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Long-term kidney outcomes of pharmacological therapies for primary IgA nephropathy: an updated systematic review of randomized trials

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Abstract

Background. Recent trials have expanded long-term treatment evidence in IgA nephropathy. We assessed their effects on kidney-function change and kidney-progression events.

Methods. We searched four databases on 23 September 2026 and repeated PubMed on 30 September for randomized trials in adults with primary IgA nephropathy reporting progression events or ≥12 months of longitudinal eGFR. Structured synthesis without meta-analysis was organized by estimand and reported using SWiM. RoB 2 assessed outcome-level bias; GRADE covered 23 results from ten principal comparisons.

Results. Fifty-one trial entries were included; for three further entries adult eligibility could not be established, and their results were not used in the adult synthesis. Iptacopan improved total eGFR slope by 3.02 mL/min/1.73 m²/year (95% CI 2.02–4.01) and reduced composite progression (HR 0.57, 0.40–0.81). Atrasentan improved total slope by 1.4 (0.5–2.3), with an imprecise composite estimate (HR 0.64, 0.39–1.05). Finerenone improved chronic slope by 1.17 (0.43–1.91) in the IgA subgroup; its total-slope interval crossed zero. MAIN reported slower annual eGFR decline with mycophenolate mofetil (1.2 versus 3.8 mL/min/1.73 m²/year) and fewer composite events

(adjusted HR 0.23, 0.09–0.63). Methylprednisolone increased serious adverse events in TESTING.

Conclusions. Long-term results strengthen evidence for treatment-specific kidney benefits. Iptacopan supports both slower eGFR decline and fewer composite progression events; atrasentan and finerenone provide clearer support for kidney-function trajectories. Endpoint definition, follow-up and certainty determine the scope of each treatment conclusion.

Systematic review registration: PROSPERO CRD420261546001.

Keywords. IgA nephropathy; systematic review; eGFR slope; kidney failure; randomized controlled trials; endothelin receptor antagonists

Background

Primary IgA nephropathy is diagnosed by kidney biopsy showing predominant or codominant mesangial IgA deposits after secondary causes have been excluded [1]. It is the most common primary glomerulonephritis worldwide (10–30% of biopsy diagnoses in Europe and North America, up to 45% in East Asia), with a reported annual incidence of about 2.5 per 100 000 adults, and a leading cause of kidney failure in young adults, with 20–40% of patients progressing to kidney failure within 20 years of diagnosis [1, 2]. Because kidney failure develops slowly, treatments are judged by their effect on long-term kidney function, and guidelines centre management on kidney protection: blood-pressure control, renin–angiotensin system blockade and, in selected patients, immunosuppression [1].

The therapeutic landscape has changed substantially. Large placebo-controlled and active-comparator trials of glucocorticoids, endothelin receptor antagonists, complement inhibitors, targeted-release budesonide and non-steroidal mineralocorticoid receptor antagonists have been reported [3–10], and in three of them (APPLAUSE-IgAN, NefIgArd and FIND-CKD) an eGFR quantity over 24–32 months was the primary endpoint. The endpoint itself has also become more complex: between-group differences in eGFR change over a fixed interval, annualized total slopes and annualized chronic slopes are all used, and they measure different things. eGFR slope has a formal surrogate basis: in a pooled analysis of individual participant data from 66 studies (186 312 participants), treatment effects on a clinical endpoint were strongly associated with effects on the

total GFR slope (median $R^2 = 0.97$) and moderately with those on the chronic slope ($R^2 = 0.55$) [11]. That analysis does not license converting a particular trial's slope difference into a number of kidney-failure events avoided.

This review evaluates how recent long-term randomized results change the evidence for pharmacological kidney protection in primary IgA nephropathy. Previous syntheses addressed selected treatments and outcomes [12–18]; final long-term reports now allow assessment of sustained kidney-function changes alongside progression events. We integrate these reports with eligible older trials and examine total and chronic eGFR slopes, time-weighted averages, fixed-time changes and progression events separately. This approach identifies the benefits supported for each treatment, the clinical meaning of the reported endpoints and the questions that remain unresolved.

Methods

Design, reporting and synthesis framework

This systematic review of randomized pharmacological trials in primary IgA nephropathy used structured synthesis without meta-analysis. Reporting follows PRISMA 2020 [19] and SWiM [20] (Additional files 1 and 2). The review was registered in PROSPERO (CRD420261546001). On 29 September 2026, after searching, partial extraction and inspection of some results, eligibility was expanded to include a trial-reported pre-specified ≥50% serum-creatinine rise as a separate progression outcome. Original-standard and amended-standard contributions are compared in Additional file 3. A post hoc exploratory synthesis of two older mycophenolate trials is reported separately (Additional file 4).

Eligibility criteria

Population. Adults with primary IgA nephropathy, including separately reported IgA subgroups of broader kidney-disease trials. Diagnostic basis is recorded per entry (Additional file 3). Two mixed adult–paediatric cohorts had adult results that could not be separated and were excluded; both also returned no outcome admissible under the original outcome standard, so population status was not the sole ground. Adult eligibility could not be established for Pozzi 1999, Manno

2009 and Liang 2022 [21–23] from the information available at completion of this review. These three entries were classified as having unresolved eligibility and were not included in the primary adult synthesis. Their five extracted progression outcomes were retained separately in Additional file 3. Intervention. Any pharmacological treatment, alone or with background therapy. Comparator. Placebo, supportive care or active treatment. Design. Randomized controlled trials. Outcomes. A trial was eligible if it reported at least one of: (i) a kidney-progression event — kidney failure (dialysis, transplantation, sustained eGFR <15 mL/min/1.73 m²), serum-creatinine doubling, a pre-specified rise of ≥50% in serum creatinine, a pre-specified percentage decline in eGFR, or an explicitly defined composite incorporating these outcomes; or (ii) a longitudinal eGFR outcome with at least 12 months of follow-up. A reported outcome did not have to be the trial's primary endpoint, and progression-event outcomes were not subject to the 12-month requirement. eGFR-decline thresholds of 25%, 30%, 40%, 50% and 57% and their composites were extracted separately; no composite was renamed in order to pool it with another, and creatinine clearance was not accepted as eGFR or as a progression event. Trials meeting the outcome standard whose numerical results could not be extracted were retained and contribute descriptively, with data not extractable kept distinct from outcome not eligible. Composite estimates were interpreted according to the full endpoint definitions reported by the original trials. Safety. Safety was not a systematic outcome and adverse events were not extracted for every agent. Systemic glucocorticoid regimens are summarized descriptively (Additional file 5) because their toxicity is substantial and several trials reported the same serious adverse events against a non-glucocorticoid arm in comparable terms. For all other agents safety data were not extracted and no safety conclusion is drawn.

Information sources, search and study selection

PubMed, Embase, Cochrane CENTRAL and Web of Science were searched on 23 September 2026. The verbatim PubMed strategy was rerun on 30 September to replace an earlier narrower execution. The retained exports comprised 2996 initial records plus 992 in the additional PubMed batch; 105 of the latter were new to the unique set. Other databases were last searched on 23 September. After merging and DOI/title-based de-duplication, 3988 records yielded 2577 unique

records and 1411 duplicates. Included-report and review reference lists were checked; database-specific strings, dates and counts are in Additional files 6 and 7.

Pre-classification (a preparatory step). Every unique record was first assigned to one of nine categories by a documented rule applied to the record's own content, with a recorded reason and one of two review states: confirmed by source or individually adjudicated (Additional file 7). This step did not by itself decide eligibility: a drug name does not establish that a record reports the same trial, so records matching only a drug name or drug class were resolved against registry number, authors, enrolment, treatment arms and recruitment dates (Additional file 8).

Screening. Two authors screened the records independently. Of the 2577 unique records, 2574 were resolved to a final category. Three reports could not be retrieved and were not assessed for eligibility (Additional file 9); they were recorded separately from eligibility exclusions and entered no numerical analysis.

Data collection, and overlapping populations

Outcome values were held in one table, one row per outcome per trial, and design and risk-of-bias information in a second; the two were not mixed. Extracted items were trial identity and registration; the relation of each report to others of the same trial; population and centre characteristics; intervention and comparator with doses, duration and background therapy; the outcome definition verbatim, including threshold, composite composition and whether persistence was required; per-arm counts with the denominator stated; the effect measure with its model; and planned and actual follow-up. Where a trial reported the same outcome in more than one publication, the final report was used for counting. Two authors independently extracted outcome data. Two reports from the same research group have potentially overlapping recruitment periods and could not be confirmed as independent [24, 25]; they form a dependency cluster (OV01), are presented separately, and their participant counts were not summed.

Grouping, prioritization and synthesis method

Grouping. Studies were grouped first by outcome family — kidney-progression events or longitudinal eGFR — and then by treatment category: supportive and renin–angiotensin system–directed therapy; systemic glucocorticoids; other immunosuppressive or immunomodulatory

therapy; agents acting on kidney haemodynamics or tubular transport (SGLT2 inhibitors, endothelin receptor antagonists, mineralocorticoid receptor antagonists, active vitamin D); and agents targeting the complement or B-cell/APRIL pathways. Gut-targeted oral budesonide is grouped with immunosuppressive therapies, because it acts on the same pathway as systemically administered glucocorticoids.

Prioritization of results. Progression events and longitudinal eGFR were prioritized over proteinuria, and pre-specified primary and key secondary kidney outcomes over exploratory analyses. Both favourable and unfavourable eligible results were reported, using final reports preferentially and labelling interim data. After extraction, ten comparisons were selected post hoc for focused presentation of long-term, practice-relevant trial or IgA-subgroup results. This presentation choice did not change eligibility; all eligible results remain in the main tables or supplements.

Synthesis method. Study-level estimates were tabulated and displayed without a pooled clinical estimate. Hazard ratios, relative risks and calculated odds ratios were labelled separately. Annualized total slopes, chronic slopes, time-weighted average eGFR and fixed-time changes were kept distinct. For the two fish-oil trials, odds ratios and Wald confidence intervals were calculated from reported event counts for individual-study display only. Whether a set of eligible results was carried into a pooled estimate was decided by whether they answer one treatment question — whether the intervention and comparator, the outcome measured and the estimand are comparable enough for a single underlying effect to be worth estimating. Differences in dose, follow-up or control condition are stated where they bear on that reading.

Numerical usability of results

Usability was decided per reported outcome, not per report. (A) An effect estimate with a defined interval, or group means with a stated dispersion, is presented with its source level labelled. (B) Values printed in a figure with their intervals are read from that figure. (C) A statement of no difference, or event counts without a randomized per-arm denominator, is summarized in text: not reported was never entered as zero and not significant was never written as no effect. Curve-,

error-bar- and point-only figures were not digitized, and no interval, event count or denominator was inferred. An abstract and the later final report of the same trial count once.

