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RESEARCH ARTICLE

Prevention of heart failure events with sodium–glucose co-transporter 2 inhibitors across a spectrum of cardio-renal-metabolic risk

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Aims Trials have tested the safety and efficacy of sodium–glucose co-transporter 2 inhibitors (SGLT2i) across various disease states. We performed a meta-analysis of randomized controlled trials (RCTs) to estimate the relative and absolute effects of SGLT2i in the prevention of heart failure (HF) events across different risk groups.

Methods and results We conducted a systematic review and meta-analysis of large, placebo-controlled RCTs with >1000 participants evaluating HF hospitalization and the composite of cardiovascular (CV) death or HF hospitalization. Due to varying durations of therapeutic exposure and follow-up, absolute risk reductions and number needed to treat were calculated based on incidence rates (per 100 patient-years). Across 71 553 patients enrolled in 10 late-phase RCTs, SGLT2i reduced the risk of HF hospitalization by 31% [hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.64–0.74; $I^2 = 0\%$] and the composite outcome of CV death or HF hospitalization by 24% (HR 0.76, 95% CI 0.72–0.80; $I^2 = 1.4\%$) compared with placebo. The number of patient-years of treatment exposure needed to prevent one CV death or HF hospitalization ranged from 19–26 (established HF) to 72–125 (chronic kidney disease) to 96–400 (high-risk type 2 diabetes). In mixed-effects meta-regression analyses, the benefits of SGLT2i on HF hospitalizations or the composite outcome (CV death or HF hospitalization) were not influenced by age, sex, or change in intermediate markers (glycated haemoglobin, systolic blood pressure, and body weight) (all $P \geq 0.10$).

Conclusion Despite wide variation in baseline risks and disease states evaluated, SGLT2i demonstrated comparable relative risk reductions in preventing HF events. Patients at highest baseline risk derived the greatest absolute benefits in preventing HF events. These composite estimates may help guide targeted implementation of SGLT2i for the prevention of HF events in type 2 diabetes and chronic kidney disease and in the treatment of HF.

Keywords Heart failure • Hospitalization • Prevention • Sodium–glucose co-transporter 2 inhibitors

Introduction

Despite their relatively recent introduction, sodium–glucose co-transporter 2 inhibitors (SGLT2i) are one of the most well-studied cardio-renal-metabolic therapies across disease domains. Trials have tested the safety and efficacy of these therapies in type 2 diabetes, chronic kidney disease, and heart failure (HF). While initially developed for glycaemic control in type 2 diabetes, it has become apparent that these therapies have important clinical benefits even among populations without diabetes.[1–3]

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The SGLT2i appear to have broad systemic effects in improving cardiovascular (CV) and kidney health. In particular, prevention of HF events has been observed across multiple clinical trials. HF is among the leading causes of hospitalization among older adults in the US and inpatient costs account for the largest proportion of total spending for HF care.[4] As such, lessening the burden of HF hospitalizations is a worthwhile patient-centred and health system goal. Prior meta-analyses of SGLT2i have mostly considered relative treatment effects (without accounting for baseline risk) and have variably included more recent published trials.[5,6] We performed an updated meta-analysis of randomized controlled trials (RCTs) to estimate the relative and absolute effects of SGLT2i in the prevention of HF events across different risk groups.

Methods

We performed a comprehensive literature search of electronic databases (MEDLINE, EMBASE, and Cochrane CENTRAL) from inception to 17 November 2020. We used the following search terms: 'empagliflozin', 'dapagliflozin', 'canagliflozin', 'ertugliflozin', 'sotagliflozin', 'myocardial infarction', 'stroke', 'major adverse cardiovascular events', 'major adverse cardiac events' and 'heart failure'. No language restrictions were applied. Presentations at major national CV meetings and bibliographies of relevant articles were also reviewed to capture more recent studies. Duplicate citations were removed and two reviewers (K.B. and V.J.) independently screened all the studies in two successive stages: title and abstract followed by full-text review. In case of any disagreement, a third reviewer was consulted to reach a consensus (M.V.). We identified RCTs comparing SGLT2i to placebo. Only trials with sample sizes >1000 participants with primary endpoints that were clinical events were included. We excluded observational studies, registry data, and post-hoc analysis of RCTs. Full texts of all included RCTs were then reviewed. Data were extracted by two independent authors (K.G and K.B.) using pre-specified electronic forms. Similar to the main trial protocols, in studies evaluating more than one dose of therapy, dosing arms were pooled for analytic purposes.

