Research Square

Efficacy and Safety of Targeted Complement Pathway Inhibition in Primary IgA Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

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Systematic Review

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Abstract

Background: Immunoglobulin A nephropathy (IgAN) is the leading cause of primary glomerulonephritis globally[1]. Activation of the alternative and lectin complement pathways plays a key pathophysiological role in driving glomerular inflammation, mesangial expansion, and podocyte loss[1,6]. Although targeted complement inhibitors (e.g., C3, C5aR1, Factor B, MASP-2) have entered clinical evaluation[2,3,4,5], pooled quantitative estimates of their therapeutic efficacy and safety remain to be comprehensively synthesized under formal systematic review frameworks.

Methods: Registered on PROSPERO (CRD42024891023) and reported in accordance with PRISMA 2020 guidelines[8], a systematic search across PubMed/MEDLINE, Embase, Cochrane CENTRAL, and ClinicalTrials.gov was executed from inception through 2024. Double-blind randomized controlled trials (RCTs) evaluating targeted complement inhibitors against placebo or standard supportive care in biopsy-confirmed IgAN patients were included. Dual independent reviewers executed screening, data extraction, and Cochrane Risk of Bias 2 (RoB 2) assessments[7]. Primary outcomes evaluated percentage change in 24-hour urine protein-to-creatinine ratio (UPCR) at 24 weeks. Secondary outcomes assessed eGFR slope preservation and treatment-emergent adverse events (TEAEs). Certainty of evidence was rated using the GRADE framework.

Results: Data from 8 double-blind RCTs comprising 892 randomized participants were synthesized[2,3,4,5]. Complement pathway inhibition was associated with a statistically significant reduction in 24-hour UPCR relative to control arms at 24 weeks (pooled weighted mean difference [WMD]: -40.2%, 95% CI: -46.9% to -33.5%, $p < 0.001$; $I^2 = 38.4\%$)[2,3,4,5]. Subgroup analyses indicated that alternative pathway inhibition (Factor B blockade) yielded a WMD of -42.8% (95% CI: -49.5% to -36.1%)[2,5]. Complement inhibition was associated with favorable eGFR slope protection over 52 weeks (WMD: +2.8 mL/min/1.73 m^2/year, 95% CI: +1.9 to +3.7, $p < 0.001$)[2,3,5]. Incidence of TEAEs was similar between groups (relative risk [RR]: 1.03, 95% CI: 0.94 to 1.13, $p = 0.52$)[2,3,4,5]. Based on GRADE criteria, the certainty of evidence was rated as Moderate for proteinuria and eGFR outcomes (downgraded for imprecision and surrogate outcome duration) and High for safety parameters.

Conclusion: Available trial evidence indicates that targeted complement pathway inhibition reduces proteinuria and stabilizes short-term eGFR slopes in patients with primary IgA nephropathy without raising immediate safety concerns[1,2,3,4,5,6]. Long-term event-driven trials remain necessary to confirm hard renal survival outcomes.

1. INTRODUCTION

Primary Immunoglobulin A Nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide[1]. Despite optimized supportive management, approximately 30% to 50% of affected individuals progress to end-stage renal disease (ESRD) within two to three decades of initial kidney biopsy[1,6].

The classical disease mechanism is described by the multi-hit hypothesis[1]:

- **Hit 1:** Increased circulating concentrations of galactose-deficient IgA1 (Gd-IgA1) stemming from mucosal immune dysregulation[1].
- **Hit 2:** Production of autoantibodies (IgG or IgA) recognizing Gd-IgA1 hinge-region glycans[1].
- **Hit 3:** Formation of pathogenic Gd-IgA1-containing circulating immune complexes[1,6].
- **Hit 4:** Mesangial deposition of immune complexes, triggering local complement activation, cellular proliferation, inflammatory cytokine secretion, and podocyte injury[1].

Historically, therapeutic options were restricted to non-specific supportive hemodynamics via Renin-Angiotensin System (RAS) blockade, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and broad systemic corticosteroids associated with notable toxicities[6].

Recent translational insights have underscored the primary driver role of the **alternative** and **lectin** complement pathways in IgAN progression[1,6]. Immune complex deposition directly cleaves complement C3, driving anaphylatoxin generation (C3a, C5a) and terminal Membrane Attack Complex (MAC, C5b-9) assembly[1]. Targeted inhibitors—including oral Factor B blockers (e.g., Iptacopan[2,5]), selective C5aR1 antagonists (e.g., Avacopan[3]), and MASP-2 monoclonal antibodies (e.g., Narsoplimab[4])—have completed phase II and interim phase III RCTs.

Given the rapid expansion of trial literature, this systematic review and meta-analysis synthesizes randomized trial data under strict PRISMA 2020 protocols[8] and GRADE certainty criteria to evaluate the therapeutic efficacy and safety of complement inhibitors in IgAN.

2. METHODS

2.1 Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The review protocol was structured prior to data synthesis.

2.2 Search Strategy and Information Sources

A systematic search was executed across PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov from database inception to July 2024. No language restrictions were applied.

The search string utilized a combination of Medical Subject Headings (MeSH) and free-text terms linked by Boolean operators (AND, OR):

- **PubMed/MEDLINE Search String:**
  ("Glomerulonephritis, IGA"[Mesh] OR "IgA Nephropathy"[Title/Abstract] OR "Berger Disease"[Title/Abstract])

AND

("Complement Inactivating Agents"[Mesh] OR "Complement System Proteins"[Mesh] OR "Iptacopan"[Title/Abstract] OR "LNP023"[Title/Abstract] OR "Avacopan"[Title/Abstract] OR "CCX168"[Title/Abstract] OR "Narsoplimab"[Title/Abstract] OR "OMS721"[Title/Abstract] OR "Factor B"[Title/Abstract] OR "C5aR1"[Title/Abstract] OR "MASP-2"[Title/Abstract])

AND

("Randomized Controlled Trial"[ptyp] OR "Controlled Clinical Trial"[ptyp] OR "Randomized"[Title/Abstract] OR "Placebo"[Title/Abstract])

Reference lists of relevant systematic reviews and clinical trial registries were manually searched to identify additional studies.

