Effective Health Care Program

Comparative Effectiveness Review
Number 166

Calcineurin Inhibitors for Renal Transplant

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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We also thank AHRQ Task Order Officer Laura Pincock, Pharm.D., M.P.H., and Nahed El-Kassar, M.D., Ph.D.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Calcineurin Inhibitors for Renal Transplant

Structured Abstract

Background. The calcineurin inhibitors (CNIs) tacrolimus and cyclosporine A (CsA) are effective immunosuppressive agents for renal transplantation, but they must be managed carefully to avoid toxicity. Routine therapeutic monitoring guides dosing, but uncertainty surrounds different monitoring methods and timepoints. Additionally, the effectiveness of strategies to reduce CNI exposure with lower therapeutic levels and other immunosuppressants is unclear. This systematic review evaluates the evidence for three Key Questions. Key Question 1 compares immunoassay analysis with liquid chromatographic or mass spectrometric analytical techniques for therapeutic monitoring of CNIs. Key Question 2 examines CsA monitoring timepoints. Key Question 3 evaluates alternatives to full-dose CNI regimens.

Methods. We searched four bibliographic databases as well as gray literature sources, covering literature published from 1994 through December 2015 (for Key Questions 1 and 2) and May 2015 (for Key Question 3). English-language studies of adult renal transplants were included. All donor types and retransplants were eligible, but multiorgan recipients were excluded. We meta-analyzed data when appropriate, assessed studies for risk of bias, and evaluated the strength of evidence.

Results. We included 105 studies; 11 addressed Key Question 1, six addressed Key Question 2, and 88 addressed Key Question 3. We included 91 randomized controlled trials and 14 nonrandomized controlled studies. Most studies examined CsA, although tacrolimus is used more widely. For Key Question 1, one study compared clinical utility outcomes associated with chromatographic techniques versus immunoassays. Evidence was insufficient to determine whether outcomes differed by technique. Eleven studies assessed analytical performance measures. Findings suggested that chromatographic techniques are more accurate and precise than immunoassays, but the clinical relevance of these differences is unclear. For Key Question 2, low-strength evidence suggested no difference in risk of acute rejection when monitoring CsA at trough versus 2-hour timepoints.

Eighty-eight studies examined regimens that limited or avoided CNI exposure. High-strength evidence suggests that early minimization with low-dose CNIs is associated with improved clinical outcomes. Moderate-strength evidence suggests that conversion from CNIs to alternative immunosuppressants results in improved renal function. High-strength evidence suggests that withdrawal of CNIs is associated with increased risk of acute rejection and graft loss. Finally, nine studies evaluated regimens that avoided CNIs and used sirolimus or belatacept immediately following transplantation. These studies were heterogeneous and were not combined for meta-analysis. Moderate-strength evidence suggests that renal function is better in patients receiving sirolimus or belatacept instead of CNIs.

Study limitations include small sample sizes, incomplete reporting of clinical outcomes, short followup periods, and multiple sources of heterogeneity (including adjunctive and induction therapies, and variation in therapeutic targets). Additionally, although tacrolimus is used more widely than CsA in current practice, most of the studies examined CsA.

Conclusions. Most studies of CNI monitoring do not directly compare strategies or assess clinical validity or utility, and are insufficient to evaluate clinical outcomes. Few studies compare 2-hour with trough monitoring of CsA, and current evidence is insufficient to suggest a superior approach. Many studies suggest that early initiation of low-dose CNIs results in improved renal function and reduced risk of harm. Strategies that employ conversion from CNIs to mTOR (mammalian target of rapamycin) inhibitors are associated with improved renal function. Regimens that withdraw CNIs are not associated with improved renal function and may increase the risk of acute rejection. Avoidance strategies based on de novo use of alternative immunosuppressive drugs are not widely studied.

Contents

Tables

Figures

Appendixes

Introduction

Background

Approximately 17,000 renal transplants occur each year in the United States, accounting for almost 60 percent of all organ transplants.[1] Kidney transplantation is the treatment of choice for end-stage renal disease. Causes of renal failure are varied, including diabetes, hypertension, glomerular and cystic kidney diseases, and autoimmune disorders. Kidney transplantation offers a better quality of life and a survival benefit over chronic dialysis for most patients. The 2013 Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients annual report showed that the conditional graft half-life (defined as the time to when half the grafts surviving at least 1 year are still functioning) was 11.9 years for deceased donor transplants and 15.9 years for living donor transplants in 2011.[2] Survival rates continue to improve; a recent analysis of more than 250,000 renal transplant recipients demonstrated that death-censored graft half-life for all deceased donor transplants increased from 10.2 years in 1989 to 14.3 years in 2005 and remained approximately 16.5 years for living donor transplants during the same time period.[3]

Calcineurin inhibitors (CNIs) are the cornerstone of immunosuppression for renal transplantation. Cyclosporine A (CsA) and tacrolimus (TAC) are the two agents composing this drug class and have been used in renal transplant recipients for more than 20 years. CsA was initially approved in 1983 by the U.S. Food and Drug Administration (FDA) for immunosuppression following organ transplantation; in 1995, a microemulsion formulation of CsA (associated with better bioavailability and more consistent absorption) was approved. CsA formulations are usually administered twice daily. TAC received FDA approval in 1994 for liver transplant recipients and in 1997 for renal transplant recipients. Tacrolimus is usually administered twice daily but recently became available as an extended-release once-daily formulation. FDA-approved generic equivalents are available for TAC immediate-release formulations, as well as modified and unmodified CsA.

TAC-based regimens are currently the mainstay at most renal transplant programs in the United States. More than 85 percent of renal transplant recipients are discharged from admission on TAC as part of their maintenance immunosuppressive regimen.[2] This is largely because TAC is more potent and associated with less rejection and nephrotoxicity than CsA.[4] However, TAC is also associated with more neurotoxicity and gastrointestinal side effects than CsA.[5] It has also been associated with an increased incidence of new-onset diabetes and the development of metabolic syndrome, which are significant concerns because the main cause of death among renal transplant recipients is cardiovascular disease.[6,7]

CNIs are effective immunosuppressants, but they have extensive toxicity profiles. TAC and CsA both require careful management to ensure sufficient dosing for therapeutic effectiveness while avoiding toxicity. Two primary strategies have been employed to balance efficacy while limiting side effects: routine monitoring of CNI drug levels to guide dosing adjustments and minimization of CNI use to the lowest therapeutic levels. Alternatively, CNI use may be withdrawn or avoided entirely in favor of other immunosuppressant therapies.

CNI Monitoring

The primary technologies used for monitoring CNI drug levels are mass spectrometry and immunoassays. CsA is measured with high-performance liquid chromatography (HPLC), liquid

chromatography-tandem mass spectrometry (LC-MS/MS), fluorescence polarization immunoassay (FPIA), and enzyme-multiplied-immunoassay techniques (EMIT). TAC can be monitored with LC-MS/MS, enzyme-linked immunosorbent assay (ELISA), or microparticle enzyme immunoassay (MEIA). Commonly used immunoassays, such as MEIA for TAC and FPIA for CsA, use monoclonal antibodies that recognize not only the parent drug but also several of its metabolites. Soldin and colleagues used data collected by the College of American Pathologists to evaluate the crossreactivity of several CsA metabolites in commonly used immunoassays for CsA.[8] The results showed significant cross-reactivity of metabolites in all the immunoassay systems tested. Such cross-reactivity can lead to overestimation of drug concentration, which could affect interpretation of patients' drug levels and lead to less-than-optimal clinical outcomes. Compared with the immunoassays, HPLC and LC-MS/MS offer more precise measures of the parent compound while minimizing measurement of metabolites, but they can also be more time-consuming, labor-intensive, and use less standardized techniques, making their performance provider-dependent. It is also unclear whether long-term health outcomes vary with each methodology.

The ability to accurately measure low-range CNI concentrations is important because CNI target therapeutic ranges have decreased over time.[9] The Report of the European Consensus Conference recommends that assays achieve a limit of quantification of 1 ng/mL.[9] However, randomized trials demonstrating the value of CNI monitoring itself are lacking. Moreover, although LC-MS/MS is one of the most popular methods for currently measuring TAC, no standardization exists between laboratories.

Selection of the appropriate timing for measuring CNI drug levels is another important component of clinical care. For TAC, single timepoint measurements have not been shown to correlate with AUC.[10] Still, it is recommended that TAC be monitored at 12 hour trough levels (C0, usually just before morning dose administration), even though the relationship between C0 and clinical outcomes is still unclear.[9] A recent publication reported that pooled data from three large randomized controlled trials (RCTs) did not show find any significant correlations between TAC trough levels at five time points (day 3, 10, and 14, and months 1 and 6 post-transplant) and the incidence of biopsy proven acute rejection in renal transplant recipients.[11]

Trough monitoring of CsA (C0) is also common, but recent research has suggested that monitoring CsA at 2 hours after dosing (C2) yields effective monitoring while enabling lower doses and less risk of toxicity.[12,13] However, C2 level monitoring is less practical because it needs to be measured within 15 minutes of the 2-hour target to avoid large shifts in concentrations, while C0 measurement can be done within a 10- to 14-hour window. The question of whether C0 monitoring should be replaced with monitoring at C2 is unresolved, and determining the optimal timepoint can lead to more efficient, safer, and higher value care.

CNI Management and Minimization Strategies

Immunosuppressive regimens designed to reduce or eliminate exposure to CNI toxicity risks have been investigated in recent years.[14] Four alternative approaches (see Table 1) to full-dose CNI therapy have emerged: (1) CNI minimization, which reduces the amount of the drug administered. This strategy may be undertaken from the time of transplant (de novo) or later post-transplant (elective) as a result of an adverse event such as nephrotoxicity or BK viral infection; (2) CNI conversion, which tapers CNI dosing at any time post-transplant until full replacement with alternative immunosuppressants is achieved. This strategy may be undertaken at any time post-transplant and is usually a result of an unacceptable CNI-related adverse event;

(3) CNI withdrawal, which slowly eliminates the amount of drug administered early or late post-transplant; (4) CNI avoidance, which avoids the use of CNI in favor of other immunosuppressive drugs from the outset. These strategies also involve the use of concurrent immunosuppressants in standard or low doses and may include induction agents to provide added immunosuppression in the immediate post-transplant period. The other immunosuppressive drugs often used include mycophenolic acid formulations such as mycophenolate mofetil (MMF) or enteric-coated mycophenolic sodium, mammalian target of rapamycin (mTOR) inhibitors such as sirolimus (SRL) or everolimus (EVR), azathioprine (AZA), and belatacept. No clear consensus exists regarding the comparative efficacy and safety of these alternatives to full-dose CNI regimens.

Table 1. Alternatives to full-dose CNI regimens

Strategy	Definition	Timing
Minimization	Lower dosage of CNI	Planned de novo or result of adverse event
Conversion	Tapering of CNI dose until eliminated and replaced with other immunosuppressant	Usually result of adverse event
Withdrawal	Tapering of CNI dose until eliminated; continuation of other immunosuppressant already in use before withdrawal	Planned de novo or result of adverse event
Avoidance	No CNI given; other immunosuppressant used	Planned de novo

CNI = calcineurin inhibitor

Another important consideration is treating high-risk populations. As the volume of patients seeking retransplantation grows, the number of highly sensitized patients has increased, as has the popularity of desensitization protocols employing plasmapheresis, high-dose induction and maintenance immunosuppression.[15] As more potent TAC-based immunosuppression has become the clinical standard, opportunistic infections such as cytomegalovirus (CMV), Epstein Barr virus, and BK viremia and nephropathy have emerged as complications, and data suggest these are more common with TAC than with CsA.[16,17] Immunosuppressive regimens that minimize or avoid CNIs may play an important role in the care of such patients.

Scope and Key Questions

This report's main objective is to conduct a systematic review and meta-analysis of the benefits and harms of CNIs as maintenance therapy for adults who have undergone a renal transplant. In this review, we address the following Key Questions (KQs):

Monitoring Assays for Calcineurin Inhibitors

Key Question 1a. In adult renal transplants, how do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of full dosing regimens of the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus?

Key Question 1b. In adult renal transplants, how do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of lower CNI doses used in minimization, conversion, or withdrawal strategies?

Cyclosporine Monitoring Timepoints

Key Question 2. In adult renal transplants, how does 2-hour post-administration cyclosporine monitoring (C2) compare with trough monitoring (C0) for health outcomes?

Management of Alternatives to Full-Dose CNI Regimens

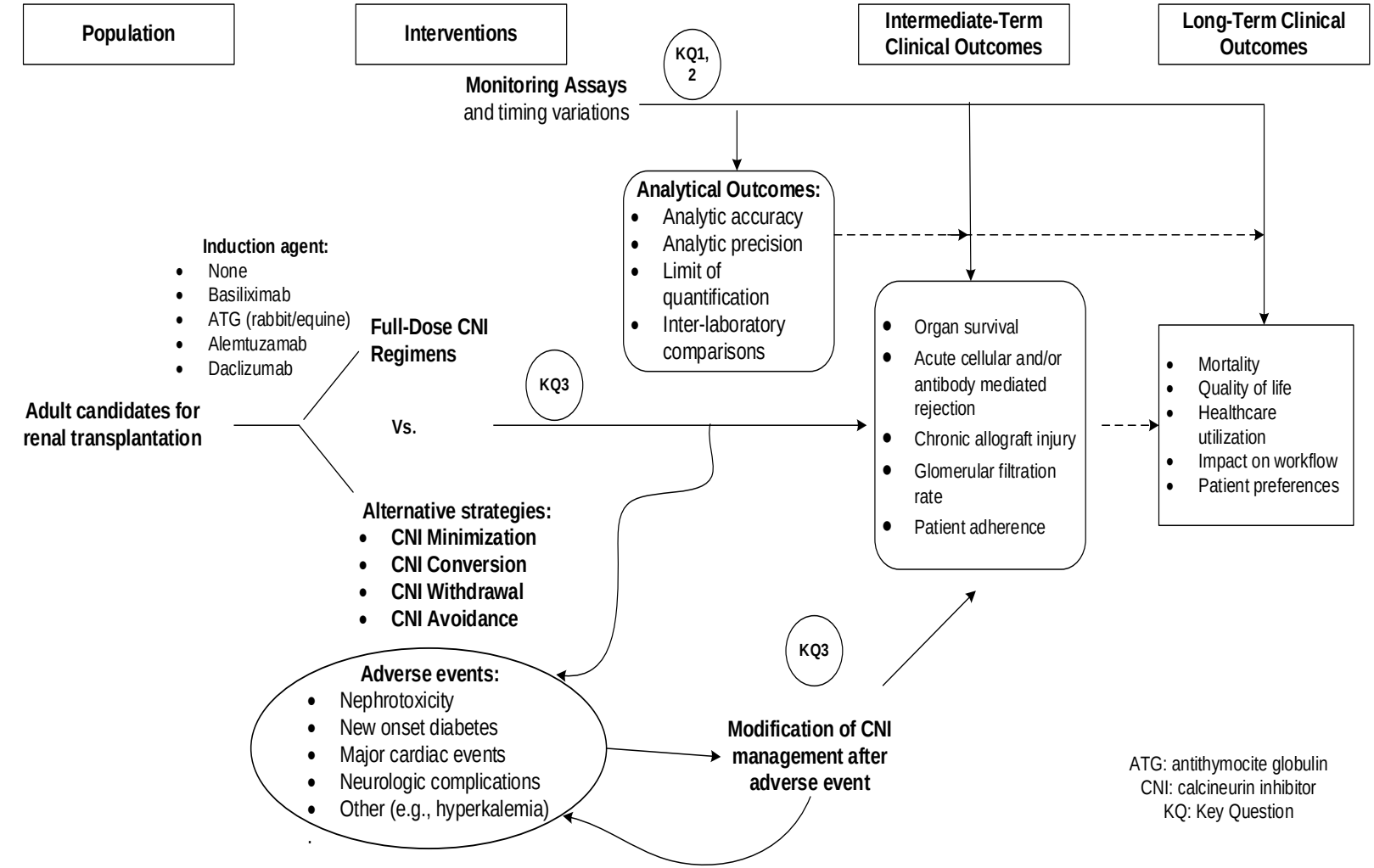
Key Question 3a. In adult renal transplants, how do immunosuppressive regimens designed to reduce or eliminate exposure to CNI toxicity compare with each other and with full-dose CNI regimens for health outcomes?

Key Question 3b. How do the type of induction agent (including when no induction is used) and the use of concurrent immunosuppressive agents affect outcomes of regimens that reduce or eliminate CNI exposure?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1).

Figure 1. Analytic framework for calcineurin inhibitors for renal transplant



ATG = antithymocyte globulin; CNI = calcineurin inhibitor; KQ = Key Question

Organization of This Report

In the remaining three chapters of this report, we discuss the methods for this systematic review, the results for each Key Question (KQ), and the findings. Within the Results chapter, we provide the results of the literature searches and screening procedures, as well as descriptions of included studies, key points, detailed syntheses of the studies, and strength-of-evidence tables for each KQ. The Discussion chapter reviews the key findings and strength of evidence for each KQ, places the findings in the context of previous systematic reviews, examines the general applicability of the studies, discusses implications for decisionmaking, describes limitations of the systematic review process and the evidence base for each KQ, and identifies knowledge gaps that require further research.

A list of acronyms and abbreviations appears after the references, followed by seven appendixes. The Appendixes include Appendix A. Search Strategy, Appendix B. Excluded Studies, Appendix C. Evidence Tables for Key Question 1a and 1b, Appendix D. Evidence Tables for Key Question 2, Appendix E. Evidence Tables for Key Question 3a and 3b, Appendix F. Forest Plots for Key Question 3a and 3b, and Appendix G. Appendix Reference List.

Methods

The methods for this systematic review follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov).

Topic Refinement and Review Protocol

This topic was initially nominated through the public Web site and was subsequently refined with input from Key Informants and public comment. We generated an analytic framework, preliminary Key Questions (KQ), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, and settings). These processes were guided by a literature scan and information provided by the topic nominator, and they were consistent with the Key Informant and public feedback. A Technical Expert Panel (TEP) was convened for this report. The TEP consisted of nine scientists and clinicians, including individuals with expertise in transplant nephrology, infectious diseases, clinical pharmacology, and therapeutic drug monitoring and assay methodology. TEP members participated in conference calls and discussions through e-mail to review the scope, analytic framework, KQs, and PICOTS; provided input on the information and categories included in evidence tables; and provided input on the data analysis plan. Lists of the TEP members and Key Informants are included in the front matter of this report. We drafted a protocol for developing this systematic review and finalized it in consultation with AHRQ and the TEP before it was posted on the Effective Health Care Web site on October 8, 2014. We note that one investigator who assisted with this review was also participating in a clinical study of an extended-release formulation of tacrolimus. This formulation was not approved by the U.S. Food and Drug Administration (FDA) at the time our review was conducted; therefore, no studies of this drug were eligible for inclusion. In consultation with AHRQ, we developed a risk-mitigation plan to manage any potential conflict of interest.

Literature Search Strategy

Literature searches were performed by Medical Librarians and followed established systematic review protocols. Searches covered the literature published from January 1, 1994, through December 10, 2015 for KQ1 and KQ2, and May 20, 2015 for KQ3. We chose 1994 as the earliest year because this reflects the timeframe in which the commonly used forms of calcineurin inhibitors (CNIs) received FDA approval. Tacrolimus (TAC) received approval in 1994 for use in liver transplants and in 1997 for use in renal transplants, and the modified formulation of cyclosporine A (CsA) received approval in 1995. Studies published before 1994 are likely to use formulations of CNIs no longer in common use.

Searches were restricted to English-language studies, given concerns that studies not published in English would be more likely to include clinical environments where post-transplant care, immunosuppressive therapy, and clinical outcomes would vary substantially from standard practices in the United States, and given the abundance of English-language studies identified in preliminary screening, including many studies conducted outside the United States or Europe.

We searched the following databases using controlled vocabulary and text words: EMBASE, MEDLINE, PubMed, and the Cochrane Library. Our searches included strategies to identify studies "in process" that were not yet indexed. The search concepts and strategies are available in Appendix A.

We also searched 21 sources for gray literature not indexed in the bibliographic databases; these sources are detailed in Appendix A. In addition, the AHRQ Scientific Resource Center requested scientific information packets from relevant pharmaceutical and test manufacturing companies, asking for any unpublished studies or data relevant for this systematic review (SR). We received six documents listing completed studies conducted by three different manufacturers, which we assessed for inclusion in the review.

Literature screening was performed using the database Distiller SR (Evidence Partners, Ottawa, Canada). Literature search results were initially screened for relevancy. Relevant abstracts were then screened against the inclusion and exclusion criteria in duplicate. Due to the highly complex methods and results of the studies, those that appeared to meet the inclusion criteria were retrieved in full and screened in duplicate by clinical experts in transplant nephrology and pharmacology, to determine whether they met the clinical criteria for inclusion. Studies that satisfied this first-pass full-text screening were then screened by methodologic experts for inclusion. Consensus discussion between the two original screeners resolved disagreements.

Study Selection

Table 2 below presents the study inclusion criteria that guided the selection of studies included in this report. The table is organized based on the PICOTS (patient, intervention, comparator, outcomes, timing, and setting) framework. In general, for clinical outcomes (e.g., organ survival, mortality), we considered randomized controlled trials (RCTs) as the best available evidence. For the analytical validity outcomes (e.g., analytic precision, limit of quantification) considered in KQs 1 and 2, we also included prospective and retrospective nonrandomized comparative trials.

Table 2. Eligibility criteria

Category	Inclusion	Exclusion
Population	• Adult renal transplant recipients treated with full-dose or alternative-dose CNI immunosuppression • All kidney donor types • Renal retransplant patients • Populations at increased risk of graft rejection	• Children (<18 years) • Multi-organ recipients
Interventions	Key Question 1a, 1b • High performance liquid chromatography (HPLC) • Liquid chromatography-tandem mass spectrometry (LC-MS/MS Key Question 2 • 2-hour postadministration monitoring of CsA (C2) Key Question 3 • CNI minimization strategies • CNI conversion strategies • CNI withdrawal strategies • CNI avoidance strategies	• Studies of investigational immunosuppressive agents that are not FDA approved, or studies using nonmodified cyclosporine formulations • Studies designed to examine the effectiveness of an induction agent as a primary intervention • Studies using muromonab OKT3
Comparators	Key Question 1a, 1b • Fluorescence polarization immunoassay (FPIA) • Enzyme-multiplied-immunoassay techniques (EMIT) • Enzyme-linked immunosorbent assay (ELISA) • Microparticle enzyme immunoassay (MEIA)	•

Category	Inclusion	Exclusion
	Key Question 2 • Trough monitoring of CsA (C0) Key Question 3 • Full-dose CNIs • CNI minimization/conversion/withdrawal/avoidance strategies compared to each other	
Outcomes	K**ey Question 1a, 1b** Analytical validity outcomes • Analytic accuracy (analytic sensitivity and specificity) • Analytic precision (e.g., intra-assay agreement, inter-assay agreement, measurement reproducibility) • Limit of quantification • Inter-laboratory comparisons (e.g., inter-laboratory agreement, measurement reproducibility) **All Key Questions** Intermediate-term clinical outcomes • Organ survival • Acute cellular and/or antibody mediated rejection (e.g., ascertained by "for cause" vs. "per protocol" biopsies) as defined by Banff criteria used in study • Chronic allograft injury (e.g., rejection or dysfunction, as defined by study) • Glomerular filtration rate (GFR), as measured by study • Serum creatinine • Infections (including timing of infections and clinical impact of infections on patients) • Malignancy • All-cause mortality • Immunosuppression regimen changed due to adverse events Adverse events • Acute and/or chronic nephrotoxicity (including method of measuring GFR threshold) • New-onset diabetes after transplant • Major adverse cardiac events • Other adverse outcomes (e.g., hyperkalemia, hypomagnesaemia, hyperuricemia, gastrointestinal complications, post-transplant hypertension or hyperlipidemia, proteinuria, hematologic side effects, neurologic complications, hair loss/gain) **Key Question 3** Long-term clinical outcomes • Health care utilization • Impact on provider workflow	
Timing	• At least 3-months post-transplant for Key Question 3	
Settings	• All settings where immunosuppressive therapy for transplant recipients is administered or monitored	
Publication Language	• English	

CNI = calcineurin inhibitors; CsA = cyclosporine; FDA = U.S. Food and Drug Administration; GFR = glomerular filtration rate

Data Extraction

Data were abstracted using Microsoft Word and Excel. Duplicate abstraction on a 10-percent random sample was used to ensure accuracy. All discrepancies were resolved by consensus discussion among the two original abstracters and an additional third person as needed. Elements abstracted included general study characteristics (e.g., country, study design, number of enrolled patients, special patient inclusion/exclusion criteria), patient characteristics (e.g., age, sex, donor type, delayed graft function), details of CNI monitoring method (e.g., type of analytic method used to measure CNI drug level, timepoint for monitoring), CNI treatment strategy (e.g., alternative CNI strategy, control strategy, induction agent), risk-of-bias items, and outcomes data.

Risk-of-Bias Assessment of Individual Studies

Risk of bias of the studies in KQ 1 that compared the analytical validity of chromatographic techniques to immunoassays for monitoring CNI drug levels was assessed using eight risk-of-bias items. These items are based on an item bank developed in part by the EPC Program to evaluate the reporting adequacy and internal validity of studies evaluating the analytical validity of medical tests. The items were based on a review of other checklists and criteria used to assess the methodological quality of studies reporting on analytical validity, such as the criteria in the ACCE and EGAPPs approaches, and expert panel consensus. The full list of the items and discussion of other methods used to assess studies of analytical validity can be found in the report titled *Addressing Challenges in Genetic Test Evaluation: Evaluation Frameworks and Assessment of Analytical Validity*.[18]

The eight items selected for this report broadly cover the following areas: adequate description of the tests under evaluation, reporting methods used to establish baseline performance of the tests, and reproducibility of the test results. When considering whether a study adequately described the tests under evaluation, we determined whether studies reported on how blood samples were collected and handled, whether and how test materials were calibrated and tested, and whether quality control/assurance measures were used to evaluate samples. When considering methods used to establish baseline performance, we determined whether studies reported on limit of detection and linearity range. Finally, when considering reproducibility, we determined whether studies reported on the test's performance over multiple testing times or across multiple laboratories. We discuss the limitations of the studies in the results section for KQ 1.

For studies addressing clinical outcomes, we used 10 items from an item bank that addresses the internal validity of comparative studies. This item bank was informed by empirical studies of the impact of study design on bias in comparative studies and is consistent with the guidance in AHRQ's "Methods Guide for Comparative Effectiveness Reviews."[19] Each item chosen addressed an aspect of study design or conduct that could help protect against bias, such as randomization of group assignment, or blinding outcome assessors to patient group assignment. Each item is phrased as a question that can be answered "Yes," "No," or "Not Reported," and each is phrased such that an answer of "Yes" indicates that the study reported a protection against bias on that aspect. The items used in this report are presented in Table E-21 of Appendix E. This table also presents the risk-of-bias ratings for all included studies.

Studies were rated as "Low," "Moderate," or "High" risk of bias. We identified three of the 10 items as most indicative of potential bias: "Was randomization adequate?"; "Was allocation

concealment adequate?"; and "Was there a <15 percent difference in completion rates in the study's groups?" A study was rated as High risk of bias if any two of these three questions were answered "No" or "Not Reported." We considered the weight of the other seven items to be equal. Thus, if at least two of the more highly weighted criteria were answered "Yes," then a study was rated as Low risk of bias if at least 75 percent of the total items were answered "Yes," as Moderate risk of bias if more than 50 percent but less than 75 percent were answered "Yes," and as High risk of bias if 50 percent or fewer of the items were answered "Yes."

Data Synthesis

For studies reporting on patient-centered clinical outcomes, we performed meta-analysis when appropriate and possible. Decisions about whether meta-analysis was appropriate depended on the judged clinical homogeneity of the different study populations, monitoring methods, CNI protocols, and outcomes. When meta-analysis was not possible (due to limitations of reported data) or was judged inappropriate, we synthesized the data using a descriptive, narrative approach.

We computed effect sizes and measures of variance using standard methods and performed random-effects meta-analysis using the Hartung-Knapp method.[20,21] We performed analyses using the statistical software program R (GNU General Public License). Forest plots were generated for each meta-analysis and were reviewed by the study team. We evaluated statistical heterogeneity of the pooled analyses using the I^2 statistic. We considered an I^2 statistic of 50 percent or more as evidence of substantial heterogeneity. For KQ 3, we performed meta-analysis on the following outcomes, as these were clinically important outcomes that were reported most consistently across studies: biopsy proven acute rejection (BPAR), graft loss, patient death, renal function, and infection-related adverse events, specifically: cytomegalovirus (CMV), BK virus infection, and other opportunistic infections. Renal function was measured by eGFR, which was assessed using a variety of commonly used analytical approaches, including the Modification of Diet in Renal Disease (MDRD) formula, the Nankivell formula, and the Cockcroft-Gault formula. Due to differences in how eGFR was measured across studies, data were pooled using the standardized mean difference (SMD) as the summary effect size metric. Due to the complex and heterogeneous nature of the studies addressing KQs 1 and 2, we did not attempt to combine data from the studies quantitatively. Instead, we provided a narrative synthesis of the general findings of the evidence addressing these questions.

For KQ 3, studies were categorized depending on the alternative CNI regimen they addressed: minimization, conversion, withdrawal, avoidance, and studies that compared alternative regimens head-to-head. Within each category of studies, subgroup analyses were performed. Subgroups were defined using the following criteria: type of CNI (CsA or TAC), type of immunosuppressant coadministered with the CNI, type of induction agent, and timing of initiation of alterative CNI strategy (<6 months vs. ≥6 months post-transplantation). We were unable to conduct subgroup analyses of kidney donor type or patients at higher risk for infections because studies rarely reported outcomes stratified by these criteria, and too few studies were identified that consisted entirely of these populations.

Results were considered to represent no difference for an outcome when the summary effect estimate was between 0.75 and 1.25 and the confidence interval (CI) included 1.0.

Strength of the Body of Evidence

For questions with clinical outcomes, we graded the strength of evidence based on the guidance established by the EPC program. Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: study limitations (including study design and aggregate risk of bias), consistency, directness, precision, and reporting bias. It also considers optional domains, such as a dose-response association, plausible confounding that would increase the observed effect, and strength of association (magnitude of effect), all of which may increase the strength of evidence. Table 3 defines the grades of evidence. We focused our assessment of the strength of evidence on studies reporting on clinical outcomes. We chose not to assess the strength of evidence for nonclinical outcomes reported in the studies of analytic validity (KQs 1a and 1b).

Table 3. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

We determined the study limitations by appraising the aggregate risk of bias of individual studies contributing to the evidence base for each comparison and clinical outcome. The evidence was downgraded when the risk of bias was judged to be high for 50 percent or more of the studies for a specific outcome.

We assessed consistency in terms of both the direction of effect and the magnitude of effect. Where quantitative synthesis was possible, the determination of inconsistency was based in part on the I^2 statistic. If I^2 was 50 percent or more, indicating the presence of substantial heterogeneity, we considered the evidence inconsistent. We downgraded the evidence for inconsistency unless the source of the heterogeneity was explained through subgroup analyses of identifiable differences in study characteristics.

The evidence was considered indirect if the populations, interventions, comparisons, or outcomes used within studies did not directly correspond to the comparisons we intended to evaluate. We downgraded evidence for indirectness if a majority of studies in a specific outcome or a heavily weighted study in the summary effect size calculation met these criteria.

We downgraded the evidence base for imprecision if the 95% CIs surrounding the summary effect estimate for relative risk exceeded both a 10-percent increase in risk as well as a 10-percent decrease in risk. If the CIs exceeded a 25-percent increase and decrease in risk, the evidence base was downgraded further due to substantial imprecision. When we identified only a single study for a specific outcome, we considered the evidence base imprecise and downgraded. We treated exceptions as they arose.

Reporting bias includes publication bias, outcome reporting bias, and analysis reporting bias. Since pharmaceutical manufacturers funded many of the studies we reviewed, we explored publication bias through a review of funnel plots. We examined funnel plots for the primary comparisons in KQ 3. We also considered outcome reporting bias for this report, particularly for the outcome of "Other Opportunistic Infections." Data ascertainment and reporting for this

outcome can vary widely, with some studies describing many different types of infections, while other studies report only one or two types of infections. We suspected reporting bias if studies appeared to selectively report incidence of specific opportunistic infections when the data favored the intervention regimen.

Applicability

We determined applicability of studies by evaluating characteristics of included patients and parameters the studies used for drug dosing and measuring immunosuppressant level targets. Studies were considered to have limited generalizability when their patient populations were at high risk for poor outcomes or were not representative of important subgroups (such as patients >65 years old, retransplants, or African-Americans). Studies were also considered to have limited applicability when CNI drug doses or immunosuppressant target levels were not considered to be within conventional standards of care (as assessed by the clinical investigators contributing to this report).

Peer Review and Public Commentary

Six external experts provided peer review on this report. In addition, the draft report was posted on the AHRQ Web site (www.effectivehealthcare.ahrq.gov) for public review. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ also reviewed the final report before publication. The dispositions of the comments are documented and will be published 3 months after publication of the report.

Results

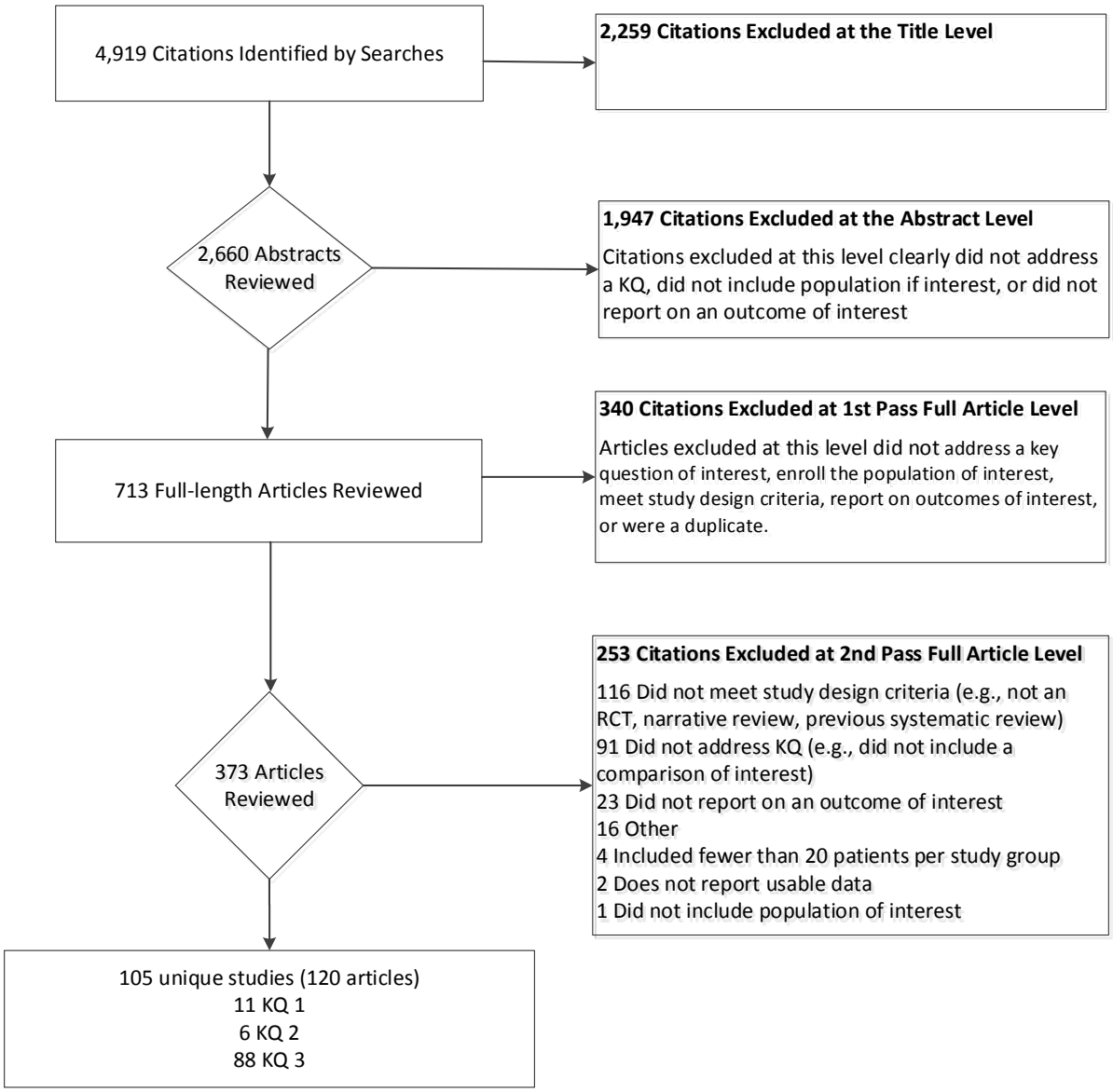
Introduction

We begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). For each KQ, we provide a detailed description of the studies, key summary points, a detailed analysis of the results, and a table that presents the strength of evidence.

Literature Searches

The literature searches identified 120 articles describing 105 studies (see Figure 2). Eleven studies (including 1 RCT) addressed KQ 1, and six studies (including 2 RCTs) examined KQ 2. The remaining 103 articles included 88 unique RCTs that addressed KQ 3. Among the 88 trials that addressed KQ 3, 32 examined reduced dosing of a calcineurin inhibitor (CNI), 22 evaluated converting from a CNI regimen to another immunosuppressive regimen, 13 assessed withdrawal of a CNI, 8 explored CNI avoidance through de novo use of non-CNI therapy, and 4 studies had more than 2 arms, which included a standard-dose CNI control group, a CNI minimization group, and either a conversion arm,[22] a withdrawal arm,[23,24] or an avoidance arm.[4] For these four multi-arm trials, data from each intervention group were analyzed with their respective regimens. Additionally, nine studies compared a low-dose CNI regimen with another type of alternative regimen without a standard-dose CNI arm to serve as a control group.

Figure 2. Study flow diagram



KQ = Key Question; RCT=randomized controlled trial

Methods for Monitoring CNI Drug Levels

Key Question 1a. How do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of full dosing regimens of CNIs?

Key Question 1b. How do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of lower dosing regimens of CNIs?

Description of Included Studies

We categorized studies that addressed this KQ according to the "ACCE" framework, which identifies four important dimensions for evaluating a medical test: (1) analytical validity; (2) clinical validity; (3) clinical utility; and (4) ethical, legal, and social implications. The first three of these criteria are meaningful for this KQ. Analytical validity refers to how well a test measures the properties or characteristics it is intended to measure, in a laboratory setting. Clinical validity (or diagnostic accuracy) refers to the accuracy with which a test predicts the presence or absence of a clinical condition. Clinical utility refers to the usefulness of the test and the value of information to medical practice. Outcomes measured in support of clinical utility may range from impact on clinical thinking to impact on therapeutic decisions to patient health outcomes.

Our literature searches identified 11 studies that compared the use of chromatographic techniques to immunoassay techniques to measure CNI (TAC and CsA) levels. None of the studies evaluated clinical validity, but one of the studies assessed clinical utility. Table 4 presents an overview of the studies addressing KQ 1.

The one study assessing clinical utility compared clinical outcomes among patients monitored with a chromatographic technique (i.e., HPLC-MS) versus an immunoassay.[25] The following clinical outcomes were evaluated: patient and graft survival, biopsy proven acute rejection (BPAR), cytomegalovirus (CMV) infection, TAC nephrotoxicity, and delayed graft function. The remaining studies focused solely on the analytical validity of the different monitoring methods. The primary outcomes reported in these studies were analytic accuracy, bias, and precision. These outcomes and other measures of analytic performance reported in the studies are defined in Table 5. Due to the limited number of studies reporting on patient-level data and heterogeneity of the data on analytic performance, we did not attempt to pool data quantitatively. Instead, we narratively summarize key findings from the studies. Detailed information on study and patient-level characteristics, outcome data, and reported adverse events are presented in evidence tables in Appendix C.

Table 4. Methods used to measure calcineurin inhibitors

Reference	Type of Study	Monitoring Methods	Outcomes
Leung et al. 2014[26]	Prospective comparison of analytical performance of tests	LC-MS/MS vs. QMS™ TAC immunoassay (QMS)	Analytic bias
Shipkova et al. 2014[27]	Prospective comparison of analytical performance of tests	LC-MS/MS vs. Elecsys TAC assay (ELCIA)	Analytic bias
Westley et al. 2007[28]	Retrospective comparison of analytical performance of tests	HPLC-MS vs. CEDIA and MEIA	Analytic bias
Borrows et al. 2006[25]	Randomized controlled trial	HPLC-MS vs. MEIA	Patient and graft survival, kidney function, biopsy proven acute rejection, TAC associated adverse events (e.g., TAC nephrotoxicity and CMV infection), and test precision.
Chan et al. 2005[29]	Prospective comparison of analytical performance	HPLC-MS vs. MEIA	Analytic accuracy
Butch et al. 2004[30]	Prospective comparison of analytical performance of tests	HPLC vs. CEDIA Plus	Analytic accuracy and bias
Staatz et al. 2002[31]	Retrospective comparison of analytical performance	LC-MS/MS vs. ELISA	Analytic accuracy and bias
Hamwi et al. 1999[32]	Prospective comparison of analytical performance of tests	HPLC-MS vs. FPIA/AxSYM, CEDIA, and modified EMIT	Analytic accuracy and bias
Schutz et al. 1998[33]	Prospective comparison of analytical performance of tests	HPLC-MS vs. FPIA/AxSYM, CEDIA, and modified EMIT	Analytic accuracy and bias
Salm et al. 1997[34]	Prospective comparison of analytical performance	HPLC-MS vs. ELISA and MEIA	Analytic accuracy
Roberts et al. 1995[35]	Prospective comparison of analytical performance of tests	HPLC-MS vs. FPIA/TDx mono and polyclonal immunoassay	Analytic accuracy and bias

CEDIA = cloned enzyme donor immunoassay; CMV = cytomegalovirus; ELCIA = electrochemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay; EMIT = enzyme multiplied immunoassay; FPIA = fluorescence polarization immunoassay; HPLC-MS = high performance liquid chromatography; LC/MS/MS = liquid chromatography-tandem mass spectrometry; MEIA = microparticle enzyme immunoassay; TAC = tacrolimus

The risk of bias of the one RCT assessing clinical utility was rated as high due to the authors not reporting on the methods used to carry out the randomization procedure and if the outcome assessors were blinded to patient assignment.

Findings for the risk-of-bias assessment of the analytic validity studies are presented in Table C-7. Most of the studies assessing analytic validity adequately described the tests under evaluation. However, the methods used to calibrate the tests and specifics about how the blood samples were collected and handled varied across studies. Only four studies reported the limit of quantification of each test[26,28,29,33] and five reported on the linearity range.[26-28,30,32] Similarly, only two studies reported that reproducibility was established before comparing the tests' analytical performance.[26,27] One of these studies was a multicenter study in which reproducibility of the tests was established over time and across participating laboratories.[27] None of the studies

reported whether the test interpreters were blinded to the testing methods used to monitor CNI levels.

Table 5. Measures of analytical performance

Term	Definition
Analytic accuracy	The analytic accuracy expresses the closeness of agreement between the true value (e.g., drug concentration) or an accepted reference value and the value found.
Precision	The degree to which the same method produces the same results on repeated measurements (repeatability and reproducibility); the degree to which values cluster around the mean of the distribution of values (i.e., the confidence limit).
Limits of Quantification	The highest or lowest concentration at which the drug can be reliably detected.
Linearity	The linearity of an analytical procedure is its ability (within a given range) to obtain test results, which are directly proportional to the concentration (amount) of drug or analyte in the sample.
Analytic Bias	The mean (overall) difference in values obtained with 2 different methods of measurement.
Confidence Limit	Range within which 95% of the differences from the bias are expected to be.
Limits of Agreement	Confidence limits for the bias. Upper LOA is computed as bias +1.96 SD. The lower LOA is computed as bias −1.96 SD. The range between the upper LOA and lower LOA is the confidence limit.

LOA = limits of agreement; SD = standard deviation
Source: www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm052377.pdf.

