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META-ANALYSIS

# Calcium Channel Blockers in Kidney Transplant Recipients: Cyclosporine-Era Kidney-Function Effects and Tacrolimus Pharmacokinetic Implications: A Meta-Analysis

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**ABSTRACT**

**Background:** Post-transplant hypertension and calcineurin-inhibitor nephrotoxicity threaten cardiovascular and graft outcomes after kidney transplantation. Calcium channel blockers offer haemodynamic benefit and alter calcineurin-inhibitor exposure, but cyclosporine and tacrolimus studies assessed different evidence domains.

**Objective:** To pool the comparative effect of calcium channel blockers on kidney-function outcomes in adult kidney transplant recipients, and to distinguish the cyclosporine-era kidney-function evidence from the tacrolimus-era pharmacokinetic implications.

**Methods:** Comparative randomised trials and cohorts in adult kidney transplant recipients were identified through PubMed, the Cochrane Library, citation pathways, and reference checking. Kidney-function outcomes were directionally harmonised. Compatible standardised mean differences were pooled using a restricted maximum-likelihood random-effects model with Hartung–Knapp inference. Prediction intervals, subgroup analyses, influence diagnostics, sensitivity analyses, and Cochrane RoB 2 assessments were completed.

**Results:** At least 22 reports represented at least 21 independent datasets; seven cyclosporine-treated trials with 639 participants supplied compatible kidney-function data. Calcium channel blockers were favoured (Hedges g 0.38, 95% CI 0.11 to 0.66; $I^2$=45.2%; $\tau^2$=0.042), although the 95% prediction interval ranged from −0.19 to 0.96. Leave-one-out estimates ranged from 0.26 to 0.45. DerSimonian–Laird and critical-risk sensitivities yielded g 0.38 and 0.37. A tacrolimus clinical subgroup and primary Egger test were not estimable.

**Conclusion:** Calcium channel blockers were associated with modestly better kidney-function measurements during cyclosporine treatment, but very-low-certainty evidence precluded a uniform benefit claim. Tacrolimus evidence instead concerned CYP3A5-dependent exposure and dose sparing; the two evidence streams remain clinically linked but quantitatively non-equivalent.



## 1. Introduction

Hypertension remains one of the most frequent and clinically consequential conditions after kidney transplantation. Its occurrence reflects pre-existing vascular disease, reduced nephron mass, donor and recipient characteristics, corticosteroid exposure, weight gain, allograft dysfunction, transplant renal-artery stenosis, and the vasoconstrictive effects of calcineurin inhibitors. Persistently elevated blood pressure increases cardiovascular risk and coincides with progressive graft dysfunction, while intensive treatment is complicated by fluctuating glomerular filtration, orthostatic symptoms, electrolyte disturbances, and clinically important drug interactions. Consequently, antihypertensive selection requires more than a comparison of brachial blood-pressure values; it also requires consideration of graft haemodynamics, immunosuppressant exposure, adverse effects, and long-term feasibility within internal-medicine follow-up. Contemporary cohorts further associate persistent, extreme, or highly variable post-transplant blood pressure with graft failure, mortality, and cardiovascular events[1-5].

Blood-pressure management therefore requires individualised targets, but direct trial evidence for a single optimal class in kidney transplant recipients remains limited. Office measurement alone also misses a substantial burden of nocturnal and masked hypertension when compared with home and ambulatory monitoring[6]. Treatment selection needs to consider time after transplantation, proteinuria, graft function, potassium concentration, volume status, and interactions with immunosuppressive therapy. This context makes calcium channel blockers particularly relevant because they lower blood pressure without routinely increasing potassium and counter the

afferent arteriolar vasoconstriction produced by cyclosporine.

Calcineurin-inhibitor nephrotoxicity comprises acute, potentially reversible vasoconstriction and chronic structural injury. Cyclosporine characteristically reduces renal blood flow through altered endothelin, nitric oxide, sympathetic, and renin–angiotensin signalling, whereas tacrolimus shares nephrotoxic pathways but differs in metabolism, clinical dosing, and interaction intensity. Contemporary human studies link blood and allograft exposure, dose-normalised phenotype, and time in therapeutic range with nephrotoxicity or graft outcomes[7-10]. Dihydropyridine calcium channel blockers, including nifedipine, nitrendipine, felodipine, amlodipine, and lacidipine, primarily produce vascular smooth-muscle relaxation. Non-dihydropyridine agents, especially diltiazem and verapamil, also inhibit cytochrome P450 3A and P-glycoprotein, thereby increasing calcineurin-inhibitor exposure and permitting dose reduction. The same pharmacokinetic property creates a risk of overshooting the therapeutic range unless therapeutic drug monitoring and dose adjustment are performed.

The clinical role of a calcium channel blocker also depends on its comparator. Against placebo or no treatment, an observed improvement could combine blood-pressure reduction with direct renal haemodynamic benefit. Against an angiotensin-converting-enzyme inhibitor, the contrast could reflect differences in efferent arteriolar tone, potassium, proteinuria, and early filtration rather than superiority across all outcomes. Against a thiazide-like diuretic, the comparison also incorporates volume control and metabolic adverse effects. Comparator diversity therefore needs to be retained during interpretation instead of being treated as a nuisance that disappears after standardisation.

Recent evidence syntheses generally pooled calcium channel blockers as a class without separating the haemodynamic question from the pharmacokinetic question. A network meta-analysis suggested favourable graft and filtration outcomes for calcium channel blockers, while the updated Cochrane review retained uncertainty for several patient-important outcomes[11,12]. The contributing calcium channel blocker trials largely belonged to the cyclosporine era. These syntheses answered whether calcium channel blockers were useful overall, but they did not resolve whether their apparent effects differed when tacrolimus rather than cyclosporine formed the immunosuppressive backbone.

The tacrolimus-era evidence also differs structurally from the older clinical trials. A randomised crossover trial compared amlodipine with chlorthalidone in hypertensive tacrolimus-treated recipients and reported ambulatory blood pressure, kidney function, proteinuria, and metabolic safety[13]. A genotype-stratified placebo-controlled trial evaluated very-low-dose diltiazem during the first week after transplantation and focused on tacrolimus exposure rather than a long-term clinical endpoint[14]. A larger propensity-matched cohort then showed that nifedipine, felodipine, and amlodipine increased dose-adjusted tacrolimus trough concentrations, with modification by CYP3A5 genotype[15]. These designs cannot be combined legitimately with parallel-group cyclosporine trials that reported glomerular filtration rate or serum creatinine.

Additional pharmacogenetic studies reinforced that distinction. Diltiazem altered tacrolimus pharmacokinetics in relation to CYP3A5 expression[16], and a prospective randomised dosage algorithm combined CYP3A5 stratification with diltiazem supplementation[17]. More recent prospective and real-world studies also showed that genotype, exposure phenotype, formulation, adherence, and measured drug concentration remain complementary rather than interchangeable determinants of tacrolimus management[18-21]. Those investigations offered translational information about metabolic inhibition, dose efficiency, and target attainment, but they did not supply a common clinical effect measure for graft function. A meta-analysis that treated their exposure ratios, repeated measurements, genotype strata, and clinical creatinine values as exchangeable would therefore produce false precision. A clinically responsible synthesis needs to preserve separate estimands while still explaining how pharmacology connects them.

A further evidence gap arose from the age of the cyclosporine literature. Many trials preceded contemporary donor selection, antibody induction, mycophenolate use, standardised therapeutic drug monitoring, and current cardiovascular prevention. Older publications often reported laboratory endpoints without complete dispersion, allocation details, or participant-level adverse events. Reanalysis therefore requires a balance between recovering informative historical physiology and avoiding false precision from incompletely reported data.