Appraisal of risk of bias and certainty

RoB 2 was applied by result to 23 outcomes from the ten focused comparisons and 41 further candidate outcomes from 32 comparisons (Additional file 10). Of these 41 additional candidate outcomes, five from three reports of unresolved adult eligibility were kept outside the primary adult synthesis, leaving 36 additional adult-eligible assessments. Allocation, deviations from assignment, missing data, measurement and selective reporting were judged separately. Each assessment was completed against the published report, and the source page and domain reasoning are recorded for that result in Additional file 10. All new or revised outcome-specific assessments were reviewed by the authors against the source reports.

Certainty was assessed with GRADE for 23 outcomes from the ten focused comparisons, separately for each comparison and outcome, with certainty starting at high and the reported grade equal to high minus the downgrades listed for that row (Additional file 11). Judging imprecision requires a stated scale, and two were used: a 25% relative reduction for outcomes reported as a ratio, and 1.0 mL/min/1.73 m² per year for annualized slope differences. Both are this review's interpretive thresholds, chosen after the results of these comparisons were known, and an effect below one is described as below that threshold. For a quantity in mL/min/1.73 m² that is not an annual rate — a fixed-time change or a multi-year time-weighted average — neither anchor applies, and imprecision was judged only from whether the interval excluded no difference. Inconsistency was not applicable, since no comparison had more than one study, and publication bias was not formally assessed. For each candidate combination of eligible results, whether it was pooled and the reasons are recorded in Additional file 12.

Additional analyses

Additional file 4 reports a post hoc exploratory synthesis of the two older mycophenolate trials, which share a treatment question (mycophenolate versus no mycophenolate, a rise of ≥50% in serum creatinine) and differ in confirmation requirement, control condition, entry criteria and achieved follow-up. Three interval methods, the two study odds ratios and a leave-one-out check

are reported. The two estimates point in opposite directions and I^2 is 52.6%, so the pooled interval is compatible with appreciable benefit and with appreciable harm; it is reported as exploratory and not used in the clinical synthesis. The two fish-oil trials were assessed separately and not synthesized, because dose, comparator, confirmation requirements and follow-up windows differ.

Use of artificial intelligence

ChatGPT/Codex (OpenAI) assisted with manuscript drafting and language revision, cross-file consistency checks, evidence-appraisal documentation and figure preparation. The authors verified the scientific content and assessment records against source materials and made the final eligibility, risk-of-bias, certainty and interpretive judgements. The authors take responsibility for the final manuscript.

Results

Study selection and characteristics

Of 3988 identified records, 1411 duplicates were removed, leaving 2577 unique records; 100 unique full-text documents were appraised. The 92 adjudicated entries comprise 51 included, three with adult eligibility unresolved, 36 excluded, one associated report without an additional usable outcome and one duplicate entry (T88 = T46; Figure 1). Counts refer to entries, not independent trials: linked reports and the unresolved OV01 cluster [24,25] are identified in Additional file 13, and participants are not summed across them. Table 1 presents the ten focused comparisons.

211 **Table 1. Characteristics of the ten principal comparisons**

Trial (reference)	Design and blinding	Randomised (n)	Intervention vs comparator	Follow-up	Kidney outcome (s) contributing to this review	Diagnostic basis (biopsy)	Report type
Barratt 2026 (APPLAUSE-IgAN) [8]	RCT, double-blind, placebo-controlled	238 vs 239	Iptacopan (oral factor B inhibitor) vs placebo; RAS blockade in both arms	24 months	Total annualized eGFR slope (primary); composite kidney-failure endpoint	Biopsy-confirmed entry requirement, all randomised	Full report, 24-month final analysis
Heerspink 2026 (ALIGN) [9]	RCT, double-blind, placebo-controlled	170 vs 170 (main stratum); 32 vs 32 (SGLT2-inhibitor stratum)	Atrasentan 0.75 mg vs placebo; RAS blockade in both arms	To week 136 (2.5 years)	Change in eGFR and total slope; composite kidney outcome	Biopsy-proven entry requirement, all randomised	Full report, final analysis
Neuen 2026 (FIND-CKD) [10]	RCT, double-blind, placebo-controlled; prespecified exploratory subgroup	226 vs 190	Finerenone vs placebo; RAS blockade in both arms	To month 32	Total and chronic eGFR slope; kidney failure or ≥40% eGFR decline	Parent trial did not require biopsy; biopsy-confirmed cases analysed separately	Subgroup of a CKD trial
Lafayette 2023 (NefIgArd) [6]	RCT, double-blind, placebo-controlled	182 vs 182	Budesonide 16 mg targeted-release vs placebo; RAS blockade and supportive care in both arms	2 years	2-year eGFR time-weighted average (primary); confirmed 30% eGFR decline or kidney failure	Biopsy-based diagnosis stated as an entry criterion	Full report
Rovin 2023 (PROTECT) [5]	RCT, double-blind, active-controlled	202 vs 202	Sparsentan vs irbesartan; RAS blockade in both arms by design	To week 110 (2 years)	Chronic and total eGFR slope; composite of 40% eGFR decline, ESKD or all-cause death	Biopsy-proven entry requirement, all randomised	Full report, 2-year results
Lv 2022 (TESTING) [3, 4]	RCT, double-blind, placebo-controlled	257 vs 246	Oral methylprednisolone (full-dose then reduced-dose phase) vs placebo; RAS blockade in both arms	Median 3.5 years	Composite of 40% eGFR decline, kidney failure or kidney death (primary); kidney failure alone; eGFR slope; serious adverse events	Kidney biopsy required at entry	Two full reports (2017, 2022)
Hou 2023 (MAIN) [26]	RCT, open-label with blinded endpoint assessment	85 vs 85	Mycophenolate mofetil plus supportive care vs supportive care	Up to 60 months	Composite of creatinine doubling, ESKD or kidney/cardiovascular death; annual rate of eGFR decline over the trial phase (secondary)	Biopsy-based diagnosis stated as an entry criterion	Full report
Rauen 2020 (STOP-IgAN) [27–29]	RCT, open-label; extended follow-up	162	Glucocorticoid, with cyclophosphamide then azathioprine in the low-GFR stratum, vs supportive care	10 years	Composite of all-cause death, ESKD or >40% eGFR decline	Biopsy-proven entry requirement, all randomised	Long-term follow-up report
Wheeler 2021 (DAPA-CKD) [30]	RCT, double-blind, placebo-controlled; prespecified subgroup	137 vs 133	Dapagliflozin vs placebo; RAS blockade in both arms	Median 2.1 years	Composite of ≥50% eGFR decline, ESKD or renal/cardiovascular death; total and chronic eGFR slope	Subgroup: 254 of 270 had biopsy-proven disease in the sensitivity analysis	Subgroup report

Trial (reference)	Design and blinding	Randomised (n)	Intervention vs comparator	Follow-up	Kidney outcome (s) contributing to this review	Diagnostic basis (biopsy)	Report type
EMPA-KIDNEY 2024 [31]	RCT, double-blind, placebo-controlled; post hoc subgroup	413 vs 404	Empagliflozin vs placebo; RAS blockade in both arms	Median 2.0 years	Composite of sustained ≥40% eGFR decline, end-stage kidney disease, sustained eGFR <10 mL/min/1.73 m² or death from kidney failure; chronic eGFR slope	Biopsy status not stated; IgA classification made post hoc	Post hoc subgroup report

Note. These are the comparisons that carry the treatment conclusions of this review and the ones assessed for risk of bias and certainty (Figure 5, Additional file 11). The remaining included entries are listed with the same fields in Additional file 13. Background renin–angiotensin system (RAS) blockade in both arms is stated for the trials whose reports specify it. ESKD, end-stage kidney disease.

Effect of the amended outcome standard

The original outcome standard is met by 53 of the 54 candidate entries. With the three reports of unresolved adult eligibility set aside, 50 of the 51 adult-eligible entries remain; Praga 2003 (T32) loses eligibility. The restriction removes six ≥50% serum-creatinine rows from the primary adult Table 2 (32 to 26 rows). A seventh such candidate result, from Pozzi 1999, is also inadmissible under the original standard. Independently reported kidney-failure, doubling or eGFR-decline results remain where eligible. Additional file 3 supplies the restricted tables and figure; creatinine-based fish-oil odds ratios and the exploratory mycophenolate synthesis are omitted. All 23 results from the ten focused comparisons remain eligible, so no conclusion drawn here rests on a removed result.

Kidney-progression events

Progression events were reported across designs from single-centre studies of fewer than 40 patients to multinational double-blind trials. Figure 2 displays the published relative effects and Figure 3 the additional outcome rows; Table 2 tabulates both. Where a trial reports counts or arm-level values without a between-group interval, the row carries exactly those values and no estimate is constructed from them; Praga 2003, Liu 2014, Li 2013 and NEFIGAN 2b are reported in this way. Where a trial reported an effect estimate only for a multivariable model, the adjustment set is stated, because that determines whether the estimate can be read as a randomized treatment effect. Systemic glucocorticoids. In TESTING (503 participants, double-blind), oral methylprednisolone reduced the composite of 40% eGFR decline, kidney failure or kidney death (hazard ratio 0.53, 0.39 to 0.72), and kidney failure alone occurred in 50/257 versus 67/246 (0.59, 0.40 to 0.87). In STOP-IgAN (162 participants), the 3-year randomized phase produced more remissions of proteinuria with added immunosuppression but no difference in its eGFR endpoint (21 of 82 versus 22 of 80 participants reaching a decrease of at least 15 mL/min/1.73 m², P = 0.75), and the 10-year follow-up reported the composite of death, ESKD or >40% eGFR decline in 35 of 77 participants assigned to added immunosuppression and 36 of 72 assigned to supportive care (hazard ratio 1.20, 0.75 to 1.92, with supportive care as the reference category). Other

glucocorticoid trials reported Pozzi 2010 five-year renal survival 88% versus 89%, Pozzi 2013 six-year 50% versus 57% (log-rank P = 0.34), Min 2017 a ≥50% creatinine rise in 20% versus 10%, and Katafuchi 2003, Wang 2013 and Stangou 2011 without an extractable estimate [32–37]. Dialysis was also reported in Pozzi 2010 (6/101 versus 4/106) and Pozzi 2013 (9/20 versus 10/26) and is tabulated separately from their creatinine-based renal-survival outcomes.