Key Points

- One small study with high risk of bias reported on clinical validity outcomes. The evidence from this study was considered insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes due to limitations in methodologic quality of the study and imprecision of the findings.
- The findings of the studies assessing analytical performance suggest that chromatographic methods are more analytically accurate and precise than commonly used immunoassays at measuring CNI drug levels, but it was unclear whether differences identified in these studies were clinically relevant such that they would change clinical management or affect patient outcomes.

Summary of Clinical Utility Outcomes

Borrows et al. conducted a RCT comparing the clinical outcomes of renal transplant recipients in whom TAC trough concentration levels were monitored using HPLC versus MEIA.[25] Table 6 below presents the findings and strength-of-evidence ratings for the outcomes this study assessed. Overall, the findings are insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes.

Table 6. Strength of evidence for clinical utility outcomes of studies of monitoring technologies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
HPLC vs. MEIA	Biopsy-proven acute rejection	Inconclusive (RR: 0.25; 95% CI: 0.02–2.14)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (too few events) (0/40 vs. 0/40)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.33; 95% CI: 0.01–7.94)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Serum creatinine levels (as measured using the Cockcroft Gault formula)	Inconclusive (SMD: 0.024; 95% CI: -0.41–0.43)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Biopsy proven acute TAC nephrotoxicity	Inconclusive (RR: 0.85; 95% CI: 0.32–2.33)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.0; 95% CI: 0.49–2.04)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Delayed graft function	Inconclusive (RR: 1.16; 95% CI: 0.62–2.20)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient

CI = confidence interval; CMV = cytomegalovirus; HPLC-MS = high-performance liquid chromatography; MEIA = microparticle enzyme immunoassay; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAC = tacrolimus

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, and Directness. Consistency was not assessed because the evidence base included only one study. Publication and reporting bias were not assessed due to insufficient number of studies.

Summary of Analytical Performance Outcomes

All 11 studies addressing KQ 1 compared the analytical performance of chromatographic techniques to an immunoassay. Among studies monitoring CsA levels, two compared HPLC to FPIA/AxSYM, CEDIA and modified EMIT,[32,33] one compared HPLC to the FPIA/TDx[35] and one compared HPLC to CEDIA plus.[30] Among studies monitoring TAC levels, three compared HPLC to either MEIA or CEDIA,[21-23] two compared LC-MS/MS to either ELISA or MEIA,[24,25] and two compared LC-MS/MS to TAC-specific immunoassays.[26,27] Most of the studies had an adequate number of participants and blood samples (30 or more participants with about 100 blood samples). The overall agreement between the chromatographic and immunoassay tests across all the studies was good (Pearson's correlation estimate: r^2 range 0.90–0.98). The most commonly reported outcomes among these studies were analytic accuracy, bias, and precision. The key findings from these studies are summarized in Table 7.

In brief, three studies compared the analytic accuracy of chromatographic techniques to immunoassay to measure TAC at various concentration levels.[29,31,34] Only two of these studies adequately reported sufficient details about the methods used to calibrate the tests or how blood samples were obtained and managed.[29,34] Only one study reported on the limit of quantification.[29] None of these studies were multicenter studies, and none of them reported on whether reproducibility of the tests was established either within blood samples or across test operators or over time. In general, the findings of these studies suggest that HPLC and LC-MS/MS were more accurate than an immunoassay in measuring TAC at lower concentration levels. However, it is unclear whether these differences are clinically relevant such that they

would change clinical management or affect patient outcomes. We did not grade the strength of evidence for these nonclinical outcomes.

Four studies reported on analytic bias between immunoassays compared to chromatographic techniques to measure TAC.[26-28,31] Three of the studies sufficiently reported details about the tests and reported on other important aspects of conducting analytical validity studies, such as the linearity and reproducibility of the tests.[26-28] The remaining study did not provide any details about how tests were calibrated or samples were obtained or handled and did not report on other details such as linearity and reproducibility.[31] The results of these studies suggest that immunoassays overestimate TAC levels compared to measurements from chromatographic techniques.

One RCT compared the precision of chromatographic techniques to immunoassays to measure TAC.[25] The findings suggest that assay precision was better for HPLC-MS than MEIA. We did not grade the strength of evidence for this nonclinical outcome. Again, it is unclear whether the differences found in these studies would change clinical management.

Finally, four studies compared the analytic accuracy and bias of chromatographic techniques to immunoassays to measure CsA levels.[30,32,33,35] In general, the tests under evaluation in these studies were sufficiently described, and all four of the studies evaluated the issue of cross-reactivity. Cross-reactivity of antibody-based CsA immunoassays with metabolites is a concern especially in situations where metabolite levels are expected to accumulate. The evaluation of cross-reactivity among these studies consistently showed that FPIA had the greatest cross-reactivity, followed by CEDIA, and EMIT showing the least cross-reactivity. The overall findings of the studies suggest that chromatographic methods are more analytically accurate and precise than commonly used immunoassays. However, it was again unclear if differences identified in these studies were clinically relevant.

Table 7. Key findings of studies comparing analytic performance of chromatographic techniques versus immunoassays

Outcome	CNI Regimen	Quantity and Type of Evidence	Key Findings
Analytic accuracy	CsA	4 prospective comparative studies[30,32,33,35]	Immunoassays show good correlation with HPLC-MS • HPLC vs CEDIA plus immunosassay: r^2=0.98; slope 0.90 (95% CI 0.87 to 0.93); intercept -18 (-26.6, -9.5), Sy/x=32.9 • HPLC vs FPIA/TDx monoclonal immunoassay: r^2=0.91 • HPLC vs FPIA/TDx polyclonal: r^2=0.98 • HPLC vs CEDIA: r^2=0.97; slope 1.31 (95% CI 1.29 to 1.47) • HPLC vs EMIT: r^2=0.97; slope 1.17 (95 CI 1.02 to 1.28) • HPLC vs FPIA/AxSYM r^2=0.98; slope 1.03 (95% CI 0.97 to 1.12) • HPLC vs FPIA/TDx r^2= 0.97 slope 1.29 (95% CI 1.19 to 1.42) • HPLC vs FPIA/AxSYM: slope=1.17 (1.04 to 1.32), intercept 13.2, Sx/y=19.2 • HPLC vs CEDIA: slope=1.19 (1.00 to 1.39), intercept -3.5, Sx/y=24.0 • HPLC vs EMIT: slope 1.07 (0.97 to 1.19), intercept 16.2, Sx/y=16.1

Outcome	CNI Regimen	Quantity and Type of Evidence	Key Findings
Analytic bias	CsA	4 prospective comparative studies[30,32,33,35]	Immunoassays measured significantly higher CsA levels than HPLC • HPLC results were 17.5% lower than CEDIA plus • HPLC values were always lower than the FPIA/TDx monoclonal with a mean difference of -109 µg/L (standard deviations [SD] 99) • Immunoassay was higher than HPLC: 14.1 % higher with CEDIA, 18.8% with EMIT, 10% with FPIA/AxSYM, 50% with FPIA/TDx • Immunoassay was higher than HPLC: 32% higher with FPIA/AxSYM, 22.5% higher with CEDIA, 23.9% higher with EMIT
Precision	CsA	4 prospective comparative studies[30,32,33,35]	HPLC demonstrated greater precision than immunoassays • For the CEDIA plus, the within assay coefficient of variance (CV) was between 2.7% and 8.7% for CsA levels ranging from 48-1,502 µg/L. • The within assay CV ranged between 2% and 5% for both the monoclonal and polyclonal FPIA/TDx • The within assay CV at the lowest CsA concentration ranged from 3.07% for the FPIA/TDx to 10.6% for the CEDIA. At the highest concentration, the CV ranged from 1.73% for FPIA/TDx to 6.45% for FPIA/AxSYM. The between assay CV ranged from 4.25% (FPIA/TDx) to 8.90% (EMIT) at the lowest CSA and from 3.12% (FPIA/TDx) to 6.77% (FPIA/AxSYM) at the highest CSA. • The within assay coefficient of variation are provided for low and high range controls: HPLC 6.8% , 7.6%; FPIA/AxSym 5.8%, 1.7%; CEDIA 11%, 5.5%; EMIT 6.5%, 4.8%
Analytic accuracy	TAC	2 prospective and 1 retrospective comparative studies[29,31,34]	HPLC and LC-MS/MS more accurate than immunoassay at measuring TAC at lower concentration levels. • TAC concentration levels measured by HPLC-MS were statistically lower than levels measured by MEIA (median difference -0.40 (2.03) µg/L; p<0.001). • Concentration measurements of TAC at 5 µg/L ng/mL, 10 µg/L ng/mL, and 20 µg/L ng/mL had corresponding relative difference in values between LC-MS/MS and immunoassay (as expressed by 95% confidence intervals) of between -50% and 60%, -24% to 31%, and -11% to 17%. • Measurement of TAC samples at various concentrations (1.0, 4.0, 15.0 and 50.0 µg/l), indicated acceptable accuracy of HPLC-MC at all levels tested (<10% deviation), and for ELISA at 1.0 and 4.0. Analytic accuracy was not acceptable for ELISA at 15.0 and 50.0 µg/L or for MEIA at all concentrations.*

Outcome	CNI Regimen	Quantity and Type of Evidence	Key Findings
Analytic bias	TAC	2 prospective and 2 retrospective comparative studies[26-28,31]	Compared to chromatographic techniques, bias for immunoassays ranged from 2% to 37%.
Precision	TAC	1 RCT[25]	Inter-assay variability using Abbott Diagnostic control samples of 5, 11, and 22 ng/ml TAC was 8.0%, 6.5%, and 5.7% for HPLC-MS, respectively, compared to 13.7%, 8.3%, and 10.9% for MEIA, respectively.

CEDIA = cloned enzyme donor immunoassay; CsA = cyclosporine; CV = coefficient of variation; ELCIA = electrochemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay; EMIT = enzyme multiplied immunoassay; FPIA = fluorescence polarization immunoassay; HPLC-MS = high performance liquid chromatography; LC/MS/MS = liquid chromatography-tandem mass spectrometry; MEIA = microparticle enzyme immunoassay; RCT = randomized controlled trial; Sy/x = dispersion of residuals;TAC = tacrolimus

*Accuracy was measured 3 times per day for 5 days, each of the weighed-in controls was assayed in triplicate by all 3 methods (HPLC-MS, ELISA, MEIA). Accuracy was calculated for each measurement as mean concentration/weight in concentration.

Applicability

The majority of the studies addressing KQ 1 were laboratory studies comparing the analytical performance of immunoassays to chromatographic techniques. These studies varied in terms of the quality controls used to prepare and handle blood samples, methods of calibrating equipment, and analytical methods used to process data. Such differences may limit the generalizability of the studies. Further, most of these studies took place in academic medical centers in which there was access to chromatographic technologies. Access to these technologies may be limited in smaller clinical settings.

Summary

Only one study at high risk of bias assessed clinical outcomes of renal recipients in whom TAC levels were measured with either a commonly used commercial immunoassay (e.g., MEIA) or HPLC. The evidence from this study was considered insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes due to limitations in methodological quality of the study and imprecision of the findings.

The findings assessing analytical performance suggest that chromatographic methods are more analytically accurate and precise than commonly used immunoassays at measuring CNI drug levels. Selection of assay methodology for measurement of calcineurin inhibitors did not have an impact on clinical outcomes after renal transplantation. This is partially due to the bias between assay methodologies. However additional factors such as the lack of standardization in laboratory procedures also impacts the wide inter-laboratory variability reported in therapeutic drug monitoring of immunosuppressive drugs.[36] However, the methodologic quality of some of the studies is questionable due to not reporting information about baseline test characteristics such as limit of detection, linearity, and reproducibility, and it was unclear whether differences identified in these studies were clinically relevant such that they would change clinical management or affect patient outcomes.

Timing for Monitoring CNI Drug Levels

Key Question 2. How does 2-hour post-administration CsA monitoring (C2) compare with trough monitoring (C0)?

Description of Included Studies

Six comparative trials addressed this question. All but one study compared C0 monitoring of CsA to C2 among new renal transplant recipients. The remaining study compared C0 monitoring to C2 monitoring of CsA among stable renal transplant recipients (>3 months post-transplant).[37] Due to the heterogeneity of the studies, we did not attempt to combine data from the studies quantitatively. Instead, we provide a narrative synthesis of the studies' general findings. Detailed evidence tables presenting information on the design of the studies, study populations, findings, and risk-of-bias assessment are located in Appendix C.

Two of the included studies were RCTs. Both studies were rated as having high risk of bias. In one study, withdrawal was higher among patients in the C2 group (6 vs. 0 in C0 group) primarily due to discomfort of giving repeated blood samples. The other RCT was rated as having high risk of bias due to not reporting on randomization procedures, blinding of outcome assessors, or completion rates.

The remaining four studies were nonrandomized comparative trials. In general, these studies were rated as high risk of bias primarily due to not using methods to ensure group comparability, not reporting whether outcome assessors were blinded, and retrospective designs.

Key Points

- Among new renal transplant recipients, risk of BPAR is similar between patients monitored at C0 and those monitored at C2. (Strength of Evidence: Low)
- Among new renal transplant recipients (within 20 days after transplant), evidence from one RCT indicated that C2 monitoring led to a significantly higher CsA mean cumulative dose increase compared to C0 monitoring. (Strength of Evidence: Low)
- Among new renal transplant recipients, evidence from one RCT demonstrated that significantly more patients in the C2 group experienced tremors than patients in the C0 group. (Strength of Evidence: Low)
- Among new renal transplant recipients, there was insufficient evidence available to draw conclusions about the association of C0 versus C2 monitoring for the outcomes of patient and graft loss, renal function, and other adverse events. This was due to the study limitations and imprecision of findings in the non-randomized trials available.
- Among stable renal transplant recipients at 3 or more months after transplant, C2 monitoring led to significantly more CsA dose reductions than C0 monitoring. (Strength of Evidence: Low)

Detailed Synthesis

Studies of New Renal Transplant Recipients

One RCT compared CsA C2 monitoring to C0 monitoring among new renal transplant patients. Kyllonen and colleagues randomly assigned 160 patients before transplantation to C0 monitoring or C2 monitoring for 20-days post-transplantation.[38] After transplantation, CsA levels

in both study groups were monitored at both C0 and C2 timepoints. However, depending on the randomization, the values of one method were blinded until the end of the 20-day study period. After 20 days, all patients were continued with C0 monitoring only. Patients at higher immunologic risk (i.e., panel reactive antibodies [PRA] >30% and/or previous graft loss within 1 year for immunologic reasons) were excluded from the study. The target C0 level was 200 to 300 µg/L, and the target C2 level was 1,500 to 2,000 µg/L. However, despite dose adjustments, 72 percent of C2 monitored patients did not reach the C2 target range by day-3 post-transplant, and 45 percent did not reach the target range by day-5 post-transplant. In contrast, 5 percent of patients did not reach the C0 target range by day-5 post-transplant.

The difficulty in reaching C2 target levels in this study likely explains the highly significant differences observed in the mean CsA doses and blood levels between the two monitoring groups. Low strength of evidence from this study indicated that C2 monitoring led to a significantly higher overall increase in CsA dose compared to C0 monitoring. The mean CsA dose in the group randomly assigned to management based on C2 monitoring was 56 percent higher than in the group randomly assigned to management based on C0 monitoring (11,409 mg vs. 7,256 mg, respectively), and the mean C0 and C2 blood levels were 98 percent and 55 percent higher in the C2 group than the C0 group. In the C0 group, the mean cumulative CsA dose increased by 7,175 mg compared to a cumulative increase of 8,460 mg in the C2 group ($p<0.01$). Such differences, however, did not lead to differences in overall acute rejection rate between the groups.

The remainder of the evidence for new renal transplant patients comes from four nonrandomized studies.[39-42] Overall, low strength of evidence from these studies and the RCT suggests no difference in the risk of acute rejection between patients monitored at C2 and those at C0 (RR 0.95, 95% CI: 0.61 to 1.45). One small non-RCT did demonstrate a significant decline in renal function among patients in the C0 group compared to those in the C2 group over the course of the study.[39] The serum creatinine level at 36 months was significantly higher among patients in the C0 group (1.46±0.52) than in patients in the C2 group (0.99±0.13, $p=0.04$). Similarly, creatinine clearance levels were significantly lower in the C0 group (55.15±19.21) than the in the C2 group (84.65±14.97, $p<0.001$). Patients in this study were followed for 36 months compared to 6 or fewer months in the other studies. For the most part, the evidence for patient and graft loss and adverse events among studies comparing C0 to C2 monitoring in new renal transplants was inconclusive due to study limitations of nonrandomized trials and imprecision of findings. However, low strength evidence from one RCT did indicate that significantly more patients in the C2 group (n=9) than in the C0 group (n=2) experienced tremors (RR 4.82, 95% CI: 1.09 to 21.78).

Studies of Stable Renal Transplant Recipients

Jirasiritham and colleagues conducted an RCT comparing CsA C0 monitoring to C2 monitoring among patients who had more than 3 months of successful renal transplantation with well-functioning renal grafts.[37] The authors randomly assigned 35 patients to convert from C0 monitoring to C2 monitoring and 35 to remain on C0 monitoring. All patients were followed for 3 months. The target C2 level among patients converted to C2 monitoring was 800 ng/mL with 10 percent variation, and the target C0 level among patients who remained on C0 monitoring was 100 to 150 ng/mL. Lack of precision due to the study's small sample size and small number of events occurring in each group prevented conclusions for the primary outcomes of interest: acute rejection, patient and graft loss, and nephrotoxicity. The findings of the study did, however,

provide low strength of evidence indicating that C2 monitoring led to more dosage reductions than C0 monitoring (34.3% vs. 14.3%, p=0.02). The discrepancy of the findings related to CsA dose between this study and the study by Kyllonen may be due to differences between the studies in the time period examined post-transplant. In the Kyllonen study, the patients were 20 days post-transplant, whereas in this study they were 3 or more months post-transplant. CsA levels tend to fluctuate more shortly after transplantation, and reaching target levels is often difficult.

Applicability

The applicability of the studies addressing this KQ is limited due primarily to the exclusion of patients at high risk of rejection. Overall, 71 percent of the studies excluded patients considered high risk. This includes patients over the age of 65 and patients with previous renal transplants. The average age range of patients enrolled in the studies was between 32 to 51 years. Few studies reported on race. Among the three studies that did, the majority of patients were Caucasian.

Summary

Table 8 presents the strength of evidence ratings for the studies addressing this KQ. Overall, low strength of evidence suggests that risk of BPAR is similar between new renal transplants monitored at C0 compared to those monitored at C2. For the most part, the evidence for patient and graft loss and adverse events among studies comparing C0 to C2 monitoring in new renal transplants was inconclusive due to study limitations of nonrandomized trials and imprecision of findings. However, low strength of evidence from one RCT indicated that C2 monitoring led to a significantly higher CsA mean cumulative dose increase compared to C0 monitoring. Low strength of evidence from this same study also indicated that significantly more patients in the C2 group than in the C0 group experienced tremors. In contrast, low strength of evidence from one small RCT indicated that C2 monitoring led to significantly more CsA dose reductions than C0 monitoring among stable renal recipients. The discrepancy of the findings related to CsA dose could be due to the difference in time post-transplant of patients in the studies. In one study, the patients were only 20-days post-transplant; in the other study, they were 3 or more months post-transplant. The difference may also reflect the fact that these conclusions come from single studies and that additional studies could overturn their conclusions.

Table 8. Strength of evidence of studies comparing C0 to C2 monitoring of CsA

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
C2 vs. C0 among new renal transplant recipients	BPAR	No difference (RR: 0.95; 95% CI: 0.61–1.45)	1 RCT, 3 non-RCTs[40-42] N=851	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 1.71; 95% CI: 0.41–7.05)	1 RCT, 2 non-RCTs[38,41,42] N=431	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.84; 95% CI: 0.33–2.14	1 RCT, 2 non-RCTs[40-42] N=635	Study Limitations Imprecision	Insufficient
	Serum creatinine levels	The findings from 1 non-RCT indicated serum creatinine level at 36 months was significantly higher among patients in the C0 group (1.46±0.52) than the C2 group (0.99±0.13, p=0.04), and creatinine clearance levels were significantly lower in the C0 group (55.15±19.21) than the C2 group (84.65±14.97, p<0.001).	1 non-RCT[39] N=37	Study Limitations Imprecision	Insufficient
	CsA dosage	Findings from 1 RCT indicated significantly higher CsA mean cumulative dose increase among patients in the C2 group compared to the C0 group (8460 mg vs. 7175 mg, p<0.01)	1 RCT[38] N=154	Study Limitations Imprecision	Low
	Chronic allograft nephrotoxicity (CAN)	Inconclusive (RR: 0.16; 95% CI: 0.02–1.09)	1 non-RCT[39] N=37	Study Limitations Imprecision	Insufficient
	Tremors	Findings from 1 RCT indicated significantly more patients in the C2 group (n=9) had tremors than the C0 group (n=2); (RR 4.82, 95% CI: 1.09–21.78)	1 RCT[38] N=154	Study Limitations Imprecision	Low
	Other Adverse Events	Inconclusive for other AEs (infections, cardiac symptoms, new onset diabetes)	1 RCTs, 2 non-RCTs[40-42] N=635	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
C2 vs. C0 among stable renal transplant recipients	BPAR	Inconclusive (RR: 0.33: 95% CI: 0.01–7.90)	1 RCT[37] N=70	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (no events)	1 RCT[37] N=70	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (no events)	1 RCT[37] N=70	Study Limitations Imprecision	Insufficient
	CsA dosage	C2 monitoring led to more dosage reductions compared to C0 monitoring (34.3% vs. 14.3%, p=0.02).	1 RCT[37] N=70	Study Limitations Imprecision	Low
	Nephrotoxicity	Inconclusive (no events)	1 RCT[37] N=70	Study Limitations Imprecision	Insufficient

AE = adverse event; BPAR = biopsy proven acute rejection; C2 = 2-hour CsA monitoring; CI = confidence interval; C0 = trough monitoring; CsA = cyclosporine A; RCT = randomized controlled trial; RR = relative risk

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, and Directness. Publication and reporting bias not assessed due to insufficient number of studies.

Alternative CNI Regimens

Key Question 3a. In adult renal transplants, how do immunosuppressive regimens designed to reduce or eliminate exposure to CNI toxicity compare with each other and with full-dose CNI regimens for health outcomes?

Key Question 3b. How do the type of induction agent (including when no induction is used) and the use of concurrent immunosuppressive agents affect outcomes of regimens that reduce or eliminate CNI exposure?

Regimens designed to reduce or eliminate CNI exposure after renal transplant were grouped into four types of strategies, as described in Table 1: minimization, conversion, withdrawal, and avoidance. Each regimen was analyzed separately, and the head-to-head studies were assessed as a separate category.

The average age of renal transplant recipients enrolled in the studies was between 30 and 55 years. Thirty-seven studies (42%) excluded patients over 75 years old, including 20 (23%) that excluded patients older than 65. Among studies reporting on patient race, the majority of enrolled patients were Caucasian males. Measures of patient socioeconomic status were not reported. In most studies, the majority of patients received their renal transplant from a deceased donor, although 11 studies (13%) enrolled only patients whose renal transplant was from a living donor. Seventy studies (80%) were conducted in the United States or Europe, while others took place in Australia, Brazil, China, Egypt, India, Iran, Japan, Korea, Mexico, and New Zealand.

In general, the studies we reviewed excluded patients at high risk for graft failure or other adverse outcomes. Clinical indications commonly used to exclude participants included active infections, history of malignancies, prior renal transplant, and/or severe metabolic or hematologic abnormalities. In thirty-five studies (40%), patients with PRA greater than 50 percent were excluded, and retransplants were not eligible for participation in 21 studies (24%). Additionally, we excluded studies conducted in multi-organ transplant populations from our analysis.

Minimization

Description of Included Studies: Minimization

The most widely studied strategy reported in the RCTs we identified in the literature search is minimization of CNI dosage. Minimization is most frequently implemented by reducing the target blood levels that are used to adjust dosing. CNI minimization has been evaluated for both CsA and TAC. CNI minimization has been supplemented with many combinations of other immunosuppressive drugs and induction agents. Thirty-six RCTs examining dose minimization met the inclusion criteria for this review (Table 9). Twenty-two studies used reduced dosing of CsA, seven studies examined TAC minimization, and seven RCTs combined populations that received CsA or TAC. Mycophenolic acid formulations (MMF or enteric-coated mycophenolic sodium) were used as the primary additional immunosuppressive drug in 19 studies, and 14 studies used mammalian target of rapamycin (mTOR) inhibitors in addition to CNI. Two studies incorporated multiple adjunct therapies, including mycophenolic acid formulations, mTOR inhibitors, and azathioprine (AZA). Vathsala et al.[43] did not use any additional maintenance

immunosuppressive therapy. Steroid therapy, usually prednisone, was administered in the intervention and control groups in nearly every study.

These trials widely used induction therapy. Sixteen studies included basiliximab induction, three used daclizumab, one used alemtuzumab, two included rabbit antithymocyte globulin (rATG), and one indicated that induction therapy was not standardized and varied according to the local practice of study sites. Two studies indicated that induction therapy was not used, while the remaining 11 studies did not report on induction. Subgroup analysis of regimens with induction agents was performed separately for studies using mycophenolic acid formulations and mTOR inhibitors.

CNI exposure was usually minimized immediately or shortly after transplant. Twenty-nine studies initiated minimization within the first 6 months following transplant, three trials waited at least 6 months, and four adopted this strategy 1 year or more after transplant. Subgroup analysis was conducted comparing early (i.e., first 6 months after transplant) and late (i.e., 6 months or later after transplant) minimization for patients receiving MMF or mycophenolate sodium (MPS). We did not examine timing of minimization for patients receiving mTOR inhibitors because minimization was initiated early in all but two studies.

Risk of bias was determined to be high for 17 of the 36 minimization studies (47%). The detailed assessments of risk of bias are presented in Table E-21 in the Appendix. Sixteen studies were categorized as moderate risk, and three studies were assessed as low risk of bias. Incomplete descriptions of randomization and allocation concealment practices were common, and many studies did not sufficiently describe whether all eligible patients were enrolled. Additionally, data on patient adherence with drug therapy were rarely included in published results. Twenty-seven trials (75%) were funded by sources that could benefit financially from the study results, such as pharmaceutical manufacturers. Five studies were funded by sources that did not appear to have a financial interest in the outcomes, and four studies did not report source of funding.

Table 9. Minimization studies

Reference	CNI	Other Immunosuppression	N, Intervention	N, Control
Xu 2011[44]	CsA, TAC	MMF	20	18
Gaston 2009[45]	CsA, TAC	MMF	243	477
Spagnoletti 2009[46]	CsA, TAC	MMF	30	30
Ekberg 2007b[4]	CsA, TAC	MMF	800	390
Hernandez 2007[47]	CsA, TAC	MMF	160	80
Tang 2006[48]	CsA, TAC	MMF, AZA	18	16
Cai 2014[49]	CsA	MPS	90	90
Chadban 2013[50]	CsA	MPS	42	33
Etienne 2010[51]	CsA	MMF	106	102
Fangmann 2010[52]	CsA	MMF	75	73
Budde 2007[53]	CsA	MPS	44	45
Cibrik 2007[54]	CsA	MPS	75	66
Ekberg 2007a[24]	CsA	MMF	183	173
Ghafari 2007[55]	CsA	MMF	42	48
Frimat 2006[56,57]	CsA	MMF	70	31
Stoves 2004[58]	CsA	MMF	13	16
Pascual 2003[59]	CsA	MMF	32	32
de Sevaux 2001[60]	CsA	MMF	152	161
Chan 2012[61]	TAC	MPS	151	141

Reference	CNI	Other Immunosuppression	N, Intervention	N, Control
Kamar 2012[62]	TAC	MPS	45	47
Bolin 2008[63]	TAC	MMF, SRL, AZA	100	223
Holdaas 2011[22]	CsA, TAC	EVR	144	123
Chadban 2014[23]	CsA	EVR	30	47
Muhlbacher 2014[64]	CsA	SRL	178	179
Cibrik 2013[65]	CsA	EVR	556	277
Takahashi 2013[66]	CsA	EVR	61	61
Oh 2014[67]	CsA	EVR	67	72
Paoletti 2012[68]	CsA	EVR	10	20
Bertoni 2011[69]	CsA	EVR	56	50
Salvadori 2009[70]	CsA	EVR	143	142
Nashan 2004[71]	CsA	EVR	58	53
Bechstein 2013[72]	TAC	SRL	63	65
Langer 2012[73]	TAC	EVR	107	117
Chan 2008[74]	TAC	EVR	49	43
Lo 2004[75]	TAC	SRL	23	16
Vathsala 2005[43]	CsA	None	20	10

AZA = azathioprine; CsA = cyclosporine; EVR = everolimus; MMF = mycophenolate mofetil; MPS = mycophenolate sodium; N = number of patients; SRL = sirolimus; TAC = tacrolimus

Key Points

- Early minimization of CNI exposure through low-dose regimens is associated with improved renal function and lower risk of acute rejection and graft loss (Strength of Evidence: High).
- Regimens using mycophenolic acid formulations and low-dose CsA are associated with better renal function, lower risk of acute rejection (Strength of Evidence: Moderate), and lower risk of graft loss (Strength of Evidence: High) compared with regimens based on standard-dose CsA. The evidence for minimization regimens using mycophenolic acid formulations and TAC suggests improvement in renal function (Strength of Evidence: High) but is insufficient to draw conclusions for the other outcomes.
- Regimens that include mTOR inhibitors and low-dose CsA are associated with improved renal function and no difference in acute rejection (Strength of Evidence: Moderate) compared with standard-dose regimens, but the evidence for mTOR inhibitors with TAC is insufficient.
- Induction with basiliximab, when used with mTOR inhibitors and low-dose CNIs, is associated with better renal function (Strength of Evidence: High), lower risk of graft loss, and no difference in risk of acute rejection (Strength of Evidence: Moderate), but the evidence is insufficient to draw conclusions when basiliximab is used with mycophenolic acid formulations.
- Minimization with low-dose CNIs and mycophenolic acid formulations, when initiated within the first 6 months after renal transplant, is associated with improved renal function (Strength of Evidence: Low), lower risk of graft loss (Strength of Evidence: Moderate), and lower risk of acute rejection and infection (Strength of Evidence: High) compared with standard-dose regimens.

- Minimization initiated 6 months after transplant or later is associated with increased risk of acute rejection (Strength of Evidence: Low). The evidence is insufficient to draw conclusions for other clinical outcomes.

Detailed Synthesis—Minimization Studies

Analysis combining results from all 36 trials (see Table 10) found that CNI minimization was associated with improved renal function, reduced risk of acute rejection and graft loss, and lower incidence of CMV and other opportunistic infections (with the exception of BK virus infection, for which the evidence was inconclusive) compared with standard-dose regimens. No difference was observed for patient death.

The strength of evidence for these findings was high for renal function, acute rejection, graft loss, and other opportunistic infections and moderate for patient death and CMV infection. The evidence for BK virus infection was insufficient based on the four studies that reported this outcome due to the small number of reported infections and substantial imprecision and inconsistency in the results. A moderate amount of heterogeneity was identified for the outcomes of eGFR and CMV infection, but this was due to the inclusion of diverse immunosuppressive regimens and the inclusion of high- and low-risk patients in these comprehensive comparisons. The effect estimate for patient death was imprecise, and the outcome of other infections was subject to reporting bias. Further analyses were conducted to separate studies according to type of adjunctive immunosuppressive therapy and choice of CNI.

Mycophenolic Acid-Based Adjunctive Therapy

Similar results were found for the 19 studies that used CNI minimization with mycophenolic acid formulations. In general, renal function improved, as measured by eGFR, and risk of acute rejection, graft loss, CMV infection, and other infections were reduced (Table 11). No difference was observed for patient death, and the two studies that reported BK infection did not yield sufficient evidence to support a conclusion. Of these 19 studies, 14 minimized CsA and 5 minimized TAC. Examination of these studies separately found high- or moderate-strength evidence that low-dose CsA was associated with improved renal function, reduced risk of acute rejection and graft loss, and lower incidence of opportunistic infections compared with standard-dose CsA (Table 12). The evidence was inconclusive for patient death, CMV infection, and BK virus infection. Low-dose TAC was also associated with improved renal function, based on high-strength evidence, compared to standard-dose regimens, but the evidence for the other important clinical outcomes we analyzed was insufficient to support conclusions.

Subgroup analyses were performed to evaluate the effect of induction therapy and timing of minimization on outcomes. Five studies used basiliximab induction in addition to CNI minimization and mycophenolic acid formulations. The evidence for each outcome was insufficient to support a conclusion due mainly to substantial imprecision in the effect size estimates. Three studies used daclizumab in the minimization arm and no induction in the control group. These studies were associated with an improvement in eGFR and lower risk of graft loss, death, and infection. However, only reduced risk of graft loss and other opportunistic infections were supported by high-strength evidence, while the other outcomes were supported by moderate- or low-strength evidence. Additionally, the results for acute rejection were inconclusive due to insufficient evidence.

Nine studies did not use induction or did not report whether induction was used. Meta-analysis of these trials found that minimization without induction, or when no induction was

reported, was associated with improved renal function and reduced risk for acute rejection, graft loss, and death. The evidence base was moderate strength for eGFR and acute rejection and low strength for graft loss and death. Analyses of infection outcomes were inconclusive.

Overall, regimens that included mycophenolic acid formulations and low-dose CNI resulted in better outcomes than standard-dose CNI regimens when induction therapy was not used, not reported, or incorporated daclizumab. Unfortunately, none of the RCTs that examined low-dose CNI regimens used different induction strategies across the minimization arm, so direct within-study comparisons of the effects of different induction agents were not possible. Further research is necessary to clarify the effect of induction therapy in CNI minimization.

Fourteen studies initiated minimization within 6 months after transplant. These trials were associated with improvement in all outcomes, except death and BK virus infection, for which the data were insufficient to support a conclusion. Interestingly, early minimization was associated with lower risk of acute rejection, as this finding may call into question conventional wisdom about the risks of low-dose strategies.

In five studies that reduced CNI dose 6 months after transplant or later, low-strength evidence indicated a higher risk of acute rejection. For the other outcomes, the evidence base was insufficient. Although we identified no studies that directly compared early with late minimization, the evidence indicates that early initiation is associated with improved outcomes while later initiation may not confer benefit and may be associated with harm. Importantly, these studies used minimization as a planned strategy in randomized populations and did not initiate lower-dose regimens in response to specific patient needs. This evidence base cannot address the potential benefits or harms of later-stage minimization in transplant recipients who experience CNI toxicity or other adverse events.

MTOR Inhibitor-Based Adjunctive Therapy

Fourteen RCTs studied SRL or EVR and reduced-dose CNI compared to standard-dose regimens. Analysis of these studies found moderate-strength evidence for improvement in renal function, and low-strength evidence suggesting no difference for risk of acute rejection and lower incidence of CMV infection (Table 13). The evidence was insufficient for the other outcomes.

Meta-analysis of the trials that specifically used low-dose CsA with an mTOR inhibitor resulted in moderate-strength evidence that suggested improved renal function and no difference for risk of acute rejection. Low-strength evidence suggested a reduced risk for graft loss and CMV infection, while the evidence was insufficient to draw conclusions about risk of death or other opportunistic infections. Only one of these studies reported on BK infection, but the authors found significantly fewer cases in the minimization group. Four studies used low-dose TAC with an mTOR inhibitor, but the evidence was insufficient for all outcomes due to substantial imprecision in the effect size estimates. The overall improvement in outcomes associated with low-dose CNI and mTOR inhibitors appears to be influenced by the studies that used CsA but not regimens based on TAC.

Induction therapy with basiliximab was employed in 10 of the trials that lowered CNI dosing and used SRL or EVR. Improved renal function and lower risk of graft loss were found in these studies, supported by moderate-strength evidence, and low-strength evidence suggested lower risk of CMV infection. No differences were observed for the risk of graft loss and death, and the evidence was insufficient to support conclusions for the outcomes of BK virus and other

infections. In the three studies that did not use or did not report induction therapy in conjunction with mTOR inhibitors, the evidence base was insufficient for all outcomes.

Applicability

The patient populations included in these studies were generally at lower risk of adverse outcomes, based on clinical and demographic characteristics, and the findings may thus be less applicable to higher-risk patients. The average age of included patients was between 40 and 50, 60 and 70 percent in most studies were men. Most of the studies excluded patients with PRA that exceeded a defined threshold (typically 50%), and patients over age 65 or 70 as well retransplant recipients were frequently excluded.

Another important consideration is that 22 of the studies used CsA, 7 used TAC, and 7 combined patients that received CsA and those that received TAC. Our overall results were generally similar to the results of subgroup analyses of studies that administered CsA. Subgroup analysis also suggested that the heterogeneity observed in several of our results might be attributed in part to the studies that used TAC. The overall findings may therefore be more representative of CsA minimization than TAC minimization.

Other features of these studies also limit the applicability of our findings. "Minimization" is not a uniform approach based on a single strategy for reducing CNI dosing, and studies varied in their selection of target levels. For example, CsA low-dose targets ranged from 25 to 50 ng/mL in some studies and 80 to 120 ng/mL in other trials. Similarly, low-dose TAC was defined as a trough target of 1.5 to 3.0 ng/mL in one study, and 5 to 10 ng/mL in another, while other studies varied within these ranges. Therefore, the target levels compared in this analysis do not represent the effect of a particular low-dose regimen. Rather, the results indicate that reduced CNI dosage is associated with improved outcomes compared with nonreduced dosing. This review cannot identify a specific target range for minimization that is associated with better clinical outcomes.

Moreover, management of immunosuppressive therapy has evolved over the past 20 years, as utilization of CNIs and adjunctive agents has increased, and as other elements of transplant medicine have changed. One important result is that current management of CNI therapy typically uses dosing and target levels that are lower than those employed in many of the studies we reviewed. In some studies, therefore, the minimization arm used dosing that would currently be viewed as a standard-dose, rather than a low-dose regimen. Another important consideration is that target ranges for therapeutic drug levels are goals that may not be achieved for every patient or even a majority of patients in a study. The appendix (Table E-3) presents data on the extent to which target levels were achieved in intervention and control groups. Wide variation existed in how this information was reported and in the achievement of targets. In many of the studies we reviewed, many patients did not, or may not, have reached a designated target level. We considered the impact of this variation on heterogeneity when we assessed the strength of evidence. However, due to incomplete and inconsistent reporting of data on achievement of target levels, it was not possible to conduct subgroup analyses based on these factors.

Summary

Overall, high- and moderate-strength evidence suggests that early CNI minimization, through low-dose regimens, improves patient outcomes and does not increase adverse event rates. The benefits associated with minimization were observed for CsA and TAC, although the evidence for TAC was frequently insufficient, and for regimens that included mycophenolic acid formulations or mTOR inhibitors as adjunct immunosuppressive therapy. Induction agents did

not clearly correlate with improved outcomes, and results for subgroup analyses of induction therapy varied by adjunct immunosuppression treatment. Timing of initiating minimization may be an important factor affecting outcomes. High strength of evidence indicated improved clinical outcomes were associated with early minimization but not late minimization. It is important to note that all these findings may be less applicable to patients at higher risk for poor clinical outcomes and may represent effects associated with CsA to a greater degree than TAC. Nevertheless, these results demonstrate that CNI minimization appears to be an effective approach to immunosuppression therapy in renal transplant recipients.

Table 10. Strength of evidence for all minimization studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
All reduced CNI vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.32; 95% CI: 0.22–0.41; I^2=60%[a])	24 RCTs[4,22,24,44,47-50,52,53,56,59-62,64,66,67,69-74] N=5,043	None	High
	BPAR	Minimization associated with reduced rejection (RR: 0.84; 95% CI: 0.75–0.95; I^2=19%)	35 RCTs[4,22-24,43-45,47-56,58-75] N=7,563	None	High
	Graft loss	Minimization associated with reduced graft loss (RR: 0.76; 95% CI: 0.61–0.94; I^2=12%)	36 RCTs[4,22-24,43-56,58-75] N=7,623	None	High
	Patient death	No difference (RR: 0.91; 95% CI: 0.72–1.14; I^2=0)	32 RCTs[4,22-24,43-45,47,49,50,52-56,58-68,70-75] N=7,215	Imprecision	Moderate
	CMV infection	Minimization associated with lower incidence of CMV (RR: 0.71; 95% CI: 0.55–0.92; I^2=57%[a])	19 RCTs[4,23,24,43,45,47,52,59,60,63-66,69-73,75] N=5,666	Study Limitations	Moderate
	BK infection	Inconclusive (RR: 0.68; 95% CI: 0.06–7.55; I^2=65%)	4 RCTs[45,59,65,73] N=1,841	Study Limitations Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Minimization associated with lower incidence of other infections (RR: 0.76; 95% CI: 0.64–0.91; I^2=0)	13 RCTs[4,24,43,48,52,54,56,59,60,62,64,71,72] N=3,065	None	High

BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = cyclosporine; eGFR = estimated glomerular filtration rate; mTOR = mammalian target of rapamycin; NS = not significant; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAC = tacrolimus

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

[a] Based on subgroup analyses, the high level of heterogeneity observed in this outcome appears to be attributable primarily to the use of multiple, diverse immunosuppressive regimens and/or the presence of high- and low-risk patients, in the included studies. Therefore, we did not decrease the strength of evidence for Inconsistency.

Table 11. Strength of evidence for minimization studies with adjunctive use of mycophenolic acid formulations

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced CNI (cyclosporine or tacrolimus) + mycophenolic acid formulations vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.32; 95% CI: 0.20–0.45; I^2=55%[a])	13 RCTs[4,24,44,47,49,50,52,53,56,59-62] N=3,178	None	High
	BPAR	Minimization associated with reduced rejection (RR: 0.80; 95% CI: 0.68–0.95; I^2=27%	18 RCTs[4,24,44,45,47,49-56,58-62] N=4,366	None	High
	Graft loss	Minimization associated with reduced graft loss (RR: 0.71; 95% CI: 0.56–0.90; I^2=5%)	19 RCTs[4,24,44-47,49-56,58-62] N=4,426	None	High
	Patient death	No difference (RR: 0.87; 95% CI: 0.66–1.15; I^2=0)	17 RCTs[4,24,44,45,47,49,50,52-56,58-62] N=4,158	Imprecision	Low
	CMV infection	Minimization associated with lower incidence of CMV (RR: 0.77; 95% CI: 0.62–0.95; I^2=36%)	7 RCTs[4,24,45,47,52,59,60] N=3,031	None	High
	BK infection	Inconclusive (RR: 0.55; 95% CI: 0.07–4.57; I^2=0)	2 RCTs[45,59] N=784	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Minimization associated with lower incidence of other infections (RR: 0.77; 95% CI: 0.61–0.98; I^2=7%)	8 RCTs[4,24,52,54,56,59,60,62] N=2,405	Reporting Bias	Moderate
Reduced cyclosporine + mycophenolic acid formulations vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.28; 95% CI: 0.10–0.46; I^2=58%)	10 RCTs[4,24,47,49,50,52,53,56,59,60] N=2,756	Inconsistency	Moderate
	BPAR	Minimization associated with reduced risk of acute rejection (RR: 0.88; 95% CI: 0.76–1.02); I^2=0)	14 RCTs[4,24,47,49-56,58-60] N=3,224	Imprecision	Moderate
	Graft loss	Minimization associated with reduced graft loss (RR: 0.70; 95% CI: 0.55–0.88; I^2=0)	14 RCTs[4,24,47,49-56,58-60] N=3,224	None	High
	Patient death	Inconclusive (RR: 0.80; 95% CI: 0.54–1.20; I^2=0)	13 RCTs[4,24,47,49,50,52-56,58-60] N=3,016	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.86; 95% CI: 0.62–1.18; I^2=47%)	6 RCTs[4,24,47,52,59,60] N=2,311	Imprecision	Insufficient
	BK infection	Inconclusive, no events observed	1 RCT[59] N=64	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Minimization associated with lower incidence of other infections (RR: 0.83; 95% CI: 0.64–1.07; I^2=0)	7 RCTs[4,24,52,54,56,59,60] N=2,313	Imprecision	Moderate

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced tacrolimus + mycophenolic acid formulations vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.42; 95% CI: 0.22–0.62; I^2=29%)	4 RCTs[4,47,61,62] N=1,814	None	High
	BPAR	Inconclusive (RR: 0.76; 95% CI: 0.40–1.43; I^2=56%)	4 RCTs[4,47,61,62] N=1,814	Imprecision Inconsistency	Insufficient
	Graft loss	Inconclusive (RR: 0.88; 95% CI: 0.32–2.46; I^2=47%)	5 RCTs[4,46,47,61,62] N=1,874	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.00; 95% CI: 0.45–2.24; I^2=0)	4 RCTs[4,47,61,62] N=1,814	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.64; 95% CI: 0.27–1.52; I^2=0)	2 RCTs[4,47] N=1,430	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.63; 95% CI: 0.01–49.02; I^2=5%)	2 RCTs[4,62] N=1,282	Imprecision	Insufficient

BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = cyclosporine; eGFR = estimated glomerular filtration rate; mTOR = mammalian target of rapamycin; NS = not significant; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAC = tacrolimus

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

[a] Based on subgroup analyses, the high level of heterogeneity observed in this outcome appears to be attributable primarily to the use of multiple, diverse immunosuppressive regimens and/or the presence of high- and low-risk patients in the included studies. Therefore, we did not decrease the strength of evidence for Inconsistency.