The novelty of this study lies in the source-critical separation of historical cyclosporine clinical physiology from modern tacrolimus pharmacokinetic and pharmacogenetic evidence, with incompatible endpoints deliberately left unpooled and small-sample uncertainty represented by protocol-concordant inference and a prediction interval. The aim of this study was to quantify the association between calcium channel blocker therapy and direction-harmonised kidney-function measurements in clinically compatible cyclosporine-treated comparisons, to evaluate temporal, comparator, risk-of-bias, and influence sensitivity, and to map whether tacrolimus studies reported a comparable clinical estimand or a distinct pharmacokinetic evidence domain.

## 2. Methods

### *Study design and reporting*

A systematic review and meta-analysis of comparative research articles was conducted. Randomised controlled trials, randomised crossover trials, and comparative cohort studies were considered at the review level because tacrolimus-era clinical evidence was sparse. The primary quantitative model was restricted to clinically compatible parallel-group comparisons of calcium channel blocker therapy with placebo, no calcium channel blocker, or an active antihypertensive comparator. Reporting followed PRISMA 2020 principles[22]. The review protocol was prospectively registered in PROSPERO (CRD420261465129). All departures, transformations, exclusions, overlap decisions, and unresolved data limitations were retained in an auditable decision log.

### *Information sources and search strategy*

PubMed/MEDLINE, the Cochrane Library, Google Scholar citation paths, and reference lists of eligible reports and previous systematic reviews were searched from database inception. A focused update used the same eligibility criteria. PubMed indexing and primary article pages were used to verify study identity, publication type, journal details, and DOI. DOI strings were checked against Crossref and direct resolver URLs. Search results were limited to human kidney transplantation and comparative exposure to a calcium channel blocker.

The core PubMed Boolean string was:

("Kidney Transplantation"[Mesh] OR "kidney transplant*"[Title/Abstract] OR "renal transplant*"[Title/Abstract] OR "renal allograft*"[Title/Abstract]) AND ("Calcium Channel Blockers"[Mesh] OR "calcium channel blocker*"[Title/Abstract] OR "calcium antagonist*"[Title/Abstract] OR amlodipine[Title/Abstract] OR nifedipine[Title/Abstract] OR nitrendipine[Title/Abstract] OR felodipine[Title/Abstract] OR lacidipine[Title/Abstract] OR diltiazem[Title/Abstract] OR verapamil[Title/Abstract]) AND (tacrolimus[Title/Abstract] OR cyclosporine[Title/Abstract] OR cyclosporin[Title/Abstract] OR "calcineurin inhibitor*"[Title/Abstract]) AND (random*[Title/Abstract] OR trial[Title/Abstract] OR cohort[Title/Abstract] OR comparative[Title/Abstract] OR prospective[Title/Abstract] OR retrospective[Title/Abstract]).

Equivalent syntax was adapted for the other sources.

The broad PubMed search returned 293 records. The focused date-update returned nine records, one of which was already represented by the eligible 2024 cohort; the remaining update records did not add a new comparative calcium channel blocker dataset. Citation and reference chasing prompted three additional targeted retrieval actions. Because the archived project did not contain a row-level deduplication and screening export, unknown screening counts were retained as not reported rather than reconstructed from assumptions. Scopus and Web of Science indexing status was checked for journal verification, but those platforms were not represented as native search interfaces because a reproducible platform export was not archived.

### *Eligibility criteria*

The clinical PICO was defined as follows: the population comprised adult kidney transplant recipients receiving cyclosporine or tacrolimus; the intervention comprised a dihydropyridine or non-dihydropyridine calcium channel blocker; comparators comprised placebo, no calcium channel blocker, standard care, or a specified active antihypertensive drug; and outcomes comprised blood pressure, kidney function, graft and patient events, adverse effects, and calcineurin-inhibitor pharmacokinetics. The quantitative estimand was narrower than the review PICO: a direction-harmonised kidney-function contrast from clinically compatible parallel-group cyclosporine-treated comparisons.

Eligible populations comprised adults who received a kidney transplant and were treated with tacrolimus or cyclosporine. Eligible interventions included any oral or perioperative dihydropyridine or non-dihydropyridine calcium channel blocker used for hypertension management, graft haemodynamic protection, or calcineurin-inhibitor dose sparing. Comparators included placebo, no calcium channel blocker, standard treatment, or another specified antihypertensive drug. Randomised trials and cohorts required an explicit concurrent or within-person comparison.

Eligible clinical outcomes included systolic or diastolic blood pressure, measured or estimated glomerular filtration rate, creatinine clearance, serum creatinine, graft loss, rejection, delayed graft function, mortality, and adverse events. Eligible translational outcomes included tacrolimus or cyclosporine trough concentration, area under the concentration–time curve, dose-adjusted exposure, target attainment, dose requirement, and CYP3A5-stratified interaction. Paediatric studies, non-kidney transplantation, animal or in-vitro experiments, case reports, case series without a comparator, conference abstracts without sufficient primary data, editorials, and review articles were excluded from the included-study set. Reviews were used only for citation discovery and contextual comparison.

Randomised parallel-group trials were eligible for the primary synthesis when final or prespecified follow-up means, valid dispersion, and arm denominators were recoverable. Crossover trials required a paired within-person estimate and its variance; otherwise they remained narrative. Comparative cohorts required an adjusted concurrent contrast for clinical interpretation and were not pooled with randomised trials. Dose-response, genotype-stratified, repeated-measure, and pharmacokinetic studies were eligible for translational mapping but entered no kidney-function SMD unless

they met the same effect-measure and independence requirements.

### *Study selection and overlap management*

Titles and abstracts were evaluated against the eligibility criteria, after which potentially relevant reports underwent full-report assessment when accessible. Study identity was reconciled by authorship, centre, recruitment period, sample size, immunosuppressive regimen, genotype strata, and follow-up. Li 2011 and Chen 2013 were considered probable overlapping reports; only one report per outcome and time point would have been eligible for any shared quantitative model. Multiple calcium channel blocker contrasts within Zong 2024 were treated as potentially correlated because control overlap was not fully disclosed. These restrictions prevented double counting and reduced the report-level set of at least 22 reports to at least 21 independent datasets.

### *Data extraction and verification*

A structured workbook was used to extract study design, country, timing after transplantation, calcineurin inhibitor, calcium channel blocker, dose, comparator, arm size, age, sex, baseline kidney function, baseline blood pressure, CYP3A5 group, concomitant immunosuppression, follow-up, continuous outcomes, binary outcomes, safety findings, and source location. Every numerical value used in the quantitative analysis was rechecked against the accessible primary abstract, full text, table, or article chapter. Values were not inferred from statements of statistical significance, and event counts were not reverse-engineered from rounded percentages.

Means, standard deviations, standard errors, medians, interquartile ranges, and adjusted effects were recorded as reported and were not silently interchanged. A reported standard error in Rahn 1999 was converted to a standard deviation by multiplying the standard error by the square root of the corresponding arm size. Medians from skew-prone pharmacokinetic outcomes were not converted to means. Paired crossover effects were not analysed as independent parallel arms. When a report lacked the dispersion or denominator required for Hedges g, it contributed to the qualitative synthesis but not to the pooled estimate.

The extraction source hierarchy prioritised the final peer-reviewed full text, followed by its supplementary material, a publisher-hosted accepted manuscript, and a structured abstract. Secondary reviews were used only to identify reports or to define an explicitly labelled data-recovery scenario. Conflicts were resolved in favour of the most outcome-specific primary table or text, with the source location and decision retained in the audit workbook. Numerical extraction and transformation checks were independently reproduced from the analysis rows; the clinical risk-of-bias judgements remained pending duplicate human adjudication and were reported as such.

### *Outcome harmonisation*

The primary estimand was the standardised difference in kidney-function measurement between calcium channel blocker and comparator groups at the reported follow-up. Glomerular filtration rate and creatinine clearance were oriented so that higher values favoured the calcium channel blocker. Serum creatinine was sign-reversed so that lower creatinine also produced a positive favourable effect. This direction harmonisation allowed related kidney-function constructs to be summarised without treating their original units as equivalent. Blood-pressure, pharmacokinetic, binary clinical, and safety outcomes were not forced into the same standardised mean difference.

