

Effect of sodium-glucose linked transporter-2 inhibitors on heart failure end points in people with type 2 diabetes mellitus: a systematic review and meta-analysis

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Abstract

Introduction: Type 2 diabetes is a condition which is frequently associated with macrovascular complications. Sodium-glucose linked transporter-2 inhibitors (SGLT2i) have been demonstrated to improve composite cardiovascular outcomes assessed via a 3-point Major Adverse Cardiovascular Events (MACE). Although they yield some benefit in reducing overall rates of cardiovascular death, stroke and myocardial infarction, it appears that the majority of the beneficial effects of SGLT2i drugs on composite outcomes are mediated by improvements in heart failure outcomes reducing cardiovascular death. This effect has been noted across multiple different drugs in the SGLT2i class. The aim of this review was to synthesise current evidence from randomised controlled trials (RCTs) comparing SGLT2i with placebo in adults with type 2 diabetes mellitus. The outcomes of interest were hazard ratios compared with placebo for hospitalisation due to heart failure (primary), death due to heart failure (secondary) and incidence rates of heart failure (secondary).

Methods: Searches were performed using recognised terms in MedLine, EMBASE, Pubmed, Cochrane CENTRAL and CINAHL. RCTs comparing SGLT2i with placebo were eligible for inclusion, providing they contained results for at least the outcome of interest. Studies were reviewed for inclusion by the two authors and data extraction and bias assessments were performed using a modified Cochrane's data extraction tool and bias assessment tool. Meta-analysis of hazard ratios (HRs) was performed in RevMan 5.4 using generic inverse variance and a fixed effects model.

Results: 3,212 records were identified of which 13 were eventually included, covering 11 clinical studies. The risk of hospi-

talisation for heart failure was significantly lower with SGLT2i compared to placebo (HR 0.69; 95% CI 0.64, 0.74). Inter-study heterogeneity was minimal ($I^2=0\%$) Only one study contained outcomes for death due to heart failure, but its results were not significant. No current studies report hazard ratios for heart failure diagnoses with SGLT2i use compared with placebo.

Conclusion: SGLT2i drugs reduce the rates of hospitalisation due to heart failure in people with type 2 diabetes. This may help mediate the improvements seen in composite cardiovascular outcomes. More evidence is needed to support their use in reducing mortality due to heart failure and incidence rates of new heart failure in this high-risk cohort.

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Introduction

Diabetes is a condition associated with significant macrovascular risk.¹ The incidence of heart failure among people with diabetes is significantly higher than in those without diabetes, especially at younger ages.² Approximately 12% of people with type 2 diabetes are estimated to have heart failure.³ Although mortality due to heart failure has improved marginally, it remains poor compared with other life-limiting conditions such as cancer.⁴ People with diabetes and heart failure with reduced or preserved ejection fraction have worse outcomes than those without diabetes.⁵ Recent estimates place hospitalisation rates for heart failure in people with type 2 diabetes at 12.4 per 1,000 person/years compared with 2.4 per 1,000 person/years in those without diabetes.⁶

Until recently, diabetes therapies have shown limited efficacy in improving cardiovascular outcomes beyond any limited effect improvements in HbA_{1c} may yield. Furthermore, some drugs such as rosiglitazone were associated with increases in adverse cardiovascular outcomes, particularly heart failure.⁷ Following the safety concerns surrounding rosiglitazone, new diabetes drugs were mandated to undergo robust trials to assess cardiovascular safety before approval,⁸ and this requirement continues.⁹

Sodium-glucose linked transporter-2 inhibitors (SGLT2i) were first introduced in the 2010s for the management of type 2 diabetes mellitus. Given the new mandate for cardiovascular outcome data prior to approval, phase III trials were designed to assess these

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outcomes using a 3-point Major Adverse Cardiovascular Events (MACE): a composite outcome of cardiovascular death, non-fatal myocardial infarction and stroke.¹⁰ Although heart failure is not part of the MACE end point, it has been assessed separately and may contribute to improved MACE by reducing cardiovascular death. The EMPA-REG trial was the first of these to report in 2015 and demonstrated reductions in mortality due to cardiovascular causes as well as MACE.¹¹ Subsequent evidence has shown similar findings for other drugs in the class.^{12,13} Most notably, SGLT2i drugs seem to be beneficial in heart failure, with more recent trials supporting their use in people with heart failure irrespective of co-morbid diabetes,^{13–15} with improvements in cardiovascular mortality and heart failure hospitalisation rates. Early meta-analyses of five studies of SGLT2i showed improvements in rates of hospitalisation for heart failure with a pooled hazard ratio (HR) of 0.68 (95% CI 0.61 to 0.76).¹⁶ Since this review, further studies have since been published. Given the significant benefits of SGLT2i on heart failure, it may be that reductions in cardiovascular death are mediated via improvements in heart failure outcomes. Some have suggested future assessments should include heart failure hospitalisation as a fourth point in the MACE outcome to better appreciate the benefit of these drugs on the condition.¹⁷

