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REVIEW

Treatments for Chronic Kidney Disease: A Systematic Literature Review of Randomized Controlled Trials

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ABSTRACT

Delaying disease progression and reducing the risk of mortality are key goals in the treatment of chronic kidney disease (CKD). New drug classes to augment renin–angiotensin–aldosterone system (RAAS) inhibitors as the standard of care have scarcely met their primary endpoints until recently. This systematic literature review explored treatments evaluated in patients with CKD since 1990 to understand what contemporary data add to the treatment landscape. Eighty-nine clinical trials were identified that had enrolled patients with estimated glomerular filtration rate 13.9–102.8 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio (UACR) 29.9–2911.0 mg/g, with (75.5%) and without (20.6%) type 2 diabetes (T2D). Clinically objective outcomes of kidney failure and all-cause mortality (ACM) were reported in 32 and 64 trials, respectively. Significant reductions ($P < 0.05$) in the risk of kidney failure were observed in seven trials: five small trials published before 2008 had evaluated the RAAS inhibitors losartan, benazepril, or ramipril in patients with ($n = 751$) or without ($n = 84$–436) T2D; two larger trials ($n = 2152$–2202) published onwards of 2019 had evaluated the sodium-glucose co-transporter 2 (SGLT2) inhibitors canagliflozin (in patients with T2D and UACR > 300–5000 mg/g) and dapagliflozin (in patients with or without T2D and UACR 200–5000 mg/g) added to a background of RAAS inhibition. Significant reductions in ACM were observed with dapagliflozin in the DAPA-CKD trial. Contemporary data therefore suggest that augmenting RAAS inhibitors with new drug classes has the potential to improve clinical outcomes in a broad range of patients with CKD.

Keywords: Albuminuria; All-cause mortality; Chronic kidney disease; Diabetes; Estimated glomerular filtration rate; Kidney failure

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Key Summary Points

Why carry out this study?

Morbidity, mortality, and the economic burden from chronic kidney disease (CKD) are growing worldwide.

This systematic literature review examined contemporary clinical trial data relative to the overall CKD treatment landscape to view the impact of novel drug classes following 20 years of little to no innovation.

What was learned from the study?

Augmenting the standard of care with canagliflozin or finerenone could significantly improve clinical outcomes in patients with type 2 diabetes (T2D).

Augmenting the standard of care with dapagliflozin could significantly improve clinical outcomes regardless of T2D status and is the only agent that has been shown to significantly reduce all-cause mortality risk.

Composite and surrogate endpoints in clinical trials have varied widely over time, likely due to changing guidelines, and may benefit from standardization.

INTRODUCTION

An estimated 840 million people worldwide have chronic kidney disease (CKD) [1], which was responsible for 1.2 million deaths and 35.8 million disability-adjusted life years in 2017 [2]. However, only 12% of sufferers are aware of their condition [3]. CKD is diagnosed when the estimated glomerular filtration rate (eGFR) declines below 60 mL/min/1.73 m^2 or the urinary albumin-to-creatinine ratio (UACR) equals or exceeds 30 mg/g for 3 months or longer [4]. As CKD progresses, healthcare costs increase and health-related quality of life (HRQoL) diminishes, with the greatest costs and HRQoL burden associated with kidney failure (eGFR $<$ 15 mL/min/1.73 m^2) [5, 6]. Adverse clinical outcomes, healthcare utilization and costs, and disease burden also increase as albuminuria worsens [7–9], and UACR 30–300 mg/g (moderately increased) and even $>$ 300 mg/g (severely increased) are now considered important predictors of risk for CKD progression, cardiovascular events, and mortality [4]. Early identification and pharmacologic intervention could therefore delay or prevent CKD progression.

Current guidelines recommend using renin–angiotensin–aldosterone system (RAAS) inhibitors (either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker) to delay or prevent CKD progression [4]. Clinical trials of other drug classes to augment RAAS inhibitors, delay progression, and improve outcomes have scarcely met their primary endpoints [10], except for sodium-glucose co-transporter 2 (SGLT2) inhibitors. Initially developed as blood glucose-lowering agents, reports of renal and cardiovascular benefits in patients with type 2 diabetes (T2D) [11–14] as well as cardiovascular benefits in patients with heart failure (HF) [15–17] have prompted the evaluation of SGLT2 inhibitors in patients with CKD who are already receiving standard of care treatment with RAAS inhibitors.

This systematic literature review explored the treatments evaluated in patients with CKD since 1990 to allow an assessment of contemporary data relative to the overall treatment landscape.

METHODS

This systematic literature review was conducted according to the recommendations of Cochrane [18], the Centre for Reviews and Dissemination [19], and the National Institute for Health and Care Excellence [20]. The protocol has been registered on PROSPERO (CRD42020190152).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Sources and Searches

Using the terms listed in the Supplementary Material, we searched MEDLINE, Embase, and the Cochrane Library for peer-reviewed articles published between 1990 and November 2, 2020, that reported results from prospective, parallel-design randomized controlled trials that evaluated pharmacologic treatments for patients aged 18 years or more with CKD and albuminuria. Search filters for MEDLINE and Embase were obtained from the Scottish Intercollegiate Guideline Network [21], and adapted for Embase by Cochrane [22]. In line with guidelines for the inclusion of gray literature [18–20, 23], the proceedings of key international conferences and trial registries were also searched (Supplementary Material).

Non-English-language publications, reviews, case studies, case reports, conference proceedings (other than those identified in the search described above), and animal studies were excluded.

Trial Selection

After removing duplicates from the combined search results, two independent reviewers screened the identified abstracts against predefined eligibility criteria (Table 1). Abstracts deemed eligible for inclusion were then compared and any discrepancies resolved mutually or by a third reviewer. This independent double-review process was repeated on the full-text articles to identify a final list of trials eligible for inclusion in this review.

Data Extraction and Quality Assessment

Data were extracted by one reviewer and validated by a second, with disagreements resolved by a third (Supplementary Material). Binary variables included trial population, number or proportion of patients experiencing an event, and incidence rates per population or person-time. Continuous and time-to-event variables included hazard ratio (HR), odds ratio, relative risk, mean, median, standard deviation, standard error, range, 95% confidence interval (CI), interquartile range, and *P* value. Outcomes reported without *P* values or 95% CIs were assumed not to be statistically significant. Outcomes reported with $P < 0.05$ or with 95% CIs not crossing 1.0 for a HR or relative risk were assumed to be statistically significant.