Other immunosuppressive and immunomodulatory therapy. In MAIN (170 participants), mycophenolate mofetil added to optimized supportive care reduced the composite of creatinine doubling, kidney failure (dialysis, transplantation, or without kidney replacement therapy) or death from a kidney or cardiovascular cause (6/85 versus 18/85; adjusted hazard ratio 0.23, 0.09 to 0.63). The annual rate of eGFR decline over the 3-year trial phase was 1.2 (0.6) versus 3.8 (0.6) mL/min/1.73 m² per year (P<0.001), an arithmetic difference of 2.6 between the published arm-level rates. The report estimated the treatment effect on eGFR slope using a linear mixed-effects model but did not provide a confidence interval for this trial-phase contrast. The 0.6 printed beside each arm mean summarises the arm mean rather than between-patient spread, so no interval for the difference was reconstructed from it. Trial-phase and post-trial results are presented separately. Two older trials reported a rise of ≥50% in serum creatinine with mycophenolate mofetil: Frisch 2005 (32 analysed, double-blind against placebo) 5/17 versus 2/15, and Tang 2005 (40 participants; mycophenolate versus continuation of ongoing treatment, not placebo-controlled) 1/20 versus 3/20. They are combined in the exploratory synthesis of Additional file 4.

Ballardie 2002 reported end-stage renal failure and therefore qualifies under the original standard. Its 72% versus 6% five-year renal-survival percentages also counted selected treatment withdrawals and are not treated as kidney-failure risks [38]. In Hou 2017, ESRD occurred in zero versus two participants by 12 months; event counts are retained without assigning an unreported analysis denominator [39]. Cruzado 2011 reported no dialysis events among 14 versus nine randomized participants at one year [40].

Supportive, antithrombotic and haemodynamic therapy. In the 1470-participant double-blind trial of Abelmoschus manihot versus losartan, the composite endpoint combined proteinuria ≥3.5 g/24 h, creatinine doubling or kidney replacement therapy, so the composite is not a kidney-progression endpoint. The eligible component was reported separately — creatinine doubling in 6 versus 10

participants (P=0.451), with one participant in the losartan arm requiring haemodialysis — and no usable effect estimate was presented. A randomized trial surfaced by the pre-classification [41] reported ESKD in 1/10 versus 4/11 over three years with dipyridamole plus low-dose warfarin; it is small, its groups differed at baseline, and it is recorded in Table 2 only. In the IgA subgroups of two SGLT2-inhibitor trials, composite kidney endpoints were reduced: dapagliflozin, a composite of sustained ≥50% eGFR decline, end-stage kidney disease or death from a kidney or cardiovascular cause, 6/137 versus 20/133 (hazard ratio 0.29, 0.12 to 0.73); empagliflozin, a composite of sustained ≥40% eGFR decline, end-stage kidney disease, sustained eGFR below 10 mL/min/1.73 m² or death from kidney failure, 51/413 versus 67/404 (0.67, 0.46 to 0.97). With sparsentan, the composite kidney failure endpoint was reached by 18 (9%) of 202 versus 26 of 202 (relative risk 0.7, 0.4 to 1.2). Cheng 2015 reported haemodialysis in 4, 1, 0 and 0 participants across four 42-person arms, retained as one multi-arm comparison [42]. Donadio 2001 contributed its randomized high- versus low-dose fish-oil comparison (ESRD 8/36 versus 10/37); the historical placebo comparison was excluded [43].

Agents targeting endothelin, complement or B-cell/APRIL pathways. Iptacopan reported a secondary composite kidney-failure endpoint and atrasentan a composite kidney outcome that did not reach significance (both in Table 2). For blisibimod, a BAFF inhibitor, the phase 2 BRIGHT-SC abstract states that one participant in each arm reached ESKD, with no per-arm randomized denominator and no event times, so no effect estimate is computed. For the remaining agents in this class the reported evidence is proteinuria-based or slope-based.

Table 2. Kidney-progression events.

Trial	Comparison	Outcome	Result	Effect measure and model
Lv 2022 (TESTING) [3]	Methylprednisolone vs placebo	40% eGFR decline, kidney failure or kidney death	HR 0.53 (0.39–0.72)	Cox, stratified
Lv 2022 (TESTING) [3]	as above	Kidney failure alone	50/257 vs 67/246; HR 0.59 (0.40–0.87)	Cox, stratified

Trial	Comparison	Outcome	Result	Effect measure and model
Rauen 2020 (STOP-IgAN) [27–29]	Immunosuppression vs supportive care	All-cause death, ESKD or >40% eGFR decline (10 y)	35/77 vs 36/72; HR 1.20 (0.75–1.92), reported with supportive care as the reference category	Cox
Hou 2023 (MAIN) [26]	MMF + supportive care vs supportive care	Creatinine doubling, kidney failure, death from a kidney or cardiovascular cause	6/85 vs 18/85; aHR 0.23 (0.09–0.63)	Cox, adjusted
Lee 1997 [41]	Dipyridamole + low-dose warfarin vs no treatment	ESKD during a 3-year trial	1/10 vs 4/11	Event counts reported; no effect estimate presented
Lv 2009 [44]	Prednisone + cilazapril vs cilazapril	Kidney survival (≥50% rise in SCr)	1 versus 7 events; post-treatment-adjusted model is not used as the randomized effect	Cox, post-treatment covariate
Frisch 2005 [45]	MMF up to 1000 mg twice daily for 1 year vs identical placebo	≥50% rise in SCr, required to be sustained for ≥2 consecutive months (the trial's primary outcome)	5/17 vs 2/15	Event counts reported; crude HR 2.28 (0.44–11.8), P=0.28; adjusted HR 1.62 (0.07–35.6); achieved mean total follow-up 59 and 75 weeks
Frisch 2005 [45]	as above	ESRD	5/17 vs 2/15	Event counts reported; crude HR 2.47 (0.48–12.8), P=0.28
Tang 2005 [46]	MMF 1.5–2 g/day for 24 weeks added to ongoing treatment vs continuation of that treatment; not placebo-controlled	≥50% rise in SCr, no persistence requirement stated	1/20 vs 3/20	Event counts reported; no effect estimate presented; 72 weeks of follow-up
Donadio 1994 [47, 48]	Fish oil 12 g/day (1.9 g EPA and 1.4 g DHA) vs olive oil placebo	≥50% rise in SCr	17/55 vs 29/51	Event counts reported; no effect estimate presented (the OR in Figure 3 b is computed from these counts, for this outcome only).

Trial	Comparison	Outcome	Result	Effect measure and model
Donadio 1999 [47]	Fish oil 12 g/day (1.9 g EPA and 1.4 DHA) vs olive oil placebo	ESRD: repeated dialysis or transplantation	8/55 vs 19/51	Event counts reported; no effect estimate presented. Same 55 versus 51 participants, so the two outcomes count as one trial. Mean follow-up 6.4 years for both outcomes: the first 2 years were the randomized phase, followed by open-label care and treatment crossover.
Alexopoulos 2004 [49]	Very-low-dose omega-3 (0.85 g EPA and 0.57 g DHA) vs symptomatic care; no placebo, blinding not described	≥50% rise in SCr at 4 years; reported separately from ≥50% GFR decline	1/14 vs 6/14	Completer counts; 18 versus 16 assigned, 14 versus 14 analysed. OR in Figure 3 b is calculated from these counts; exclusions limit an assignment-effect interpretation.
Praga 2003 [50]	Enalapril vs antihypertensive therapy without ACE inhibitors or ARBs	Renal survival (≥50% rise in baseline SCr), the trial's primary outcome	3/23 vs 12/21; log-rank P<0.05; renal survival 100% vs 70% at 4 years and 92% vs 55% at 7 years	Event counts and Kaplan-Meier estimates reported; no hazard ratio presented
Liu 2014 [51]	Methylprednisolone + cyclosporine A vs methylprednisolone alone	≥25% fall in eGFR within 12 months (secondary kidney endpoint)	2/23 vs 0/25	Event counts reported; no effect estimate presented
Wheeler 2021 (DAPA-CKD) [30]	Dapagliflozin vs placebo	Composite of sustained ≥50% eGFR decline, end-stage kidney disease or death from a kidney or cardiovascular cause	6/137 vs 20/133; HR 0.29 (0.12–0.73)	Cox, pre-specified subgroup

Trial	Comparison	Outcome	Result	Effect measure and model
EMPA-KIDNEY 2024 [31]	Empagliflozin vs placebo	Composite of sustained ≥40% eGFR decline, end-stage kidney disease, sustained eGFR <10 mL/min/1.73 m² or death from kidney failure	51/413 vs 67/404; HR 0.67 (0.46–0.97)	Cox, post hoc classification
Rovin 2023 (PROTECT) [5]	Sparsentan vs irbesartan	Composite kidney failure endpoint (confirmed 40% eGFR reduction, ESKD or all-cause death)	18 (9%) vs 26; RR 0.7 (0.4–1.2)	Relative risk, as reported
Lafayette 2023 (NefIgArd) [6]	Targeted-release budesonide vs placebo	Confirmed 30% eGFR reduction or kidney failure	21 (12%) vs 39 (21%); HR 0.45 (0.26–0.75)	Cox
Barratt 2026 (APPLAUSE-IgAN) [8]	Iptacopan vs placebo	Composite kidney-failure endpoint (sustained ≥30% eGFR decline, sustained eGFR <15, dialysis, transplant, kidney-failure death)	21.4% vs 33.5%; HR 0.57 (0.40–0.81)	Cox, secondary endpoint
Heerspink 2026 (ALIGN) [9]	Atrasentan vs placebo	Composite kidney outcome (≥30% eGFR decline, kidney failure, all-cause death)	26/170 (15%) vs 37/170 (22%); HR 0.64 (0.39–1.05)	Cox, secondary endpoint (not significant)
Neuen 2026 (FIND-CKD) [10]	Finerenone vs placebo	Kidney failure or ≥40% eGFR decline (sustained ≥4 weeks)	52/226 (23.0%) vs 51/190 (26.8%); HR 0.82 (0.56–1.21)	Cox, pre-specified exploratory subgroup
Li 2020 [52]	A. manihot vs losartan	Creatinine doubling (the eligible component of the trial's composite)	6 vs 10 (P=0.451); 1 participant in the losartan arm required haemodialysis	No effect estimate reported for the component

Trial	Comparison	Outcome	Result	Effect measure and model
Masutani 2016 [53]	Steroid-pulse therapy plus mizoribine vs steroid-pulse therapy alone	Creatinine doubling or ≥50% eGFR decline	No participant reached the endpoint in either group	Event counts reported; no relative effect estimate presented
Lv 2009 [44]	Prednisone + cilazapril vs cilazapril	CKD stage 5 during follow-up	0 versus 2	33 versus 30 randomized; three lost overall. Distinct from the ≥50% SCr outcome; no borrowed HR.
Alexopoulos 2004 [49]	Very-low-dose omega-3 vs symptomatic care	Author-reported ESRD over 4 years	1/14 vs 6/14	Completer analysis of 18 versus 16 assigned; dialysis/SCr definition and exclusions described in Additional file 10.
Tang 2010 [54]	Original MMF vs control assignment	Creatinine doubling or ESRD over ≥6 years	3/20 vs 10/20	Same 40-patient Tang 2005 cohort, not a new trial. ESRD 2 vs 9; all patients alive; Methods composite also included death.
Pozzi 2010 [33]	Azathioprine + corticosteroids vs corticosteroids	Dialysis during follow-up	6/101 vs 4/106	Reported separately from the ≥50% SCr renal-survival endpoint; no borrowed HR; outcome-specific RoB 2: some concerns; not graded.
Pozzi 2013 [34]	Azathioprine + corticosteroids vs corticosteroids	Dialysis during follow-up	9/20 vs 10/26	Related protocol/reporting programme to Pozzi 2010; not assumed independent; outcome-specific RoB 2: some concerns; not graded.
Hou 2017 [39]	MMF + reduced-dose prednisone vs full-dose prednisone	ESRD by 12 months	0 versus 2	87 vs 89 randomized; 86 vs 88 efficacy set. ESRD analysis denominator not specified; counts only.