These data from randomised controlled trials (RCTs) are further supported by real-world evidence. One striking study compared SGLT2i with dipeptidylpeptidase-4 inhibitors and showed significant reductions in hospitalisation for heart failure and all-cause mortality with HRs of 0.69 (95% CI 0.61 to 0.77; $p < 0.0001$) and 0.59 (95% CI 0.52 to 0.67; $p < 0.0001$), respectively.¹⁸

The exact mechanism of action is not clear and there are many suggested possibilities but is thought to be independent of glycaemic outcomes and the osmotic diuretic effect of these drugs.¹⁹ One suggested mechanism of action is attenuation of sodium-hydrogen exchanger activity, which is often increased in heart failure and contributes to diuretic resistance and fluid retention.^{19,20} Other mechanisms of action have also been suggested including effects on cardiac remodelling, left ventricular hypertrophy and decreasing oxidative stress.^{19,21}

It seems plausible that many of the beneficial effects of SGLT2i drugs may be mediated through improvements in heart failure outcomes, both in people with and without type 2 diabetes. The aim of this review was to assess current RCT evidence reporting heart failure outcomes in adults with type 2 diabetes to see whether this assumption may hold true.

Aims

The aim of this systematic review is to assess the effect of SGLT2i drugs on heart failure outcomes in adults with type 2 diabetes mellitus in RCTs. A summary of the population, intervention, comparison and outcomes (or PICO) model for this systematic review is shown in Table 1.

Methods

Protocol and registration

This systematic review and meta-analysis was prospectively registered with PROSPERO (registration number: CRD4202023256) and the reporting of this review has been undertaken in accordance with PRISMA guidelines.²² The search was performed on 14 March 2021.

Table 1. Summary of the PICO (population, intervention, comparison and outcome) model used for this systematic review and meta-analysis

	Description
P (Population)	Adults aged ≥ 18 years
I (Intervention)	Treatment with any sodium-glucose linked transporter-2 inhibitor
C (Comparison)	Placebo
O (Outcomes)	Primary: Mortality due to heart failure Secondary: Admission to hospital due to heart failure Incident diagnosis of heart failure

Eligibility criteria

Randomised controlled trials comparing SGLT2i with placebo in adults (aged ≥ 18 years) with type 2 diabetes were eligible for inclusion. Relevant sub-analyses of studies containing a broader population were eligible. Other study designs were not considered. Included studies contained data for at least one of the outcomes of interest. Studies including those with other types of diabetes or including pregnant individuals or children were excluded. No exclusions were made on grounds of data or language.

The primary outcome of interest was hospitalisation due to heart failure. Death due to heart failure, and incident diagnosis of heart failure were both secondary outcomes.

Data sources and search strategy

EMBASE, MedLine, PubMed, Cochrane CENTRAL and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched electronically. An example of the search terms used in OVID: Medline is shown in Table 2. These terms were adapted for each database as required. Language and date limits were not applied.

Study screening and selection

Identified studies were imported into EndNote v9.3 for reference management. Following the removal of duplicate manuscripts, titles and abstracts were screened for relevance. Potentially

Table 2. Example of search terms for retrieval of studies, in this case from Ovid: Medline electronic database at <http://ovidsp.ovid.com/>

1.	diabet*
2.	"heart failure" OR "cardiac failure" OR ("left ventricular" OR LV OR systolic OR diastolic) ADJ2 impairment) OR HFpEF OR HFrEF OR CCF OR HF
3.	("sodium-glucose" OR "sodium glucose") ADJ3 transport*
4.	SGLT2* OR "SGLT-2*" OR -gliflozin
5.	3 OR 4
6.	1 AND 3 AND 5

relevant manuscripts were then reviewed in full-text against the inclusion and exclusion criteria before a decision was made regarding final inclusion. Review articles identified by the search were cross-referenced to ensure no potentially relevant studies were missed. All identified full-text articles were readily accessible for inclusion; no data or manuscript requests to authors were required on this occasion.