Risk of bias and quality of reporting were assessed using eight questions from the PMG24 Company Evidence Submission Template (NICE single technology appraisal process) [24], developed based on previous recommendations [19]. Answers of "yes," "no," or "unclear due to inadequate reporting" were required. Depending on the question, answers of "yes" or "no" could indicate a higher or lower risk of bias (Supplementary Material).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Search Results

Overall, 40,550 records were identified (Fig. 1). After removal of 20,773 duplicates, 19,777 abstracts were reviewed against eligibility criteria, and 19,557 were excluded. The full texts of 220 articles were reviewed, and 121 were excluded (Table S1). The addition of one more article, identified during a search of conference proceedings, resulted in 100 eligible articles providing data for 89 randomized controlled trials (Table 2).

Trial Characteristics

Thirty-seven trials were multinational, 18 were conducted in Japan, and seven each were conducted in China and Italy, with the remaining trials conducted in a range of countries worldwide.

Sixty-six trials (74.2%) were published onwards of 2010, and 23 (25.8%) were

Table 1 Eligibility criteria

	Inclusion	Exclusion
Population	Adults aged ≥ 18 years with CKD and albuminuria,[a,b,c] with or without T2D	Subjects without CKD or with an acute kidney injury (note that acute kidney injury in subjects with CKD is an outcome of interest in the DAPA-CKD trial)
		According to DAPA-CKD eligibility criteria, subjects with CKD were excluded if they met one or more of the following criteria:
		Type 1 diabetes
		Organ transplantation (any organ, including kidneys)
		Receiving dialysis
		Polycystic kidney disease (any type), lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis
		New York Heart Association class IV congestive heart failure
		Malignancies
		Blood-borne diseases (e.g., HIV, hepatitis)
Intervention/comparators	Pharmacological agents for the treatment of CKD	Treatments for secondary conditions associated with CKD (e.g., anemia, mineral and bone disorder)
	Placebo	Non-pharmacological treatments (e.g., devices, diagnostics, transplants, dialysis)
		As per DAPA-CKD eligibility criteria, cytotoxic therapy
Outcomes	Clinical outcomes (see Data extraction variables in the Supplementary Material)	Pharmacokinetics
		Pharmacodynamics
	Adverse events	
	Health-related quality of life	
	Patient-reported outcomes	

Table 1 continued

	Inclusion	Exclusion
Study type	Prospective, parallel-design, phase 3–4 RCTs (only publications reporting the randomization phase)	Any trials using a crossover design
		Any trials described as pilot studies
		Any non-randomized studies, including (but not limited to) parallel non-randomized clinical trials, single-arm clinical trials, case studies and reports, and any observational studies
		Reviews, including systematic literature reviews
		Editorials, letters, and commentaries
Others	Language: English	Other languages
	Publication years: 1990 to November 2, 2020	Older publications
	Study duration: ≥ 12 weeks	
	≥ 50 patients per randomized arm	

CKD chronic kidney disease, *HIV* human immunodeficiency virus, *RCT* randomized controlled trial, *T2D* type 2 diabetes
[a]Including proxies: albumin-to-creatinine ratio, urinary protein-to-creatinine ratio, or reagent strip qualitative recording
[b]This was required to be reported in the trial eligibility criteria or as a baseline characteristic; trials were excluded if no information on albuminuria was reported or if patients with severely increased albuminuria were explicitly excluded from the trial
[c]Albuminuria could be reported using multiple methods

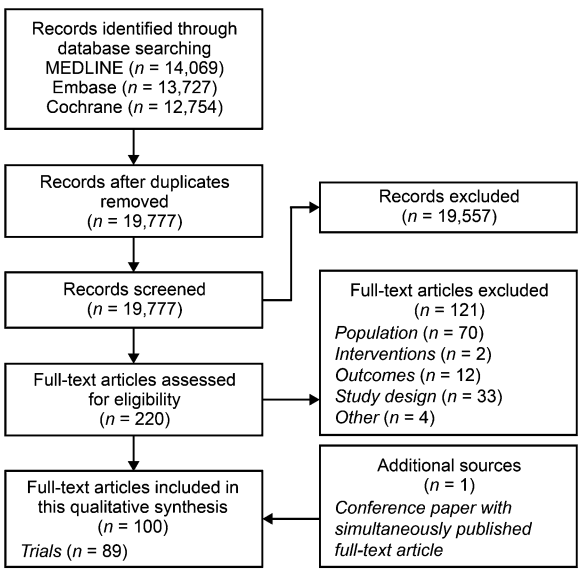

Fig. 1 Study selection PRISMA diagram

published before 2010. Forty-three trials (48.3%) were phase 3 (n = 29), phase 4 (n = 10), phase 2/3 (n = 3), or phase 3/4 (n = 1), and most were double blind (61.8%) or open label (32.6%) (Fig. S1a, b). Forty-six trials (51.7%) did not report their trial phase.

Most trials enrolled 50–100 patients per arm, although 10 conducted onwards of 2004 enrolled more than 1000 patients per arm [25–27, 34, 47, 60, 73–75, 93]. Forty-three trials (48.3%) enrolled patients with T2D, 29 enrolled patients with or without T2D (32.6%), and 17 enrolled patients without T2D (19.1%). Across all included trials, 75.5% of patients had T2D (Fig. S2a, b). All patients were followed for at least 12 weeks, although mean or median follow-up extended to at least 12 months in 60 trials (67.4%) and at least 24 months in 38 trials (42.7%).

Table 2 Relevant characteristics of included trials

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
DAPA-CKD/ NCT03036150	Heerspink et al. 2020 [25]	NA	2–4/± T2D/–	Dapagliflozin 10	Placebo	–	–	Antihyperglycemic[a]
FIDELIO-DKD/ NCT02540993	Bakris et al. 2020 [26]	NA	2–4/T2D/–	Finerenone	Placebo	–	–	Antihypertensive
CREDENCE/ NCT02065791	Perkovic et al. 2019 [27]	NA	2–3/T2D/–	Canagliflozin 100	Placebo	–	–	Antihyperglycemic[a]
	Mahaffey et al. 2019 [28]	Subgroup info		Canagliflozin 100	Placebo	–	–	
	Jardine et al. 2020 [29]	Secondary analysis by baseline kidney function		Canagliflozin 100	Placebo	–	–	
Lui 2020/NR	Liu et al. 2020 [30]	NA	–/T2D/ Microalbuminuria	Epalrestat	Placebo	–	–	Antihyperglycemic
Yagoglu 2020/NR	Yagoglu et al. 2020 [31]	NA	3–4/T2D/–	Linagliptin	Insulin titration	–	–	Antihyperglycemic
Allegretti 2019/ NCT02836873	Allegretti et al. 2019 [32]	NA	3/T2D/–	Bexagliflozin 20	Placebo	–	–	Antihyperglycemic[a]
DELIGHT/ NCT02547935	Pollock et al. 2019 [33]	NA	2–4/T2D/–	Dapagliflozin 10	Dapagliflozin 10 + saxagliptin 2.5	Placebo	–	Antihyperglycemic[a]
CARMELINA/ NCT01897532	Rosenstock et al. 2019 [34]	NA	2–4/T2D/–	Linagliptin	Placebo	–	–	Antihyperglycemic
DERIVE/ NCT02413398	Fioretto et al. 2018 [35]	NA	3/T2D/–	Dapagliflozin 10	Placebo	–	–	Antihyperglycemic[a]