Outcomes of interest included HF hospitalization and the composite of CV death or HF hospitalization. Pre-specified hazard ratio (HR) and their 95% confidence interval (CI) were pooled using a random-effects DerSimonian and Laird model.[7] Weights were assigned for each study based on the inverse of the variance. In light of varying durations of therapeutic exposure and follow-up, absolute risk reduction (ARR) and number needed to treat (NNT) were also calculated based on incidence rates (per 100 patient-years).

Heterogeneity among studies was assessed using the Higgins I^2 value.[8] We conducted a meta-regression analysis using mixed-effects modelling to explain any observed heterogeneity for HF hospitalization and the composite outcome of CV death or HF hospitalization. Meta-regression model inputs were selected *a priori* and included baseline characteristics (mean age and proportion of women in the placebo arm) and interval effects on intermediate markers [mean between-arm changes in glycated haemoglobin (HbA1c), systolic blood pressure, and body weight]. Each trial measured effects on intermediate markers at variable follow-up time-points. For the purposes of this meta-regression analysis, changes in HbA1c were captured between 12–52 weeks post-randomization and changes in systolic blood pressure and body weight were selected from 34–338 weeks across trials. For trials that did not report pooled effects on intermediate markers by dose, data from the higher SGLT2i dose were considered. Subgroup analysis was conducted to assess for variability of treatment effect across the different trial populations. Publication bias was assessed visually with funnel plots. Study quality was assessed using version 2 of the Cochrane risk-of-bias tool.[7] All *P*-values were 2-tailed with statistical significance specified at 0.05. Stata version 16 (Stata Corp., College Station, TX, USA) and R package, metafor, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for analyses.

Results

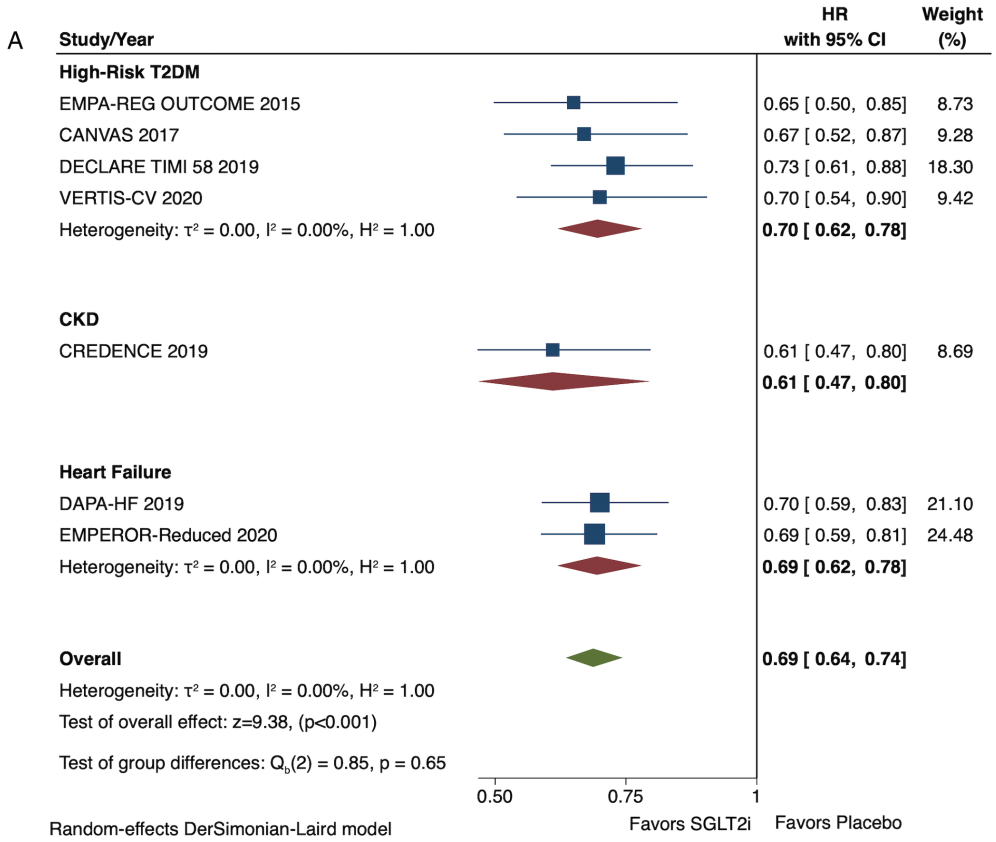
Our search strategy yielded 594 original records, of which 18 were selected for full-text review. Ten RCTs[1–3,5,6,8–12] enrolling 71 553 patients met our inclusion criteria. There were 39 057 and 32 496 patients in the SGLT2i and placebo arm, respectively. The main design features and baseline characteristics of individual RCTs are displayed in *Table 1*. The average follow-up period ranged from 0.75 years (in SOLOIST-WHF) to 4.2 years (in DECLARE-TIMI 58). All trials that met the inclusion criteria had an overall low risk of bias (online supplementary *Table S1*).