Trial	Comparison	Outcome	Result	Effect measure and model
Cruzado 2011 [40]	Sirolimus + enalapril/atorvastatin vs enalapril/atorvastatin	Dialysis at 1 year	0/14 vs 0/9	All alive and dialysis-free; no relative effect estimable. Measured GFR is not relabelled as eGFR.
Cheng 2015 [42]	Valsartan alone / plus clopidogrel / plus leflunomide / plus both	Haemodialysis during 24 months	4/42; 1/42; 0/42; 0/42	One four-arm trial; shared control not counted repeatedly. Retain haemodialysis label; maintenance status not specified.
Donadio 2001 [43]	High-dose vs low-dose omega-3 fatty acids	ESRD during follow-up	8/36 vs 10/37	Minimum 2 years of treatment; follow-up up to 5 years. Randomized dose comparison only; historical placebo excluded.

Each row retains its reported endpoint, analysis population and follow-up. Outcome-specific RoB 2 and GRADE coverage is mapped in Additional files 10 and 11; ungraded or unassessed results are identified there. Shared control arms and repeated endpoints are not independent comparisons. Results from the three reports of unresolved adult eligibility are retained separately in Additional file 3. Rows whose source reports counts or arm-level values only carry those values; no effect estimate or interval is reconstructed for them.

Footnote to Table 2: HR, hazard ratio; RR, relative risk; aHR, adjusted hazard ratio; CV, cardiovascular; ESKD, end-stage kidney disease; SCr, serum creatinine. Estimates are reported as published; they are not pooled and are not compared between trials. Rows within the same trial are not independent studies.

Long-term eGFR outcomes, reported by estimand

Table 3 lists the longitudinal eGFR results, and Figure 4 displays published between-group differences by estimand in panels (a) to (c) and, in panel (d), arm-level values from two trials that report no between-group contrast. Three definitional points govern their reading: whether the quantity is a fixed-time change or an annualized slope; whether a slope is total (from

randomization) or chronic (excluding the initial period, typically from week 6); and over what window.

Table 3. Longitudinal eGFR outcomes.

Trial	Quantity	Result	Notes
Barratt 2026 (APPLAUSE-IgAN) [8]	Total annualized eGFR slope over 24 months	−3.10 vs −6.12; difference 3.02 mL/min/1.73 m² per year (2.02 to 4.01), P<0.001	Primary endpoint
Heerspink 2026 (ALIGN) [9]	Total eGFR slope to week 136	Difference 1.4 mL/min/1.73 m² per year (0.5 to 2.3), nominal P=0.0033	Supportive analysis
Heerspink 2026 (ALIGN) [9]	Between-group difference in eGFR change to week 136	2.4 mL/min/1.73 m² (−0.1 to 4.8), P=0.057	Key secondary endpoint
Heerspink 2026 (ALIGN) [9]	Between-group difference in eGFR change to week 136	9.1 mL/min/1.73 m² (3.0 to 15.2)	Exploratory stratum; 64 participants
Rovin 2023 (PROTECT) [5]	Chronic eGFR slope, week 6 to 110	Difference 1.1 mL/min/1.73 m² per year (0.1 to 2.1), P=0.037	Key secondary endpoint
Rovin 2023 (PROTECT) [5]	Total eGFR slope, day 1 to week 110	Difference 1.0 mL/min/1.73 m² per year (−0.03 to 1.94), P=0.058	Supportive
Neuen 2026 (FIND-CKD) [10]	Total eGFR slope to month 32	0.61 mL/min/1.73 m² per year (−0.14 to 1.36)	Pre-specified exploratory; crosses zero
Neuen 2026 (FIND-CKD) [10]	Chronic eGFR slope	1.17 mL/min/1.73 m² per year (0.43 to 1.91)	Same trial and subgroup as above
Lafayette 2023 (NefIgArd) [6]	Time-weighted average of eGFR over 2 years	Difference 5.05 mL/min/1.73 m² (3.24 to 7.38), P<0.0001; change −2.47 vs −7.52	Regression model, full analysis set
Lv 2022 (TESTING) [3]	eGFR slope	Difference 2.46 mL/min/1.73 m² per year (0.94 to 3.99)	Secondary analysis

Trial	Quantity	Result	Notes
Hou 2023 (MAIN) [26]	Annual rate of eGFR decline over the 3-year trial phase	1.2 (0.6) vs 3.8 (0.6) mL/min/1.73 m² per year, P<0.001; no between-group interval reported	Trial-phase decline; linear mixed-effects model specified for treatment effect. No interval for this contrast; 2.6 is the arithmetic difference between published rates. RoB 2: some concerns; GRADE: low (allocation concern and unresolved precision around the review's annual-rate threshold). Post-trial values kept separate.
EMPA-KIDNEY 2024 [31]	Chronic eGFR slope	Relative difference −43% (−59 to −27)	Post hoc disease classification
O'Shaughnessy 2024 (ENVISION) [55]	Change in eGFR at month 12	LSM change −2.7, 0.2, −1.5 (2, 4, 8 mg) vs −7.4 mL/min/1.73 m² (placebo)	Secondary endpoint; the three dose arms share one placebo group
Floege 2025 (IGNAZ) [56]	Change in eGFR at month 24	Difference about 8.1 mL/min/1.73 m² (−3.5 to 19.7)	Secondary endpoint; 35 participants evaluable at 24 months; dose arms share one placebo group
Joo 2026 [57]	Annual eGFR decline over 12 months	−0.32 mL/min/1.73 m² (−2.54 to 1.99) vs −3.64 (−5.70 to −1.58), P=0.02	Double-blind placebo-controlled; primary outcome included eGFR change
Yang 2026 [58]	Between-group difference in eGFR change to month 12	3.30 mL/min/1.73 m² (0.50 to 6.10) for 12 mg; 5.22 (2.44 to 7.99) for 16 mg	Change, not slope; abstract-level
Hirai 2017 [59]	eGFR absolute change over 36 months	No significant between-group difference; baseline eGFR 67.5±30.4 vs 67.4±33.6 mL/min/1.73 m²	Secondary outcome; ~40% dropout
Yu 2017 [60]	eGFR over the 5-year follow-up after discontinuation	No significant between-group difference	Observational phase after a short treatment course
Barratt 2022 (JANUS) [61]	Renal function over 72 weeks	Reported as declining with placebo and stable with atacicept	eGFR values shown graphically only; not numerically extractable

Trial	Quantity	Result	Notes
Lafayette 2017 [62]	Change in eGFR over 1 year	Reported as unchanged in both groups	Co-primary outcome; no group values reported
Wheeler 2021 (DAPA-CKD) [30]	Total and chronic eGFR slope to end of treatment	Total: difference 1.2 mL/min/1.73 m² per year (−0.12 to 2.51); chronic: 2.4 (1.08 to 3.71)	Pre-specified subgroup; chronic window from week 2; total slope crosses zero
Cheng 2015 [42]	eGFR over 24 months, four treatment arms	Group trajectories shown in Figure 3 of the source; exact contrast and CI not supplied	Methods and Table 1 name different eGFR formulas; dialysis-related missing values unclear. Graphical result retained descriptively; no digitized estimate.
Li 2013 [63]	eGFR at 60 months	108.1±29.0 vs 105.7±17.7 mL/min/1.73 m² (P=0.7)	Arm-level means as reported; no between-group estimate reported
Li 2013 [63]	Rate of decline of eGFR over 60 months	−0.39±2.57 vs −0.59±1.63 mL/min/1.73 m² per year (P=0.7)	Arm-level rates as reported; no between-group estimate reported
Fellström 2017 (NEFIGAN) [64]	Mean percentage change from baseline in eGFR at 12 months	0.7% vs −10.9%; ratio 1.11 (1.01–1.225), P=0.0134	Percentage change as reported; absolute eGFR not reported in the material held

Total slope, chronic slope, fixed-time change and time-weighted average are reported separately. Appraisal coverage is mapped by outcome in Additional files 10 and 11; an appraisal of one outcome does not cover every result from that trial. Rows whose source reports arm-level values only carry those values; no between-group estimate is constructed for them. Panel (d) of Figure 4 displays such values for two trials; the other arm-level rows are tabulated only.

Footnote to Table 3: LSM, least-squares mean. A total slope and a chronic slope answer different questions and are not interchangeable; a fixed-time difference and a slope are different quantities. No between-trial comparison of these values was undertaken, because units, windows, slope definitions and populations differ.

Reading the endpoints of a single trial together

The principal comparisons illustrate how kidney-function and event endpoints jointly inform treatment interpretation. APPLAUSE-IgAN, ALIGN, FIND-CKD and NefIgArd show different patterns of effect and precision across these outcomes.

APPLAUSE-IgAN (iptacopan versus placebo). In the 477-participant trial, the primary annualized total eGFR slope over 24 months favoured iptacopan by 3.02 mL/min/1.73 m²/year (95% CI 2.02–4.01). The secondary composite of sustained ≥30% eGFR decline, sustained eGFR <15 mL/min/1.73 m², dialysis, transplantation or kidney-failure death occurred in 21.4% versus 33.5% (HR 0.57, 0.40–0.81). These findings support slower eGFR decline and fewer composite progression events over two years. The composite interval encompasses reductions smaller than the review's 25% interpretive threshold.