Table 12. Strength of evidence for subgroup analyses of minimization studies with adjunctive use of mycophenolic acid formulations

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Induction subgroup: Basiliximab + reduced CNI + mycophenolic acid formulations	Renal function	Inconclusive (SMD: 0.42; 95% CI: -0.78–1.62; I^2=84%)	3 RCTs[50,53,61] N=456	Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 0.86; 95% CI: 0.57–1.30; I^2=0)	4 RCTs[50,53,54,61] N=597	Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.57; 95% CI: 0.61–4.07; I^2=0)	5 RCTs[46,50,53,54,61] N=657	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.10; 95% CI: 0.16–7.43; I^2=0)	4 RCTs[50,53,54,61] N=597	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 1.14; 95% CI: 0.66–1.95; p=0.64)	1 RCT[54] N=141	Imprecision	Insufficient
Induction subgroup: no induction or not reported + reduced CNI + mycophenolic acid formulations	Renal function	Minimization with no induction or not reported associated with improved eGFR (SMD: 0.25; 95% CI: 0.05–0.45; I^2=9%)	6 RCTs[44,49,56,59,60,62] N=788	Study Limitations	Moderate
	BPAR	Minimization with no induction or not reported associated with lower risk of rejection (RR: 0.83; 95% CI: 0.74–0.95; I^2=0)	9 RCTs[44,45,49,55,56,58-60,62] N=1,627	Study Limitations	Moderate
	Graft loss	Minimization with no induction or not reported associated with lower risk of graft loss (RR: 0.79; 95% CI: 0.60–1.04; I^2=0)	9 RCTs[44,45,49,55,56,58-60,62] N=1,627	Study Limitations Imprecision	Low
	Patient death	Minimization with no induction or not reported associated with lower risk of death (RR: 0.81; 95% CI: 0.61–1.08; I^2=0)	9 RCTs[44,45,49,55,56,58-60,62] N=1,627	Study Limitations Imprecision	Low
	CMV infection	Inconclusive (RR: 1.01; 95% CI: 0.50–2.01; I^2=17%)	3 RCTs[45,59,60] N=1,097	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (RR: 0.55; 95% CI: 0.07–4.57; I^2=0)	2 RCTs[59,76] N=784	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 1.08; 95% CI: 0.52–2.24; I^2=0)	4 RCTs[56,59,60,62] N=570	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Induction subgroup: daclizumab only in minimization group + reduced CNI + mycophenolic acid formulations	Renal function	Minimization with daclizumab induction associated with improved eGFR (SMD: 0.25; 95% CI: 0.05–0.44; I^2=54%)	3 RCTs[4,24,52] N=1,694	Inconsistency	Moderate
	BPAR	Inconclusive (RR: 0.58; 95% CI: 0.16 to 2.15; I^2=93%)	3 RCTs[4,24,52] N=1,694	Imprecision Inconsistency	Insufficient
	Graft loss	Minimization with daclizumab induction associated with lower risk of graft loss (RR: 0.53; 95% CI: 0.31–0.91; I^2=8%)	3 RCTs[4,24,52] N=1,694	None	High
	Patient death	Minimization with daclizumab induction associated with lower risk of death (RR: 0.65; 95% CI: 0.40–1.05; I^2=0)	3 RCTs[4,24,52] N=1,694	Imprecision	Low
	CMV infection	Minimization with daclizumab induction associated with lower incident of CMV infection (RR: 0.81; 95% CI: 0.58–1.13; I^2=0)	3 RCTs[4,24,52] N=1,694	Imprecision	Low
	Other opportunistic infections	Minimization with daclizumab induction associated with lower risk of other infections (RR: 0.68; 95% CI: 0.50–0.94; I^2=0%)	3 RCTs[4,24,52] N=1,694	None	High
Early minimization subgroup: reduced CNI + mycophenolic acid formulations	Renal function	Early minimization associated with improved eGFR (SMD: 0.33; 95% CI: 0.16–0.45; I^2=61%)	10 RCTs[4,24,44,47,49,50,52,53,60,61] N=2,921	Study Limitations Inconsistency	Low
	BPAR	Early minimization associated with lower risk of rejection (RR: 0.79; 95% CI: 0.66–0.96; I^2=33%)	13 RCTs[4,24,44,45,47,49,50,52-55,60,61] N=3,872	None	High
	Graft loss	Early minimization associated with lower risk of graft loss (RR: 0.72; 95% CI: 0.54–0.95; I^2=9%)	14 RCTs[4,24,44-47,49,50,52-55,60,61] N=3,932	Study Limitations	Moderate
	Patient death	Inconclusive (RR: 0.87; 95% CI: 0.63–1.20; I^2=0)	13 RCTs[4,24,44,45,47,49,50,52-55,60,61] N=3,872	Study Limitations Imprecision	Insufficient
	CMV infection	Early minimization associated with lower risk of CMV (RR: 0.77; 95% CI: 0.61–0.96; I^2=39%)	6 RCTs[4,24,45,47,52,60] N=2,967	None	High
	BK infection	Inconclusive (RR: 0.53; 95% CI: 0.18–1.57; p=0.25)	1 RCT[45] N=720	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
	Other opportunistic infections	Early minimization associated with lower risk of other infections (RR: 0.76; 95% CI: 0.57 of 1.00; I^2=9%)	5 RCTs[4,24,52,54,60] N=2,148	Imprecision	Moderate
Late minimization subgroup: reduced CNI + mycophenolic acid formulations	Renal function	Inconclusive (SMD: 0.42; 95% CI: -0.17–1.02; I^2=6%)	3 RCTs[56,59,62] N=257	Imprecision	Insufficient
	BPAR	Late minimization associated with increased risk of acute rejection (RR: 1.48; 95% CI: 0.81–2.71; I^2=0)	5 RCTs[51,56,58,59,62] N=494	Imprecision	Low
	Graft loss	Inconclusive (RR: 0.62; 95% CI: 0.30–1.30; I^2=0)	5 RCTs[51,56,58,59,62] N=494	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.87; 95% CI: 0.43–1.77; I^2=0)	4 RCTs[56,58,59,62] N=286	Imprecision	Insufficient
	CMV infection	Inconclusive, no events observed	1 RCT[59] N=64	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive, no events observed	1 RCT[59] N=64	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 2.35; 95% CI: 0.72–7.66; I^2=0)	3 RCTs[56,59,62] N=257	Imprecision	Insufficient

BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = cyclosporine; eGFR = estimated glomerular filtration rate; mTOR = mammalian target of rapamycin; NS = not significant; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAC = tacrolimus

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

Table 13. Strength of evidence for minimization studies with adjunctive use of mTOR inhibitors

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced CNI (cyclosporine or tacrolimus) + mTOR inhibitors vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.31; 95% CI: 0.12–0.50; I^2=68%[a])	10 RCTs[22,64,66,67,69-74] N=1,831	Study Limitations	Moderate
	BPAR	No difference (RR: 0.95; 95% CI: 0.77–1.17; I^2=0)	14 RCTs[22,23,64-75] N=2,810	Study Limitations Imprecision	Low
	Graft loss	Inconclusive (RR: 0.79; 95% CI: 0.47–1.33; I^2=24%)	14 RCTs[22,23,64-75] N=2,810	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.97; 95% CI: 0.59–1.60; I^2=0)	13 RCTs[22,23,64-68,70-75] N=2,704	Imprecision	Insufficient
	CMV infection	Minimization associated with lower incidence of CMV (RR: 0.52; 95% CI: 0.29–0.93; I^2=55%)	10 RCTs[23,64-66,69-73,75] N=2,282	Study Limitations Inconsistency	Low
	BK infection	Inconclusive (RR: 0.84; 95% CI: 0.03–27.74; I^2=86%)	2 RCTs[65,73] N=1,057	Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.75; 95% CI: 0.29–1.91; I^2=0)	3 RCTs[64,71,72] N=596	Study Limitations Imprecision	Insufficient
Reduced cyclosporine + mTOR inhibitors vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.36; 95% CI: 0.08–0.64; I^2=69%[a])	6 RCTs[64,66,67,69-71] N=1,120	Study Limitations	Moderate
	BPAR	No difference (RR: 0.88; 95% CI: 0.70–1.10; I^2=0)	9 RCTs[23,64-71] N=2,060	Imprecision	Moderate
	Graft loss	Minimization associated with reduced risk of graft loss (RR: 0.56; 95% CI: 0.26–1.18; I^2=31%)	9 RCTs[23,64-71] N=2,060	Imprecision	Low
	Patient death	Inconclusive (RR: 0.86; 95% CI: 0.42–1.77; I^2=0)	8 RCTs[23,64-68,70,71] N=1,954	Imprecision	Insufficient
	CMV infection	Minimization associated with reduced risk for CMV infection (RR: 0.51; 95% CI: 0.25–1.06; I^2=69%)	7 RCTs[23,64-66,69-71] N=1,891	Imprecision Inconsistency	Low
	BK infection	Minimization associated with reduced incidence of BK infection (RR: 0.15; 95% CI: 0.03–0.67; p=0.01)	1 RCT[65] N=833	Imprecision	Low
	Other opportunistic infections	Inconclusive (RR: 0.59; 95% CI: 0.15–2.30; I^2=30%)	2 RCTs[64,71] N=468	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced tacrolimus + mTOR inhibitors vs. Standard	Renal function	Inconclusive (SMD: 0.37; 95% CI: -0.12–0.85; I^2=23%)	3 RCTs[72-74] N=444	Imprecision	Insufficient
	BPAR	Inconclusive (RR: 1.50; 95% CI: 0.78–2.91; I^2=0)	4 RCTs[72-75] N=483	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.88; 95% CI: 0.56–6.39; I^2=0)	4 RCTs[72-75] N=483	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.02; 95% CI: 0.31–3.35; I^2=0)	4 RCTs[72-75] N=483	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.59; 95% CI: 0.21–1.65; I^2=0)	3 RCTs[72,73,75] N=391	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (RR: 5.46; 95% CI: 0.65–45.99; p=0.12)	1 RCT[73] N=224	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.52; 95% CI: 0.10 to 2.72; p=0.43 for candida; RR: 1.03; 95% CI: 0.07–16.15; p=0.98 for herpes)	1 RCT[72] N=128	Study Limitations Imprecision	Insufficient

BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = cyclosporine; eGFR = estimated glomerular filtration rate; mTOR = mammalian target of rapamycin; NS = not significant; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAC = tacrolimus

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

[a] Based on subgroup analyses, the high level of heterogeneity observed in this outcome appears to be attributable primarily to the use of multiple, diverse immunosuppressive regimens and/or the presence of high- and low-risk patients in the included studies. Therefore, we did not decrease the strength of evidence for Inconsistency.

Table 14. Strength of evidence for subgroup analyses of minimization studies with adjunctive use of mTOR inhibitors

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Induction subgroup: basiliximab + reduced CNI + mTOR inhibitors	Renal function	Induction with basiliximab associated with improved eGFR (SMD: 0.34; 95% CI: 0.10 to 0.58; I^2=61%[a)]	7 RCTs[66,67,69-71,73,74] N=1,079	None	High
	BPAR	No difference (RR: 0.94; 95% CI: 0.77–1.14; I^2=0)	10 RCTs[23,65-71,73,74] N=2,019	Imprecision	Moderate
	Graft loss	Induction with basiliximab associated with reduced risk of graft loss (RR: 0.57; 95% CI: 0.32–1.03; I^2=28%)	10 RCTs[23,65-71,73,74] N=2,019	Imprecision	Moderate
	Patient death	No difference (RR: 0.97; 95% CI: 0.62–1.54; I^2=0)	9 RCTs[23,65-68,70,71,73,74] N=1,913	Imprecision	Low
	CMV infection	Induction with basiliximab associated with lower incidence of CMV infection (RR: 0.47; 95% CI: 0.20–1.09; I^2=62%)	7 RCTs[23,65,66,69-71,73] N=1,758	Imprecision Inconsistency	Low
	BK infection	Inconclusive (RR: 0.84; 95% CI: 0.03–27.74; I^2=86%)	2 RCTs[65,73] N=1,057	Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Inconclusive for herpes simplex infections (RR: 0.13; 95% CI: 0.01–2.47; p=0.18)	1 RCT[71] N=111	Study Limitations Imprecision	Insufficient
Induction subgroup: no induction or not reported + reduced CNI + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.26; 95% CI: -0.58–1.10; I^2=84%)	3 RCTs[22,64,72] N=752	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 1.34; 95% CI: 0.22–8.08; I^2=64%)	3 RCTs[22,64,72] N=752	Study Limitations Imprecision Inconsistency	Insufficient
	Graft loss	Inconclusive (RR: 1.26; 95% CI: 0.21–7.50; I^2=0)	3 RCTs[22,64,72] N=752	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.20; 95% CI: 0.02–71.29; I^2=29%)	3 RCTs[22,64,72] N=752	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.85; 95% CI: 0.10–7.30; I^2=0)	2 RCTs[64,72] N=485	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.78; 95% CI: 0.25–2.50; I^2=0)	2 RCTs[64,72] N=485	Study Limitations Imprecision	Insufficient

BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = cyclosporine; eGFR = estimated glomerular filtration rate; mTOR = mammalian target of rapamycin; NS = not significant; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; TAC = tacrolimus

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

[a] Based on subgroup analyses, the high level of heterogeneity observed in this outcome appears to be attributable primarily to the use of multiple, diverse immunosuppressive regimens and/or the presence of high- and low-risk patients in the included studies. Therefore, we did not decrease the strength of evidence for Inconsistency.

Conversion

Description of Conversion Studies

Overall, 23 studies assessed the benefits and harms of converting from a CNI to another maintenance immunosuppressive regimen. The majority of the studies (n=18) evaluated conversion from a CNI to an mTOR-based inhibitor (SRL or EVR). The other studies assessed conversion from CNI to AZA, MMF, MPS, or belatacept. Table 15 presents the immunosuppressive regimens assessed in the studies. In most of the studies, conversion took place within 3- to 6-months post-transplantation. Additional information about the dosing of the regimens is provided in Table E-5.

All the studies evaluating the impact of conversion were RCTs in which all patients were initially on a CNI regimen and then randomly assigned to either remain on the CNI regimen or convert to another immunosuppressive agent. The majority of the studies were rated as having high (53%) or moderate (30%) risk of bias. In most cases, the sources of potential bias were due to not reporting if there was allocation concealment or if outcome assessors were blinded, differential loss to followup, and potential conflict of interest of the funding source. The majority of studies (96%) were either industry funded or did not report the funding source. Four studies were rated as having a low risk of bias.[77-79] These studies clearly reported allocation concealment and did not have differential loss to followup. See Table E-21 for risk-of-bias ratings.

Table 15. Conversion studies

Reference	Type of Intervention	N, Intervention	N, Control
Budde 2015[80]	CNI to EVR	46	47
Bensal 2013[77]	CNI to SRL	31	29
Holdaas 2011[22]	CNI to EVR	127	123
Weir 2011[81]	CNI to SRL	148	151
Schena 2009[82]	CNI to SRL	555	275
Watson 2005[79]	CNI to SRL	19	19
Chhabra 2013[83]	TAC to SRL	123	64
Silva 2013[84]	TAC to SRL	97	107
Heilman 2011[85]	TAC to SRL	62	60
Rostaing 2015[86]	CsA to EVR	96	98
Mjornstedt 2012[87]	CsA to EVR	102	100
Nafar 2012[88]	CsA to SRL	50	50
Guba 2010[89]	CsA to SRL	69	71
Bemelman 2009[90]	CsA to EVR or MPS	74	39
Lebranchu 2009[91]	CsA to SRL	95	97
Durrbach 2008[92]	CsA to SRL	33	36
Barsoum 2007[93]	CsA to SRL	76	37
Budde 2012[78]	CsA to EVR	155	146
Bakker 2003[94]	CsA to AZA	60	68
MacPhee 1998[95]	CsA to AZA	102	114
Hilbrands 1996[96]	CsA to AZA	60	60
Dudley 2005[97]	CsA to MMF	73	70
Rostaing 2011[98]	CNI to belatacept	84	89

AZA = azathioprine; CNI = calcineurin inhibitor; CsA = cyclosporine; EVR = everolimus; MMF = mycophenolate mofetil; MPS = mycophenolate sodium; SRL = sirolimus; TAC = tacrolimus

Key Points

- Patients converted to an mTOR inhibitor demonstrated modest improvement in renal function compared to patients who remained on a CNI regimen. (Strength of Evidence: Moderate)
- Patients converted to an mTOR inhibitor experienced lower incidence of cytomegalovirus infection than patients remaining on a CNI regimen. (Strength of Evidence: High)
- Graft loss was similar among patients remaining on a CNI and those converting to an mTOR inhibitor or AZA. (Strength of Evidence: Low)
- The overall risk of BPAR was higher among patients converted to MPS than those who remained on a CNI regimen. (Strength of Evidence: Moderate)
- The evidence was insufficient due to lack of precision to permit conclusions for the outcomes from studies that evaluated conversion from CsA to MMF.

Detailed Synthesis: Conversion Studies

Table 16 shows the findings and the strength-of-evidence ratings for all the outcomes analyzed. Seventeen studies contributed data to a pooled analysis comparing renal function as measured by glomerular filtration rate among patients converted to an mTOR inhibitor to renal function among those remaining on a CNI. Moderate-strength evidence suggested modest improvement in renal function among those converted to an mTOR inhibitor (SMD: 0.37; 95% CI: 0.14–0.60). When the analysis was stratified based on type of CNI, high-strength evidence suggested improved renal function among those converted to an mTOR compared to patients remaining on CsA (SMD: 0.62; 95% CI: 0.23–1.01). However, low-strength evidence indicated no difference in renal function between patients converted to an mTOR inhibitor and those remaining on TAC (SMD: -0.11; 95% CI: -0.47–0.25).

Pooled analyses revealed substantial heterogeneity for renal function for both the overall CNI versus mTOR analysis (I^2= 89%) and the CsA versus mTOR subanalysis (I^2= 88%). When we removed the Barsoum et al. study from the analysis, the I^2 for the overall CNI analysis dropped to 74 percent and to 14 percent in the CsA subanalysis.[93] One primary difference between this study and the other studies in the analyses was a delay in the addition of MMF among patients converted to SRL from CsA. The addition of MMF among these patients occurred 3-months postconversion and 6-months post-transplant. In the other studies, MMF or MPS were initiated immediately or shortly after renal transplantation. This might explain why the between-group difference in eGFR was substantially higher in this study than the others.

The only other difference observed between patients converted to an mTOR inhibitor and those remaining on a CNI regimen was in the reported incidence of cytomegalovirus (CMV). High-strength evidence suggested that conversion to an mTOR inhibitor was associated with lower reported incidence of CMV (RR: 0.61; 95% CI: 0.38 to 0.98; I^2=37%). This difference, however, was no longer present when the analysis was stratified by type of CNI (CsA vs. TAC). Finally, low-strength evidence indicated no difference between groups in the TAC subanalysis for graft loss. The evidence was insufficient for this outcome for the overall CNI analysis and for the CsA subanalysis. The evidence was also insufficient to draw any conclusions for incidence of BPAR, patient death, or other infection-related adverse events among patients converted to an mTOR and those remaining on a CNI regimen.

Similarly, evidence from three studies that evaluated conversion from CsA to AZA was insufficient to support conclusions for the outcomes of acute rejection, patient death, and

incidence of infection.[94-96] However, low-strength evidence from these studies did suggest that graft loss was similar among patients who converted to AZA and those who remained on CsA (RR: 0.84; 95% CI: 0.55–1.28, I^2=0).

Moderate-strength evidence from one study in which patients were converted from CsA to MPS indicated a significantly higher risk of BPAR among patients converted to MPS.[90] In this study, eight patients in the MPS group experienced an episode of acute rejection compared to only one patient in the CsA group (RR: 8.61; 95% CI: 1.14–65.9; p=0.04). The evidence was insufficient to permit conclusions for patient death, graft loss, or risk of infection among patients converted to MMF or MPS and those who remained on CsA.

Finally, the findings of one study in which patients were converted from CsA to belatacept showed a modest improvement in GFR among patients who converted to belatacept (60.5±11.01 mL/min/MDRD vs. 56.5±14.42 mL/min/MDRD; mean change from baseline 2.1±10.34, p<0.01). The evidence from this study was inconclusive for patient death, graft loss, or infection risk.

We did not conduct subgroup analyses of these studies to identify effects associated with induction agents. Induction therapy is expected to affect patient outcomes immediately after transplantation and shortly thereafter but is less likely to have an impact during the later timeframes when most studies initiated CNI conversion. Moreover, subgroups were too small for analysis due to heterogeneity and frequent nonreporting of induction therapy.

Applicability

The applicability of the findings of the studies assessing conversion from a CNI to another immunosuppression regimen is limited due to lack of reporting about key patient characteristics such as race and exclusion of high-risk patients. Overall, 38 percent of the studies evaluating conversion did not report on race. Among those that did, the majority of the enrolled patients were male Caucasians. Thirteen studies (62%) excluded high-risk patients. This includes older patients (≥65 years of age) and patients who had a previous renal transplant. Overall, eight studies (38%) excluded patients aged 65 years or older, and six (28%) excluded patients who had a previous renal transplant.

Summary

Overall, moderate-strength evidence indicated that conversion to an mTOR inhibitor was associated with modest improvement in renal function. The strength of evidence was high for the finding that conversion to an mTOR was associated with a decreased risk in the incidence of CMV infection. Finally, low-strength evidence suggests no difference in graft loss between patients remaining on TAC and those converting to an mTOR inhibitor or AZA. For BPAR, patient death, or incidence of other infection-related adverse events, the findings of our analyses were inconclusive due to study limitations and/or lack of precision. In general, the followup period in the majority of studies addressing conversion was relatively short (12 months) and limited primarily to low-risk patients.

Table 16. Strength of evidence for conversion studies

Comparison	Outcome	Conclusions	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
CNI (cyclosporine or tacrolimus) to mTOR inhibitors	BPAR	Inconclusive (RR: 1.38; 95% CI: 0.96–1.99; I^2=49%)	18 RCTs[22,77,79,81-85,87-93,99] N=3,442	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.11; 95% CI: 0.73–1.69; I^2=2%)	14 RCTs[22,81-85,87,89,91-93,99] N=3,165	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.19; 95% CI: 0.66–2.15; I^2=0)	14 RCTs[22,81-85,87,89,91-93,99] N=3,165	Study Limitations Imprecision	Insufficient
	Renal function	Conversion to mTOR associated with improved renal function (SMD: 0.37; 95% CI: 0.14–0.60; I^2=87%)	17 RCTs[22,77,79,81-85,87,89,91-93,99] N=3,254	Inconsistency	Moderate
	CMV Infection	Conversion to mTOR associated with lower incidence of CMV (RR: 0.61; 95% CI: 0.38–0.98; I^2=37%)	10 RCTs[77,81,83-85,87,89,90,92,99] N=1,660	None	High
	BK infection	Inconclusive (RR: 0.59; 95% CI: 0.20–1.79; I^2=40%)	7 RCTs[77,81,83-85,87,91,99] N=1,332	Imprecision	Insufficient
	Other infection	Inconclusive (RR: 1.28; 95% CI: 0.84–1.97; I^2=28%)	10 RCTs[77,79,81-85,87,93,99] N=1,660	Imprecision	Insufficient
Tacrolimus to mTOR inhibitors	BPAR	Inconclusive (RR: 1.75; 95% CI: 0.35–8.08; I^2=0%)	3 RCTs[83-85] N=513	Imprecision	Insufficient
	Graft loss	No difference (RR: 0.88; 95% CI: 0.55–1.39; I^2=0%)	3 RCTs[83-85] N=513	Imprecision	Low
	Patient death	Inconclusive (RR: 1.46; 95% CI: 0.24–8.83; I^2=0%)	3 RCTs[83-85] N=513	Imprecision	Insufficient
	Renal function	No difference (SMD: -0.11; 95% CI: -0.47–0.25; I^2=0%	3 RCTs[83-85] N=513	Imprecision	Low
	CMV Infection	Inconclusive (RR: 0.70; 95% CI: 0.07–6.91; I^2=56%)	3 RCTs[83-85] N=513	Imprecision	Insufficient
	BK infection	Inconclusive (RR: 0.35; 95% CI: 0.11–1.14; I^2=0%)	2 RCTs[83,85] N=309	Study Limitations Imprecision	Insufficient
	Other infection	Inconclusive (RR: 0.58; 95% CI: 0.05–6.47; I^2=0%)	3 RCTs[83-85] N=513	Imprecision	Insufficient

Comparison	Outcome	Conclusions	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Cyclosporine to mTOR inhibitors	BPAR	Inconclusive (RR: 1.37; 95% CI: 0.76–2.46; I^2=64%)	9 RCTs[87-93,99] N=1,357	Imprecision Inconsistency	Insufficient
	Graft loss	Inconclusive (RR: 1.27; 95% CI: 0.42–3.81; I^2=25%)	7 RCTs[87,89,91-93,99] N=1,180	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.78; 95% CI: 0.43–1.42; I^2=0%)	7 RCTs[87,89,91-93,99] N=1,180	Imprecision	Insufficient
	Renal function	Conversion to mTOR associated with improved renal function (SMD: 0.62; 95% CI: 0.23–1.01; I^2=86%; with 1 outlier study removed SMD: 0.48; 95% CI: 0.32–0.65; I^2=14%)[a]	8 RCTs[87-91,93,99] N=1,288	None	High
	CMV infection	Inconclusive (RR: 0.56; 95% CI: 0.23–1.38; I^2=54%)	5 RCTs[87,89,90,92,99] N=788	Imprecision	Insufficient
	BK infection	Inconclusive (RR: 1.59; 95% CI: 0.33–7.61; I^2=0%)	3 RCTs[87,91,99] N=534	Imprecision	Insufficient
	Other infection	Inconclusive (RR: 1.30; 95% CI: 0.28–6.11; I^2=57%)	3 RCTs[87,91,99] N=534	Imprecision	Insufficient
Cyclosporine to azathioprine	BPAR	Inconclusive (RR: 0.93; 95% CI: 0.52–1.68; I^2=0%)	3 RCTs[94-96] N=464	Study Limitations Imprecision	Insufficient
	Graft loss	No difference (RR: 0.84; 95% CI: 0.55–1.28; I^2=0%)	3 RCTs[94-96] N=464	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 0.92; 95% CI: 0.41–2.04; I^2=14%)	3 RCTs[94-96] N=465	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 3.35; 95% CI: 0.13–82.5)	1 RCT[96] N=120	Study Limitations Imprecision	Insufficient
Cyclosporine to mycophenolic acid formulations	BPAR	Conversion to MPS associated with higher incidence of acute rejection (RR: 8.67; 95% CI: 1.14–65.9)	1 RCTs[90] N=103	Imprecision	Moderate
	Graft loss	Inconclusive (RR: 0.473, 95% CI: 0.09–2.50)	1 RCT[97] N=143	Imprecision	Insufficient
	Patient death	Inconclusive (too few events) (RR: 7.0, 95% CI: 0.36 to 133)	1 RCT[97] N=143	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.62; 95% CI: 0.20–12.9; I^2=0%)	2 RCTs[90,97] N=256	Imprecision	Insufficient

Comparison	Outcome	Conclusions	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
CNI (cyclosporine or tacrolimus) to Belatacept	BPAR	Inconclusive (RR: 13.76, 95% CI: 0.78–240)	1 RCT[98] N=173	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (no events) (0/84 vs. 0/89)	1 RCT[98] N=173	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.35, 95% CI: 0.01–8.54)	1 RCT[98] N=173	Study Limitations Imprecision	Insufficient
	Renal function	Inconclusive (SMD: 0.31; 95% CI: -0.02–0.64)	1 RCT[98] N=173	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (too few events) (RR: 1.06, 95% CI: 0.15–7.35)	1 RCT[98] N=173	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (too few events) (RR: 7.41, 95% CI: 0.39–141)	1 RCT[98] N=173	Study Limitations Imprecision	Insufficient
	Other infection	Inconclusive (RR: 1.06, 95% CI: 0.22–5.10)	1 RCT[98] N=173	Study Limitations Imprecision	Insufficient

BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; eGFR = estimated glomerular filtration rate; mTOR = mammalian target of rapamycin; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

[a] The primary difference between the outlier study and the other studies in this analysis was a delay in the addition of MMF among patients converted to SRL from CsA. The addition of MMF in the outlier study occurred 3-months postconversion and 6-months post-transplant. In the other studies, MMF or MPS were initiated immediately or shortly after renal transplantation.

Withdrawal

Description of Withdrawal Studies

Renal transplant patients on a CNI-based regimen may benefit from having CNI withdrawn while continuing alternative immunosuppression therapies. Withdrawal is different from conversion because the non-CNI immunosuppressive agent is included in the regimen before withdrawal, while conversion strategies do not introduce the alternative drug until discontinuation of the CNI.

Fifteen RCTs examined CNI withdrawal (Table 17). Nine studies included MMF as the primary alternative to CNI, and six studies used mTOR inhibitors. CsA was withdrawn in 10 studies (6 with MMF and 4 with SRL or EVR). TAC was withdrawn in two studies that used SRL. Three studies that used MMF combined data on patients receiving CsA or TAC. Seven studies included fewer than 100 patients, while the largest study enrolled 430 transplant recipients. Nine studies initiated withdrawal within 6 months following transplant, five studies withdrew CNI 6 months or more post-transplant, and one study began withdrawal between 2 and 16 months after renal transplant.

Overall risk of bias was assessed as high for 10 of the withdrawal studies, moderate for 4 studies, and 1 study was at low risk of bias.[100] Only 1 study declared funding support from a noncommercial source,[101] 2 studies did not disclose any funding information,[102,103] and 12 of the 15 studies received funding from sources that could benefit financially from favorable study results.

Table 17. Withdrawal studies

Reference	Withdrawn	Maintained	N, Intervention	N, Control
Mourer 2012[104]	CNI	MMF	79	79
Pascual 2008[100]	CNI	MMF	20	20
Suwelack 2004[105]	CNI	MMF	18	20
Asberg 2012[106]	CsA	MMF	20	19
Ekberg 2007a[24]	CsA	MMF	179	173
Hazzan 2006[101]	CsA	MMF	54	54
Abramowicz 2002[107]	CsA	MMF	85	85
Schnuelle 2002[103]	CsA	MMF	44	40
Smak Gregoor 2002[108]	CsA	MMF	63	149
Chadban 2014[23]	CsA	EVR	49	47
Stallone 2003[102]	CsA	SRL	20	20
Gonwa 2002[109]	CsA	SRL	100	97
Johnson 2001[110]	CsA	SRL	215	215
Flechner 2011[111]	TAC	SRL	152	139
Freitas 2011[112]	TAC	SRL	23	24

CNI = calcineurin inhibitor; CsA = cyclosporine; EVR = everolimus; MMF = mycophenolate mofetil; SRL = sirolimus; TAC = tacrolimus

Key Points

- Withdrawal was associated with increased risk of acute rejection for patients maintained on mycophenolate acid formulations (Strength of Evidence: High) or mTOR inhibitors (Strength of Evidence: Moderate) compared to patients who remained on both a CNI and other adjunctive therapy.
- Risk of graft loss was higher when CNI was withdrawn from patients remaining on MMF (Strength of Evidence: Low) compared to patients maintained on both CNIs and MMF. The evidence for the outcome of graft loss was insufficient to support conclusions for studies that maintained patients on mTOR inhibitors after CNI withdrawal (Strength of Evidence: Insufficient) compared to patients who continued to receive both CNIs and mTOR inhibitors.
- Maintenance of MMF after CNI withdrawal was associated with improvement in renal function (Strength of Evidence: High) compared to continuation of both therapies.
- The evidence base is insufficient to support conclusions for the risk of infections in patients withdrawn from CNIs.

Detailed Synthesis of Withdrawal Studies

Withdrawal of CNI therapy was associated with increased risk of BPAR, regardless of whether patients received MMF or mTOR inhibitors as the primary alternative immunosuppressive agent. High-strength evidence demonstrated a large magnitude of effect, with risk of rejection more than three times greater in patients maintained on MMF after CNI withdrawal compared with recipients continued on both MMF and CNI. A smaller but still significant effect was observed in regimens using mTOR inhibitors, with a relative risk of rejection greater than 1.7. Risk of graft loss was also higher when CNI was withdrawn from patients remaining on MMF based on low-strength evidence, but the evidence base was inconclusive for this outcome in studies that maintained patients on mTOR inhibitors after CNI withdrawal.

High-strength evidence also supported the finding that maintenance of MMF after CNI withdrawal was associated with improvement in renal function, but the evidence for eGFR was inconclusive for the subset of studies using CsA. Evidence for other outcomes, including infections and death, was insufficient to support conclusions.

Timing of withdrawal with respect to renal transplant was assessed in subgroup analyses of the nine studies that included MMF, since all six studies that used mTOR inhibitors used early withdrawal. Three studies initiated CNI withdrawal during the first 6-months post-transplant (designated “early withdrawal”), and five studies initiated withdrawal 6 months or later after transplant (“late withdrawal”). One study included both early and late withdrawal.[100] Low-strength evidence was found for improved renal function in the late withdrawal subgroups. Early withdrawal was associated with higher risk of graft loss and death, and the evidence was insufficient to make conclusions for acute rejection and renal function. For studies of late withdrawal, maintenance of MMF after CNI withdrawal was associated with greater risk of acute rejection based on moderate-strength evidence. The evidence was insufficient to support any conclusions regarding infection outcomes in these subgroups.

We did not conduct subgroup analyses of these studies to identify effects associated with induction agents. As with conversion strategies, induction therapy is not expected to have a clinically significant impact during the later timeframes when most studies initiated CNI

withdrawal. Moreover, subgroups were too small for analysis due to heterogeneity and frequent nonreporting of induction therapy.

Applicability

The studies of CNI withdrawal have similar limits on applicability as described elsewhere. Nine of the 15 studies excluded patients who exceeded a defined PRA threshold. In 10 studies that reported patient race, at least 75 percent of participants were Caucasian. These studies are therefore most applicable to average- or low-risk patients. However, only one study excluded patients over 65 years old, and just one study excluded retransplants. Moreover, seven studies reported the proportion of patients who experienced DGF, which was present in at least 13 percent of intervention group patients in each study. Finally, 10 studies enrolled patients receiving CsA, three studies combined patients on either CsA or TAC, and only two studies focused exclusively on the use of TAC. Our findings may thus be more relevant to withdrawal of CsA than to withdrawal of TAC.

Summary

High-strength evidence based on 15 RCTs indicates that CNI withdrawal is associated with greater risk of acute rejection for renal transplant recipients (Table 18). Moderate-strength evidence suggests that withdrawal may be associated with increased graft loss in patients maintained on MMF. Renal function may improve after withdrawal in some patients, and the evidence base is inconclusive for death and infection outcomes.

Table 18. Strength of evidence for withdrawal studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
CNI withdrawal + mycophenolate	Renal function	Withdrawal associated with improved renal function (SMD: 0.49; 95% CI: 0.26–0.72; I^2=21%)	5 RCTs[24,100,103,104,113] N=742	None	High
	BPAR	Withdrawal associated with higher risk of rejection (RR: 3.17; 95% CI: 1.78–5.66; I^2=46%)	9 RCTs[24,100,103-108,113] N=1,201	None	High
	Graft loss	Withdrawal associated with higher risk of graft loss (RR: 1.35; 95% CI: 0.80–2.26; I^2=0)	9 RCTs[24,100,103-108,113] N=1,201	Imprecision	Low
	Patient death	No difference (RR: 0.99; 95% CI: 0.67 to 1.48; I^2=0)	8 RCTs[24,100,103,104,106-108,113] N=1,163	Imprecision	Low
	CMV infection	Inconclusive (RR: 1.12; 95% CI: 0.39 to 3.21; I^2=22%)	5 RCTs[24,100,103,105,108] N=726	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.73; 95% CI: 0.47–1.12; I^2=35%)	5 RCTs[24,100,103,105,108] N=726	Imprecision	Insufficient
Cyclosporine withdrawal + mycophenolate	Renal function	Inconclusive (SMD: 0.54; 95% CI: -0.07–1.15; I^2=54%)	3 RCTs[24,103,113] N=544	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Withdrawal associated with higher risk of rejection (RR: 3.23; 95% CI: 1.39–7.47; I^2=60%)	6 RCTs[24,103,106-108,113] N=965	Study Limitations Inconsistency	Low
	Graft loss	Withdrawal associated with higher risk of graft loss (RR: 1.56; 95% CI: 0.95–2.54; I^2=0)	6 RCTs[24,103,106-108,113] N=965	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 1.11; 95% CI: 0.66–1.87; I^2=0)	6 RCTs[24,103,106-108,113] N=965	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.49; 95% CI: 0.26–8.62; I^2=41%)	3 RCTs[24,103,108] N=648	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.73; 95% CI: 0.31–1.69; I^2=54%)	3 RCTs[24,103,108] N=648	Imprecision Inconsistency	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Early withdrawal subgroup: CNI + mycophenolate	Renal function	Inconclusive (SMD: 0.54; 95% CI: -0.07–1.15; I^2=54%)	3 RCTs[24,103,113] N=544	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 1.69; 95% CI: 0.59–4.85; I^2=26%)	3 RCTs[24,103,113] N=544	Study Limitations Imprecision	Insufficient
	Graft loss	Early withdrawal associated with higher risk of graft loss (RR: 1.34; 95% CI: 0.75–2.39; I^2=0)	3 RCTs[24,103,113] N=544	Study Limitations Imprecision	Low
	Patient death	Early withdrawal associated with higher risk of death (RR: 1.45; 95% CI: 0.87–2.40; I^2=0)	3 RCTs[24,103,113] N=544	Study Limitations Imprecision	Low
	CMV infection	Inconclusive (RR: 0.98; 95% CI: 0.04–21.99; I^2=0)	2 RCTs[24,103] N=436	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.60; 95% CI: 0.11–3.22; I^2=0)	2 RCTs[24,103] N=436	Study Limitations Imprecision	Insufficient
Late withdrawal subgroup: CNI + mycophenolate	Renal function	Late withdrawal associated with improved eGFR (61.1 vs. 52.9, p<0.01;[104] 66 vs. 63, p=NS;[107] increase of 4.5 mL/min, p=0.16[108])	3 RCTs[104,107,108] N=540	Imprecision	Low
	BPAR	Late withdrawal associated with higher risk of rejection (RR: 6.16; 95% CI: 3.11–12.21; I^2=0)	5 RCTs[104-108] N=617	Imprecision	Moderate
	Graft loss	Inconclusive (RR: 1.40; 95% CI: 0.33–5.95; I^2=0)	5 RCTs[104-108] N=617	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.83; 95% CI: 0.37–1.83; I^2=0)	4 RCTs[104,106-108] N=579	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.83; 95% CI: 0.05–13.36; I^2=80%)	2 RCTs[105,108] N=250	Study Limitations Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.98; 95% CI: 0.08–11.73; I^2=0)	2 RCTs[105,108] N=250	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
CNI withdrawal + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.16; 95% CI: -0.25–0.57; I^2=69%)	5 RCTs[23,102,110-112] N=904	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Withdrawal associated with higher risk of rejection (RR: 1.71; 95% CI: 1.19–2.45; I^2=5%)	6 RCTs[23,102,109-112] N=1,101	Study Limitations	Moderate
	Graft loss	Inconclusive (RR: 0.97; 95% CI: 0.45–2.09; I^2=30%)	6 RCTs[23,102,109-112] N=1,101	Study Limitations Imprecision	Insufficient
	Patient death	No difference (RR: 1.03; 95% CI: 0.64–1.66; I^2=0)	6 RCTs[23,102,109-112] N=1,101	Study Limitations Imprecision	Low
	CMV infection	Inconclusive (RR: 0.91; 95% CI: 0.01–119.68; I^2=0)	2 RCTs[23,110] N=526	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.68; 95% CI: 0.39–1.18; p=0.17)	1 RCT[110] N=430	Study Limitations Imprecision	Insufficient
Cyclosporine withdrawal + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.26; 95% CI: -0.71–1.23; I^2=71%)	3 RCTs[23,102,110] N=566	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Withdrawal associated with higher risk of acute rejection (RR: 1.67; 95% CI: 0.87–3.22; I^2=22%)	4 RCTs[23,102,109,110] N=763	Study Limitations Imprecision	Low
	Graft loss	Withdrawal associated with lower risk of graft loss (RR: 0.64; 95% CI: 0.37–1.12; I^2=0)	4 RCTs[23,102,109,110] N=763	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 0.82; 95% CI: 0.39–1.74; I^2=0)	4 RCTs[23,102,109,110] N=763	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.91; 95% CI: 0.01–119.68; I^2=0)	2 RCTs[23,110] N=526	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.68; 95% CI: 0.39–1.18; p=0.17)	1 RCT[110] N=430	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Tacrolimus withdrawal + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.00; 95% CI: -2.48–2.48; I^2=43%)	2 RCTs[111,112] N=338	Study Limitations Imprecision	Insufficient
	BPAR	Withdrawal associated with higher risk of rejection (RR: 1.93; 95% CI: 1.43–2.60; I^2=0)	2 RCTs[111,112] N=338	Study Limitations	Moderate
	Graft loss	Inconclusive (RR: 2.15; 95% CI: 0.29–16.01; I^2=0)	2 RCTs[111,112] N=338	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.40; 95% CI: 0.31–6.19; I^2=0)	2 RCTs[111,112] N=338	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.
BPAR=biopsy proven acute rejection; CI=confidence interval; CMV=cytomegalovirus; CNI=calcineurin inhibitor; eGFR=estimated glomerular filtration rate; mTOR=mammalian target of rapamycin; NS=not significant; RCT=randomized controlled trial; RR=relative risk; SMD=standardized mean difference

Avoidance

Description of Avoidance Studies

Another strategy to prevent CNI-associated toxicity is complete avoidance of CNI regimens. Immunosuppressive treatment based on SRL or belatacept has been studied in nine RCTs (Table 19). Sirolimus was used with MMF in five studies, with AZA in one study, and alone in one study. Six of the SRL studies were small and included fewer than 150 patients each, while 1 study included nearly 800 patients.[4] Two large multinational trials, BENEFIT[114] and BENEFIT-EXT,[115] compared belatacept and MMF to CsA and MMF, with basiliximab induction in both groups. BENEFIT-EXT enrolled only extended criteria donors, who are typically associated with poorer clinical outcomes. Both BENEFIT studies included and compared more and less intensive schedules for administration of belatacept. We attempted to combine the BENEFIT studies for meta-analysis, but the results masked individual study effects and exhibited high heterogeneity, probably due to the differences in patient populations. Therefore, we report these two studies separately in the synthesis of results and the assessment of strength of evidence.

The seven remaining studies used SRL, but one did not use an induction agent while the others varied widely in choice of induction, including basiliximab, alemtuzumab, daclizumab, and ATG. The studies also differed in whether induction was used solely in the intervention arm or in the control arm as well.