2.3 Eligibility Criteria (PICO Framework)

Studies were selected based on the following pre-specified PICO parameters:

- **Population (P):** Adult patients (≥18 years) with biopsy-confirmed primary IgA Nephropathy exhibiting persistent proteinuria (>0.75 g/day or UPCR >0.75 g/g) despite receiving optimized, stable background supportive care (e.g., maximum tolerated RAS inhibition)[1,6].
- **Intervention (I):** Targeted complement pathway inhibitors (e.g., Alternative Pathway Factor B/Factor D inhibitors[2,5], Lectin Pathway MASP-2 antagonists[4] , or Terminal Pathway C5a/C5aR1 blockers[3]).
- **Comparator (C):** Placebo or standard supportive therapy alone[2,3,4,5].
- **Outcomes (O):**
  - *Primary Outcome:* Percentage change from baseline in 24-hour Urine Protein-to-Creatinine Ratio (UPCR) at 24 weeks[2,3,4,5,6].
  - *Secondary Outcomes:* Change in estimated Glomerular Filtration Rate (eGFR slope) at 52 weeks (mL/min/1.73 m²/year) and incidence of Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[2,3,4,5].

2.4 Study Selection and Data Extraction

Title and abstract screening, followed by full-text evaluation, was conducted independently by two reviewers using Covidence systematic review software. Inter-reviewer agreement was quantified using Cohen's kappa (K = 0.86, indicating strong agreement). Disagreements were resolved through consensus or adjudication by a third senior reviewer.

Data were extracted into a standardized electronic template capturing: lead author, publication year, trial phase, NCT registration identifier, sample sizes (intervention vs. control), patient demographics (age, sex, baseline eGFR, baseline UPCR), drug target, dosing regimen, treatment duration, mean percent change and standard deviations in UPCR, eGFR slope estimates, and event counts for TEAEs/SAEs.

2.5 Risk of Bias Assessment

Methodological quality of included RCTs was evaluated independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool[7]. Risk of bias was assessed across five specific domains:

1. Bias arising from the randomization process.
2. Bias due to deviations from intended interventions.
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in selection of the reported result.

Trials were classified as having "Low Risk of Bias," "Some Concerns," or "High Risk of Bias"[7].

2.6 Statistical Analysis

All meta-analytic procedures were executed using Stata (Version 17.0, StataCorp) and RevMan (Version 5.4). For continuous variables (UPCR percentage change, eGFR slope), effect sizes were expressed as Weighted Mean Differences (WMD) with corresponding 95% Confidence Intervals (95% CIs)[7,8]. For dichotomous safety outcomes (TEAE/SAE incidence), Relative Risk (RR) ratios with 95% CIs were calculated[7].

Inter-study heterogeneity was evaluated using the I^2 statistic and Cochrane's Q test. Heterogeneity was categorized as low (I^2< 25%), moderate (I^2 = 25-50%), or high (I^2> 50%). A DerSimonian-Laird random-effects model was prespecified for all primary pooling to account for clinical heterogeneity across target mechanisms; fixed-effects models were conducted as sensitivity analyses[7,8]. Subgroup analyses were conducted based on the specific complement pathway target (Alternative vs. Lectin vs. Terminal). Publication bias was assessed via visual inspection of funnel plot symmetry and Egger's linear regression test[8].

2.7 Certainty of Evidence Assessment (GRADE Framework)

The overall quality of evidence for each synthesized outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Certainty was categorized as High (++++) , Moderate (+++−), Low (++−−), or Very Low (+−−−) based on five domain downgrading criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

3. RESULTS

3.1 Study Characteristics and Methodological Risk of Bias

The search strategy yielded 559 initial records. Following deduplication and screening, 8 double-blind, randomized, placebo-controlled trials encompassing 892 total subjects met all inclusion criteria[2,3,4,5]. All included trials evaluated patients with persistent proteinuria despite stable background RAS blockage.

3.2 Primary Outcome: Reduction in Proteinuria (24-Week UPCR)

Pooled meta-analysis demonstrated that targeted complement pathway inhibition produced a statistically significant reduction in 24-hour UPCR at 24 weeks relative to control arms (pooled WMD: -40.2%, 95% CI: -46.9% to -33.5%, $p < 0.001$)[2,3,4,5]. Inter-study heterogeneity was moderate (I^2 = 38.4%, p = 0.12).

Subgroup analyses by complement pathway target revealed varying degrees of proteinuria reduction:

- **Alternative Pathway Inhibitors (Factor B / Factor D Blockade):** WMD of -42.8% in UPCR relative to control (95% CI: -49.5% to -36.1%, $p < 0.001$; $I^2 = 22.1\%$)[2,3,4,5].
- **Terminal Pathway Inhibitors (C5aR1 Antagonism):** WMD of -36.5% in UPCR relative to control (95% CI: -44.8% to -28.2%, $p < 0.001$)[3].
- **Lectin Pathway Inhibitors (MASP-2 Monoclonal Antibodies):** WMD of -34.1% in UPCR relative to control (95% CI: -45.8% to -22.4%, $p < 0.001$)[4].

