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SYSTEMATIC REVIEW & META-ANALYSIS

Calcineurin Inhibitor–Based versus Cyclophosphamide-Based Immunosuppression for Primary Membranous Nephropathy: A Meta-Analysis of Remission and Relapse

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ABSTRACT

Background: Primary membranous nephropathy (MN) is a leading cause of the nephrotic syndrome in adults. Calcineurin inhibitor (CNI)-based and cyclophosphamide-based regimens are both endorsed as first-line therapy, but their comparative efficacy and the durability of the remission they induce remain uncertain.

Objective: To compare CNI-based versus cyclophosphamide-based regimens for total remission, complete remission and relapse in adults with primary MN.

Methods: PubMed/MEDLINE, with Scopus and Web of Science indexing checks and manual reference screening, was searched for randomised controlled trials comparing a CNI-based regimen (tacrolimus or cyclosporine) with a cyclophosphamide-based regimen. Risk ratios (RRs) were pooled with a DerSimonian–Laird random-effects model; heterogeneity was quantified with I^2; risk of bias used the Cochrane RoB 2 tool.

Results: Nine RCTs (eleven articles; 599 participants) were included. Total remission did not differ between strategies (RR 1.02, 95% CI 0.86–1.20; I^2=67%; 95% prediction interval 0.61–1.72). Complete remission did not differ (RR 0.84, 95% CI 0.34–2.04). Relapse tended to be more frequent after CNI-based therapy (RR 1.76, 95% CI 0.95–3.24; I^2=0%) without reaching significance. Estimates were stable across all sensitivity analyses, and no small-study effect was detected (Egger p=0.87).

Conclusion: CNI-based and cyclophosphamide-based regimens produced comparable remission in primary MN; a non-significant signal towards more frequent relapse after CNI therapy supports individualised, durability- and toxicity-aware treatment selection.

1. Introduction

Primary (idiopathic) membranous nephropathy is among the most common causes of the nephrotic syndrome in non-diabetic adults. It is an organ-specific autoimmune disease in which subepithelial immune-complex deposition along the glomerular basement membrane provokes proteinuria; in approximately seven of ten patients the responsible autoantibody targets the M-type phospholipase A2 receptor (PLA_2R); the antibody is termed anti-PLA_2R[1]. Its incidence appears to be rising in some regions, an increase linked in part to environmental exposures, which underscores the continuing clinical importance of optimising therapy[2].

The natural history is notably heterogeneous, with roughly a third of patients undergoing spontaneous remission, a third maintaining persistent proteinuria, and a third progressing towards kidney failure over a decade[3]. This heterogeneity underlies a longstanding therapeutic dilemma: whom to treat, when, and with which agent. For patients judged to be at moderate or high risk of progression—on the basis of persistent nephrotic-range proteinuria, declining kidney function or high antibody titres—immunosuppression is indicated, and current international guidance lists both cyclophosphamide-based and calcineurin inhibitor (CNI)-based regimens as acceptable first-line options without firmly ranking them[4]. Because spontaneous remission is common, the decision to commit a patient to prolonged immunosuppression is consequential, and the comparative merits of the two principal regimens bear directly on the balance between benefit and harm[5].

Risk stratification has become central to this decision. The advent of the anti-PLA_2R antibody as a non-invasive marker of disease activity, alongside the degree and persistence of proteinuria and the trajectory of kidney function, now allows clinicians to identify the patients most likely to progress and therefore most likely to benefit from immunosuppression, while sparing those with a high probability of spontaneous remission[1]. Against this background, the question is rarely whether to use a calcineurin inhibitor or an alkylating agent in isolation, but which of the two established strategies offers the better balance of remission, durability and safety for a given patient—precisely the comparison this synthesis was designed to inform[4].

Cyclophosphamide-based regimens, given as alternating monthly cycles with corticosteroids (the Ponticelli and modified-Ponticelli regimens), have the longest and most robust evidence for inducing durable remission and protecting kidney function, but they carry dose-dependent risks of infection, marrow suppression, gonadal toxicity and malignancy[5]. Calcineurin inhibitors—tacrolimus and cyclosporine—act through both immunological and direct, reversible podocyte-stabilising mechanisms and offer a corticosteroid- and alkylator-sparing alternative; however, their effect is widely held to depend on continued exposure, with proteinuria prone to recur after the drug is tapered or withdrawn[6].

The evidence underpinning the current equipoise is nonetheless fragmented. Most constituent trials were individually small and open-label; the regimens grouped under the CNI label range from monotherapy to corticosteroid combination and to sequential or multitarget protocols incorporating rituximab or mycophenolate mofetil; and several influential trials, including a sequential tacrolimus–rituximab comparison[7] and a cyclosporine-based multitarget comparison[8], were reported only in the last few years and were absent from older syntheses. In parallel, B-

cell–depleting therapy has emerged as a potentially more durable, relapse-sparing alternative[9,10], changing the therapeutic context in which the two classic regimens are now used.

The novelty of this study lies in its focused and contemporary synthesis of randomised evidence comparing CNI-based with cyclophosphamide-based immunosuppression specifically in primary membranous nephropathy, incorporating trials reported in the last few years and jointly analysing remission together with relapse rather than remission alone. The aim of this study was to quantify and compare the effect of CNI-based versus cyclophosphamide-based regimens on total remission, complete remission and relapse in adults with primary membranous nephropathy, and to characterise the robustness and consistency of these effects through pre-specified sensitivity and subgroup analyses.