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
VERTIS-RENAL/ NCT01986855	Grunberger et al. 2018 [36]	NA	3/T2D/–	Ertugliflozin 10	Ertugliflozin 5	Placebo	–	Antihyperglycemic[a]
AWARD-7/ NCT01621178	Tuttle et al. 2018 [37]	NA	3–4/T2D/–	Dulaglutide 1.5	Dulaglutide 0.75	Insulin glargine	–	Antihyperglycemic
MARLINA-T2D/ NCT01792518	Groop et al. 2017 [38]	NA	1–3/T2D/–	Linagliptin	Placebo	–	–	Antihyperglycemic
GUARD/ NCT01968044	Yoon et al. 2017 [39]	NA	3–4/T2D/–	Gemigliptin	Placebo	–	–	Antihyperglycemic
	Han et al. 2018 [40]	40-week extension; placebo transitioned to linagliptin		Gemigliptin	Placebo	–	–	
LIRA-RENAL/ NCT01620489	Davies et al. 2016 [41]	NA	3/T2D/–	Liraglutide 1.8	Placebo	–	–	Antihyperglycemic
EMPA-REG-RENAL/ NCT01164501	Barnett et al. 2014 [42]	NA	2–4/T2D/–	Empagliflozin 25	Empagliflozin 10	Placebo	–	Antihyperglycemic[a]
Kohan 2014/ NCT00663260	Kohan et al. 2014 [43]	NA	2–3/T2D/–	Dapagliflozin 10	Dapagliflozin 5	Placebo	–	Antihyperglycemic[a]
Yale 2014/ NCT01064414	Yale et al. 2014 [44]	52-week results	3/T2D/–	Canagliflozin 300	Canagliflozin 100	Placebo	–	Antihyperglycemic[a]
	Yale et al. 2013 [45]	NA		Canagliflozin 300	Canagliflozin 100	Placebo	–	
DNETT-Japan/ NCT00253786	Shikata et al. 2020 [46]	NA	–/T2D/ Macroalbuminuria	Intensive treatment	SOC	–	–	Antihypertensive
SONAR/ NCT01858532	Heerspink et al. 2019 [47]	NA	1–3/T2D/ Macroalbuminuria	Atrasentan	Placebo	–	–	Antihypertensive
Chen 2018/NR	Chen et al. 2018 [48]	NA	1–3/T2D/–	Irbesartan 150	Irbesartan 300	Irbesartan 150 + spironolactone 20	Irbesartan 300 + spironolactone 20	Antihypertensive

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
Scheele 2016/NR	Scheele et al. 2016 [49]	NA	3–4/T2D/ Macroalbuminuria	PF-00489791	Placebo	–	–	Antihypertensive
Han 2015/ NCT01382303	Han et al. 2015 [50]	NA	–/T2D/–	Pentoxifylline	Placebo	–	–	Antihypertensive
PREDIAN/EudraCT #2007–005985–10	Navarro-González et al. 2015 [51]	NA	3–4/T2D/–	Pentoxifylline	Placebo	–	–	Antihypertensive
Pan 2015/ NCT00774904	Pan et al. 2015 [52]	NA	–/T2D/–	Losartan 100	Amlodipine	–	–	Antihypertensive
VA NEPHRON-D/ NCT00555217	Fried et al. 2013 [53]	NA	2–4/T2D/ Macroalbuminuria	Losartan 100	Losartan 100 + lisinopril	–	–	Antihypertensive
	Palevsky et al. 2016 [54]	Acute kidney injury incidence and severity		Losartan 100	Losartan 100 + lisinopril	–	–	
Lewis 2012/NR	Lewis et al. 2012 [55]	NA	–/T2D/–	Pyridoxamine dihydrochloride 300	Pyridoxamine dihydrochloride 150	Placebo	–	Antihyperglycemic
ORIENT/ NCT00141453	Imai et al. 2011 [56]	NA	–/T2D/ Macroalbuminuria	Olmesartan	Placebo	–	–	Antihypertensive
ASCEND/ NCT00120328	Mann et al. 2010 [57]	NA	3–4/T2D/–	Avosentan 50	Avosentan 25	Placebo	–	Antihypertensive
AMADEO/ NCT00168857	Bakris et al. 2008 [58]	NA	–/T2D/–	Telmisartan	Losartan 100	–	–	Antihypertensive
DETAIL/NR	Barnett et al. 2004 [59]	NA	–/T2D/–	Telmisartan	Enalapril	–	–	Antihypertensive
DIABHYCAR/NR	Marre et al. 2004 [60]	NA	–/T2D/–	Ramipril	Placebo	–	–	Antihypertensive
RENAAL/NR	Brenner et al. 2001 [61]	NA	–/T2D/–	Losartan 100	Placebo	–	–	Antihypertensive

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
IDNT/NR	Lewis et al. 2001 [62]	NA	–/T2D/ Macroalbuminuria	Irbesartan 300	Amlodipine	Placebo	–	Antihypertensive
	Atkins et al. 2005 [63]	Proteinuria		Irbesartan 300	Amlodipine	Placebo	–	
	Berl et al. 2003 [64]	CV outcomes		Irbesartan 300	Amlodipine	Placebo	–	
EUCLID/NR	Chaturvedi 1997 [65]	NA	–/T2D/–	Lisinopril	Placebo	–	–	Antihypertensive
Lewis 1993/NR	Lewis et al. 1993 [66]	NA	–/T2D/–	Captopril	Placebo	–	–	Antihypertensive
Voroneanu 2017/NR	Voroneanu et al. 2017 [67]	NA	1–4/T2D/ Macroalbuminuria	Silymarin	Placebo	–	–	Antioxidant
SAKURA/NR	Endo et al. 2013 [68]	NA	–/T2D/ Macroalbuminuria	Probucol	SOC	–	–	Lipid-lowering
PANDA/ ISRCTN 58196433	Rutter et al. 2011 [69]	NA	–/T2D/–	Atorvastatin 80	Atorvastatin 10	–	–	Lipid-lowering
Abe 2011 (+ T2D)/NR	Abe et al. 2011b [70]	NA	1–2/T2D/–	Rosuvastatin	SOC	–	–	Lipid-lowering
Endo 2006/NR	Endo et al. 2006 [71]	NA	–/T2D/ Macroalbuminuria	Probucol	SOC	–	–	Lipid-lowering
Sun-MACRO/ NCT00130312	Packham et al. 2012 [72]	NA	3–4/T2D/ Macroalbuminuria	Sulodexide	Placebo	–	–	Antithrombotic
BEACON/ NCT01351675	de Zeeuw et al. 2013 [73]	NA	4/T2D/–	Bardoxolone methyl	Placebo	–	–	Triterpenoid
ALTITUDE/ NCT00549757	Parving et al. 2012 [74]	NA	1–3/T2D/–	Aliskiren	Placebo	–	–	Uric acid lowering
TREAT/ NCT00093015	Pfeffer et al. 2009 [75]	NA	3–4/T2D/–	Darbepoetin alfa	Placebo	–	–	ESA