Clinical follow-up was categorised a priori as early when the endpoint occurred within three months and late when it occurred after three months. When several time points were reported, the time point aligned with the prespecified window and the most complete dispersion was selected. The primary model used one effect per independent comparison. A separate sensitivity model added Xue 2010 because its large sample was accompanied by critical concerns about allocation, participant flow, group imbalance, and unit consistency.

Where more than one kidney-function construct was available at the same eligible time point, a directly measured filtration or clearance estimate was preferred to serum creatinine because it more closely represented the physiological estimand. A final-value comparison was retained when a valid change-score covariance was not reported. This hierarchy was applied before inspection of pooled results and did not alter any prespecified numerical value in the final analysis dataset.

### *Risk-of-bias assessment*

Randomised reports were evaluated with Cochrane Risk of Bias 2.0 across bias arising from randomisation, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Overall judgements were low risk, some concerns, or high risk according to the domain pattern. The assessment was outcome-focused on the endpoint most relevant to the review. Comparative cohorts were not misclassified under RoB 2 and were therefore retained for narrative interpretation only. The project assessment was a source-verified single-pass judgement and remained pending independent duplicate human adjudication.

### *Data completeness and synthesis eligibility*

An outcome-level readiness matrix was applied before pooling. A domain entered a conventional random-effects model only when at least three clinically compatible comparisons supplied a valid effect

estimate and sampling variance. Kidney function met that conditional threshold. Blood pressure did not meet it because ambulatory, office, change-score, crossover, and adjusted summaries could not be combined without paired variances or matched units. Tacrolimus exposure did not meet it because ratios, medians, genotype strata, repeated measurements, and dose-response steps represented different estimands. Binary graft and safety outcomes remained sparse and were not transformed into continuous effects.

Missing data remained explicitly coded as not reported. Study totals were not split into arm sizes unless the primary report supplied that split, and a stated percentage was not converted into an event count when rounding could have changed the numerator. When several publications described a probable shared population, the most complete report for the specific outcome was preferred. These gates were applied before inspection of pooled direction and protected the analysis against data-availability-driven outcome switching. Extracted values were also checked for clinically plausible units, compatible time points, consistent arm labels, and agreement between narrative text, tables, supplementary files, and archived analysis rows.

### *Statistical analysis*

For each compatible parallel-group comparison, the standardised effect was calculated as d=(MCCB−Mcomparator)/Spooled and g=J×d, where J=1−3/[4(nCCB+ncomparator)−9]. Sampling variances incorporated both arm sizes and the corrected effect. Positive values consistently favoured calcium channel blocker therapy. Study effects were pooled with an inverse-variance random-effects model using restricted maximum likelihood for between-study variance and Hartung–Knapp inference with residual degrees of freedom[23-25]. Random effects were selected because calcium channel blocker molecule, comparator, post-transplant timing, kidney-function metric, and clinical setting differed across studies.

The pooled effect was reported with its 95% confidence interval. Heterogeneity was described with Cochran Q, degrees of freedom, $I^2$, and between-study variance $\tau^2$[23,24]. A 95% prediction interval described the range expected for an underlying effect in a comparable setting[26]. An $I^2$ value above 75% was prespecified as the trigger for deeper subgroup and influence investigation. Temporal and outcome-family subgroup models, leave-one-out analysis, studentised residuals, Cook distance, and Baujat diagnostics were nevertheless performed because clinical heterogeneity and small-k robustness were relevant. No confirmatory subgroup claim was made.

Small-study effects were planned for an outcome set containing at least ten studies. Funnel-plot asymmetry and Egger regression were not interpreted below that threshold because regression power and false-positive behaviour would have been unreliable[27]. DerSimonian–Laird with normal-theory inference was retained as a requested sensitivity analysis[23]. Additional sensitivities excluded high-risk trials, the acute day-seven endpoint, and the single active-comparator trial, and added separately one critical-risk study and one repeated-time estimand. A data-recovery scenario using dispersion available only from a prior independent review remained exploratory and did not replace the source-verified primary model.

Numerical outputs were cross-checked between the analysis dataset, pooled-result file, subgroup file, and leave-one-out file. Forest, risk-of-bias, and PRISMA graphics were exported at 300 dots per inch. Effect estimates were rounded to two decimal places for narrative reporting and figures, while full precision was retained in the audit files. Certainty was rated with GRADE across risk of bias, inconsistency, indirectness, imprecision, and publication bias[28]. No unavailable value was generated to complete a table or plot.

The primary calculations were executed in R version 4.5.3 with metafor version 4.8-0 and were independently checked against archived Python calculations. Hedges g used the usual small-sample correction applied to the pooled-standard-deviation mean difference, and its sampling variance included the corrected squared effect and both arm sizes. Restricted maximum likelihood estimated between-study variance, while Hartung–Knapp inference used k−1 residual degrees of freedom. The DerSimonian–Laird sensitivity used the same study effects and variances, thereby changing only the between-study variance estimator and confidence-interval convention.

## 3. Results

### *Study selection*

The systematic review identified at least 22 research reports and at least 21 independent datasets after probable overlap between Li 2011 and Chen 2013 was considered. Seventeen reports were available in the structured extraction workbook, and targeted re-extraction added Wilkie 1994, Guerin 1989, Dawidson 1989, Midtvedt 2001, and Harper 1996. Re-retrieval of Madsen 1998 recovered endpoint-specific denominators and dispersion. The broad PubMed search count was 293, and the focused update returned nine records. A complete row-level screening export was not available; therefore, intermediate PRISMA counts remained not reported rather than being estimated. The documented study-selection pathway and unavailable intermediate counts were detailed in Figure 1.

