Reviews in Cardiovascular Medicine

IMR Press

Systematic Review

Cardiovascular outcomes of glucose lowering therapy in chronic kidney disease patients: a systematic review with meta-analysis

Anna Kamdar[1], Robert Sykes[1,2,*], Andrew Morrow[1,2], Kenneth Mangion[1,2,3], Colin Berry[1,2,3]

[1] *Institute of Cardiovascular and Medical Sciences, University of Glasgow, G12 8TA Glasgow, UK*

[2] *West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, G81 4DY Glasgow, UK*

[3] *Department of Cardiology, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde Health Board, G51 4TF Glasgow, UK*

*Correspondence: robert.sykes@glasgow.ac.uk (Robert Sykes)

DOI:10.31083/j.rcm2204152

Submitted: 5 September 2021 Revised: 13 October 2021 Accepted: 19 October 2021 Published: 22 December 2021

Chronic kidney disease (CKD) and cardiovascular disease share common risk factors such as hypertension, diabetes mellitus and dyslipidemia. Patients with CKD carry a high burden of cardiovascular disease and may be excluded from clinical trials on the basis of safety. There are an increasing number of clinical trials which predefine sub-group analysis for CKD. This systematic review with fixed-effect meta-analysis investigates glucose lowering therapy and cardiovascular outcomes in relation to CKD. We included randomized controlled trials (RCT) of glucose lowering treatments performed in adults (aged $\geq$18 years), humans, with no restriction on date, and English-language restriction in patients with pre-existing CKD regardless of diabetes status. Embase & Ovid Medline databases were searched up to April 2021. Risk of bias was assessed according to Revised Cochrane risk-of-bias tool. We included 7 trials involving a total of 48,801 participants. There were 4 sodium-glucose cotransporter-2 inhibitors (SGLT2i), 2 glucagon-like peptide-1 receptor (GLP-1R) agonists and 1 Dipeptidyl-peptidase 4 (DPP4) inhibitor identified. SGLT2i (relative risk (RR) = 0.90, 95% confidence interval (CI) [0.79–1.02]) and GLP-1R agonists (RR = 0.83, 95% CI [0.72–0.96]) were associated with a reduction in cardiovascular death. SGLT2i (RR = 0.69, 95% CI [0.63–0.75]) are also associated with a reduction in hospitalization for heart failure. In summary, this meta-analysis of large, RCTs of glucose lowering therapies has demonstrated that treatment with SGLT2i or GLP-1R agonists may improve 3 point-MACE and cardiovascular outcomes in patients with chronic renal failure compared with placebo. This systematic review was registered with the PROSPERO network (registration number: CRD42021268563) and follows the PRISMA guidelines on systematic reviews and metanalysis.

Keywords

Cardiovascular outcomes; Randomized controlled trials; Chronic kidney disease; Mortality; Myocardial infarction; Heart failure; Cardiorenal syndrome

1. Introduction

Cardiac dysfunction in the presence of chronic kidney disease (CKD) is a well-established phenomenon. End-stage renal disease (ESRD) is associated with adverse cardiac events in up to 64% of patients undergoing hemodialysis. Developing evidence-based medicines for cardiovascular disease (CVD) through randomized, controlled trials (RCTs) in this population is a current priority [1, 2]. Cardiovascular death accounts for 50% of deaths in CKD patients representing an unmet clinical therapeutic need for safe and effective therapies in these patients [2]. Many of the risk factors of cardiac dysfunction and CKD are shared, including hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease [3]. Additionally; anemia, hypovolemia, proteinuria and mineral metabolism abnormalities associated with CKD are associated with increased likelihood of adverse cardiovascular outcomes [3].

Diabetic nephropathy is the leading cause of CKD. Patients with CKD and diabetes carry a high burden of CVD [4]. The mainstay of reducing diabetes-associated cardiovascular (CV) death is through modification of underlying risk factors, including glycemic control, dyslipidemia, smoking, physical inactivity, and hypertension, which are shared risks in myocardial infarction (MI) [5] and stroke [6, 7]

Type 2 diabetes mellitus (T2DM) is also associated with cardiovascular disease, with a 2–3 times increased risk of cardiovascular disease [8]. Around 40% of T2DM patients develop diabetic kidney disease, which portends an even greater risk of adverse cardiovascular outcomes [9]. Randomized controlled trials in patients with diabetes mellitus have demonstrated the beneficial cardiovascular effects of antihyperglycemic agents such as sodium-glucose co-transporter inhibitors (SGLT2i), glucagon-like peptide-1 receptor (GLP-1R) agonists [10, 11]. Previous systematic reviews and meta-analysis have focused on the identification of RCTs involving patients with T2DM [12, 13], however cardiovascular outcomes in the context of CKD and ESRD patients are less well-established as CKD patients are frequently excluded from clinical trials, and only recently that focused trials have been designed to address this patient group [14]. Shared risk factors and the prevalence of concomitant CKD and CVD in clinical practice demonstrate the need for rigorous safety and efficacy data in this population.

This systematic review with meta-analysis investigates the data available on cardiovascular outcomes specifically in CKD/ESRD patients involved in clinical trials of glucose-lowering therapies.

2. Methods

2.1 Search strategy and selection criteria

This review focuses on cardiovascular outcomes in trials in chronic kidney disease patients and was registered within the PROSPERO network (registration number: CRD42021268563) [15]. An electronic database search was performed of Embase & Ovid Medline up to April 2021 through the Ovid Gateway system in addition to screening of review articles generated during this search. The search was restricted to randomized controlled trials (RCT) performed in adults (aged $\geq$18 years), humans, with no restriction on date. Language was restricted to English.

The MeSH terms of the search strategy were created following an initial scoping of existing reviews and primary study literature. These included 'cardiovascular disease', 'chronic heart failure', 'chronic kidney disease', 'chronic renal disease' and variants. These terms were then combined with Boolean operators in addition to limitations.

The search was designed to be sensitive to the tautological array of alternative terminologies included in studies of CKD and CVD and was performed on 31st March 2021. Identified studies were de-duplicated prior to screening of title and abstract to exclude irrelevant or ineligible articles. The manuscripts of remaining articles were then reviewed. Studies were included if they met the following conditions: primary RCT or subsequent subgroup analysis of larger RCT in a population of patients with chronic kidney disease stages 1–5 with native kidneys; Sample size greater than 300; Follow-up $\geq$3 months; Cardiovascular outcome data and antihyperglycemic intervention. Reasons for exclusion included: conference abstract only with lack of sufficient data for inclusion; if the parent study of a sub-group analysis had already been included; or if it did not meet inclusion due to short follow-up or small sample size. In addition, a screen of the reference list of existing reviews and included trials was performed to identify any further studies not included in the search results. Studies were then included if they included a glucose lowering therapy as the intervention and did not meet any exclusion criteria.

All references were uploaded to Rayyan [16], a web-based computational reference manager. These were then independently screened in two stages. Initially through title and abstract, and then by full text. AK and RS reviewed eligibility. Discordance was adjudicated by AM. These were recorded in a PRISMA workflow and reported according to the PRISMA guidelines for systematic review and metanalysis [17] (**Supplementary Table 1**).