All studies were reviewed independently by two reviewers (TSCJ and REJR). No disputes occurred in performing this review; a third reviewer was available to adjudicate the inclusion of manuscripts/studies if needed.

Data extraction

Data were extracted using a modified Cochrane's data collection form for RCTs specific to the needs of this review²³ and is included as an appendix to this manuscript (See Appendix 1 online at www.bjd-abcd.com). Key data to be extracted included the number of participants in each arm of the trial, the baseline characteristics of the study participants (weight, BMI, HbA_{1c}, age, ethnicity, duration of diabetes) and relevant co-morbidities including but not limited to pre-existing renal or cardiovascular disease. Outcomes were captured as the number of participants in each arm experiencing the outcome by the end of the study period. Bias assessment was performed using Cochrane's Collaboration bias assessment tool for RCTs.²⁴

Synthesis of results

All data available for the primary outcome of hospitalisation due to heart failure in a suitable format, was incorporated into meta-analysis. Any studies which could not be included in meta-analysis have been synthesised narratively. Meta-analysis was conducted using generic inverse variance, $\log[\text{hazard ratios}]$ and standard error in RevMan 5.4 using a fixed-effects model and inter-study heterogeneity was assessed and reported using I^2 statistics. For the secondary outcomes of death due to heart failure or incident diagnosis of heart failure, a narrative synthesis was conducted due to limited available data from the identified studies.

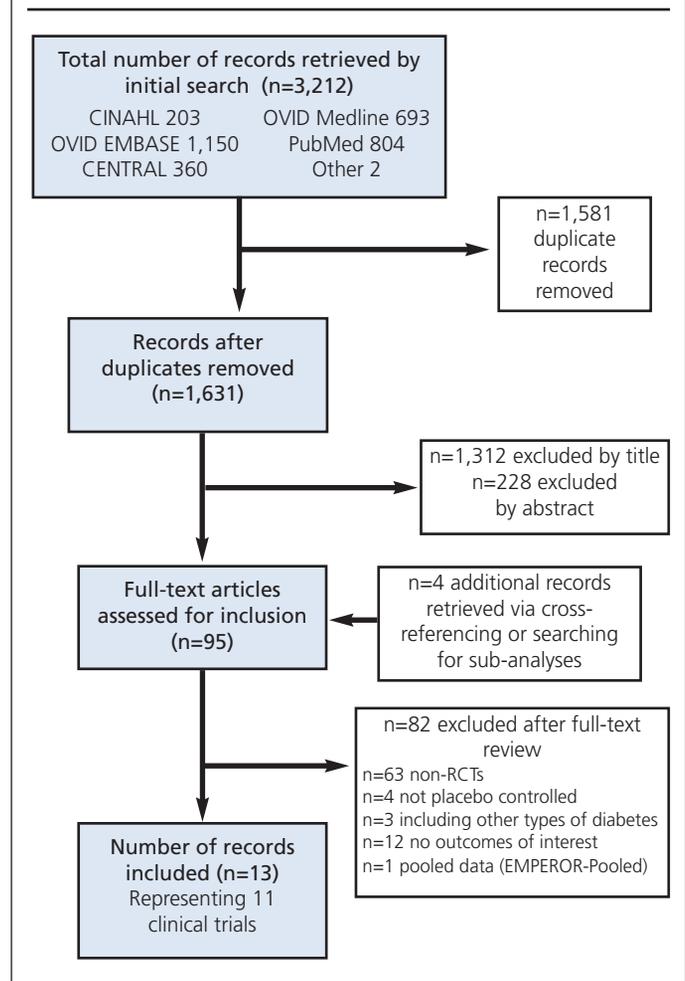
Results

A total of 3,210 records were identified, subsequently 1,581 duplicates immediately removed. The remaining 1,629 were screened, of which 89 were identified for full-text review following screening. Four additional studies of potential relevance were identified from cross-referencing pre-existing review articles. Eleven records covering nine clinical studies were eventually identified for inclusion in this review. Eight of these had data available in a format suitable for meta-analysis for hospitalisation due to heart failure; the other has been included in narrative form. At a later stage two further key studies were added following their presentation and publication (listed as other in the flow-chart). The review process is summarised in the flow chart shown in Figure 1. The characteristics of the identified studies are summarised in Table 3.