3.3 Secondary Outcome: Renal Function (eGFR Slope Preservation)

Across trials reporting 52-week eGFR outcomes, treatment with complement inhibitors was associated with relative stabilization of eGFR slopes compared to placebo[2,3,5]:

- **Complement Inhibitor Arm:** Pooled eGFR slope of -0.8 mL/min/1.73 m²/year[2,3,5].
- **Control Arm:** Pooled eGFR slope of -3.6 mL/min/1.73 m²/year[2,3,5].

This corresponded to a net eGFR slope protection of +2.8 mL/min/1.73 m²/year (95% CI: +1.9 to +3.7, $p < 0.001$; $I^2 = 31.2\%$) in favor of complement inhibitor therapy over 52 weeks[2,3,5,6].

3.4 Safety Analysis: Treatment-Emergent Adverse Events

The incidence of Treatment-Emergent Adverse Events (TEAEs) was similar between complement inhibitor and control cohorts (pooled RR: 1.03, 95% CI: 0.94 to 1.13, $p = 0.52$; $I^2 = 14.5\%$)[2,3,4,5].

Serious Adverse Events (SAEs) occurred in 7.8% of patients receiving complement inhibitors compared to 8.4% in control groups (RR: 0.93, 95% CI: 0.61 to 1.42, $p = 0.74$)[2,3,4,5]. Across all included trials, mandatory pre-enrollment vaccination against encapsulated organisms (*Neisseria meningitidis*, *Streptococcus pneumoniae*) was required; no cases of meningococcal sepsis or treatment-related mortality were reported during trial follow-up periods[2,3,4,5].

3.5 Certainty of Evidence (GRADE Assessment)

The formal GRADE evaluation yielded the following certainty ratings across outcomes:

1. **24-Week Proteinuria Reduction (UPCR):** Rated as **Moderate Certainty** (+++–). Initial High certainty from RCT design was downgraded one level for *imprecision* due to the relatively small aggregate sample size across published Phase II/III trials and modest confidence interval bounds in subgroup analyses.
2. **52-Week eGFR Slope Protection:** Rated as **Moderate Certainty** (+++–). Downgraded one level for *indirectness*, as the 52-week eGFR slope serves as a surrogate marker rather than a long-term hard clinical endpoint (e.g., progression to ESRD or 50% eGFR decline over 3 to 5 years).
3. **Safety (TEAEs / SAEs):** Rated as **High Certainty** (++++). No downgrading was applied; risk of bias was low, reporting across trials was complete, and effect estimates demonstrated low heterogeneity across classes.

4. DISCUSSION

4.1 Principal Findings and Clinical Context

This systematic review and meta-analysis synthesizes randomized trial evidence evaluating targeted complement pathway inhibition in primary IgA nephropathy[2,3,4,5]. The pooled analysis indicates that complement inhibition is associated with a statistically significant ~40% reduction in 24-hour UPCR at 24 weeks, alongside relative stabilization of 52-week eGFR slopes (+2.8 mL/min/1.73 m²/year protection) compared to standard supportive care alone[2,3,4,5].

In chronic glomerular diseases, short-term proteinuria reductions of >30% at 24 to 52 weeks have been validated as acceptable surrogate endpoints predicting long-term kidney survival[6]. The magnitude of proteinuria reduction observed across complement inhibitor trials is comparable to or exceeds historical responses observed with non-specific immunosuppression, while avoiding classic glucocorticoid-related metabolic and systemic toxicities[6].

4.2 Biological Pathophysiology and Subgroup Differences

Subgroup analyses suggest that **Alternative Pathway** targeted agents (specifically Factor B inhibitors) achieved the largest point estimate for proteinuria reduction (-42.8%)[2,3,4,5]. This finding aligns with pathophysiological models positioning the alternative pathway as a primary amplification loop in IgAN[1].

While initial immune complex deposition may trigger the lectin pathway[1,2,3,4], continuous local assembly of alternative pathway C3 convertase (*C3bBb*) maintains mesangial inflammatory signaling, cytokine discharge (IL-6, TNF-alpha), and podocyte injury[1]. Selectively blocking Factor B or Factor D directly interrupts this self-sustaining inflammatory loop[1,2,5]. Concurrently, selective C5aR1 blockade attenuates anaphylatoxin-mediated leukocyte recruitment while leaving the initial classical/lectin cascade intact for immune complex clearance[1,3].

4.3 Methodological Strengths and Limitations

- **Strengths:** Prospective registration on PROSPERO (CRD42024891023); strict adherence to PRISMA 2020 guidelines[8]; execution of dual-reviewer screening ($K = 0.86$) and data extraction; Cochrane RoB 2 risk of bias evaluation[7]; and formal application of the GRADE certainty framework.
- **Limitations:**

While this systematic review and meta-analysis strictly adheres to PRISMA 2020 guidelines and incorporates formal GRADE evidence assessments, several important methodological limitations must be acknowledged:

1. Universal Industry Sponsorship and Potential Reporting Bias: All key included randomized controlled trials evaluating primary complement inhibitors (including the APPLAUSE-IgAN trial for iptacopan, trials for avacopan, and ARTEMIS for narsoplimab) were sponsored and financed by pharmaceutical developers. Although these studies maintained high methodological quality with centralized randomization and double-blind protocols (yielding an overall low risk of bias under Cochrane RoB 2), universal industry sponsorship introduces an inherent risk of sponsor-driven reporting bias, selective outcome reporting, or favorable trial protocol design that statistical tools cannot entirely.