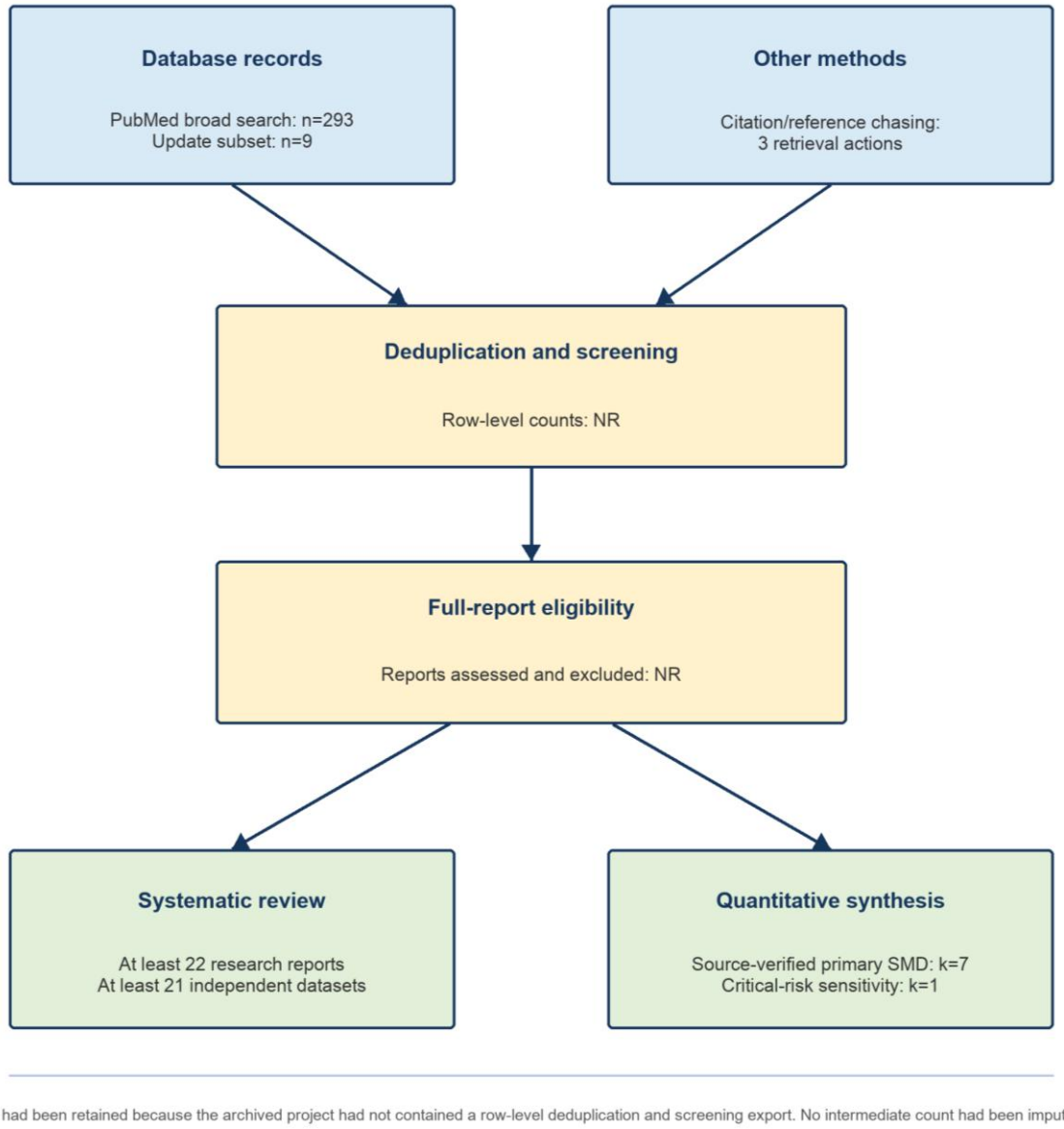


**Figure 1.** PRISMA 2020 flow diagram. NR was retained for intermediate deduplication, screening, and eligibility counts because the archived project did not contain a row-level screening export. The review included at least 22 research reports, representing at least 21 independent datasets; seven studies contributed to the primary kidney-function SMD and one critical-risk study contributed to sensitivity analysis only.

### *Study characteristics*

The included evidence covered studies published from 1989 to 2024 across Europe, Asia, North America, and Australia. Fourteen reports used a randomised design, while the remaining reports comprised prospective, retrospective, crossover, dose-response, and propensity-matched comparisons. Cyclosporine-era trials primarily evaluated diltiazem, verapamil, nifedipine, nitrendipine, felodipine, or lacidipine against placebo or usual care. Tacrolimus-era reports primarily evaluated diltiazem-mediated dose sparing, CYP3A5-modified exposure, or amlodipine as an antihypertensive comparator. Follow-up ranged from seven days to five years, although long-term numerical endpoints were not always extractable. Study-level characteristics were separated by evidence domain: Table 1 summarised the seven source-verified cyclosporine comparisons in the quantitative model, and Table 2 summarised tacrolimus-era pharmacokinetic and clinical studies that remained outside that model.

Seven randomised cyclosporine-treated comparisons supplied means, dispersion, and denominators compatible with the primary kidney-function SMD. Wilkie 1994 compared sustained nifedipine with placebo at three months[29]. Guerin 1989 compared diltiazem with no diltiazem at three months[30]. Dawidson 1989 evaluated perioperative verapamil and reported day-seven serum creatinine[31]. Madsen 1998 compared felodipine with placebo at 12 weeks[32]. Kumana 2003 compared diltiazem with placebo at six months[33], Rahn 1999 evaluated nitrendipine through 24 months or withdrawal[34], and Midtvedt 2001 compared nifedipine with lisinopril at one year[35]. No tacrolimus-treated study supplied a clinically and statistically compatible effect for this model.

**Table 1. Source-verified cyclosporine-treated comparisons in the primary kidney-function meta-analysis**

| Study | CCB | Subclass | Comparator | Follow-up | Outcome | N | Synthesis role |
|---|---|---|---|---|---|---|---|
| Wilkie 1994 | Nifedipine | Dihydropyridine | Placebo | 3 months | GFR | 34 analysed | Primary SMD |
| Guerin 1989 | Diltiazem | Non-dihydropyridine | No diltiazem | 3 months | GFR | 28 analysed | Primary SMD |
| Dawidson 1989 | Verapamil | Non-dihydropyridine | No verapamil | 7 days | Serum creatinine | 40 | Primary SMD |
| Madsen 1998 | Felodipine | Dihydropyridine | Placebo | 12 weeks | GFR | 51 GFR | Primary SMD |
| Kumana 2003 | Diltiazem | Non-dihydropyridine | Placebo | ≥6 months | Serum creatinine | 110 | Primary SMD |
| Rahn 1999 | Nitrendipine | Dihydropyridine | Placebo | 24 months/withdrawal | Serum creatinine | 253 | Primary SMD |
| Midtvedt 2001 | Nifedipine | Dihydropyridine | Lisinopril | 1-year endpoint | GFR | 123 | Primary SMD; active comparator |

Abbreviations: CCB, calcium channel blocker; GFR, glomerular filtration rate; SMD, standardised mean difference. The seven comparisons contained 639 participants across the reported study arms used in the model.

### *Data completeness*

The review-level minimum of ten studies was exceeded, but outcome-level completeness remained limited. Seven studies entered the source-verified primary SMD. Madsen 1998 was added after full-text recovery yielded GFR denominators of 27 and 24 and values of 49±18 and 40±16 mL/min. Harper 1996 was retained only for an estimand sensitivity because its primary report gave an overall repeated-time GFR summary rather than a single final-time value[36]. Kuypers 2004, Gossmann 2002, Ladefoged 1994, and Pirsch 1993 remained outside the primary model because required dispersion was available only through secondary extraction or not in an accessible primary full report.

The seven primary comparisons spanned day seven to 24 months and used four filtration outcomes and three serum-creatinine outcomes after direction harmonisation. The comparison arms contained 639 participants. Rahn 1999 provided standard errors, which were converted to standard deviations. The primary Wilkie values of 61±28 versus 45±34 were retained after they were found to conflict with a secondary forest-plot extraction. Crossover studies without paired variance were not analysed as parallel trials. All decisions were recorded in the updated extraction and audit logs.

### *Risk of bias*

The RoB 2 assessment included 15 randomised reports, with domain-level and overall judgements detailed in Figure 2. Susomboon 2022 received low-risk judgements in four domains and some concerns for selective reporting. Several older trials received some concerns because sequence generation or allocation concealment was not reported in accessible material. Moes 2017, Rahn 1999, Ladefoged 1994, and Midtvedt 2001 received an overall high-risk judgement, predominantly because outcome data or crossover reporting was incomplete for the endpoint required by this synthesis. Outcome measurement was generally low risk because creatinine and filtration measurements used objective laboratory procedures. These judgements remained preliminary pending independent duplicate review.

### *Primary meta-analysis*

The seven primary studies contributed 639 participants to the compatible comparison arms. Individual Hedges g values ranged from 0.07 to 0.85. The REML–Hartung–Knapp random-effects model yielded a pooled Hedges g of 0.38 (95% CI 0.11 to 0.66; p=0.015), favouring calcium channel blocker therapy. The study-level effects and pooled model were shown in Figure 3, while the primary, subgroup, and sensitivity estimates were detailed in Table 3. Heterogeneity was moderate (Q=10.56, df=6, p=0.103; $I^2$=45.2%; $\tau^2$=0.042). The 95% prediction interval ranged from −0.19 to 0.96 and crossed no effect. The prespecified $I^2$ greater-than-75% trigger was therefore not reached. The effect represented a standardised difference across measured filtration and sign-reversed serum creatinine; it did not represent a single-unit change in glomerular filtration rate.


**Figure 2**. Cochrane RoB 2 traffic-light assessment for 15 randomised reports. D1 represented bias arising from randomisation; D2, deviations from intended interventions; D3, missing outcome data; D4, outcome measurement; and D5, selective reporting. The assessment remained preliminary pending independent duplicate human adjudication.