2. Methods

2.1 Design, protocol and reporting

This study was conducted and reported as a systematic review with meta-analysis of randomised controlled trials, in accordance with the principles of the PRISMA 2020 statement. The eligibility criteria, the primary and secondary outcomes, and the analysis plan—including the random-effects model, the prediction interval, the subgroup analyses and the four pre-specified sensitivity analyses—were defined before quantitative synthesis. Subgroup analyses were designated exploratory. The review was not registered in a prospective register.

2.2 Information sources and search strategy

PubMed/MEDLINE was searched as the primary information source, and the indexing of each retrieved trial was cross-checked in Scopus and Web of Science. The reference lists of eligible trials, narrative reviews and previous meta-analyses were screened manually. Reliance on a single primary database is acknowledged as a constraint and discussed in the limitations. The Boolean search string combined disease and intervention concepts:

("membranous nephropathy" OR "membranous glomerulonephritis" OR "idiopathic membranous nephropathy") AND (tacrolimus OR cyclosporine OR "calcineurin inhibitor") AND (cyclophosphamide OR "alkylating agent" OR Ponticelli) AND (random *OR "controlled trial").*

2.3 Eligibility criteria

Studies were eligible if they were randomised controlled trials enrolling adults with biopsy-proven primary membranous nephropathy; compared a CNI-based regimen (tacrolimus or cyclosporine, with or without corticosteroids or additional agents) against a cyclophosphamide-based regimen; and reported remission or relapse. Reviews, meta-analyses, network meta-analyses, protocols, single-arm studies, and trials of secondary or lupus-associated membranous nephropathy were excluded. Where one trial cohort was reported in several publications, the cohort was counted once for pooling, as detailed in Section 3.9.

2.4 Data extraction and quality assurance

For each trial the following were extracted: first author, year, country, CNI agent and regimen, comparator regimen, follow-up duration, number randomised per arm, and event counts for total remission, complete remission and relapse, together with available safety data and, where reported, baseline proteinuria, serum albumin, kidney function and anti-PLA_2R status. Data were verified against the source records. Where an abstract reported remission only as a group percentage, the event count was reconstructed from that percentage and the randomised arm size and was flagged as back-calculated; robustness to these reconstructions was tested in a pre-specified sensitivity analysis restricted to trials with directly reported counts.

2.5 Risk-of-bias assessment

Risk of bias was appraised with the Cochrane Risk-of-Bias 2 (RoB 2) tool across five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Because remission is defined on objective laboratory thresholds, the outcome-measurement domain was generally judged at low risk even in open-label trials; the absence of blinding contributed to some concerns in the deviations domain.

2.6 Statistical analysis

The primary effect measure for the dichotomous outcomes was the risk ratio (RR) with 95% confidence interval (CI), expressing the risk of the event with CNI-based therapy relative to cyclophosphamide-based therapy. A random-effects model with the DerSimonian–Laird estimator of between-study variance (τ^2) was used throughout, and a 95% prediction interval was computed for the primary outcome. Heterogeneity was quantified with I^2 and the Cochran Q test, with values near 25%, 50% and 75% regarded as low, moderate and substantial. A continuity correction of 0.5 was applied to any zero cell. For the continuous proteinuria outcome the planned measure was the standardised mean difference (Hedges' g); however, dispersion statistics were too inconsistently reported to permit valid pooling, so this outcome was summarised narratively.

Robustness was examined through four pre-specified sensitivity analyses: leave-one-out omission of each trial in turn; restriction to trials with directly reported event counts; exclusion of the atypical sequential and multitarget regimens; and exclusion of the trial rated at high risk of bias. Exploratory subgroup analyses examined CNI type, regimen structure and follow-up duration (≤6 versus ≥12 months). Small-study effects were assessed by funnel-plot inspection and Egger's regression test, interpreted with caution because fewer than ten trials contributed. Analyses were performed in R and Python; two-sided $p<0.05$ denoted significance.

3. Results

3.1 Study selection

The database search and manual screening yielded nine randomised controlled trials meeting all eligibility criteria. These nine trials were reported across eleven articles, because one trial cohort—from the Postgraduate Institute of Medical Education and Research, Chandigarh—was described in three sequential publications reporting 12-month, 24-month and 6-year outcomes[11–13]. The flow of identification, screening, eligibility and inclusion is shown in Figure 1.