2.2 Data extraction and analysis

Data was extracted by AK then reviewed by RS and AM for discrepancies. Demographic data and the definitions of CVD and CKD used within the RCT were extracted from the studies or attached supplementary data. Baseline characteristics including presence of congestive heart failure, hypertension, diabetes, and cerebrovascular disease were also gathered. The definition of the primary outcome for each study was collated.

Hazard ratios were collected, and where not available calculated from reported or supplementary data for primary composite outcomes, all-cause mortality, renal and cardiac outcomes. Forest plots were created for primary outcome, all-cause mortality, Fatal/Non-fatal MI and hospitalizations for heart failure (HHF) where available with the aid of RevMan software [18]. Two-tailed statistical analysis was performed with a significance threshold of $p < 0.05$. Risk ratios and 95% confidence intervals were calculated using Mantel-Haenszel method. A fixed effect analysis model was used due to the inclusion criteria of sample size >300 and low levels of heterogeneity between studies.

Heterogeneity of studies was assessed prior to subgroup analysis with an I^2 of 25%, 50% and 75% correlating to low, medium and high heterogeneity respectively. The parameters assessed were age, sex, baseline estimated glomerular filtration rate (eGFR). A further sensitivity analysis was carried out to account for differences in study populations across the RCTs due to two RCTs enrolling patients without diabetes. A risk of bias assessment was undertaken for all included studies using the Revised Cochrane risk-of-bias tool [19] by AK, RS and AM independently. Studies were categorized into low, high and unclear risk of bias. Studies with a high risk of bias were then excluded in a sensitivity analysis. Begg's funnel plots were used to assess for publication bias for CV mortality, fatal/non-fatal MI and HHF with 95% confidence interval applied.

3. Results

3.1 Study characteristics

Our initial search yielded 1561 abstracts. Sixty-seven studies were identified as RCTs with cardiovascular outcomes which involved CKD patients. Of these we identified 7 RCTs for inclusion which involved diabetes medications. The PRISMA workflow is shown in Fig. 1. These were CARMELINA [20], CREDENCE [21], DAPA-CKD [22], EMPEROR-REDUCED [23], HARMONY [24], LEADER [25] and SCORED [26]. A risk of bias assessment can be viewed in Fig. 2. Most studies had a low risk of bias, however SCORED had high bias in terms of its outcome analysis. This was due to the change in definition of primary outcome from time-to-event to number of events. The study also used investigator-reported outcomes for the analysis.

Four studies involved SGLT2i, two involved GLP-1R agonists, and one assessed a DPP-4 inhibitor versus placebo in patients with chronic renal failure. A total of 47,879 participants were enrolled across all 7 trials. Trial participants were predominantly male and aged greater than 60 years of age. Only one study, SCORED, included patients with CKD stage

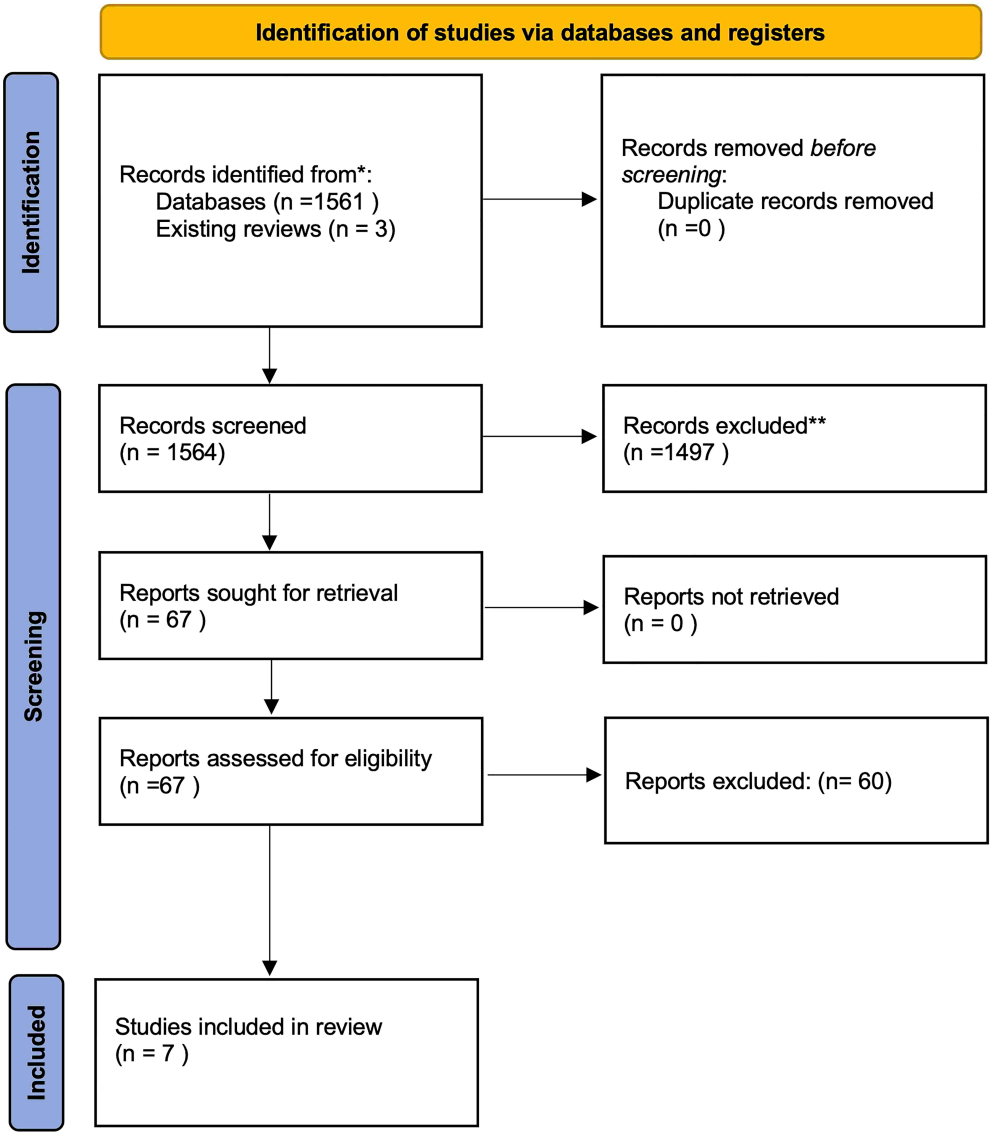

Fig. 1. PRISMA [17] workflow of included studies. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

5, whereas other studies only included stages 1–4. A summary of the included studies can be viewed in Table 1 (Ref. [20–26]) alongside the intervention details.

Included trial demographics were assessed for heterogeneity in addition to the degree of renal impairment. Heterogeneity assessment from the SCORED required estimation of mean and standard deviations from median and interquartile ranges provided. Mean eGFR was unable to be calculated for LEADER as the supplementary appendix grouped eGFR by class. These were normal, mild, moderate, and severe with 2.5% of liraglutide and 2.3% of placebo patients categorized as severe impairment (eGFR <30 mL/min/1.73 m^2). Overall, 65.3% of liraglutide and 64.6% of placebo patients in LEADER had an eGFR <90 mL/min/1.73 m^2.

Between all trials, age yielded a Chi^2 of 14.05 ($p = 0.03$) and I^2 of 57% suggesting moderate heterogeneity between study populations. However, eGFR had a Chi^2 of 2.76 ($p = 0.74$) and I^2 of 0% so the level of renal impairment between studies was comparable.