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
CASSIOPEIR/ NCT01090037	Nakamoto et al. 2020 [76]	NA	–/± T2D/–	TRK-100STP 120	TRK-100STP 240	Placebo	–	Antihypertensive
UK HARP-III/ ISRCTN11958993	Haynes et al. 2018 [77]	NA	3–4/± T2D/–	Irbesartan 300	Sacubitril + valsartan	–	–	Antihypertensive
Ameen 2016/NR	Ameen et al. 2016 [78]	NA	–/± T2D/–	Valsartan	Valsartan + amlodipine	–	–	Antihypertensive
Hosoya 2014/ JapicCTI-101171	Hosoya et al. 2014 [79]	NA	3/± T2D/–	Topiroxostat	Placebo	–	–	Uric acid lowering
COSMO-CKD/ UMIN000002143	Ando et al. 2014a [80]	NA	1–3/± T2D/–	Benidipine	Hydrochlorothiazide	–	–	Antihypertensive
Ando 2013/ UMIN000001247	Ando et al. 2013 [81]	NA	–/± T2D/ Microalbuminuria	Cilnidipine	Amlodipine	–	–	Antihypertensive
Wang 2013/NR	Wang et al. 2013 [82]	NA	1–3/± T2D/–	Spironolactone	SOC	–	–	Antihypertensive
KVT/NCT00190580	Yasuda et al. 2013 [83]	NA	–/± T2D/–	Valsartan	SOC	–	–	Antihypertensive
Abe 2011 (± T2D)/ UMIN000002644	Abe et al. 2011a [84]	NA	2–3/± T2D/–	Benidipine	Amlodipine	–	–	Antihypertensive
ACCOMPLISH/ NCT00170950	Bakris et al. 2010 [85]	Prespecified analysis, therefore included	–/± T2D/–	Benazepril 40 + amlodipine	Benazepril 40 + hydrochlorothiazide	–	–	Antihypertensive
ESPLANADE/ NCT00199927	Ruggenenti et al. 2010 [86]	NA	–/± T2D/–	Benazepril 20 + valsartan + fluvastatin	Benazepril 20 + valsartan	–	–	Antihypertensive
Abe 2010/NR	Abe et al. 2010 [87]	NA	3–5/± T2D/–	Benidipine	Cilnidipine	–	–	Antihypertensive
JLIGHT/NR	Iino et al. 2004 [88]	NA	–/± T2D/–	Losartan 100	Amlodipine	–	–	Antihypertensive

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
AIPRI/NR	Maschio et al. 1996 [89]	NA	–/± T2D/–	Benazepril 10	Placebo	–	–	Antihypertensive
	Maschio et al. 1999 [90]	NA		Benazepril 10	Placebo	–	–	
ASUCA/ UMIN000001778	Kimura et al. 2017 [91]	NA	3/± T2D/–	Atorvastatin	SOC	–	–	Lipid-lowering
Sukuki 2013/ UMIN000002935	Suzuki et al. 2013 [92]	NA	1–2/± T2D/–	Ezetimibe	Statin uptitration	–	–	Lipid-lowering
SHARP/NCT00125593	Baigent et al. 2011 [93]	NA	–/± T2D/–	Simvastatin + ezetimibe	Placebo	–	–	Lipid-lowering
	Haynes et al. 2014 [94]	LDL		Simvastatin + ezetimibe	Placebo	–	–	
LORD/ANZCTR: 012605000693628	Fassett et al. 2010 [95]	NA	–/± T2D/–	Atorvastatin	Placebo	–	–	Lipid-lowering
	Fassett et al. 2014 [96]	NA		Atorvastatin	Placebo	–	–	
K-STAR/NCT00860431	Cha et al. 2016 [97]	NA	3–4/± T2D/–	AST-120	SOC	–	–	Uremic toxins adsorbent
EPPIC-1/NCT00500682	Schulman et al. 2015 [98]	NA	–/± T2D/–	AST-120	Placebo	–	–	Uremic toxins adsorbent
EPPIC-2/NCT00501046		NA		AST-120	Placebo	–	–	
CAP-KD/NCT00456859	Akizawa et al. 2009 [99]	NA	–/± T2D/–	AST-120	SOC	–	–	Uremic toxins adsorbent
CKD-FIX/ ACTRN12611000791932	Badve et al. 2020 [100]	NA	3–4/± T2D/–	Allopurinol	Placebo	–	–	Uric acid lowering
FEATHER/ UMIN000008343	Kimura et al. 2018 [101]	NA	3/± T2D/–	Febuxostat	Placebo	–	–	Uric acid lowering

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
Goicoechea 2010/NR	Goicoechea et al. 2010 [102]	NA	2–5/± T2D/–	Allopurinol	SOC	–	–	Uric acid lowering
Tsubakihara 2012/ CRG030600049	Tsubakihara et al. 2012 [103]	NA	–/± T2D/–	Darbepoetin alfa	Epoetin alfa	–	–	ESA
Wesson 2019/ NCT03317444	Wesson et al. 2019 [104]	NA	3–4/± T2D/–	Veverimer	Placebo	–	–	Hydrochloric acid binder
AASER/ NCT01709994	Goicoechea et al. 2018 [105]	NA	3–4/± T2D/–	Aspirin	SOC	–	–	NSAID
PREDICT/ NCT01581073	Hayashi et al. 2020 [106]	NA	4–5/no T2D/–	Darbepoetin alfa (high Hb target)	Darbepoetin alfa (low Hb target)	–	–	ESA
EVALUATE/ UMIN000001803	Ando et al. 2014b [107]	NA	1–3a/no T2D/–	Eplerenone	Placebo	–	–	Antihypertensive
Woo 2014/NR	Woo et al. 2014 [108]	NA	2–5/no T2D/–	Aliskiren	Losartan 100	Aliskiren + losartan 100	–	Antihypertensive
Shen 2012/NR	Shen et al. 2012 [109]	NA	3/no T2D/–	Losartan 50	Placebo	–	–	Antihypertensive
Bianchi 2010/ ACTRN12610000034033	Bianchi et al. 2010 [110]	NA	1–3/no T2D/–	Ramipril + atorvastatin	Ramipril + atorvastatin + irbesartan + spironolactone	–	–	Antihypertensive
AVER/NR	Esnault et al. 2008 [111]	NA	–/no T2D/–	Amlodipine	Enalapril	–	–	Antihypertensive