ALIGN (atrasentan versus placebo, main stratum). Over 136 weeks, the total eGFR slope favoured atrasentan by 1.4 mL/min/1.73 m²/year (95% CI 0.5–2.3) in a supportive analysis. The key secondary fixed-time eGFR difference was 2.4 mL/min/1.73 m² (−0.1 to 4.8), and the secondary composite of ≥30% eGFR decline, kidney failure or all-cause death occurred in 26/170 versus 37/170 participants (HR 0.64, 0.39–1.05). The remaining secondary endpoints were not formally tested. The exploratory SGLT2-inhibitor stratum (32 per arm) yielded a week-136 eGFR difference of 9.1 (3.0–15.2). The strongest support in the main stratum concerns the total slope; the fixed-time and event estimates remain imprecise.

FIND-CKD (finerenone versus placebo, IgA subgroup). In the prespecified exploratory subgroup (226 versus 190 participants), the month-32 total-slope difference was 0.61 mL/min/1.73 m²/year (95% CI −0.14 to 1.36) and the chronic-slope difference was 1.17 (0.43–1.91). Kidney failure or sustained ≥40% eGFR decline occurred in 52/226 versus 51/190 participants (HR 0.82, 0.56–1.21). The chronic slope supports slower decline after the initial treatment period, whereas the total-slope and progression-event estimates remain imprecise.

NefIgArd (targeted-release budesonide versus placebo). Over two years, the primary time-weighted average eGFR favoured budesonide by 5.05 mL/min/1.73 m² (95% CI 3.24–7.38). Confirmed 30% eGFR reduction or kidney failure occurred in 21/182 versus 39/182 participants

(HR 0.45, 0.26–0.75). The two-year kidney-function difference and lower composite-event risk were both supported by high-certainty evidence.

The SGLT2-inhibitor IgA subgroups also support kidney-function and event benefits. Dapagliflozin reduced its composite of sustained ≥50% eGFR decline, end-stage kidney disease or death from a kidney or cardiovascular cause (HR 0.29, 95% CI 0.12–0.73) and improved chronic slope by 2.4 mL/min/1.73 m²/year (1.08–3.71); its total-slope difference was less precise (1.2, −0.12 to 2.51). Empagliflozin reduced its composite of sustained ≥40% eGFR decline, end-stage kidney disease, sustained eGFR below 10 mL/min/1.73 m² or death from kidney failure (HR 0.67, 0.46–0.97) and the rate of chronic eGFR decline by 43%. These estimates apply to the reported IgA subgroups.

Clinical interpretation combines the trajectory and event findings within each trial, retaining the endpoint hierarchy, analysis population and follow-up window. This identifies whether the evidence supports slower kidney-function decline, fewer composite progression events, or both.

What the recent reports add to the existing evidence

Table 4 answers three questions for each report, in this order: what the previous syntheses had already covered, what result this review adds, and how that result strengthens or qualifies what was already there. The first column also records the relation between the two, because a later analysis of the same trial and a result from a different trial of the same drug are different additions.

Table 4. What the recent reports add, separated into three questions

Report and relation to what was already covered	Q1. What the previous syntheses covered	Q2. What this review adds	Q3. How the added result strengthens or qualifies that
Barratt 2026 (APPLAUSE-IgAN) [8]. Different trial, same drug	Phase 2 trial covered by Jeyabalan 2025, Chen B 2025, Chen R 2026, Kim 2025 and the Wu 2026 node; the 24-month report itself is in Li 2026	Total eGFR slope difference 3.02 mL/min/1.73 m² per year (2.02–4.01); secondary composite kidney-failure endpoint 21.4% versus 33.5%, HR 0.57 (0.40–0.81)	Adds completed phase 3 evidence on eGFR decline and a composite kidney outcome. The composite estimate supports a lower hazard, although its confidence interval includes reductions smaller than the review's 25% interpretive threshold; it does not isolate an effect on kidney failure alone.
Heerspink 2026 (ALIGN) [9]. Same trial, later report	Kim 2025 includes the week-36 proteinuria analysis; Jeyabalan 2025 lists it as ongoing with no results; Chen B 2025 and Chen R 2026 do not mention atrasentan; the Wu 2026 endothelin node draws on the PROTECT 2-year and ALIGN interim reports	eGFR change at week 136, 2.4 mL/min/1.73 m² (−0.1 to 4.8); total slope difference 1.4 (0.5–2.3); composite kidney endpoint 15% versus 22%, HR 0.64 (0.39–1.05)	Converts a trial known only through its proteinuria result into one with long-term eGFR and event data. The slope favours atrasentan while the fixed-time difference and the composite do not reach significance: a difference in quantity and precision, not a contradiction
Neuen 2026 (FIND-CKD) [10]. Not covered	Finerenone is absent from all six documents	Total slope difference 0.61 mL/min/1.73 m² per year (−0.14 to 1.36); chronic slope difference 1.17 (0.43–1.91); composite 52/226 (23.0%) versus 51/190 (26.8%), HR 0.82 (0.56–1.21)	Adds a non-immunosuppressive agent, with the IgA-specific estimates. The composite and the total slope cross their null while the chronic slope does not, so the direction is strengthened without the size being established

Report and relation to what was already covered	Q1. What the previous syntheses covered	Q2. What this review adds	Q3. How the added result strengthens or qualifies that
Wheeler 2021 (DAPA-CKD) [30]. Subgroup of a trial used by the previous syntheses for other purposes	Kim 2025 states that unpublished data were obtained; whether the IgA result was extracted cannot be determined, so coverage is uncertain. No other document reports the subgroup	Composite of sustained ≥50% eGFR decline, end-stage kidney disease or renal or cardiovascular death: 6/137 versus 20/133, HR 0.29 (0.12–0.73), median follow-up 2.1 years	Enters the graded set with an interval whose upper limit lies below this review's 25% interpretive anchor, so imprecision was not deducted. Limited to the subgroup; the number of events remains small
EMPA-KIDNEY 2024 [31]. Subgroup of a trial used by the previous syntheses for other purposes	Kim 2025 states that it included a prespecified secondary analysis; the IgA split is post hoc, and whether the IgA result was extracted cannot be determined — uncertain	Kidney disease progression 51/413 versus 67/404, HR 0.67 (0.46–0.97); chronic eGFR slope reduced by 43% (95% CI 27 to 59), median follow-up 2.0 years	Adds the largest event count among the graded subgroups, and is the one graded comparison whose IgA disease subgroup was defined post hoc; strengthens the evidence while limiting what its interval can establish
Joo 2026 [57]. Not covered	Absent from all six documents	Annual eGFR decline over 12 months: −0.32 mL/min/1.73 m² (−2.54 to 1.99) versus −3.64 (−5.70 to −1.58), P=0.02; no progression events reported	Adds a 12-month slope result with no progression events, so it bears on eGFR change only
Floege 2025 (IGNAZ) [56]. Not covered	Jeyabalan 2025 lists IGNAZ as ongoing with no results; the other five do not mention felzartamab	Change in eGFR at month 24, about 8.1 mL/min/1.73 m² in favour of felzartamab (−3.5 to 19.7); 35 participants evaluable at 24 months; no progression events	Adds month-24 data for a trial previously listed as ongoing. The interval includes no difference, so the direction is qualified rather than established
Yang 2026 [58]. Not covered	Absent from all six documents	Between-group difference in eGFR change at month 12: 3.30 (0.50–6.10) and 5.22 (2.44–7.99) mL/min/1.73 m²; no progression events; abstract-level	Abstract-level and ungraded; reported for completeness, not used in any conclusion

Report and relation to what was already covered	Q1. What the previous syntheses covered	Q2. What this review adds	Q3. How the added result strengthens or qualifies that
Hou 2023 (MAIN) [26]. Different trial, same drug	Other mycophenolate trials are covered by Jeyabalan 2025 and Chen B 2025, and Kim 2025 excluded mycophenolate trials for insufficient size and duration; whether MAIN's progression data were extracted cannot be determined — uncertain	Composite of creatinine doubling, end-stage kidney disease or death from a kidney or cardiovascular cause: 6/85 versus 18/85, adjusted HR 0.23 (0.09–0.63) Trial-phase annual eGFR decline was 1.2 versus 3.8 mL/min/1.73 m² per year (P<0.001).	Adds randomized progression-event and trial-phase kidney-function results for mycophenolate. Composite certainty is moderate; certainty for the annual eGFR result is low.
Rauen 2020 (STOP-IgAN) [27–29]. Same trial, later report	Included by Jeyabalan 2025 (five references) and by Kim 2025 (a post hoc analysis of the same trial)	Composite of all-cause death, end-stage kidney disease or >40% eGFR decline at a median of 7.4 years: 35 of 77 versus 36 of 72, HR 1.20 (0.75–1.92, supportive care as the reference category)	Extends a trial already covered from its 3-year randomized phase to a 10-year horizon. Long-term follow-up did not establish a kidney-outcome benefit; the interval remained compatible with benefit and harm
O'Shaughnessy 2024 (ENVISION) [55], Barratt 2022 (JANUS) [61], both phase 2. Same drug, different trial from the phase 3 programme	Both are covered; whether the specific quantity reported here was extracted depends on supplementary material not obtained — uncertain	Reported for completeness	The relation is to a programme already covered, and the extracted quantity cannot be shown to be new

Footnote to Table 4: the comparison syntheses were examined in full text (Jeyabalan 2025, Chen B 2025, Chen R 2026, Kim 2025, Wu et al. 2026, Li et al. 2026) and each was searched for the trials concerned; the document-by-document verification is in Additional file 14. Coverage describes the text, tables and stated scope of those documents, not the literature as a whole.

Risk of bias and certainty of the evidence

The principal modern trials used blinded randomized comparisons, but this alone does not settle every outcome-specific bias domain: TESTING reported trial completion for 493 of 503 participants, so premature treatment discontinuation cannot be equated with missing endpoint data, and ALIGN reported 154 of 170 and 142 of 170 participants completing the study and used

prespecified models for missing and intercurrent-event data. The assessment limits are in Additional file 10.

The 23 outcomes from the ten focused comparisons comprised four at low risk of bias and 19 at some concerns (Figure 5). Concerns principally involved incomplete outcome-availability or allocation reporting; the EMPA-KIDNEY IgA split was also post hoc. The 36 additional adult-eligible outcome assessments comprised one at low risk of bias, 31 at some concerns and four at high risk. Five candidate assessments from these entries are reported separately. Outcome coverage and the source record for each assessment are given in Additional file 10. The standalone TESTING kidney-failure component was assessed from its own report, and the composite and eGFR judgements were not transferred to it.