SCORED was unfortunately prematurely terminated due to financial reasons related to the coronavirus pandemic [26]. Due to this, the primary endpoint definition was altered to include total number of events rather than a time-to-event analysis.

3.2 Study outcomes

Table 2 lists outcomes for each individual trial. Confidence intervals were calculated based on this information in Table 3 and corresponding *p*-values provided.

Table 1. Baseline study characteristics of included trials.

Parent trial	CARMELINA [20]	CREDENCE [21]	DAPA-CKD [22]	EMPEROR-REDUCED [23]	HARMONY [24]	LEADER [25]	SCORED [26]
Subgroup	Secondary analysis of T2DM with coexisting kidney disease	Patient with type 2 diabetes and CKD with prior history of HF	-	Pre-specified analysis of EMPORER-REDUCED	-	-	-
Author	Rosenstock *et al.*	Mahaffey *et al.*	Heerspink *et al.*	Packer *et al.*	Hernandez *et al.*	Marso *et al.*	Bhatt *et al.*
Year of study	2019	2019	2020	2020	2018	2016	2021
Drug action	DPP-4 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor	GLP-1R agonist	GLP-1R agonist	SGLT2 inhibitor
Intervention	Linagliptin	Canagliflozin	Dapagliflozin	Empagliflozin	Abiglutide	Liraglutide	Sotagliflozin
Number of participants	6979	4401	4304	3730	9463	9340	10584
Mean age (years)	65.9	63	61.9	67.2	64.1	64.3	69**
Male, (%)	62.9	66.1	66.9	76.5	70	64.3	55.7**
CKD stage*	CKD1-4	CKD2-4	CKD2-4	CKD1-3b	CKD1-3b	CKD 1-4	CKD 3-5
Mean. eGFR (mL/min/1.73 m^2)	54.6	56.2	43.1	61.8	79.1	-	44.4
Median UACR (mg/g)	162	927	949.5	-	-	-	74
Diabetes, (%)	100	100	67.5	49.8	100	100	100
Stroke/Cerebrovascular disease, n (%)	-	-	-	-	17	16.1	8.9
Atrial fibrillation, (%)	9.6	-	-	35.6	8	-	-
Hypertension, (%)	91	96.8		72.4	86	90	-
Ischemic heart disease, (%)	58.5	-	-	-	47	-	-
NYHA class at baseline	-	0–III	0–III	II–IV	-	II–III	0–IV
Prevalence of HF at baseline, (%)	26.8	14.8	10.9	100	20	-	31
Other treatment	Standard care	Standard care	ACEI or ARB 4 weeks prior	Standard care	Standard care	Standard care	Standard care
RAAS-inhibitor, (%)	81.1	69.0	-	69.7	-	-	88.5
ACE-inhibitor (%)	-	-	31.5	-	49.0	51.0	38.3
Angiotensin receptor blocker (%)	-	-	66.7	-	33.0	31.9	49.0
Angiotensin receptor-neprilysin inhibitor (%)	-	-	-	19.5	-	-	1.2
Mineralcorticoid-receptor antagonist (%)	-	-	-	71.3	-	-	15.0
Beta-blocker, (%)	59.5	40.2	-	94.7	-	55.5	62.5
Diuretic, (%)	54.9	46.7	43.7	-	-	41.8	65.2
Statin, (%)	71.9	69.0	64.9	-	-	72.2	-
Antithrombotic*** (%)	62.2	59.6	-	-	77.0	67.8	-
Mean Follow-up (months)	26.4	31.44	28.8	16	19.2	45.6	16

*CKD stages: Stage 1 with normal or high GFR (GFR >90 mL/min/1.73 m^2); Stage 2 Mild CKD (GFR = 60–89 mL/min/1.73 m^2); Stage 3A Moderate CKD (GFR = 45–59 mL/min/1.73 m^2); Stage 3B Moderate CKD (GFR = 30–44 mL/min/1.73 m^2); Stage 4 Severe CKD (GFR = 15–29 mL/min/1.73 m^2); Stage 5 End Stage CKD (GFR <15 mL/min/1.73 m^2).

** Median value reported.

*** Anticoagulation or antiplatelet agent, including aspirin.

SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1R, glucagon-like peptide-1 receptor; DPP4, Dipeptidyl-peptidase 4; CKD, Chronic Kidney disease; eGFR, estimated Glomerular Filtration Rate; UACR, Urinary albumin to creatinine ratio; NYHA, New York Heart Association functional classification; RAAS, Renin-Aldosterone-Angiotensin System; ACE, angiotensin converting enzyme; ACEI, Angiotensin coverting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Outcomes of parent trials.

Parent trial	CARMELINA		CREDENCE		DAPA-CKD		EMPORER-REDUCED		HARMONY		LEADER		SCORED	
Arm	Linagliptin	Placebo	Canagliflozin	Placebo	Dapagliflozin	Placebo	Empagliflozin	Placebo	Albiglutide	Placebo	Liraglutide	Placebo	Sotagliflozin	Placebo
Participants, N	3494	3485	2202	2199	2152	2152	1863	1867	4731	4732	4668	4672	5292	5292
Primary composite outcome	Time to first occurrence of CV death, non-fatal MI or non-fatal stroke		Composite. of ESRD (dialysis, transplantation, or a sustained estimated. GFR of <15 or a doubling of the serum creatinine level, or renal/CV death		Composite of sustained decline in the eGFR of at least 50%, ESRD, or death from renal or CV causes		Composite of adjudicated CV death or hospitalization for heart failure, analyzed as the time to the first event		First occurrence of CV death, myocardial infarction, or stroke		First occurrence of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke		Total number of deaths from CV causes, hospitalizations for HF and urgent visits for HF	
Primary composite outcome, n (%)	**434 (12.4)***	**420 (12.1)***	**245 (11.1)***	**339 (15.4)***	**198 (9.2)***	**312 (14.5)***	**361 (19.4)***	**461 (24.7)***	**338 (7)***	**428 (9)***	**607 (13)***	**696 (14.9)***	**400 (7.6)***	**530 (10.0)***
All-cause mortality, n (%)	367 (10.5)	10.7	167 (7.6)	201 (9.1)	**101 (4.7)***	**146 (6.8)***	250 (13.4)	265 (14.2)	196 (4.0)	205 (4.0)	**383 (8.2)***	**449 (9.6)***	246 (4.7)	246 (4.7)
Cardiovascular mortality, n (%)	221 (7.3)	225 (7.6)	110 (5.0)	140 (6.4)	65 (3.0)	80 (3.7)	186 (10)	202 (10.8)	122 (2.6)	130 (2.7)	**219 (4.7)***	**280 (6.0)***	155 (2.9)	170 (3.2)
Fatal/non-fatal Myocardial infarction, n (%)	165 (4.7)	146 (4.2)	83 (3.8)	95 (4.3)	32 (1.5)	45 (2.1)	-	-	**181 (4.0)***	**240 (5.0)***	**294 (6.3)***	**341 (7.3)***	-	-
Stroke (fatal/non-fatal), n (%)	81 (2.3)	88 (2.5)	62 (2.4)	80 (3.0)	26 (1.2)	30 (1.4)	-	-	94 (2.0)	108 (2.3)	173 (3.7)	201 (4.3)	-	-
Progression to ESRD disease, n (%)	63 (1.8)	64 (1.8)	117 (5.3)	165 (7.5)	110 (5.1)	161 (7.5)	-	-	-	-	-	-	-	-
Doubling of baseline creatinine/change in eGFR, n (%)	-	-	119 (5.4)	187 (8.5)	112 (5.2)	200 (9.3)	-	-	-	-	-	-	37 (0.7)	52 (1.0)
Hospitalisation for heart failure, n (%)	209 (6.0)	226 (6.5)	89 (4.0)	141 (6.4)	-	-	**388 (20.8)***	**553 (29.6)***	-	-	218 (4.7)	248 (5.3)	**245 (3.5)***	**360 (5.1)***

Change in eGFR = decrease $\geq$30 mL/min/1.73 m^2 if eGFR previously $\geq$60 mL/min/1.73 m^2 or relative decrease $\geq$50% *bold text = statistically significant result ($p < 0.05$).