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
ROAD/NR	Hou et al. 2007 [112]	NA	–/no T2D/–	Benazepril 10	Benazepril 40	Losartan 50	Losartan 200	Antihypertensive
Hou 2006/ NCT00270426	Hou et al. 2006 [113]	NA	–/no T2D/–	Benazepril 10	Placebo	–	–	Antihypertensive
REIN-2/NR	Ruggenenti et al. 2005 [114]	NA	3b–5/no T2D/ PER < 3 and ≥ 3 g/day	Ramipril + felodipine	Ramipril	–	–	Antihypertensive
AASK/NCT04364139	Agodoa et al. 2001 [115]	NA	2–4/no T2D/–	Ramipril	Amlodipine	–	–	Antihypertensive
Cinotti 2001/NR	Cinotti and Zucchelli 2001 [116]	NA	–/no T2D/–	Lisinopril	SOC	–	–	Antihypertensive
Nephros/NR	Herlitz et al. 2001 [117]	NA	–/no T2D/–	Ramipril + felodipine	Ramipril	Felodipine	–	Antihypertensive
REIN-1 (Stratum 1)/NR	Ruggenenti et al. 1999 [118]	NA	–/no T2D/–	Ramipril	Placebo	–	–	Antihypertensive
REIN-1 (Stratum 2)/NR	Remuzzi et al. 1997 [119]	NA	2–4/no T2D/–	Ramipril	Placebo	–	–	Antihypertensive
Stefoni 1996/NR	Stefoni et al. 1996 [120]	NA	–/no T2D/–	Ibopamine	SOC	–	–	Antihypertensive

Table 2 continued

Study ID/NCT (or other) number	Author(s)	Details in secondary publication	CKD stage/T2D status/albuminuria status	Treatment				Treatment class
				1	2	3	4	
Zucchelli 1992/NR	Zucchelli et al. 1992 [121]	NA	–/no T2D/–	Captopril	Nifedipine	–	–	Antihypertensive
CRIB-PHOS/ NCT00806481	Chue et al. 2013 [122]	NA	3/no T2D/–	Sevelamer	Placebo	–	–	Phosphate binder

ACTRN Australian Clinical Trials Registration Number, *ANZCTR* Australian New Zealand Clinical Trials Registry, *CKD* chronic kidney disease, *CRG* Cochrane Renal Group, *EAS* erythropoiesis-stimulating agent, *EudraCT* European Union Drug Regulating Authorities Clinical Trials, *ISRCTN* International Standard Randomised Controlled Trials Number, *JapicCTI* Japan Pharmaceutical Information Center, *NA* not available, *NCT* national clinical trial, *NR* not reported, *NSAID* non-steroidal anti-inflammatory drug, *PER* protein excretion rate, *SGLT2* sodium-glucose co-transporter 2, *SOC* standard of care, *T2D* type 2 diabetes, *UMIN* University Hospital Medical Information Network

[a]Primary/previous treatment class: Initially developed as blood glucose-lowering agents, observations of renal and cardiovascular benefits in patients with T2D [11–14] as well as cardiovascular benefits in patients with heart failure [15–17] has prompted the evaluation of SGLT2 inhibitors in patients with CKD

Antihypertensive agents were the most common intervention assessed overall, but were approximately twice as common in trials of patients without T2D (88%) than trials of patients with (42%), or with or without (45%) T2D. Blood glucose-lowering agents were also common in trials of patients with T2D (37%). The most common comparators were placebo in trials of patients with T2D (53%) and active comparators in trials of patients without (53%), or with or without (38%) T2D. Placebo was also common in trials of patients without (35%), or with or without (34%) T2D (Fig. S3a, b).

Baseline Patient Characteristics

In more than 80% of trials, 50–100% of patients were male (Fig. S4). Mean age ranges were 51.0–72.1 years in trials of patients with or without T2D (except one trial with a mean age range of 34–35 years [82]), 53.8–70.2 years in trials of patients with T2D (except one trial with a mean age range of 34.0–35.0 years [66], and one trial with a median age of 33 years [65]), and 44.4–71.0 years in trials of patients without T2D.

While CKD etiologies other than diabetic nephropathy were infrequently reported in trials of patients with T2D, 13 trials (14.6%) of patients without T2D and 16 (18.0%) of patients with or without T2D reported glomerulonephritis as a key CKD etiology (Table S2a, b).

Mean eGFR ranged between 13.9 and 102.8 mL/min/1.73 m^2, including two trials that enrolled patients with mean eGFR > 90 mL/min/1.73 m^2 (Table S3) [38, 59]. Trials most commonly reported albuminuria as UACR (50.6%), with mean UACR ranging between 29.9 and 2911.0 mg/g. Other trials reported UACR via categorization into normo-, micro-, or macroalbuminuria (16.9%), albumin excretion rate (12.4%), protein excretion rate (20.2%), protein-to-creatinine ratio (18.0%), or urinary albumin value (13.5%) (Table S4a–f).

Thirty-one trials (34.8%) included patients with prior histories of cardiovascular disease, with the proportion of patients ranging from 1.7% to 92.0%, although cardiovascular disease history was either inconsistently defined or not defined at all (Table S5). Fourteen trials (15.7%) included patients with HF, with the proportion of patients ranging from 0.6% to 43.1% (Table S6). Eighty-two trials (92.1%) reported systolic and diastolic blood pressure (Table S7).

Composite Outcomes

Fifty-seven composite endpoints were identified, only 13 of which were used in more than one trial (Fig. S5a, b). Composite outcomes are summarized in Table S8.

Twelve trials (13.5%) reported significant reductions in the risks of composites comprising kidney failure plus one or more of doubling of serum creatinine, eGFR reduction (≥ 40% or ≥ 50%), mortality (all-cause, renal, or cardiovascular), myocardial infarction (MI), stroke, albuminuria progression, or other (Table 3). These included trials published before 2013 evaluating RAAS inhibitors losartan (RENAAL, ROAD) [61, 112], ramipril (REIN-1, AASK) [115, 123], irbesartan (IDNT) [62], valsartan (KVT) [83], and benazepril (ROAD, and an unnamed trial) [112, 113] in patients with, without, or with or without T2D. Also included were trials published onwards of 2019 evaluating dipeptidyl peptidase 4 inhibitor linagliptin (CARMELINA) [34], endothelin A receptor antagonist atrasentan (SONAR) [47], and the non-steroidal mineralocorticoid receptor antagonist finerenone (FIDELIO-DKD) [26] in patients with T2D, as well as the SGLT2 inhibitor canagliflozin (CREDENCE) [27] in patients with T2D and UACR > 300–5000 mg/g. Another SGLT2 inhibitor, dapagliflozin, significantly reduced the risk of composite endpoints comprising kidney failure and at least 50% eGFR reduction plus cardiovascular and/or renal mortality in patients with or without T2D and UACR 200–5000 mg/g (DAPA-CKD) [25]. Kidney failure as an independent outcome is reported below.