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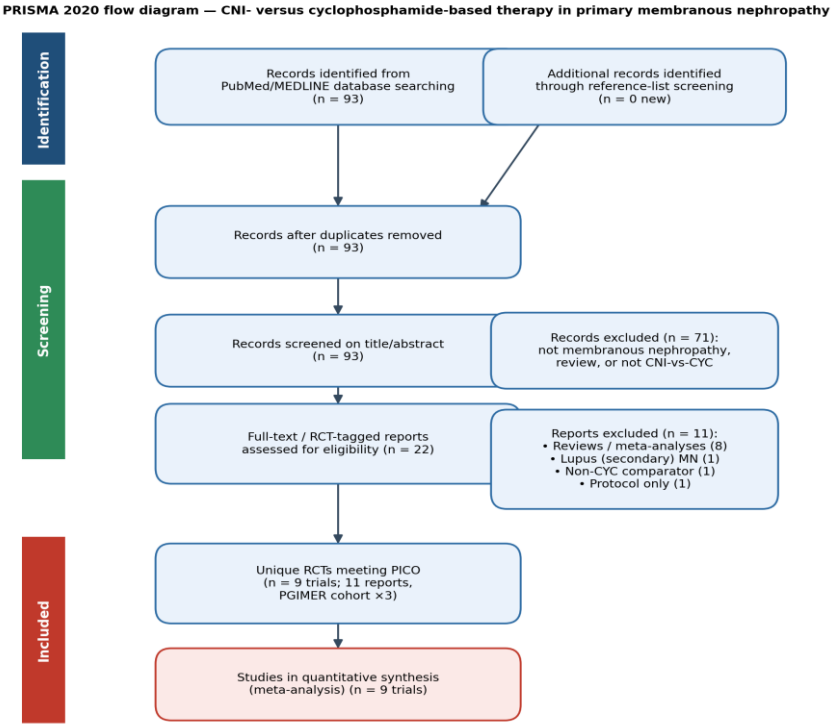

Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility and inclusion.

3.2 Characteristics of included studies

The nine trials enrolled 599 participants and were conducted in China, India, a multinational European setting and Greece between 2010 and 2023[7,8,11,14–19]. Seven trials used tacrolimus as the CNI and two used cyclosporine; the comparator was a cyclical or modified-Ponticelli cyclophosphamide–corticosteroid regimen in every trial. Follow-up for the primary report ranged from 2 to 24 months, with extended follow-up to 6 years available for one cohort. The study-level characteristics are summarised in Table 1, and the remission and relapse definitions and assessment timepoints of each trial are detailed in Table 2.

Table 1. Characteristics of the nine included randomised controlled trials.

Study (year)	Country	CNI arm (n)	Cyclophosphamide arm (n)	Follow-up	Total remission, CNI vs CYC
Fernández-Juárez 2021 (STARMEN)	Spain/EU	Tacrolimus→rituximab (43)	Cyclical CS–CYC (43)	24 mo	25/43 vs 36/43
Chen 2010	China	Tacrolimus + steroid (39)	CYC + steroid (34)	6–12 mo	33/39 vs 22/34*
Xu 2013	China	Tacrolimus + steroid (43)	CYC + steroid (57)	≥18 mo	28/43 vs 25/57*
Ramachandran 2016/17/21 (PGIMER)	India	Tacrolimus + steroid (35)	Modified-Ponticelli CYC (35)	12 mo–6 yr	25/35 vs 27/35*
He 2013	China	Low-dose tacrolimus + steroid (28)	IV CYC + steroid (28)	12 mo	25/28 vs 18/28
Liang 2017	China	Tacrolimus monotherapy (30)	CYC + steroid (28)	~12 mo	24/30 vs 23/28
Peng 2016	China	Tacrolimus + steroid (30)	CYC + steroid (30)	9 mo	25/30 vs 22/30*
Duan 2023	China	Cyclosporine + MMF + steroid (39)	Cyclical CS–CYC (39)	12 mo	31/39 vs 34/39
Kosmadakis 2010	Greece	Cyclosporine + steroid (10)	CYC + steroid (8)	9 mo	6/10 vs 8/8

Notes: \ Event counts back-calculated from reported remission proportions and randomised arm size. CS, corticosteroid; CYC, cyclophosphamide; MMF, mycophenolate mofetil; IV, intravenous; CNI, calcineurin inhibitor.*

3.3 Outcome definitions and baseline comparability

As detailed in Table 2, complete remission was generally defined as proteinuria below 0.3–0.5 g/day with preserved or stable kidney function, and partial remission as a reduction in proteinuria of at least 50% to a sub-nephrotic level; total remission was the sum of the two. Relapse was generally defined as recurrence of proteinuria above a nephrotic or pre-specified threshold after a remission, although the precise definition and timing varied. Baseline severity was broadly comparable but not identical: reported baseline proteinuria clustered between approximately 5 and 9 g/day and serum albumin between approximately 22 and 28 g/L, with preserved or only mildly reduced kidney function at entry in most trials. Anti-PLA_2R status was reported inconsistently and could not be incorporated; this residual clinical variability is one plausible contributor to the heterogeneity observed for the remission outcomes.

Table 2. Remission and relapse definitions and primary assessment timepoint for each trial.

Trial	Remission definition (CR / PR)	Relapse definition	Primary assessment
STARMEN	CR <0.3 g/day; PR <3.5 g/day and ≥50% fall	Proteinuria >3.5 g/day after remission	24 months
Chen 2010	CR <0.3 g/day; PR ≥50% fall to <3.5 g/day	Not separately reported	6–12 months
Xu 2013	CR <0.3 g/day; PR ≥50% fall	Not separately reported	Early + ≥18 months
Ramachandran (PGIMER)	CR <0.3 g/day; PR ≥50% fall to <3.5 g/day	Nephrotic-range recurrence after remission	12 months (to 6 years)
He 2013	CR <0.3 g/day; PR ≥50% fall	Not separately reported	12 months
Liang 2017	CR <0.3 g/day; PR ≥50% fall	Recurrence after remission	~12 months
Peng 2016	CR <0.3 g/day; PR ≥50% fall	Not separately reported	9 months
Duan 2023	CR <0.3 g/day; PR ≥50% fall to <3.5 g/day	Not separately reported	12 months
Kosmadakis 2010	CR <0.3 g/day; PR ≥50% fall	Not separately reported	9 months

Notes: CR, complete remission; PR, partial remission. Definitions are paraphrased from the source reports and were broadly but not identically specified.