ESRD, End-stage renal disease; Egfr, estimated glomerular filtration rate.

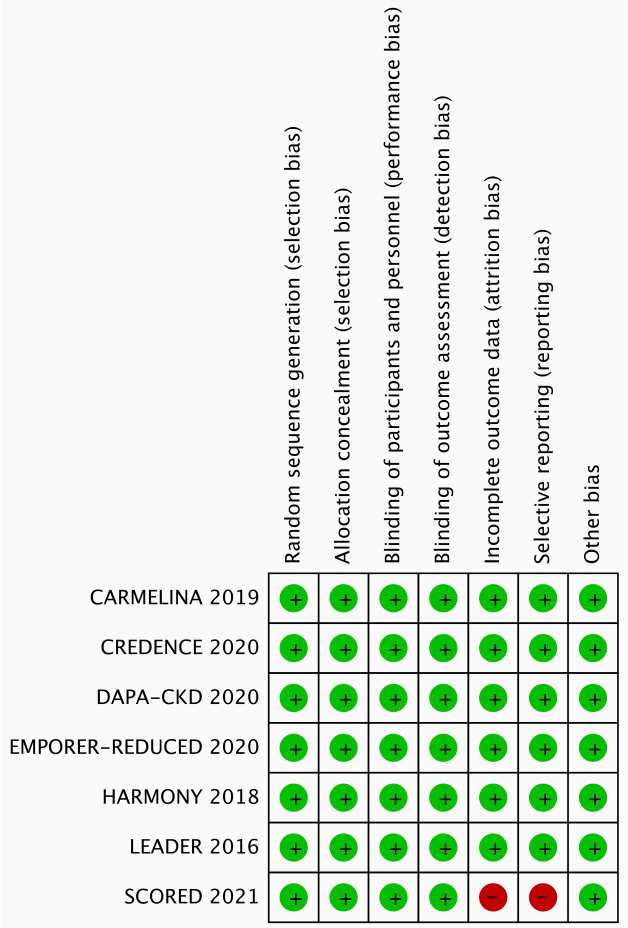

Fig. 2. Risk of bias summary of included trials. Reviewers' judgements for risk of bias within each included study.

3.2.1 Primary composite outcomes

All primary composite outcomes included CV death. Across all studies, interventions were associated with statistically significant reductions in the primary outcome compared with placebo (Table 3). CREDENCE and DAPA-CKD had primary composite outcomes which included renal outcomes as well as cardiovascular outcomes. All remaining studies shared a similar primary outcome of 3-point major adverse cardiac events (MACE) involving CV death, MI and stroke.

3.2.2 All-cause mortality

All-cause mortality was reduced in DAPA-CKD (6.8% vs 4.7% p = 0.004) and LEADER (9.6% vs 8.2% p = 0.02) (Fig. 3A).

There were no between-group differences in mortality in CARMELINA, CREDENCE, or HARMONY. p-values were not provided by EMPORER-REDUCED and SCORED.

The effect size of SGLT2i (Z = 2.43 [p = 0.03]) and GLP-1R agonists (Z = 2.21 [p = 0.03]) was similar in reducing mortality.

3.2.3 Fatal/Non-fatal MI

Data were unavailable for fatal/non-fatal MI in EMPORER-REDUCED and SCORED. HARMONY (4.0% vs 5.0% p = 0.003) and LEADER (6.3% vs 7.3% p = 0.046) had a statically significant reduction in fatal/non-fatal MI (Table 2). Overall, GLP-1R agonists had the greatest effect in the prevention of fatal/non-fatal MI (Z = 3.35 [p = 0.0008]) when compared to DPP4i (Z = 1.08 [p = 0.28]) and SGLT2i (1.60 [p = 0.11]) (Fig. 3B). There were no between group differences observed between CREDENCE and DAPA-CKD in prevention of MI (Chi^2 = 0.56, [p = 0.45]; I^2 = 0%) and similarly between GLP-1R agonists (Chi^2 = 1.19, [p = 0.27]; I^2 = 16%).

3.2.4 Cardiovascular mortality

CV mortality reduction was significantly reduced in LEADER (6.3% vs 7.3% p = 0.007).

SGLT2i (Z = 2.35 [p = 0.02]) and GLP-1R agonists (Z = 2.56 [p = 0.01]) had a similar effect size in reducing CV mortality (Fig. 3C). Additionally, there did not appear to be between group differences in this reduction in SGLT2i (Chi^2 = 1.42, [p = 0.70]; I^2 = 0%). There may be a moderate difference between GLP-1R agonists (Chi^2 = 1.42, [p = 0.23]; I^2 = 30%).

3.2.5 Hospitalizations for heart failure

Data were not available for HHF in DAPA-CKD and HARMONY.

HHF were decreased across remaining trials and significantly reduced in EMPORER-REDUCED (20.8% vs 29.6% $p < 0.001$) and SCORED (5.1% vs 3.5% $p < 0.001$). In all studies with data, there was a decrease in HHF. This reduction was most prominent in SGLT2i (Z = 8.50 [$p < 0.00001$]) (Fig. 3D).

3.3 Sensitivity analysis

An initial sensitivity analysis was performed for studies which included 3-point MACE as the primary outcome (Table 4). This only affected the SGLT2i group, but did not lead to any significant change (Z = 5.91 [$p < 0.0001$], I^2 = 0).

The populations of DAPA-CKD and EMPORER-REDUCED varied substantially from other studies as there were individuals without diabetes included in the trial designs. Sensitivity analysis of all-cause mortality, fatal/non-fatal MI, CV mortality and HHF were performed for SGLT2i excluding these trials (Table 4). Reductions in CV mortality and HHF remained significant for SGLT2i.

A further sensitivity analysis was performed excluding SCORED from the SGLT2i group due to the high risk of reporting bias on outcomes. All-cause mortality (Z = 2.94 [p = 0.003]), CV mortality (Z = 2.26 [p = 0.02]) and HHF (Z = 7.05 [$p < 0.00001$]) remained significant.

3.4 Risk of publication bias assessment

Begg's funnel plots were created for the CV outcomes of CV mortality (Fig. 4A), Fatal/non-fatal MI (Fig. 4B) and HHF (Fig. 4C). Fatal/non-fatal MI showed slight asymmetry from

Table 3. Hazard ratios by drug class and test for overall effect size.