Five of the avoidance studies were assessed to have moderate risk of bias, while four were categorized as high risk of bias. Adherence with treatment regimen was of particular concern as a threat to validity in these studies, as five of nine studies did not achieve at least 85-percent adherence. Six studies were funded by sources with a commercial interest in the outcome, while three studies did not report a funding source.

Table 19. Avoidance studies

Reference	Intervention	Control	Induction	N, Intervention	N, Control
Vincenti 2010[114]	Belatacept, MMF	CsA, MMF	Basiliximab	445	221
Durrbach 2010[115]	Belatacept, MMF	CsA, MMF	Basiliximab	359	184
Flechner 2002[116]	SRL, MMF	CsA, MMF	Basiliximab	31	30
Ekberg 2007b[4]	SRL, MMF	CsA, MMF	Daclizumab (non-CNI arm)	399	390
Asher 2013[117]	SRL, MMF	TAC, MMF	Daclizumab	19	19
Glotz 2010[118]	SRL, MMF	TAC, MMF	rATG (non-CNI arm)	71	70
Schaefer 2006[119]	SRL, MMF	TAC, MMF	ATG	41	78
Groth 1999[120]	SRL, AZA	CsA, AZA	None used	41	42
Refaie 2011[121]	SRL	TAC	Alemtuzumab	10	11

ATG = anti-thymocyte globulin; AZA = azathioprine; CNI = calcineurin inhibitor; CsA = cyclosporine; MMF = mycophenolate mofetil; r-ATG = rabbit anti-thymocyte globulin; SRL = sirolimus; TAC = tacrolimus

Key Points

- The evidence base for these CNI avoidance regimens was small and mainly inconclusive.
- The studies were heterogeneous in their use of immunosuppressive therapies and induction agents.

- Belatacept was associated with improved renal function (Strength of Evidence: Moderate) and no difference in risk of graft loss or death (Strength of Evidence: Low) compared to use of CsA.
- Studies that used mTOR inhibitors and MMF instead of CNI were associated with improved renal function but higher risk of graft loss compared with tacrolimus regimens (Strength of Evidence: Low) and no difference in risk of graft loss compared with cyclosporine regimens (Strength of Evidence: Low). Results for the other outcomes were generally inconclusive.

Detailed Synthesis of Avoidance Studies

Each BENEFIT study found that belatacept was associated with improved renal function based on moderate-strength evidence, and low-strength evidence suggested it was noninferior to CsA for the outcomes of graft loss and death (Table 20). The study that used standard-criteria donors also found that belatacept was associated with increased risk for acute rejection, while the study conducted with extended-criteria donors found that belatacept was noninferior to CsA for this outcome. These studies did not provide sufficient evidence to draw conclusions for the infection outcomes.

Two studies compared SRL to CSA, with MMF in both arms.[4,116] SRL was associated with no difference in risk of graft loss, based on low-strength evidence. The evidence was insufficient to support conclusions for the other outcomes.

Three studies compared SRL to TAC, with MMF in both arms.[117-119] SRL was associated with improved renal function and lower risk of CMV infection but a higher risk of graft loss, based on low-strength evidence. The evidence was insufficient to support conclusions for other outcomes.

Groth studied a regimen of SRL and AZA compared with CsA and AZA in 83 patients. Moderate- to low-strength evidence showed no difference in renal function or acute rejection and an increased risk of other opportunistic infections. The evidence was inconclusive for the outcomes of graft loss, death, and CMV infection.

Finally, a small study[121] of 21 kidney recipients compared SRL to TAC, with alemtuzumab induction in both groups but no additional immunosuppressive therapy. Renal function as measured by creatinine clearance was observed to improve in the SRL group; the evidence base for other outcomes was insufficient to draw conclusions.

We did not conduct subgroup analyses of these studies to identify effects associated with induction agents. Although induction therapy could be important in explaining differences in patient outcomes in these studies, subgroups were too small for analysis.

Applicability

The BENEFIT-EXT study is one of few studies included in this report that specifically enrolled patients at higher risk for poor clinical outcomes. The other eight studies were similar to those described in the sections on CNI minimization, conversion, and withdrawal. Four studies excluded patients based on a PRA threshold, four excluded older patients, and two excluded retransplants. These studies are generally applicable to average or low-risk renal transplant recipients but may be limited in their generalizability to other populations. As is the case in other sections of this report, the majority of studies (five of nine) used CsA rather than TAC as the CNI.

Summary

Moderate- or low-strength evidence, based on a small number of heterogeneous studies, indicates that regimens that use belatacept or SRL from the time of transplantation are associated with few differences in clinical outcomes compared with standard-dose CNI regimens. Belatacept, however, was associated with increased risk of acute rejection compared to CsA, when used in recipients of standard-criteria donors.

Table 20. Strength of evidence for avoidance studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Belatacept + MMF vs. CsA + MMF, with basiliximab induction in both groups, with standard-criteria donors	Renal function	Associated with improved eGFR (Less intensive belatacept regimen: SMD: 0.55; 95% CI: 0.36–0.74; p<0.001); more intensive belatacept regimen: SMD: 0.58; 95% CI: 0.39–0.77; p<0.001)	1 RCT[114,115] N=666	Imprecision	Moderate
	BPAR	Associated with increased risk of acute rejection (RR: 2.73; 95% CI: 1.64–4.54; p<0.001)	1 RCT[114,115] N=666	Imprecision	Moderate
	Graft loss	Belatacept noninferior to CsA (RR: 0.56; 95% CI: 0.22–1.43; p=0.22)	1 RCT[114,115] N=666	Imprecision	Low
	Patient death	Belatacept noninferior to CsA (RR: 0.71; 95% CI: 0.27–1.84; p=0.48)	1 RCT[114,115] N=666	Imprecision	Low
	CMV infection	Inconclusive (RR: 0.78; 95% CI: 0.45–1.36; p=0.39)	1 RCT[114,115] N=666	Imprecision	Insufficient
	BK infection	Inconclusive (RR: 0.72; 95% CI: 0.31–1.65; p=0.44)	1 RCT[114] N=666	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.61; 95% CI: 0.33–1.14; p=0.12)	1RCT[114,115] N=666	Imprecision	Insufficient
Belatacept + MMF vs. CsA + MMF, with basiliximab induction in both groups, with extended-criteria donors	Renal function	More intensive belatacept regimen associated with improved eGFR (SMD: 0.32; 95% CI: 0.11 to 0.53; p<0.01); inconclusive for less intensive belatacept regimen (SMD: 0.18; 95% CI: -0.02–0.39; p=0.08)	1 RCT[115] N=543	Imprecision	Moderate
	BPAR	Belatacept noninferior to CsA (RR: 1.26; 95% CI: 0.83–1.92; p=0.28)	1 RCT[115] N=543	Imprecision	Moderate
	Graft loss	Belatacept noninferior to CsA (RR: 0.85; 95% CI: 0.50–1.43; p=0.53)	1 RCT[115] N=543	Imprecision	Low
	Patient death	Belatacept noninferior to CsA (RR: 0.77; 95% CI: 0.32–1.85; p=0.56)	1 RCT[115] N=543	Imprecision	Low
	CMV infection	Inconclusive (RR: 0.96; 95% CI: 0.61–1.53; p=0.87)	1 RCT[115] N=543	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.51; 95% CI: 0.23–1.12; p=0.09)	1 RCT[115] N=543	Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
mTOR inhibitors + mycophenolate mofetil vs. Cyclosporine + mycophenolate mofetil	Renal function	Inconclusive (SMD: 0.46; 95% CI: -0.53–1.45; I^2=92%)	2 RCT[4,116] N=850	Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 0.93; 95% CI: 0.31–2.81; I^2=58%)	2 RCT[4,116] N=850	Imprecision Inconsistency	Insufficient
	Graft loss	No difference (RR: 1.01; 95% CI: 0.64–1.59; I^2=0)	2 RCT[4,116] N=850	Imprecision	Low
	Patient death	Inconclusive (RR: 0.96; 95% CI: 0.46–2.04; I^2=0)	2 RCT[4,116] N=850	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.58; 95% CI: 0.19–1.77; I^2=49%)	2 RCT[4,116] N=850	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.82; 95% CI: 0.56–1.21; p=0.32)	1 RCT[4] N=789	Imprecision	Insufficient
mTOR inhibitors + mycophenolate mofetil vs. Tacrolimus + mycophenolate mofetil	Renal function	Regimen associated with improved eGFR at 12 months (68 mL/min vs. 62 mL/min; p=0.06)[118] and improved serum creatinine at 3 months (1.3 vs. 1.5, p=0.01)[119]	2 RCT[118,119] N=260	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 1.61; 95% CI: 0.75–3.43; I^2=0)	3 RCT[117-119] N=298	Study Limitations Imprecision	Insufficient
	Graft loss	Regimen associated with higher risk of graft loss (RR: 3.40; 95% CI: 0.97-11.92; I^2=0)	3 RCT[117-119] N=298	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 2.48; 95% CI: 0.27–22.87; I2=0)	3 RCT[117-119] N=298	Study Limitations Imprecision	Insufficient
	CMV infection	Regimen associated with lower incidence of CMV (RR: 0.07; 95% CI: 0.01–0.52; p=0.009)	1 RCT[118] N=141	Study Limitations Imprecision	Low
	BK infection	Inconclusive (RR: 4.93; 95% CI: 0.24–100.89; p=0.30)	1 RCT[118] N=141	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 1.77; 95% CI: 0.63–5.03; p=0.28)	1 RCT[118] N=141	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
mTOR inhibitors + azathioprine vs. Cyclosporine + azathioprine	Renal function	No difference (69.5±4.1 mL/min vs. 58.7±3.6 mL/min, p=NS)	1 RCT[120] N=83	Imprecision	Moderate
	BPAR	Inconclusive (RR: 1.09; 95% CI: 0.64–1.85; p=0.75)	1 RCT[120] N=83	Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.26; 95% CI: 0.03–2.20; p=0.21)	1 RCT[120] N=83	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.34; 95% CI: 0.01–8.14; p=0.51)	1 RCT[120] N=83	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.23; 95% CI: 0.41–3.72; p=0.71)	1 RCT[120] N=83	Imprecision	Insufficient
	Other opportunistic Infections	Associated with higher incidence of other infections (RR: 2.22; 95% CI: 0.93–5.28; p=0.07)	1 RCT[120] N=83	Imprecision	Low
mTOR inhibitors vs. Tacrolimus, with alemtuzumab induction in both groups	Renal function	SRL associated with improved renal function (1.83±0.88 mL/second vs. 1.38±0.48 mL/second, p<0.05)	1 RCT[121] N=21	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 0.44; 95% CI: 0.11–1.78; p=0.25)	1 RCT[121] N=21	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 2.20; 95% CI: 0.23–20.72; p=0.49)	1 RCT[121] N=21	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.36; 95% CI: 0.02–8.03; p=0.52)	1 RCT[121] N=21	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 0.44; 95% CI: 0.11–1.78; p=0.25)	1 RCT[121] N=21	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 2.20; 95% CI: 0.23–20.72; p=0.49)	1 RCT[121] N=21	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.36; 95% CI: 0.02–8.03; p=0.52)	1 RCT[121] N=21	Study Limitations Imprecision	Insufficient

AZA = azathioprine; BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CsA = cyclosporine; eGFR = estimated glomerular filtration rate; MMF = mycophenolate mofetil; mTOR = mammalian target of rapamycin; NS = not significant; rATG = rabbit anti-thymocyte globulin; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SRL = sirolimus; TAC = tacrolimus

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

Head-to-Head Studies

Description of Head-to-Head Studies

Nine studies directly compared a CNI minimization regimen to CNI conversion, withdrawal, or avoidance strategies (Table 21). These studies did not have a standard-dose CNI arm to serve as a conventional control group. Five studies compared minimization to conversion: two converted patients from low-dose CsA to SRL,[122,123] one converted patients from low-dose TAC to SRL,[124] and two converted subjects from low-dose CNI (CsA or TAC) to EVR[125] or unspecified "rapamycin."[126] In addition to the studies comparing minimization to conversion, two studies compared low-dose TAC to withdrawal of TAC.[127,128] Finally, two studies compared low-dose TAC to avoidance strategies based on SRL.[129,130]

These studies differed from the previous sets of trials in population as well as design. Head-to-head studies were generally smaller than the other studies reviewed. Seven of the 9 studies (78%) enrolled fewer than 100 patients, while just 29 of the 79 studies (37%) addressing other regimens had populations of fewer than 100. The head-to-head studies also included populations at higher risk for poor outcomes. Four of the 9 head-to-head trials included only patients with chronic allograft nephropathy, while only 4 of the other 79 studies we reviewed (3 minimization studies and 1 withdrawal study) were limited to that population. Another of the head-to-head trials[130] focused more generally on higher-risk participants, including a large proportion of African-American patients (71%), older patients (30% were older than 50 years old), and a large proportion of patients with delayed graft function (47%).

Seven studies were evaluated as high risk of bias, due to poor adherence to study regimens, low rates of study completion, industry funding, and failure to report important characteristics of study randomization and enrollment.

Table 21. Head-to-head studies

Reference	Minimization	Other Intervention	N, Intervention	N, Control
Stallone 2005[126]	CNI, MMF	Conversion to SRL	50	34
Han 2011[122]	CsA, MMF	Conversion to SRL, MMF	29	22
Liu 2007[123]	CsA, MMF	Conversion to SRL, MMF	54	56
Pankewycz 2011[124]	TAC, MPS	Conversion to SRL, MMF	29	23
Cataneo-Davila 2009[125]	CNI, EVR	Conversion to EVR	10	10
Rivelli 2015[128]	TAC, SRL	Withdrawal of TAC	22	23
Burkhalter 2012[127]	TAC, SRL, MPS	Withdrawal of TAC	19	18
Hamdy 2005[129]	TAC, SRL	Avoidance with SRL, MMF	65	65
Lo 2004[130]	TAC	Avoidance with SRL	41	29

CNI = calcineurin inhibitor; CsA = cyclosporine; MMF = mycophenolate mofetil; MPS = mycophenolate sodium; SRL = sirolimus; TAC = tacrolimus

Key Points

- Head-to-head studies were smaller and included more high-risk patients than other types of studies evaluated in this report.
- Two studies that compared a regimen of low-dose TAC and SRL to CNI avoidance using SRL and MMF found that the avoidance strategy was associated with better renal function (Strength of Evidence: Low). Results were inconclusive for other outcomes.

- One study that compared a regimen using low-dose CsA and MMF to a regimen that used conversion to an mTOR inhibitor found that the conversion regimen was associated with improved renal function (Strength of Evidence: Moderate) and reduced risk of graft loss (Strength of Evidence: Low).
- Additional direct comparative studies are needed to inform the evidence base.

Detailed Synthesis of Head-to-Head Studies

Two studies that compared low-dose CsA with conversion from CsA to an mTOR inhibitor provided low-strength evidence suggesting that conversion was associated with improved renal function and lower risk of graft loss (Table 22).[123,126] These two studies were inconclusive for the outcome of acute rejection. The other three conversion studies did not provide sufficient evidence to draw conclusions for any of the outcomes we assessed.[125-127]

Two studies comparing low-dose TAC to CNI avoidance with SRL found low-strength evidence that treatment with an mTOR inhibitor was associated with improved eGFR.[129,130] Results were inconclusive for all other outcomes.

Rivelli et al.[128] compared a regimen of low-dose TAC and SRL to a regimen that withdrew TAC while maintaining SRL. Renal function, as measured by creatinine clearance, was better in patients in the withdrawal arm than those who continued to receive TAC. However, this study was limited to 45 patients, and results for other outcomes were inconclusive.

Finally, Burkhalter et al.[127] compared a regimen of low-dose TAC, SRL, and MPS to a regimen that maintained SRL and MPS while withdrawing TAC. The study did not provide conclusive findings at 6 months. After 1 year, SRL had been discontinued for most of the patients in both study groups due to adverse events.

Applicability

As noted above, these studies were more likely than others in this report to include patients at higher risk for adverse outcomes. These studies are therefore potentially more relevant to important population subgroups. However, adherence to study groups and study completion rates was low in several studies, which may limit the generalizability of the results. Interestingly, five of the nine studies included TAC, two included CsA, and two combined patients on either CNI. These studies were the only ones we examined that focused primarily on TAC rather than CsA, and they may therefore have greater relevance to contemporary immunosuppressive treatment.

Summary

We identified only nine RCTs that conducted head-to-head comparisons of CNI minimization with other alternative immunosuppressive regimens. Four studies reported improved renal function in patients who did not receive or were converted from CNI, and two studies found conversion was associated with lower risk of graft loss. This evidence base was not sufficient to support conclusions for the other comparisons and outcomes examined. Additional head-to-head studies are needed to further build the evidence base for the comparative effectiveness of CNI minimization versus other alternative immunosuppressive strategies.

Table 22. Strength of evidence for head-to-head studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced CNI + mycophenolate mofetil vs. Conversion from CNI to mTOR inhibitor	Renal function	Inconclusive (47 mL/min vs. 53 mL/min; p=0.22)	1 RCT[126] N=84	Imprecision	Insufficient
	BPAR	Inconclusive; no events observed	1 RCT[126] N=84	Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 5.44; 95% CI: 0.71–41.53; p=0.10)	1 RCT[126] N=84	Imprecision	Insufficient
	Patient death	Inconclusive; no events observed	1 RCT[126] N=84	Imprecision	Insufficient
Reduced cyclosporine + mycophenolate mofetil vs. Conversion from cyclosporine to mTOR inhibitor	Renal function	Conversion associated with improved renal function (one study reported higher eGFR in conversion group, p<0.05, data not available;[123] one study reported eGFR: 37 mL/min for minimization vs. 50 mL/min for conversion; p<0.05[124])	2 RCT[122,123] N=161	Study Limitations	Moderate
	BPAR	Inconclusive (RR: 0.76; 95% CI: 0.12–4.97; p=0.77)	1 RCT[123] N=51	Study Limitations Imprecision	Insufficient
	Graft loss	Conversion associated with reduced risk of graft loss (1 study reported "graft survival estimate" favoring conversion: 55% vs. 77%;[123] 1 study reported "graft survival ratio was markedly higher in conversion group"[124])	2 RCT[122,123] N=161	Study Limitations Imprecision	Low
Reduced tacrolimus + mycophenolate mofetil vs. Conversion from tacrolimus to mTOR inhibitor, with rATG induction	Renal function	Inconclusive (74 mL/min vs. 66 mL/min; p=0.09)	1 RCT[124] N=52	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 0.27; 95% CI: 0.01–6.26; p=0.41)	1 RCT[124] N=52	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.27; 95% CI: 0.01–6.26; p=0.41)	1 RCT[124] N=52	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (RR: 2.40; 95% CI: 0.10–56.30; p=0.59)	1 RCT[124] N=52	Study Limitations Imprecision	Insufficient
Reduced CNI + mTOR inhibitors vs. Conversion from CNI to mTOR inhibitors + either mycophenolate mofetil or azathioprine	Renal function	Inconclusive (76 mL/min vs. 66 mL/min; p=0.26)	1 RCT[125] N=20	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 3.00; 95% CI: 0.14–65.90; p=0.49)	1 RCT[125] N=20	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive; no events observed	1 RCT[125] N=20	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive; no events observed	1 RCT[125] N=20	Study Limitations Imprecision	Insufficient

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced tacrolimus + mTOR inhibitors + mycophenolic sodium vs. Withdrawal of tacrolimus + mTOR inhibitors + mycophenolic sodium	Renal function	Inconclusive (52 mL/min vs. 45 mL/min; p=0.25)	1 RCT[127] N=37	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 0.47; 95% CI: 0.05l-4.78; p=0.53)	1 RCT[127] N=37	Study Limitations Imprecision	Insufficient
Reduced tacrolimus + mTOR inhibitors vs. Withdrawal of tacrolimus + mTOR inhibitors	Renal function	Minimization associated with lower CrCl compared to withdrawal (57.0 mL/min vs. 68.1 mL/min; p<0.05)	1 RCT[128] N=45	Imprecision	Low
	BPAR	Inconclusive (RR: 1.05; 95% CI: 0.35l-3.12; p=0.94)	1 RCT[128] N=45	Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.57; 95% CI: 0.29l-8.51; p=0.60)	1 RCT[128] N=45	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.52; 95% CI: 0.05l-5.36; p=0.59)	1 RCT[128] N=45	Imprecision	Insufficient
Reduced tacrolimus + mTOR inhibitors + basiliximab induction vs. mTOR inhibitors + mycophenolate mofetil + basiliximab induction	Renal function	Minimization associated with lower eGFR compared to avoidance (79.6 mL/min vs. 94.9 mL/min; p<0.05)	1 RCT[129] N=130	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 1.33; 95% CI: 0.60–2.95; p=0.48)	1 RCT[129] N=130	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.33; 95% CI: 0.31–5.72; p=0.70)	1 RCT[129] N=130	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 5.00; 95% CI: 0.24–102.16; p=0.30)	1 RCT[129] N=130	Study Limitations Imprecision	Insufficient
	Other opportunistic Infections	Inconclusive (RR: 0.09; 95% CI: 0.01–1.61; p=0.10)	1 RCT[129] N=130	Study Limitations Imprecision	Insufficient
Reduced tacrolimus + mTOR inhibitors + rATG induction vs. mTOR inhibitors + mycophenolate mofetil + rATG induction	Renal function	Minimization associated with lower eGFR compared to avoidance (52.9 mL/min vs. 72.4 mL/min; p<0.05)	1 RCT[130] N=70	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 1.41; 95% CI: 0.28–7.22; p=0.68)	1 RCT[130] N=70	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.89; 95% CI: 0.55–6.51; p=0.32)	1 RCT[130] N=70	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 2.14; 95% CI: 0.09–50.82; p=0.64)	1 RCT[130] N=70	Study Limitations Imprecision	Insufficient

BPAR = biopsy proven acute rejection; CI = confidence interval; CMV = cytomegalovirus; CNI = calcineurin inhibitor; eGFR = estimated glomerular filtration rate; mTOR = mammalian target of rapamycin; rATG = rabbit anti-thymocyte globulin; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations, Precision, Consistency, Directness, Reporting Bias.

Discussion

Below, we summarize the main findings and their strength of evidence. We then discuss the findings in relation to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions. When we have graded evidence as insufficient, it indicates that evidence is either unavailable, does not permit estimation of an effect, or does not permit us to draw a conclusion with at least a low level of confidence. It does not indicate that a treatment has been proven to lack efficacy.

Key Findings and Strength of Evidence

Key Question 1

One small study with high risk of bias reported on clinical validity outcomes. The evidence from this study was considered insufficient to permit conclusions about the comparative performance of high-performance liquid chromatography (HPLC) versus immunoassay for clinical outcomes. The findings of eleven studies assessing analytical performance suggest that chromatographic methods are more accurate and precise than commonly used immunoassays at measuring CNI drug levels. However, it is unclear whether the differences identified in these studies are clinically meaningful such that they would change clinical management or affect patient outcomes.

Key Question 2

The findings of the studies composing the evidence base for this question showed low strength of evidence, suggesting that risk of biopsy proven acute rejection (BPAR) is similar between new renal transplants monitored at trough level (C0) and those monitored at 2 hours (C2). For the most part, the evidence for patient and graft loss and adverse events among studies comparing C0 to C2 monitoring in new renal transplants was inconclusive due to study limitations and imprecise findings.

However, low-strength evidence from one randomized controlled trial (RCT) indicated that C2 monitoring led to a significantly higher Cyclosporine A (CsA) mean cumulative dose increase than C0 monitoring. Low-strength evidence from this study also indicated that significantly more patients in the C2 group than in the C0 group experienced tremors. In contrast, low-strength evidence from one small RCT indicated that C2 monitoring led to significantly more CsA dose reductions than C0 monitoring among stable renal recipients.

The discrepancy of the findings related to CsA dose may be due to the difference in time post-transplant of patients in the studies. In one study, the patients were only 20-days post-transplant, whereas in the other study they were stable transplants, with 3 or more months since transplant. CsA levels tend to fluctuate more shortly after transplantation, and reaching target levels is often more difficult. In addition, the C2 target levels in the study examining newer transplants were somewhat higher than in the other studies that address this question. Target C2 levels in the other studies ranged from 1,100 to 1,400 µg/L compared to 1,500 to 2,000 µg/L in the study of newer transplants. Alternatively, the explanation may be the single-study evidence base for each conclusion; future studies could overturn these conclusions.

Key Questions 3a and 3b

Four types of immunosuppressive regimens designed to reduce calcineurin inhibitor (CNI) exposure were assessed. High- and moderate-strength evidence suggests that minimization strategies based on lower doses of CsA or TAC result in significantly better clinical outcomes than with standard-dose regimens and provide a superior combination of increased benefits and reduced harms than approaches using conversion, withdrawal, or avoidance. Low-dose therapy was associated with reduced risk for acute rejection, graft loss, and opportunistic infections. Minimization was also associated with improved renal function as measured by estimated glomerular filtration rate (eGFR). These benefits were associated with both CsA and TAC, and with adjunctive use of either mycophenolic acid–based therapy such as mycophenolate mofetil (MMF) or mycophenolic sodium (MPS), or mammalian target of rapamycin (mTOR) inhibitors, including sirolimus (SRL) and everolimus (EVR). High-strength evidence also indicates that minimization may be most effective when initiated immediately or shortly following transplant and may be less effective when implemented 6 or more months after transplant.

The evidence base addressing induction therapy used in conjunction with CNI minimization is inconclusive and needs further research, although studies suggest that use of induction therapy may not be necessary to achieve the improved outcomes associated with CNI minimization. We were unable to evaluate the role of induction therapy for conversion, withdrawal, or avoidance strategies because subgroups were too small for analysis due to heterogeneity of regimens and nonreporting of induction agent use. Additionally, induction therapy likely has limited clinical relevance to many of these studies because conversion and withdrawal strategies were usually initiated at least several months post-transplant, when the impact of induction treatment would be minimized.

Similarly, moderate-strength evidence indicated that conversion to an mTOR inhibitor or belatacept was associated with modest improvement in renal function compared to standard-dose CNI regimens. High-strength evidence also suggested that conversion to an mTOR inhibitor was associated with a decreased risk in the incidence of cytomegalovirus (CMV) infection. However, moderate-strength evidence suggested that conversion from a CNI regimen to MPS was associated with an increased risk of BPAR. The evidence for converting to an mTOR inhibitor was inconclusive for other outcomes, such as BPAR, patient death, and other infection-related adverse events. More controlled trials with longer followup may be needed to better understand the impact of conversion on longer-term outcomes, such as patient death and graft loss, and among higher-risk patients for these outcomes.

High- and moderate-strength evidence suggests that planned withdrawal of CNI may result in improved renal function but is also associated with increased risk of acute rejection. Risk for acute rejection was higher in studies that used either mycophenolic acid–based treatment or mTOR inhibitors. The evidence base was insufficient to support conclusions for most of the outcomes examined. An important question the studies we reviewed did not adequately address is the interaction between the timeframe of withdrawal and the emergence of adverse outcomes. If events such as acute rejection, graft loss, or infection occur very soon after withdrawal of a CNI and replacement with a non-CNI agent, we may conclude that the non-CNI agent is inferior. However, an alternative explanation may be that because withdrawal protocols include a period during which the CNI dose is reduced but not eliminated, an adverse event may result primarily from the use of a low-dose CNI regimen during the transition phase rather than the agent that eventually replaced the CNI. Conversely, if poor outcomes present several weeks or months after

a CNI has been completely withdrawn, we may be more confident attributing the results to non-CNI therapy.

Avoidance strategies were examined in only nine studies, each of which used either SRL or belatacept as the primary alternative to CNI therapy. The evidence base for most outcomes was considered insufficient, although moderate-strength evidence suggests that belatacept is associated with improved renal function and, when standard-criteria donors are used, with increased risk of acute rejection. Further research on de novo avoidance of CNI treatment is necessary.

All these studies compared standard-dose CNI regimens with strategies designed to reduce CNI toxicity. Our review also identified nine trials that examined head-to-head comparisons between low-dose CNI and approaches that used conversion, withdrawal, or avoidance. Some of these studies suggest a beneficial effect on renal function associated with conversion, withdrawal, or avoidance. However, the studies are heterogeneous and enrolled small numbers of patients, and the overall evidence base is insufficient to draw conclusions.

Findings in Relation to What Is Already Known

Several systematic reviews have examined different aspects of CNI management in renal transplant patients. A recent survey of 76 laboratories providing immunosuppressant therapeutic drug monitoring describes the lack of standardization in laboratory procedures as a major factor impacting inter-laboratory variability.[36] While HPLC is the gold standard for monitoring CNI, many laboratories do not use appropriate reference materials such as isotope-labeled internal standards to determine the true value of CNI concentrations.[36] Levine and Holt, regarding proficiency testing of tacrolimus by 22 clinical laboratories, reported the following total error rate for each assay evaluated compared with exact matching isotope dilution mass spectrometry: 17.6-21.4% for CMIA, 28.0-33.4% for LC-MS, and 17.6-54.0% for ACMIA.[131] The total error reported in their study was defined as 2 times the total coefficient of variation plus the average bias. Analytical assay comparisons for commonly used cyclosporine assays reported biases in the range of 29-57% for FPIA as compared with HPLC.[132] Based on our review, selection of assay methodology for measurement of calcineurin inhibitors did not have an effect on clinical outcomes after renal transplantation, but this could be partially due to the bias between assay methodologies and lack of standardization in laboratory procedures.

On the question of C2 monitoring of CsA, one previous review examined studies comparing the clinical outcomes of patients on CsA-based therapy monitored with C2 levels to those monitored by C0 levels. Knight and Morris evaluated the evidence from trials evaluating the impact of C2 versus C0 monitoring on clinical outcomes among renal, liver, and cardiac transplant recipients.[12] The evidence base for renal transplant recipients consisted of 13 studies, most of which were single-group pre-post studies. This review does not include these studies. However, despite differences in the evidence base, the conclusions that Knight and Morris drew were similar to those in this review. These authors found evidence that C2 monitoring was associated with detecting higher levels of CNI than C0, but no clear evidence that C2 monitoring affects renal function or acute rejection. Thus, Knight and Morris concluded that little evidence from prospective studies supports the theoretical benefits of C2 monitoring.

The other previous reviews focused on evaluating the benefits and harms associated with changing from a standard CNI regimen to an alternative regimen, specifically minimization and withdrawal,[14,133] avoidance and withdrawal,[134,135] and conversion to an mTOR inhibitor.[136]

Su and colleagues[133] recently completed a systematic review of seven RCTs that examined CNI minimization or withdrawal with use of the mTOR inhibitor EVR. The alternative strategies used in these studies were associated with increased eGFR, lower serum creatinine, and no difference in graft loss or death. Low-dose regimens were associated with no difference in BPAR, while rejection risk was higher in studies that avoided CNI. Additionally, patients on EVR had lower risk of CMV infection but were at greater risk for nonfatal adverse events. Moore et al.[14] reviewed 19 RCTs that evaluated CNI minimization or withdrawal with use of MMF or MPS. Minimization regimens were associated with improved renal function, as measured by GFR, and reduced risk of graft loss. No harms were increased in the minimization trials. Conversely, withdrawal studies were associated with greater risk of BPAR and improved GFR and serum creatinine. These results are consistent with our meta-analyses, which found significant benefits associated with low-dose approaches to CNI management, but lesser benefits and potential harms resulting from CNI withdrawal regimens.

Yan and colleague's review[134] identified 11 RCTs of withdrawal strategies and 16 RCTs that used CNI avoidance. Early withdrawal and SRL-based avoidance were associated with improved renal function and no difference in graft loss, patient survival, or adverse events. These regimens also resulted in higher risk of BPAR at 1 year, but no significant differences were observed at 2 years after transplant. Bai and colleagues' very recent review evaluated seven RCTs that examined CNI withdrawal.[135] Withdrawal from a CNI was associated with greater risk of acute rejection and thrombocytopenia but also with improved renal function and decreased risk of hypertension.

Lim and colleagues conducted a recent systematic review of RCTs comparing delayed conversion from CNIs to mTOR inhibitors versus remaining on CNIs.[136] The overall evidence base for this review consisted of 27 trials; however, only 13 trials reported on outcomes of interest to the review and contributed to primary analyses conducted in the review. Most of these trials were included in the present review. The primary outcomes the Lim review analyzed included renal function (as measured by GFR), acute rejection, mortality, graft loss, and adverse events. Similar to the results in this review, Lim et al. found that patients converted to an mTOR inhibitor had slightly higher GFR at 1-year followup than patients remaining on a CNI. The results of their GFR analysis also indicated the presence of substantial heterogeneity (I^2=68%) that was not explained by time post-transplant or type of mTOR inhibitor. Lim et al.'s findings also indicated that rejection risk was higher among patients converted to an mTOR inhibitor. Finally, like this review, Lim et al. found that conversion to an mTOR inhibitor was associated with fewer reported incidences of CMV. However, they indicated that discontinuation secondary to adverse events was generally higher among patients converting to an mTOR inhibitor.

Another important point to address is the safety of SRL as an alternative to CNI-based treatment. A recent meta-analysis by Knoll et al. examined the effectiveness and harms associated with SRL-based regimens after renal transplantation.[137] They found a significantly increased risk of death associated with SRL use, in contrast to our review. However, their analysis included all SRL trials, not just SRL in the context of CNI minimization, and so the difference in findings is not surprising. However, these findings do suggest the need for more research on the safety of SRL.

Similarly, the ELITE-Symphony study[4] reported that renal function improved in its low-dose TAC arm when compared with SRL, while the three head-to-head studies that we reviewed found that TAC was associated with poorer renal function compared with alternative SRL-based regimens. This inconsistency is likely attributable to differences in the patient populations and

the adjunctive and induction therapies used in each study, suggesting that further research is needed to clarify the effect of these strategies on renal function.

Applicability

Five important factors limit the applicability of these findings to patient care, specifically when considering the evidence examining alternative regimens. First, most of the patients enrolled in the studies we reviewed were at average or low risk for poor outcomes, while populations at higher risk for graft rejection, infection, or adverse events are not well-represented in the evidence base. Many of the RCTs included in this review excluded highly sensitized populations, retransplants, and patients with significant comorbid conditions. These trials did not report socioeconomic status, and 21 studies excluded patients over age 65. No studies focused exclusively on graft recipients with demographic characteristics often associated with greater risk for acute rejection, such as African-Americans, and almost no studies stratified results by this factor or by age or immunologic risk. Additionally, we excluded studies in multi-organ transplant populations. Therefore, this evidence base may primarily represent the effects of alternative CNI regimens on average- or low-risk patients and may not indicate how changes in standard CNI regimens might affect higher-risk groups or other important subpopulations of renal transplant recipients.

Second, these RCTs implemented alternative CNI regimens as planned strategies in patients randomly assigned to treatment or control groups. Transplant recipients who required a regimen change due to CNI toxicity were not specifically studied in these trials and were not analyzed separately. Thus, the evidence base may not reflect how minimization, conversion, or withdrawal strategies affect outcomes in patients who have experienced CNI-related adverse events.

Third, the studies included in this review disproportionately examined CsA rather than TAC. Contemporary immunosuppressive practice, however, favors use of TAC over CsA. Therapeutic effectiveness, as well as toxicity, vary between the two types of CNIs. Our overall findings were generally consistent with the results of subgroup analyses of studies using CsA but were less similar to studies that administered TAC. However, most of the outcomes we focused on throughout this review, including acute rejection, graft loss, and risk of infection, may not be expected to vary substantially between TAC and CsA. Other outcomes, such as renal function, may be more sensitive in the different therapies. Perhaps the most important outcome that we might expect to vary between CsA and TAC regimens is toxicity. However, data on nephrotoxicity and neurotoxicity were rarely reported in the studies we reviewed. It is therefore unclear how the results of studies on alternative CsA regimens apply to regimens using TAC.

Fourth, minimization regimens varied widely in selection of low-dose target levels. Standard definitions for low-dose targets have not been codified, and the evidence base does not indicate optimal levels for reducing CsA or TAC exposure. Similarly, achievement of low-dose CNI target levels for minimization regimens was poorly and inconsistently reported and varied across studies. Moreover, levels that were considered “low” when some studies were conducted may now be considered “standard,” so the evidence base may not fully reflect current patterns of CNI use.

Finally, it is important to note that we examined only immunosuppression for renal transplant recipients. The results of these studies may not apply to CNI therapy for patients with liver, pancreas, other solid organ transplants, or to patients who receive sequential or combination organ transplants.

Implications for Clinical and Policy Decisionmaking

The evidence base examined in this systematic review has important implications for clinicians involved in the care of renal transplant recipients, most notably transplant surgeons, nephrologists, pharmacists, nurses, and infectious disease specialists. To reduce the risk of CNI-associated toxicity and adverse events, treatment with low-dose CsA or TAC in combination with MMF, MPS, or mTOR inhibitors may provide sufficient immunosuppressive therapy to reduce risk of acute rejection and opportunistic infection while enabling improved renal function. Conversion or withdrawal strategies may also help improve renal function but can result in higher risk for acute rejection. The potential benefits and risks of de novo CNI avoidance are unclear.

The evidence base examined in this report includes a disproportionate number of studies of CsA and relatively few studies of TAC, although TAC is utilized more frequently than CsA in the United States. Clinicians should recognize that the findings discussed throughout this report might characterize more precisely the effects of CsA rather than TAC. However, we do not suggest that CsA should be preferred over TAC or that current use of TAC is inappropriate. Instead, we wish to highlight the need for additional research to identify optimal strategies for administering and managing CNI immunosuppression.

Therapeutic drug monitoring of adjunctive therapies such as MMF or mTOR inhibitors were not evaluated in this review. There is an emerging view that mycophenolic acid (MPA) exposure rather than CNI exposure better predicts clinical outcomes following renal transplantation. However, whether TDM should be performed for MPA is a matter of debate.[138,139] Prospective, randomized trials performing MPA TDM have shown conflicting results.[140,141] However, a recent study by Abdi employing a time-to-event model demonstrated that acute rejection, graft loss and death following renal transplantation was significantly associated with MPA and not CNI exposure.[142]

We did review studies comparing trough level monitoring to C2 monitoring for CsA. However, CsA is less commonly used in clinical practice today. There is still a question of the best timepoint or timepoints for monitoring TAC, as TAC trough levels are not well correlated with total exposure.[143]

Adjunctive therapies such as MMF or mTOR inhibitors were not evaluated independently from CNI utilization in this review. Although these currently used therapeutic agents were not compared head-to-head, regimens that paired each with low-dose CNI regimens were associated with good patient outcomes. We also did not perform independent assessments of induction therapy. Our analyses found the evidence was insufficient to support strong conclusions about induction agents, and the results do not indicate whether specific induction strategies, when used with low-dose CNIs, yield greater or lesser benefits. Lack of induction was even associated with positive patient outcomes. However, it is important to note that most of the immunosuppressive regimens we evaluated in this report included multiple therapeutic agents. Distinguishing the effects of individual strategies within complex multicomponent treatments is a significant challenge for clinicians and researchers.[144]

Carefully selecting the optimal time for implementing an alternative immunosuppressive strategy may be important for achieving positive patient outcomes. Minimization and avoidance regimens can be planned in advance for the care of new renal transplant recipients. Conversion and withdrawal regimens, on the other hand, are most frequently initiated in response to adverse events in patients receiving CNIs, but they can also be planned. Early minimization appears to be more beneficial than later minimization and is also associated, somewhat surprisingly, with

lower risk of acute rejection compared to standard regimens. Conversion and withdrawal may confer some benefits but are also associated with increased risks. Avoidance strategies have not been widely studied yet. Clinicians treating new renal transplant recipients may therefore find value in deciding on a long-term approach early in the treatment process.

Clinicians must carefully weigh many therapeutic options when evaluating which immunosuppressive regimen to implement and must consider each patient's immunologic risk and comorbid medical conditions. The studies assessed in this review were conducted primarily in low-risk populations. When clinicians treat higher-risk patients they should consider how the balance of potential benefits and risks evaluated in our evidence tables may differ for those populations. However, it is important for clinicians to understand how CNI-based immunosuppression and current alternative strategies affect low- or average-risk patients, since the latter compose a majority of the renal transplant population. Studies in relatively healthier patients may also be necessary for establishing benchmarks that can be used when evaluating immunosuppressive therapy in higher-risk populations.

For all of the results described in this review, clinicians must evaluate the clinical significance of our findings. For example, renal function was often identified as an outcome that improved after implementation of an alternative regimen, but the absolute change in eGFR or creatinine clearance was sometimes of limited clinical relevance. Clinicians should consider how the effect sizes we described for renal function and other outcomes may translate into patient well-being.

Clinicians must also consider patient adherence to medication regimens when evaluating therapeutic options. A recent survey of 60 renal transplant patients found that low adherence was associated with poorer renal function, and the most frequently cited reason for nonadherence was patient forgetfulness.[145] Clinicians should discuss with patients and their families potential barriers to adherence, including unwanted drug side effects, interactions between immunosuppressive drugs and other medications, complexity of medication regimens, and cost.

Medication costs are an important consideration for patients, clinicians, health insurers, and policymakers. While Medicare often provides 80 percent of coverage of immunosuppression for up to 3 years following renal transplantation, the burden of paying for immunosuppression in the longer term may fall disproportionately on patients and their families if Medicare entitlement was based solely on end-stage renal disease. CsA, TAC, MMF, MPS, and SRL are available in generic formulations, but belatacept is not.

Another important consideration is the growing body of research on pharmacogenetic testing. Development of validated biomarkers may help clinicians better individualize immunosuppressive regimens and potentially prolong patient and graft survival by minimizing long-term drug toxicity.

Monitoring therapeutic drug levels is a critical component of CNI management. Although the evidence base for KQ 1 is limited, the ease of use of immunoassays may outweigh any potential improvements in analytic validity resulting from the use of HPLC methodologies. Similarly, the evidence base for KQ2 was limited, and preferences for C0 or C2 monitoring of CsA may be most influenced by practical considerations, such as patient convenience. C2 level monitoring is less practical because it needs to be measured within 15 minutes of the 2-hour target to avoid large shifts in concentration during the absorption phase, while C0 measurement can be done within a 10- to 14-hour window as it represents the elimination phase.[12,13] Finally, other factors also influence drug dose, such as eating habits and use of certain over-the-counter medications or herbal supplements.

Limitations of the Comparative Effectiveness Review Process

Due to the broad scope of the KQs, the many potentially relevant studies, and the time and resources available to complete the review, we confined our final analyses to RCTs for KQ 3. Many observational studies have been published that address this topic, and by excluding non-RCTs we may have omitted important findings, especially those related to adverse events. However, our systematic searches did not exclude observational studies; thus, we reviewed their characteristics and found they were generally small, did not have extended followup periods, and their reported outcomes were represented adequately by the available RCTs.

We also limited our review to studies published in English, which could have excluded important articles published in other languages. However, we included 22 studies representing 1,939 subjects from countries outside North America, Western Europe, and Australia, including studies conducted in Asia, the Middle East, and South America.

Another limitation of the systematic review and meta-analytic process is that combining multiple studies into broad analytic categories can mask important sources of heterogeneity. For example, studies that used an mTOR inhibitor were frequently combined, whether they used SRL or EVR, because their pharmacologic mechanisms are similar. Studies also varied in whether and how they excluded higher-risk patients, in how they measured renal function, and in the selection of medication dosing and therapeutic targets. We performed numerous subgroup analyses to address important types of study variation and conducted sensitivity analyses to explore heterogeneity. However, we could not explore every potentially important source of variance given the complexity of immunosuppression management in transplant recipients.

Limitations of the Evidence Base

Very few studies addressed KQs 1 and 2. They were highly complex and heterogeneous, and we were not able to conduct meta-analysis given these limitations. Only one RCT examined clinical outcomes of different monitoring methods. Most of the studies were not randomized and used pre-post study designs. While many of the studies examining analytical accuracy consider HPLC as the gold standard, most of these studies did not use appropriate reference materials such as isotope-labeled internal standards to determine the true value of CNI concentrations. In addition, assays and methods have improved over the past 10 years, thus assays utilized in an early era may not be comparable to newer assay technologies.

We identified 88 unique RCTs that addressed KQ 3, which is a robust evidence base. However, variations in patient populations and medication regimens may limit the generalizability of individual studies as well as our meta-analyses.