Four trials (4.5%) reported significant reductions in the risks of composites comprising cardiovascular mortality without kidney failure, plus at least one of doubling serum creatinine, renal mortality, MI, stroke, hospitalization for HF, or hospitalization for HF or unstable angina

Table 3 Composite endpoints with significant outcomes

Endpoints			Trial	Active arm	Control arm	Outcome	*P* value	HR (95% CI)
Kidney failure	≥ 50% eGFR reduction	–	AASK	Ramipril	Amlodipine	Secondary	0.01	38[c,e] (10–58)
		Mortality		Ramipril	Amlodipine	Secondary	0.005	38[c,e] (13–56)
		Renal mortality, albuminuria progression, or other[a]	CARMELINA	Linagliptin	Placebo	Exploratory	0.003	0.86 (0.78–0.95)
		Renal or cardiovascular mortality	DAPA-CKD	Dapagliflozin	Placebo	Primary	< 0.001	0.61 (0.51–0.72)
		Renal mortality	DAPA-CKD	Dapagliflozin	Placebo	Secondary	< 0.001	0.56 (0.45–0.68)
		Renal or cardiovascular mortality	CREDENCE	Canagliflozin	Placebo	Primary	0.00001	0.70 (0.59–0.82)
	Doubling of serum creatinine	–	SONAR	Atrasentan	Placebo	Primary	0.0047	0.65 (0.49–0.88)
			RENAAL	Losartan	Placebo	Secondary	0.01	21[c] (5–34)
			REIN-1 (stratum 2)	Ramipril	Placebo	Unsure	0.02	–
			FIDELIO-DKD	Finerenone	Placebo	Secondary	–	0.76 (0.65–0.90)
		Cardiovascular mortality, non-fatal MI, or stroke	SONAR	Atrasentan	Placebo	Secondary	0.049	0.8 (0.64–0.99)
		Mortality	RENAAL	Losartan	Placebo	Primary	0.02	16[c] (2–28)
			IDNT	Irbesartan	Placebo	Primary	0.02	0.80[d,f] (0.66–0.97)
					Amlodipine	Primary	0.006	0.77[d,f] (0.63–0.93)
			KVT	Valsartan	SOC	Unsure	0.007	–
							0.008	38.3[c,f] (11.9–56.9)
							0.004	42.6[c,e] (16.4–60.6)
				Valsartan + SOC	SOC	Unsure	0.004	0.57 (0.39–0.84)
			ROAD	Benazepril[g]	Benazepril[h]	Primary	0.028	51[c] (4.8–73.3)
				Losartan[g]	Losartan[h]		0.022	53[c] (5.5–74.1)
			Hou 2006	Benazepril	Placebo	Primary	0.004	43.0[c]
	Renal mortality	≥ 40% eGFR reduction	FIDELIO-DKD	Finerenone	Placebo	Primary	0.001	0.82 (0.73–0.93)
		Cardiovascular mortality	CREDENCE	Canagliflozin	Placebo	Exploratory	–	0.73 (0.61–0.87)
	Mortality		RENAAL	Losartan	Placebo	Secondary	0.01	20[c] (5–32)
			AASK	Ramipril	Amlodipine	Secondary	0.007	41[c,e] (14–60)

Table 3 continued

Endpoints			Trial	Active arm	Control arm	Outcome	*P* value	HR (95% CI)
Cardiovascular mortality[b]	MI, stroke	–	CREDENCE	Canagliflozin	Placebo	Secondary	0.01	0.80 (0.67–0.95)
			CARMELINA	Linagliptin	Placebo	Primary	< 0.001[i]	1.02 (0.89–1.17)
		Hospitalization for HF	FIDELIO-DKD	Finerenone	Placebo	Secondary	0.03	0.86 (0.75–0.99)
		Hospitalization for HF or unstable angina	BEACON	Bardoxolone methyl	Placebo	Secondary	< 0.001	1.71 (1.31–2.24)
			CREDENCE	Canagliflozin	Placebo	Secondary	–	0.74 (0.63–0.86)
	Hospitalization for HF		CREDENCE	Canagliflozin	Placebo	Secondary	< 0.001	0.69 (0.57–0.83)
			DAPA-CKD	Dapagliflozin	Placebo	Secondary	0.009	0.71 (0.55–0.92)

CI confidence interval, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *HR* hazard ratio, *MI* myocardial infarction, *SOC* standard of care

[a]Retinal photocoagulation, anti-vascular endothelial growth factor injection therapy for diabetic retinopathy, vitreous hemorrhage, and diabetes-related blindness

[b]Kidney failure not included as an endpoint

[c]Risk reduction

[d]Relative risk

[e]Adjusted

[f]Unadjusted

[g]Uptitrated (optimal antiproteinuric) dose

[h]Conventional dose

[i]*P* value for noninferiority

(Table 3). These included the CARMELINA [34], FIDELIO-DKD [26], and CREDENCE [27] trials, as well as the DAPA-CKD trial of dapagliflozin, which significantly reduced the risk of a composite endpoint comprising cardiovascular mortality and hospitalization for HF [25]. Conversely, the risk of a composite endpoint comprising cardiovascular mortality and hospitalization for HF or unstable angina increased in the BEACON trial of bardoxolone methyl, a nuclear 1 factor (erythroid-derived 2)-related factor 2 activator, although patients in this trial had CKD stage 4, T2D, and median UACR 320 mg/g [73].

Renal Outcomes

Kidney Failure

Kidney failure (previously end-stage kidney disease or end-stage renal disease [124]) ensues when eGFR declines below 15 mL/min/1.73 m^2 (CKD stage 5) and the patient requires kidney replacement therapy (previously renal replacement therapy [124]) in the form of a transplant or dialysis [4].

Thirty-two trials (36.0%) reported numbers of patients progressing to kidney failure (Table S9). Significant risk reductions were observed in seven trials (7.9%): the RENAAL trial of losartan in patients with T2D and UACR $\geq$ 300 mg/g ($P = 0.002$) [61], the ROAD trial of optimal antiproteinuric doses of losartan ($P = 0.046$) and benazepril ($P = 0.042$) in patients without T2D [112], an unnamed trial of conventionally dosed benazepril in patients without T2D ($P = 0.02$) [113], the REIN-1 and AASK trials of ramipril in patients without T2D (both $P = 0.01$) [115, 118], the CREDENCE trial of canagliflozin ($P = 0.002$) [27], and the DAPA-CKD trial of dapagliflozin (HR 0.64; 95% CI 0.50–0.82) [25].