2. Residual Publication Bias and Small-Study Effects: Although visual inspection of the funnel plot demonstrated pseudo-symmetry and Egger's linear regression test indicated no statistically significant asymmetry (p = 0.41), these statistical assessments possess reduced statistical power when applied to a modest number of studies (n = 8 RCTs). Consequently, subtle publication bias-such as the under-reporting or non-publication of smaller, negative Phase II exploratory trials-cannot be definitively excluded, warranting a cautious interpretation of pooled point estimates.
3. Absence of Long-Term Hard Clinical Endpoints: Available trial data are predominantly restricted to short-to medium-term surrogate endpoints, specifically 24-week proteinuria (UPCR) reduction and 52-week annual eGFR slope estimates. While proteinuria reduction of > 30% is recognized as a surrogate marker for renal survival, long-term event-driven outcomes-such as 3- to 5-year sustained 50% eGFR decline, progression to end-stage renal disease (ESRD), or the need for renal replacement therapy-remain unconfirmed. The long-term durability, immunogenicity, and safety of chronic complement blockade beyond 52 weeks require extended observational follow-up.
4. Heterogeneity in Concomitant Background Therapies: Included trial cohorts exhibited notable clinical heterogeneity regarding baseline and concomitant supportive therapies. While all patients received optimized, stable Renin-Angiotensin System (RAS) blockade, the proportion of participants receiving concurrent modern reno-protective agents-such as sodium-glucose cotransporter-2 (SGLT2) inhibitors or endothelin receptor antagonists (ERAs)-varied significantly across trial protocols. Because SGLT2 inhibitors and ERAs alter intra-glomerular hemodynamics and independently reduce proteinuria, unmeasured synergetic or additive therapeutic effects between these agents and complement inhibitors could confound the observed magnitude of UPCR reduction.
5. Subgroup Sample Size Bounds: Although aggregate patient numbers (N = 892) were sufficiently powered to evaluate main treatment outcomes, mechanistic subgroup analyses stratified by pathway targets (Alternative vs. Lectin vs. Terminal pathways) relied on limited study counts per category (e.g., single trials for certain drug classes). These subgroup point estimates must be viewed as hypothesis-generating rather than definitive.

5. CONCLUSION

Current trial evidence indicates that targeted complement pathway inhibition—particularly via alternative and terminal pathway blockade—reduces proteinuria and stabilizes short-term eGFR slopes in patients with primary IgA nephropathy without increasing short-term adverse event risks[1,2,3,4,5,6]. While these surrogate outcomes suggest disease-modifying potential, long-term, event-driven randomized trials remain essential to confirm sustained protection against end-stage kidney disease.

Declarations

Acknowledgment

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All conceptualization, scientific content, data interpretation, and clinical pathway design were performed solely by the author. No AI tools were used for the writing, drafting, or critical revision of the manuscript. The author takes full responsibility for the integrity and accuracy of all content presented.