Small sample size was an important limitation in many studies. Although we were able to perform meta-analyses of many key outcomes, small studies can yield imprecise statistical estimates. Sample size was an especially notable limitation in our evaluation of low-frequency events, such as patient death and graft loss. As a result, the most robust findings associated with alternative CNI regimens are based on changes in renal function and risk of acute rejection, while other important outcomes are not well addressed. Moreover, measures of improvement in renal function that achieve statistical significance may not indicate clinically meaningful differences in patient care. In addition, for the outcome of BPAR, the studies we reviewed varied in their use of biopsy testing, with some studies implementing routine “per-protocol” biopsies,

while other studies used biopsy primarily to confirm suspected cases of organ rejection. These different strategies may have introduced variation in the study data we evaluated.

Similarly, incomplete and inconsistent reporting of adverse events limited our ability to adequately assess the potential impact of alternative CNI strategies on patient harms. This was particularly important for CNI-related nephrotoxicity and chronic allograft dysfunction, which were not assessed systematically in this review because too few studies reported comparable data for these outcomes. Infections were also reported inconsistently, and in many comparisons we lacked sufficient data to support conclusions about the effect of alternative CNI strategies on infection rates. This is a major limitation of the evidence base because infection risk is a critical factor that clinicians must consider when managing immunosuppressive regimens.

Another major limitation is the short followup period reported in most studies. We used 1-year outcome data whenever possible in our review because that was the time period reported most consistently. Incidence of major adverse outcomes (such as acute rejection or graft loss) within 1 year also provides the most direct evidence on the effects of alternative regimens, since events occurring relatively soon after implementation of a new approach are more likely to be associated with that approach, while events that emerge later may be attributed to other changes in the patient's management or morbidity. Nevertheless, longer-term outcomes are important to patients and clinicians and provide important insight into the effect of CNI management strategies. Outcome measures beyond 1 year can also inform clinicians about the sustainability of alternative strategies or identify unforeseen risks. However, very few studies examined long-term results.

Patient adherence to prescribed CNI regimens is another important factor that limits our findings. Measures of adherence were not consistently reported, and failure of patients to remain on CNI regimens may account for poorer outcomes or limited clinical improvement. Similarly, imperfect fidelity to monitoring protocols (e.g., variation in when clinical staff actually collect samples for laboratory testing) was an inherent limitation of many RCTs. Another limitation is the potential imprecision in laboratory results, between and within labs, which may affect the validity of individual study results.

The disproportionate number of studies that used CsA rather than TAC may also limit the generalizability of the evidence base to current immunosuppressive practice. Finally, we again emphasize that most of the studies we reviewed were conducted in low- or average-risk populations and were implemented as planned strategies rather than therapeutic responses to patients who exhibited CNI-related adverse events. The effects of alternative strategies on high-risk patients remain largely unknown.

Research Gaps

For KQs 1 and 2, insufficient evidence directly compares analytical and clinical outcomes between different monitoring techniques. Current studies also do not adequately consider the resources and costs associated with different monitoring methods, lack of standardization in laboratory procedures, patient and clinician preferences, and availability of specific methods, such as HPLC. In addition, the followup periods reported in most studies are not long enough for assessing many relevant outcomes. Comparisons of monitoring techniques are particularly important because long-term overexposure to immunosuppression could potentially contribute to post-transplant complications such as infection, malignancy, cardiovascular disease, diabetes, and related allograft changes (formerly known as chronic allograft nephropathy).

Although our review identified many studies examining KQ 3, significant knowledge gaps emerged. Insufficient evidence addresses the management of immunosuppression in high-risk populations, including elderly renal transplant patients, African-Americans, those of lower socioeconomic status, patients who have undergone retransplantation, and those living with significant comorbidities, including HIV.

We also found the evidence base lacks many studies that compare low-dose TAC to standard-dose TAC, in the context of various adjunctive therapies and induction agents. It is unclear how the evidence we reviewed, based largely on studies of CsA, should be interpreted compared to current practices that favor TAC. Our analyses detected heterogeneity in our findings that may be attributed partly to variation in the immunosuppressive regimens that were evaluated. Moreover, subgroup analysis found that the outcomes reported in studies using TAC tended to vary more from our overall findings compared to the studies that administered CsA.

Similarly, the evidence on the role of induction agents is insufficient and inconsistent, particularly in low-dose CNI regimens and avoidance strategies. While many studies have examined induction therapy independently, data on their effectiveness within these alternative regimens are missing. Also, too few studies directly compare alternative regimens to each other, as most studies instead compare alternative regimens to standard, full-dose CNI therapy. We also did not find sufficient evidence to adequately evaluate belatacept therapy.

The current evidence base does not measure and report important patient-centered outcomes, including preferences for different medications, adherence to immunosuppressive therapy, and side effects of CNIs and other immunosuppressants. Many other outcomes are not reported or are described inconsistently, such as CNI-associated toxicity, graft dysfunction, and infections. Finally, data from longer-term followup are lacking. Almost no studies have assessed the effectiveness, harms, or levels of patient adherence associated with alternative regimens after 5, 10, or 15 years.

Conclusions

We identified 105 studies published between 1994 and 2015 that addressed management of CNI immunosuppression and met our inclusion criteria. Eleven studies examined technologies used to monitor therapeutic drug levels in patients on CNI therapy. Six studies compared monitoring of CsA levels at trough compared with 2 hours after administration. The remaining 88 trials evaluated a variety of alternative strategies to full-dose CNI therapy.

The findings of the studies addressing analytic validity suggest that chromatographic techniques (e.g., HPLC, LC-MS/MS) more accurately measure CNI concentration levels than commonly used immunoassays. However, it is unclear whether the differences identified in these studies are clinically meaningful such that they would change clinical management or affect patient outcomes. In addition, these techniques are typically time-consuming, labor-intensive, and less standardized, and thus their results may be more provider-dependent.

For KQ 2, the current state of the evidence does not suggest any clear clinical benefit of C2 monitoring over C0; however, low strength of evidence suggests that risk of BPAR is similar between new renal transplants monitored at C0 and those monitored at C2. One RCT indicated that C2 monitoring led to a significantly higher CsA mean cumulative dose increase compared to C0 monitoring in recent transplant recipients. Low-strength evidence from this same study also indicated that significantly more patients in the C2 group than in the C0 group experienced tremors. In contrast, another small RCT indicated that C2 monitoring led to significantly more CsA dose reductions than C0 monitoring among stable renal recipients. Whether this reflects

actual differences between recent and stable renal recipients, or simply reflects the fact that each is based on a single study, is uncertain. Future studies might overturn these conclusions.

For KQ 3, high-strength evidence suggests that immunosuppression with low-dose CsA or TAC, in combination with mycophenolic acid formulations or mTOR inhibitors, results in lower risk of acute rejection and graft loss and improved renal function. The benefits of minimization strategies may be most significant when initiated from the time of transplant or shortly thereafter. Use of induction agents is not strongly associated with improved outcomes in minimization regimens, but additional research is necessary to clarify the effect of induction therapy. Conversion from a CNI to an mTOR inhibitor is associated with modest improvement in renal function. Conversion is also associated with a slightly lower risk of CMV, but the evidence was inconclusive for other opportunistic infections. Withdrawal of a CNI is not associated with improvements in renal function and may increase the risk of acute rejection. Avoidance strategies employing de novo use of SRL, EVR, or belatacept have not been studied widely, and further research is necessary to identify potential benefits or harms of CNI avoidance.

These regimens have been studied primarily in low-risk populations, and the evidence base therefore can directly inform care of most renal transplant recipients. However, further research is necessary to generate evidence of optimal immunosuppression strategies for high-risk patients. More comprehensive and consistent reporting of clinically important and patient-centered outcomes is needed, including measures of renal function, CNI-related toxicity, side effects, and patient adherence to immunosuppressive regimens.

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Abbreviations and Acronyms

AR	Acute Rejection
ABS	Affect balance scale
AUC	Areas under curve
AZA	Azathioprine
ATG/rATG	Anti-thymocyte globulin
BEL	Belatacept
BPAR	Biopsy proven acute rejection
BP	Blood Pressure
BK	Polyomavirus
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitors
CsA	Cyclosporine A
CES-D	Center of epidemiological studies depression scale
CrCl	Creatinine Clearance
CAN	Chronic Allograft Nephropathy
DGF	Delayed Graft Function
EVR	Everolimus
FPIA/FPLA	Fluorescence polarization immunoassay
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
GGT	Gamma glutamyltransferase
HBV	Hepatitis B
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
IFTA	Interstitial fibrosis and tubular atrophy on kidney allograft biopsy
IA	Immunoassay
LC	Liquid Chromatography
LDL	Low Density Lipoprotein
MMF	Mycophenolate mofetil group
MPS	Mycophenolate Sodium
MS	Mass Spectrometry
MPA	Medroxyprogesterone acetate
NR	Not Reported
NA	Not Applicable
PRED	Prednisone
PRA	Panel Reactive Antibody
PCP	Pneumocystis carinii pneumonia
SIP	Sickness impact profile
SRL	Sirolimus
STER	Steroid
TAC	Tacrolimus
TACex	Patients receiving TAC without criteria to undergo intervention at month 3
UTI	Urinary tract infection

Appendix A. Search Strategy

Resources Searched

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for the bibliographic databases appear below.

Table A-1. Bibliographic databases searched

Name	Date Limits	Platform/Provider
The Cochrane Central Register of Controlled Trials (CENTRAL)	1994 through July 11, 2014	Wiley
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	1994 through May 20, 2015	Wiley
Database of Abstracts of Reviews of Effects (DARE)	1994 through May 20, 2015	Wiley
EMBASE (Excerpta Medica)	1994 through December 10, 2015 (for KQ1 and KQ2) 1994 through May 20, 2015 (for KQ3)	Embase.com
Health Technology Assessment Database (HTA)	1994 through June 2014	Wiley
MEDLINE	1994 through May 20, 2015	Embase.com
PubMed (In-process and published records)	1994 through December 10, 2015 (for KQ1 and KQ2) 1994 through May 20, 2015 (for KQ3)	NLM
U.K. National Health Service Economic Evaluation Database (NHS EED)	1994 through June 2014	Wiley

Table A-2. Gray literature resources searched

Name	Date Limits	Platform/Provider
American Society of Transplantation (AST)	Searched July 24, 2014*	AST
American Society of Transplant Surgeons (ASTS)	Searched July 24, 2014*	ASTS
American Transplant Congress	2013 and 2014 meeting abstracts	ASTS
Clinical Trials.gov	1994 through July 15, 2014	U.S. National Institutes of Health (NIH)
Centre for Evidence in Transplantation (CET)	Website searched July 24, 2014* Trial Watch database searched January 1, 2013 through July 24, 2014	CET
Centers for Disease Control and Prevention (CDC)	Searched July 24, 2014*	CDC
Centers for Medicare and Medicaid	1994 through July 15, 2014	CMS
Health Devices	1994 through July 15, 2014	ECRI Institute
Health Technology Assessment Information Service (HTAIS) website	1994 through July 15, 2014	ECRI Institute
Healthcare Product Comparison Systems (HPCS) website	1994 through July 20, 2014	ECRI Institute
Healthcare Standards database	1994 through July 15, 2014	ECRI Institute
Infectious Diseases Society of America (IDSA)	1994 through September 9, 2014	IDSA (searched via Google search engine)
MedlinePlus	Searched July 24, 2014	National Library of Medicine (NLM)

Table A-2. Gray literature resources searched (continued)

Name	Date Limits	Platform/Provider
Medscape	2009 through July 23, 2014	WebMD
National Guideline Clearinghouse™ (NGC)	Searched July 14, 2014*	Agency for Healthcare Research and Quality (AHRQ)
National Institute of Health and Clinical Excellence (NICE)	Searched July 25, 2014*	National Health Service (UK)
National Kidney Foundation (NKF)	Searched July 24, 2014*	NKF
Organ Procurement and Transplantation Network (OPTN)	Searched Aug 12, 2014*	Health Resources and Services Administration (HRSA)
Scientific Registry of Transplant Recipients	Searched Aug 12, 2014*	Health Resources and Services Administration (HRSA)
U.S. Food and Drug Administration (FDA)	Searched July 14, 2014*	FDA
World Transplant Congress (WTC)	2014 meeting abstracts	WTC

*Search date limits were not applied.

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature).

Topic-Specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table A-3. Controlled vocabulary and keywords

Concept	Controlled Vocabulary	Keywords
Calcineurin Inhibitors	***EMBASE (EMTREE)***	advagraf
	'advagraf'/exp	astagraf
	'astagraf'/exp	calcineurin NEAR/2 inhibit*
	'calcineurin inhibitor'/exp	cipol
	'ciclosporine'/exp	'cni'
	'cipol'/exp	cyclokat
	'cyclokat'/exp	cyclosporin
	'cyclosporin'/exp	cyclosporine
	'deximune'/exp	'CSA-neoral'
	'gengraf'/exp	'cya-nof'
	'hecoria'/exp	deximune
	'immunosporin'/exp	gengraf
	'implanta'/exp	hecoria
	'mustopic oint'/exp	immunosporin

Table A-3. Controlled vocabulary and keywords (continued)

Concept	Controlled Vocabulary	Keywords
	'neoral'/exp 'prograf'/exp 'tacrolimus'/exp 'tsukubaenolide'/exp 'vekacia'/exp	implanta imusporin 'mustopic oint' neoral 'ol-27-400' prograf tacrolimus tsukubaenolide vekacia
CNI Minimization	'low drug dose'/exp 'dosage schedule comparison'/exp 'treatment withdrawal'/exp 'drug withdrawal'/exp	Alternative AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) avoid* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) eliminate* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) low AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) lower* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) minimize AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) minimization AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) minimal AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) reduce AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) reduction AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) taper* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) withdraw* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen)
CNI alternative drugs	'alemtuzumab'/exp 'belatacept'/exp 'everolimus'/exp 'rapamycin'/exp 'sotrastaurin'/exp 'tofacitinib'/exp	alemtuzumab belatacept' everolimus' rapamycin sirolimus sotrastaurin tofacitinib

Table A-3. Controlled vocabulary and keywords (continued)

Concept	Controlled Vocabulary	Keywords
Drug Monitoring timepoints (Cyclosporine)	**NA**	('area under' NEXT/1 curve) ('2' OR 'two') NEAR/1 hour* "c1" "c0" "c2" (time OR 'time point' OR timepoint* OR timing OR duration) AND (cyclospor* NEAR/2 level*) time NEAR/1 series trough
Drug Monitoring Terms	'area under the curve'/exp 'drug monitoring'/exp 'pharmacodynamics'/exp 'pharmacokinetics'/exp	('area under' NEXT/4 curve) bioequivalence 'drug monitoring' (drug OR therapy OR therapeutic) AND (monitor* OR measure* OR surveillance) drug NEAR/3 (clearance OR activation OR adsorp* OR absorp* OR bioavailabilit* OR distribution) (limit NEXT/3 quantification) 'loq'
Immunoassays/Mass Spectrometry	'immunoassay'/exp 'mass spectrometry'/exp 'high performance liquid chromatography'/exp	ACMIA 'antibody conjugated magnetic immunoassay' 'elisa' 'emit' 'enzyme linked immmunosorbent assay' 'enzyme multiplied immunoassay' fluorescence NEAR/1 polarization 'fpia' 'gc-ms' 'high performance liquid chromatography hplc' 'hplc-ms' immunoassay* 'lc-ms' 'liquid chromatography' NEAR/2 'mass spectrometry' 'mass spectrometry' (mass NEAR/1 spectrometr*) 'meia' 'microparticle enzyme immunoassay' 'ms'
Kidney Transplantation	**EMBASE (EMTREE)** 'kidney graft'/exp	'kidney graft' 'kidney transplantation' 'renal graft dysfunction' (kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft* OR recipient*)

*EMTREE terms are mapped to corresponding Medical Subject Heading (MeSH) terms in Embase.com.

Search Strategies

Table A-4. EMBASE/MEDLINE for Key Question 1 and Key Question 3b (presented in Embase.com syntax)

Set Number	Concept	Search Statement
1	Kidney transplantation	'kidney graft'/exp OR 'kidney graft' OR 'kidney transplantation' OR 'renal graft dysfunction'/exp OR 'renal graft dysfunction' OR ((kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft* OR recipient*))
2	Immunosuppressive drugs	'tacrolimus'/exp OR tacrolimus OR 'cyclosporin'/exp OR cyclosporin OR 'cyclosporine'/exp OR cyclosporine OR 'ciclosporine'/exp OR ciclosporine OR 'mustopic oint'/exp OR 'mustopic oint' OR 'tsukubaenolide'/exp OR tsukubaenolide OR 'cipol'/exp OR cipol OR 'cyclokat'/exp OR cyclokat OR 'deximune'/exp OR deximune OR 'implanta'/exp OR implanta OR 'immunosporin'/exp OR immunosporin OR imusporin OR 'vekacia'/exp OR vekacia OR 'prograf'/exp OR prograf OR 'advagraf'/exp OR advagraf OR 'hecoria'/exp OR hecoria OR 'neoral'/exp OR 'gengraf'/exp OR gengraf OR 'astagraf'/exp OR astagraf OR 'ol-27-400' OR 'CSA-neoral' OR 'cya-nof' OR neoral
3		'calcineurin inhibitor'/exp OR calcineurin NEAR/2 inhibit* OR 'cni'
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Monitoring assays	'immunoassay'/exp OR immunoassay* OR 'mass spectrometry'/exp OR 'mass spectrometry' OR 'high performance liquid chromatography'/exp OR (mass NEAR/1 spectrometr*) OR 'ms' OR 'gc-ms' OR 'hplc-ms' OR 'high performance liquid chromatography' OR 'hplc' OR (fluorescence NEAR/1 polarization) OR 'fpia' OR 'enzyme multiplied immunoassay' OR 'emit' OR 'enzyme linked immmunosorbent assay' OR 'elisa' OR 'microparticle enzyme immunoassay' OR 'meia' OR ('liquid chromatography' NEAR/2 'mass spectrometry') OR 'lc-ms' OR 'antibody conjugated magnetic immunoassay' OR ACMIA
7	Drug monitoring	'drug monitoring'/exp OR 'drug monitoring' OR ((drug OR therapy OR therapeutic) AND (monitor* OR measure* OR surveillance)) OR 'pharmacodynamics'/exp OR 'area under the curve'/exp OR 'pharmacokinetics'/exp OR bioequivalence OR (drug NEAR/3 (clearance OR activation OR adsorp* OR absorp* OR bioavailabilit* OR distribution)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq'
8	Combine sets	5 AND 6 AND 7
9	Diagnostic test Hedge	8 AND ('diagnostic accuracy'/exp OR 'diagnosis':lnk OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR 'sensitivity' OR 'specificity' OR 'accuracy':de OR 'precision'/exp OR 'precision':de OR 'prediction and forecasting'/exp OR 'prediction and forecasting' OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'test retest reliability'/exp OR (test NEXT/3 reliability) OR 'reliability'/exp OR 'validity'/exp OR 'measurement repeatability'/exp OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR 'ppv' OR ((false OR true) NEAR/1 (positive OR negative)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq' OR (('inter assay' OR 'inter-assay' OR 'inter laboratory' OR 'inter-laboratory') NEAR/2 (agreement OR measurement OR reproducibility))

Table A-4. EMBASE/MEDLINE for Key Question 1 and Key Question 3b (presented in Embase.com syntax) (continued)

Set Number	Concept	Search Statement
10	Clinical trials filter	8 AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR 'randomization' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'placebo'/exp OR 'placebo' OR 'latin square design'/exp OR 'latin square design' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'controlled study'/exp OR 'controlled study' OR 'clinical trial'/exp OR 'clinical trial' OR 'comparative study'/exp OR 'comparative study' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'follow up'/exp OR 'follow up' OR 'intermethod comparison'/exp OR 'intermethod comparison' OR 'parallel design'/exp OR 'parallel design' OR 'control group'/exp OR 'control group' OR 'prospective study'/exp OR 'prospective study' OR 'retrospective study'/exp OR 'retrospective study' OR 'case control study'/exp OR 'case control study' OR 'major clinical study'/exp OR 'major clinical study' OR 'evaluation study'/exp OR 'evaluation study' OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR 'blind'/exp OR blind OR sham)) OR 'latin square' OR isrctn* OR actrn* OR (nct* NOT nct))
11	Systematic Review/Meta-analysis filter	8 AND ('research synthesis' OR pooled OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis' OR (('evidence base' OR 'evidence based'/exp OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search*) AND ('review'/exp OR 'review' OR 'review'/it)))
12	Combine sets	9 OR 10 OR 11
13	Remove unwanted publication types	12 NOT 'book'/exp OR 'book' OR 'conference paper'/exp OR 'conference paper' OR 'editorial'/exp OR 'editorial' OR 'letter'/exp OR 'letter' OR 'note'/exp OR 'note' OR book:it,pt OR 'edited book':it,pt OR 'case report':it,pt OR 'case reports':it,pt OR comment:it,pt OR conference:it,pt OR editorial:it,pt OR letter:it,pt OR news:it,pt OR note:it,pt OR proceeding:it,pt

Table A-5. EMBASE/MEDLINE for Key Question 2 (presented in Embase.com syntax)

Set Number	Concept	Search Statement
1	Kidney transplantation	'kidney graft'/exp OR 'kidney graft' OR 'kidney transplantation' OR 'renal graft dysfunction'/exp OR 'renal graft dysfunction' OR ((kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft* OR recipient*))
2	Cyclosporine	Cyclosporin/exp OR Cyclosporine OR cyclosporin OR cipol OR cyclokat OR deximune OR implanta OR imusporin OR vekacia OR ciclosporin OR 'CsA-Neoral' OR 'CyA-NOF' OR 'Neoral' OR 'OL 27-400'
3	Combine sets	1 AND 2
4	Drug monitoring/ pharmacodynamics	'drug monitoring'/exp OR 'drug monitoring' OR ((drug OR therapy OR therapeutic) AND (monitor* OR measure* OR surveillance)) OR 'pharmacodynamics'/exp OR 'area under the curve'/exp OR 'pharmacokinetics'/exp OR bioequivalence OR (drug NEAR/3 (clearance OR activation OR adsorp* OR absorp* OR bioavailabilit* OR distribution)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq'
5	Monitoring timepoints	(('2' OR 'two') NEAR/1 hour*) OR trough OR ((time OR 'time point' OR timepoint* OR timing OR duration) AND (cyclospor* NEAR/2 level*)) OR 'c1' OR 'c0' OR 'c2' OR ('area under' NEXT/1 curve) OR time NEAR/1 series
6	Combine sets	3 AND 4 AND 5

Table A-5. EMBASE/MEDLINE for Key Question 2 (presented in Embase.com syntax) (continued)

Set Number	Concept	Search Statement
7	Diagnostic test Hedge	6 AND ('diagnostic accuracy'/exp OR 'diagnosis':lnk OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR 'sensitivity' OR 'specificity' OR 'accuracy':de OR 'precision'/exp OR 'precision':de OR 'prediction and forecasting'/exp OR 'prediction and forecasting' OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'test retest reliability'/exp OR (test NEXT/3 reliability) OR 'reliability'/exp OR 'validity'/exp OR 'measurement repeatability'/exp OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR 'ppv' OR ((false OR true) NEAR/1 (positive OR negative)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq' OR (('inter assay' OR 'inter-assay' OR 'inter laboratory' OR 'inter-laboratory') NEAR/2 (agreement OR measurement OR reproducibility))
8	Clinical Trials	6 AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR 'randomization' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'placebo'/exp OR 'placebo' OR 'latin square design'/exp OR 'latin square design' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'controlled study'/exp OR 'controlled study' OR 'clinical trial'/exp OR 'clinical trial' OR 'comparative study'/exp OR 'comparative study' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'follow up'/exp OR 'follow up' OR 'intermethod comparison'/exp OR 'intermethod comparison' OR 'parallel design'/exp OR 'parallel design' OR 'control group'/exp OR 'control group' OR 'prospective study'/exp OR 'prospective study' OR 'retrospective study'/exp OR 'retrospective study' OR 'case control study'/exp OR 'case control study' OR 'major clinical study'/exp OR 'major clinical study' OR 'evaluation study'/exp OR 'evaluation study' OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR 'blind'/exp OR blind OR sham)) OR 'latin square' OR isrctn* OR actrn* OR (nct* NOT nct))
9	Systematic Review/Meta-analysis filter	6 AND ('research synthesis' OR pooled OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis' OR (('evidence base' OR 'evidence based'/exp OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search*) AND ('review'/exp OR 'review' OR 'review'/it)))
10	Combine sets	7 OR 8 OR 9
11	Remove unwanted publication types	10 NOT 'book'/exp OR 'book' OR 'conference paper'/exp OR 'conference paper' OR 'editorial'/exp OR 'editorial' OR 'letter'/exp OR 'letter' OR 'note'/exp OR 'note' OR book:it,pt OR 'edited book':it,pt OR comment:it,pt OR conference:it,pt OR editorial:it,pt OR letter:it,pt OR news:it,pt OR note:it,pt OR proceeding:it,pt
12	Remove overlap from KQ1	11 NOT (results from KQ1)

Table A-6. EMBASE/MEDLINE for Key Question 3a (presented in Embase.com syntax)

Set Number	Concept	Search Statement
1	Kidney transplantation	'kidney graft'/exp OR 'kidney graft' OR 'kidney transplantation' OR 'renal graft dysfunction'/exp OR 'renal graft dysfunction' OR (kidney OR renal) NEAR/2 (allograft* OR alograft* OR transplant* OR homograft* OR graft*)
2	Immunosuppressive drugs	'tacrolimus'/exp OR tacrolimus OR 'cyclosporin'/exp OR cyclosporin OR 'cyclosporine'/exp OR cyclosporine OR 'ciclosporine'/exp OR ciclosporine OR 'mustopic oint'/exp OR 'mustopic oint' OR 'tsukubaenolide'/exp OR tsukubaenolide OR 'cipol'/exp OR cipol OR 'cyclokat'/exp OR cyclokat OR 'deximune'/exp OR deximune OR 'implanta'/exp OR implanta OR 'immunosporin'/exp OR immunosporin OR imusporin OR 'vekacia'/exp OR vekacia OR 'prograf'/exp OR prograf OR 'advagraf'/exp OR advagraf OR 'hecoria'/exp OR hecoria OR 'neoral'/exp OR 'gengraf'/exp OR gengraf OR 'astagraf'/exp OR astagraf OR 'ol-27-400' OR 'CSA-neoral' OR 'cya-nof' OR neoral
3		'calcineurin inhibitor'/exp OR calcineurin NEAR/2 inhibit* OR 'cni'
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Dose minimization	'low drug dose'/exp OR 'dosage schedule comparison'/exp OR 'treatment withdrawal'/exp OR 'drug withdrawal'/exp OR ((low OR lower* OR reduce OR reduction OR minimize OR minimization OR minimal OR withdraw* OR avoid* OR eliminate* OR taper* OR alternative OR conversion) NEAR/4 (dose* OR dosing OR dosage* OR drug* OR calcineurin OR tacrolimus OR cyclosporine* OR 'CNI' OR strategy OR strategies OR regimen*))
7	CNI alternatives (major concepts)	'rapamycin'/exp/mj OR 'rapamycin':ti OR 'everolimus'/exp/mj OR 'everolimus':ti OR 'alemtuzumab'/exp/mj OR 'alemtuzumab':ti OR 'sotrastaurin'/exp/mj OR 'sotrastaurin':ti OR 'tofacitinib'/exp/mj OR 'tofacitinib':ti OR 'belatacept'/exp/mj OR 'belatacept':ti OR sirolimus:ti
8	Combine sets	5 AND (6 OR 7)
9	Controlled trials filter	8 AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR 'randomization' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'placebo'/exp OR 'placebo' OR 'latin square design'/exp OR 'latin square design' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'controlled study'/exp OR 'controlled study' OR 'clinical trial'/exp OR 'clinical trial' OR 'comparative study'/exp OR 'comparative study' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'follow up'/exp OR 'follow up' OR 'intermethod comparison'/exp OR 'intermethod comparison' OR 'parallel design'/exp OR 'parallel design' OR 'control group'/exp OR 'control group' OR 'prospective study'/exp OR 'prospective study' OR 'retrospective study'/exp OR 'retrospective study' OR 'case control study'/exp OR 'case control study' OR 'major clinical study'/exp OR 'major clinical study' OR 'evaluation study'/exp OR 'evaluation study' OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR 'blind'/exp OR blind OR sham)) OR 'latin square' OR isrctn* OR actrn* OR (nct* NOT nct))
10	Systematic Review/Meta-analysis filter	8 AND ('research synthesis' OR pooled OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis' OR (('evidence base' OR 'evidence based'/exp OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search*) AND ('review'/exp OR 'review' OR 'review'/it)))
11	Combine sets	9 OR 10

Table A-6. EMBASE/MEDLINE for Key Question 3a (presented in Embase.com syntax) (continued)

Set Number	Concept	Search Statement
12	Remove unwanted publication types	11 NOT 'book'/exp OR 'book' OR 'conference paper'/exp OR 'conference paper' OR 'editorial'/exp OR 'editorial' OR 'letter'/exp OR 'letter' OR 'note'/exp OR 'note' OR book:it,pt OR 'edited book':it,pt OR 'case report':it,pt OR comment:it,pt OR conference:it,pt OR editorial:it,pt OR letter:it,pt OR news:it,pt OR note:it,pt OR proceeding:it,pt

Embase.com Syntax:

*	=	truncation character (wildcard)
NEAR/*n*	=	search terms within a specified number (*n*) of words from each other in any order
NEXT/*n*	=	search terms within a specified number (*n*) of words from each other in the order specified
/	=	search as a subject heading
exp	=	"explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
mj	=	denotes a term that has been searched as a major subject heading
:de	=	search in the descriptors field (controlled terms and keywords)
:lnk	=	floating subheading
:it,pt.	=	source item or publication type
:ti.	=	limit to title
:ti,ab.	=	limit to title and abstract fields

Table A-7. PUBMED (PreMEDLINE) for Key Question 1 and Key Question 3b

Set Number	Concept	Search Statement
1	Kidney transplantation	(kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft* OR recipient*)
2	Immunosuppressive drugs	tacrolimus OR cyclosporin OR cyclosporine OR ciclosporine OR "mustopic oint" OR tsukubaenolide OR cipol OR cyclokat OR deximune OR implanta OR immunosporin OR imusporin OR vekacia OR prograf OR advagraf OR hecoria OR gengraf OR astagraf OR "ol-27-400" OR "CSA-neoral" OR "cya-nof" OR neoral
3		(calcineurin AND inhibit*) OR "cni"
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Immunoassay/ Mass Spectrometry	immunoassay* OR "mass spectrometry" OR "high performance liquid chromatography" OR (mass AND spectrometr*) OR "gc-ms" OR "hplc-ms" OR "hplc" OR (fluorescence AND polarization) OR "fpia" OR "enzyme multiplied immunoassay" OR "emit" OR "enzyme linked immmunosorbent assay" OR "elisa" OR "microparticle enzyme immunoassay" OR "meia" OR ("liquid chromatography" AND "mass spectrometry") OR "lc-ms" OR "antibody conjugated magnetic immunoassay" OR "ACMIA"
7	Combine sets	5 AND 6
8	Remove unwanted publication types	7 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
9	Limit to in process citations	10 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])

Table A-8. PUBMED (PreMEDLINE) for Key Question 2

Set Number	Concept	Search Statement
1	Kidney transplantation	(kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft* OR recipient*)
2	Immunosuppressive drugs	cyclosporine OR cyclosporin OR cipol OR cyclokat OR deximune OR implanta OR imusporin OR vekacia OR ciclosporin OR "CsA-Neoral" OR "CyA-NOF" OR "Neoral" OR "OL 27-400"
3	Combine sets	1 AND 2
4	Monitoring time points	(("2"[tiab] OR two[tiab]) AND hour*) OR trough OR ((time OR "time point" OR timepoint* OR timing OR duration) AND cyclospor* AND level*) OR "c1"[tiab] OR "c0"[tiab] OR "c2"[tiab] OR "area under the curve" OR "time series"
5	Combine sets	3 AND 4
6	Remove unwanted publication types	5 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
9	Limit to in process citations	6 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])

Table A-9. PUBMED (PreMEDLINE) for Key Question 3a

Set Number	Concept	Search Statement
1	Kidney transplantation	(kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft*)
2	Immunosuppressive drugs	tacrolimus OR cyclosporin OR cyclosporine OR ciclosporine OR "mustopic oint" OR tsukubaenolide OR cipol OR cyclokat OR deximune OR implanta OR immunosporin OR imusporin OR vekacia OR prograf OR advagraf OR hecoria OR gengraf OR astagraf OR "ol-27-400" OR "CSA-neoral" OR "cya-nof" OR neoral
3		(calcineurin AND inhibit*) OR "cni"
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Dose minimization	(low[tiab] OR lower*[tiab] OR reduce[tiab] OR reduction[tiab] OR minimize[tiab] OR minimization[tiab] OR minimal[tiab] OR withdraw*[tiab] OR avoid*[tiab] OR eliminate*[tiab] OR taper*[tiab] OR alternative[tiab] OR conversion[tiab]) AND (dose*[tiab] OR dosing[tiab] OR dosage*[tiab] OR calcineurin[tiab] OR tacrolimus[tiab] OR cyclosporine*[tiab] OR "CNI"[tiab] OR strategy[tiab] OR strategies[tiab] OR regimen*[tiab])
7	CNI Alternatives	rapamycin OR everolimus OR alemtuzumab OR sotrastaurin OR tofacitinib OR belatacept OR sirolimus
8	Combine sets	5 AND (6 OR 7)
9	Remove unwanted publication types	8 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
10	Limit to in process citations	9 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
11	Controlled trials filter	10 AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR meta-analysis[mh] OR meta-analysis[pt] OR outcomes research[mh] OR multicenter study[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square" OR placebos[mh] OR placebo* OR random* OR "control group" OR prospective* OR retrospective* OR volunteer* OR sham OR "meta-analysis"[tw] OR cohort OR ISRCTN* OR ACTRN* OR NCT*)
12	Systematic Review/Meta-analysis filter	10 AND (meta-analysis OR meta-analysis[pt] OR ((evidence base* OR methodol* OR systematic* OR quantitativ* OR studies OR overview* OR search) AND review[pt]))
13	Combine sets	11 OR 12

PubMed Syntax:

* = truncation character (wildcard)

[ti] = limit to title field

[tiab] = limit to title and abstract fields

[tw] = text word

Appendix B. Excluded Studies

Does not meet study design criteria (e.g., not a randomized controlled trial, previous systematic review, narrative review, or commentary):

An open label, prospective, randomized, controlled, multi-center study assessing fixed dose vs concentration controlled CellCept regimens for patients following a single organ renal transplantation in combination with full dose and reduced dose calcineurin inhibitors. Dev Behav Pediatr Online. 2004. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/645/CN-00487645/frame.html

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Appendix C. Evidence Tables for Key Questions 1a and 1b

Table C-1. Study characteristics

Reference	Country	Type of Study Study Design (n)	CNI Regimen	Intervention Monitoring Method	Comparative/Reference Monitoring Method	Outcomes	Followup
Leung et al. 2014[1]	USA	Analytical accuracy of tests measuring TAC, prospective comparative study (145)	TAC regimen	QMS TAC immunoassay (QMS)	LC-MS/MC (in house)	Analytical performance	Not reported
Shipkova et al. 2014[2]	Germany	Analytical accuracy of tests measuring TAC, prospective comparative study (60)	TAC regimen	Elecsys TAC assay (ELCIA)	LC-MS/MC	Analytical performance	Not reported
Westley et al. 2007[3]	Australia	Analytical accuracy of tests measuring TAC, retrospective comparative study (67)	TAC regimen	CEDIA and MEIA	HPLC-MS	TAC concentrations and analytical performance	Not reported
Borrows et al. 2006[4]	United Kingdom	Clinical utility of test measuring TAC, RCT (80)	TAC (10-15 ng/ml)+ MMF (750 mg/twice daily) and induction anti-CD25 monoclonal	HPLC-MS	MEIA	Patient and graft survival, graft function, BPAR, bacterial infection, incidence of CMV, NODM, other adverse events; inter-assay variability	6 months
Chan et al. 2005[5]	China	Analytical accuracy of tests measuring TAC, prospective comparative study (30)	TAC+ prednisolone and AZA	HPLC-MS	MEIA	TAC concentration, analytical performance, clinical management	Not reported
Butch et al. 2004[6]	United States	Analytical accuracy of tests measuring CsA, prospective comparative study (165)	CsA regimen	CEDIA	HPLC-MS	Analytical performance	Not reported
Staatz et al. 2002[7]	Australia	Analytical accuracy of tests measuring TAC, retrospective comparative study (76)	TAC+ MMF or AZA and steroids	LC/MS/MS	ELISA	TAC concentrations and analytical performance	Data collected from patients who received either a liver or kidney transplant from 1994 to 2000

Table C-1. Study characteristics (continued)

Reference	Country	Type of Study Study Design (n)	CNI Regimen	Intervention Monitoring Method	Comparative/Reference Monitoring Method	Outcomes	Followup
Hamwi et al. 1999[8]	Austria	Analytical accuracy of tests measuring CsA, prospective comparative study (49)	CsA regimen	FPIA/AxSYM, CEDIA, and modified EMIT	HPLC-MS	Analytical performance	Not reported
Schutz et al. 1998[9]	Germany	Analytical accuracy of tests measuring CsA, prospective comparative study (99)	CsA regimen	FPIA/AxSYM, CEDIA, and modified EMIT	HPLC-MS	Analytical performance	Not reported
Salm et al. 1997[10]	Australia	Analytical accuracy of tests measuring TAC, prospective comparative study (67)	TAC regimen	ELISA and MEIA	HPLC-MS[2] Developed by the authors of the study; HPLC-MS tandem mass spectrometry	TAC concentrations and analytical performance	4 months
Roberts et al. 1995[11]	United Kingdom	Analytical accuracy of tests measuring CsA, prospective comparative study (70)	CsA regimen	FPIA/TDx mono and polyclonal immunoassay	HPLC-MS	Analytical performance	Not reported

BPAR=biopsy proven acute rejection; CEDIA=cloned enzyme donor immunoassay; CMV=cytomegalovirus; CsA=cyclosporine; ELCIA=electrochemiluminescence immunoassay; ELISA=enzyme-linked immunosorbent assay; EMIT= enzyme multiplied immunoassay; FPIA=fluorescence polarization immunoassay; HPLC-MS=high performance liquid chromatography; LC/MS/MS=liquid chromatography-tandem mass spectrometry; MEIA=microparticle enzyme immunoassay; MMF=mycophenolate mofetil; NODM=new onset diabetes mellitus; RCT=randomized controlled trial; RIA=radio-immunoassay; TAC=tacrolimus

Table C-2. Patient characteristics

Reference	Number of Patients	Mean Age	Percent Male	Number Live Donor Recipients	Percent Ethnicity
Shipkova et al. 2014[2]	60 patients who underwent kidney transplant (other patient in the study underwent heart and liver transplants)	Not reported	Not reported	Not reported	Not reported
Leung et al. 2014[1]	145 whole blood samples	Not reported	Not reported	Not reported	Not reported
Westley et al. 2007[3]	88 patients who underwent kidney transplant (other patients in study underwent liver transplant)	Range: 9 to 69 years	66%	Not reported	Not reported
Borrows et al. 2006[4]	MEIA: 40 HPLC: 40 All patients underwent kidney transplant	MEIA: 46 years HPLC: 44 years	MEIA: 65% HPLC-MS: 45%	MEIA: 18 HPLC-MS: 19	MEAI: 45% Caucasian, 25% Indo-Asian, 20% Afro-Caribbean, 5.0% Mid-Eastern, 5.0% Asian HPLC-MS: 60% Caucasian, 22% Indo-Asian, 17% Afro-Caribbean, 0% Mid-Eastern and Asian
Chan et al. 2005[5]	30 patients; all patients underwent kidney transplant	42.6 years	53%	Not reported	Not reported
Butch et al. 2004[6]	165 specimens from patients who underwent kidney transplant (other patients in the study underwent bone marrow, heart and liver transplants)	Not reported	Not reported	Not reported	Not reported
Staatz et al. 2002[7]	76 patients who underwent kidney transplant (other patients in study underwent liver transplant)	Patients aged 15 years or older	Not reported	Not reported	Not reported
Hamwi et al. 1999[8]	49 specimens from patients who underwent kidney transplant (other patients in the study underwent bone marrow, heart and liver transplants)	Not reported	Not reported	Not reported	Not reported
Schutz et al. 1998[9]	99 specimens from patients who underwent kidney transplant (other patients in the study underwent bone marrow, heart and liver transplants)	Not reported	Not reported	Not reported	Not reported
Salm et al. 1997[10]	37 patients who underwent kidney transplant (other patients in study underwent liver transplant)	No reported	Not reported	Not reported	Not reported
Roberts et al. 1995[11]	86 whole blood samples from 70 patients	Not reported	Not reported	Not reported	Not reported

HPLC-MS=high-performance liquid chromatography; MEIA=microparticle enzyme immunoassay

Table C-3. Primary findings of study measuring clinical utility

Reference	Number of Patients	Followup	TAC Level (ng/ml)	Patient Survival	Graft Survival	BPAR	DGF	TAC Nephrotoxicity	Serum Creatinine (µmol/l)
Borrows et al. 2006[4]	MEIA: 40 HPLC-MS: 40	6 months	MEIA: 11.1±2.7 HPLC: 9.2±2.3 (p=0.02)	MEIA: 100% HPLC-MS: 100%	MEIA: 100% HPLC-MS: 97.5%	MEIA: 4 patients (10%) HPLC-MS: 1 patient (2.5%) No significant difference (p=0.17)	MEIA: 14 patients (35%) HPLC-MS: 12 patients (30%) No significant difference	MEIA: 6 patients (15%) HPLC-MS: 7 patients (17.5%)	MEIA: 142±39 HPLC-MS: 141±45 No significant difference

BPAR=biopsy proven acute rejection; DGF=delayed graft function; HPLC-MS=high performance liquid chromatography-mass spectrometry; MEIA=microparticle enzyme immunoassay; TAC=tacrolimus

Table C-4. Analytical validity outcomes

Reference	Number of Patients (Blood Samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC_{12} Values	Mean Bias	Precision
Leung et al. 2014[1]	145 whole blood samples	QMS TAC immunoassay (QMS) vs. LC-MS/MS (in house)	Whole blood samples collected from patients undergoing routine TAC monitoring; samples stored at below -20 C until tested.	Not reported	r^2=0.99 Slope 1.13 (range 4.0 to 84.6 ng/mL)	NR	NR	31% (overall per Bland/Altman analysis = 2.4 ng/mL)	Coefficient of variance for intra-assay and inter-assay precision studies ranged from 3.9% to 8.1% and 4.7% to 10.0%.
Shipkova et al. 2014[2]	60 whole blood	Elecsys TAC assay (ELCIA) vs. LC-MS/MC	Blood samples collected from 5 different sites; samples stored at room temperature if tested within 8 hours of collection or at below -15 C if tested at a later time; all samples were measured within 6 months of collection.	Slope 1.0±0.10, intercept <1/10 of the low end of the therapeutic concentration range of 3.0 µg/L for kidney	r^2=0.97 Slope: 1.13 (95% CI: 1.09 to 1.16 According to the authors, this value fell out of the acceptance value of 1.0±0.1	NR	NR	5.9% (95% CI: -27.8% to -39.5%)	For ELCIA only: Linearity: 0.5 to 40 µg/L; functional sensitivity: 0.3 µg/L (CV≤20%) Intermediate imprecision for TAC concentration ≥6.8 µg/L was ≤6.5% Lower imprecision for TAC to 1.5 µg/L was consistently ≤10%

Table C-4. Analytical validity outcomes (continued)

