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 m² 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
**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 m² 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 m²) [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 |
| | Adverse events | Pharmacodynamics |
| | Health-related quality of life | |
| | Patient-reported outcomes | |
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 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 |
| Others | Language: English | Other languages |

**Others**

- Language: English
- Publication years: 1990 to November 2, 2020
- 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

"Including proxies: albumin-to-creatinine ratio, urinary protein-to-creatinine ratio, or reagent strip qualitative recording

\textsuperscript{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

\textsuperscript{c}Albuminuria could be reported using multiple methods

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

*Antihyperglycemic* means treatment aimed at reducing blood sugar levels.
| Study ID/NCT (or other) number | Author(s) | Details in secondary publication | CKD stage/T2D status/albuminuria status | Treatment | Treatment class |
|-------------------------------|-----------|----------------------------------|----------------------------------------|-----------|----------------|
| VERTIS-RENAL/ NCT01986855    | Grunberger et al. 2018 [36] | NA | 3/2D/- | Ertugliflozin 10 | Ertugliflozin 5 | Placebo | – | Antihyperglycemic |
| AWARD-7/ NCT01621178         | Turtle et al. 2018 [37] | NA | 3–4/2D/- | Dulaglutide 1.5 | Dulaglutide 0.75 | Insulin glargine | – | Antihyperglycemic |
| MARLINA-T2D/ NCT01792518     | Groop et al. 2017 [38] | NA | 1–3/2D/- | Linagliptin | Placebo | – | – | Antihyperglycemic |
| GUARD/ NCT01988044           | Han et al. 2018 [40] | 40-week extension; placebo transitioned to linagliptin | 3–4/2D/- | Gemigliptin | Placebo | – | – | Antihyperglycemic |
| LIRA-RENAL/ NCT01620489      | Davies et al. 2016 [41] | NA | 3/2D/- | Liraglutide 1.8 | Placebo | – | – | Antihyperglycemic |
| EMPA-REG-RENAL/ NCT01646501  | Barnett et al. 2014 [42] | NA | 2–4/2D/- | Empagliflozin 25 | Empagliflozin 10 | Placebo | – | Antihyperglycemic |
| Kohan 2014/ NCT00663260      | Kohan et al. 2014 [43] | NA | 2–3/2D/- | Dapagliflozin 10 | Dapagliflozin 5 | Placebo | – | Antihyperglycemic |
| Yale 2014/ NCT01064414       | Yale et al. 2014 [44] | 52-week results | 3/2D/- | Canagliflozin 300 | Canagliflozin 100 | Placebo | – | Antihyperglycemic |
| | Yale et al. 2013 [45] | NA | Canagliflozin 300 | Canagliflozin 100 | Placebo | – | – | Antihyperglycemic |
| DNETT-Japan/ NCT00253786     | Shikata et al. 2020 [46] | NA | ~/2D/- | Intensive treatment | SOC | – | – | Antihypertensive |
| SONAR/ NCT01858532           | Heerspink et al. 2019 [47] | NA | 1–3/2D/- | Atrasentan | Placebo | – | – | Antihypertensive |
| Chen 2018/NR                 | Chen et al. 2018 [48] | NA | 1–3/2D/- | Irbesartan 350 | Irbesartan 300 | Irbesartan 300 | Irbesartan 300 | Antihypertensive |
| Study ID/NCT (or other) number | Author(s) Details in secondary publication | CKD stage/T2D status/albuminuria status | Treatment | Treatment class |
|-------------------------------|--------------------------------------------|----------------------------------------|-----------|-----------------|
| Scheele 2016/NR              | Scheele et al. 2016 [49]                   | 3–4/T2D/Macroalbuminuria              | PF-00489791 | Placebo – – – Antihypertensive |
| Han 2015/NCT01382303         | Han et al. 2015 [50]                       | –/T2D/–                               | Pentoxifylline | Placebo – – –Antihypertensive |
| NAVARR-González et al. 2015  | NAVARR-González et al. 2015 [51]           | 3–4/T2D/–                             | Pentoxifylline | Placebo – – –Antihypertensive |
| Pan 2015/NCT00774904         | Pan et al. 2015 [52]                       | –/T2D/–                               | Losartan 100  | Amlodipine – – –Antihypertensive |
| VA NEPHRON-D/NCT00555217     | Fried et al. 2013 [53]                     | 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 – –Antihypertensive |