3.4 Risk of bias

The principal limitations across the nine trials were the open-label design and, in several trials, incomplete reporting of allocation concealment and of the pre-specified analysis. Seven trials were rated as having some concerns overall, driven chiefly by the deviations-from-intended-interventions domain; outcome measurement was judged at low risk in all because remission relied on objective proteinuria thresholds. The trial reporting partial participant self-selection was rated at high risk overall and was removed in a sensitivity analysis. The domain-level judgements are presented in Figure 2.

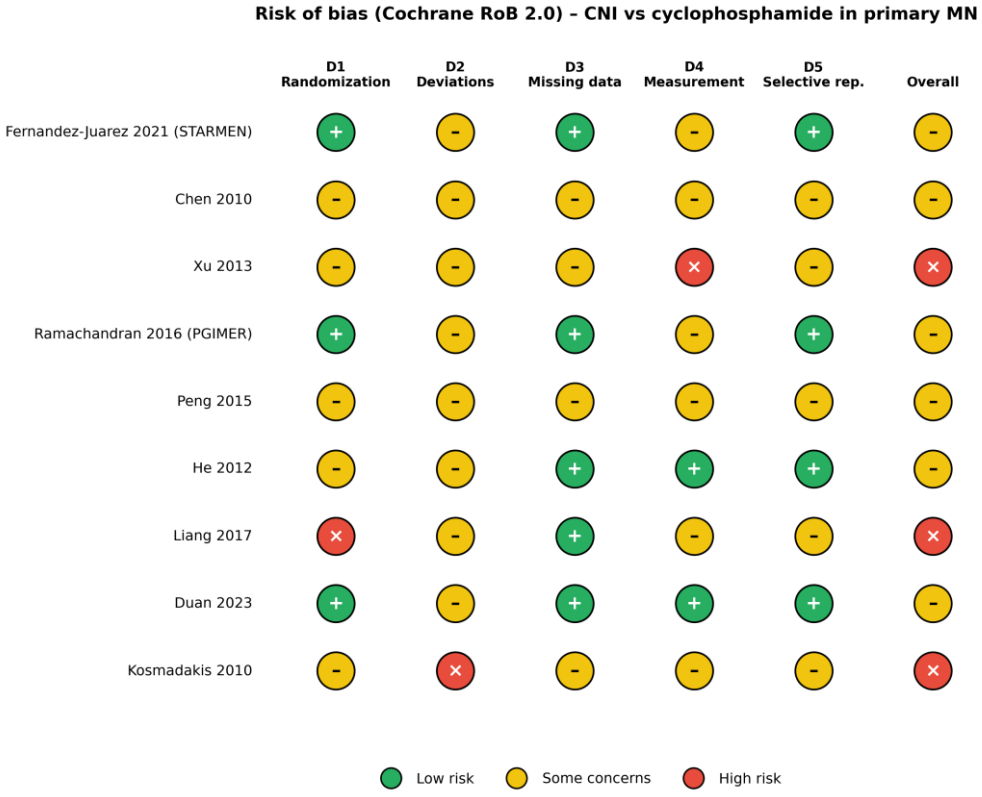

Figure 2. Cochrane RoB 2 domain-level and overall risk-of-bias judgements for the included trials.

3.5 Primary outcome: total remission

Nine trials contributed to the primary outcome, with 222 of 297 participants achieving total remission on CNI-based therapy versus 215 of 302 on cyclophosphamide-based therapy (Table 1). Total remission did not differ significantly between the strategies: the pooled risk ratio was 1.02 (95% CI 0.86–1.20; Z=0.21; p=0.83). Between-study heterogeneity was moderate-to-substantial (I^2=67%, τ^2=0.043, Cochran Q=24.6, df=8, p=0.002), and the 95% prediction interval was wide (0.61–1.72), indicating that a future trial could plausibly favour either regimen. Individual estimates ranged from 0.69 (favouring cyclophosphamide) in the STARMEN trial to 1.49 (favouring tacrolimus) in Xu 2013, as displayed in Figure 3.

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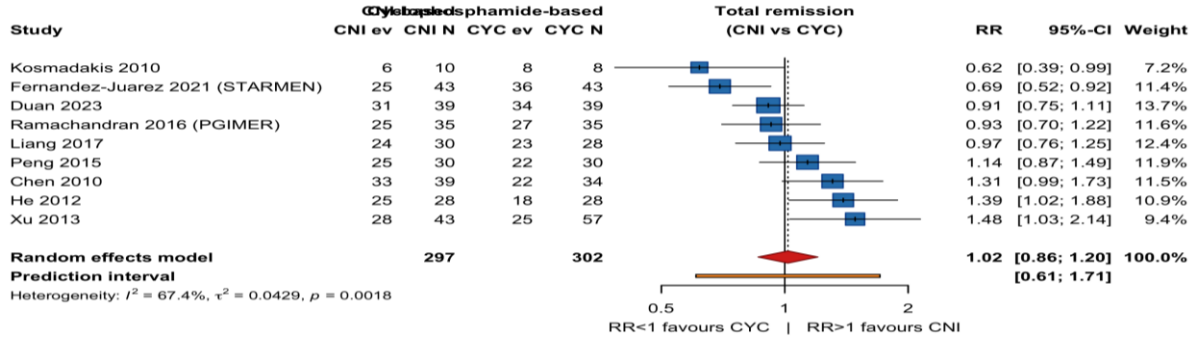

Figure 3. Random-effects forest plot of total remission (complete plus partial), CNI-based versus cyclophosphamide-based therapy. Squares are proportional to study weight; the diamond is the pooled DerSimonian–Laird estimate.

