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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 71553 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; I² = 0%] and the composite outcome of CV death or HF hospitalization by 24% (HR 0.76, 95% CI 0.72–0.80; I² = 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 ≥ 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
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. 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. 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. Weights were assigned for each study their 95% confidence interval (CI) were pooled using a random-effects model. Outcome of interest included HF hospitalization and the composite outcome of CV death or HF hospitalization with placebo (Figure 1). Treatment effects were consistent across trials without apparent statistical heterogeneity for HF hospitalization (I² = 0%) and minimal statistical heterogeneity for CV death or HF hospitalization (I² = 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 HF hospitalization ranged from 21–35 (in HF) to 104 (in chronic kidney disease) to 196–435 (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 ≥ 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).

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

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG-OUTCOME</th>
<th>CANVAS/CANVAS-R</th>
<th>DECLARE-TIMI 58</th>
<th>VERTIS-C</th>
<th>CREDENCE</th>
<th>DAPA-CRD</th>
<th>SCORED</th>
<th>DAPA-HF</th>
<th>EMPEROR-Reduced</th>
<th>SOLOIST-WHF</th>
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</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Randomized double-blind</td>
<td>Randomized double-blind</td>
<td>Randomized double-blind</td>
<td>Randomized double-blind</td>
<td>Randomized double-blind</td>
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<td>Randomized double-blind</td>
<td>Randomized double-blind</td>
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<tr>
<td><strong>Average follow-up (years)</strong></td>
<td>3.1</td>
<td>2.4</td>
<td>4.2</td>
<td>3.5</td>
<td>2.6</td>
<td>2.4</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>0.75</td>
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<tr>
<td><strong>Trial participants</strong></td>
<td>Type 2 DM with established CVD</td>
<td>Type 2 DM with established CVD or multiple risk factors for CVD</td>
<td>Type 2 DM with established CVD</td>
<td>Type 2 DM with established CVD</td>
<td>Albuminuric CKD with type 2 DM</td>
<td>Albuminuric CKD with or without type 2 DM</td>
<td>Type 2 DM with CKD and additional CV risk factors</td>
<td>HF (EF ≤ 40% and NYHA class II–IV) with or without type 2 DM</td>
<td>HF patients (EF ≤ 40% and NYHA class II–IV) with or without type 2 DM</td>
<td>Type 2 DM and recently hospitalized for worsening HF (included EF &gt;40%)</td>
</tr>
<tr>
<td><strong>Treatment arm</strong></td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Ertagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Soragliflozin</td>
<td>Dapagliflozin</td>
<td>Empagliflozin</td>
<td>Soragliflozin</td>
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<tr>
<td><strong>Primary outcome</strong></td>
<td>Composite of CV death, non-fatal MI, and non-fatal stroke</td>
<td>Composite of CV death, non-fatal MI, and ischemic stroke</td>
<td>Composite of CV death, MI, and ischemic stroke</td>
<td>Composite of CV death, MI, and non-fatal stroke</td>
<td>Composite of ESKD, doubling of serum creatinine/death from renal/CV cause</td>
<td>Composite of CV death, MI, and non-fatal stroke</td>
<td>Composite of worsening HF and CV death</td>
<td>Composite of worsening HF and CV death</td>
<td>Composite of HF hospitalization and CV death</td>
<td>Composite of worsening HF and CV death</td>
</tr>
<tr>
<td><strong>Patients randomized</strong></td>
<td>7020</td>
<td>10142</td>
<td>17160</td>
<td>8246</td>
<td>4401</td>
<td>4304</td>
<td>10584</td>
<td>4744</td>
<td>3730</td>
<td>1222</td>
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<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean age (years)</td>
<td>63.1</td>
<td>63.3</td>
<td>63.9</td>
<td>64.4</td>
<td>63.0</td>
<td>62.0</td>
<td>69</td>
<td>66.3</td>
<td>66.8</td>
<td>70</td>
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<tr>
<td>Women (%)</td>
<td>28.5</td>
<td>35.8</td>
<td>37.4</td>
<td>30.0</td>
<td>33.9</td>
<td>33.0</td>
<td>44.9</td>
<td>23.4</td>
<td>23.9</td>
<td>33.7</td>
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<tr>
<td>White race (%)</td>
<td>72.4</td>
<td>78.3</td>
<td>79.6</td>
<td>69.9</td>
<td>66.0</td>
<td>53.0</td>
<td>82.6</td>
<td>70.2</td>
<td>70.5</td>
<td>93.2</td>
</tr>
<tr>
<td>HF (%)</td>
<td>10.1</td>
<td>14.4</td>
<td>10.0</td>
<td>23.7</td>
<td>14.8</td>
<td>10.9</td>
<td>31</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min/1.73 m² (%)</td>
<td>25.9</td>
<td>20.1</td>
<td>7.4</td>
<td>21.9</td>
<td>59.8</td>
<td>89.5</td>
<td>100</td>
<td>40.7</td>
<td>48.2</td>
<td>69.8</td>
</tr>
</tbody>
</table>

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.
Effects of SGLT2i on HF across spectrum of risk

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,\textsuperscript{13} it is estimated that 34 million have diabetes mellitus\textsuperscript{14} and 37 million have chronic kidney disease.\textsuperscript{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.\textsuperscript{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

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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 sitagliptin 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, Cytokinetiks, and Relypsa, and participates in clinical

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