Dialysis and Transplantation

Dialysis, kidney transplantation, or both were reported in 17 (19.1%), seven (7.9%), and two trials (2.2%), respectively (Table S10). Significant outcomes were limited to three trials (3.4%). The lipid-lowering agent probucol lengthened mean time to starting dialysis in a trial of patients with T2D and UACR > 300 mg/g ($P = 0.009$) [71], and the number of patients starting dialysis was significantly reduced in a trial of patients without T2D receiving the RAAS inhibitor captopril ($P < 0.005$) [121], as well as patients receiving dapagliflozin in the DAPA-CKD trial (HR 0.66; 95% CI 0.48–0.90) [25].

Kidney Function Decline

Percentage eGFR declines, mean eGFR declines, and final eGFR measurements at end of follow-up were reported in 11 (12.4%), 30 (33.7%), and 25 (28.1%) trials, respectively (Table S11a–c).

The number of patients reaching an eGFR decline of 50% was significantly reduced in four trials (4.5%): the SONAR trial of atrasentan in patients with T2D and UACR 300–5000 mg/g ($P = 0.038$) [47], the LORD trial of lipid-lowering agent atorvastatin in patients with or without T2D ($P = 0.023$) [95], and the DAPA-CKD trial of dapagliflozin (HR 0.53; 95% CI 0.42–0.67) [25]. In the PREDICT trial of erythropoiesis-stimulating agent darbepoetin alfa, the number of patients without T2D reaching an eGFR decline of 50% was also significantly reduced among those targeting a higher (11–13 g/dL) versus lower (9–11 g/dL) hemoglobin level ($P = 0.008$); however, targeting a higher hemoglobin level did not improve kidney outcomes overall [106]. The number of patients reaching an eGFR decline of at least 40% was significantly reduced in the FIDELIO-DKD trial of finerenone (HR 0.81; 95% CI 0.72–0.92) [26].

Twenty trials (22.5%) reported numbers of patients doubling their serum creatinine (Table S12). Significant risk reductions were observed in seven trials (7.9%): the SONAR trial of atrasentan ($P = 0.0055$) [47], the FIDELIO-DKD trial of finerenone (HR 0.68; 95% CI 0.55–0.82) [26], the RENAAL trial of losartan ($P = 0.006$) [61], the ROAD trial of optimal antiproteinuric doses of losartan ($P = 0.040$) and benazepril ($P = 0.041$) [112], an unnamed trial of conventional doses of benazepril ($P = 0.02$) [113], the IDNT trial of irbesartan ($P < 0.001$ vs amlodipine, $P = 0.003$ vs placebo) [62], and the CREDENCE trial of canagliflozin ($P < 0.001$) [27].

Cardiovascular Outcomes

Heart Failure

Fourteen trials (15.7%) reported incidences of HF (Table S13), with significant reductions observed in two trials (2.2%): the ASCEND trial of endothelin type A receptor antagonist avosentan in patients with T2D ($P = 0.008$ with a 25-mg dose, $P = 0.05$ with a 50-mg dose) [57] and the IDNT trial of irbesantan ($P = 0.004$ vs amlodipine, $P = 0.048$ vs placebo) [64].

Hospitalization for HF or Unstable Angina

Hospitalization for HF and hospitalization for unstable angina were reported in 10 (11.2%) and two trials (2.2%), respectively (Table S14). Significant reductions in hospitalization for HF were observed in two trials (2.2%): the RENAAL trial of losartan ($P = 0.005$) [61] and the CREDENCE trial of canagliflozin ($P < 0.001$) [27]. Conversely, bardoxolone methyl significantly increased hospitalization for HF in the BEACON trial ($P < 0.001$) [73].

MI and Stroke

Twenty-four trials (27.0%) reported acute, non-fatal, or fatal MI, and 25 trials (28.1%) reported non-fatal or fatal stroke (Tables S15 and S16). A significant reduction in MI was observed in patients receiving the calcium channel blocker amlodipine in the IDNT trial ($P = 0.021$ vs placebo) [64]. A significant reduction in non-fatal stroke was observed in the SONAR trial of atrasentan ($P = 0.0021$) [47], and significant reductions in ischemic ($P = 0.0073$) or any stroke ($P = 0.01$) were observed in the SHARP trial of a combination of lipid-lowering agents simvastatin and ezetimibe in patients with or without T2D [93]. Conversely, a significant increase in fatal or non-fatal stroke was observed in the TREAT trial of patients with CKD stages 3–4 and T2D receiving darbepoetin alfa ($P < 0.001$) [75].

Mortality Outcomes

All-Cause Mortality

Sixty-three trials (70.8%) reported all-cause mortality (ACM) (Table S17), with a significant reduction observed in the DAPA-CKD trial of dapagliflozin ($P = 0.004$) [25].

Cardiovascular and Renal Mortality

Cardiovascular and renal mortality were reported in 18 (20.2%) and nine trials (10.1%), respectively, with no significant outcomes observed (Table S18).

Other Renal Outcomes

eGFR Slopes

eGFR slopes were reported in 15 trials (16.9%), with eGFR declines significantly reduced in three trials (3.4%): the RENAAL trial of losartan ($P = 0.01$) [61], an unnamed trial of benazepril ($P = 0.006$) [113], and the REIN-1 trial of ramipril ($P = 0.036$) [118] (Table S19).

Albuminuria

UACR changes from baseline and final UACR measurements at end of follow-up were reported in 20 (22.5%) and 17 (19.1%) trials, respectively (Table S20a, b). Significant UACR decreases from baseline were observed in eight trials (9.0%): the GUARD, ASCEND, AWARD-7 and EMPA-REG-RENAL trials of dipeptidyl peptidase 4 inhibitor gemigliptin ($P < 0.001$) [39], avosentan 25 or 50 mg ($P < 0.001$) [57], glucagon-like peptide-1 receptor agonist dulaglutide 1.5 mg ($P = 0.0024$) [37], and the SGLT2 inhibitor empagliflozin 25 mg ($P = 0.0257$–0.0031) [42], respectively, in patients with T2D; unnamed trials of calcium channel blocker benidipine ($P < 0.0001$ vs amlodipine) [84] and xanthine oxidase inhibitor topiroxostat ($P = 0.0092$) [79] in patients with or without T2D; the ACCOMPLISH trial of a combination of benazepril and amlodipine ($P = 0.0001$ vs benazepril combined with hydrochlorothiazide) in patients with or without T2D [85]; and the EVALUATE trial of selective aldosterone antagonist eplerenone in patients without T2D ($P = 0.0222$) [107].

When final UACR measurements at end of follow-up were used, significant decreases in UACR from baseline were observed in four trials (4.5%): an unnamed trial of lipid-lowering agent rosuvastatin in patients with T2D ($P < 0.01$ vs standard of care) [70], the AMADEO

trial of RAAS inhibitors telmisartan and losartan in patients with T2D (both $P < 0.0001$) [58], the RENAAL trial of losartan ($P < 0.001$) [61], and an unnamed trial of benidipine ($P < 0.01$ vs amlodipine) in patients with or without T2D [84].