3.6 Secondary outcomes: complete remission and relapse

Four trials reported complete remission separately. The pooled risk ratio was 0.84 (95% CI 0.34–2.04; p=0.69) with substantial heterogeneity (I^2=83%), indicating no significant difference but marked inconsistency. Relapse after remission was reported in three trials, using the definitions in Table 2. Pooled analysis suggested a higher relapse risk with CNI-based therapy, but the estimate did not reach significance and the confidence interval crossed unity (RR 1.76, 95% CI 0.95–3.24; I^2=0%); it should therefore be described as a tendency rather than an established difference. The consistency of this signal (I^2=0%) is clinically coherent with the dependence of CNI efficacy on continued exposure and with long-term follow-up within the included Chandigarh cohort, in which early parity in remission gave way to more frequent relapse in the tacrolimus arm[12,13]. Reported adverse events were broadly comparable; where detailed, tacrolimus-based therapy was associated with fewer infective events but more frequent glucose intolerance[17].

3.7 Subgroup analyses (exploratory)

The exploratory subgroup analyses, which were underpowered, did not identify a statistically significant effect modifier. Tacrolimus-based trials yielded a pooled risk ratio of 1.09 (95% CI 0.90–1.31; k=7) and cyclosporine-based trials 0.80 (95% CI 0.56–1.15; k=2), with no significant difference between subgroups (p=0.14). Trials with follow-up of at least 12 months gave a pooled risk ratio of 0.95 (95% CI 0.78–1.15) versus 1.12 (95% CI 0.84–1.51) for shorter follow-up (p=0.35), consistent with attenuation of any early CNI advantage over time. The subgroup analysis by CNI type is shown in Figure 4.

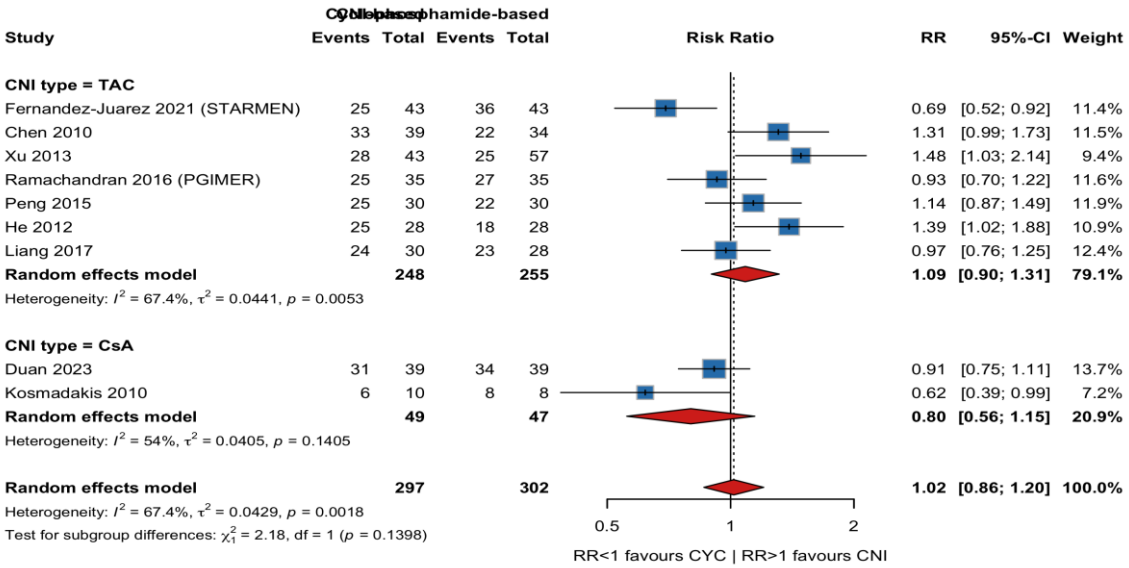

Figure 4. Exploratory subgroup forest plot of total remission by calcineurin inhibitor type (tacrolimus versus cyclosporine).

3.8 Sensitivity analyses and small-study effects

The primary estimate was robust across all four pre-specified sensitivity analyses, summarised in Table 3. Leave-one-out omission produced pooled risk ratios between 0.98 and 1.07, all non-significant. Restriction to the five trials with directly reported counts yielded 0.91 (95% CI 0.72–1.15; I^2=69%; p=0.42), indicating that the back-calculated trials did not materially distort the synthesis. Exclusion of the atypical sequential and multitarget regimens gave 1.11 (95% CI 0.93–1.32; k=7; p=0.23), and exclusion of the single high-risk trial gave 1.03 (95% CI 0.85–1.25; k=8; p=0.77). Funnel-plot inspection was approximately symmetrical and Egger's test showed no small-study effect (intercept 0.48, p=0.87); with nine trials this assessment was underpowered, as shown in Figure 5.