Reference	Number of Patients (Blood Samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC_{12} Values	Mean Bias	Precision
Westley et al. 2007[3]	88 (88) Samples underwent approximately three freeze/thaw cycles during the study period between the two study centers.	CEDIA and MEIA vs. HPLC-MS	NR	See precision data	CEDIA vs. HPLC-MS: r^2=0.77 CEDIA vs. MEIA: r^2=0.72 MEIA vs. HPLC-MS: r^2=0.90	NR	NR	CEDIA vs. HPLC-MS: 33.3% (±3.9) CEDIA vs. MEIA: 13.9% (±4.4%) MEIA vs. HPLC-MS: 20.1 (±2.5%)	CEDIA vs. HPLC-MS: RMSE=5.7 µg/L CEDIA vs. MEIA: RMSE=3.7 µg/L MEIA vs. HPLC-MS: RMSE=2.8 µg/L
Borrows et al. 2006[4]	40 (total samples not reported)	HPLC-MS vs. MEIA	TAC levels measured daily from first day post-transplant to discharge from hospital and at each clinic visit	Median/Range TAC at 6 months: MIEA: 12.8 (6.7 to 22.0) ng/ml HPLC-MS: 9.9 (5.5 to 18.9) ng/ml	NR	NR	NR	NR	Inter-assay variability at 5, 11, and 22 ng/ml TAC: MEIA 13.7%, 8.3%, 10.9% HPLC 8.0%, 6.5%, 5.7%
Chan et al. 2005[5]	30 (134)	HPLC-MS vs. MEIA	50 pairs of 2-hour post-dose (C2) and 4-hour post-dose (C4) were used; with an estimation of the 12-hour AUC done using a two-point sampling method; TAC concentrations measured at a median 13.5 months post-transplant	HPLC-MS: median TAC 9.75 (7.08) µg/L MEIA: 10.30 (8.08) µg/L Median difference -0.40 (2.03) µg/L; p<0.001; % difference 5.04%; concentrations significantly, but not clinically, lower for HPLC-MS	r^2= 0.94; p<0.001; indicates good correlation between methods	95% LoA 2.98 to -4.10 µg/L; 90% of patients had an absolute difference of less than 3.1 µg/L	Mean difference: 3.4±11.6 hr. µg/L; p=0.059; % difference 2.6±11.4%; p=0.107	NR	NR

Table C-4. Analytical validity outcomes (continued)

Reference	Number of Patients (Blood Samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC_{12} Values	Mean Bias	Precision
Butch et al. 2004[6]	165 specimens from patients who underwent kidney transplant (other patients in the study underwent bone marrow, heart and liver transplants)	CEDIA Plus vs HPLC	Whole blood samples collected over an eight-week period and assayed within an 8-h period of specimen receipt.	Ranged from 28-1,289 µg/L	HPLC vs CEDIA plus immunosassay r2=0.98; HPLC was lower than CEDIA plus with a mean difference of -17.5%; slope 0.90 (95% CI 0.87 to 0.93)	CEDIA plus has low range calibrators 25-450 µg/L and high range calibrators 450-2000 µg/L	NR	17.5% lower by HPLC compared with CEDIA	Within-run imprecision (coefficient of variation) ranged from 1.7% to 3.3%; between day imprecision ranged from 2.7% to 7.8%.
Staatz et al. 2002[7]	29 (98)	LC/MS/MS vs. ELISA	12-hour trough monitoring; immediate post-transplant and subsequent at each clinical visit. Samples for concentration monitoring ranged from 2 to 402 days post-transplant; samples per subject ranged from 1 to 6 (median 4)	ELISA TAC ranged from 1.9 to 43.4 ng/mL LC/MS/MS ranged from 1.7 to 44 ng/mL	r^2=0.95; SE.EST: 1.37	NR	NR	ELISA vs. LC/MS/MS 0.47 (±1.37) At TAC 0 to 6 ng/ml, Mean Bias: 4.7 (±19.6)	Relative difference between 2 assays at 5, 10, and 20 ng/ml TAC: Reported as 95% CIs: -50% to 60%, -24% to 31%, and -11% to 17%

Table C-4. Analytical validity outcomes (continued)

Reference	Number of Patients (Blood Samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC_{12} Values	Mean Bias	Precision
Hamwi et al. 1999[8]	49 samples	HPLC-MS vs. FPIA/AxSYM, CEDIA, and modified EMIT	Whole blood samples in which CsA levels were monitored no more than 5 days after collection of these specimens. Samples were stored 4 C.	NR	HPLC vs CEDIA: r^2=0.97; slope 1.31 (95% CI 1.29 to 1.47); HPLC vs EMIT: r^2=0.97; slope 1.17 (95 CI 1.02 to 1.28); HPLC vs FPIA/AxSYM r^2=0.98; slope 1.03 (95% CI 0.97 to 1.12); HPLC vs FPIA/TDx r^2= 0.97 slope 1.29 (95% CI 1.19 to 1.42).	NR	NR	Immunoassay was higher than HPLC: 14.1 % higher with CEDIA, 18.8% with EMIT, 10% with FPIA/AxSYM, 50% with FPIA/TDx	The within assay CV at the lowest CsA concentration ranged from 3.07% for the FPIA/TDx to 10.6% for the CEDIA. At the highest concentration, the CV ranged from 1.73% for FPIA/TDx to 6.45% for FPIA/AxSYM. The between assay CV ranged from 4.25% (FPIA/TDx) to 8.90% (EMIT) at the lowest CSA and from 3.12% (FPIA/TDx) to 6.77% (FPIA/AxSYM) at the highest CSA
Schutz et al. 1998[9]	99 specimens from patients who underwent kidney transplant	HPLC-MS vs. FPIA/AxSYM, CEDIA, and modified EMIT	To evaluate accuracy, drug free whole blood samples with CsA added as well as using the metabolites in methanol solutions.	50, 100, and 400 µg/L.	FPIA slope= 1.17 (1.04 to 1.32), mean difference of measurement to HPLC 32%; CEDIA slope=1.19 (1.00 to 1.39), 22.5%; EMIT 1.07 (0.97 to 1.19), 23.9%	Detection limits: 13µg/L for the FPIA, 25 µg/L, for CEDIA, and 17.0 µg/L for EMIT	NR	Immunoassay was higher than HPLC: 32% higher with FPIA/AxSYM, 22.5% higher with CEDIA, 23.9% higher with EMIT.	The within assay coefficient of variation are provided for low and high range controls: HPLC 6.8% , 7.6%; FPIA/AxSym 5.8%, 1.7%; CEDIA 11%, 5.5%; EMIT 6.5%, 4.8%

Table C-4. Analytical validity outcomes (continued)

Reference	Number of Patients (Blood Samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC_{12} Values	Mean Bias	Precision
Salm et al. 1997[10]	37 (129)	ELISA and MEIA vs. HPLC-MS2 Developed by the authors of the study; HPLC-MS tandem mass spectrometry	12-hour trough monitoring; first sample within 1 week of transplant; additional samples collect each month for 4 months	HPLC-MS2 TAC ranged from 1.7 to 26.1 µg/l; ELISA ranged from 1.9 to 24.4 µg/l; MEIA 0.9 to 28.5 µg/l	ELISA vs. HPLC-MS: SE. EST 1.26; MEIA vs. HPLC-MS: SE.EST 2.13	NR	NR	ELISA vs. HPLC-MS: 0.171 (±1.27) MEIA vs. HPLC-MS: 1.78 (±2.24)	Relative difference between assays at 5, 10, 20 µg/l TAC: Reported as 95% CIs: ELISA vs. HPLC-MS 2.9 to 7.9, 7.7 to 12.7, and 17.2 to 22.2 MEIA vs. HPLC-MS 1.7 to 10.2, 7.5 to 16.0, 19.2 to 27.6
Roberts et al. 1995[11]	70 patients (86 whole blood samples)	HPLC-MS vs. FPIA/TDx mono and polyclonal immunoassay	Whole blood samples collected 12 hours after oral dose of CsA were obtained from patients on twice daily CsA (4 to 10 mg/kg)	HPLC-MS and FPIA/TDx monoclonal CsA concentration ranged from 25 to 1,200 µg/L; polyclonal concentrations ranged from <50 to 3,800 µg/L	HPLC vs FPIA/TDx monoclonal immunoassay r2=0.91; HPLC values were always lower than the FPIA/TDx monoclonal with a mean difference of -109 µg/L (standard deviations [SD] 99); HPLC vs. FPIA/TDx polyclonal r2=0.98.	NR	NR	HPLC values was always lower than the FPIA/TDx monoclonal with a mean difference of -109 µg/L (standard deviations [SD] 99)	The within assay coefficient of variance varied from 4.0% to 7.0% and the between assay variance varied from 5.0% to 7.0%.

AUC=area under the curve; CEDIA=cloned enzyme donor immunoassay; CI=confidence interval; CMIA=chemiluminescent microparticle immunoassay; CsA=cyclosporine; CV=coefficients of variance; ELCIA=electrochemiluminescence immunoassay; ELISA=enzyme-linked immunosorbent assay; EMIT= enzyme multiplied immunoassay; FPIA=fluorescence polarization immunoassay; HPLC=high performance liquid chromatography; LC-MS/MS=liquid chromatography-mass spectrometry; LC/MS/MS=liquid chromatography-tandem mass spectrometry; LoA=limits of agreement; HPLC-MS=high performance liquid chromatography-mass spectrometry; MEIA=microparticle enzyme immunoassay; ng/mL=nanogram/milliliter; NR=not reported; RMSE=root mean squared error; SE. EST=standard error of the estimate; TAC=tacrolimus; µg/l=micrograms per liter

Table C-5. Adverse events

Reference	Number of Patients	Bacterial Infection	Cytomegalovirus	Biopsy Proven Nephrotoxicity	New Onset Diabetes	Tremor
Borrows et al. 2006[4]	MEIA: 40 HPLC-MS: 40	MEAI: 11 patients (32.5%) HPLC-MS: 11 patients (32.5%)	MEIA: 2 patients (5.0%) HPLC-MS: 0 patients	MEAI: 6 (15%) HPLC-MS: 7 (17.5%)	MEIA; 1 patient (2.5%) HPLC-MS: 0 patients	MEIA: 2 patients (5.0%) HPLC-MS: 2 patients (5.0%)

HPLC=high performance liquid chromatography mass spectrometry; MEIA=microparticle enzyme immunoassay

Table C-6. Risk of bias assessment of clinical outcomes

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar in terms of demographic and clinical factors (e.g. kidney function) at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which the patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Overall Risk of Bias
Borrows et al. 2006[4]	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	Low

NR=not reported

Table C-7. Risk of bias assessment of analytical validity studies

Author, Year	Were the tests under evaluation described in sufficient detail to permit replication of the tests?	Were the testing results interpreted by blinded interpreters?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Has the issue of cross-reactivity been thoroughly evaluated?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established (across operators/ instruments/ reagent lots/ different days of the week/ different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
Leung et al. 2014[1]	Yes	NR	Yes	Yes	NR	Yes	Yes	No
Shipkova et al. 2014[2]	Yes	NR	No	Yes	NR	Yes	Yes	Yes
Westley et al. 2007[3]	Yes	NR	Yes	Yes	NR	Yes	NR	No
Chan et al. 2005[5]	Yes	NR	Yes	No	NR	NR	NR	No
Butch et al. 2004[6]	Yes	NR	No	Yes	Yes	Yes	No	No
Staatz et al. 2002[7]	No	NR	No	No	NR	NR	NR	No
Hamwi et al. 1999[8]	Yes	NR	No	Yes	Yes	Yes	No	No
Schutz et al. 1998[9]	Yes	NR	Yes	NR	Yes	Yes	Yes	No
Salm et al. 1997[10]	Yes	NR	No	No	NR	NR	NR	No
Roberts et al. 1995[11]	Yes	NR	No	No	Yes	NR	NR	No

Appendix D. Evidence Tables for Key Question 2

Table D-1. Study characteristics

Reference	Country	Type of Study (n)	Immunosuppressive Regimen	Monitoring Procedure	Assay Type	Target CNI Level	Outcomes	Followup
Kyllonen & Salmela 2006[12]	Finland	RCT (154)	CsA, steroids and MMF	Patients randomized to C0 or C2 monitoring for first 3 weeks post-transplant; C0 monitoring only starting week 4	FPIA	By day 5 post-transplant C0 250 µg/mL (range 200 to 300) C2 1,700 µg/mL (range 1,500 to 2,000)	C0 and C2 levels, serum creatinine, BPAR, and adverse events	12 months
Paydas et al. 2005[13]	Turkey	Retrospective comparative trial (37)	CsA, prednisone and MMF or AZA	C0 and C2 levels evaluated local hospital from month 1 to month 36 post-transplant; C2 blood samples taken 2 hours ±15 mins	Cobas Integra (Roche)	C0 after 1 year: <200 ng/mL C2 after 1 year: 800 ng/mL	C0 and C2 levels, serum creatinine levels, creatinine clearance levels, cholesterol	36 months
Praditpornsilpa et al. 2005[14]	Thailand	Historically controlled comparative trial (210)	C0 group: CsA and steroids (100%), AZA (60.2%) or MMF (39.8%) C2 group: CsA and steroids (100%), AZA (79.5%), MMF (20.5%)	NR	NR	CsA C0 at 12 and 24 months: 220±42 and 167±44 ng/mL CsA C2 at 12 and 24 months: 1,000±177 and 814±15 ng/mL	C0 and C2 levels, serum creatinine level and incident of BPAR	24 months
Birsan et al. 2004[15]	Austria	Historically controlled comparative trial (177)	CsA, steroids and MMF	89 patients managed prospectively by C2 monitoring; blood collected daily at 2 hours post morning dose Patients compared retrospectively to 88 patients managed by C0 monitoring	FPIA	CsA C0: 250±50 ng/mL CsA: 1,500±200ng/mL	BPAR, time to first rejection, incidence of delayed graft function, and discontinuation of study protocol	30 days and 12 months (for some outcomes)

Table D-1. Study characteristics (continued)

Reference	Country	Type of Study (n)	Immunosuppressive Regimen	Monitoring Procedure	Assay Type	Target CNI Level	Outcomes	Followup
Hardinger et al. 2004[16]	USA	Prospective, non-randomized comparative trial (100)	CsA, steroids and MMF or AZA	NR	FPIA	CsA C2: 1,000 to 1,200 ng/mL months 0 to 3 and 600 to 1,000 ng/mL thereafter CsA C0: 250 to 350 ng/mL months 0 to 3 and 100 to 250 thereafter	BPAR, renal function, infection, adverse events, and drug costs	6 months
Jirasiritham et al. 2003[17]	Thailand	RCT	CsA regimen	Blood CsA levels monitored bi-weekly	NR	CsA C2: 800 ng/mL with 10% variation CsA C0: 100 to 150 ng/mL	BPAR, nephrotoxicity, need for CsA dose adjustment	3 months

AUC=area under the curve; AZA=azathioprine; BPAR=biopsy proven acute rejection; C0=CsA trough level; C2=2 hour post CsA dosage level; C3=3 hour post CsA dosage level; CNI=calcineurin inhibitor; CsA=cyclosporine; EMIT=enzyme multiplied immunoassay technique; FPIA=fluorescence polarization immunoassay; MMF=mycophenolate mofetil group; NR=not reported; RCT=randomized controlled trial; µg·h/L=micrograms per hour per liter

Table D-2. Study inclusion/exclusion criteria

Reference	Inclusion Criteria	Exclusion Criteria
Kyllonen & Salmela 2006[12]	Adult renal transplant recipients using CsA	Patients who had lost their previous graft within one year for immunologic reasons
Paydas et al. 2005[13]	Adult renal transplant recipients using CsA	Not reported
Praditpornsilpa et al. 2005[14]	Adult renal transplant recipients using CsA	Patients who had vascular or urologic complications post-transplantation.
Birsan et al. 2004[15]	Adult patients who received their first kidney transplant from a cadaveric donor	Multi-organ transplant, human leukocyte antigen-identical donor, kidney from a non-heart beating donor, panel reactive antibody level higher than 50% at any time or higher than 30% at the time of transplantation and the need for plasmapheresis
Hardinger et al. 2004[16]	Adult renal recipients receiving triple immunosuppression with CsA	Patients with a known allergy to CsA or documentation of malignancy within 2 years, with the exception of skin malignancies. Pregnant women or nursing mothers, women of childbearing years not practicing a reliable form of birth control and patients with active infection

ALG=antilymphocyte globulin; ATG=antithymocyte globulin; CsA=cyclosporine; OKT3=orthoclone; PRA=panel reactive antibody

Table D-3. Patient characteristics

Reference	Number of Patients	Mean Age	Percent Male	Percent White	Weight	Percent Live Donor Recipients	Time Since Transplant	Prior Transplant
Kyllonen & Salmela 2006[12]	160 (C0 80 and C2 74)	C0: 51.4 years C2: 49.7 years	C0: 67.5% C2: 71.2%	NR	C0: 72.0 kg C2: 74.9 kg	0%	NR	C0: 2 patients re-transplantation C2: 3 patients re-transplantation
Paydas et al. 2005[13]	37 (C0 25; C2 12)	C0: 32.3 years C2: 35.0 years	C0: 72% C2: 75%	NR	NR	C0: 84% C2: 83%	36 months	NR
Praditpornsilpa et al. 2005[14]	210 (C0 128; C2 82)	C0: 40.8 years C2: 43.1 years	C0: 54.7% C2: 60.3%	All Asian	NR	C0: 28.9% C2: 29.2%	NR	NR
Birsan et al. 2004[15]	177 (C0 88; C2 89)	C0: 48.9 years C2: 51.4 years	C0: 64.8% C2: 68.6%	NR	NR	100%	NR	NR
Hardinger et al. 2004[16]	100 (C0 50; C2 50)	C0: 43 years C2: 51 years	C0: 62% C2: 70%	C0: 86% C2: 84%	C0: 82 kg C2: 86 kg	C0: 48% C2: 40%	NR	C0: 86% first transplant C2: 94% first transplant
Jirasiritham et al. 2003[17]	70 (C0 35; C2 35)	NR	NR	NR	NR	NR	NR	NR

Note: The authors of Jirasiritham et al. reported no significant between group differences in the demographic profiles including: age, sex, donor type, previous episode of acute rejection, CsA nephrotoxicity, duration after kidney transplantation, and basic maintenance immunosuppressants. CsA=cyclosporine; C0=CsA trough level; C2=2 hour post CsA dosage level; kg=kilogram
NR=not reported

Table D-4. Primary clinical outcomes

Reference	Number of Patients	Mean Baseline CNI Level	Followup Mean CNI Level	Percent Above/Below Target Level CNI	Patient and Graft Survival	Mean Serum Creatinine	Graft Dysfunction	Mean Total Cholesterol
Kyllonen & Salmela 2006[12]	160 (C0 80; C2 74)	NR	Over 21 days: CsA C0 level: 235 (224 to 245) µg/mL CsA C2 level: 1,645 (1,574 to 1,716) µg/mL Mean CsA dose: C0 4.9 mg/kg C2 7.6 mg/kg	NR	At 12 months: C0: 98.7% patient, 92.5% graft C2: 100.0% patient, 94.6% graft	Mean at 3 months: C0: 107.1 µmol/L C2: 109.2 µmol/L	Total BPAR C0: 6 patients (7.5%) and C2: 8 patients (10.8%); no difference in CsA level between rejectors and non-rejectors; DGF C0: 25 (31%); C2: 23 (31%)	NR

Table D-4. Primary clinical outcomes (continued)

Reference	Number of Patients	Mean Baseline CNI Level	Followup Mean CNI Level	Percent Above/Below Target Level CNI	Patient and Graft Survival	Mean Serum Creatinine	Graft Dysfunction	Mean Total Cholesterol
Paydas et al. 2005[13]	37 (C0 25; C2 12)	C0: 251.44±143.33 ng/mL C2: 1,382.85±536.29 ng/mL	At 36 months: C0: 128.03±69.49 ng/mL C2: 715.84±226.58 ng/mL p<0.001	NR	NR	Baseline: C0: 1.17±0.32 mg/Dl C2: 0.97±0.29 At 36 months: C0: 1.46±0.52 C2: 0.99±0.13; p=0.039 CrCl – Baseline: C0: 72.32±23.10 mL/min C2: 78.73±22.42 At 36 months: C0: 55.15±19.21 C2: 84.65±14.97 (p<0.001)	CAN developed in 13 C0 patients and 1 C2 (p=0.013)	At 36 months: C0: 234.94±48.93 C2: 206.57±38.08
Praditpornsilpa et al. 2005[14]	210 (C0 128; C2 82)	C0: 332±109 ng/mL C2: 1,447±208 ng/mL	C0:167±44 ng/mL C2: 814±115 ng/mL	NR	NR	At 6 months, patients with C2 level >1,300 ng/mL had higher serum creatinine levels than patients with C2 <1,100 ng/mL (1.96±0.29 vs. 1.37±0.34, p<0.001); no significant differences at months 12 and 24	BPAR: C0: 7 (6.0%) C2: 9 (10%), no significant difference	NR

Table D-4. Primary clinical outcomes (continued)

Reference	Number of Patients	Mean Baseline CNI Level	Followup Mean CNI Level	Percent Above/Below Target Level CNI	Patient and Graft Survival	Mean Serum Creatinine	Graft Dysfunction	Mean Total Cholesterol
Birsan et al. 2004[15]	177 (C0 88; C2 89)	Level not reported	Level not reported Mean daily dose 1.7 to 2.0 times higher in C2 group compared to C0 group	At followup (30 days): 10.11% of patients did not reach target CsA (1,500 ng/mL)	100% for patient and graft in both groups	No significant difference in serum creatinine at 30 days post-transplant; at one year no significant difference in mean creatinine clearance	C0: 45.4% (n=40) pts. Received treatment for rejection; C2: 28.1% (n=25) received treatment (p=0.017) Banff grade I or higher: C0: 20.45%; C2:13.48% (p=0.318)	NR
Hardinger et al. 2004[16]	100 (C0 50; C2 50)	At 1 month: C0: 289±126 mg/dL C2: 1,141±316 mg/dL Significant difference (p<0.05)	At 3 months: C0: 177±60 mg/dL C2: 805±mg/dL At 6 months: C0: 160±60 mg/dL C2: 575±202 mg/dL Dose at 6 months: C0: 273± mg/dL C2: 199±73 mg/dL Significant difference (p<0.001)	NR	100% patient and graft for both groups	At 6 months: C0: 1.5±0.5 mg/dL C2: 1.5±0.6 mg/mL	C0: 3 patients experienced rejections (6.0%) C2: 2 patients experienced rejection (4.0%)	At baseline: C0: 160±46 C2: 170±44 At 6 months: C0: 177±35 C2: 191±48
Jirasiritham et al. 2003[17]	70 (C0 35; C2 35)	Conversion to C2: CsA C0: 128 ng/mL C0 only: CsA C0: 156 ng/mL	C2 after conversion: 856 ng/mL C0: 137 ng/mL	C2 group: 12 (34.3%) patients needed reductions in CsA dosage and 2 (5.7%) needed increases to obtain the C2 target level; vs. C0 group: 17 (49%) needed increases in dose and 5 (15%) decreases in dose; p=0.02	100% both groups	NR	Group 1 (C2) 0 BPAR; Group 2 C0 only) 1 BPAR 0 Nephrotoxicity in both groups	NR

BPAR=biopsy proven acute rejection; C0=CsA trough level; C2=2 hour post CsA dosage level; C3=3 hour post CsA dosage level; Cr/Cl=creatinine clearance; CsA=cyclosporine; DGF=delayed graft function; mg/Dl=milligrams per deciliter; mL/min=milliliter per minute; ng/mL=nanogram per milliliter; NR=not reported; µg/L=micrograms per liter; µg/mL=micrograms per milliliter; µmol/L=micromoles per liter

Table D-5. Adverse events and withdrawal

Reference	Adverse Events	Withdrawal or Discontinuation of CNI
Kyllonen & Salmela 2006[12]	No difference between C0 and C2 for infections, vomiting, heartburn, upper and lower gastrointestinal symptoms, headache, diarrhea, vertigo, fatigue, insomnia, neurological symptoms, cardiac symptoms, or NODM Significantly more patients in C2 group (9) compared to C0 (2) experienced tremor ($p<0.05$)	5 patients withdrew due to discomfort with repeated blood samples
Birsan et al. 2004[15]	NR	16.8% (25 patients) in C2 group and 11.4% (10 patients) in C0 group switched to tacrolimus due to acute rejection (n=17), CsA toxicity (n=8), slow/low absorbers (n=5) or other (n=5)
Hardinger et al. 2004[16]	No serious fungal or viral infections (including CMV) during study period; NODM occurred in 1 patient in each group, and 20% of patients in C2 group and 27% in C0 group required treatment of new onset hypercholesterolemia	14% (7 patients) in C2 group switched to TAC (3 hirsutism, 2 hemolytic uremic syndrome, and 2 acute rejection); 10% (5 patients) switched to TAC in C0 group (2 for hirsutism and 3 for acute rejection)

C0=CsA trough level; C2=2 hour post CsA dosage level; C3=3 hour post CsA dosage level; CMV=cytomegalovirus; CNI=calcineurin inhibitor; CsA=cyclosporine; NODM: new onset diabetes mellitus; NR=not reported; TAC=tacrolimus

Table D-6. Risk of bias assessment for RCTs addressing Key Question 2

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar in terms of demographic and clinical factors (e.g., kidney function) at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both study groups?	Were outcome assessors blinded to the group to which the patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study groups?	Overall Risk of Bias
Kyllonen & Salmela 2006[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Jirasiritham et al. 2003[17]	NR	NR	Yes	NR	Yes	NR	Yes	Yes	NR	Low

NR=not reported

Table D-7. Risk of bias assessment for non-randomized comparative trials addressing Key Question 2

Author, Year	Did the study employ any other methods to enhance group comparability?	Was the process of assigning patients to groups made independently from physician and patient preference?	Were groups similar in terms of demographic and clinical factors (e.g., kidney function) at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was the comparison of interest prospectively planned?	Was compliance with treatment ≥85% in both study groups?	Were outcome assessors blinded to the group to which the patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study groups?	Overall Risk of Bias
Paydas et al. 2005[13]	No	No	Yes	NR	No	Yes	No	Yes	Yes	Yes	Low
Praditpornsilpa et al. 2005[14]	No	No	Yes	NR	No	Yes	No	Yes	Yes	Yes	Low
Birsan et al. 2004[15]	No	No	Yes	NR	Yes	Yes	No	Yes	Yes	No	Low
Hardinger et al. 2004[16]	No	No	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Low

NR=not reported

Appendix E. Evidence Tables for Key Questions 3a and 3b

Table E-1. Study design characteristics of minimization studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Cai et al. 2014[18]	Minimization of CsA	CsA (75–90 ng/mL, C2 target 350–400 ng/mL) + EC-MPS (1,440 mg) + STER (5 mg)	CsA (150–180 ng/mL, C2 target 700–800 ng/mL) + EC-MPS (1,440 mg) + STER (5 mg)	NR	NR	3 days	Excluded age>72, PRA >20%
Chadban et al. 2014[19]	Minimization of CsA	CsA (50% reduction from baseline) + EVR (6–10 ng/mL) + withdrawal of EC-MPS and STER	CsA (C2 target 500–700 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	2 weeks	Excluded age>65, PRA >50%, retransplants
Muhlbacher et al. 2014[20]	Minimization of CsA	CsA (75–100 ng/mL) + SRL (4–12 ng/mL) + STER	CsA (150–200 ng/mL) + SRL (4–12 ng/mL)+ STER	IA	NR	1 month	Excluded PRA >50%, African-Americans
Oh et al. 2014[21]	Minimization of CsA	CsA (25–50 ng/mL) + EVR (3–8 ng/mL) + STER (prednisolone ≥5 mg)	CsA (100–200 ng/mL) + EC-MPS (720–1,440 mg) + STER (prednisolone ≥5 mg)	NR	Basiliximab	1 month	Excluded age>65, retransplants
Bechstein et al. 2013[22]	Minimization of TAC	TAC (3–7 ng/mL) + SRL (8–15 ng/mL) + STER (prednisone 5 mg)	TAC (8–12 ng/mL) + SRL (5–10 ng/mL) + STER (prednisone 5 mg)	HP/LC-MS	Not used	Within 7 days	Excluded PRA>50% and "Patients at high risk"
Chadban et al. 2013[23]	Minimization of CsA	CsA (C2 target 550–700 ng/mL) + EC-MPS (1,440 mg) + STER	CsA (C2 target 850–1,000 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	4 weeks	Excluded age>75, PRA>50%, retransplants
Cibrik et al. 2013[24]	Minimization of CsA	CsA (25–50 ng/mL) + EVR (3–8 ng/mL OR 6–12 ng/mL) + STER	CsA (100–250 ng/mL) + MPA (1,440 mg) + STER	LC-MS	Basiliximab	24 hours	Excluded age>70, PRA>50%
Takahashi et al. 2013[25]	Minimization of CsA	CsA (25–50 ng/mL) + EVR (3–8 ng/mL) + STER (minimum 5 mg)	CsA (100–250 ng/mL) + MMF (2,000 mg) + STER (minimum 5 mg)	NR	Basiliximab	24 hours	Excluded age>65, PRA >50%, delayed graft function

Table E-1. Study design characteristics of minimization studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Chan et al. 2012[26]	Minimization of TAC	TAC (3–6 ng/mL) + EC-MPS (1,440 mg) + STER (prednisone 5 mg)	TAC (8–12 ng/mL) + EC-MPS (1,440 mg) + STER (prednisone 5 mg)	NR	Basiliximab	24 hours	Excluded age>70, PRA >20%, retransplants
Kamar et al. 2012[27]	Minimization of TAC	TAC (2–4.5 ng/mL) + EC-MPS (1,440 mg) + STER	TAC (5.5–10 ng/mL) + EC-MPS (720 mg) + STER	IA	NR	Minimum 1 year	Excluded age>75
Langer et al. 2012[28]	Minimization of TAC	TAC (1.5–3 ng/mL) + EVR (3–8 ng/mL) + STER (prednisone 5 mg)	TAC (4–7 ng/mL) + EVR (3–8 ng/mL) + STER (prednisone 5 mg)	LC-MS	Basiliximab	3 months	Excluded PRA >50%, retransplants
Paoletti et al. 2012[29]	Minimization of CsA	CsA (50–100 ng/mL) + EVR (3–8 ng/mL) + STER	CsA (125–250 ng/mL) + MMF (dose not reported) + STER	NR	Basiliximab	Immediate	Excluded age>70
Bertoni et al. 2011[30]	Minimization of CsA	CsA (C2 target 250–300 ng/mL) + EVR (8–12 ng/mL) + STER	CsA (C2 target 500–700 ng/mL) + EC–MPS (1,440 mg) + STER	NR	Basiliximab	Immediate	Excluded age>65, PRA >50%, retransplants
Holdaas et al. 2011[31]	Minimization of CNI	CNI (CsA or TAC) at 70%–90% reduction from baseline + EVR (3–8 ng/mL) + prior therapy (could include MPA, AZA, and/or STER)	CsA (C2 target ≥400 ng/mL) or TAC (≥4 ng/mL) + prior therapy (could include MPA, AZA, and/or STER)	NR	NR	Minimum 6 months	NR
Xu et al. 2011[32]	Minimization of CNI	CNI (CsA 80–120 ng/mL or TAC 3–6 ng/mL) + MMF (1,500 mg) + STER (prednisone 5 mg)	CNI (CsA 120–180 ng/mL or TAC 6–10 ng/mL) + MMF (1,500 mg) + STER (prednisone 5 mg)	IA	NR	Immediate	Excluded retransplants
Etienne et al. 2010[33]	Minimization of CsA	CsA (2.0–2.6 mg h/L) + MMF (2,000 mg)	CsA (3.5–4.8 mg h/L) + MMF (2,000 mg)	LC-MS	rATG (72%) Interleukin-2 receptor antagonists (28/%)	1 year	Excluded age>75, PRA>80%
Fangmann et al. 2010[34]	Minimization of CsA	CsA (50–75 ng/mL) + MMF (2,000 mg) + STER (minimum 5mg)	CsA (100–150 ng/mL) + MMF (2,000) + STER (minimum 5mg)	NR	Daclizumab in intervention group	Shortly after transplant	Excluded PRA >20%, retransplants

Table E-1. Study design characteristics of minimization studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Gaston et al. 2009[35]	Minimization of CNI	CNI (CsA 95–145 ng/mL or TAC 3–5 ng/mL) + MMF (≥1.3 µg/mL for patients on CsA or ≥1.9 µg/mL for patients on TAC) + STER	CNI (CsA 190–220 ng/mL or TAC 6–8 ng/mL) + either MMF (≥1.3 µg/mL for patients on CsA or ≥1.9 µg/mL for patients on TAC) or MMF fixed dose (mean 1,834 mg for patients on CsA or mean 1,663 mg for patients on TAC) + STER (both comparison groups)	NR	"administered according to center practice"	Within 24 hours	NR
Salvadori et al. 2009[36]	Minimization of CsA	CsA (C2 target 150–300 ng/mL) + EVR (8–12 ng/mL) + STER (prednisone 5 mg)	CsA (C2 target 350–450 ng/mL) + EVR (3–8 ng/mL) + STER (prednisone 5 mg)	NR	Basiliximab	Within 24 hours	Excluded age>65, PRA >50%
Spagnoletti et al. 2009[37]	Minimization of CNI and switch from CsA to TAC	TAC (5–8 ng/mL) + MMF (1,000 mg) + STER	CsA (C2 target 150–400 ng/mL) + EVR (3–8 ng/mL) + STER	NR	Basiliximab	24 hours	NR
Bolin et al. 2008[38]	Minimization of TAC	TAC (3.0–5.9 ng/mL) + continuation of previous adjunct therapy (AZA, MMF, SRL, and/or STER)	TAC (6.0–8.9 ng/mL) or CsA (50–250 ng/mL) + continuation of previous adjunct therapy (AZA, MMF, SRL, and STER)	NR	NR	Minimum 6 months	NR
Chan et al. 2008[39]	Minimization of TAC	TAC (3–6 ng/mL) + EVR (3–12ng/mL) + STER (≥5 mg)	TAC (7–10 ng/mL) + EVR (3–12ng/mL) + STER (≥5 mg)	LC-MS	Basiliximab	Within 24 hours	Excluded age>65, PRA >50%
Budde et al. 2007[40]	Minimization of CsA	CsA (C2 target 550–700 ng/mL) + EC-MPS (1,440 mg) + STER	CsA (C2 target 850–1,000 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	2 months	Excluded age>75, PRA >50%
Cibrik et al. 2007[41]	Minimization of CsA	CsA (C2 target 600–800 ng/mL) + EC-MPS (1,440 mg; high risk patients could receive up to 2,160 mg) + STER	CsA (C2 target 800–1,000 ng/mL) + EC-MPS (1,440 mg; high risk patients could receive up to 2,160 mg) + STER	HPLC or IA	Basiliximab	2 months	Excluded age>70, PRA >20%
Ekberg et al. 2007a[42]	Minimization of CsA	CsA (50–100 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	NR	Daclizumab in intervention group	Immediate	Excluded PRA >20%, retransplants
Ekberg et al. 2007b[43]	Minimization of CNI	CsA (50–100 ng/mL) or TAC (3–7 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	IA	Daclizumab in intervention group	Immediate	Excluded age>75, PRA >20%

Table E-1. Study design characteristics of minimization studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Ghafari et al. 2007[44]	Minimization of CsA	CsA (125–175 ng/mL) + MMF (30 mg/kg) + STER (methylprednisone 0.10 mg)	CsA (150 ng/mL) + MMF (30 mg/kg) + STER (methylprednisone 0.10 mg)	IA	None used	Immediate	Excluded retransplants
Hernandez et al. 2007[45]	Minimization of CNI	CsA (125–175 ng/mL) or TAC (7–10 ng/mL) + MMF (2,000 mg) + STER (prednisone 5–10 mg)	CsA (150–200 ng/mL) + AZA (1.5 mg/kg/day) + STER (prednisone 5–10 mg)	IA	Basiliximab (intervention group) and ATG (control group)	Within 24 to 48 hours	Excluded PRA >30%
Frimat et al. 2006[46] Frimat et al. 2010[47]	Minimization of CsA	CsA (reduced by 50% from previous regimen) + MMF (2,000 mg) + STER	CsA with or without AZA + STER	NR	NR	Minimum 1 year	All patients had chronic allograft dysfunction; excluded age>65
Tang et al. 2006[48]	Minimization of CsA	CsA (80–100 ng/mL) + "other medications according to centre protocol" including MMF, AZA	Conversion from previous CsA regimen to TAC (6–8 ng/mL)	IA	NR	Minimum 12 months	All patients had chronic allograft dysfunction; excluded age>65
Vathsala et al. 2005[49]	Minimization of CsA	CsA (90–110 ng/mL) + Alemtuzumab (20 mg twice)	CsA (180–225 ng/mL) + AZA (1 mg/kg/day) + STER	NR	Alemtuzumab in intervention group	Immediate	Excluded age>65, PRA >85%
Lo et al. 2004[50]	Minimization of TAC	TAC (5–10 ng/mL) + SRL (10–15 ng/mL) + STER (prednisone 5 mg)	TAC (10–15 ng/mL) + SRL (5–10 ng/mL) + STER (prednisone 5 mg)	IA (TAC) HPLC (SRL)	rATG	Within 2 days	NR
Nashan et al. 2004[51]	Minimization of CsA	CsA (50–100 ng/mL) + EVR (3 mg) + STER (prednisone ≥ 5 mg)	CsA (125–250 ng/mL) + EVR (3 mg) + STER (prednisone ≥ 5 mg)	NR	Basiliximab	Within 24 hours	Excluded age>65, PRA >80%
Stoves et al. 2004[52]	Minimization of CsA	CsA (75–100 ng/mL) + MMF (2,000 mg)	CsA ("per unit protocol"; data not reported) + AZA	NR	NR	Minimum 6 months	All patients had chronic allograft dysfunction
Pascual et al. 2003[53]	Minimization of CsA	CsA (50–150 ng/mL) + MMF (1,500–2,000 mg) + STER (prednisone 7.5–10 mg)	CsA (100–300 ng/mL) + MMF (1,500–2,000 mg) + STER (prednisone 7.5–10 mg)	IA	NR	Minimum 12 months	NR

Table E-1. Study design characteristics of minimization studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
de Sevaux et al. 2001[54]	Minimization of CsA	CsA (150 ng/mL) + MMF (2,000 mg) + STER (prednisone 0.1 mg/kg)	CsA (150 ng/mL) + MMF (2,000 mg) + STER (prednisone 0.1 mg/kg)	IA	NR	48 hours	NR

AR=acute rejection; AZA=azathioprine; ATG/rATG=antithymocyte globulin; CNI=calcineurin inhibitors; CsA=cyclosporine; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; h/L=hectoliter; HPLC=high performance liquid chromatography; IA=immunoassay; LC=liquid chromatography; mg=milligram; mg/kg=milligram per kilogram; MMF=mycophenolate mofetil group; MPA=medroxyprogesterone acetate; MPS=mycophenolate sodium; MS=mass spectrometry; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; SRL=sirolimus; STER=steroid; TAC=tacrolimus; µg/mL=micrograms per milliliter

Table E-2. Study population characteristics of minimization studies

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Cai et al. 2014[18]	Minimization of CsA	China	90	90	Living related Living unrelated	34 vs. 33	73%	NR	12% vs. 18%
Chadban et al. 2014[19]	Minimization of CsA	Asia Australia New Zealand	30	47	Deceased: 52 Living related: 51 Living unrelated: 23	43 vs. 46	71%	51%	NR
Muhlbacher et al. 2014[20]	Minimization of CsA	Europe	178	179	Deceased: 314 Living related: 39 Living unrelated: 2	47 vs. 46	68%	94%	6% vs. 9%
Oh et al. 2014[21]	Minimization of CsA	Korea	67	72	Deceased: 25 Living related: 79 Living unrelated: 35	42 vs. 47	60%	NR	NR
Bechstein et al. 2013[22]	Minimization of TAC	Europe	63	65	Deceased	48 vs. 45	65%	100%	30% vs. 31%
Chadban et al. 2013[23]	Minimization of CsA	Australia	42	33	Deceased: 41 Living: 34	44 vs. 48	63%	85%	NR
Cibrik et al. 2013[24]	Minimization of CsA	Worldwide	556	277	Deceased: 385 Living related: 311 Living unrelated: 135	46 vs. 45 vs. 47	67%	68%	NR
Takahashi et al. 2013[25]	Minimization of CsA	Japan	61	61	Deceased: 2 Living related: 79 Living unrelated: 41	42 vs. 39	68%	NR	NR
Chan et al. 2012[26]	Minimization of TAC	USA	151	141	Deceased, living related and living unrelated	48 vs. 45	69%	86%	24% overall

Table E-2. Study population characteristics of minimization studies (continued)

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Kamar et al. 2012[27]	Minimization of TAC	France	45	47	Deceased: 88 Live unrelated: 4	51 vs. 54	66%	96%	NR
Langer et al. 2012[28]	Minimization of TAC	Worldwide	107	117	Deceased: 160 Living related: 39 Living unrelated: 25	45 vs. 47	57%	83%	NR
Paoletti et al. 2012[29]	Minimization of CsA	Italy	10	20	Deceased	47 vs. 51	70%	NR	NR
Bertoni et al. 2011[30]	Minimization of CsA	Italy	56	50	NR	46 vs. 50	NR	NR	23% vs. 41%
Holdaas et al. 2011[31]	Minimization of CNI	Worldwide	144	123	Deceased: 158 Living: 107 Missing: 4	50 vs. 48	65%	72%	NR
Xu et al. 2011[32]	Minimization of CNI	China	20	18	Living related	29 vs. 32	82%	NR	NR
Etienne et al. 2010[33]	Minimization of CsA	France	106	102	Deceased	52 vs. 51	69%	98%	3% vs. 4%
Fangmann et al. 2010[34]	Minimization of CsA	Europe	75	73	Deceased	52 vs. 54	62%	NR	27% vs. 27%
Gaston et al. 2009[35]	Minimization of CNI	USA	243	477	Deceased: 361 Living related: 206 Living unrelated: 148	48 vs. 49 (MMF concentration controlled) vs. 50 (MMF fixed dose)	67%	69%	NR
Salvadori et al. 2009[36]	Minimization of CsA	Italy	143	142	Deceased: 278 Living: 7	45 vs. 46	40%	64%	23% vs. 31%
Spagnoletti et al. 2009[37]	Minimization of CNI and switch from CsA to TAC	Italy	30	30	Deceased	NR	NR	100%	NR
Bolin et al. 2008[38]	Minimization of TAC	USA	100	223	Deceased: 168 Live: 155	50 vs. 48 (TAC) vs. 51 (CsA)	66%	73%	NR
Chan et al. 2008[39]	Minimization of TAC	USA	49	43	Deceased: 31 Living related: 36 Living unrelated: 25	47 vs. 47	62%	66%	DGF Intervention: 4 (8.2%) of Control: 4 (9.3%)
Budde et al. 2007[40]	Minimization of CsA	Germany	44	45	Deceased: 64 Living: 35	45 vs. 49	69%	93%	NR

Table E-2. Study population characteristics of minimization studies (continued)

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Cibrik et al. 2007[41]	Minimization of CsA	USA	75	66	Deceased: 73 Living related: 62 Living unrelated: 29	49 vs. 47	61%	61%	NR
Ekberg et al. 2007a[42]	Minimization of CsA	Worldwide	183	173	Deceased: 277 Living related: 47 Living unrelated: 32	48 vs. 49	65%	84%	20% vs. 22%
Ekberg et al. 2007b[43]	Minimization of CNI	Worldwide	CsA: 399 TAC: 401	390	Deceased: 764 Living related: 345 Living unrelated: 79	47 (CsA) vs. 45 (TAC) vs. 46	65%	93%	NR
Ghafari et al. 2007[44]	Minimization of CsA	Iran	42	48	Living	49 vs. 47	47%	NR	NR
Hernandez et al. 2007[45]	Minimization of CNI	Spain	160	80	Deceased	48 vs. 47 vs. 47	64%	NR	32% vs. 40% vs. 27%
Frimat et al. 2006[46] Frimat et al. 2010[47]	Minimization of CsA	France	70	31	Deceased Living	44 vs. 45	81%	NR	NR
Tang et al. 2006[48]	Minimization	Hong Kong	18	16	Deceased: 26 Living related: 8	45 vs. 48.5	62%	NR	NR
Vathsala et al. 2005[49]	Minimization of CsA	Asia	20	10	Deceased: 14 Living related: 14 Living unrelated: 2	Median: 38 vs. 41	50%	NR	20% vs. 10%
Lo et al. 2004[50]	Minimization of TAC	USA	23	16	Deceased	Median: 49 vs. 46	59%	21%	57% vs. 63%
Nashan et al. 2004[51]	Minimization of CsA	USA Europe	58	53	Deceased: 89 Living related: 17 Living unrelated: 5	44 vs. 46	61%	75%	NR
Stoves et al. 2004[52]	Minimization of CsA	United Kingdom	13	16	NR	NR	NR	NR	NR
Pascual et al. 2003[53]	Minimization of CsA	USA	32	32	Deceased: 37 Living related: 18 Living unrelated: 9	47 vs. 45	75%	64%	0 vs. 3%
de Sevaux et al. 2001[54]	Minimization of CsA	Netherlands	152	161	Deceased: 233 Living: 80	49 vs. 48	62%	NR	NR