Outcome	Drug class	Trial	Risk ratio [95% CI]	*p*-value
Primary composite outcome	DPP-4 inhibitor	CARMELINA	1.03 [0.91, 1.17]	<0.001
		Test for overall effect: Z = 0.47 (*p* = 0.64)		
	SGLT2 inhibitor	CREDENCE	0.72 [0.62, 0.84]	0.00001
		DAPA-CKD	0.63 [0.54, 0.75]	<0.001
		EMPORER-REDUCED	0.78 [0.69, 0.89]	<0.001
		SCORED	0.75 [0.67, 0.85]	<0.001
		Total	0.73 [0.68, 0.79]	N/A
		Test for overall effect: Z = 8.80 (*p* < 0.00001)		
	GLP-1R agonist	LEADER	0.87 [0.79, 0.97]	0.01
		HARMONY	0.79 [0.69, 0.91]	<0.0001
		Total	0.84 [0.78,0.91	N/A
		Test for overall effect: Z = 4.17 (*p* < 0.0001)		
All-cause mortality	DPP-4 inhibitor	CARMELINA	0.98 [0.82, 1.17]	0.74
		Test for overall effect: Z = 0.27 (*p* = 0.79)		
	SGLT2 inhibitor	CREDENCE	0.83 [0.68, 1.01]	0.61
		DAPA-CKD	0.81 [0.59, 1.12]	0.004
		EMPORER-REDUCED	0.92 [0.76, 1.11]	N/A
		SCORED	0.91 [0.74, 1.13]	N/A
		Total	0.89 [0.81, 0.98]	N/A
		Test for overall effect: Z = 2.43 (*p* = 0.02)		
	GLP-1R agonist	LEADER	0.78 [0.66, 0.93]	0.02
		HARMONY	0.94 [0.74, 1.20]	0.644
		Total	0.89 [0.80, 0.99]	N/A
		Test for overall effect: Z = 2.21 (*p* = 0.03)		
Cardiovascular mortality	DPP-4 inhibitor	CARMELINA	0.98 [0.82, 1.17]	0.63
		Test for overall effect: Z = 0.22 (*p* = 0.82)		
	SGLT2 inhibitor	CREDENCE	0.78 [0.62, 1.00]	0.86
		DAPA-CKD	0.81 [0.59, 1.12]	N/A
		EMPORER-REDUCED	0.92 [0.76, 1.11]	N/A
		SCORED	0.91 [0.74, 1.13]	0.35
		Total	0.90 [0.79, 1.02]	N/A
		Test for overall effect: Z = 2.35 (*p* = 0.02)		
	GLP-1R agonist	LEADER	0.78 [0.66, 0.93]	0.007
		HARMONY	0.94 [0.74, 1.20]	0.578
		Total	0.83 [0.72, 0.96]	N/A
		Test for overall effect: Z = 2.56 (*p* = 0.01)		
Fatal/Non-fatal MI	DPP-4 inhibitor	CARMELINA	1.13 [0.91, 1.40]	0.3
		Test for overall effect: Z = 1.08 (*p* = 0.28)		
	SGLT2 inhibitor	CREDENCE	0.87 [0.65, 1.16]	0.37
		DAPA-CKD	0.71 [0.45, 1.11]	N/A
		EMPORER-REDUCED	-	-
		SCORED	-	-
		Total	0.82 [0.64, 1.05]	N/A
		Test for overall effect: Z = 1.60 (*p* = 0.11)		
	GLP-1R agonist	LEADER	0.86 [0.74, 1.00]	0.046
		HARMONY	0.75 [0.62, 0.91]	0.003
		Total	0.82 [0.73, 0.92]	N/A
		Test for overall effect: Z = 3.35 (*p* = 0.0008)		
Hospitalizations for heart failure	DPP-4 inhibitor	CARMELINA	0.92 [0.77, 1.11]	0.26
		Test for overall effect: Z = 0.87 (*p* = 0.38)		
	SGLT2 inhibitor	CREDENCE	0.63 [0.49, 0.82]	0.98
		DAPA-CKD	-	-
		EMPORER-REDUCED	0.70 [0.63, 0.79]	<0.001
		SCORED	0.68 [0.58, 0.80]	<0.001
		Total	0.69 [0.63, 0.75]	N/A
		Test for overall effect: Z = 8.50 (*p* < 0.00001)		
	GLP-1R agonist	LEADER	0.88 [0.74, 1.05]	0.14
		HARMONY	-	-
		Test for overall effect: Z = 1.42 (*p* = 0.16)		

SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1R, glucagon-like peptide-1 receptor; DPP4, Dipeptidyl-peptidase 4; CI, Confidence interval; N/A, not applicable; -, no data available.

Table 4. Sensitivity analysis of Type 2 diabetes mellitus trials.

Outcome	Number of participants		Risk ratio [95% CI]	Effect size (Z)	*p*-value	I^2
	SGLT2 inhibitor	Placebo				
All-cause mortality	7494	7491	0.92 [0.81, 1.05]	1.21	0.23	0.49
Cardiovascular mortality	7494	7491	0.85 [0.73, 1.00]	1.92	0.05	0.00
Fatal/Non-Fatal MI *	2202	2199	0.87 [0.65, 1.16]	0.93	0.35	N/A
Hospitalisations for heart failure	7494	7491	0.67 [0.58, 0.76]	5.91	$p < 0.00001$	0.00

SGLT2i, sodium-glucose cotranporter 2 inhibitor; *, data only available for CREDENCE; N/A, not applicable.