Table 3. Pre-specified sensitivity analyses for the primary outcome (total remission).

Sensitivity analysis	k	Pooled RR (95% CI)	I^2	p
Primary (all trials)	9	1.02 (0.86–1.20)	67%	0.83
Directly reported data only	5	0.91 (0.72–1.15)	69%	0.42
Excluding sequential + multitarget regimens	7	1.11 (0.93–1.32)	55%	0.23
Excluding high-risk trial	8	1.03 (0.85–1.25)	70%	0.77
Leave-one-out (range)	8	0.98–1.07 (all NS)	59–71%	—

Notes: NS, non-significant. All analyses used the DerSimonian–Laird random-effects model.

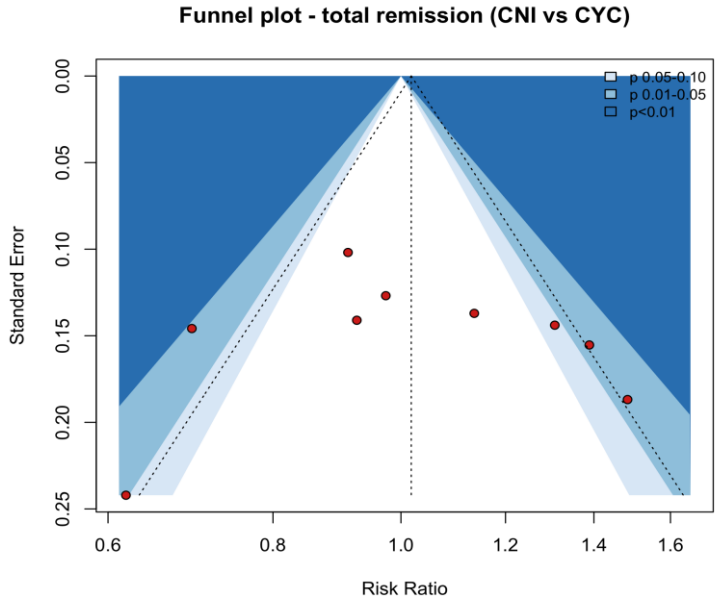

Figure 5. Funnel plot of the total-remission comparison with pseudo-95% confidence limits.

3.9 Handling of the repeated cohort

To make explicit how the single repeated cohort was used, **Table 4** maps each extracted value to its source report. The cohort contributed once to the pooled remission estimate, through the 12-month primary report; the 24-month and 6-year reports supplied relapse and long-term data only.

Table 4. Mapping of extracted values to the three reports of the single repeated (PGIMER) cohort.

Report	Role in this synthesis	Values used
Ramachandran 2016 (12-month)	Primary remission estimate (counted once)	Total remission 25/35 vs 27/35
Ramachandran 2017 (2-year)	Relapse and durability narrative	Higher relapse in tacrolimus arm
Ramachandran 2021 (6-year)	Long-term outcome narrative	Long-term remission/relapse trends

Notes: The cohort was counted once for the remission meta-analysis to avoid double-counting.

4. Discussion

This meta-analysis of nine randomised controlled trials comprising 599 adults with primary membranous nephropathy found that CNI-based and cyclophosphamide-based regimens produced statistically comparable overall remission (RR 1.02, 95% CI 0.86–1.20), with a confidence interval that excluded any clinically important advantage in either direction. Complete remission likewise did not differ. The most clinically salient observation was a consistent, although non-significant, tendency towards more frequent relapse after CNI-based therapy (RR 1.76, 95% CI 0.95–3.24)—an outcome with no measurable heterogeneity that accords with the dependence of this drug class on continued exposure. The two strategies thus appear interchangeable for inducing remission but may differ in the durability of the response.

4.1 Comparison with previous syntheses

The direction of these findings is consistent with prior work, and the value added is one of updating, focusing and the joint analysis of remission with relapse. The most recent Cochrane review concluded that calcineurin inhibitors and alkylating agents were of comparable efficacy for inducing remission while differing in adverse effects[20], and network meta-analyses have ranked tacrolimus and cyclophosphamide closely for remission while separating them on infection risk[21,22]. A recent network meta-analysis comparing rituximab, tacrolimus, cyclophosphamide and cyclosporine reached similar conclusions regarding remission parity among the conventional agents[23]. By confining inclusion to head-to-head randomised comparisons in primary disease and incorporating trials reported after those syntheses[7,8], this analysis provides a contemporary, focused estimate, and its explicit attention to relapse adds a dimension frequently omitted from earlier remission-only syntheses.

Beyond the qualitative agreement, the magnitude and precision of the present estimate are informative. The pooled

risk ratio for total remission (1.02) sat almost exactly on the line of no effect, and its confidence interval (0.86–1.20) was sufficiently narrow to exclude any relative difference greater than approximately one fifth in either direction. This precision, achieved by pooling nine randomised comparisons, exceeds that of any single constituent trial and lends the conclusion of equivalence a firmer empirical footing than the individual studies, several of which were too small to detect even moderate differences, could provide on their own.