In the pooled overall analysis that included all patients, SGLT2i reduced the risk of HF hospitalization by 31% (HR 0.69, 95% CI 0.64–0.74) and the composite outcome of CV death or HF hospitalization by 24% (HR 0.76, 95% CI 0.72–0.80) compared with placebo (*Figure 1*). Treatment effects were consistent across trials without apparent statistical heterogeneity for HF hospitalization ($I^2 = 0\%$) and minimal statistical heterogeneity for CV death or HF hospitalization ($I^2 = 1.4\%$). Subgroup analysis revealed no significant heterogeneity in treatment effects across the key trial populations (HF, chronic kidney disease, high-risk type 2 diabetes). Absolute risks of HF hospitalization in placebo-treated participants ranged widely from 0.23 per 100 patient-years in DECLARE-TIMI 58 to 4.8 per 100 patient-years in EMPEROR-Reduced. Absolute risks of CV death or HF hospitalization in placebo-treated participants ranged from 0.25 per 100 patient-years to 5.2 per 100 patient-years (*Figure 2*). Absolute rates for time-to-first events were not reported in SCORED or SOLOIST-WHF. The number of patient-years of treatment exposure needed to prevent one HF hospitalization ranged from 21–35 (in HF) to 104 (in chronic kidney disease) to 196–435 (in high-risk type 2 diabetes). The number of patient-years of treatment exposure needed to prevent one CV death or HF hospitalization event ranged from 19–26 (in HF) to 72–125 (in chronic kidney disease) to 96–400 (in high-risk type 2 diabetes) (*Figure 3*). Mixed-effects meta-regression models were constructed to explain the minimal observed heterogeneity of effects of SGLT2i on HF events. Age, sex, and effects on intermediate markers (HbA1c, systolic blood pressure, body weight) were not associated with risk reductions in HF hospitalization alone or the composite of CV death or HF hospitalization with SGLT2i ($P \geq 0.10$ for both outcomes). Funnel plots were symmetric, and Egger's test found no significant small study bias for the outcome of HF hospitalization ($P = 0.44$) or the composite of CV death or HF hospitalization ($P = 0.12$).

Table 1 **Study designs and baseline characteristics of 10 randomized controlled trials**