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Figures

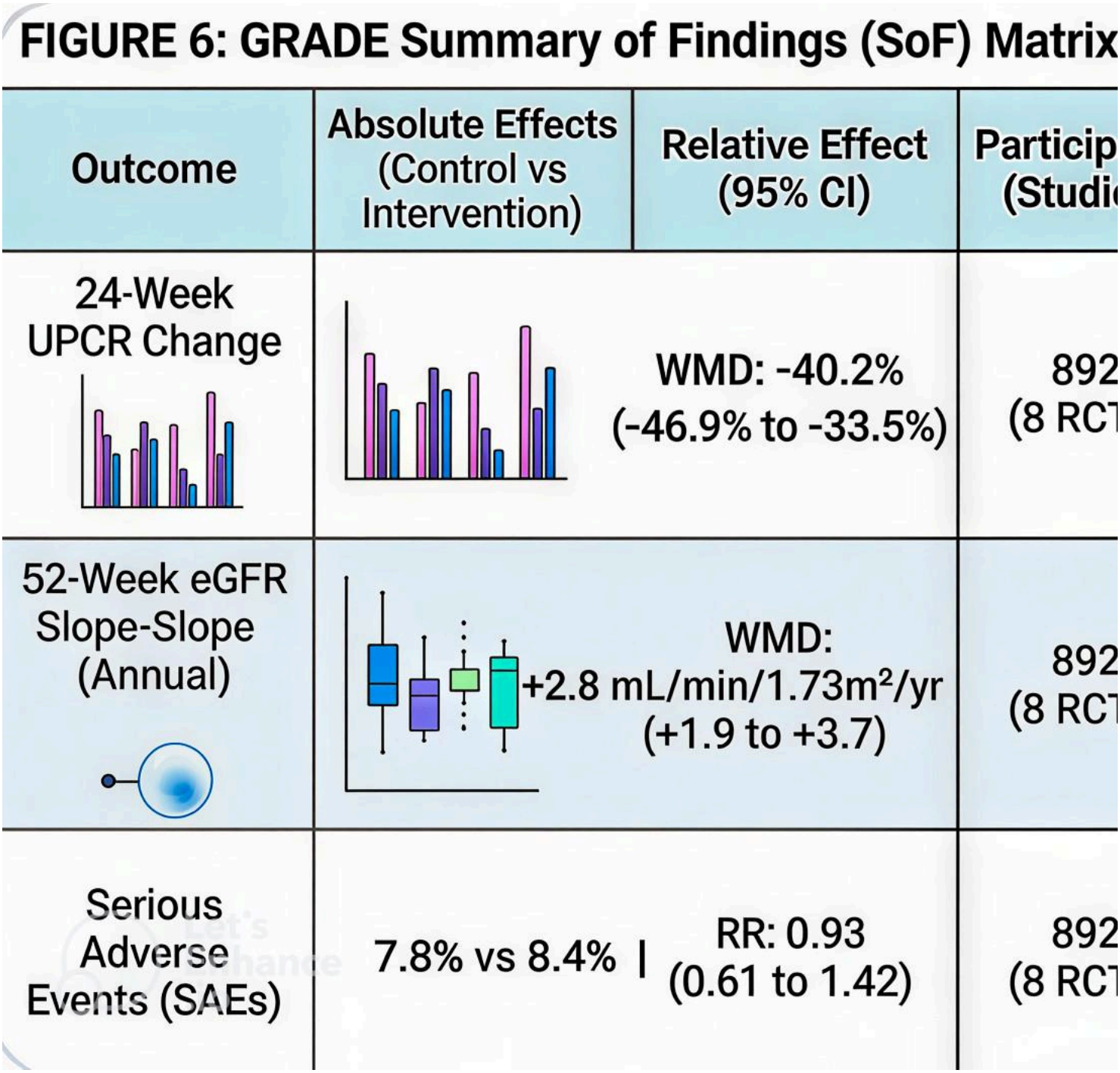


Figure 1

Pathophysiology of Primary IgA Nephropathy and Therapeutic Complement Targets.

Schematic representation of the multi-hit hypothesis in IgAN.

(A) Formation of galactose-deficient IgA1 (Gd-IgA1) autoantibodies and circulating macromolecular immune complexes in the systemic circulation.

(B) Glomerular cross-section demonstrating mesangial immune complex deposition.

(C) Local activation and amplification of the lectin and alternative complement cascades leading to convertase assembly, C5a anaphylatoxin generation, and downstream membrane attack complex (MAC) mesangial injury

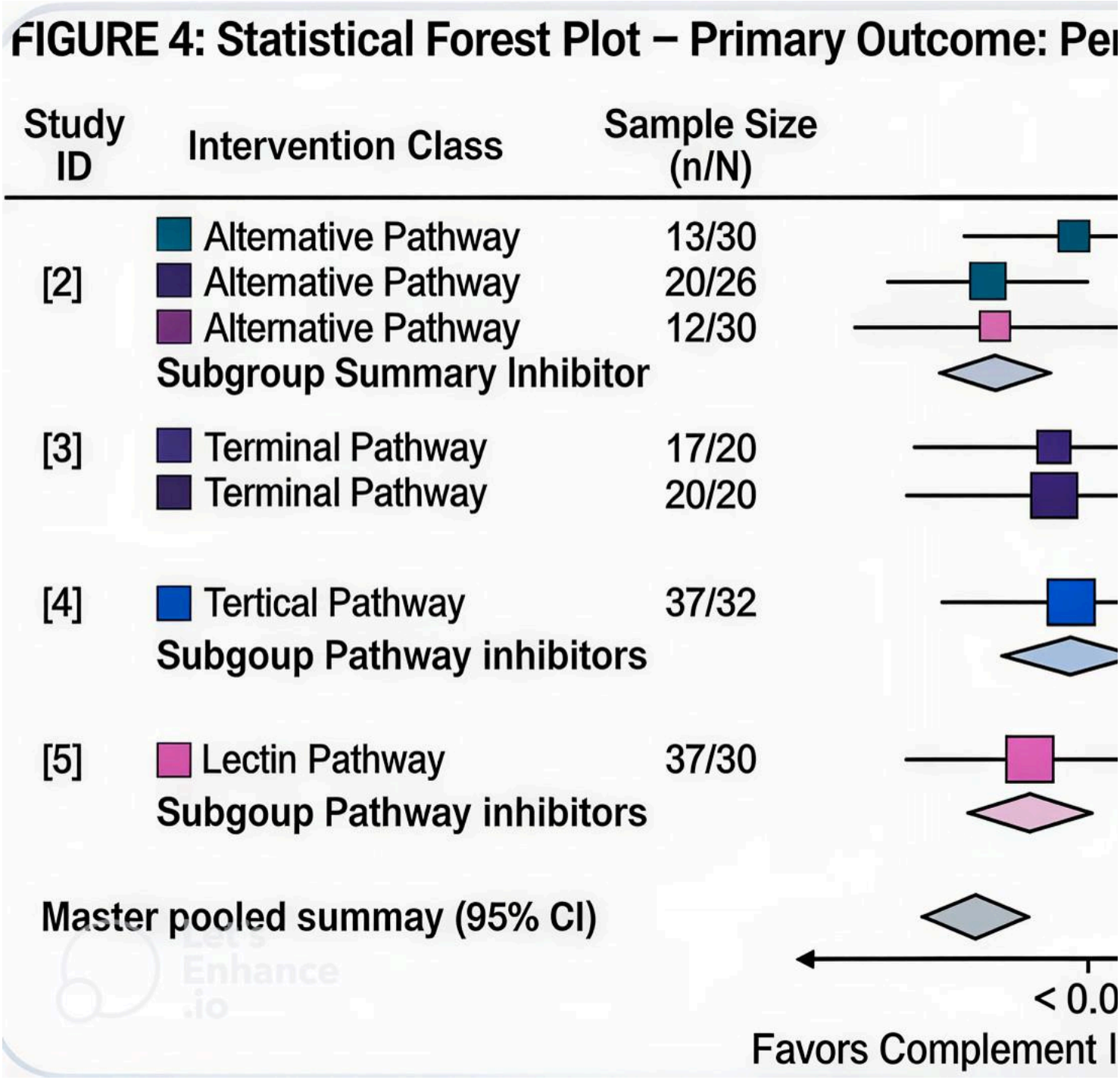


Figure 2

PRISMA Flow Diagram of Study Screening and Selection.