4.2 Heterogeneity

Moderate-to-substantial heterogeneity was observed for the remission outcomes (I^2=67% for the primary outcome). The pooled point estimate therefore represents an average across genuinely different effects, and the wide prediction interval (0.61–1.72) communicates that a future trial could favour either regimen. Plausible sources include differing remission definitions and assessment timepoints; the diversity of CNI regimens; and differences in baseline proteinuria, kidney function and antibody status[1]. The contrast between the heterogeneous remission outcomes and the perfectly consistent relapse outcome (I^2=0%) suggests that the strategies converge on similar short-term remission through different routes but diverge predictably once CNI exposure is withdrawn.

The exploratory subgroup analyses did not isolate a single dominant source of heterogeneity. Neither calcineurin inhibitor type nor follow-up duration produced a significant between-subgroup difference, which is itself consistent with the view that the dispersion of effects reflects genuine, multifactorial clinical diversity—differences in regimen intensity, ethnicity, baseline severity and outcome timing—rather than a single methodological artefact that a simple stratification could remove.

4.3 Position relative to newer therapies

Although this synthesis compared the two classic immunosuppressive strategies, neither arm involved a B-cell–depleting agent. Rituximab has become central to first-line decision-making in many settings, having shown efficacy relative to cyclophosphamide in a randomised trial[9], and newer anti-CD20 agents such as obinutuzumab are being evaluated in rituximab-refractory disease[10,24]. The present comparison should therefore be read as characterising the relationship between two established options rather than defining the optimal first-line agent overall[6]. The relapse signal observed for CNIs strengthens the rationale for positioning durable, B-cell–directed strategies against both classic regimens in future trials.

The broader therapeutic pipeline reinforces this point. Agents directed at the antibody-producing plasma cell, complement-modulating therapies and dual endothelin–angiotensin receptor antagonists are progressing through evaluation, and each is being judged increasingly on its capacity to deliver durable, treatment-free remission rather than transient proteinuria reduction[6]. Within this evolving landscape, the calcineurin inhibitors and alkylating agents examined here remain the accessible, affordable backbone of care in most of the world, and a clear understanding of how they compare—and where each falls short on durability—remains the necessary reference point against which newer, costlier options must be measured.

4.4 Mechanistic considerations

The comparable induction of remission but divergent durability is biologically plausible. Cyclophosphamide, by depleting autoreactive B-cell clones and reducing pathogenic anti-PLA_2R antibody, can interrupt the immunological driver of the disease and thereby produce remission that persists after the drug is stopped[1]. Calcineurin inhibitors lower proteinuria partly through a direct, reversible stabilising effect on the podocyte actin cytoskeleton, which can reduce proteinuria without necessarily extinguishing the underlying autoimmune process, so that proteinuria recurs once the podocyte effect is withdrawn[6]. This framework accounts both for the early parity in remission and for the later relapse signal, and it implies that monitoring anti-PLA_2R titres during and after therapy could identify patients in whom immunological remission has not been achieved.

4.5 Clinical implications

Because overall remission is comparable, the choice of regimen can reasonably prioritise patient-specific factors. A younger patient of reproductive age, for whom the gonadal and oncological toxicity of cumulative cyclophosphamide is a concern, may be directed towards a CNI-based or B-cell–directed approach despite the relapse risk. A patient for whom durable, treatment-free remission is paramount may reasonably be offered a time-limited cyclophosphamide course. Where a CNI is chosen, the heightened relapse tendency argues for a slow, monitored taper with surveillance of proteinuria and, where available, anti-PLA_2R titres; where cyclophosphamide is chosen, cumulative-dose limitation and gonadal protection remain priorities. These recommendations are consistent with current guidance[4].

In practical terms, a calcineurin inhibitor strategy may reasonably be accompanied by measurement of trough drug levels, periodic assessment of serum creatinine and proteinuria, and, where the assay is accessible, serial anti-PLA_2R antibody titres to gauge immunological response before any attempt at withdrawal. An alkylating-agent strategy, by contrast, calls for vigilance over the leucocyte count during each cycle, attention to the cumulative lifetime dose, and counselling about fertility preservation in those of reproductive age. Framing the two regimens in terms of these distinct monitoring requirements, rather than a presumed efficacy difference, more accurately reflects what the present evidence supports.

4.6 Considerations for resource-limited settings

For a general internal medicine readership, including practitioners in resource-limited settings, the comparable efficacy of the two strategies has practical resonance. Cyclophosphamide and the older calcineurin inhibitors are widely available and inexpensive relative to biologic agents, so the choice between them can be made largely on clinical grounds. Where laboratory-monitoring capacity is limited, the simpler, time-limited nature of a cyclical cyclophosphamide course may be operationally attractive, whereas calcineurin inhibitors require drug-level monitoring and surveillance of kidney function to balance efficacy against nephrotoxicity.