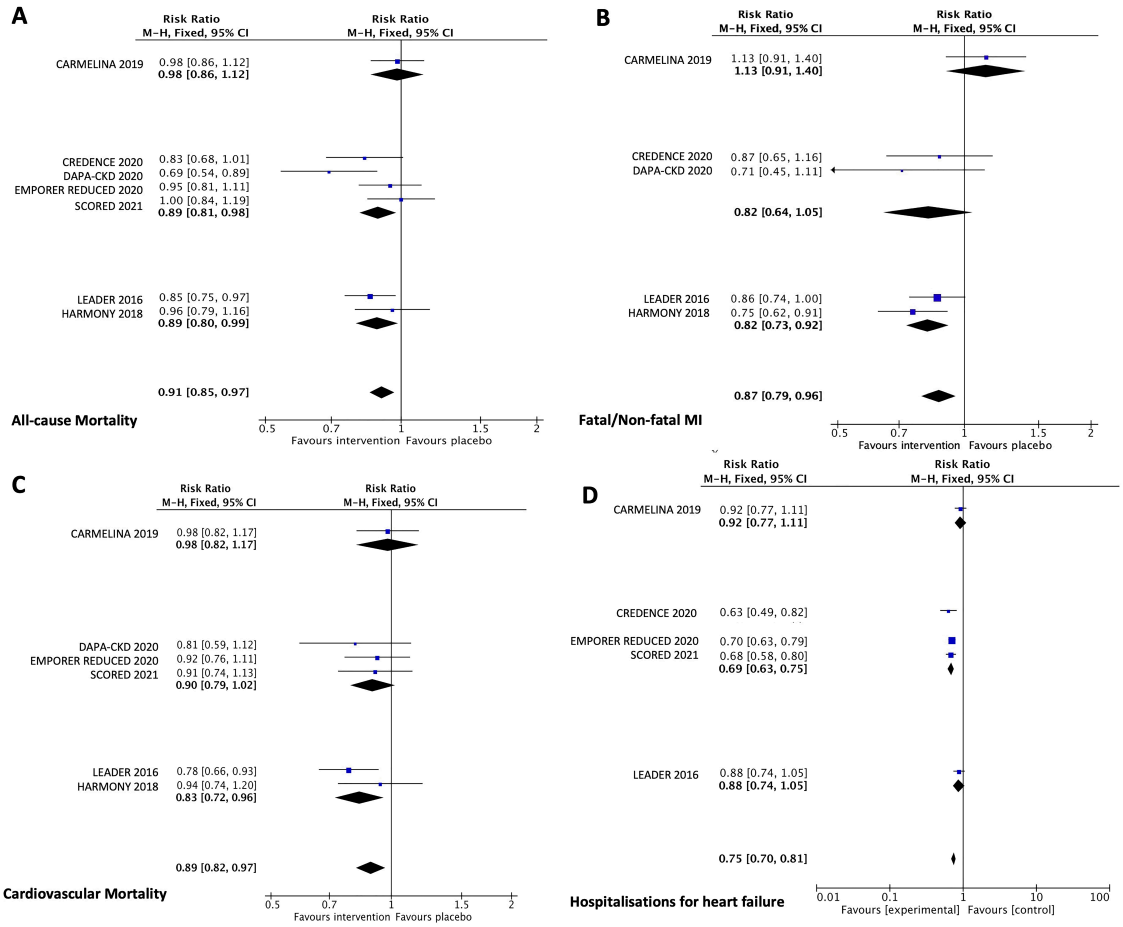

Fig. 3. Forest plots of primary composite outcomes. (A) All-cause mortality. (B) Fatal/Non-fatal MI. (C) Cardiovascular Mortality. (D) Hospitalization for heart failure.

the CARMELINA trial, however due to five trials being included the power to detect asymmetry was reduced.

4. Discussion

Our systematic review yielded three main classes of diabetic drugs which have had their cardiovascular outcomes studied in large-scale clinical trials. These were a DPP-4 inhibitor, SGLT2i, and GLP-1R agonists. In patients with CKD, SGLT2i and GLP1R agonists were associated with a reduction in cardiovascular death and all-cause death, and SGLT2i, GLP1R agonists and DPP4 inhibitors were associated with a reduction in hospitalization for heart failure.

DPP-4 inhibitors and GLP-1R agonists are incretin-based therapies. GLP-1 is a peptide hormone with multiple actions including insulin secretion stimulation, inhibition of gastric emptying and appetite suppression [27].

Ordinarily, GLP-1 exerts its effects through the GLP-1 receptor. GLP-1 can be cleaved by DPP-4 and neutral endopeptidase 24.11 into smaller fragments which can also exert their effects on surrounding tissues although this is not well understood [27]. DPP-4 is largely responsible for the inactivation of GLP-1 [27].

There are several overlaps between the actions of incretin-based therapies due to their effects on different aspects of signaling pathways. However, several contrasting actions do exist. Notably, GLP-1R agonists have been shown to improve

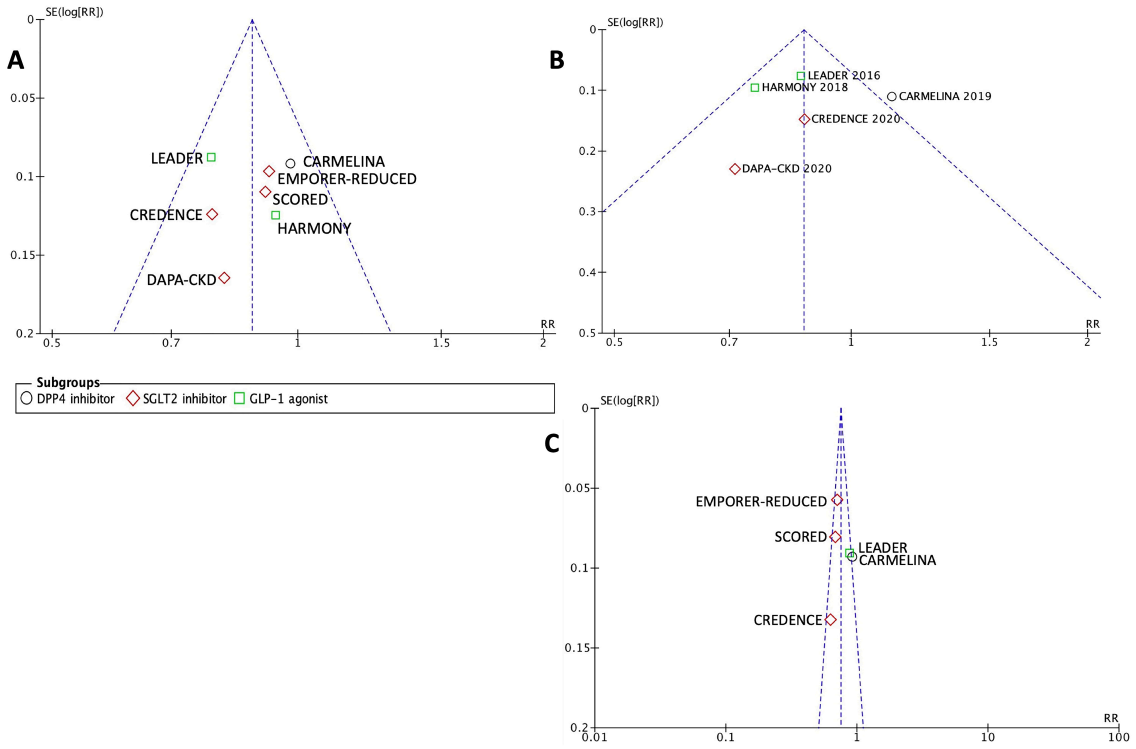

Fig. 4. Risk of publication bias assessment. Funnel plots to assess risk of bias in (A) Cardiovascular mortality, (B) Fatal/Non-Fatal myocardial infarction and (C) Hospitalisations for heart failure.

left ventricular (LV) function and heart rate and decrease body weight and blood pressure [27]. DPP-4 inhibitors, on the contrary, have little effect on blood pressure and none on body weight, but have modest effect on improving LV function [27].

At the centre of modern therapy in CKD and T2DM is the modification of underlying risk factors including glycemic control, hypertension and dyslipidemia. In 2021, the multicentre study 'Nephropathy in Diabetes type 2 (NID-2)' showed intensive management of these three factors in diabetic nephropathy patients with albuminuria reduced the incidence of MI and stroke [28].

Heart failure is the predominant cardiovascular complication in CKD. The presence of HF before the commencement of renal replacement therapy is a significant independent predictor of mortality, with estimated average survival reduced to three years from five when compared to those without HF. More than half of patients with HF have renal impairment, which increases the likelihood of premature mortality [29]. The management of HF and concomitant CKD or ESRD is complicated by having to balance the nephrotoxicity of mainstay HF therapies and the cardiovascular risks associated with hemodialysis.

Evidence-based medical therapy for HF includes renin-angiotensin-aldosterone (RAAS) inibition, beta-blocke therapy, and manangement of risk factors, including smoking, hypertension, obesity, glycemic control, proteinuria, lipid-lowering therapy, and anemia [30, 31]. The current guidelines for guided-medical therapy for HF with reduced ejection fraction (HFrEF) have recently been updated to include SGLT2i with or without T2DM, in addition to angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, diuretics and aldosterone antagonists as treatments for HF [32].