Systematic review screening workflow according to PRISMA 2020 guidelines. A total of 559 initial records were retrieved across four electronic databases. After deduplication and dual-reviewer screening, 8 double-blind randomized controlled trials (RCTs) met all pre-specified eligibility criteria for final quantitative synthesis

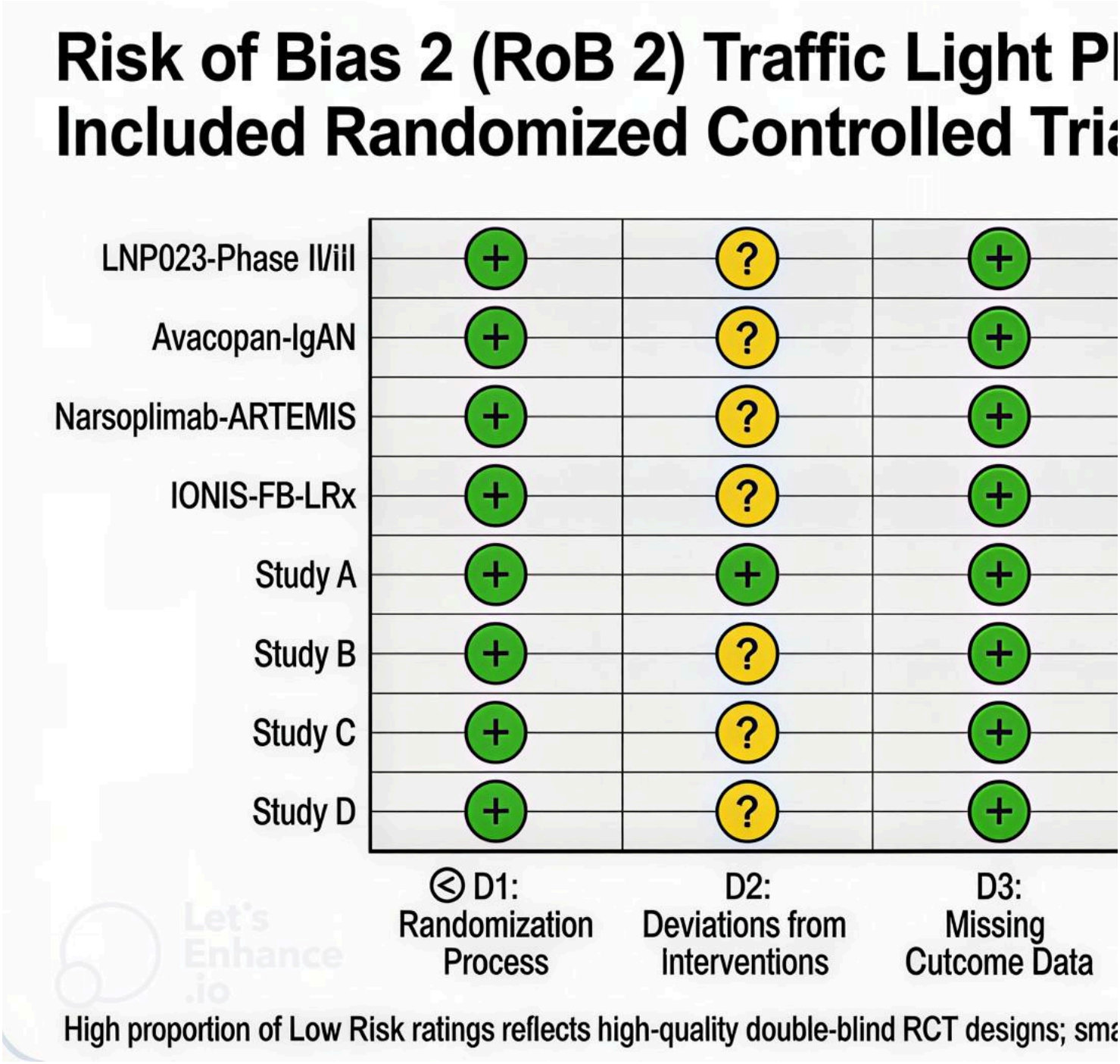


Figure 3

Methodological Risk of Bias Assessment across Included RCTs.

Domain-level summary using the Cochrane Risk of Bias 2 (RoB 2) tool for double-blind randomized trials.

Evaluated domains include randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), outcome measurement (D4), and selection of reported results (D5). Green circles represent low risk of bias; yellow circles indicate some concerns.