CNI=calcineurin inhibitors; CsA=cyclosporine; DGF=delayed graft function; MMF=mycophenolate mofetil group; NR=not reported; TAC=tacrolimus

Table E-3. Clinical outcomes of minimization studies

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Cai et al. 2014[18]	1 year	Mean CsA C2 level: 363±149 ng/mL vs. 739±174 ng/mL	12/90 vs. 15/90 (BPAR, graft loss, patient death, lost to follow up)	10 vs. 12	1 vs. 2	1 vs. 1	63±19 vs. 59±15 (Cockcroft-Gault)	137±176 vs. 142±118	19 vs. 20	NR
Chadban et al. 2014[19]	1 year		11 vs. 8	5 vs. 6 Banff (year not reported): Grade 1A: 5 vs. 3 Grade 1B: 0 vs. 4 Grade 2A: 0 vs. 0 Grade 2B: 0 vs. 1 Grade 3: 0 vs. 1 Unspecified: 0 vs. 2	0 vs. 2	0 vs. 1	NR	NR	NR	NR
Muhlbacher et al. 2014[20]	1 year	Mean CsA level lower in intervention group, specific data NR	NR	20/178 vs. 29/179, p=NS Bannf 97: Grade 1A: 9 vs. 14; Grade 1B: 3 vs. 9; Grade 2A: 4 vs. 3; Grade 2B: 3 vs. 2; Grade 3: 1 vs. 1	6 months: 0 vs. 2 12 months: 1 vs. 2	6 months: 0 12 months: 0 vs. 3	6 months: 55.9±1.67 vs. 51.0±1.67, p=0.04 12 months: 57.8±1.78 vs. 49.5±2.46, p<0.01 (Nankivell)	6 months: 1.79 vs. 2.00, p=0.03 12 months: 1.75 vs. 1.97, p<0.01	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Oh et al. 2014[21]	1 year	Mean trough level: 54.1 ng/mL vs. 120.4 ng/mL Intervention group mean above target range, but lower than control group (p<0.01)	NR	5/67 vs. 8/72	0 vs. 1	0	5 months: 66.7±17.5 vs. 59.5±16.4, p=0.02 12 months: 69.5±17.2 vs. 61.2±17.9, p=0.01 (MDRD)	NR	NR	NR
Bechstein et al. 2013[22]	6 months	Mean TAC levels achieved throughout study	NR	11/63 vs. 5/65 Banff 97: Grade 1A: 4 vs. 4; Grade 2A: 5 vs. 0; Grade 2B: 2 vs. 1	4 vs. 1	3 vs. 2	63.8±17.3 vs. 52.7±18.9, p=0.005 (Nankivell)	136 vs. 153, p=NS	NR	NR
Chadban et al. 2013[23]	1 year	Mean C2 target achieved in both groups: 640±216 vs. 876±250	6 months: 15/42 vs. 10/33 12 months: 18 vs. 12 (BPAR, graft loss, patient death)	6 months: 12 vs. 8 12 months: 15 vs. 10	6 month: 3 vs. 1 12 months: 3 vs. 1	6 months: 0 vs. 1 12 months: 0 vs. 1	6 months: 63.2±24.3 vs. 60.2±17.6 12 months: 60.7±20.1 vs. 63.3±17.5 (Cockcroft-Gault)	NR	8 vs. 13	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Cibrik et al. 2013[24]	2 years	Mean trough CsA level: 42.7 ng/mL (low EVR) vs. 47.9 ng/mL (high EVR) vs. 120.5 ng/mL (standard dose EVR and CsA)	91/277 (low EVR) vs. 75/279 (high EVR) vs. 76/277 (standard) (BPAR, graft loss, patient death, lost to follow-up)	55 (low EVR) vs. 42 (high EVR) vs. 53 (standard) Banff 03: Grade 1A: 25 vs. 20 vs. 27 Grade 1B: 13 vs. 10 vs. 8 Grade 2A: 10 vs. 9 vs. 17 Grade 2B: 2 vs. 4 vs. 3 Grade 3: 2 vs. 0 vs. 2	16 (low EVR) vs. 17 (high EVR) vs. 11 (standard)	9 (low EVR) vs. 10 (high EVR) vs. 8 (standard)	Median: 54.0 vs. 55.4 vs. 51.4 (MDRD) Median: 64.7 vs. 64.4 vs. 62.1 (Nankivell) Median: 67.4 vs. 66.4 vs. 65.0 (Cockcroft-Gault)	NR	80 vs. 85 vs. 57, p<0.05 compared with both groups	NR
Takahashi et al. 2013[25]	1 year	Median CsA trough level: 63.0 ng/mL vs. 130.5 ng/mL, but "a higher proportion of EVR patients were above the cyclosporine target range versus the MMF group"	7/61 vs. 7/61 (BPAR, graft loss, patient death, lost to follow-up)	3 vs. 5 Banff 03: Grade 1A: 2 vs. 2 Grade 1B: 0 vs. 1 Grade 2A: 1 vs. 2	0	0	62.09±18.99 vs. 56.34±15.23, p=NS (MDRD)	NR	9 vs. 8	NR
Chan et al. 2012[26]	6 months	24%–52% of intervention group exceeded trough target; 31%–53% of control group below trough target	22/151 vs. 16/141 (BPAR, graft loss, patient death)	16 vs. 14 Banff 97: Grade 1A: 6 vs. 6 Grade 1B: 2 vs. 3 Grade 2A: 5 vs. 3 Grade 2B: 2 vs. 2 Missing: 1 vs. 0	6 vs. 2	1 vs. 2	63.6±4.8 vs. 61.0±4.9, p=NS (Nankivell) 62.1 vs. 59.5, p=NS (Cockcroft-Gault)	144 vs. 135, p=NS	4 vs. 4	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Kamar et al. 2012[27]	6 months	Mean TAC levels for intervention group not reached until 3 months into study	NR	0	0	0	6 months: 49.1±11.1 vs. 44.7±11.5, p=0.07 Change from baseline: 2.48±0.95 vs. -0.48±0.93, p=0.03 (aMDRD)	6 months: 137±33 vs. 147±39, p=0.30 Change from baseline: 6.2±2.8 vs. 4.3±2.8, p=0.01	2 vs. 1	NR
Langer et al. 2012[28]	1 year	56% of intervention group exceeded trough target; 30% of control group not in target range	5/107 vs. 4/117 (BPAR, graft loss, patient death, lost to follow-up) Treatment/Efficacy failure: 29 vs. 14 [12 months]	2 vs. 1	1 vs. 1	2 vs. 1	57.1±19.5 vs. 51.7±20 (MDRD) 67.1 ±23.0 vs. 61.1±19.7 (Cockcroft-Gault)	1.44±0.51 mg/dL vs. 1.60±0.71 mg/dL	19 vs. 12	NR
Paoletti et al. 2012[29]	1 year	NR	NR	1/10 vs. 2/20	0	0	NR	Change from baseline: -0.04±0.4 mg/dL vs. -0.08±0.3 mg/dL, p=NS	0 vs. 1	NR
Bertoni et al. 2011[30]	1 year	NR	NR	11/56 vs. 9/50	3 vs. 6	NR	81.64±32.67 vs. 62.62±22.81, p<0.01 (Cockcroft-Gault)	NR	5 vs. 3	Mean length of hospital stay: 24.77±11.13 days vs. 24.57±12.20 days
Holdaas et al. 2011[31]	2 years	CsA dose reduced by mean 78%, TAC by mean 66%	17/144 vs. 11/123	8 vs. 3 Grade 1A: 4 vs. 1 Grade 2A: 2 vs. 0 Grade 3: 1 vs. 0 Missing: 1 vs. 2	8 vs. 6	3 vs. 0	52.0±18.7 vs. 53.6±21.1 (Cockcroft-Gault)	171±102 vs. 168±81	25 vs. 5	NR
Xu et al. 2011[32]	1 year	NR	NR	4/20 vs. 3/18	0 vs. 1	0 vs. 1	59.4±27.4 vs. 58.9±29.8	No significant difference	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Etienne et al. 2010[33]	2 years	Intervention group mean trough levels were significantly lower than control group, p<0.01	19/106 vs. 37/101, p<0.01 (BPAR, graft loss, CsA toxicity, >15% increase in mean SCr)	6 vs. 3 Bannf 97: Grade 1: 0 vs. 2 Grade 2: 5 vs. 1 Grade 3: 1 vs. 0	0 vs. 1	NR	Change from baseline: 0.57±8.80 vs. -4.27±8.06	Change from baseline: 0±0.34 mg/dL vs. 0.18±0.82 mg/dL	NR	CAN: 2 vs. 2
Fangmann et al. 2010[34]	1 year	NR	NR	2/75 vs. 19/73, p<0.05	5 vs. 15	2 vs. 5	34.1±17.4 vs. 29.4±16.5, p<0.05 (Cockcroft-Gault)	NR	4 vs. 8	NR
Gaston et al. 2009[35]	1 year	Mean target for intervention group not achieved, but was statistically significantly lower than both comparison groups	55/243 vs. 137/477 (BPAR, graft loss, patient death, lost to follow-up, withdrawn consent)	15 vs. 46	5 vs. 8	4 vs. 8	Change from baseline: 12.3% vs. 5.4% vs. 8.2% (Nankivell)	NR	18 vs. 68, p<0.05	NR
Salvadori et al. 2009[36]	6 months	Mean CsA levels exceeded target range in intervention group	NR	16/142 vs. 20/143	3 vs. 14, p<0.01	2 vs. 2	6 months: 60.0±16.4 vs. 62.3±15.6 12 months: 63.8±18.3 vs. 64.8±17.7 (Nankivell) 6 months: 57.8±19.3 vs. 59.9±18.6 12 months: 61.3±22.0 vs. 62.5±20.7 (Cockcroft-Gault)	6 months: 1.63 vs. 1.56 mg/dL 12 months: 1.55 vs. 1.51 mg/dL	33 vs. 25	NR
Spagnoletti et al. 2009[37]	6 months	NR	NR	NR	1/30 vs. 2/30	0	NR	NR	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Bolin et al. 2008[38]	1 year	24% of intervention group exceeded TAC trough target; 34% of control group lower than TAC trough target	NR	2/100 vs. 2/112 (standard TAC) vs. 3/111 (standard CsA) Grade 1A 0 vs. 1 vs. 1 Grade 1B: 1 vs. 1 vs. 1 Grade 2A: 1 vs. 0 vs. 1	0 vs. 1	0	Median change from baseline: 1.65 vs. -0.60 (standard TAC) vs. -0.80 (standard CsA) (Cockcroft-Gault)	Median change from baseline: -0.10 mg/L vs. 0	1 vs. 8 vs. 7	NR
Chan et al. 2008[39]	6 months	Intervention: Mean TAC trough levels higher than target; at 6 months intervention TAC level = 7.1, control TAC level = 7.2	7/49 vs. 7/43	7 vs. 6 Banff 97: Grade 1: 5 vs. 4 Grade 2A: 1 vs. 1 Unknown: 1 vs. 1	0 vs. 1	0	75.3±16.6 vs. 72.5±15.2 (Nankivell) 82.8±26.8 vs. 77.2±21.8 (Cockcroft-Gault)	112±31 mg/dL vs. 127±50 mg/dL	5 vs. 4	CAN: 0 vs. 2
Budde et al. 2007[40]	1 year	Intervention group achieved target (mean: 688±238 ng/mL) at 12 months Control group below target (mean: 781±215 ng/mL) at 12 months Intervention group 10-15% below control group	6 months: 7/44 vs. 8/45 1 year: 8 vs. 9 (BPAR, graft loss, patient death)	6 months: 6 vs. 8 1 year: 7 vs. 8 Banff 97: Grade 1: 4 vs. 7 Grade 2: 3 vs. 2 (1 patient had two episodes)	0	6 months: 2 vs. 0 1 year: 3 vs. 1	6 months: 61.5±3.7 vs. 55.3±3.2 1 year: 59.7±4.1 vs. 56.6±3.2 (Cockcroft-Gault)	6 months: 145 vs. 160 1 year: 1 62 vs. 163	5 vs. 3	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Cibrik et al. 2007[41]	1 year	From months 3–12, 18%-37% of intervention group achieved target C2, 26%-40% of control group achieved target C2	13/75 vs. 16/66 (BPAR, graft loss, patient death)	11 vs. 16 Banff 97: Grade 1A: 8 vs. 10 Grade 1B: 2 vs. 3 Grade 2A: 0 vs. 1 Grade 2B: 1 vs. 2	1 vs. 1	1 vs. 0	79.2 vs. 71.0, p<0.05 Change from baseline: 9.6 vs. 6.6 (Cockcroft-Gault)	132 vs. 141	NR	NR
Ekberg et al. 2007a[42]	1 year	9% of intervention group patients exceeded target level some time during the study	NR	46/183 vs. 48/173	6 vs. 9	4 vs. 5	50.9±6.4 vs. 48.6±6.9 (Cockcroft-Gault)	1.5 mg/dL vs. 1.6 mg/dL	NR	NR
Ekberg et al. 2007b[43]	1 year	Mean trough levels were within the target levels for all groups	Low dose CsA: 81 Low dose TAC: 49 Standard dose CsA: 89 (Graft loss, death, use of additional immuno-suppression, discontinuation of study medication for >14 consecutive or 30 cumulative days)	6 months: Low dose CsA: 87 Low dose TAC: 45 Standard dose CsA: 94 1 year: Low dose CsA: 109 Low dose TAC: 62 Standard dose CsA: 117	Low dose CsA: 23 Low dose TAC: 14 Standard dose CsA: 32	Low dose CsA: 7 Low dose TAC: 11 Standard dose CsA: 13	Low dose CsA: 59.4±25.1 (Cockcroft-Gault) 50.2±23.1 (MDRD) Low dose TAC: 65.4±27.0 (Cockcroft-Gault) 54.3±23.9 (MDRD) Standard dose CsA: 57.1±25.1 (Cockcroft-Gault) 46.2±23.1 (MDRD)	NR	NR	NR
Ghafari et al. 2007[44]	2 years	NR	NR	20/42 vs. 25/48	8 vs. 10	1 vs. 1	NR	No significant difference (data not reported)	3 vs. 3	No difference in length of hospital stay or readmissions

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Hernandez et al. 2007[45]	2 years	Low dose CsA trough level: 133±61 Low dose TAC trough level: 7.5±2 Standard CsA trough level: 126±46	NR	Low dose CsA: 11 Banff 97: Grade 1: 6 Grade 2: 4 Grade 3: 1 Low dose TAC: 13 Grade 1: 7 Grade 2: 4 Grade 3: 2 Standard CsA: 12 Grade 1: 9 Grade 2: 2 Grade 3: 1	Low dose CsA: 4 vs. 4 Low dose TAC: 7 vs. 4	Low dose CsA: 4 vs. 3 Low dose TAC: 8 vs. 3	Low dose CsA: 66±20 (Cockcroft-Gault) 56±21 (Jelliffe 2) 59±24 (MDRD) Low dose TAC: 70±27 (Cockcroft-Gault) 59±20 (Jelliffe 2) 62±22 (MDRD) Standard dose CsA: 58±14 (Cockcroft-Gault) 51±17 (Jelliffe 2) 52±18 (MDRD)	NR	Low dose CsA: 10 Low dose TAC: 6 Standard dose CsA: 10	CAN: 1 in low dose CsA group
Frimat et al. 2006[46] Frimat et al. 2010[47]	5 years	Intervention group trough levels were lower than control group at study completion: 71 vs. 117 ng/mL	NR	2 years: 0 5 years: 0 vs. 1	2 years: 1/70 vs. 1/31 5 years: 2 vs. 2	2 years: 0 5 years: 0 vs. 1	2 years: 56.2±16.6 vs. 45.1±16.4 (Cockcroft-Gault) 5 years: 51.8±20.2 vs. 41/3±18.9	NR	NR	NR
Tang et al. 2006[48]	15 months	NR	NR	0/18 vs. 2/16	0 vs. 2	NR	39.8±20.2 vs. 32.9±11.1	NR	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Vathsala et al. 2005[49]	6 months	Median CsA trough level: 119 vs. 172 ng/mL	NR	5/20 vs. 2/10 Banff 97: Border line: 2 vs. 1 Grade 1: 2 vs. 1 Grade 2A: 1 vs. 0	3 vs. 0	1 vs. 0	No significant difference (data not reported)	No significant difference (data not reported)	5 vs. 1	NR
Lo et al. 2004[50]	6 months	Mean TAC 12 hour trough: 4.4±1.2 vs. 15.8 ±9.3	4/23 vs. 1/23 (BPAR, graft loss, patient death)	1/23 vs. 1/16	4/23 vs. 1/16	0/23 vs. 1/16	NR	1.6±0.9 mg/dL vs. 1.9±0.7 mg/dL, p=NS	6 vs. 9	Median hospital stay: 6 days (range 4–27) vs. 7 days (range 4–15) All-cause hospital re-admission: 44% vs. 56%
Nashan et al. 2004[51]	3 years	Over 3 years, mean daily CsA dose significantly lower in intervention group (3.2 mg/kg vs. 2.0 mg/kg) Over first 6 months, CsA trough levels were 35% lower in intervention than control group	6 months: 2/53 vs. 8/58, p<0.05 1 year: 5 vs. 15, p<0.05 3 years: 10 vs. 19, p<0.05 (BPAR, graft loss, patient death, lost to follow-up)	6 months: 2 vs. 8 1 year: 4 vs. 9 3 years: 7 vs. 10	6 months: 1 vs. 1 1 year: 1 vs. 3 3 years: 2 vs. 7	6 months: 0 1 year: 0 vs. 2 3 years: 2 vs. 5	6 months: 59.7±11.7 vs. 51.1±15.0, p<0.01 1 year: 60.9±11.3 vs. 53.5±12.1, p<0.01 3 years: 56.6±20.0 vs. 51.7±13.1, p=NS (Nankivell)	NR	19 vs. 29, p<0.05	CAN: 1 year: 0 vs. 3 3 years: 7 vs. 11
Stoves et al. 2004[52]	6 months	Median CsA trough level: 99 ng/mL vs. 163 ng/mL Mean dose reduction from baseline: 24%	6 (3-patient death, 3-lost to follow-up)	0	0	3 (during 9 months)	Median change over baseline: 2.5 vs. -0.7, p=0.05	NR	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Pascual et al. 2003[53]	6 months	Mean CsA trough level at 6 months: 86 vs. 193 ng/mL	NR	0/32 vs. 0/32	0	0	64.6±20 vs. 61.0±19 Change from baseline: 7.1, p=0.01	1.33±0.26 vs. 1.40±0.25 Change from baseline: -0.06, p=0.06	NR	NR
de Sevaux et al. 2001[54]	6 months	Median CsA trough level at 3 months: 154 vs. 248	NR	29/152 vs. 36/161, p=NS Banff 93: Grade 1: 16 vs. 20 Grade 2: 10 vs. 16 Grade 3: 3 vs. 0	8 vs. 14, p=NS	3 vs. 5	3 months: 66±36 vs. 59±32 6 months: 69±31 vs. 65±28	3 months: 142 vs. 151 6 months: 136 vs. 141	20 vs. 27	NR

aMDRD=abbreviated modification of diet in renal disease; BPAR=biopsy proven acute rejection; CAN=chronic allograft nephropathy; C2=2 hour post CsA dosage level; CsA=cyclosporine; EVR=everolimus; MDRD=modification of diet in renal disease; mg/dL=milligram per deciliter; MMF=mycophenolate mofetil group; ng/mL=nanogram per milliliter; NR=not reported; NS=not significant; SCr=serum creatinine; TAC=tacrolimus

Table E-4. Adverse events reported in minimization studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Cai et al. 2014[18]	Minimization of CsA	NR	NR	Gastroenteritis: 5/90 vs. 4/90 UTI: 0 vs. 2	NR	NR	No difference	No difference for GI, anemia, leukopenia
Chadban et al. 2014[19]	Minimization of CsA	12 vs. 13	0 vs. 1	CMV: 2 vs. 4 All infections: 18 vs. 34	NR	0 vs. 1	No difference between groups for cholesterol	No difference between groups for GI, anemia
Muhlbacher et al. 2014[20]	Minimization of CsA	NR	1/178 (lymphoma-like reaction) vs. 2/179 (lymphoma-like reaction and renal carcinoma)	CMV: 13 vs.14 Pneumonia: 10 vs. 16 Herpes: 10 vs. 9 Candida: 11 vs. 17 UTI: 47 vs. 45 Wound infection: 13 vs. 4	NR	NR	No difference for BP, cholesterol; control group had higher triglycerides	No difference for anemia, leukopenia, edema
Oh et al. 2014[21]	Minimization of CsA	NR	NR	All infections: 36/67 vs. 60/72	NR	NR	No difference	No difference for GI, respiratory, vascular, nervous system
Bechstein et al. 2013[22]	Minimization of TAC	9/63 vs. 8/65	1 (basal cell carcinoma) vs. 1 (post-transplant lymphoma)	CMV: 3/63 vs. 5/65 Candida: 2 vs. 4 Sepsis: 1 vs. 3 Pneumonia: 2 vs. 6 UTI: 8 vs. 3 Herpes: 1 vs. 1 Lymphocele: 6 vs. 7 Dehiscence: 3 vs. 1 Wound infection: 1 vs. 1	NR	NR	No difference	No difference for GI, anemia, leukopenia, edema
Chadban et al. 2013[23]	Minimization of CsA		4 total (2 skin carcinoma, 1 post-transplant lymphoma, 1 Hodgkins; “no significant difference between groups”)	30 vs. 26 (details not reported)	NR	NR	NR	No difference for GI

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Cibrik et al. 2013[24]	Minimization of CsA	28/274 vs. 40/278 vs. 20/273	9 vs. 7 vs. 13	CMV infection: 4 vs. 1 vs. 25 CMV syndrome: 4 vs. 5 vs. 15 CMV disease: 2 vs. 3 vs. 8 BK virus: 2 vs. 4 vs. 13 UTI: 66 vs. 73 vs. 74 Upper respiratory tract: 54 vs. 49 vs. 63	8 vs. 21 vs. 11	NR	No difference for BP; total cholesterol and triglycerides lower in intervention group	No difference for GI; stomatitis higher in intervention group; leukopenia lower in intervention group
Takahashi et al. 2013[25]	Minimization of CsA	7 vs. 3	2 (thyroid cancer; b-cell lymphoma) vs. 0	CMV infection: 3 vs. 21 CMV test positive: 4 vs. 19 Nasopharyngitis: 21 vs. 26	NR	8 vs. 5	No difference	Nephrotoxicity: 13 vs. 6; No difference in GI, anemia, headache, stomatitis, hirsutism; edema higher in intervention group
Chan et al. 2012[26]	Minimization of TAC	19/114 vs. 33/119	1/151 (renal cell carcinoma) vs. 2/141 (basal cell carcinoma, malignant melanoma)	Bacterial: 59 vs. 65 Viral: 33 vs. 27	NR	NR	NR	No difference for GI, anemia, edema
Kamar et al. 2012[27]	Minimization of TAC	NR	NR	Any: 10 vs. 9 Bronchitis: 3 vs. 1 Pneumocystis jirovecii: 1 vs. 0 UTI: 1 vs. 2 Gastroenteritis: 1 vs. 4 Pyelonephritis: 0 vs. 1 Infected hygroma: 0 vs. 1	NR	NR	No difference for cholesterol, triglycerides	No difference for GI, anemia, edema
Langer et al. 2012[28]	Minimization of TAC	14/109 vs. 18/119	NR	CMV: 2 vs. 3 BK: 5 vs. 1 UTI: 36 vs. 42 Bacterial: 39.4% vs. 35.3% Viral: 9.2% vs. 10.9% Fungal: 5.9% vs. 7.3%	NR	12 vs. 9	No difference for cholesterol	No difference for GI, anemia, edema, nervous system, hypokalemia, hyperkalemia

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Paoletti et al. 2012[29]	Minimization of CsA	2/10 vs. 2/20	NR	NR	NR	3 vs. 2	No difference for BP; cholesterol and triglycerides higher in intervention group	NR
Bertoni et al. 2011[30]	Minimization of CsA	NR	NR	CMV infection: 26% vs. 27% (specific data not reported) CMV disease rate: 8% vs. 10%	NR	519.7±77.31 mg/24 hours vs. 296.7±33.42 mg/24 hours, p=0.01	No difference for cholesterol; systolic BP lower in intervention group	NR
Holdaas et al. 2011[31]	Minimization of CNI	7/144 vs. 4/123	11 vs. 7	Any infection: 89 vs. 75 UTI: 24 vs. 13 Upper respiratory tract: 16 vs. 16	NR	19 vs. 11	No difference for triglycerides or hypertension; cholesterol and hyperlipidemia higher in intervention group	Higher incidence of edema, pyrexia, rash in intervention group; no difference for GI, anemia
Xu et al. 2011[32]	Minimization of CNI	NR	NR	Pulmonary: 1 vs. 3 (1 of these confirmed CMV)	NR	None	No difference for BP	Nephrotoxicity: 0/20 vs. 5/18 (p<0.05)
Etienne et al. 2010[33]	Minimization of CsA	2 vs. 7	3 (1 skin cancer, 2 solid carcinoma) vs. 7 (5 skin cancer, 2 solid carcinoma)	Bacterial: 22/106 vs. 19/101 Viral: 4/106 vs. 9/101)	NR	NR	No difference for cholesterol, triglycerides; BP lower in intervention group	Nephrotoxicity: 5/106 vs. 12/101 (p=0.08)
Fangmann et al. 2010[34]	Minimization of CsA	NR	0	CMV: 19/75 vs. 15/73 Herpes: 6 vs. 11 Other viral: 9 vs. 4 Bacterial: 40 vs. 39 Fungal: 9 vs. 3	9 vs. 5; type unspecified	NR	No difference for BP and lipids	Neurological: 17 vs. 13 Metabolic: 22 vs. 14 GI: 13 vs. 10 Hematological: 14 vs. 19
Gaston et al. 2009[35]	Minimization of CNI	2 (CsA) and 32 (TAC) vs. 3 (CsA) and 41 (TAC)	2 (CsA) and 3 (TAC) vs. 1 (CsA) and 12 (TAC)	All “opportunistic infections”: 22/238 vs. 55/471 CMV: 12/238 vs. 32/471 BK virus infection: 4/238 vs. 15/471 BK virus nephropathy: 0/238 vs. 8/471	NR	NR	No difference for hypertension, hyperlipidemia	No difference for GI, leukopenia

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Salvadori et al. 2009[36]	Minimization of CsA	7/142 vs. 3/143	2 vs. 2 (1 basal cell carcinoma, 1 epithelioma, 2 unspecified)	All infections: 88 vs. 96 CMV requiring hospitalization: 3 vs. 2 Pneumonia requiring hospitalization: 3 vs. 2	"Cardiac disorders": 7 vs. 4	NR	No difference	No difference for GI, anemia, edema, vascular, metabolic
Spagnoletti et al. 2009[37]	Minimization of CNI and switch from CsA to TAC	1/30 vs. 4/30	NR	NR	NR	NR	No difference for BP; higher mean serum cholesterol and higher serum triglycerides for intervention group	NR
Bolin et al. 2008[38]	Minimization of TAC	3/63 vs. 2/66 (standard TAC) vs. 3/66 (standard CsA)	9/100 vs. 6/112 (standard TAC) vs. 3/111 (standard CsA) (mainly basal and squamous cell carcinoma)	CMV: 0 vs. 3 (standard TAC) vs. 1 (standard CsA); 3 of these were donor derived All other infections: 16 vs. 30 (standard TAC) vs. 22 (standard CsA)	NR	NR	No difference for cholesterol, triglycerides	No difference for overall quality of life; lower GI distress for intervention group
Chan et al. 2008[39]	Minimization of TAC	8/21 vs. 4/17	0 vs. 1 (adrenal neoplasm)	9/49 vs. 8/43 Pneumonia: 1 vs. 0 UTI: 6 vs. 7 Wound infection: 2 vs. 1	NR	0 vs. 1	Hypercholesterolemia: 5 (10.2%) vs. 4 (9.3%) Hypertriglyceridemia: 1 (2.0%) vs. 3 (7.0%) No difference for lipids, triglycerides	No difference for GI, edema, hematological Peripheral edema: 23 (47%) vs. 9 (20.9%)
Budde et al. 2007[40]	Minimization of CsA	NR	NR	All infections (details NR): 30/44 vs. 35/45	NR	NR	No difference for BP	No difference for GI
Cibrik et al. 2007[41]	Minimization of CsA	4 (groups not specified)	2 (groups not specified)	Candidiasis: 9/75 vs. 8/66 Oral candidiasis: 13 vs. 9 UTI: 9 vs. 21 Upper respiratory: 13 vs. 6	NR	NR	NR	No difference for GI, anemia, leukopenia, hirsutism
Ekberg et al. 2007a[42]	Minimization of CsA	NR	5 (including 1 post-transplant lymphoproliferative disorder) vs. 1	CMV: 20 vs. 24 Candida: 8 vs. 16 Herpes simplex: 13 vs. 11 Herpes zoster: 12 vs. 9 UTI: 8 vs. 7	NR	NR	No difference	No difference for lymphocele, hypertension

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Ekberg et al. 2007b[43]	Minimization of CNI	Low dose CsA: 17 Low dose TAC: 34 Standard dose CsA: 23	Low dose CsA: 4 (Kaposi's sarcoma, transitional-cell, renal-cell, basal-cell) Low dose TAC: 8 (3 basal-cell, 2 renal-cell, prostate, cerebral lymphoma, squamous cell) Standard dose CsA: 5 (2 basal-cell, squamous-cell, oral mucosa, Kaposi's sarcoma)	Low dose CsA: All "opportunistic infections" (per study designation): 93 CMV: 45 Candida: 19 Herpes simplex: 15 All other infections: 206 UTI: 97 Pneumonia: 5 Nasopharyngitis: 32 Low dose TAC: All "opportunistic infections" (per study designation): 80 CMV: 39 Candida: 12 Herpes simplex: 18 All other infections: 211 UTI: 95 Pneumonia: 13 Nasopharyngitis: 32 Standard dose CsA: All "opportunistic infections" (per study designation): 100 CMV: 55 Candida: 29 Herpes simplex: 21 All other infections: 208 UTI: 109 Pneumonia: 18 Nasopharyngitis: 22	Low dose CsA: 15 Low dose TAC: 13 Standard dose CsA: 15	Low dose CsA: 8 Low dose TAC: 20 Standard dose CsA: 9	No difference in hypercholesterolemia, hyperlipidemia, hypertriglyceridemia between low and standard dose CsA groups; hypercholesterolemia and hyperlipidemia lower in low dose TAC group	No difference for anemia, leukopenia, edema, pyrexia, lymphoceles, disorders of the nervous system, respiratory system, or vascular system; higher incidence of serious GI events in low dose TAC group
Ghafari et al. 2007[44]	Minimization of CsA	No difference between groups (data not specified)	NR	No difference between groups (data not specified)	No difference between groups (data not specified)	NR	Lower hypertension, higher triglycerides in intervention group	Nephrotoxicity: 1 vs. 4; No difference for GI, hematological

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Hernandez et al. 2007[45]	Minimization of CNI	Low dose CsA: 9/58 vs. 10/55 Low dose TAC: 15/55 vs. 10/55	Low dose CsA: 2 vs. 3 Low dose TAC: 2 vs. 3	Low dose CsA: CMV: 19 vs. 40 Pneumonia: 4 vs. 1 UTI: 25 vs. 23 Other viral: 8 vs. 5 Low dose TAC: CMV: 29 vs. 40 Pneumonia: 3 vs. 1 UTI: 28 vs. 23 Other viral: 5 vs. 5	NR	No difference	No difference for cholesterol, triglycerides	Nephrotoxicity: Low dose CsA: 12 vs. 18 Low dose TAC: 20 vs. 18 No difference for GI, anemia, leukopenia
Frimat et al. 2006[46] Frimat et al. 2010[47]	Minimization of CsA	NR	2 years: 3/70 vs. 2/33 5 years: 3 vs. 3	2 years: All infections: 33 vs. 10 Herpes simplex: 2 vs. 0 Herpes zoster: 3 vs. 1 Other herpes: 1 vs. 0 Bronchitis: 13 vs. 3 5 years: All infections: 6 vs. 2 Opportunistic infections: 0	2 years: NR 5 years: 4 vs. 1	2 years: 39% vs. 62%	NR	2 years: Higher incidence of GI, anemia in intervention group; no difference for leucopenia 5 years: no difference for GI, urinary system, kidney, thoracic, respiratory, mediastinal disorders
Tang et al. 2006[48]	Minimization	NR	NR	UTI: 0/18 vs. 1/16 Gastroenteritis: 1 vs. 0 Herpes zoster: 0 vs. 1	NR	No difference	No difference	NR
Vathsala et al. 2005[49]	Minimization of CsA	NR	0	CMV: 9/20 vs. 2/10 Herpes zoster: 1 vs. 0 Septicimia: 2 vs. 0 Pneumonia: 6 vs. 0 UTI: 9 vs. 6	NR	NR	No difference for BP	NR
Lo et al. 2004[50]	Minimization of TAC	5/23 vs. 4/16	0	1 CMV in control group	1 idiopathic pulmonary hemorrhage in control group	NR	No difference for cholesterol, triglycerides	Nephrotoxicity: 7 cases in control group; No difference for leukopenia

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Nashan et al. 2004[51]	Minimization of CsA	NR	3 vs. 2	CMV: 0 vs. 1 Herpes simplex: 0 vs. 3 Bacterial: 24 vs. 23 Fungal: 5 vs. 5 Pneumocystis carinii: 0 vs. 1	5 vs. 2 (myocardial infarction, angina pectoris, sudden death)	13 vs. 5	No difference	Nephrotoxicity: 2/58 vs. 6/53; No difference for GI
Stoves et al. 2004[52]	Minimization of CNI	0	NR	UTI: 1 (control group)	NR	NR	No difference for BP, lipids	NR
Pascual et al. 2003[53]	Minimization of CsA	NR	0	0	NR	NR	No difference	NR
de Sevaux et al. 2001[54]	Minimization of CsA	6 vs. 6	0	CMV: 35 vs. 31 UTI: 38 vs. 34 Oral candidiasis: 12 vs. 14	NR	NR	No difference	Nephrotoxicity: 4/152 vs. 13/161, p=0.06

BK=BK polyomavirus; BP=blood pressure; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporine; GI=gastrointestinal; NR=not reported; UTI=urinary tract infection; TAC=tacrolimus

Table E-5. Study design characteristics of conversion studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Budde et al. 2015[55] Budde et al. 2015[56]	Conversion from CNI to EVR	EVR (6-10 ng/mL) + EC-MPS ≥ 720 mg/day + STER	CsA (80-150 ng/mL) or TAC (5-10 ng/mL)	NR	NR	3 months	NA
Rostaing et al. 2015[57]	Conversion from CsA to EVR	EVR (6-10 ng/mL) + EC-MPS (720 mg) + STER	CsA (100-150 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	3 months	Excluded age >70 and PRA >20%
Bansal et al. 2013[58]	Conversion from Control Regimen to SRL	SRL (8–15 ng/mL)	CsA (150–250 ng/mL) or TAC (6–8 ng/mL) + MMF + STER (prednisone 5 mg)	HPLC	NR	3 months	Only live donors included
Chhabra et al. 2013[59]	Conversion from TAC to SRL	SRL (5–8 ng/mL) + MMF (2,000 mg)	TAC (6–8 ng/mL) + MMF (2,000 mg)	HPLC	Alemtuzumab	1 year	NA
Silva et al. 2013[60]	Conversion from TAC to SRL	SRL (8 and 12 ng/mL) + EC-MPS (1,440 mg) + STER	TAC (5 and 15 ng/mL) + EC-MPS (1,440 mg) + STER	HPLC	Basiliximab	3 months	NA

Table E-5. Study design characteristics of conversion studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Budde et al. 2015[61] Budde et al. 2012[62] Budde et al. 2011[63]	Conversion from CsA to EVR	EVR (6–10 ng/mL) + MPS (1,440 mg) + STER (prednisolone ≥5 mg)	CsA (100–150 ng/mL) + MPS (1,440 mg) + STER (prednisolone ≥5 mg)	NR	Basiliximab	4.5 months	NA
Mjornstedt et al. 2015[64] Mjornstedt et al. 2012[65]	Conversion from CsA to EVR	EVR (6–10 ng/mL) + EC-MPS (1,440 mg) + STER	CsA (C2 target 600–800 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	7 weeks	NA
Nafar et al. 2012[66]	Conversion from CsA to SRL	SRL (8–15 ng/mL) + CsA changed to MMF in the 4th month + STER (5 mg) administered during the first 3 months	CsA (150–250 ng/mL) + MMF (1,000–2,000 mg) + STER	NR	NR	4 months	Excluded DGF
Heilman et al. 2011[67]	Conversion from TAC to SRL	SRL (8 ng/mL) + MMF (1,000 mg) + rapid STER withdrawal	TAC (5–8 ng/mL) + MMF (2,000 mg) + rapid STER withdrawal	NR	rATG	1 month	NA
Holdaas et al. 2011[31]	Conversion from CNI to EVR	Conversion from CNI to EVR (8–12 ng/mL) + prior therapy (could include MPA, AZA and/or STER)	CsA (C2 target ≥400 ng/mL) or TAC (≥4 ng/mL) + prior therapy (could include MPA, AZA, and/or STER)	NR	NR	Minimum 6 months	NA
Rostaing et al. 2011[68]	Conversion from CNI to belatacept	Belatacept (10–12 µg/mL) + MMF, MPS, SRL or AZA	CsA (100–250 ng/mL) or TAC (5–10 ng/mL) + MMF, MPS, SRL or AZA	NR	NR	During 28-day period	NA
Weir 2011[69]	Conversion from CNI to MMF	SRL (2.9 mg at 24 months) + MMF + STER	CsA (240.4 mg at 24 months) or TAC (7.1 mg at 24 months) + MMF + STER	NR	ATG: 105 Basiliximab: 80 Daclizumab: 32 Muromonab-CD3: 1	30–180 days	NA
Guba et al. 2010[70]	Conversion from CsA to SRL	SRL (5–10 ng/mL) + MMF (1,500 mg) + STER	CsA (100–150 ng/mL) + MMF (2,000 mg) + STER	NR	ATG-F	10–24 days	Excluded PRA >30% and persistent DGF
Bemelman et al. 2009[71]	Conversion from CsA to MPS or EVR	MPS (>2 mg) or EVR (target AUC 12–150 mg h/L) + STER	CsA (target AUC 120–3,250 µg h/L) + STER	NR	Basiliximab	6 months	Excluded PRA >50%

Table E-5. Study design characteristics of conversion studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Schena et al. 2009[72]	Conversion from CNI to SRL	SRL + MMF or AZA +STER	CsA or TAC + MMF or AZA +STER	HPLC (SRL) IA (CNI)	NR	Minimum 6 months	NA
Lebranchu et al. 2011[73] Lebranchu 2009[74]	Conversion from CsA to SRL	SRL (5–10 ng/mL) + MMF + STER	CsA (C2 target 500–800 ng/mL) + MMF +STER	NR	Daclizumab	3 months	Excluded PRA >30%, living donors
Durrbach et al. 2008[75]	Conversion from CsA to SRL	SRL (10–20 ng/mL) + MMF + STER	CsA (75–200 ng/mL) + MMF + STER	NR	ATG	NR	Excluded PRA >50%
Barsoum et al. 2007[76]	Conversion from CsA to SRL	SRL (11.4±2.6 ng/mL) + MMF + STER	CsA (811±137.5 ng/mL) + MMF + STER	NR	NR	3 months	Excluded deceased donors
Dudley et al. 2005[77]	Conversion from CsA to MMF	MMF (2,000 mg) + STER (10 mg)	CsA (≥80 ng/mL)	NR	NR	10 weeks	NA
Watson et al. 2005[78]	Conversion from CNI SRL	SRL (5–15 ng/mL) + AZA or mycophenolic acid + STER	CsA or TAC + AZA or mycophenolic acid + STER	HPLC	NR	Minimum 6 months	NA
Bakker et al. 2003[79]	Conversion from CsA to AZA	AZA (2–2.5 mg/kg) + STER	CsA (5 mg/kg) + STER	NR	NR	3 months	NA
MacPhee et al. 1998[80]	Conversion from CsA to AZA	AZA (1.6–1.9 mg/kg) + STER (10 mg)	CsA (2.5–3 mg/kg) + STER (10 mg)	IA/FPIA	NR	1 year	NA
Hilbrands et al. 1996[81]	Conversion from CsA to AZA	AZA (3 mg/kg) + STER (10 mg)	CsA (100–200 ng./mL) + STER withdrawn	NR	ATG	3 months	NA

AZA=azathioprine; ATG=antithymocyte globulin; C2=2 hour post CsA dosage level; CNI=calcineurin inhibitors; CsA=cyclosporine; DGF=delayed graft function; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; FPIA=fluorescence polarization immunoassay; h/L=hectoliter; HPLC=high performance liquid chromatography; IA=immunoassay; mg=milligram; MMF=mycophenolate mofetil group; MPA=medroxyprogesterone acetate; MPS=mycophenolate sodium; NA=not applicable; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; STER=steroid; SRL=sirolimus; TAC=tacrolimus; μg=micrograms

Table E-6. Study population characteristics of conversion studies

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Budde et al. 2015[55] Budde et al. 2015[56]	Conversion from CNI to EVR	Germany	46	47	Deceased: 66 Living related: 19 Living unrelated: 7	51 vs. 50	69%	100%	NR
Rostaing et al. 2015[57]	Conversion from CsA to EVR	France	96	98	Deceased: 174 Living: 20	48 vs. 50	66%	NR	19% vs. 24%
Bensal et al. 2013[58]	Conversion from CNI to SRL	India	31	29	Living	34 vs. 30	87%	100% Asian	NR
Chhabra et al. 2013[59]	Conversion from TAC to SRL	USA	123	64	Deceased: 57 Living related: 76 Living unrelated: 55	49 vs. 49	57%	51%	13% overall
Silva et al. 2013[60]	Conversion from TAC to SRL	Brazil	97	107	Deceased: 146 Living: 151	44 vs. 44	69%	57%	NR
Budde et al. 2015[61] Budde et al. 2012[62] Budde et al. 2011[63]	Conversion from CsA to EVR	Germany	155	146	Deceased: 220 Living related: 57 Living unrelated: 23	46 vs. 46	63%	97%	NR
Mjornstedt et al. 2015[64] Mjornstedt et al. 2012[65]	Conversion from CsA to EVR	Europe	102	100	Deceased: 144 Living: 58	55 vs. 53	71%	99%	NR
Nafar et al. 2012[66]	Conversion from CsA to MMF	Iran	50	50	Living	38 vs. 42	55%	100% (Iranian)	NR
Heilman et al. 2011[67]	Conversion from TAC to SRL	USA	62	60	Deceased	52 vs. 54	62%	77%	9% overall
Holdaas et al. 2011[31]	Conversion from CNI to EVR	Worldwide	127	123	Deceased: 154 Living related: 93 Missing: 3	49 vs. 48	67%	72%	NR
Rostaing et al. 2011[68]	Conversion from CNI to belatacept	France	84	89	Deceased: 86 Living: 83	45 vs. 44	73%	56%	NR
Weir 2011[69]	Conversion of CNI to SRL	USA	148	151	Deceased: 180 Living related: 79 Living unrelated: 40	48 vs. 48	63%	50%	NR