GRADE ratings for the 23 focused comparison–outcome results were three high, eight moderate and twelve low (Additional file 11). MAIN's composite was moderate certainty; its trial-phase eGFR result was low certainty because allocation methods were incompletely reported and uncertainty around the 1.0 mL/min/1.73 m²/year interpretive threshold could not be established from the reported model summary. The 0.6 printed beside those arm means is not a between-patient SD: at a mean of 3.8, an SD of 0.6 would leave about 2% of participants above a 5 mL/min/1.73 m²/year decline, against the 32.9% the trial reports, so the value describes the arm mean and no interval was reconstructed from it. DAPA-CKD certainty was moderate for the composite and chronic slope and low for total slope. Other results were not graded.

Safety of systemic glucocorticoid regimens

As defined in Methods, safety is summarized for one class only. Data for systemic glucocorticoid regimens are separated according to whether the comparator arm also received a glucocorticoid, and no pooled estimate was calculated, because definitions, observation periods and denominators were not standardized. In TESTING, the largest glucocorticoid trial with a placebo comparator, serious adverse events occurred in 28 (10.9%) versus 7 (2.8%) participants and serious infections in 17 versus 3; the excess was larger in the full-dose phase than in the reduced-dose phase, but because the phases also differed in antibiotic prophylaxis, enrolment period and follow-up, this difference is reported as observed and not attributed to dose alone. In STOP-IgAN, serious

adverse events occurred in 29 versus 21 participants and impaired glucose tolerance or diabetes in 9 versus 1. Most older trials reported safety only in narrative terms.

Discussion

Principal clinical findings

Recent trials extend the treatment evidence in primary IgA nephropathy from proteinuria reduction to long-term kidney-function trajectories and progression events. Iptacopan now has final results supporting both slower eGFR decline and fewer composite events. Atrasentan and finerenone add evidence on kidney-function trajectories, with greater uncertainty around their event endpoints. Targeted-release budesonide, methylprednisolone in TESTING and mycophenolate mofetil in MAIN, with lower certainty for its eGFR result, also showed benefits on kidney-function and composite-event outcomes, as did the reported SGLT2-inhibitor IgA subgroups. The 10-year STOP-IgAN follow-up found no established benefit of added immunosuppression on its composite outcome. Together, these results sharpen treatment-specific conclusions and show how endpoint choice and follow-up determine their clinical scope.

What the new long-term results change or qualify

For iptacopan, the 24-month APPLAUSE-IgAN analysis advances the evidence from interim proteinuria reduction to a total-slope benefit of 3.02 mL/min/1.73 m²/year and a lower risk of its secondary composite kidney outcome (HR 0.57). ALIGN provides a more qualified picture for atrasentan: total slope favoured treatment by 1.4 mL/min/1.73 m²/year, whereas the week-136 eGFR difference (2.4, 95% CI −0.1 to 4.8) and composite kidney outcome (HR 0.64, 0.39–1.05) remained imprecise. Thus, the two final reports strengthen evidence on long-term kidney function while supporting different levels of confidence in progression-event benefits.

Finerenone's IgA-subgroup findings distinguish the chronic treatment phase from the overall eGFR trajectory: the chronic-slope difference was 1.17 mL/min/1.73 m²/year, while the total-slope difference of 0.61 included zero. Initial haemodynamic effects may contribute to this distinction. NefIgArd provides complementary evidence from a sustained eGFR difference over two years and fewer confirmed 30% eGFR reductions or kidney-failure events. MAIN likewise combines slower

trial-phase eGFR decline with fewer composite events, extending the evidence for mycophenolate mofetil in its enrolled population. By contrast, STOP-IgAN's 10-year composite estimate (HR 1.20) leaves the value of additional immunosuppression unestablished in patients receiving optimized supportive care.

Earlier-stage programmes extend the evidence base for subsequent confirmation. Calcitriol showed a 12-month difference in eGFR decline (−0.32 versus −3.64 mL/min/1.73 m²), with no progression events. Sibeprenlimab and felzartamab yielded secondary eGFR results at 12 and 24 months, respectively, with multiple dose arms sharing a placebo group. HR19042 remains supported by a conference abstract with discrepant endpoint descriptions between the abstract and registration. These reports contribute emerging kidney-function evidence, while their designs and reporting maturity limit treatment-specific conclusions.

How endpoint definition and estimand shape interpretation

Endpoint definitions determine what a kidney benefit means. A composite containing an eGFR threshold captures progression earlier than kidney failure alone, and a proteinuria-containing composite includes a different clinical outcome. A composite whose death component is not restricted to kidney death: kidney or cardiovascular death in MAIN and DAPA-CKD, all-cause death in ALIGN and PROTECT, all-cause death in STOP-IgAN, includes non-kidney events and is not a kidney-specific effect. Total slopes include the initial treatment period; chronic slopes describe the subsequent trajectory; time-weighted averages and fixed-time changes quantify eGFR over their stated windows. These distinctions explain why treatment estimates can differ within one trial. The surrogate validation of slope [11] supports its use as an endpoint, while trial-specific event data remain necessary to quantify kidney-failure risk.

What this review adds to the previous syntheses

This review brings final long-term analyses and eligible older trials into a common clinical framework: what each treatment changes in kidney function, and what its progression-event data support. Organizing the evidence by outcome and estimand makes the additional long-term information visible and preserves differences in clinical meaning and precision.

Previous syntheses provide complementary perspectives. A narrative review of 76 randomized trials in 100 reports, searched to December 2023, organized proteinuria, eGFR, kidney failure and safety findings by treatment category [15]. A meta-analysis of 14 multicentre phase 2b/3 trials, searched to 21 May 2025, focused on proteinuria and eGFR slope [12], while network meta-analyses compared remission, proteinuria, kidney damage or failure and adverse events [13, 14]. The present review adds the interpretation of specific long-term kidney outcomes now available across these treatment categories.

More recent comparisons include a 37-trial network meta-analysis searched to 15 November 2024, whose endothelin-receptor-antagonist evidence used the PROTECT two-year and ALIGN interim reports and whose iptacopan evidence used the phase 2 trial [17]. A Bayesian network meta-analysis compared immunosuppressants and targeted agents across 17 trials [14]. A complement-targeted review searched to June 2026 incorporated the APPLAUSE-IgAN 24-month results [18], and a preprint searched to 24 June 2026 estimated antiproteinuric effects by mechanism [16]. These differences in scope and timing establish the context for the specific long-term additions mapped in Additional file 14.

Full-text verification of the comparison syntheses identified four additions absent from the documents examined: the ALIGN 2.5-year final analysis, the FIND-CKD IgA subgroup, the calcitriol trial and felzartamab's 24-month data. APPLAUSE-IgAN's 24-month analysis was already covered by the later complement-targeted review. The added contribution therefore lies in these newly available outcomes and their integrated clinical interpretation, including additional follow-up from previously represented trials.

Clinical implications

Clinical decisions can now draw on treatment-specific long-term evidence beyond proteinuria. The strongest interpretation matches each result to its endpoint, observation window, population and certainty: a two-year slope describes a treatment-period trajectory, an IgA-subgroup composite estimates progression within that subgroup, and extended follow-up addresses durability after the randomized phase. Baseline kidney function, proteinuria and background

therapy remain essential to applicability. Direct comparative trials are needed to establish treatment rankings and the incremental value of combinations.

Limitations

Interpretation is limited by source availability and uneven outcome reporting. Blisibimod and HR19042 were reported from abstracts, and three reports could not be retrieved. Potential overlap between two entries [24, 25] remains unresolved; they were retained separately without summing participants, while a confirmed duplicate was counted once. Some kidney-failure counts have unresolved denominators, one ESKD result [65] was recorded descriptively, and several older reports provide event curves or graphical eGFR results without extractable numerical data. GRADE covered ten principal comparisons, and RoB 2 additionally covered 36 adult-eligible results. Incomplete documentation of outcome availability lowered confidence in several long-term estimates. Adult eligibility could not be established for three reports at completion of this review. These five outcomes were not included in the primary adult synthesis or used to formulate its conclusions. The original-standard restricted synthesis is reported in Additional file 3. Safety coverage was limited to systemic glucocorticoids, and missing-result bias was not formally assessed.

Conclusions

Long-term randomized evidence strengthens treatment-specific conclusions on kidney protection in primary IgA nephropathy. Iptacopan's final results support slower eGFR decline and fewer composite progression events, while atrasentan and finerenone provide clearer evidence on kidney-function trajectories than on event reduction. Established and newer therapies should be interpreted through their specific endpoints, populations, follow-up and certainty. Future trials should report progression events alongside clearly defined eGFR measures and standardized safety outcomes to clarify durable benefit and inform treatment selection.

List of abbreviations

APRIL: a proliferation-inducing ligand; BAFF: B-cell activating factor; CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate;

ERA: endothelin receptor antagonist; ESKD: end-stage kidney disease; HR: hazard ratio; IgA: immunoglobulin A; IgAN: IgA nephropathy; LSM: least-squares mean; MMF: mycophenolate mofetil; MRA: mineralocorticoid receptor antagonist; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RAS: renin–angiotensin system; RCT: randomized controlled trial; RoB 2: Risk of Bias 2; RR: relative risk; SCr: serum creatinine; SGLT2: sodium–glucose cotransporter 2; SWiM: Synthesis Without Meta-analysis; UPCR: urine protein-to-creatinine ratio.

Declarations

Ethics approval and consent to participate. Not applicable; only published, aggregate data from randomized trials were analysed.

Consent for publication. Not applicable.

Availability of data and materials. The search strings, screening ledger and adjudication, outcome extraction table, risk-of-bias and GRADE assessments, verification against previous syntheses, exploratory analysis, safety tables and machine-readable data files are provided as additional files (Additional files 1–14). No new primary data were generated.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. Ting Li: conceptualization, methodology, investigation (study screening and data extraction), and writing – original draft. Min Tong: investigation (independent study screening and data extraction) and validation of the results. Xue Liu: investigation (evidence appraisal), data curation, validation of figures and tables, and writing – review and editing. Jian Zheng: supervision, methodology, funding acquisition, and writing – review and editing.

Acknowledgements. Not applicable.

Additional files

Additional file 1 (Additional_file_1_prisma_2020_checklist.pdf). PRISMA 2020 checklist, completed against this manuscript, with the location of each item and procedures not performed marked as not done.

Additional file 2 (Additional_file_2_swim_checklist.pdf). SWiM checklist, completed item by item.