	EMPA-REG OUTCOME[8]	CANVAS/ CANVAS-R[9]	DECLARE–TIMI 58[10]	VERTIS-CV[12]	CREDENCE[11]	DAPA-CKD[3]	SCORED[6]	DAPA-HF[1]	EMPEROR-Reduced[2]	SOLOIST-WHF[5]
Year of reporting	2015	2017	2019	2020	2019	2020	2020	2019	2020	2020
Study design	Randomized double-blind	Randomized double-blind	Randomized double-blind	Randomized double-blind	Randomized double-blind	Randomized double-blind	Randomized double-blind	Randomized double-blind	Randomized double-blind	Randomized double-blind
Average follow-up (years)	3.1	2.4	4.2	3.5	2.6	2.4	1.3	1.5	1.3	0.75
Trial participants	Type 2 DM with established CVD	Type 2 DM with established CVD or multiple risk factors for CVD	Type 2 DM with established CVD or multiple risk factors for CVD	Type 2 DM with established CVD	Albuminuric CKD with type 2 DM	Albuminuric CKD with or without type 2 DM	Type 2 DM with CKD and additional CV risk factors	HF (EF ≤40% and NYHA class II–IV) with or without type 2 DM	HF patients (EF ≤40% and NYHA class II–IV) with or without type 2 DM	Type 2 DM and recently hospitalized for worsening HF (included EF >40%)
Treatment arm	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Canagliflozin	Dapagliflozin	Sotagliflozin	Dapagliflozin	Empagliflozin	Sotagliflozin
Primary outcome	Composite of CV death, non-fatal MI, and non-fatal stroke	Composite of CV death, non-fatal MI, and non-fatal stroke	Composite of CV death, MI, and ischaemic stroke	Composite of CV death, non-fatal MI, and non-fatal stroke	Composite of ESKD, doubling of serum creatinine/death from renal/CV cause	Composite of ESKD, sustained ≥50% eGFR decline, death from renal or CV cause	Total number of CV death and hospitalizations and urgent visits for HF	Composite of worsening HF and CV death	Composite of HF hospitalization and CV death	Total number of CV death and hospitalizations and urgent visits for HF
Patients randomized	7020	10 142	17 160	8246	4401	4304	10 584	4744	3730	1222
Baseline characteristics										
Mean age (years)	63.1	63.3	63.9	64.4	63.0	62.0	69	66.3	66.8	70
Women (%)	28.5	35.8	37.4	30.0	33.9	33.0	44.9	23.4	23.9	33.7
White race (%)	72.4	78.3	79.6	69.9	66.6	53.0	82.6	70.2	70.5	93.2
HF (%)	10.1	14.4	10.0	23.7	14.8	10.9	31	100	100	100
eGFR < 60 mL/ min/1.73 m^2 (%)	25.9	20.1	7.4	21.9	59.8	89.5	100	40.7	48.2	69.8
Background therapies										
RAASi (%)	80.7	80.0	81.2	81.1	99.9	97.0	88.5	94.4	89.1	91.3
β-blocker (%)	64.5	53.5	52.7	69.3	40.2	39	62.5	96.1	94.7	92
Diuretics (%)	43.2	44.3	40.6	42.9	46.7	43.7	35.3	96.5	NR	95
MRA (%)	6.3	NR	NR	8.2	NR	5.3	36	71.0	71.3	64.5

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NR, not reported; NYHA, New York Heart Association; RAASi, renin–angiotensin–aldosterone system inhibitor.



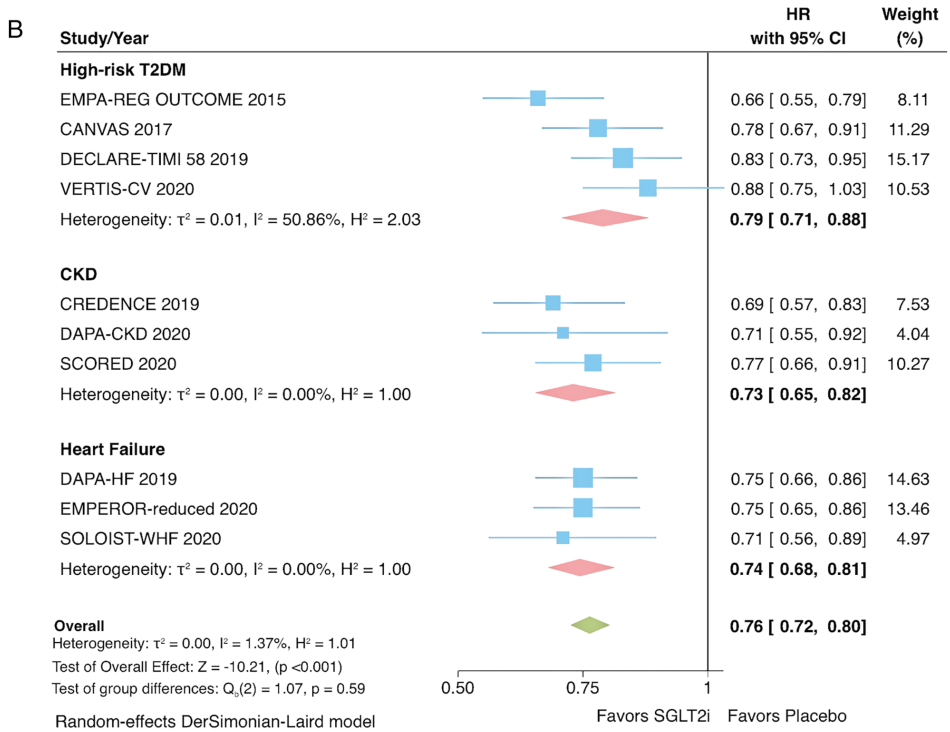


Figure 1 Pooled relative effect sizes of sodium–glucose co-transporter 2 inhibitors (SGLT2i) on heart failure hospitalization (*A*) and the composite of cardiovascular death or heart failure hospitalization (*B*) across trials. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; T2DM, type 2 diabetes mellitus.