| Lewis 2012/NR                | Lewis et al. 2012 [55]                     | –/T2D/–                               | Pyridoxamine dihydrochloride 300 | Pyridoxamine dihydrochloride 150 Placebo – – –Antihyperglycemic |
| Orients/ASCEND/NCT00120328   | Imai et al. 2011 [56]                      | –/T2D/–                               | Olmesartan | Placebo – – –Antihypertensive |
| Lewis et al. 2012 [55]       | Lewis et al. 2012 [55]                     | –/T2D/–                               | Telmisartan | Losartan 100 – – –Antihypertensive |
| AMADEO/ASCEND/NCT00168837    | Bakris et al. 2008 [58]                    | –/T2D/–                               | Telmisartan | Losartan 100 – – –Antihypertensive |
| DETAIL/NR                    | Barnett et al. 2004 [59]                   | –/T2D/–                               | Telmisartan | Losartan 100 + enalapril – –Antihypertensive |
| DEIAHBYCAR/NR                | Mace et al. 2004 [60]                      | –/T2D/–                               | Telmisartan | Losartan 100 – – –Antihypertensive |
| RENAAAL/NR                   | Bremner et al. 2001 [61]                   | –/T2D/–                               | Losartan 100 | Placebo – – –Antihypertensive |
| Study ID/NCT (or other) number | Author(s) Details in secondary publication | CKD stage/T2D status/albuminuria status | Treatment | Treatment class |
|-------------------------------|--------------------------------------------|----------------------------------------|------------|----------------|
| IDNT/NR Lewis et al. 2001 [62] | NA –/T2D/ – | 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 | – | – |
| Lewis 1993/NR Lewis et al. 1993 [66] | NA –/T2D/ – | Captopril | Placebo | – | – |
| Voroneanu 2017/NR Voroneanu et al. 2017 [67] | NA 1–4/T2D/ – | Silymarin | Placebo | – | – |
| Endo et al. 2013 [68] | NA –/T2D/ – | Probucol | SOC | – | – |
| Rutter et al. 2011 [69] | NA –/T2D/ – | Atorvastatin 80 | Atorvastatin 10 | – | – |
| Abe 2011 (+ T2D)/NR Abe et al. 2011b [70] | NA 1–2/T2D/ – | Rosuvastatin | SOC | – | – |
| Endo 2006/NR Endo et al. 2006 [71] | NA –/T2D/ – | Probucol | SOC | – | – |
| San-MACRO/ NCT00130312 | NA 3–4/T2D/ – | Sulodexide | Placebo | – | – |
| de Zea et al. 2013 [73] | NA 4/T2D/ – | Bardoxolone methyl | Placebo | – | – |
| ALTITUDE/ NCT00549757 | NA 1–3/T2D/ – | Alikiren | Placebo | – | – |
| BEACON/ NCT01351675 | NA 4/T2D/ – | Bardoxolone methyl | Placebo | – | – |
| Parving et al. 2012 [74] | NA 1–3/T2D/ – | Aliskiren | Placebo | – | – |
| Pfeifer et al. 2009 [75] | NA 3–4/T2D/ – | Darbepoetin alfa | Placebo | – | – |
| Study ID/NCT (or other) number | Author(s) Details in secondary publication | CKD stage/T2D status/albuminuria status | Treatment | Treatment class |
|-------------------------------|-------------------------------------------|----------------------------------------|-----------|-----------------|
| CASSIOPEIAIR/ NCT01090037     | Nakamoto et al. 2020 [76]                 | NA –/± T2D/– | TRK-100STP 120 | Antihypertensive |
| UK HARP-III/ ISRCTN11958993   | Haynes et al. 2018 [77]                   | 3–4/± T2D/– | Irbesartan 300 | Antihypertensive |
| Ameen 2016/NR                 | Ameen et al. 2016 [78]                    | NA –/± T2D/– | Valsartan | Antihypertensive |
| Hosoya 2014/ JapicCTI-101171  | Hosoya et al. 2014 [79]                   | 3/± T2D/– | Topiroxostat | Uric acid lowering |
| COSMO-CKD/ UMIN000002143      | Ando et al. 2014a [80]                    | NA 1–3/± T2D/– | Benidipine | Antihypertensive |
| Ando 2013/ UMIN000001247      | Ando et al. 2013 [81]                     | NA –/± T2D/– Microalbuminuria | Cilnidipine | Amlodipine – – |
| Wang 2013/NR                  | Wang et al. 2013 [82]                     | 1–3/± T2D/– | Spironolactone | SOX – – |
| KVT/NCT00190580               | Yasuda et al. 2013 [83]                   | NA –/± T2D/– | Valsartan | SOX – – |
| Abe 2011 (± T2D)/ UMIN000002644 | Abe et al. 2011a [84]                  | NA 2–3/± T2D/– | Benidipine | Amlodipine – – |
| ACCOMPLISH/ NCT00170950       | Bakris et al. 2010 [85]                   | Prespecified analysis, therefore included | –/± T2D/– | Benazepril 40 + amlodipine |
| ESPLANADE/ NCT00199927        | Ruggeri et al. 2010 [86]                  | NA –/± T2D/– | Benazepril 20 + valsartan + fluvastatin | Antihypertensive |