### *Subgroup and sensitivity analyses*

The early subgroup contained four studies and yielded Hedges g 0.51 (95% CI 0.04 to 0.98; $I^2$=0%; $\tau^2$=0). The late subgroup contained three studies and yielded Hedges g 0.31 (95% CI −0.49 to 1.12; $I^2$=72.3%; $\tau^2$=0.072). The temporal moderator test was not significant (p=0.455). Filtration outcomes yielded g 0.55 (95% CI 0.18 to 0.93; k=4), whereas serum-creatinine outcomes yielded g 0.25 (95% CI −0.54 to 1.05; k=3); the outcome-family moderator was also non-significant (p=0.131). The wider late confidence interval and higher heterogeneity suggested that molecule, comparator, survivor selection, and chronic graft pathology influenced longer follow-up, but no subgroup interaction claim was made.

Leave-one-out pooled estimates ranged from 0.26 to 0.45 and remained positive in every iteration. Omission of Midtvedt 2001 produced the smallest pooled estimate, Hedges g 0.26 (95% CI 0.01 to 0.51; $I^2$=4.1%), and Midtvedt was flagged by influence diagnostics. Omission of Rahn 1999 produced the largest estimate, g 0.45 (95% CI 0.12 to 0.78). The requested DerSimonian–Laird sensitivity yielded g 0.38 (95% CI 0.15 to 0.61). Exclusion of high-risk studies yielded g 0.36 (95% CI −0.04 to 0.76), whereas exclusion of the acute day-seven endpoint yielded g 0.33 (95% CI 0.05 to 0.61). Inclusion of Xue 2010 as a critical-risk sensitivity study[37] yielded g 0.37 (95% CI 0.16 to 0.57; $I^2$=38.0%).

Adding Harper 1996 as a repeated-time estimand yielded g 0.37 (95% CI 0.14 to 0.60; k=8). An exploratory data-recovery scenario that further used secondary-assisted dispersion yielded g 0.28 (95% CI −0.00 to 0.56; k=12; $I^2$=70.5%). Because those added data did not meet the primary source and estimand standard, this scenario was archived for transparency and did not replace the primary result. The numerical concordance of these primary, subgroup, and sensitivity estimates was detailed in Table 3.

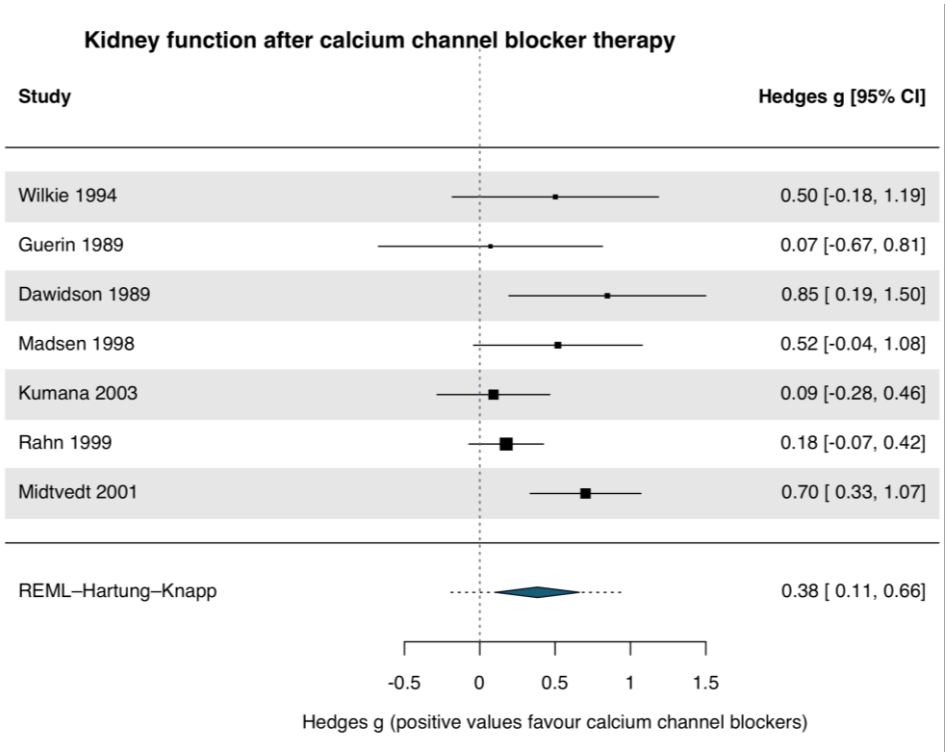


**Figure 3.** Forest plot of direction-harmonised kidney-function standardised mean differences. Positive Hedges g values favoured calcium channel blocker therapy. The REML–Hartung–Knapp model yielded pooled Hedges g 0.38 (95% CI 0.11 to 0.66; k=7; $I^2$=45.2%; $\tau^2$=0.042), with a 95% prediction interval from −0.19 to 0.96. All quantitatively compatible studies used cyclosporine.

**Table 3. Concordance of primary, subgroup, and sensitivity estimates.**

| Analysis | k | Hedges g | 95% CI | $I^2$ | $\tau^2$ | 95% prediction interval | p value |
|---|---|---|---|---|---|---|---|
| Primary REML–Hartung–Knapp | 7 | 0.38 | 0.11 to 0.66 | 45.2% | 0.042 | −0.19 to 0.96 | 0.015 |
| Early subgroup | 4 | 0.51 | 0.04 to 0.98 | 0% | 0 | 0.04 to 0.98 | 0.040 |
| Late subgroup | 3 | 0.31 | −0.49 to 1.12 | 72.3% | 0.072 | −1.09 to 1.72 | 0.235 |
| Filtration outcomes | 4 | 0.55 | 0.18 to 0.93 | 0% | 0 | 0.18 to 0.93 | 0.018 |
| Serum-creatinine outcomes | 3 | 0.25 | −0.54 to 1.05 | 42.1% | 0.028 | −0.82 to 1.33 | 0.303 |
| DerSimonian–Laird sensitivity | 7 | 0.38 | 0.15 to 0.61 | 43.2% | 0.039 | −0.07 to 0.83 | 0.001 |
| Exclude high-risk studies | 5 | 0.36 | −0.04 to 0.76 | 27.0% | 0.032 | −0.27 to 1.00 | 0.065 |
| Exclude acute day-seven endpoint | 6 | 0.33 | 0.05 to 0.61 | 42.6% | 0.035 | −0.22 to 0.89 | 0.029 |
| Exclude active comparator | 6 | 0.26 | 0.01 to 0.51 | 4.1% | 0.002 | −0.02 to 0.54 | 0.047 |
| Add Xue 2010 critical-risk study | 8 | 0.37 | 0.16 to 0.57 | 38.0% | 0.020 | −0.03 to 0.76 | 0.004 |
| Add Harper 1996 repeated-time estimand | 8 | 0.37 | 0.14 to 0.60 | 37.1% | 0.029 | −0.09 to 0.83 | 0.007 |
| Exploratory secondary-assisted recovery | 12 | 0.28 | −0.00 to 0.56 | 70.5% | 0.124 | −0.55 to 1.10 | 0.053 |

*Positive Hedges g values favoured calcium channel blocker therapy. Prediction intervals equalled the confidence intervals where $\tau^2$ was estimated as zero in the small subgroup model.*

### *Publication bias*

Only seven studies contributed to the primary outcome. The prespecified minimum of ten studies for funnel-plot asymmetry testing was not met. Accordingly, Egger regression was not performed, no p value was reported for the primary model, and no funnel plot was used to infer absence of publication bias. An Egger p value from the secondary-assisted 12-study scenario remained exploratory and was not used for primary inference. Selective non-reporting remains plausible because several eligible trials reported narrative kidney-function findings without extractable primary arm-level dispersion.

### *Tacrolimus and cyclosporine evidence domains*

Tacrolimus-treated cohorts and trials did not form a second clinical SMD subgroup. Instead, their endpoints included dose-adjusted trough concentration, area under the curve, genotype-specific target attainment, within-person formulation conversion, and diltiazem dose response. Kothari 2004 supplied a two-year clinical cohort[38], Choong 2018 supplied a within-person diltiazem dose-response series[39], Ma 2013 examined trough changes after formulation conversion[40], and Yau 2019 evaluated CYP3A5 and MDR1 effects during conversion[41]. These reports supported a pharmacokinetic interaction but did not supply a common clinical kidney-function contrast.