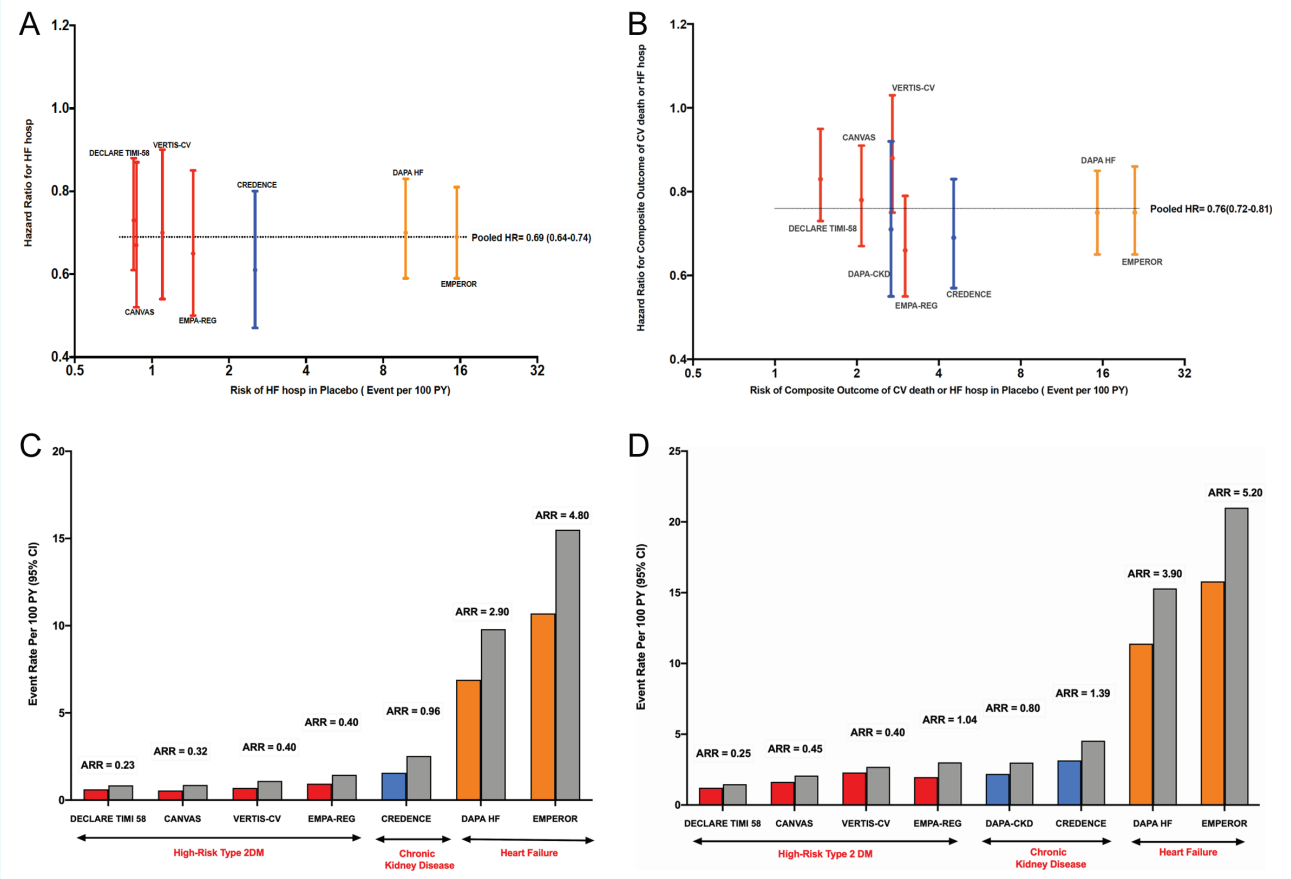


Figure 2 Relative effect sizes of sodium–glucose co-transporter 2 inhibitors on heart failure (HF) hospitalization (*A*) and the composite of cardiovascular (CV) death or HF hospitalization (*B*) across a range of baseline risk. Absolute risk reductions with sodium–glucose co-transporter 2 inhibitors on HF hospitalization (*C*) and composite of CV death or HF hospitalization (*D*) across trials. ARR, absolute risk reduction; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; PY, patient-years.