Risk of bias assessment

Bias assessment concluded potential sources of bias in most of the studies, although much of this was due to lack of clarity in

Figure 1. Flow chart showing the systematic review process and the numbers excluded at each stage



the reviewed manuscripts. The effect of potential bias introduced by changes in protocol mid-way through many of the studies is uncertain. This was the case with multiple studies, where adaptations were made in light of new published outcome data from other drugs in the class. On assessment, these protocol amendments were done in a valid way without unblinding or affecting the outcomes. Included studies with major protocol revisions for this reason have therefore be highlighted as having an "unclear" risk of bias in the "other bias" domain. The risk of bias assessment for this systematic review is summarised in Table 4.

Primary outcome

All of the identified studies had outcome data for hospitalisation due to heart failure. Ten of the studies were included in meta-analysis. One study, DAPA-CKD,²⁵ did not report a HR for this outcome for the sub-group of people with type 2 diabetes and was therefore not included in the meta-analysis. However, data were available to calculate the number of events in the intervention and comparator arms during the follow-up period of the study, with 30 hospitalisations due to heart failure occurring in the intervention arm (n=1,455) compared with 63 in the control

Table 3. Summary of baseline characteristics and design of studies included in this review

Study name or reference	Drug	Study region	Number in intervention group, n/total, N [†]	Follow-up duration, median (weeks)	Age (years) mean±SD	Ethnicity (% white)	HbA _{1c} (%) [*] mean±SD	BMI (kg/m ²) mean±SD	Outcomes of interest (all due to heart failure)
CANVAS ²⁵	Canagliflozin	Global	5,795/10,142	126.1	63.3±8.3	78.3%	8.2±0.9	32.0±5.9	Hospitalisation Death
CREDESCENCE ²⁶	Canagliflozin	Global	2,202/4,401	136.8	63.0±9.2	66.6%	8.3±1.3	31.3±6.2	Hospitalisation
DAPA-CKD ^{27‡}	Dapagliflozin	Global	1,455/2,906	125.3	56.0±14.6	54%	5.6±0.4	n/a [¶]	Hospitalisation
DAPA-HF ^{28,29*}	Dapagliflozin	Global	1,075/2,139	79.2	66.3±9.9	69.2%	7.4±1.5	29.4±6.1	Hospitalisation
DECLARE-TIMI 58 ^{30*}	Dapagliflozin	Global	8,582/17,160	219.2	63.9±6.8	79.7%	8.3±1.2	32.1±6.0	Hospitalisation
EMPA-REG ^{11*}	Empagliflozin	Global	4,687/7,020	161.8	63.1±8.6	72.6%	8.1±0.9	30.6±5.3	Hospitalisation
EMPEROR-Preserved ^{33*∞}	Empagliflozin	Global	1,466/2,938	113.4	71.8±9.3	76.3%	Not reported	29.8±5.8	Hospitalisation
EMPEROR-Reduced ^{14,15*}	Empagliflozin	Global	927/1,856	69.6	66.8±10.0	69.7%	7.4±1.6	28.8±5.5	Hospitalisation
SCORED ^{*34}	Sotagliflozin	Global	5,292/10,584	69.3	69 (63–74)‡	83.2%	8.3 (7.6–9.3)	31.9 (28.1–36.2) [§]	Hospitalisation
SOLOIST ^{31*}	Sotagliflozin	Global	608/1,222	40	69 (63–76) [§]	93.2%	7.2 (6.4–8.2) [§]	30.4 (26.3–34.3) [§]	Hospitalisation
VERTIS-CV ³²	Ertugliflozin	Global	5,499/8,246	182.7	64.4±8.1	87.8%	8.2±1.0	31.9±5.4	Hospitalisation

*Combined placebo/intervention baseline data not available. Groups noted to be broadly similar, intervention group characteristics reported in table.
[†]Numbers for people with type 2 diabetes only in studies containing both people with and without diabetes.
[‡]Data not in a suitable format for meta-analysis therefore included in narrative review only.
[¶]Although BMI data were not available, baseline weight (kg) was reported as 78.3±19.9.
[§]Reported as median (interquartile range).
[∞]Baseline characteristics for only people with diabetes not yet reported, therefore available characteristics include the entire cohort

Table 4. Risk of bias assessment for included randomised controlled trials (RCTs) using the Cochrane Risk of Bias assessment tool for randomised controlled trials²⁴