SGLT2i have exhibited improved glycemic control, renal and cardiovascular outcomes in large-scale clinical trials. Their mechanism of action is through inhibition of glucose reabsorption in the proximal convoluted tubule in the nephron, leading to increased glucose excretion in the urine [9]. The exact mechanism of how SGLT2i improve cardiovascular outcomes is not well established. However, it is hypothesized that a combination and interplay of several factors, including improved glycemic control, reduction in systemic blood pressure, improved endothelial function, and reduced systemic inflammation, contribute to this [9].

CARMELINA [20] evaluated the DPP-4 inhibitor Linagliptin, the only DPP4i RCT identified in our inclusion criteria. This study showed similar cardiovascular outcomes in placebo and intervention groups and no between-group differences in our other selected outcomes. While Linagliptin did not improve these outcomes compared to placebo, it is promising that there were no apparent adverse effects of introducing linagliptin [20]. The selected study population for CARMELINA was at high risk of negative CV and renal outcomes, which may not be indicative of

the clinical population. Additionally, the follow-up time of 2.2 years may not have been sufficient to establish further progression to ESRD [20].

CREDENCE [21] was stopped early based on recommendations from its Independent Data Monitoring Committee (IDMC) when a planned interim analysis showed the trial had achieved pre-specified criteria for the primary composite endpoint. The planned duration of the trial was 5 years, however it was was stopped after 2.5 years. There was a 34% relative reduction in its primary composite outcome when compared to placebo. Moreover, there was significant improvement in cardiovascular outcomes, including a 39% reduction in hospitalizations for heart failure [21]. This was one of the first studies to include patients with significant diabetic kidney disease, in patients with eGFR of 30–90 mL/min/1.73 m^2. There was promising data in the cardiovascular and renal outcomes of canagliflozin in these patients, however like the other included studies in this analysis, with the exception of SCORED [26], there were no patients with eGFR <30 mL/min/1.73 m^2. CREDENCE did not involve kidney disease unrelated to diabetes. A recent meta-analysis and review of CREDENCE and related trials in 2021 has raised doubts over the role of SGLT2i for reducing the overall incidence of stroke in patients with diabetic nephropathy [33]. However, it was shown that there may be a modest reduction in hemorrhagic stroke [34] and atrial fibrillation [33]. This reduction is most prominent in patients with lower baseline eGFR [33]. Similarly, SGLT2i may reduce MI in patients with T2DM and pre-existing atherosclerotic disease with a greater reduction in those with a lower eGFR [35]. The early termination of trials meeting pre-defined end points may limit the power to detect outcomes related to treatment safety, and has the potential to overestimate treatment effect size. Continued collection of rigorous follow-up data for clinical outcomes is therefore encouraged.

DAPA-CKD included CKD patients both with and without diabetic kidney disease [22]. Dapagliflozin has become the first SGLT2 inhibitor to be approved for CKD regardless of diabetes status due to its strong performance in reducing the decline of eGFR, hospitalization for HF, and cardiovascular death in CKD patients [36]. The DAPA-CKD trial was discontinued by the data monitoring committee when an interim analysis showed a statistically significant effect of dapagliflozin on the primary composite outcome, that would not be expected to change with additional enrolment. These patients had a lower risk of a decline in eGFR $>50\%$, progression to ESRD or death from renal or CV causes when compared to placebo-control. The premature closure of the trial may decrease the power of secondary outcomes investigated by the team [22, 36].

EMPORER-REDUCED focused on the renal and cardiovascular outcomes of patients with reduced ejection fraction heart failure. Some data were available for patients included with CKD, however not all of this could be related to specifically designed CKD trials. However, the data that was available showed that Empagliflozin has some role in the slowing of eGFR decline and some reduction in all-cause mortality, though the reduction in CV mortality is slim. Furthermore, secondary outcomes were treated in a stepwise hierarchical manner to reduce multiplicity. The mean follow-up period for EMPEROR-REDUCED was relatively short at 1.3 years. Further follow-up studies would be required to ascertain if this improvement is long-standing [23].

EMPORER-REDUCED and DAPA-CKD were the only trials included which had participants enrolled both with and without CKD. The findings of these trials provide the possibility that SGLT2i may have some benefit in CKD patients without diabetes, though subgroup analysis of these patients would be required as well as long-term follow up due to the differing pathology.

SCORED was the only study to evaluate an SGLT2i in the presence of varying albuminuria [26]. Other SGLT2i studies defined the presence of albuminuria as a urinary albumin to creatinine ratio of >300 mg/g [11, 21]. Despite early termination, the study was able to show statistically significant improvement in cardiovascular outcomes including a significant reduction in hospitalizations for heart failure. However, this study requires additional funding for the intended follow-up, limiting assessment of long-term outcomes beyond 1.3 years. Due to funding, the initial primary endpoint criteria were changed to total number of events which may overestimate the benefits of Sotagliflozin. Termination of the study did not allow for adjudication of events, which may have introduced bias towards intervention, particularly for the assessment of secondary outcomes [26]. Longer trial follow-up data are required to evaluate the safety and systemic effects of Sotagliflozin in patients with CKD

Liraglutide and Albiglutide are GLP-1R agonists which were investigated in the LEADER and HARMONY [21, 22] trials. Liraglutide is DPP-4 resistant human GLP-1 analogue, whilst Albiglutide is a GLP-1 dimer fused to albumin with a position 2 replacement of alanine to glycine making it resistant to DPP4 degradation [37].

LEADER intervention group had a sustained improvement in cardiovascular outcomes over the course of the trial and a reduction in cardiovascular death as well as reduced hospitalization for heart failure [25]. The study however selected patients with high risk of CV events for inclusion, and so the translation of benefit to those with low risk may not be to the extent seen in the clinical trial. Moreover, as the trial was terminated early the data is restricted to 3.5 year follow-up rather than the anticipated 5-year period [25]. Additionally, outcomes of fatal/non-fatal stroke and MI were not pre-specified outcomes of the study and exploratory outcome p-values were not adjusted for multiplicity, hence these results may not be confirmatory [25]. Further trials with pre-specified analysis would be required to establish this finding fully.

HARMONY results exhibited reduced CV events and improved glycemic control in patients given Albiglutide [24].

HARMONY did not collect data on urinary albumin so inferences of renal safety in CKD should be treated with some caution. Like EMPEROR-REDUCED, the short mean follow-up of 2.2 years may not provide sufficient detail of long-term safety outcomes in CKD patients. Though LEADER and HARMONY had improved CV outcomes, other GLP-1R agonists have not shown improvement [38, 39]. This effect may not be synonymous with all GLP-1R agonists.

5. Limitations

This meta-analysis finds that glucose lowering therapies may be beneficial for CV outcomes in CKD patients, however there are some limitations. Notably, EMPORER-REDUCED and DAPA-CKD included participants both with and without T2DM. As data in these were not clearly separated out to account for this difference the data was excluded within a sensitivity analysis.

Moreover, individual studies had differening eligibility criteria including baseline CV risk, influencing cardiovascular outcome data between study populations. Reporting of events across studies was also inconsistent, with some outcome data unavailable.