Discussion

In this study-level meta-analysis of RCTs enrolling nearly 72 000 participants, we found that SGLT2i significantly reduced the risk of HF events across a broad spectrum of baseline cardio-renal-metabolic risk. Despite the varied populations evaluated, the relative benefits in preventing HF events were remarkably consistent with minimal evidence of statistical heterogeneity. The absolute benefits of SGLT2i in preventing HF events thus varied by baseline risk, such that patients with established HF derived the greatest absolute benefits. On the other end of the risk spectrum for HF events, lower-risk, more prevalent populations (such as type 2 diabetes without established CV disease) encompass a much larger cohort at risk. For instance, while the estimated number of patients with HF with reduced ejection fraction is ~3 million in the US,[13] it is estimated that 34 million have diabetes mellitus[14] and 37 million have chronic kidney disease.[15]

Our meta-analysis suggests that 19 to 26 patients would need to be treated for a year to prevent a CV death or HF hospitalization among patients with HF with reduced ejection fraction. This NNT aligns well with other established components of evidence-based therapies. For instance, in the PARADIGM-HF trial, 14 patients were estimated to have to be treated with sacubitril/valsartan to prevent one CV death or HF hospitalization over 5 years. With lifetime use, the benefits of SGLT2i in extending survival and keeping patients out of the hospital may be substantial.[16] SGLT2i, as a once daily fixed dose therapy without important attendant haemodynamic consequences may be easily added to multi-drug regimens for the treatment of high-risk patients with HF and reduced ejection fraction. Ongoing trial programmes are further evaluating their role in myocardial infarction (EMPACT-MI and DAPA-MI), HF with preserved ejection fraction (DELIVER, EMPEROR-Preserved, and CHIEF-HF), acute HF (EMPULSE-HF, DICTATE-AHF, and DAPA ACT HF-TIMI 68), and even COVID-19 (DARE-19).

The mechanisms underlying the substantial risk reduction on HF events may be multifactorial and remain under active investigation. We conducted meta-regression analyses leveraging select commonly reported parameters to attempt to explain the minimal heterogeneity observed. Meta-regression analyses are subject to limitations given the limited number of trials included, lack of patient-level data, and variable time-points of measurement of