Bias Assessment - RCTs	CANVAS ²⁵	CREDESCENCE ²⁶	DAPA-CKD ²⁷	DAPA-HF ^{28,29}	DECLARE-TIMI 58 ³⁰	EMPEROR-Reduced ^{14,15}	EMPA-REG ¹¹	SOLOIST ³¹	VERTIS-CV ³²	SCORED ³⁴	EMPEROR-Preserved ³³
1. Random sequence generation	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
2. Allocation concealment	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
3. Blinding of participants and personnel	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
4. Blinding of outcome assessment	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
5. Incomplete outcome data	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low
6. Selective reporting	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Low	Unclear	Low
7. Other sources of bias	Unclear	Low	Low	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear

arm (n=1,451). The rate of hospitalisation due to heart failure with dapagliflozin was 2.1 per 100 person-years versus 3.8 per 100 person-years with placebo. One of the secondary outcomes for this study was a composite of cardiovascular mortality or hospitalisation due to heart failure and reported a HR of 0.7 (95% CI 0.52 to 0.92).

The meta-analysis of the results from the other 10 trials is shown in Figure 2. The studies included 65,708 patients of which 36,133 were taking an SGLT2i drug. The pooled hazard ratio for hospitalisation due to heart failure was 0.69 (95% CI 0.64, 0.74) significantly favouring SGLT2i to placebo. Inter-study heterogeneity was very low with an I^2 value of 0%. Of note, this is also comparable to the HRs for the composite outcome of hospitalisation due to heart failure or cardiac death in DAPA-CKD.

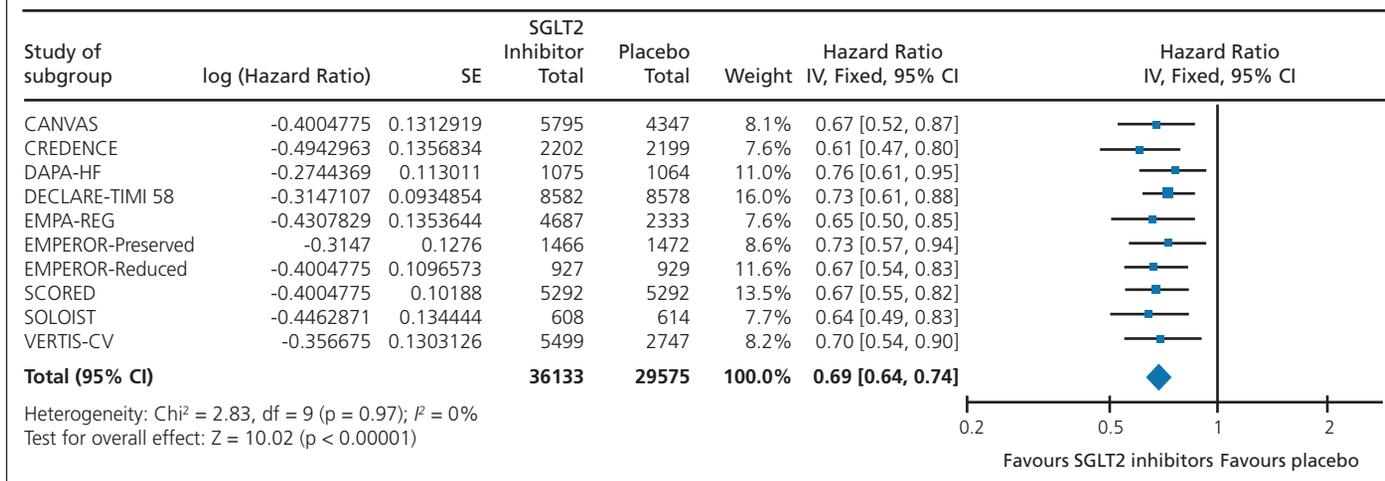
Secondary outcomes

Only one study reported mortality rates due specifically to heart failure. This study, the CANVAS study, reported a HR of 0.89 (95% CI 0.49 to 1.6) for canagliflozin compared with placebo. This fails to reach statistical significance. No studies reported the rates of incident new heart failure diagnoses with SGLT2i drugs compared with placebo.

Discussion

The cardiovascular outcome trials of SGLT2i drugs to date have provided robust and consistent evidence that their use in people with type 2 diabetes is associated with improved cardiac outcomes. In this systematic review looking specifically at heart failure outcomes, all identified studies favoured SGLT2i drugs to placebo (HR 0.69; 95% CI 0.64, 0.74) with very limited inter-study heterogeneity. This is comparable to the earlier meta-analysis of the five studies published at that point (HR 0.68; 0.61 to 0.76).¹⁶ This is strong evidence that SGLT2i drugs reduce the risk of hospital admission due to heart failure and that this is likely to be a class effect. Several of the studies feature a composite outcome of death due to cardiovascular causes and hospitalisation due to heart failure – the significance of SGLT2i drugs in reducing this outcome may be primarily mediated by reductions in hospitalisation due to heart failure.