6. Conclusions

In summary, large, randomized control trials of oral antihyperglycemic agents in patients with chronic renal failure have demonstrated some improvement in cardiovascular outcomes compared with placebo. There is encouraging evidence from existing trial data that SGLT2i and GLP1R agonists are safe in patients with chronic renal failure. SGLT2i have significantly lower rates of all-cause mortality and HHF. GLP1R agonists appear to reduce fatal/non-fatal MI, but across the class have differing effects on other CV outcomes. Additionally, long-term follow-up data is required with wider inclusion of patients with eGFR <30 mL/min/1.73 m^2 in order to confidently evaluate the safety of these medications in patients with CKD 4 or above, as well as dialysis-dependent patients. Further studies specifically designed for patients with CKD without T2DM are also of merit to account for the differences in disease progression.

Author contributions

AK, RS and AM designed the review and performed data extraction and analysis. KM and CB provided advice on study design and interpretation of data. All authors contributed to editorial changes to the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all individuals who helped in our investigation and to the peer-reviewers for their suggestions.

Funding

Professor Colin Berry is supported by research funding from the British Heart Foundation (PG/17/25/32884; RE/13/5/30177; RE/18/6/34217). Dr Andrew Morrow is supported by research funding from the Medical Research Council (MR/S018905/1). Dr Kenneth Mangion is supported by research funding from the Chief Scientist Office (COV/LTE/20/10, COV/GLA/20/05).

Conflict of interest

Professor Colin Berry is employed by the University of Glasgow which holds consultancy and research agreements for his work with companies that have commercial interests in the diagnosis and treatment of angina. The companies include Abbott Vascular, Astra Zeneca, Boehringer Ingelheim, GSK, HeartFlow, Menarini, Novartis, and Siemens Healthcare. The other authors do not have any potential conflicts of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm2204152.

References

[1] Schreiber BD. Congestive Heart Failure in Patients with Chronic Kidney Disease and on Dialysis. The American Journal of the Medical Sciences 2003; 325: 179–193.

[2] Bagshaw SM, Cruz DN, Aspromonte N, Daliento L, Ronco F, Sheinfeld G, *et al.* Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. Nephrology, Dialysis, Transplantation. 2010; 25: 1406–1416.

[3] Segall L, Nistor I, Covic A. Heart failure in patients with chronic kidney disease: a systematic integrative review. BioMed Research International. 2014; 2014: 937398.

[4] Pálsson R, Patel UD. Cardiovascular Complications of Diabetic Kidney Disease. Advances in Chronic Kidney Disease. 2014; 21: 273–280.

[5] Zhan C, Shi M, Wu R, He H, Liu X, Shen B. MIRKB: a myocardial infarction risk knowledge base. Database. 2019; 2019: baz125.

[6] Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. Circulation Research. 2017; 120: 472–495.

[7] Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World Journal of Diabetes. 2015; 6: 1246–1258.

[8] Liu L, Simon B, Shi J, Mallhi AK, Eisen HJ. Impact of diabetes mellitus on risk of cardiovascular disease and all-cause mortality: Evidence on health outcomes and antidiabetic treatment in United States adults. World Journal of Diabetes. 2016; 7: 449¬–461.

[9] Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nature Reviews Cardiology. 2020; 17: 761–772.

[10] Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, *et al.* Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Circulation. 2021; 143: 516–525.

[11] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England Journal of Medicine. 2015; 373: 2117–2128.

[12] Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, *et al.* Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2019; 21: 1237–1250.
[13] Yamada T, Wakabayashi M, Bhalla A, Chopra N, Miyashita H, Mikami T, *et al.* Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and network meta-analysis. Cardiovascular Diabetology. 2021; 20: 14.
[14] Bangalore S, Maron DJ, Fleg JL, O'Brien SM, Herzog CA, Stone GW, *et al.* International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease (ISCHEMIA-CKD): Rationale and design. American Heart Journal. 2018; 205: 42–52.
[15] Kamdar A, Sykes R, Morrow A, Mangion K, Berry C. Cardiovascular outcomes of diabetic medications used in chronic kidney disease patients. PROSPERO. 2021. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021268563 (Accessed: 28 October 2021).
[16] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Systematic Reviews. 2016; 5: 210.
[17] 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. British Medical Journal. 2021; 372: n71.s
[18] The Cochrane Collaboration. RevMan Web. 2020. Available at: revman.cochrane.org (Accessed: 28 October 2021).
[19] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. British Medical Journal. 2019; 366: l4898.
[20] Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, *et al.* Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA. 2019; 321: 69–79.
[21] Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, *et al.* Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England Journal of Medicine. 2019; 380: 2295–2306.
[22] Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F, *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. The New England Journal of Medicine. 2020; 383: 1436–1446.
[23] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.* Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The New England Journal of Medicine. 2020; 383: 1413–1424.
[24] Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, *et al.* Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018; 392: 1519–1529.
[25] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, *et al.* Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine. 2016; 375: 311–322.
[26] Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, *et al.* Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. The New England Journal of Medicine. 2021; 384: 129–139.
[27] Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circulation Research. 2014; 114: 1788–1803.
[28] Sasso FC, Pafundi PC, Simeon V, De Nicola L, Chiodini P, Galiero R, *et al.* Efficacy and durability of multifactorial intervention on mortality and MACEs: a randomized clinical trial in type-2 diabetic kidney disease. Cardiovascular Diabetology. 2021; 20: 145.
[29] Delanaye P, Glassock RJ, De Broe ME. Epidemiology of chronic kidney disease: think (at least) twice! Clinical Kidney Journal. 2017; 10: 370–374.
[30] K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. American Journal of Kidney Diseases. 2005; 45: S1–S153.
[31] House AA. Management of Heart Failure in Advancing CKD: Core Curriculum 2018. American Journal of Kidney Diseases. 2018; 72: 284–295.
[32] Maddox TM, Januzzi JL, Allen LA, Breathett K, Butler J, Davis LL, *et al.* 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues about Heart Failure with Reduced Ejection Fraction. Journal of the American College of Cardiology. 2021; 77: 772–810.
[33] Zhou Z, Jardine MJ, Li Q, Neuen BL, Cannon CP, de Zeeuw D, *et al.* Effect of SGLT2 Inhibitors on Stroke and Atrial Fibrillation in Diabetic Kidney Disease: Results From the CREDENCE Trial and Meta-Analysis. Stroke. 2021; 52: 1545–1556.
[34] Tsai W, Chuang S, Liu S, Lee C, Chien M, Leung C, *et al.* Effects of SGLT2 inhibitors on stroke and its subtypes in patients with type 2 diabetes: a systematic review and meta-analysis. Scientific Reports. 2021; 11: 15364.
[35] Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, *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: 31–39.
[36] Singh V. Farxiga approved in the US for the treatment of chronic kidney disease in patients at risk of progression with and without type-2 diabetes. 2021. Available at: https://www.astrazeneca.com/media-centre/press-releases/2021/farxiga-approved-in-the-us-for-ckd.html (Accessed: 24 July 2021).
[37] Baggio LL, Huang Q, Brown TJ, Drucker DJ. A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. Diabetes. 2004; 53: 2492–2500.
[38] Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, *et al.* Effects of once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine. 2017; 377: 1228–1239.
[39] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, *et al.* Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine. 2016; 375: 1834–1844.