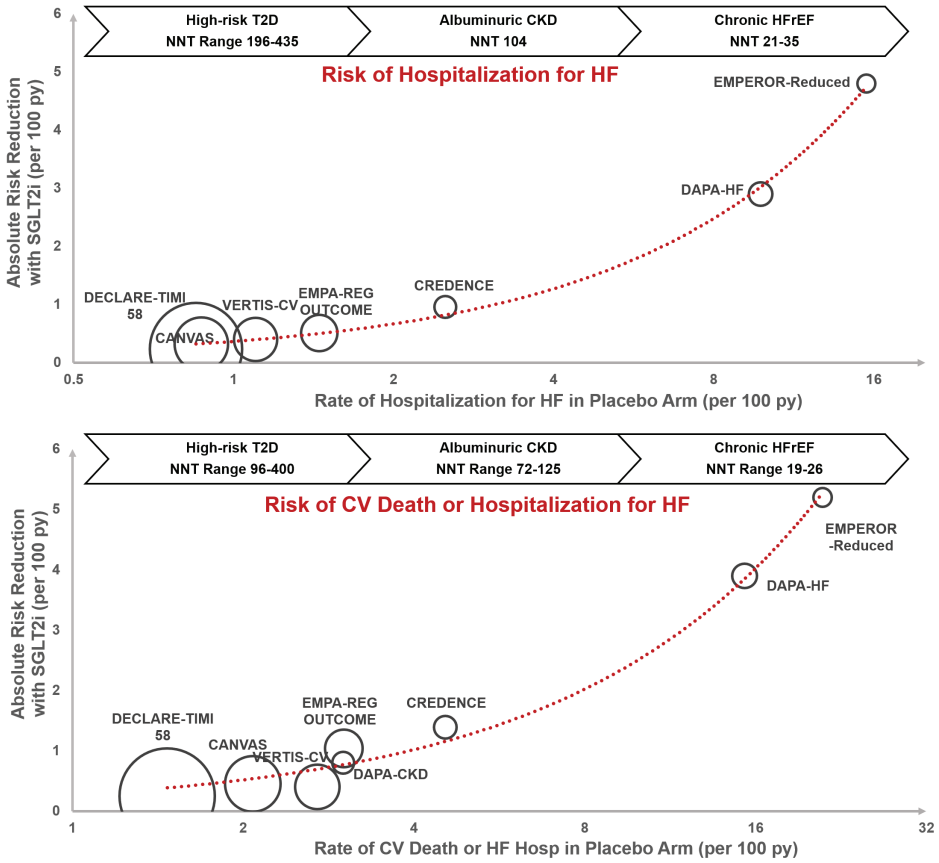


Figure 3 Relationship between baseline risk and treatment benefits with sodium–glucose co-transporter 2 inhibitors (SGLT2i) on heart failure (HF) hospitalization (upper panel) and the composite of cardiovascular (CV) death or HF hospitalization (lower panel). Size of circles corresponds to sample size of the trial population. Red dotted line reflects fitted line across trials. Number needed to treat (NNT) estimated based on incidence rates [per 100 patient-years (py)] and reflects the number of patient-years exposure to prevent one HF event. CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes.

intermediate markers. Despite these limitations, reduction in HF events were observed to be independent of the effects of SGLT2i on intermediate markers (glycaemia, blood pressure, and weight). Taken together with the modest magnitude of treatment effect on these markers across trials, the observed haemodynamic and metabolic effects of SGLT2i alone are unlikely to fully explain HF risk reduction.

Our study inherits certain limitations from the included trials. To evaluate the effects of SGLT2i across a broad range of risk, the trial populations included in our analysis were highly variable. However, treatment effects on HF events were remarkably similar across different at-risk populations of interest. The sotagliflozin trials (SOLOIST-WHF and SCORED) were prematurely terminated by the sponsor due to the COVID-19 pandemic with lower than anticipated enrolment/follow-up. This resulted in revision of the study endpoints to include cumulative events rather than time to first event for HF-related endpoints. Absolute event rates from these trials were thus excluded while reporting ARR and NNT. However, despite these limitations, our study adds to the growing literature supporting SGLT2i.[17]

Despite wide variations in baseline risks and underlying disease states, SGLT2i demonstrated comparable relative risks reductions in preventing HF events. Successful implementation of SGLT2i has the potential to have a meaningful impact on population-level HF events and may have important economic considerations in the health valuation of this therapy.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: A.Q. reports receiving fees for educational activities from the American College of Cardiology, Society for Vascular Medicine, Society for Cardiovascular Angiography and Interventions, Janssen and Janssen, Pfizer, Medscape, and Clinical Exercise Physiology Association. M.V. has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, and Relypsa, and participates in clinical

endpoint committees for studies sponsored by Galmed, Novartis, and the NIH. All other authors have nothing to disclose.

References

McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CE, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.

2. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
3. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JF, McMurray JJ, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446.
4. Echouffo-Tcheugui JB, Bishu KG, Fonarow GC, Egede LE. Trends in health care expenditure among U.S. adults with heart failure: the Medical Expenditure Panel Survey 2002–2011. *Am Heart J* 2017;**186**:63–72.
5. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–128.
6. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, Cherney DZI, Dwyer JP, Scirica BM, Bailey CJ, Díaz R, Ray KK, Udell JA, Lopes RD, Lapuerta P, Steg PG; SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021;**384**:129–139.
7. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.
8. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
9. 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;**377**:644–657.
10. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Ruff CT, Gause-Nilsson IA, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
11. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–2306.
12. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZ, McGuire DK; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**:1425–1435.
13. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MS, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UK, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2020 update: a report from the American Heart Association. *Circulation* 2020;**141**:e139–e596.
14. U.S. Department of Health and Human Services. National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf (22 February 2021).
15. Centers for Disease Control and Prevention. Chronic Kidney Disease (CKD) Surveillance System: CKD Stages among U.S. Adults, 1988–1994 vs. 1999–2006 vs. 2007–2014 vs. 2015–2016. https://nccd.cdc.gov/CKD/detail.aspx?Qnum=Q8#refreshPosition (22 February 2021).
16. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJ, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet* 2020;**396**:121–128.
17. Salah HM, Al'Aref SJ, Khan MS, Al-Hawwas M, Vallurupalli S, Mehta JL, Mounsey JP, Greene SJ, McGuire DK, Lopes RD, Fudim M. 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* 2020;**232**:10–22.