Additional file 3 (Additional_file_3_eligibility_robustness_and_diagnostic_basis.zip). Entry-level original-standard decisions, actual restricted outcome tables and figure, diagnostic and age evidence, and the source review of previous exclusions. The archive contains the PDF document and six machine-readable CSV files; their roles are listed in the contents file inside the archive.

Additional file 4 (Additional_file_4_exploratory_synthesis.pdf). Exploratory synthesis: mycophenolate mofetil versus no mycophenolate, ≥50% rise in serum creatinine. The post hoc synthesis of the two older mycophenolate trials, with fixed-effect, DerSimonian–Laird and Hartung–Knapp–Sidik–Jonkman intervals, the study odds ratios, heterogeneity and a leave-one-out check; not used in the clinical synthesis.

Additional file 5 (Additional_file_5_safety_tables.pdf). Safety tables for systemic glucocorticoid regimens. Tables 5 A and 5 B in full: regimens where only the intervention arm received a glucocorticoid, and trials where both arms did.

Additional file 6 (Additional_file_6_search_strings.pdf). Search strings and search dates. The four verbatim database search strings, the date each search was executed (23 September 2026), and the re-execution of the PubMed string on 30 September 2026.

Additional file 7 (Additional_file_7_screening_ledger.pdf). Screening ledger: reader's guide and record-level counts. The structure of the ledger, the de-duplication rule, the nine record-level categories with counts, and the review state of each record; the machine-readable ledger is Additional file 13.

Additional file 8 (Additional_file_8_registry_link_check.pdf). Re-checking of records recorded as resolved to a trial ID, against registry fields.

Additional file 9 (Additional_file_9_record_adjudication.pdf). Record-level adjudication, and the three reports that could not be retrieved: the adjudication of records previously held only as rule output, and the disposition of the three candidate reports whose eligibility was not assessed, with the retrieval attempts.

Additional file 10 (Additional_file_10_risk_of_bias.pdf). Outcome-specific RoB 2 assessments, source-supported additions and a coverage map identifying unassessed results and results of unresolved adult eligibility.

Additional file 11 (Additional_file_11_grade.pdf). Certainty of the evidence (GRADE). Certainty by comparison and outcome, with a per-row downgrade ledger and the basis of each judgement; the remaining estimates are listed with their specific limitations instead of a grade.

Additional file 12 (Additional_file_12_no_pooling_reasons.pdf). Pooling decisions for each candidate combination of eligible results: whether it was carried into a pooled estimate or reported side by side, whether a single treatment question is shared, and how differences in dose, follow-up, control condition, endpoint composition and estimand bear on a common effect. The two mycophenolate trials and the two fish-oil trials are examined item by item.

Additional file 13 (Additional_file_13_data.xlsx). Machine-readable screening, eligibility and outcome datasets: the 2577-record ledger; decisions for 92 entries; original-standard checks for 54 candidates; primary adult and unresolved-eligibility outcome sets; restricted results; and result-level appraisal and GRADE linkage. Counting units and verification status are retained separately.

Additional file 14 (Additional_file_14_comparison_reviews.pdf). Verification against previous syntheses, document by document. What each comparison synthesis covers, separating the formal final report from the trial, with the search cut-off date of each document.

Figure legends

Figure 1. Adapted PRISMA flow of records and trial entries. Of 2577 unique records, 335 were available for linkage and adjudication; these are not 335 full-text reports. The full-text set contains 100 unique documents. Three reports were not retrieved and are outside the 92 adjudicated entries. These comprise 51 included, three with adult eligibility unresolved, 36 excluded, one associated report and one duplicate entry. Dashed connectors indicate report linkage and a change of counting unit. Entries may represent linked reports; participants were not summed across them (Additional files 7 and 13).

Figure 2. Kidney-progression outcomes: published relative effects. Relative effects are hazard ratios except PROTECT (relative risk) and Frisch 2005 (crude hazard ratio). These are the Table 2

entries for which the source reported an effect estimate; rows carrying counts or arm-level values only are shown in Figure 3, and no estimate is constructed for them. No pooled estimate or cross-trial comparison is implied. Additional file 3 provides the original-standard display of 26 results after removing ≥50% serum-creatinine endpoints. Results of unresolved adult eligibility are listed separately.

Figure 3. Kidney-progression outcomes: additional outcome rows and calculated odds ratios. (a) Additional primary adult outcome rows, retaining their reported event definitions and denominators. (b) Odds ratios calculated from the two fish-oil counts already included in (a); these are repeated displays, not additional outcomes. Panel (a) of Figure 2 and panel (a) of this figure together represent 32 distinct Table 2 results. No pooled estimate or cross-trial comparison is implied. Alexopoulos counts are from 28 completers among 34 assigned participants.

Figure 4. Long-term eGFR results by estimand. (a) Annualized total slope differences, including the initial treatment period. (b) Annualized chronic slope differences, after that period. (c) Non-slope eGFR differences, with time-weighted averages and fixed-time changes labelled separately. (d) Arm-level eGFR values reported without a between-group estimate. Positive between-group differences favour the experimental treatment; arm-level values in panel (d) are not treatment contrasts, and panels (c) and (d) are not directly comparable with the annualized slopes in panels (a) and (b). No pooled estimate was calculated. In ENVISION the dose arms share one placebo group.

Figure 5. RoB 2 across the ten focused comparisons. (a) Five domain judgements for each of 23 outcome-specific assessments. (b) Summary: four low risk, 19 some concerns, none high risk. Additional file 10 separately tabulates 36 further adult-eligible outcome assessments and five candidate assessments from the three unresolved-eligibility entries. The figure reports risk of bias, not GRADE certainty.

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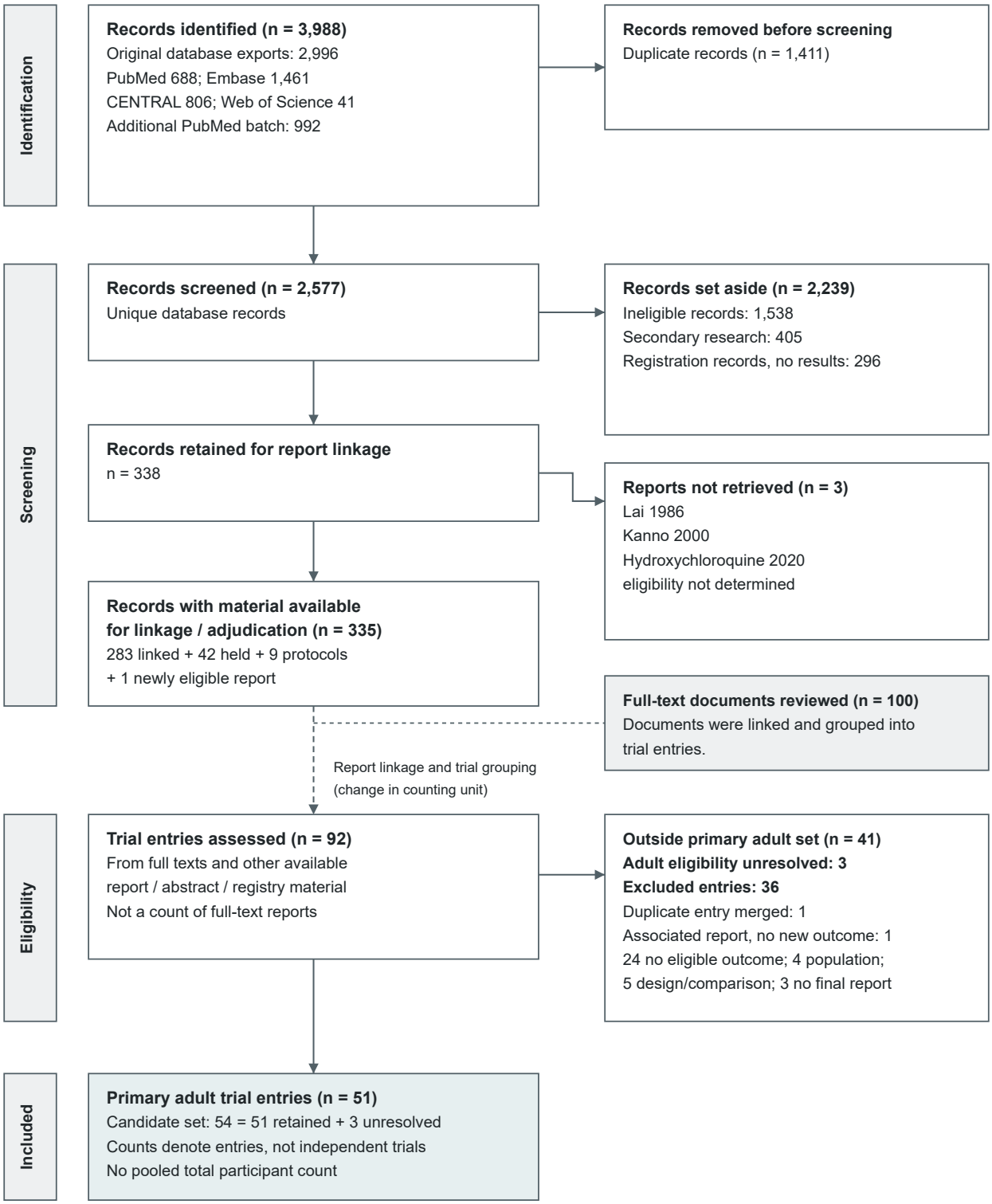
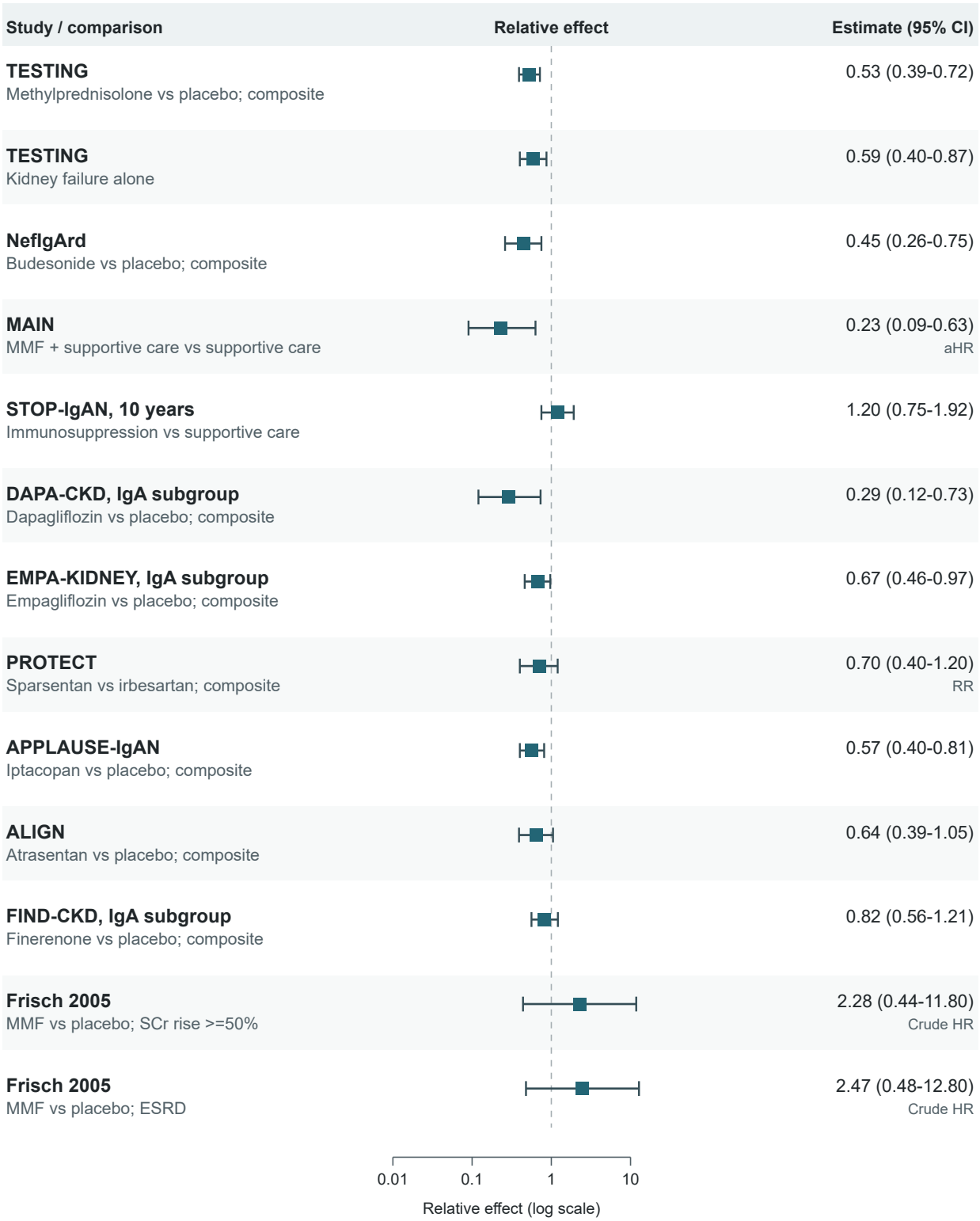