Unfortunately, the available studies did not consistently report mortality rates due to heart failure. The one study with this outcome demonstrated a trend towards reduced mortality, but failed to reach statistical significance. Further studies or sub-analysis of current works is needed to establish whether SGLT2i drugs improve heart failure-specific mortality.

Figure 2. Forrest plot showing meta-analysis of hazard ratios for hospitalisation due to heart failure for included studies

No studies reported the incident rates of new heart failure diagnoses. Most studies to date have been in people with significant cardiovascular risk factors. Further work is needed to assess incident heart failure diagnosis rates in those with these significant risk factors but without heart failure at baseline.

The paucity of data from studies for two of the outcomes limits the conclusions we are able to draw at present from this review. SGLT2i drugs appear to be well tolerated by most, but potential side effects including ketoacidosis and urinary tract infection may limit their use in some people with diabetes.³⁵

Both SGLT2i and long acting GLP1-receptor agonists improve cardiovascular outcomes and they appear to provide benefit by entirely different mechanisms.^{19,36} Although SGLT2i drugs appear to reduce rates of cardiovascular disease and heart outcomes more than metformin,³⁷ the cost difference between these drugs makes cost-effectiveness less certain. Further health-economic analyses will be needed to establish this moving forwards. Cardiovascular benefit is also well established for pioglitazone¹⁹ and it has been argued that SGLT2i, long-acting GLP-1 receptor agonists, pioglitazone and metformin could complement each other, if used in combination, to further improve cardiovascular outcomes.¹⁹ Nevertheless, the benefits of SGLT2i drugs in improving cardiovascular outcomes are clear, and we welcome their inclusion in the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) joint type 2 diabetes treatment algorithm – especially their use as second-line therapy in those at increased risk.³⁸ Furthermore, we look forward to seeing their evolving role in the management of type 1 diabetes and future evidence that they improve cardiovascular outcomes beyond the positive glycaemic and weight outcomes demonstrated by the DEPICT trials.³⁹

Conclusion

SGLT2i drugs significantly reduced heart failure hospitalisation rates in adults with type 2 diabetes in RCTs compared with placebo. This occurs, without any heterogeneity, in all drugs across the class in the studies identified for inclusion in this review. This may be the main mediator of improved composite



Key messages

- SGLT2i are proven to reduce the rates of 3-point MACE (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke)
- Reductions in cardiovascular death may be mediated by significant improvements in heart failure
- This meta-analysis provides additional evidence using all available studies to date for reductions in hospitalisation due to heart failure
- The reporting of death specifically due to heart failure is limited and should be considered as an outcome of interest for future sub-analyses or works. Where reported, reduction in mortality due to heart failure are clear

cardiovascular outcomes reported in many of the trials. It is not clear whether SGLT2i drugs reduce mortality rates due to heart failure or incident diagnosis. We eagerly await further work to clarify the benefits of SGLT2i drugs in this regard.

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Appendix 1. Data extraction form

Review Title/ID					
Study ID					
Link					
Ref					
Notes					
General information					
Date form completed					
Person ID/name					
Publication Type					
Study Eligibility					
RCT?					
Intervention?					
Comparator?					
Outcomes?					(one or more of interest as per protocol)
INCLUDE					
Methods					
Aim of study					
Design					
Unit of allocation					
Start date					
End date					
Duration of participation					
Ethics?					
Participants					
Population					
Setting					
Inclusion criteria					
Exclusion criteria					
Method of recruitment					
Consent?					
Number randomised					
Clusters					
Age					
Sex					
Race					
Co-morbidty					
Diabetes duration					
Other drugs					
HbA1c					
Weight/BMI					
eGFR					
Subgroups measured?					
Subgroups reported?					
Group (intervention)					
Intervention randomised					
Co-interventions					
Group (comparator)					
Comparator randomised					
Co-interventions					
Outcomes					
		Intervention		Comparator	
HF hospitalisation					
HF death					
Incident HF					
Bias					
		Hi	Unclear	Lo	
Random seq?					
Allocation concealment?					
Blinding part and pers					
Blinding of outcome assessment					
Incomplete outcome data?					
Selective outcome reporting?					
Other Bias					