminal pro-B-type natriuretic peptide and clinical outcomes: vericiguat heart failure with reduced ejection fraction study. JACC Heart Fail 2020;8:931-9.
13. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med 2021;384:105-16.
14. Lim J, Kim B, Choi YJ, Lee HJ, Han KD, Lee H, et al. Abstract 12476: Dapagliflozin versus empagliflozin and the risk for cardiovascular outcomes in patients with type 2 diabetes: a nationwide population-based study. Circulation 2022;146:A12476.
15. Lim J, Hwang IC, Choi HM, Yoon YE, Cho GY. Comparison of cardiovascular and renal outcomes between dapagliflozin and empagliflozin in patients with type 2 diabetes without prior cardiovascular or renal disease. PLoS One 2022;17:e0269414.
16. Azuri J, Aboalhasan E, Hammerman A, Arbel R. Abstract 9946: Dapagliflozin versus empagliflozin for improving outcomes of type 2 diabetes mellitus patients with heart failure and reduced ejection fraction. Circulation. 2021;144:A9946.

Online supplementary material:
Document 1. PRISMA checklist.
Figure S1. Risk of bias assessment of the included studies.