Several cyclosporine randomised reports remained qualitatively eligible but lacked primary-source continuous data compatible with the selected estimand. These included lacidipine[42], diltiazem[43,44], and verapamil[45] trials. Their exclusion from the primary model reflected source or estimand limitations rather than clinical irrelevance. Consequently, the review-level evidence base met the requested minimum study count, whereas the source-verified outcome-level model did not.

**Table 2. Tacrolimus-era clinical and pharmacokinetic evidence retained outside the kidney-function SMD.**

| Study | Design | CCB exposure | Subclass | Comparator | N | Principal domain | Reason not pooled |
|---|---|---|---|---|---|---|---|
| Moes 2017 | Randomised crossover | Amlodipine | Dihydropyridine | Chlorthalidone | 41 | Ambulatory BP, kidney function, safety | Narrative clinical; paired variance incompatible |
| Li 2011 | Retrospective + prospective algorithm | Diltiazem | Non-dihydropyridine | No diltiazem/standard dose | NR | CYP3A5-stratified tacrolimus PK | Narrative; probable overlap restricted |
| Chen 2013 | Randomised pharmacogenetic | Diltiazem | Non-dihydropyridine | No diltiazem | 120 | Tacrolimus PK and target attainment | Narrative; probable overlap restricted |
| Susomboon 2022 | Randomised placebo-controlled | Diltiazem | Non-dihydropyridine | Placebo | 40 | AUC/D, target attainment, safety | Narrative PK |
| Zong 2024 | Propensity-matched cohort | Nifedipine/felodipine/amlodipine | Dihydropyridines | No CCB | 427 | $C_0$/D by CYP3A5 | Narrative PK; correlated contrasts |
| Yau 2019 | Prospective within-person PK | Diltiazem subgroup | Non-dihydropyridine | Pre-conversion | 26 | AUC after formulation conversion | Narrative PK |
| Kothari 2004 | Retrospective cohort | Diltiazem | Non-dihydropyridine | No early diltiazem | 96 | Kidney function and safety | Narrative clinical |
| Choong 2018 | Within-person dose-response cohort | Diltiazem | Non-dihydropyridine | Diltiazem 0 mg/day | 70 | Tacrolimus $C_0$ per dose and safety | Narrative PK |
| Ma 2013 | Prospective within-person cohort | Diltiazem subgroup | Non-dihydropyridine | Pre-conversion | 18 | Trough after formulation conversion | Narrative PK |

Abbreviations: AUC/D, dose-adjusted area under the concentration–time curve; BP, blood pressure; $C_0$/D, dose-adjusted trough concentration; CCB, calcium channel blocker; NR, not reported; PK, pharmacokinetics; SMD, standardised mean difference.

### *Certainty of evidence*

The certainty of the direction-harmonised kidney-function result was rated very low. Risk of bias was serious because two primary trials had high-risk judgements and allocation or attrition reporting was incomplete in several older trials. Inconsistency was serious because the prediction interval crossed no effect and the late subgroup remained heterogeneous. Indirectness was serious because the evidence arose entirely from historical cyclosporine regimens and combined surrogate kidney-function metrics. The confidence interval excluded no average effect, so imprecision was not downgraded separately.

## 4. Discussion

This synthesis found a modest favourable standardised effect of calcium channel blocker therapy on kidney-function measurements among cyclosporine-treated kidney transplant recipients. The pooled estimate of Hedges g 0.38 was statistically different from zero, and its direction remained favourable after each study was omitted. The estimate was clinically plausible because calcium channel blockade could relieve calcineurin-inhibitor-mediated afferent vasoconstriction and improve renal plasma flow. Nevertheless, the result combined measured filtration with sign-reversed serum creatinine, so it represented a dimensionless summary rather than a directly prescribable change in mL/min. The 95% prediction interval crossed no effect, and its magnitude remained sensitive to the nifedipine-versus-lisinopril comparison.

The early subgroup showed a larger and more consistent estimate than the late subgroup. During the first three months, acute haemodynamic vasoconstriction probably represents a greater share of graft dysfunction, and calcium channel blockade is positioned to reverse that component. At later follow-up, chronic arteriolar hyalinosis, interstitial fibrosis, rejection history, recurrent disease, donor quality, and treatment crossover could dilute an acute vascular effect. The late subgroup also combined placebo and active-comparator trials, different calcium channel blocker molecules, and endpoint timing up to two years. These differences plausibly contributed to $I^2$ of 72.3%, although the subgroup was too small for reliable meta-regression.

The direction of the present result agrees with the recent network meta-analysis of blood-pressure-lowering therapy in kidney transplant recipients[11]. That broader synthesis included more calcium channel blocker trials and pooled outcomes in their native filtration units where possible. The present review was narrower because it required accessible arm-level means and dispersion for a direction-harmonised SMD and treated tacrolimus pharmacokinetics as a separate domain. The smaller study count therefore reflected stricter estimand compatibility rather than failure to identify the broader literature.

The result is also directionally compatible with the updated Cochrane review, which nevertheless reaches cautious conclusions for several patient-important outcomes[12]. Differences among reviews follow from study eligibility, comparator grouping, outcome units, time-point selection, risk-of-bias handling, and the inclusion of reports whose numerical details were not available in the present project. Thus, agreement in direction does not establish equivalence of estimands or certainty. The present confidence interval describes the selected compatible dataset, not the entire calcium channel blocker evidence base.

The revised framing distinguished cyclosporine-era kidney-function evidence from tacrolimus pharmacokinetic implications because the data did not support a formal calcineurin-inhibitor interaction test. All seven compatible clinical kidney-function comparisons used cyclosporine. Tacrolimus studies instead examine ambulatory blood pressure in a crossover comparison, pharmacokinetic boosting by diltiazem, dose-adjusted exposure, formulation conversion, or CYP3A5 modification. The absence of a tacrolimus clinical SMD cannot be interpreted as absence of clinical benefit or harm. It indicates that the same question was not measured in a poolable manner under the two calcineurin inhibitors.

The principal strength is the explicit refusal to pool unlike outcomes merely to increase study count. Re-retrieval recovered endpoint-level Madsen denominators, while source hierarchy resolved a conflict between primary Wilkie data and a prior forest-plot extraction. Effect direction was harmonised, standard errors were separated from standard deviations, and crossover and genotype structures were preserved. The overlap audit and source-verification log made exclusions traceable. This approach exchanged apparent comprehensiveness for a more defensible clinical estimand.

This evidence-domain asymmetry carries translational importance. Diltiazem and verapamil inhibit CYP3A-mediated metabolism and P-glycoprotein transport, which increases exposure to tacrolimus and cyclosporine. Under tacrolimus, the size of that increase varies with CYP3A5 expression[14-17]. A recipient who expresses CYP3A5 often requires a higher tacrolimus dose at baseline, and metabolic inhibition could change dose-normalised exposure differently from that in a non-expresser. A favourable reduction in tablet requirement therefore coexists with a risk of supratherapeutic exposure, acute kidney injury, neurotoxicity, and unstable trough concentration if dose adjustment lags.

Dihydropyridine calcium channel blockers offer a different balance. Amlodipine, nifedipine, felodipine, nitrendipine, and lacidipine produce arteriolar relaxation with less deliberate use as metabolic boosters, although clinically meaningful tacrolimus interactions are still reported[15]. Their adverse-effect

profile includes peripheral oedema, headache, flushing, and gingival overgrowth, all of which could affect adherence or obscure fluid-status assessment. Non-dihydropyridine agents additionally raise concern for bradycardia, conduction delay, and stronger drug interaction. The class is therefore not pharmacologically homogeneous even when the pooled kidney-function direction was favourable.