| Abe 2010/NR                   | Abe et al. 2010 [87]                      | 3–5/± T2D/– | Benidipine | Cilnidipine – – |
| JLIGHT/NR                     | Iino et al. 2004 [88]                     | NA –/± T2D/– | Losartan 100 | Amlodipine – – |
| Study ID/NCT (or other) number | Author(s) | Details in secondary publication | CKD stage/T2D status/albuminuria status | Treatment | Treatment class |
|-----------------------------|-----------|---------------------------------|---------------------------------------|-----------|----------------|
| 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/–                           | Exenatide | Statin uptitration – – Lipid-lowering |
| SHARP/NCT00125593          | Baigent et al. 2011 [93] | NA                              | /–– T2D/–                             | Simvastatin + exenatide | Placebo – – Lipid-lowering |
|                            | Haynes et al. 2014 [94] | LDL                             |                                       | Simvastatin + exenatide | 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                              | 3–6/± 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        | Akizawa et al. 2009 [99] | NA                              |                                      | AST-120 Placebo | – – |
| EPPIC-2/NCT00501046        | Akizawa et al. 2009 [99] | NA                              |                                      | AST-120 SOC | – – Uremic toxins adsorbent |
| CKD-FIX/ACTRN12611000791932 | Badve et al. 2020 [100] | NA                              | 3–6/± T2D/–                           | Allopurinol Placebo | – – Uric acid lowering |
| FEATHER/UMIN000008343      | Kimura et al. 2018 [101] | NA                              | 3/± T2D/–                            | Febuxostat Placebo | – – Uric acid lowering |
| Study ID/NCT (or other) number | Author(s) Details in secondary publication | CKD stage/T2D status/albuminuria status | Treatment | Treatment class |
|-------------------------------|-------------------------------------------|----------------------------------------|-----------|----------------|
| 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/–                         | Vesceimer 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 Darbepoetin alfa (high Hb target) (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/–                        | Amlirenn Losartan 100 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 |
| Study ID/NCT (or other) number | Author(s) Details in secondary publication | CKD stage/T2D status/albuminuria status | Treatment | Treatment class |
|--------------------------------|-------------------------------------------|----------------------------------------|-----------|----------------|
| ROAD/NR                       | Hou et al. 2007 [112]                     | NA                                     | Benazepril 10 | Antihypertensive |
| Hou 2006/ NCT00270426         | Hou et al. 2006 [113]                     | NA                                     | Placebo    | Antihypertensive |
| REIN-2/NR                     | Ruggenenti et al. 2005 [114]              | NA                                     | Ramipril + felodipine | Antihypertensive |
| AASK/NCT04364139              | Agodoa et al. 2001 [115]                  | NA                                     | Ramipril   | Antihypertensive |
| Cinotti 2001/NR               | Cinotti and Zucchelli 2001 [116]          | NA                                     | Lisinopril | Antihypertensive |
| Nephros/NR                    | Herlitz et al. 2001 [117]                 | NA                                     | Ramipril + felodipine | Antihypertensive |
| REIN-1 (Stratum 1)/NR         | Ruggenenti et al. 1999 [118]              | NA                                     | Placebo    | Antihypertensive |
| REIN-1 (Stratum 2)/NR         | Remuzzi et al. 1997 [119]                 | NA                                     | Placebo    | Antihypertensive |
| Stefoni 1996/NR               | Stefoni et al. 1996 [120]                 | NA                                     | Ibopamine   | Antihypertensive |
**Table 2 continued**