Adapted PRISMA layout; records, documents and trial entries are separate units.

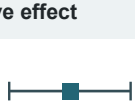
A **Reported relative effect estimates**



A Additional kidney-progression and kidney-failure results

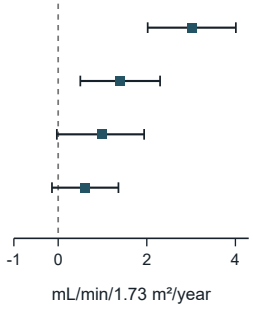
Study	Outcome	Treatment / arm order	Reported result
Lee 1997	ESKD at 3 years	Dipyridamole + low-dose warfarin vs no treatment	1/10 vs 4/11
Lv 2009	SCr rise >=50%	Prednisone + cilazapril vs cilazapril	1 vs 7
Tang 2005	SCr rise >=50%	MMF + ongoing treatment vs ongoing treatment	1/20 vs 3/20
Mayo / Dobos 1994	SCr rise >=50%	Fish oil vs original placebo group	17/55 vs 29/51
Alexopoulos 2004	SCr rise >=50%	Very-low-dose omega-3 vs control	1/14 vs 6/14
Praga 2003	SCr rise >=50%	Enalapril vs non-ACE-inhibitor therapy	3/23 vs 12/21
Liu 2014	eGFR fall >=25%	MP + CsA vs methylprednisolone	2/23 vs 0/25
A. manihot trial	Creatinine doubling	A. manihot vs losartan	6 vs 10
Mizoribine trial	Creatinine doubling / >=50% eGFR decline	Steroid pulse + mizoribine vs steroid pulse alone	0 vs 0; n = 40
Lv 2009	CKD stage 5	Prednisone + cilazapril vs cilazapril	0 vs 2; assigned 33/30
Alexopoulos 2004	ESRD	Very-low-dose omega-3 vs control	1/14 vs 6/14
Mayo / Donadio 1999	ESRD	Fish oil vs original placebo group	8/55 vs 19/51
Tang 2010 follow-up	Creatinine doubling / ESRD over >=6 years	Original MMF vs control assignment	3/20 vs 10/20
Pozzi 2010	Dialysis	Azathioprine + steroids vs steroids	6/101 vs 4/106
Pozzi 2013	Dialysis	Azathioprine + steroids vs steroids	9/20 vs 10/26
Hou 2017	ESRD	MMF + reduced-dose prednisone vs full-dose prednisone	0 vs 2*
Cruzado 2011	Dialysis	Sirolimus + ACE inhibitor + statin vs ACE inhibitor + statin	0/14 vs 0/9
Cheng 2015	Haemodialysis	Control / clopidogrel / leflunomide / both (all groups received valsartan)	4/42; 1/42; 0/42; 0/42
Donadio 2001	ESRD	High-dose vs low-dose omega-3	8/36 vs 10/37

B Calculated odds ratios for two SCr-rise outcomes already listed in panel A

Study / comparison	Relative effect	Estimate (95% CI)
Mayo / Dobos 1994 Fish oil vs original placebo assignment		0.34 (0.15-0.75) OR
Alexopoulos 2004 Very-low-dose omega-3 vs control		0.10 (0.01-1.02) OR

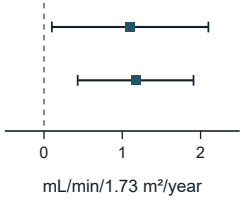
A

Study / comparison	Estimate (95% CI)
APPLAUSE-IgAN Total slope to month 24	3.02 (2.02–4.01)
ALIGN Total slope to week 136	1.40 (0.50–2.30)
PROTECT Total slope: day 1 to week 110	1.00 (-0.03–1.94)
FIND-CKD, IgA subgroup Total slope to month 32	0.61 (-0.14–1.36)



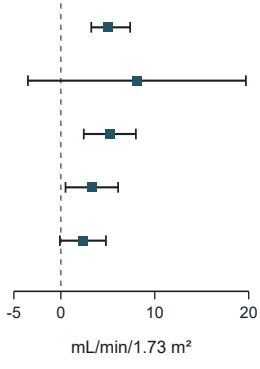
B

Study / comparison	Estimate (95% CI)
PROTECT Chronic slope: weeks 6–110	1.10 (0.10–2.10)
FIND-CKD, IgA subgroup Chronic slope	1.17 (0.43–1.91)



C

Study / comparison	Estimate (95% CI)
NeflgArd Time-weighted average over 2 years	5.05 (3.24–7.38)
IGNAZ Change to month 24	8.10 (-3.50–19.70)
HR19042, 16 mg Change to month 12; abstract-level	5.22 (2.44–7.99)
HR19042, 12 mg Change to month 12; abstract-level	3.30 (0.50–6.10)
ALIGN Change to week 136	2.40 (-0.10–4.80)



D

ENVISION: change at month 12

mL/min/1.73 m²

Sibeprenlimab 2 mg/kg	-2.7
Sibeprenlimab 4 mg/kg	0.2
Sibeprenlimab 8 mg/kg	-1.5
Placebo	-7.4

Calcitriol: annual change over 12 months

mL/min/1.73 m²/year

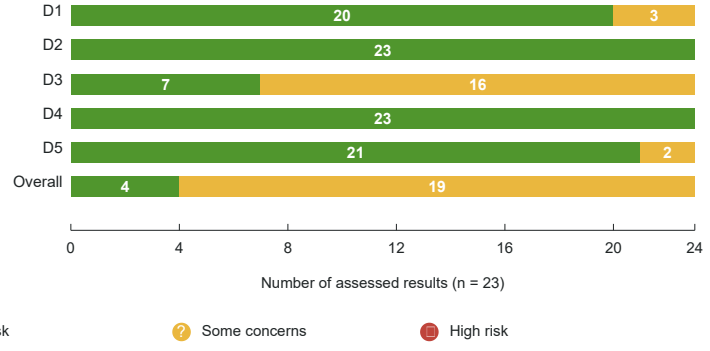
Calcitriol 0.25 microgram/day	-0.32
Placebo	-3.64

Arm-level values in panel D are not between-group effects; no confidence intervals are shown.

A **Study / outcome**

Study / outcome	D1 Randomisation process	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Outcome measurement	D5 Selection of the reported result	Overall
APPLAUSE-IgAN						
24-month annuali□ ed total slope	+	+	?	+	+	?
Composite kidney-failure endpoint	+	+	?	+	+	?
ALIGN						
Week-136 eGFR change	+	+	?	+	+	?
Total slope to week 136	+	+	?	+	+	?
Composite kidney outcome	+	+	?	+	+	?
FIND-CKD (IgA subgroup)						
Chronic slope	+	+	?	+	+	?
Total slope	+	+	?	+	+	?
Composite kidney outcome	+	+	?	+	+	?
NefIgArd						
2-year time-weighted average eGFR	+	+	+	+	+	+
Composite kidney outcome	+	+	+	+	+	+
PROTECT						
Chronic slope (weeks 6-110)	+	+	?	+	+	?
Total slope (day 1 to week 110)	+	+	?	+	+	?
Composite kidney endpoint	+	+	?	+	+	?
TESTING						
Composite kidney outcome	+	+	+	+	+	+
eGFR slope	+	+	+	+	+	+
MAIN						
Composite: creatinine doubling, KRT or death	?	+	+	+	+	?
Trial-phase annual rate of eGFR decline	?	+	+	+	+	?
STOP-IgAN (10-year follow-up)						
Composite: death, ESKD or >40% eGFR loss	?	+	+	+	+	?
DAPA-CKD (IgA subgroup)						
Composite: □ 50% eGFR loss, ESKD or death	+	+	?	+	+	?
Total eGFR slope to end of treatment	+	+	?	+	+	?
Chronic eGFR slope from week 2	+	+	?	+	+	?
EMPA-KIDNEY (IgA subgroup)						
Kidney disease progression	+	+	?	+	?	?
Chronic eGFR slope (relative)	+	+	?	+	?	?

B **Summary of assessed results**



Ten comparisons; 23 outcome-specific assessments. Results are not independent trials.

Unassessed entries are omitted. Assessment scope and domain definitions are in the figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile10riskofbias.pdf
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