A three-pathway translational framework clarifies how those observations relate without treating them as one outcome. The first pathway is vascular: dihydropyridine-predominant arteriolar relaxation could lower systemic pressure and oppose calcineurin-inhibitor-associated afferent vasoconstriction. The second is metabolic: CYP3A and P-glycoprotein inhibition, strongest with diltiazem and verapamil, could increase calcineurin-inhibitor exposure and reduce the dose needed to reach a trough target. The third is safety-mediated: excessive exposure, oedema, hypotension, bradycardia, or conduction disturbance could offset haemodynamic or dose-sparing advantages. Table 4 and Figure 4 linked each pathway to its evidential support, clinical risk, and monitoring response.

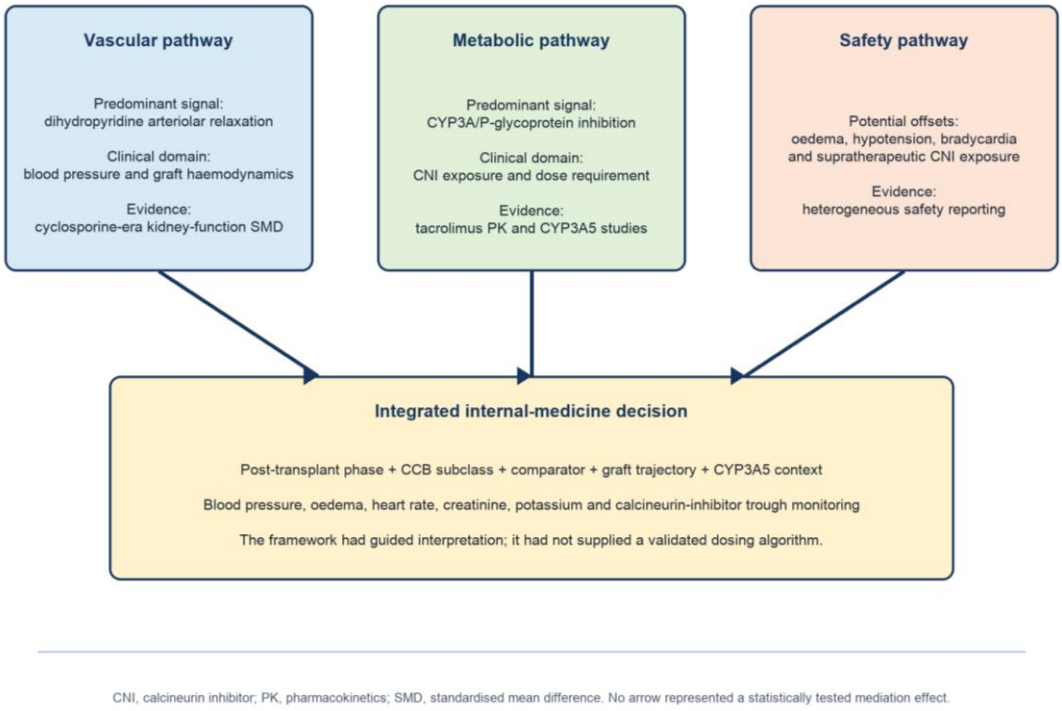


**Figure 4.** Translational framework linking vascular, metabolic, and safety pathways. Cyclosporine-era quantitative evidence informed kidney-function physiology, whereas tacrolimus studies principally informed CYP3A5-dependent exposure and dose management. The framework integrated post-transplant phase, calcium channel blocker subclass, graft trajectory, and monitoring without implying a statistically tested mediation pathway or validated dosing algorithm.

Post-transplant phase modifies the relevance of each pathway. During the immediate perioperative period, intravascular volume, delayed graft function, vasopressor exposure, changing corticosteroid doses, and rapidly adjusted calcineurin-inhibitor targets make both renal perfusion and drug exposure unstable. A calcium channel blocker initiated at that stage therefore requires close assessment of pressure, urine output, creatinine trajectory, and trough concentration. During the early outpatient phase, stable oral absorption and repeated blood-pressure measurement make titration more interpretable, but rejection treatment and interacting medicines could still change exposure. In the late phase, chronic graft pathology, proteinuria, cardiovascular comorbidity, oedema, and adherence become relatively more important than reversal of acute vasoconstriction. These phase-specific hypotheses explain some clinical heterogeneity but do not constitute statistically confirmed effect modification.

Comparator choice further limits direct prescribing claims. The active nifedipine-versus-lisinopril study contrasts two biologically active strategies rather than calcium channel blockade with no treatment. Its omission reduced the pooled estimate to g 0.26, showing that the class signal was partly dependent on how an alternative antihypertensive affected filtration. This finding does not establish inferiority of renin–angiotensin-system blockade, which could offer different benefits for proteinuria and long-term cardiovascular risk while transiently lowering filtration. The pooled SMD therefore informs a physiological comparison, whereas individual therapy still requires a clinical choice among competing benefits, contraindications, and monitoring burdens.

For internal-medicine practice, the findings support a mechanism-informed rather than class-only approach. In a cyclosporine-treated recipient with hypertension and preserved perfusion reserve, a dihydropyridine calcium channel blocker could provide blood-pressure control while countering renal vasoconstriction. In a tacrolimus-treated recipient, diltiazem could be considered when dose sparing is desirable, but only with a preplanned tacrolimus reduction, early repeat trough measurement, creatinine and potassium monitoring, and review of interacting medicines. Genotype information, when already available, could refine the expected exposure change but could not replace therapeutic drug monitoring.

Implementation also requires coordination between transplant nephrology, general internal medicine, clinical pharmacy, and primary care. A calcium channel blocker started outside the transplant service could change calcineurin-inhibitor exposure before the next routine appointment. Medication reconciliation, explicit interaction alerts, agreed trough-monitoring intervals, and communication of the intended dose-sparing strategy are therefore essential. Home blood-pressure records and serial creatinine complement, but do not substitute for, measured drug concentration. Contemporary adherence monitoring supports the importance of verifying actual antihypertensive exposure rather than relying on prescription records alone[18].

The practical monitoring sequence differs by subclass. After starting or increasing diltiazem or verapamil, the transplant team needs to confirm the intended calcineurin-inhibitor dose change, obtain an early trough concentration, and repeat creatinine, potassium, blood pressure, and heart rate. Symptoms of tremor, headache, confusion, gastrointestinal disturbance, bradycardia, or hypotension could signal toxicity or intolerance. After starting a dihydropyridine, blood pressure response and peripheral oedema remain central, while tacrolimus or cyclosporine exposure still requires review when the molecule, dose, genotype, or co-medication profile suggests an interaction. Table 4 presented these actions as monitoring principles rather than validated dosing rules because the included studies did not support a universal schedule.

**Table 4. Mechanism-informed clinical translation and monitoring principles**

| Clinical context | Predominant mechanism | Potential benefit | Principal risk | Monitoring emphasis |
|---|---|---|---|---|
| Dihydropyridine CCB | Predominantly vascular smooth-muscle relaxation; possible CNI exposure change | Blood-pressure reduction and opposition to afferent vasoconstriction | Oedema, headache, flushing, hypotension; residual PK interaction | Blood pressure, oedema, creatinine trajectory, medication interactions, CNI trough when indicated |
| Diltiazem or verapamil | Vascular effect plus CYP3A and P-glycoprotein inhibition | Blood-pressure control and potential CNI dose sparing | Supratherapeutic CNI exposure, nephrotoxicity, neurotoxicity, bradycardia, conduction delay | Preplanned CNI dose review, early repeat trough, creatinine, potassium, blood pressure, heart rate |
| Phase-specific application | Relative contribution of acute vasoconstriction, unstable exposure, or chronic graft disease | Mechanism-informed selection according to perioperative, early, or late post-transplant phase | Volume instability, rejection treatment, changing steroid/CNI targets, chronic comorbidity | Urine output and perfusion early; adherence, proteinuria, cardiovascular status and graft trajectory later |

*Abbreviations: CCB, calcium channel blocker; CNI, calcineurin inhibitor; PK, pharmacokinetic. These principles synthesise study mechanisms and safety considerations; they do not represent a validated dosing schedule.*

The pooled effect does not justify treating serum creatinine improvement as a surrogate for long-term graft survival. Acute haemodynamic improvement might lower creatinine without modifying chronic immune or fibrotic injury. Conversely, a calcium channel blocker that raises calcineurin-inhibitor exposure could improve blood pressure while increasing nephrotoxic risk. Patient-important outcomes such as graft loss, cardiovascular events, rejection, hospitalisation, and mortality were reported sparsely or with incompatible definitions. Treatment choice therefore needs to integrate blood pressure, albuminuria, potassium, heart rate, oedema, graft trajectory, and immunosuppressant concentration rather than rely on the pooled SMD alone.