Health-Related Quality of Life

Five trials (5.6%) [75, 97, 99, 100] reported HRQoL during treatment. In one trial (1.1%), Kidney Disease and Quality of Life physical function score improved significantly from baseline ($P < 0.0001$) in patients with CKD and metabolic acidosis treated with veverimer, a first-in-class hydrochloric acid binder [104].

Early Trial Discontinuation

Ten trials (11.8%) were stopped early due to low recruitment or low event rates ($n = 2$) [47, 100], safety concerns ($n = 5$) [53, 57, 73, 74, 115], negative results reported in a sister trial ($n = 1$) [72], other reasons ($n = 1$) [61], or for reasons not provided ($n = 1$) [113]. On the advice of independent data monitoring committees, the CREDENCE [27] and DAPA-CKD [25] trials were stopped early after meeting prespecified efficacy criteria for early cessation and after demonstrating overwhelming efficacy, respectively.

Risk of Bias Assessment

For seven of eight questions, 65–100% of trials had a "lower" or "unclear" risk of bias, while 35% of trials were not double blind and therefore at a "higher" risk of bias. Potential conflicts of interest were identified in 57% of trials (Fig. S6a, b).

Safety

Key safety outcomes are provided in Table S21.

The highest overall incidence of treatment-related adverse events (AEs) was reported in a trial of phosphodiesterase type 5 inhibition for patients with diabetic nephropathy (active arm, 54.7%; placebo arm, 56.3%) [49]. In this trial, the most common treatment-related AEs occurred in the placebo arm, and included headache (7.8%), diarrhea (3.6%), dyspepsia (3.6%), and peripheral edema (1.6%) [49].

The highest overall incidence of serious AEs was reported in the TREAT trial of darbepoetin alfa (active arm, 61.6%; placebo arm, 60.4%), which was stopped early due to safety concerns [75]. The most common serious AE, reported in the placebo arm, was hypertension (24.5%) [75].

DISCUSSION

The 89 clinical trials identified by this systematic literature review included a broad range of patients with any stage of CKD (eGFR 13.9–102.8 mL/min/1.73 m^2) and albuminuria (UACR 29.9–2911.0 mg/g), with (75.5%) or without (20.6%) T2D.

Many trials evaluated the impact of treatment on one or more composite endpoints, and 16 trials reported significant reductions in risks of composites comprising kidney failure ($n = 12$) or cardiovascular mortality without kidney failure ($n = 4$) while evaluating RAAS inhibitors, SGLT2 inhibitors, finerenone, or other drug classes. However, these composites were diverse and assessed in a broad range of patients, hindering comparisons.

Clinically objective independent outcomes, such as kidney failure and ACM, were more consistently defined. Of 32 trials reporting incidences of kidney failure, seven observed significant risk reductions following treatment. These included a small trial of losartan ($n = 751$) in patients with T2D [61] and four smaller trials of losartan, benazepril, and ramipril ($n = 84$–436) in patients without T2D [112, 113, 115, 118], all published before 2008. Consequently, RAAS inhibition became the standard of care for patients with CKD [4]. However, there had been a lack of success in developing new agents to augment RAAS inhibitors, delay progression, and improve outcomes, with trials of other drug classes scarcely meeting their primary endpoints until recently. Two large trials ($n = 2152$ and 2202) published onwards of 2019 demonstrated significant

reductions in the risk of kidney failure among patients with UACR ≥ 200 mg/g treated with SGLT2 inhibitors [25, 27]. While the CREDENCE trial of canagliflozin only enrolled patients with T2D, the DAPA-CKD trial of dapagliflozin showed that kidney-protective effects from SGLT2 inhibition could be extended to patients with or without T2D [25]. A significant reduction in ACM observed in the same trial of dapagliflozin is the only example of a marked prolongation of survival reported to date in patients with CKD [25], and evidence from a recent systematic review confirms that well-designed clinical trials are required to optimize existing treatments to meet this unmet need [125].

Kidney failure and other clinical outcomes develop late in CKD, requiring trials with relatively long durations to enroll large patient populations [10]. Surrogate endpoints can be used to monitor disease progression and evaluate treatments in earlier stages of CKD [10, 126–129]. However, this review identified a diverse range of surrogate endpoints, including specific eGFR changes from baseline (33.7%), final eGFR values at end of follow-up (28.1%), eGFR slopes (16.9%), and percentage eGFR declines from baseline (12.4%). Future clinical trials evaluating new treatments for patients in the earlier stages of CKD may therefore benefit from the standardization of surrogate endpoints.

While it has been shown elsewhere that HRQoL diminishes with progression of CKD [5, 6], this review highlights the paucity of data showing that improvements with treatment are accompanied by improvements in HRQoL. Only five trials (5.6%) were identified that assessed HRQoL during treatment, with significant improvements limited to a trial of a hydrochloric acid binder for patients with metabolic acidosis [104]. Difficulties capturing changes in HRQoL, including the number of instruments used and differences in their sensitivities, have been highlighted recently [6].

This review has several limitations, including the exclusion of non-English-language publications and of trials enrolling patients without albuminuria. Phase was not reported in 51.7% of trials, and it is possible that some phase 2 trials were included against eligibility criteria. A "higher" risk of bias was identified for 35% of trials that were not double blind. Finally, eligibility criteria were broad and this review included patients with any stage of CKD, with or without T2D, and treated with any drug class since 1990. CKD etiologies differed markedly between patients with T2D and without T2D, and a diverse range of comparators was also identified. Surrogate and clinically objective measurements of declining kidney function and treatment efficacy have also evolved over time, and 57 different composite outcomes were identified. Given the breadth and diversity of the data acquired, the performance of a meta-analysis was considered to be infeasible.

CONCLUSION

Until recently, only RAAS inhibitors had shown that they could delay CKD progression and reduce the risk of kidney failure; however, this evidence was generated in just one small trial of patients with T2D and four smaller trials of patients without T2D. Contemporary data from the CREDENCE, DAPA-CKD, and FIDELIO-DKD trials suggest that adding an appropriate SGLT2 inhibitor or finerenone on top of standard of care RAAS inhibition can significantly improve a range of both kidney and cardiovascular outcomes in patients with or without T2D. Moreover, data from DAPA-CKD suggest that dapagliflozin added to standard of care RAAS inhibition can significantly decrease all-cause mortality in patients with or without T2D. Given the morbidity and mortality burden of CKD, the impact of CKD progression on HRQoL and healthcare costs, and the increasing prevalence of risk factors such as hypertension and diabetes in aging populations, these new drug classes potentially have an important role in the future treatment and management of CKD.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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