4.7 Strengths and limitations

The strengths of this synthesis include its restriction to primary disease and to head-to-head randomised comparisons, the incorporation of recently reported trials, the joint analysis of remission and relapse, the use of a prediction interval, and an extensive set of pre-specified sensitivity analyses. Several limitations must be weighed. First, the search relied principally on a single database with indexing cross-checks; eligible trials, particularly those in regional or non-English journals, may have been missed, and the predominance of trials from a small number of Asian centres may limit generalisability. Second, most trials were small and open-label, several were rated as having some concerns and one as high risk. Third, complete remission and relapse were reported separately in only a minority of trials, and several remission counts were reconstructed from published proportions; a sensitivity analysis restricted to directly reported data nonetheless preserved the conclusion. Fourth, moderate-to-substantial heterogeneity means the

pooled estimates are averages across diverse regimens, and the small number of trials rendered the assessment of small-study effects underpowered. Fifth, anti-PLA_2R serology was inconsistently reported and could not be incorporated[1]. Finally, the comparator cyclophosphamide regimens were generally short, cyclical courses, so the toxicity argument for preferring a CNI is weaker than against prolonged alkylator exposure.

At the review level, three further constraints deserve mention. The absence of prospective registration limits formal protection against selective reporting within the review process, although the analysis plan was fixed before synthesis. The reliance on aggregate, study-level data precluded analyses that individual-participant data would have permitted, such as adjustment for baseline proteinuria or antibody status. And progression to kidney failure—the outcome of greatest long-term importance to patients—was too sparsely and heterogeneously reported across the included trials to support a meaningful pooled estimate, so the synthesis necessarily centred on remission and relapse as proximate surrogates.

4.8 Implications for future research

Adequately powered randomised trials are needed that standardise the definition and timing of remission, stratify enrolment by anti-PLA_2R antibody status, and report relapse and long-term kidney outcomes uniformly, so that durability becomes a routine endpoint. Trials should position the two classic regimens against contemporary B-cell–depleting therapy and, ideally, against antibody-guided strategies[24]. Greater consistency in the reporting of arm-level event counts, adverse events and cumulative drug exposure would also improve the quality of future syntheses, and the inclusion of patient-reported and fertility-related endpoints would better align the evidence base with real treatment decisions.

4.9 Interpretation of the magnitude of effect

Taken together, the precise central estimate and the wide prediction interval express the two halves of the synthesis. On average, the two strategies are equivalent for inducing remission, and a clinician constrained by drug availability or patient preference can proceed with either in the reasonable expectation of a similar group-level remission rate. Yet the wide prediction interval (0.61–1.72) signals that, in any particular setting—shaped by the specific regimen, the population and the timing of assessment—the true effect could still depart appreciably from equivalence. This juxtaposition is faithfully reproduced in the forest plot in Figure 3, where individual trial estimates span both sides of the line of no effect, and in the sensitivity analyses in Table 3, where the pooled estimate remained close to unity under every reasonable definition of the comparison. The clinical corollary is that population-level equivalence does not guarantee equivalence for the individual patient, and that the durability of remission, rather than its initial achievement, is the more discriminating consideration in practice.

5. Conclusion

In this meta-analysis of nine randomised controlled trials enrolling 599 adults with primary membranous nephropathy, calcineurin inhibitor–based and cyclophosphamide-based regimens achieved statistically comparable overall remission (RR 1.02, 95% CI 0.86–1.20) and did not differ in complete remission. The principal clinically meaningful observation was a consistent, although non-significant, tendency towards more frequent relapse after calcineurin inhibitor–based therapy, coherent with the dependence of this drug class on sustained exposure. The pooled estimate was stable across leave-one-out analysis, restriction to directly reported data, exclusion of atypical regimens and exclusion of the high-risk trial, and showed no detectable small-study effect; nonetheless, heterogeneity was moderate-to-substantial and the prediction interval wide. The decision between a calcineurin inhibitor and an alkylating agent should therefore not rest on anticipated differences in inducing remission, which are similar, but on the durability of response and on patient-specific considerations of tolerability and risk—particularly fertility preservation, infection susceptibility and the cumulative toxicity of cyclophosphamide. Calcineurin inhibitor–based therapy is a reasonable first-line option, especially where alkylator toxicity is undesirable, but it warrants a cautious, monitored taper and an explicit relapse plan; cyclophosphamide-based therapy remains valuable where durable, treatment-free remission is the priority. Future adequately powered trials that standardise remission definitions, stratify by anti-PLA_2R status, and position both classic regimens against contemporary B-cell–depleting therapy are needed to move beyond the present equipoise.

In aggregate, the message is one of reassurance coupled with redirected attention. Either established regimen can be expected to induce remission in a broadly similar proportion of patients, so the decision that genuinely matters is less which agent achieves remission than how durable that remission proves and at what cumulative cost in toxicity it is obtained. For the practising internist and nephrologist, this reframing—efficacy as a shared baseline, durability and tolerability as the discriminating considerations—offers a practical and evidence-consistent basis for individualising care in a disease whose heterogeneity has long resisted a single, universal treatment rule.

Declarations

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Author contributions (CRediT)

L.P.S.: conceptualization, methodology, formal analysis, investigation, writing — original draft. H.H.: conceptualization, supervision, validation, writing — review & editing. Both authors reviewed and approved the final manuscript.

Ethics and consent

Not applicable. This study was a systematic review and meta-analysis of previously published, de-identified aggregate data and did not involve new human participants. The review was not registered in a prospective register.

Conflict of interest

The authors declare no conflict of interest.

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Use of AI / Data availability

Generative AI: none used in writing the scientific content. Data availability: all data analysed are contained within the published source articles cited; the extracted dataset and analysis code are available from the corresponding author on reasonable request.

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