Moderate overall heterogeneity is expected from variation in molecule, dose, comparator, timing, transplant era, and kidney-function measurement. The four early studies ranged from perioperative verapamil to three-month nifedipine, diltiazem, and felodipine. The late studies ranged from placebo-controlled diltiazem and nitrendipine to an active lisinopril comparison. Cyclosporine formulations and target concentrations also changed across decades. REML–Hartung–Knapp inference preserved small-sample uncertainty, and the prediction interval showed that a comparable future trial could plausibly yield no benefit. The requested DerSimonian–Laird model produced a similar mean effect in sensitivity analysis, but it was not promoted above the registered primary method.

The leave-one-out analysis showed that no single study reversed the pooled direction. However, persistence of a positive point estimate does not remove concerns about selective reporting. Several eligible trials lacked extractable standard deviations, denominators, or matched time points, and their unavailable effects

could differ from the included effects. Egger regression was not performed because seven primary studies fell below the prespecified threshold. This decision prevented an unstable p value from being mistaken for evidence against publication bias. The 12-study secondary-assisted scenario and its Egger result therefore remained non-confirmatory.

The critical-risk sensitivity analysis added a large comparative report and slightly reduced the pooled estimate while narrowing its confidence interval. That apparent gain in precision did not warrant primary inclusion because large sample size cannot correct unclear allocation, marked group imbalance, post-allocation exclusions, or inconsistent units. Keeping that report outside the primary model reduced the risk that a potentially biased study would dominate weighting. The sensitivity result nevertheless showed that its numerical direction did not contradict the primary synthesis.

The risk-of-bias pattern reinforces the need to separate numerical stability from evidential certainty. Objective creatinine and filtration measurements reduced measurement bias, but incomplete reporting of randomisation, attrition, and selective time points affected several trials. A narrow confidence interval from inverse-variance weighting cannot correct those design limitations. The pooled estimate is therefore interpreted as a very-low-certainty signal that supports clinical plausibility and future trial design, rather than as a definitive treatment threshold.

The comparison with previous meta-analyses also illustrates why updated synthesis remains useful despite overlap in primary trials. Earlier reviews focused on class-level efficacy and patient-important outcomes, while the present analysis mapped the transition from cyclosporine haemodynamic trials to tacrolimus pharmacogenetic studies. That mapping exposed a measurement discontinuity across transplant eras. It also clarified that additional tacrolimus studies would not automatically strengthen a kidney-function meta-analysis unless they reported a compatible clinical endpoint.

Several limitations constrain the review. First, the archived screening project lacked a complete row-level deduplication and exclusion log, so the intermediate PRISMA counts could not be reconstructed without invention. Second, only seven studies contributed to the primary SMD, all of which used cyclosporine; the requested calcineurin-inhibitor subgroup interaction was therefore inestimable. Third, glomerular filtration, creatinine clearance, and serum creatinine were standardised across different time points, which improved comparability at the cost of direct clinical units.

Fourth, accessible reports for several older trials omitted arm-level dispersion or denominators, and secondary-assisted recovery could not substitute for primary source verification. Fifth, risk-of-bias judgements and the quantitative re-extraction remain pending independent duplicate human verification, despite source-level checking. Sixth, the prediction interval crossed no effect and limited generalisation of the statistically significant mean. Seventh, comparative cohorts were retained only narratively; residual confounding limited causal interpretation of their pharmacokinetic and clinical findings. Eighth, patient-important endpoints and adverse effects were too heterogeneous for a unified quantitative model.

Future trials need to enrol recipients under contemporary tacrolimus and cyclosporine protocols, stratify randomisation by calcineurin inhibitor and CYP3A5 status, and report ambulatory blood pressure, measured or estimated filtration, albuminuria, trough exposure, dose requirement, adverse events, graft loss, and cardiovascular outcomes at common time points. Individual-participant data would allow interaction testing without ecological subgroup bias and would handle repeated exposure measurements appropriately. Standardised reporting of means, standard deviations, adjusted contrasts, and participant-level event counts would make a clinically interpretable network or multivariate synthesis possible.

A pragmatic future protocol could randomise recipients within tacrolimus and cyclosporine strata to a dihydropyridine calcium channel blocker, a non-dihydropyridine calcium channel blocker, or an active comparator. It could use 24-hour ambulatory systolic pressure and measured filtration as co-primary outcomes, with prespecified trough-guided dose adjustments and central adjudication of graft events. Such a design would distinguish blood-pressure efficacy, renal haemodynamics, and metabolic boosting while preserving the safety procedures required in routine transplant medicine.

Until such evidence becomes available, the most defensible interpretation is that calcium channel blockers offer a modest kidney-function advantage in the historical cyclosporine-treated population, while tacrolimus-era evidence mainly defines a pharmacokinetic management problem. The two evidence streams inform different clinical decisions. They support cautious use of calcium channel blockers within an integrated transplant-hypertension strategy, but they do not establish that one calcineurin inhibitor modifies the clinical efficacy of the class.

## 5. Conclusion

Calcium channel blocker therapy was associated with a modest improvement in direction-harmonised kidney-function measurements among cyclosporine-treated kidney transplant recipients. Across seven source-verified randomised comparisons involving 639 participants, the registered REML–Hartung–Knapp model yielded Hedges g 0.38, with a 95% confidence interval from 0.11 to 0.66 and moderate heterogeneity. The 95% prediction interval ranged from −0.19 to 0.96, so a favourable average effect does not guarantee

benefit in every comparable setting. The direction remained positive in all leave-one-out analyses and under DerSimonian–Laird, acute-endpoint exclusion, and critical-risk sensitivities. Midtvedt 2001 remained influential, and exclusion of high-risk studies widened the confidence interval across no effect. The result represents a standardised composite of filtration measures and sign-reversed serum creatinine rather than a uniform change in mL/min. Evidence certainty is therefore very low because of risk of bias, inconsistency, and indirectness to contemporary tacrolimus-based care. Tacrolimus studies did not supply a comparable clinical kidney-function subgroup; they instead described CYP3A5-dependent changes in dose-adjusted exposure and dose sparing. Consequently, the apparent tacrolimus–cyclosporine difference reflects different evidence domains rather than a proven treatment interaction. For internal-medicine practice, calcium channel blocker selection needs to integrate blood-pressure phenotype, graft function, oedema, heart rate, interacting medicines, and calcineurin-inhibitor concentrations. Diltiazem or verapamil require planned dose adjustment and prompt therapeutic drug monitoring, whereas dihydropyridines require surveillance for oedema and residual pharmacokinetic interaction. Contemporary trials stratified by calcineurin inhibitor and CYP3A5 status, with common clinical endpoints and complete dispersion reporting, remain necessary before a differential treatment effect can be claimed.

## Declarations

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### *Conflict of interest*
The authors declare that there are no competing interests.

### *Author contributions*
All authors contributed to the conception and design of the review. Harnavi Harun and Evelin Veronike performed the literature search, study selection, and data extraction. Harnavi Harun and Garri Prima Decroli undertook the statistical analysis and interpretation of the results. Muhammad Ridhwan Fatharanifurqan contributed to data verification and manuscript preparation. All authors drafted and critically revised the manuscript and approved the final version.

### *Data availability*
All data analysed in this study are derived from the published articles cited in the reference list and from the PROSPERO-registered protocol; further details are available from the corresponding author on reasonable request.

### *Generative AI disclosure*
The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

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