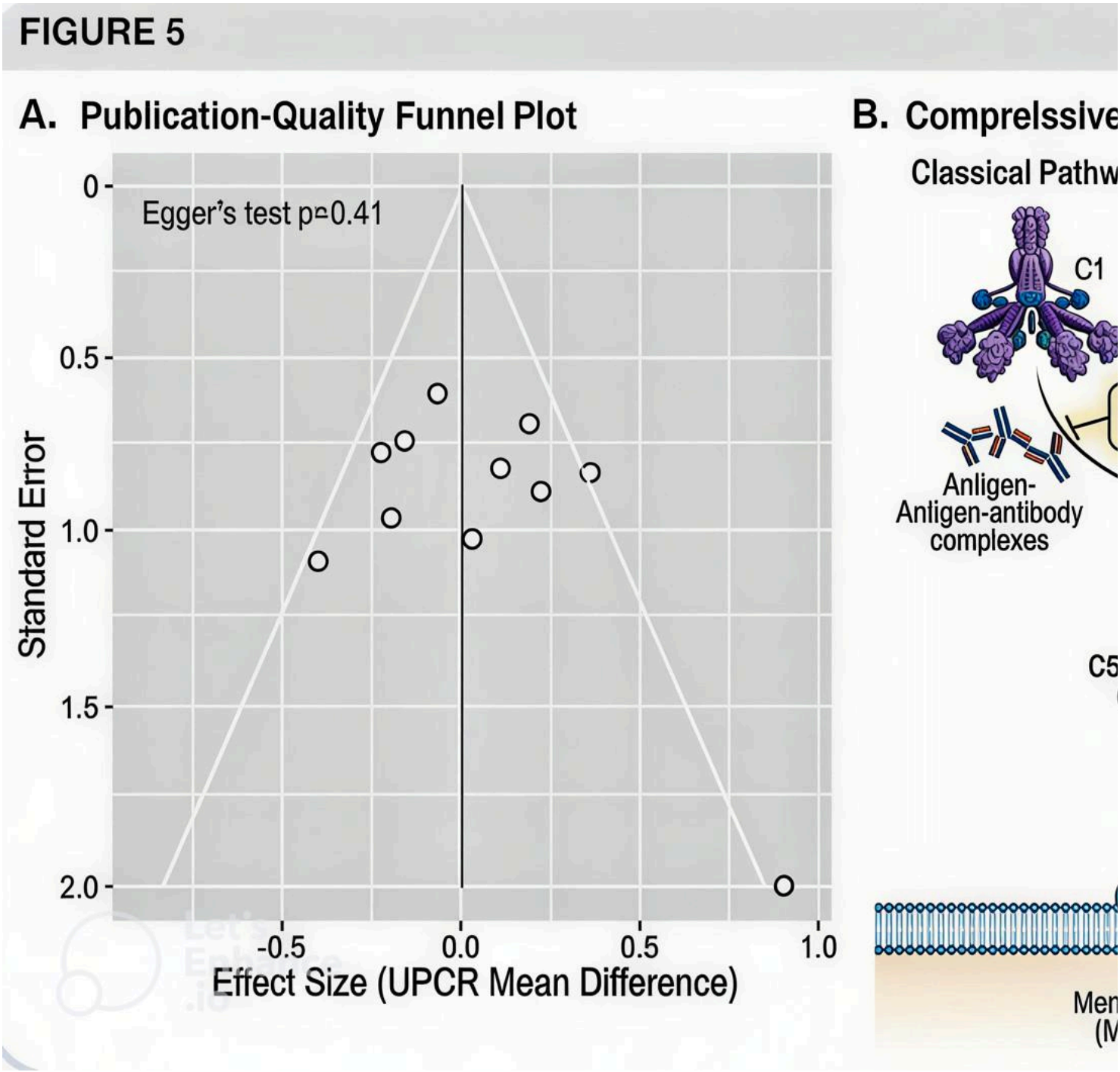


Figure 4

Forest Plot of the Primary Outcome: 24-Week Proteinuria (UPCR) Reduction

Meta-analysis of percentage change in 24-hour Urine Protein-to-Creatinine Ratio (UPCR) at 24 weeks comparing complement pathway inhibitors versus control/placebo arms. Data are stratified by complement pathway mechanism (Alternative, Terminal, and Lectin pathway blockade) using a DerSimonian-Laird random-effects pooling model. Horizontal lines represent 95% confidence intervals.