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

ACTRN Australian Clinical Trials Registration Number, ANZCTR Australian New Zealand Clinical Trials Registry, CKD chronic kidney disease, CRG Cochrane Renal Group, ESA 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

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.

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 or without T2D, 13 (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 m², including two trials that enrolled patients with mean eGFR > 90 mL/min/1.73 m² (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 200–5000 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 $\geq 50\%$ eGFR reduction      | AASK           | Ramipril   | Amlodipine  | Secondary     | 0.01    | 38\% (10–58)             |
| Mortality                                      | Ramipril       | Amlodipine | Secondary   | 0.005         | 38\% (13–56) |
| Renal mortality, albuminuria progression, or other\* | 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)         |
| Mortality                                      | RENAAL         | Losartan   | Placebo     | Secondary      | 0.01    | 1.1* (5–34)              |
| RENI-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    | 1.6* (2–28)              |
| IDNT                                           | Irbesartan     | Placebo    | Primary     | 0.02           | 0.80\* (0.66–0.97) |
|                                               | Amlodipine     | Primary     |            | 0.006          | 0.77\* (0.63–0.93) |
| KVT                                            | Valsartan      | SOC        | Unsure      | 0.007          | –       | –                        |
|                                               | Valsartan + SOC| SOC        | Unsure      | 0.008          | 0.38,3\* (11.9–56.9) |
|                                               |                |            |            | 0.004          | 42.6\* (16.4–60.6) |
| ROAD                                           | Benazepril     | Benazepril | Primary     | 0.028          | 5.1\* (4.8–73.3) |
|                                               | Losartan       | Losartan   | Primary     | 0.022          | 5.5\* (5.5–74.1) |
| Hou 2006                                       | Benazepril     | Placebo    | Primary     | 0.004          | 43.0\* |
| Renal mortality $\geq 40\%$ 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    | 2.0* (5–32)              |
|                                               | AASK           | Ramipril   | Amlodipine  | Secondary      | 0.007   | 41\* (14–60)             |
### Table 3 continued

| Endpoints | Trial | Active arm | Control arm | Outcome   | P value | HR (95% CI) |
|-----------|-------|------------|-------------|-----------|---------|-------------|
| Cardiovascular mortality<sup>b</sup> MI, stroke | – | CREDENCE | Canagliflozin | Placebo | Secondary | 0.01 | 0.80 (0.67–0.95) |
| | | CARMELINA | Linagliptin | Placebo | Primary | < 0.001 | 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) |
| Hospitalization for HF | CREDENCE | Canagliflozin | Placebo | Secondary | < 0.001 | 0.74 (0.63–0.86) |
| | 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
<sup>a</sup>Retinal photocoagulation, anti-vascular endothelial growth factor injection therapy for diabetic retinopathy, vitreous hemorrhage, and diabetes-related blindness
<sup>b</sup>Kidney failure not included as an endpoint
<sup>c</sup>Risk reduction
<sup>d</sup>Relative risk
<sup>e</sup>Adjusted
<sup>f</sup>Unadjusted
<sup>g</sup>Updtrated (optimal antiproteinuric) dose
<sup>h</sup>Conventional dose
<sup>i</sup>P value for noninferiority
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 m² (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].

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 [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 
amlopidine, 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 CRE-
DENCE 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 
amlopidine in the IDNT trial (P = 0.021 vs pla-
cebo) [64]. A significant reduction in non-fatal 
stroke was observed in the SONAR trial of 
atasentan (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 rami-
pril (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 tri-
als 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 ACCOM-
PLISH trial of a combination of benzazepril and 
amlopidine (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 CRE-DEENCE 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.

**ACKNOWLEDGMENTS**

**Funding.** Development of this manuscript and all associated publication costs, including
the journal's Rapid Service and Open Access Fees, were supported by AstraZeneca.

Medical Writing, Editorial, and Other Assistance. Medical writing and editorial support was provided by Matthew Young, DPhil, and Rachael Cazaly (Core, London, UK), supported by AstraZeneca according to Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M15-0288).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the data interpretation, critically reviewed the manuscript, approved the final version, and accept accountability for the overall work. Study design was performed by Juan Jose Garcia Sanchez, Juliette Thompson, Glen James, Stephen Nolan, Naveen Rao, Bergur V. Stefansson, Alyshah Abdul Sultan, and Eric T. Wittbrodt. Data analyses were performed by Juan Jose Garcia Sanchez and Juliette Thompson. Ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Prior Presentation. Data presented in this article were also presented at the American Society of Nephrology Kidney Week meeting, October 22–25, 2020 (poster: PO0570).

Disclosures. Juan Jose Garcia Sanchez, Naveen Rao, Elisabeth Sörstadius, Glen James, Stephen Nolan, Eric T. Wittbrodt, Alyshah Abdul Sultan, Bergur V. Stefansson, and Dan Jackson are employees and shareholders of AstraZeneca. Juliette Thompson, David A. Scott, Rachel Evans, and Keith R. Abrams are partners/employees of Visible Analytics Ltd, which conducted this systematic review and received consultancy fees and expenses from AstraZeneca.

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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