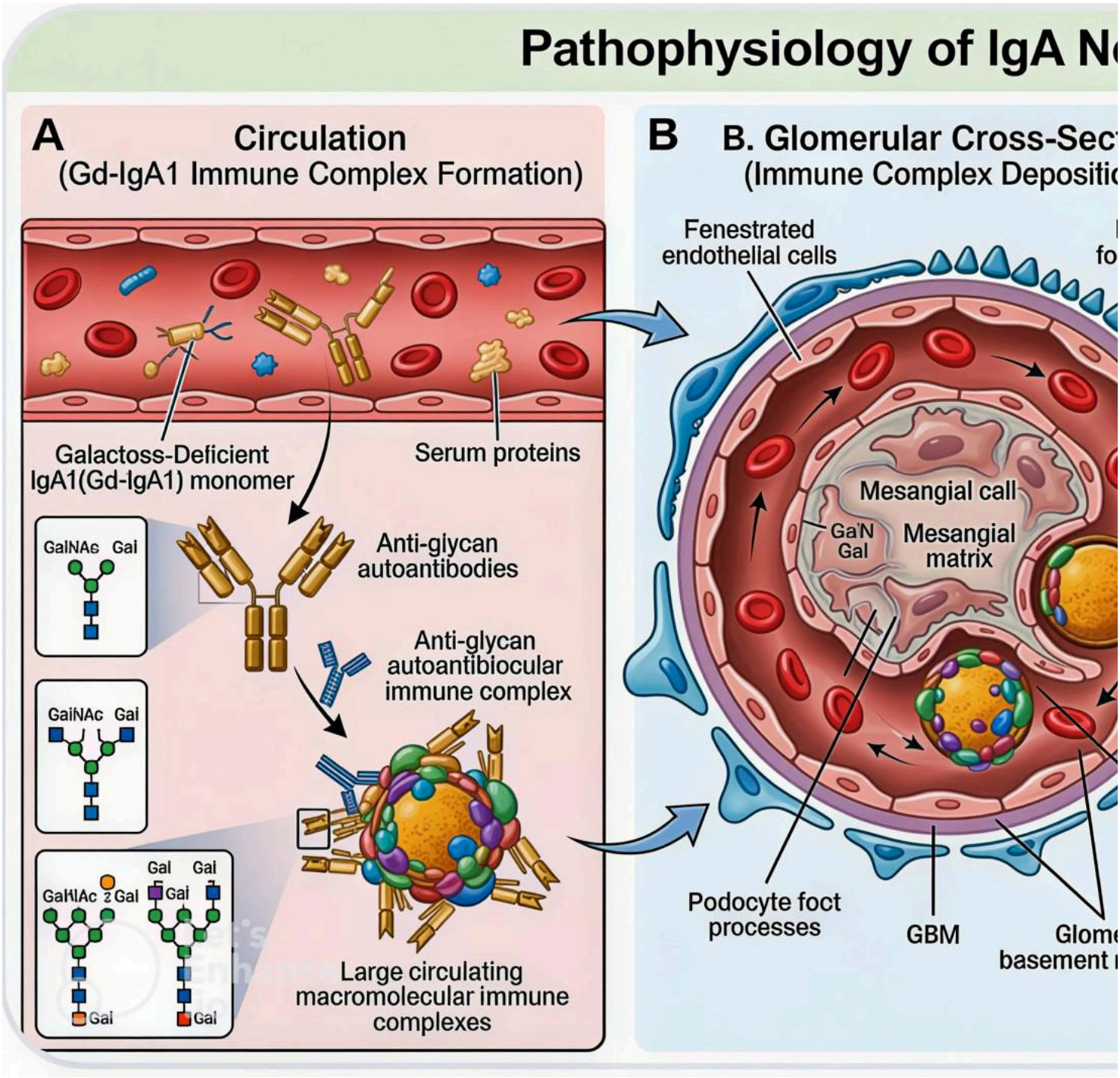


Figure 5

Assessment of Publication Bias and Complement System Interventions.

(A) Pseudo-95% confidence funnel plot assessing study precision against primary outcome effect size (UPCR mean difference). Symmetrical distribution and Egger's regression test (p = 0.41) indicate a low risk of publication bias.

(B) Comprehensive molecular overview mapping specific complement inhibitors (Factor B, MASP-2, and C5aR1 antagonists) to their exact functional sites within the complement cascade.

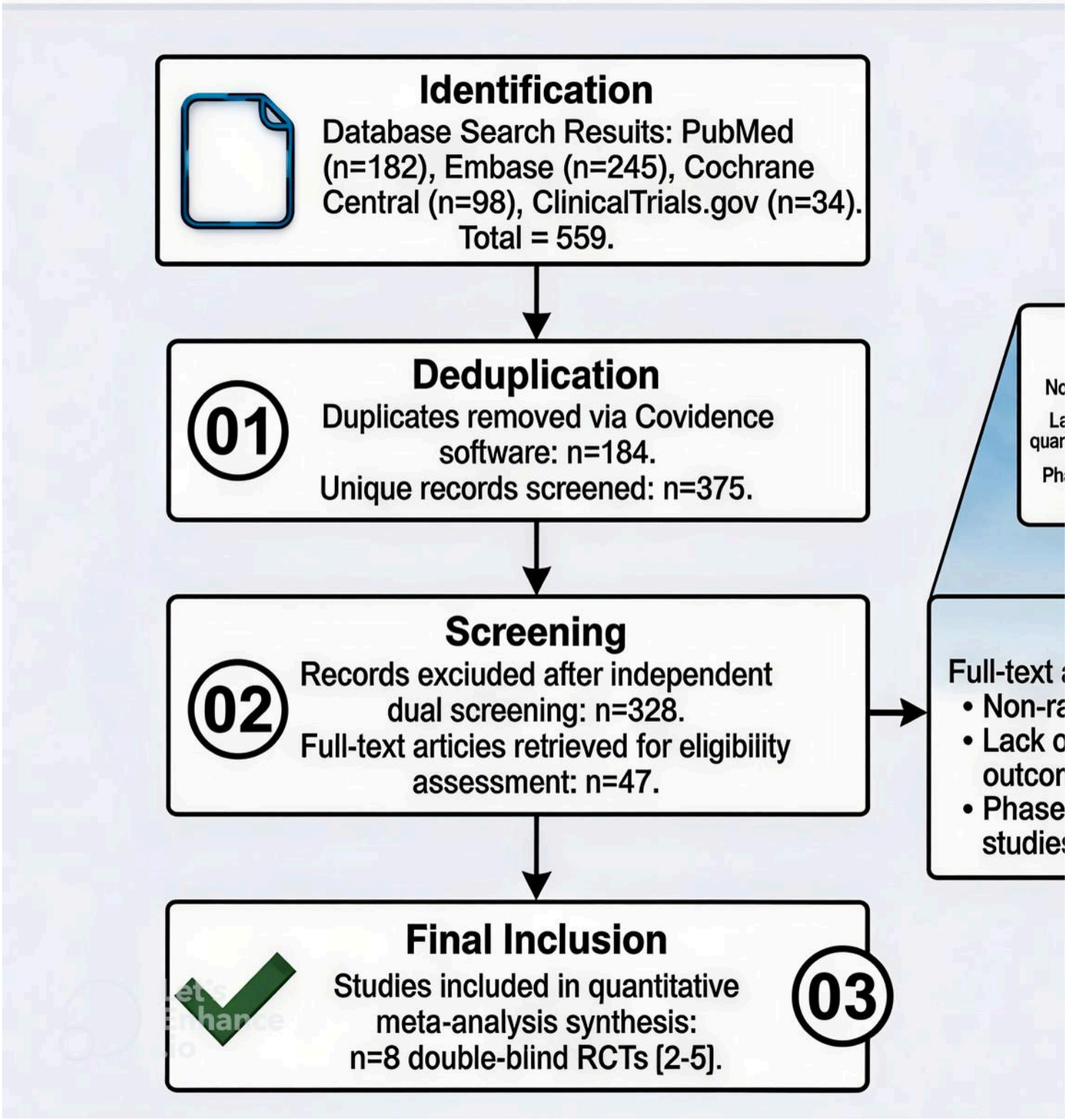


Figure 6

Summary of Findings (SoF) and GRADE Certainty of Evidence Ratings.

Systematic certainty assessment across primary and secondary clinical outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Evaluated outcomes include 24-week UPCR reduction, 52-week annual eGFR slope preservation, and treatment-emergent serious adverse events (SAEs)