Table E-6. Study population characteristics of conversion studies (continued)

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Guba et al. 2010[70]	Conversion from CsA to SRL	Germany	69	71	Brain death: 125 Living: 15	47 vs. 47	68%	99%	24% overall
Bemelman et al. 2009[71]	Conversion from CsA to MPS or EVR	Netherlands	74 (MPS 36, EVR 38)	39	Deceased: 63 Living: 50	52 (MPS) vs. 49 (EVR) vs. 51 (CsA)	57%	86%	NR
Schena et al. 2009[72]	Conversion from CNI to SRL	Worldwide	555	275	Deceased: 520 Living: 303	44 vs. 43	70%	66%	NR
Lebranchu et al. 2011[73] Lebranchu 2009[74]	Conversion from CsA to SRL	France	95	97	Deceased	46 vs. 47	71%	NR	14% overall
Durrbach et al. 2008[75]	Conversion from CsA to SRL	France	33	36	Living	52 vs. 57	NR	NR	38% overall
Barsoum et al. 2007[76]	Conversion from CsA to SRL	Egypt	76	37	Living	45 vs. 44	65%	NR	29% overall
Dudley et al. 2005[77]	Conversion from CsA to MMF	United Kingdom	73	70	Deceased: 119 Living: 24	43 vs. 45	62%	NR	NR
Watson et al. 2005[78]	Conversion from CNI to SRL	United Kingdom	19	19	Deceased: 28 Living: 10	47 vs. 48	82%	NR	NR
Bakker et al. 2003[79]	Conversion from CsA to AZA	Netherlands	60	68	Deceased	46 vs. 43	62%	NR	NR
MacPhee et al. 1998[80]	Conversion from CsA to AZA	Scotland	102	114	Deceased: 194 Living: 22	41 vs. 39	59%	NR	NR
Hilbrands et al. 1996[81]	Conversion from CsA to AZA	Netherlands	60	60	Deceased	43 vs. 43	63%	NR	NR

CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; MMF=mycophenolate mofetil group; MPS=mycophenolate sodium; NR=not reported; SRL=sirolimus; TAC=tacrolimus

Table E-7. Clinical outcomes of conversion studies

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Budde et al. 2015[55] 1 year followup	1 year	Target C0 CsA 100 to 150 ng/mL (mean 113), TAC 5-10 ng/mL (mean 5.6) EVR: 6 to 10 ng/mL (mean concentration 6.4 ng/mL)	CNI: 5 EVR: 17	CNI: 0 EVR: 0	CNI: 0 EVR: 0	CNI: 1 EVR: 1	CNI: 58.2 ± 16.6 mL/min/Nankivell EVR: 61.6 ± 19.8 mL/min/Nankivell	NR	NR
Budde et al. 2015[56] 5 year followup	5 years	Target C0 CsA 100 to 150 ng/mL (mean 113), TAC 5-10 ng/mL (mean 5.6) EVR: 6 to 10 ng/mL (mean concentration 6.4 ng/mL)	NR	CNI: 0 EVR: 0	CNI: 1 EVR: 3	CNI: 3 EVR: 2	CNI: 60.4 ± 16.8 mL/min/Nankivell EVR: 66.7 ± 17.4 mL/min/Nankivell	NR	NR
Rostaing et al. 2015[57]	1 year	At month 6, 38% of control group below CsA trough target; at month 12, 21% below target. For intervention group, 3% below EVR trough level at 6 months, and 4% below target at 12 months	CsA: 6 EVR: 25	CsA: 5 EVR: 24	CsA: 1 EVR: 5	CsA: 0 EVR: 0	Mean eGFR at 3 months CsA: 50.2±15.3 mL/min/MDRD EVR: 52.1±15.9 mL/min/MDRD Mean eGFR at 1 year: CsA: 53.5±16.9 mL/min/MDRD EVR: 60.1±20.0 mL/min/MDRD	NR	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Bensal et al. 2013[58]	6 months	Target C0 TAC 6 to 8 ng/mL; CsA 150 to 250 ng/mL; SRL 8 to 15 ng/mL	NR	CNI: 2 SRL: 2	Authors report no difference between groups; data not reported	Authors report no difference between groups; data not reported	Mean eGFR CNI: 80.6±16.5 mL/min/MDRD SRL: 88.9±11.8	CNI: 1.14±0.17 mg/dL SRL: 0.99±0.11	SRL group had a mean gain of eGFR of 12 mL/min
Chhabra et al. 2013[59]	2 years	Target C0 TAC 6 to 8 ng/mL SRL C0 6 to 8 ng/mL	NR	TAC: 7 SRL: 4	TAC: 2 SRL: 3	TAC: 0 SRL: 4	Mean eGFR at 12 months TAC: 66.6 mL/min/MDRD SRL: 67.5	NR	NR
Silva et al. 2013[60]	2 years	NR	NR	TAC: 62 SRL: 22	TAC: 4 SRL: 1	TAC: 9 SRL: 3	Mean eGFR TAC: 70.7±25.1 mL/min/MDRD SRL: 66.2±25.3	TAC: 1.3±0.3 mg/dL SRL: 1.4±0.4	NR
Budde et al. 2015[61] 5 year followup	5 years	Target C0 CsA 100 to 150 ng/mL EVR: 6 to 10 ng/mL	CsA: 35 EVR: 48	CsA: 11 EVR: 21	CsA: 3 EVR: 4	CsA: 3 EVR: 4	CsA: 60.9 mL/min/Nankivell (95% CI: 57.3 to 64.4) EVR: 66.2 mL/min/Nankivell (95% 62.8 to 69.6)	NR	NR
Budde et al. 2012[62] 3 year followup	3 years	Target C0 CsA 100 to 150 ng/mL EVR: 6 to 10 ng/mL	CsA: 23 EVR: 46	CsA: 7 EVR: 20	CsA: 1 EVR: 1	CsA: 3 EVR: 3	24 months CsA: 62.4 mL/min/Nankivell (95% CI: 58.7 to 66.1) EVR: 70.0 (95% CI: 66.6 to 73.5) 36 months CsA: 61.0 (95% CI: 56.4 to 65.6) EVR: 68.5 (95% CI: 64.0 to 73.0)	NR	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Budde et al. 2011[63] 1 year followup	1 year	Target C0 CsA 100 to 150 ng/mL EVR: 6 to 10 ng/mL	CsA: 42 EVR: 39	CsA: 22 EVR: 23	CsA: 0 EVR: 0	CsA: 1 EVR: 0	CsA: 61.9 mL/min/Nankivell (95% CI: 59.0 to 64.9) EVR: 71.8 (95% CI: 68.9 to 74.6) Mean difference: -9.8 (95% CI: -12.2 to -7.5, p<0.001)	NR	NR
Mjornstedt et al. 2015[64] 3 year followup	3 year	At months 6 and 12 all patients within C0 target range from EVR (6 to 10 ng/mL) and CsA (117 ng/mL at 6 months; 105 at 12 months)	CsA: 6 EVR: 3	CsA: 10 EVR: 12	CsA: 0 EVR: 0	CsA: 3 EVR: 1	CsA: 46.1 ± 17.0 ml/min; EVR: 48.2 ± 14.7 ml/min	NR	NR
Mjornstedt et al. 2012[65] 1 year followup	1 year	At months 6 and 12 all patients within C0 target range from EVR (6 to 10 ng/mL) and CsA (117 ng/mL at 6 months; 105 at 12 months)	CsA: 12 EVR: 29	CSA: 11 EVR: 28	CsA: 0 EVR: 0	CsA: 2 EVR: 2	CsA: 47.8±15.4 mL/min/ measured GFR EVR: 51.2±14.1	CsA: 132±45 µmol/L EVR: 122±35	NR
Nafar et al. 2012[66]	4 years	SRL target C0 levels 8 ng/mL to 15 ng/mL CsA C0 levels 150 ng/mL to 250 ng/mL	NR	CsA: 9 pts. (34 episodes) SRL: 4 pts. (20 episodes)	Authors report no significant difference between groups; data reported in figure	Authors report no significant difference between groups; data reported in figure	<u>At 1 year</u> CsA: 73.2±19.2 mL/min/ Cockcroft SRL: 82.3±24.3 <u>At 4 years</u> CsA: 70.3±23.6 SRL: 79.8±22.3	<u>At 1 year</u> CsA: 1.4±0.35 mg/dL SRL: 1.26±0.32 <u>At 4 years</u> CsA: 1.57±0.33 SRL: 1.24±0.24	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Heilman et al. 2011[67]	2 years	SRL level at 1 year 9.8±3.6 ng/dL TAC level at 1 year 6.9±4.6 ng/dL	NR	TAC: 3 SRL: 8	At 1 year TAC: 0 SRL: 0 At 2 year TAC: 2 SRL: 1	At 1 year TAC: 0 SRL: 0 At 2 year TAC: 2 SRL: 1	At 1 year TAC: 62.7±26.5 mL/min/ iothalomate clearance SRL: 57.4±20.7 At 2 years TAC: 62.8±21.6 SRL: 64.3±29.0	At 1 year TAC: 1.39±0.81 mg/dL SRL: 1.26±0.37 At 2 years TAC: 1.26±0.36 SRL: 1.39±0.54	Total withdraws TAC: 11 SRL: 39, 23 of which were for drug side effects
Rostaing et al. 2011[68]	1 year	BEL C0 level maintained at 10 to 12 µg/ml; CsA C0 serum level maintained at 100 to 250 ng/ml TAC at 5 to 10 ng/ml	NR	CNI: 0 BEL: 6	CNI: 0 BEL: 0	CNI: 2 BEL: 0	CNI: 56.5±14.42 mL/min/MDRD BEL: 60.5±11.01	NR	NR
Weir et al. 2011[69]	2 years	Authors report that mean C0 levels of TAC remained stable over study and CsA levels decreased due to dosage reduction	12 months CNI: 29 SRL: 36 24 months CNI: 42 SRL: 50	CNI: 9 SRL: 11	CNI: 4 SRL: 3	CNI: 5 SRL: 0	1 year CNI: 71.5±21.2 ml/min/ Nankivell SRL: 74.6±17.9 2 years CNI: 71.2±23.4 SRL: 75.5±19.2	1 year CNI: 145.0±96.5 µmol/L SRL: 126.2±82.8 2 years CNI: 151.8±117.0 SRL: 127.1±83.9	Creatinine Clearance 1 year CNI: 58.0±23.3 mL/min SRL: 61.9±20.1 2 years CNI: 56.9±23.0 SRL: 62.3±22.1
Guba et al. 2010[70]	1 year	Authors report C0 level generally met CsA C0: 100 to 150 ng/mL SRL: 5 to 10 ng/mL	CsA: 23 SRL: 35	CsA: 11 SRL: 12	CsA; 3 SRL: 1	CsA: 1 SRL: 1	CsA: 53.4±18.0 mL/min/ Nankivell SRL: 64.5±25.2	SRL: 1.51±0.59 (mg/dL) CsA: 1.87±0.98 (mg/dL)	Drug withdrawals significantly higher in SRL group (36.2%) than in CsA group (19.0%)

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Bemelman et al. 2009[71]	2 years	Target CsA AUC_{12} 3,250 µg·h/L EVR 150 mg·h/L	NR	CsA: 1 MPS: 8 EVR: 0	NR	NR	Mean eGFR at baseline (for all groups) 58±18 mL/min/MDRD At follow-up CsA: 44±15 MPS: 56±23 EVR: 55±20	At conversion[2] CsA: 124±11 µmol/L MPS: 116±11 EVR: 118±12 At follow-up[2] CsA: 139±14 µmol/L MPS: 135±21 EVR: 110±7	NR
Schena et al. 2009[72] 24 months followup	2 years	Target C0 CsA 50 to 250 ng/mL TAC 4 to 10 ng/ng/mL; SRL 8 to 20 ng/mL	CNI: 40 SRL: 89	CNI: 19 SRL: 44	CNI: 26 SRL: 58	CNI: 12 SRL: 32	Pts baseline GFR >40 mL/min (n=743) CNI: 52.1 SRL 53.7 Diff: 1.6 (95% CI: -1.43 to -4.6) Pts baseline GFR 20 to 40 mL/min CNI: 17.9 SRL: 21.7 Diff: 3.8 (95% CI: -12.27 to -6.91	Mean urinary protein/creatinine ration CNI: 0.22±0.40 SRL: 0.72±1.50	NR
Schena et al. 2009[72] 12 months followup	1 year	NR	CNI: 11 SRL: 36	CNI: 4 SRL: 17	CNI: 8 SRL: 27	CNI: 2 SRL: 14	Pts baseline GFR >40 mL/min/Nankivell (n=743) CNI: 57.7 SRL: 59.0 Diff: 1.3 (95% CI: -1.06 to -3.69) Pts. baseline GFR 20 to 40 mL/min (n=87) CNI: 27.2 SRL: 24.6 Diff: -2.6 (95% CI: -12.27 to -6.91)	Mean urinary protein/creatinine ratio CNI: 0.23±0.25 SRL: 0.36±0.53	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Lebranchu et al. 2011[73]	4 year	Target CsA C2 500 to 800 ng/mL	NR	CsA: 2 SRL: 2	CsA: 0 SRL: 1	CsA: 2 SRL: 2	CsA: 51.4 mL/min/MDRD (95% CI: 47.9 to 54.9) SRL: 58.7 (95% CI: 55.1 to 62.4)	NR	NR
Lebranchu et al. 2009[74]	1 year	Target CsA C2 500 to 800 ng/mL	NR	CsA: 8 SRL: 16	CsA: 0 SRL: 1	CsA: 0 SRL: 0	CsA: 53.9±51 mL/min/MDRD SRL: 61.2±58	CsA: 132.3 µmol/L (126.1 to 138.5) SRL: 117.4 (110.7 to 124.2)	NR
Durrbach et al. 2008[75]	6 months	At 6 months, SRL C0 level 13.0±4.0 ng/mL at 6.8±4.9 g/d CsA dose 233±77 mg/d	NR	SRL: 4 CsA: 3	SRL: 4 CsA: 1	SRL: 1 CsA: 0	SRL: 44.7±16.6 mL/min/ Cockcroft CsA: 41.9±15.2 mL/min	SRL: 171±53 µmol/L CsA: 171±65	Delayed graft function: SRL: 15 CsA: 11 Withdrawal SRL: 16 CsA: 6
Barsoum et al. 2007[76]	2 years	At 12 to 24 months, CsA C2 level 1,000 ng/mL; SRL C0 level 10 to 15 ng/mL	NR	SRL: 10 CsA: 7	SRL: 4 CsA: 4	SRL: 3 CsA: 3	Mean eGFR Baseline SRL: 61.85±10.45 mL/min/ MDRD CsA: 63.77±8.9 2 years SRL: 70.2 ±8.0 CsA: 55.86±7.8	SRL: 96.8 µmol/L CsA: 126.72	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Dudley et al. 2005[77]	1 year	Target CsA C0 at 12 months 117.0±49 ng/mL	NR	CsA: 0 MMF: 0	CsA: 4 MMF: 2	CsA: 0 MMF: 3	NR	Serum creatinine clearance 6 months CsA: 244.1 (±55) µmol/L (increase of 22.3 from baseline) MMF: 200.7 (±61) (decrease of -21 from baseline) 12 months CsA: 245.1 (±50) (increase of 22.2) from baseline MMF: 198.0 (±53) (decrease of -24.9 from baseline)	Number of responders (experienced a significant improvement in renal function) 6 months CsA: 18 MMF: 36 12 months CsA: 21 MMF: 30
Watson et al. 2005[78]	1 year	Median daily dose of SRL at 12 months 2.5 mg; whole blood levels 8.5 ng/mL (4.9 to 12.5) Median C0 TAC: 10.6 ng/mL; median CsA: 187 ng/mL	NR	CNI: 0 SRL: 0	NR	NR	Baseline GRF CNI: 36.1 mL/min SRL: 37.8 Mean difference between groups at 3 months: 7.9 mL/min (95% CI: 4.1 to 11.7, p=<0.001); at 12 months: 12.9 (95% CI: 6.1 to 19.7, p=<0.001) This indicates a GFR improvement of 8.5 ml/min among SRL group and a decline of 4.3 in the CNI group.	Mean difference between groups: -67 µmol/L (-148 to 14)	1 patient in each group returned to dialysis

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Bakker et al. 2003[79]	15 years	Mean dose of CsA 5.1±1.4 mg/kg	NR	CsA: 2 AZA: 3	CsA: 24 AZA: 14	CsA: 29 AZA: 27	CsA: 59.3 mL/min/ Nankivell SRL: 71.7 Diff: 15.7 (95% CI: 0 to 30.6)	NR	NR
Bakker et al. 2003[79]	≤10 years	Mean dose of CsA 5.1±1.4 mg/kg	NR	See above	CsA: 17 AZA: 9	CsA: 19 AZA: 16	3 months CsA: 56.5 mL/min/ Nankivell SRL: 53.5 Diff: 3.0 (95% CI: -2.6 to 8.6) 1 year CsA: 55.7 SRL: 72.9 Diff: 17.1 (95% CI: 11.6 to 22.7) 10 years CsA: 52.8 SRL: 71.7 Diff: 19.0 (95% CI: 10.0 to 27.8)	NR	NR
MacPhee et al. 1998[80]	10 year	Target levels of CsA (97±34 nmol/L) achieved at dose 2.5 to 3.0 mg/kg Target maintenance dose of AZA 1.6 to 1.9 mg/kg	NR	CsA: 17 AZA: 16	CsA: 48 AZA: 39	CsA: 12 AZA: 6	NR	CsA: 153 µmol/L AZA: 153 µmol/L	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Followup	Achievement of CNI Target Levels	Treatment Failure Composite[1] (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Hilbrands et al. 1996[81]	1 year	CsA C0 levels 100 to 200 ng/ml	NR	CsA: 20 AZA: 16	CsA: 1 AZA: 1	CsA: 1 AZA: 1	NR	Mean creatinine clearance At 3 months CsA: 57 (40 to 69) ml/min AZA: 52 (42 to 66) At 1 year CsA: 53 (43 to 67) 64 (53 to 84)	Quality of Life at 1 year[3] Median SIP score CsA: 3.8 (1.3 to 6.5) AZA: 3.5 (0.5 to 10.4) Median ABS score CsA: 7.5 (6 to 8.5) AZA: 7 (5.5 to 8) Median CES-D score CsA: 1 (0 to 4) AZA: 1 (0 to 5.5)

[1] Composite variable defined as biopsy-proven acute rejection, graft loss, death and loss to follow-up, discontinuation due to lack of efficacy or toxicity, conversion to another regimen up to or at 12 month after transplantation.

[2] The mean creatinine levels and standard deviations were estimated based on data presented in a figure.

[3] Lower scores on the ABS, CES-D, and SIP indicate better quality of life.

ABS=affect balance scale; AUC=area under the curve; AZA=azathioprine; BEL=belatacept; C0=CsA trough level; C2=2 hour post CsA dosage level; CES-D=Center for Epidemiologic Studies Depression Scale; CI=confidence interval; CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; g/d=gram per day; GFR/eGFR=glomerular filtration rate/estimated glomerular filtration rate; h/L=hectoliter; k/L=kiloliter; MDRD=modification of diet in renal disease; mg/kg=milligram per kilogram; mL/min=milliliter per minute; MMF=mycophenolate mofetil group; MPS=mycophenolate sodium; ng/mL=nanogram per milliliter; nmol/L=nanogram per liter; NR=not reported; SIP=sickness impact profile; SRL=sirolimus; TAC=tacrolimus; µmol/L=micromoles per liter

Table E-8. Adverse events reported in conversion studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Budde et al. 2015[55]	Conversion from CNI to EVR	NR	NR	Any infection: EVR 28 vs. CNI 26 Any serious infection: EVR 8 vs. CNI 4 CMV colitis: EVR 1 vs. CNI 1 CMV gastroenteritis: EVR	NR	EVR: 15 vs. CNI 3	Hyper-lipidemia: EVR 6 vs. CNI 0 Hyper-cholesterol-emia: EVR 5 vs. CNI 0 Total cholesterol: EVR 6.2 mmol/L vs. CNI 5.2 mmol/L Triglycerides: EVR 2.6 vs. CNI 2.6	Aphthous stomitis: EVR 12 vs. CNI 0 Nasopharyngitis: EVR 11 vs. CNI 11 Peripheral edema: EVR: 11 vs. CNI 3 Anemia: EVR 8 vs. CNI 4 Diarrhea: EVR 8 vs. CNI 11 Neutropenia: EVR 0 vs. CNI 0 Leukopenia: EVR 6 vs. CNI 2 Puritis: EVR 5 vs. CNI 0 Thrombocytopenia: EVR 2 vs. CNI 1

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Rostaing et al. 2015[57]	Conversion from CsA to EVR	NR	NR	CMV: EVR 3 vs. CsA 7 BK viremia: EVR 0 vs. CsA 3 Urinary tract infection: EVR 9 vs. CsA 7	NR	NR	Dyslipidemia: EVR 9 vs. CsA 6 Hypertension: EVR 5 vs. CsA 6 Total cholesterol and LDL cholesterol: lower in CsA group HDL cholesterol: no difference between groups	Peripheral edema; EVR 15 vs. CsA 17 Aphthous stomatitis: EVR 19 vs. CsA 4 Anemia: EVR 9 vs. CsA 7 Diarrhea: EVR 8 vs. CsA 6 Bronchitis: EVR 7 vs. CsA 6 Neutropenia: EVR 6 vs. CsA 7 Pyrexia: EVR 6 vs. CsA 6 Leukopenia: EVR 2 vs. CsA 8 Gingival hypertrophy: EVR 0 vs. CsA 8 Acne: EVR 6 vs. CsA 1 Cough: EVR 2 vs. CsA 5 Rash: EVR 7 vs. CsA 0
Bensal et al. 2013[58]	Conversion from Control Regimen to SRL	Authors report no difference between groups 9 (31%) in CNI group vs. 7 (22.6%) in SRL group; p=0.459	NR	Herpes simplex virus infection: 1 patient in CNI group Herpes zoster: 1 patient in SRL group Fulminant bacterial pneumonia: 1 patient in SRL group 0 CMV or BK Respiratory infection: 1 patient in each group Skin infection: 1 patient in CNI group	0 patients	No between-group differences	NR	Tuberculosis: 1 patient in CNI group Enthesitis: 4 patients in the SRL group. Seizure: 1 SRL patient with a history of seizures developed a seizure during treatment. Aphthous stomatitis: 1 patient in SRL group

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Chhabra et al. 2013[59]	Conversion from TAC to SRL	Authors report no difference between groups, data not included	TAC 4/123 vs. SRL 1/64	CMV: TAC 7 vs. SRL 3 BK: TAC 5 vs. SRL 2 Pneumonia: TAC 3 vs. SRL 1 Herpes: TAC 4 vs. SRL 2 Nasopharyngitis: TAC 5 vs. SRL 1 Cyclosporidia: TAC 1 vs. SRL 0 Cellulitis: TAC 2 vs. SRL 0 Histoplasmosis: TAC 0 vs. SRL 1 UTI: TAC 20 vs. SRL 7	Authors report no difference between groups, data not included	TAC 11 vs. SRL 5	Hyperlipidemia higher in SRL vs. TAC group Cholesterol-lowering medication use: SRL: 45% CNI: 22%	Histoplasmosis: TAC 0 SRL 1 Cyclosporidia: TAC 1 SRL 0
Silva et al. 2013[60]	Conversion from TAC to SRL	NR	Kaposi's sarcoma: TAC: 1/107 Emryonal testicular carcinoma: TAC: 2/107	TAC group: Polyomavirus nephropathy: 2/107 (2%) CMV Virus: months 4-24 SRL: 5% TAC: 4% Herpes zoster: months 4-24 SRL: 4% TAC: 7% Polyomavirus: months 4-24 SRL: 3% TAC: 4% Pneumonia: TAC: 2 (2%)	2 patients suffered a cardiovascular event leading to death. SRL: 1/97 TAC: 1/107	SRL: 3 (3%)	Blood Pressure: No difference Dyslipidemia SRL: 6 TAC: 3 Total cholesterol (mg/dL) SRL: 219 TAC: 181 Triglycerides, HDL, VLDL, LDL higher in SRL group	6 combined deaths recorded in SRL and TAC groups (2 due to infection and 1 due to cardiovascular event each) SRL: zygomycosis Diarrhea TAC: 2/107 (2%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Budde et al. 2015[61] FOLLOW-UP: Budde et al. 2012[62] Budde et al. 2011[63]	Conversion from CsA to EVR	Diabetes mellitus CsA: 15 (10%); 20 (13%) p=0.4667	13 malignancies were reported within 36 months after randomization Basalioma CSA: 11/145 EVR: 5/155 Squamous cell carcinoma CSA: 3/145 EVR: 2/155 Spinalioma (left arm) CSA: 1/145 Post-transplant lympho-proliferative disease EVR: 1/155	Herpes virus CsA: 17 (12%); EVR: 24 (15%); Pneumocystis jirovecii pneumonia CsA: 1 (<1%); EVR: 1 (<1%) BK virus CsA: 5 (3%); EVR: 11 (7%) Cytomegalovirus CsA: 32 (22%); EVR: 32 (20%) Pneumonia CsA: 23 (16%); EVR: 25 (16%) Infections during months 12–24 CSA: 30 (20.7%); EVR: 35 (22.6%) Infections during months 24–36 CSA: 29 (20.0%); EVR: 31 (20.0%) Infections during months 12-60 CsA: 127 (87.6%); EVR: 137 (88.4%) UTI infection CsA: 109 (75%); EVR: 120 (77%); p=0·4866	Myocardial infarction CsA: 1 (Death of patient not related to drug)	CsA: 24 (17%) EVR: 24 (15%)	Hyperlipidemia CsA: 15 (10%) EVR: 22 (14%) Hypercholes-terolemia CsA: 40 (28%) EVR: 45 (29%) Hypertriglyc-eridemia CsA: 5 (3%) EVR: 10 (6%) Hypertension CsA: 20 (14%) EVR: 8 (12%) Hypotension CsA: 32 (22%) EVR: 22 (114%)	Nasopharyngitis CsA: 49 (34%) EVR: 58 (37%) Aphthous stomatitis CsA: 4 (3%) EVR: 26 (17%) Diarrhea CsA: 45 (31%) EVR: 68 (44%) Impaired healing CsA: 5 (3%) EVR: 6 (4%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Mjornstedt et al. 2012[65]	Conversion from CsA to EVR	NR	Malignant parathyroid tumor EVR: 1 Adenocarcinoma of the prostate EVR: 1 Squamous cell carcinoma CsA: 1 Testicular cancer CsA: 1 At 3 year followup, authors report that 5 patients in each group developed a malignancy during 12 to 36 months	Urinary tract infection EVR: 15 (14.7%) CsA: 28 (28.0%) At 12 to 36 months, 27.2% of patients with EVR had a UTI vs. CNI 18.9% Polyoma virus infection EVR: 2 (2.0%) CsA: 1 (1.0%) CMV EVR: 9 (8.8%) CsA: 13 (13.0%) Herpes simplex EVR: 5 (4.9%) CsA: 1 (1.0%) Pneumonia EVR: 12 (11.8%) CsA: 2 (2.0%) Upper respiratory tract infection EVR: 5 (4.9%) CsA: 4 (4.0%) Herpes zoster EVR: 1 (1.0%) CsA: 6 (6.0%) Oral candidiasis EVR: 5 (4.9%) CsA: 2 (2.0%) BK virus nephropathy EVR: 1 CsA: 2 Sepsis EVR: 5 Gastroenteritis EVR: 5	NR	EVR: 5 (4.9%)	Hyperlipidemia EVR: 13 (12.7%) CsA: 9 (9.0%) Hypercholesterolemia EVR: 10 (9.8%) CsA: 2 (2.0%) Blood pressure lower in EVR vs. CsA	Edema EVR: 30 (29.4%) CsA: 21 (21.0%) Anemia EVR: 17 (16.7%) CsA: 6 (6.0%) Leukopenia EVR: 14 (13.7%) CsA: 11 (11.0%) Acne EVR: 13 (12.7%) CsA: 2 (2.0%) Mouth ulceration EVR: 13 (12.7%) CsA: 1 (1.0%) Lymphocele EVR: 10 (9.8%) CsA: 6 (6.0%) Dermatitis EVR: 9 (8.8%) CsA: 5 (5.0%) Cough EVR: 7 (6.9%) CsA: 4 (4.0%) Headache EVR: 6 (5.9%) CsA: 4 (4.0%) Hypokalemia EVR: 6 (5.9%) Venous thrombosis EVR: 6 (5.9%) CsA: 3 (3.0%) Myalgia EVR: 5 (4.9%) CsA: 2 (2.0%) Sinusitis EVR: 5 (4.9%) CsA: 1 (1.0%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
								Diarrhea EVR: 5(4.9%) CsA: 11(11.0%) Fatigue EVR: 2 (2.0%) CsA: 7 (7.0%) Hirsutism EVR: 1 (1.0%) CsA: 6 (6.0%) Arthralgia EVR: 4 (3.9%) CsA: 5 (5.0%) Dizziness EVR: 1 (1.0%) CsA: 5 (5.0%) Hydronephrosis EVR: 4 Pyelonephritis CsA: 3
Nafar et al. 2012[66]	Conversion from CsA to MMF	No significant findings. Fasting blood glucose, (mg/dL) 1 year followup values: SRL: 96 CsA: 105	NR	NR	CsA: 4 patients suffered cardio events coupled with sepsis leading to death.	NR	Serum cholesterol (mg/dL) SRL: 194 CsA: 190 Serum triglyceride (mg/dL) SRL: 205 CsA: 189	Hospitalization – 4 year period SRL: 52 CsA: 44

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Heilman et al. 2011[67]	Conversion from TAC to SRL; rapid STER withdrawal for all patients	NR	Cancer SRL: 1	CMV SRL: 8 TAC: 8 BK virus Nephropathy SRL: 2 TAC: 3 Pneumonitis SRL: 2 Fever SRL: 1	NR	SRL: 4	Hyperlipidemia SRL: 4 No difference in blood pressure	Oral ulcers SRL: 7 Edema SRL: 3 Cytopenia SRL: 2 Rash SRL: 2 IFTA TAC: 2
Holdaas et al. 2011[31]	Conversion from CNI to EVR	6/127 vs. 4/123	9 vs. 7	Any infection: 83 vs. 75 UTI: 22 vs. 13 Upper respiratory tract: 15 vs. 16	NR	21 vs. 11	Cholesterol, triglycerides, hyperlipidemia higher in intervention group; no difference for hypertension	Higher incidence of GI, anemia, edema, pyrexia, in intervention group

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Rostaing et al. 2011[68]	Conversion from CNI to Belatacept	Diabetes Belatacept: 7 (8%) CNI: 10 (11%)	Basal cell carcinoma Belatacept: 1 (1%) CNI: 2 (2%) Kaposi's sarcoma Belatacept: 1 (1%)	Herpes infections Belatacept: 4 (5%) CNI 3 (3%) BK polyoma virus Infection Belatacept: 3 (4%) Polyomavirus associated nephropathy Belatacept: 1 (1%) CMV infection Belatacept: 2 (2%) CNI: 2 (2%) Kaposi's sarcoma Belatacept: 1 (1%) Urinary tract infection Belatacept: 2 (2%) Total fungal Infections Belatacept: 11 (13%) CNI: 3 (3%) Tinea versicolor Belatacept: 5 (6%) Fungal infection Belatacept: 1 (1%) CNI: 1 (1%) Onychomycosis Belatacept: 1 (1%) CNI: 1 (1%) Body tinea Belatacept: 1 (1%) Skin candida Belatacept: 1 (1%) Vulvovaginal mycotic infection Belatacept: 1 (1%) Pyrexia Belatacept: 3 (4%)	Myocardial infarction CNI: (1/89)		BP over the 12 months Belatacept: 4.0/3.5 mmHg CNI group 1.6/1.7 mmHg	Congenital, Familial, and Metabolic Disorders Belatacept: 3 (4%) CNI: 3 (3%) Other causes Belatacept: 35 (42%) CNI: 43 (48%) Glomerulonephritis Belatacept: 23 (27%) CNI: 14 (16%) Polycystic kidneys Belatacept: 9 (11%) CNI: 9 (10%) Renovascular/hyper-tensive nephrosclerosis Belatacept: 7 (8%) CNI: 10 (11%) Pyelonephritis Belatacept: 2 (2%) CNI- 1 (1%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Weir 2011[69]	Conversion from CNI to SRL + MMF	Diabetes CNI: 2 (6%)	Malignancies SRL: 7 (4.7%) CNI: 10 (6.5%)	Aspergillus CNI: 1(0.9%) BK virus infection CNI: 9 (6%) Candida SRL: 8 (5.4%) CNI: 12 (7.8%) CMV SRL: 7 (4.7%) CNI: 15 (9.8%) Herpes simplex SRL: 6 (4.1%) CNI: 1 (0.7%) Herpes zoster SRL: 12 (8.1%) CNI: 8 (5.2%) Pneumocystis SRL: 2 (1.4%) Cryptococcus CNI: 1 (0.7%)	Pulmonary embolism CNI: 1 (lead to death) Cardiac arrest CNI: 1 (lead to death)	SRL: 3 (4.4%)	Diastolic blood pressure was lower after 24 months in SRL group Hyperlipidemia SRL: 120 (81.1%) CNI: 97 (63.4%) Hypertension SRL: 30 (20.3%) CNI: 25 (16.3%)	Diarrhea SRL: 51 (34.5%) CNI: 50 (32.7%) Peripheral edema SRL: 42 (28.4%) CNI: 20 (13.1%) Leukopenia SRL: 36 (24.3%) CNI: 29 (19%) Mouth Ulceration SRL: 21 (14.2%) Urosepsis CNI: 1 (lead to death) Focal segmentation SRL: 2 (3%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Guba et al. 2010[70]	Conversion from CsA to SRL	Diabetes mellitus SRL: 7.3% CsA: 5.6% p=0.7430	CsA: 4 (6%) patients; including renal cell cancer, colon cancer, squamous cell cancer of the nasal cavity, and non-Hodgkin lymphoma of the transplanted kidney. SRL: No cancers This between group difference was not significant; p=0.1198	CMV infection SRL: 7.3%; CsA: 28.2%; p=0.0016 Pneumonia SRL: 11.6%; CsA: 9.9%; p=0.7901 Urinary tract infections SRL: 18.8%; CsA: 29.6%; p=0.1691 Infections and infestations (overall) SRL: 52.2%; CsA: 60.6%; p=0.3942 Skin infections SRL: 8.70%; CsA: 1.41%; p=0.0608 Respiratory SRL: 13.0%; CsA: 7.0%; p=0.2711	Cardiac disorders SRL: 13.0%; CsA: 5.6%; p=0.1545	Proteinuria: SRL: 5 (7.3%) CsA: 1 (1.4%) (p=0.113)	Hyperlipidemia SRL: 20.3%; CsA: 7.0%; p=0.0269	Serious adverse events SRL: 53.6% CsA: 66.2% p=0.1675; severity similar in both groups Lymphocele SRL: 27.5% CsA: 23.9%; p=0.7005 Gastrointestinal disorders (overall) SRL: 29.0% CsA: 33.8%; p=0.5877 Diarrhea SRL: 13.0% CsA: 9.9%; p=0.6037 Metabolism and nutrition disorders (overall) SRL: 30.4% CsA: 29.6%; p=1.0 Blood and lymphatic disorders (overall) SRL: 26.1% CsA: 23.9%; p=0.8462 Anemia SRL: 13.0% CsA: 5.6%; p=0.1545 Thrombopenia SRL: 2.9% CsA: 4.2%; p=1.0 Leucopenia SRL: 10.1% CsA: 11.3%; p=1.0 Vascular disorders (overall) SRL: 10.1% CsA: 18.3%; p=0.2277 Hypertonia

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
								SRL: 0% CsA: 4.2%; p=0.2448 <u>Skin and subcutaneous tissue disorders (overall)</u> SRL: 20.3% CsA: 7.0%; p=0.0269 <u>Acne</u> SRL: 7.25% CsA: 0%; p=0.0270 <u>Hepatobiliary disorders</u> SRL: 11.6% CsA: 9.9%; p=0.7901 <u>Nervous system disorders</u> SRL: 10.1% CsA: 9.9%; p=1.0
Bemelman et al. 2009[71] Interim report of 2 year study	Conversion from CsA to MPS or EVR	NR	Posttransplant lymphopro-liferative disease EVR: 1	Cytomegalovirus disease CSA: 0(0%); MPS: 1(1%); EVR: 0(0%) Pneumonia CSA: 1(1%); MPS: 3(3%); EVR: 2(2%) Transplant pyelonephritis and urosepsis CSA: 1(1%); MPS: 0(0%); EVR: 5(5%) Lower urinary tract infection CSA: 2(2%); MPS: 3(3%); EVR: 9(6%) Flu-like syndrome EVR: 3(3%)	Cardio events CSA: 1(1%); MPS: 4(4%); EVR: 2(2%)	Not reported	No between group differences	Other (diarrhea, abdominal pain, varicella zoster, anemia, leucopenia) MPS: 7(7%) Other (abdominal pain, dysmenorrhea, urethral syndrome) EVR: 7(7%) Ankle edema CSA: 0(0%); MPS: 0(0%); EVR: 2(2%) Diarrhea CSA: 0(0%); MPS: 1(1%); EVR: 1(1%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Schena et al. 2009[72]	Conversion from CNI to SRL	Frequency of diabetes mellitus SRL: 4.7% CNI: 4.4%	Malignancies, Total SRL: 21 (3.8%) CNI: 30 (11.0%) Skin carcinoma SRL: 12 (2.2%) CNI: 21 (7.7%)	Infection Pneumonia SRL: 70 (12.7%) CNI: 14 (5.1%) Herpes simplex SRL: 48 (8.7%) CNI: 12 (4.4%) Fever SRL: 113 (20.5%) CNI: 25 (9.2%)	NR	Proteinuria higher in the CNI vs. SRL group.	Hyperlipidemia SRL: 295 (53.5%) CNI: 72 (26.4%)	Other Aphthous stomatitis SRL: 23 (4.2%) CNI: 1 (0.4%) Stomatitis SRL: 21 (3.8%) CNI: 1 (0.4%) Acne SRL: 10 (1.8%) Hyperlipidemia SRL: 295 (53.5%) CNI: 72 (26.4%) Diarrhea SRL: 216 (39.2%) CNI: 63 (23.1%) Anemia SRL: 200 (36.3%) CNI: 45 (16.5%) Peripheral edema SRL: 176 (31.9%) CNI: 37 (13.6%) Albuminuria SRL: 130 (23.6%) CNI: 35 (12.8%) Acne SRL: 89 (16.2%) CNI: 11 (4.0%) Thrombocytopenia SRL: 77 (14.0%) CNI: 9 (3.3%) Leukopenia SRL: 74 (13.4%) CNI: 12 (4.4%) Skin rash SRL: 67 (12.2%) CNI: 11 (4.0%) Lactic dehydrogenase increased

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
								SRL: 64 (11.6%) CNI: 3 (1.1%) Hyperglycemia SRL: 62 (11.3%) CNI: 18 (6.6%) Hyperuricemia SRL: 41 (7.4%) CNI: 42 (15.4%)
Lebranchu et al. 2011[73] Lebranchu 2009[74]	Conversion of CsA to SRL	More frequent in the SRL group (2 vs. 1); difference not significant	Metastatic gastric adeno-carcinoma SRL: 1 Lung adeno-carcinoma SRL: 1 Two patients (2.4%) Angiosarcoma CsA: 1 Kaposi Sarcoma CsA: 1	BK virus infection CsA: 1 SRL: 1	NR	Proteinuria (>1 g per 24 hr) CSA: 2; SRL: 3	No difference in mean blood pressure, lipids level at 6 months	Diabetes showed a significant association with more severe fibrosis: 92% (12/13) of diabetic patients had IF grade >I at 1 year compared to 49% (53/108) in non-diabetic recipients. Gastrointestinal disorders reported in six cases (6.5%) in the SRL group and three (3.5%) in the CsA group
Durrbach et al. 2008[75]	Conversion from CsA to SRL	NR	Prostate cancer SRL: 1 patient Kaposi's sarcoma CsA: 1	CMV infection CsA: 4; SRL: 0 patients; p=0.12	NR	Proteinuria (>1 g per 24 hr) CSA: 2; SRL: 3	No significant differences in blood pressure and total lipid panels	Lymphocele CsA: 2%; SRL: 24.2%; p=0.04) Pancytopenia CsA: 0%; SRL: 12.1%; p=0.005) Abdominal pain CsA: 2.8%; SRL: 15.2%; p=0.1 Aphthous stomatitis CsA: 0%; SRL: 12.1%; p=0.05 Epistaxis CsA: 0%; SRL: 12.1%; p=0.05

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Barsoum et al. 2007[76]	Conversion from CsA to SRL	SRL: 3.6% CsA: 8.1% Authors report no significant difference	Lung malignancy SRL: 2.7%; CsA: 0%, authors report no significant difference Prostate malignancy SRL: 2.7%; CsA: 0%; authors report no significant difference	Herpes viral infection SRL: 15.8%; CsA: 21.1%; authors report no significant difference Pneumonia SRL: 11.8%; CsA: 10.8%; authors report no significant difference	Cardiovascular events SRL: 1.3% (Arm A) CsA: 8.1% (Arm B)	Proteinuria SRL: 36.8%; CsA: 18.6%; p<0.05	Hypertension SRL: 52.6%; CsA: 91.8%; p<0.05 Hyperlipidemia (peak cholesterol >7.75 mmol/L); SRL: 32.9%; CsA: 23.7%; p<0.05	Lymphoceles SRL: 14.5% CsA: 10.6% Peripheral edema SRL: 36.8% CsA: 37.8% Thrombotic microangiopathy SRL: 1.3% CsA: 0% Deep venous thrombosis SRL: 7.9% CsA: 13.5% Pulmonary embolism SRL: 2.6% CsA: 5.4% Oral ulcers SRL: 13.2% CsA: 5.4% Rectal ulcers SRL: 1.3% CsA: 0% >2-fold elevation of ALT SRL: 11.8% CsA: 10.8% >2-fold elevation of AST SRL: 6.6% CsA: 2.7% >2-fold elevation of GGT SRL: 21.1% CsA: 21.6%

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Dudley et al. 2005[77]	Conversion from CsA to MMF	NR	NR	CMV MMF: 1 CsA: 1 Herpes zoster MMF+ CsA: 11 Herpes simplex MMF+ CsA: 3 Candida albicans MMF+ CsA: 5 Chronic Hepatitis B MMF: 1 (lead to death) UTI MMF: 10 (14%) CsA: 5 (7%)	Myocardial Infarction MMF: 1 (lead to death)	NR	Significant differences in cholesterol in MMF group vs. CsA group. Lower blood pressure observed in MMF group vs. CsA group. Hypotension MMF: 11 (15%) CsA: 4 (6%) Hypertension MMF: 5 (7%) CsA: 8 (11%)	Diarrhea MMF: 33(45%) CsA: 4 (6%) Abdominal Pain MMF: 17 (23%) CsA: 8 (11%) Anemia MMF: 16 (22%) CsA: 6 (9%) Weight Loss MMF: 11 (15%) Vomiting/Nausea MMF: 12 (16%) CsA: 6 (9%) Anorexia MMF: 7 (10%) CsA: 4 (6%) Polycystic Kidney disease MMF: 1 (lead to death)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Watson et al. 2005[78]	Conversion from CNI to SRL	NR	NR	Chest infection CNI: 2/19 SRL: 4/19 Herpes stomatitis CNI: 1/19 SRL: 2/19 UTI CNI: 4/19 SRL: 6/19	NR	Lower levels of proteinuria after conversion to SRL	No significant changes in blood pressure and total cholesterol levels.	Acneiform rash SRL: 2 Diarrhea CNI: 4/19 SRL: 6/19 Acute gout CNI: 2/19 SRL: 1/19 Pulmonary embolism SRL: 1/19 Bone pain CNI: 2/19 SRL: 3/19 Coryza CNI: 1/19 SRL: 7/19 Dysmenorrhoea SRL: 3/19 Epistaxis CNI: 1/19 SRL: 3/19 Indigestion CNI: 3/19 SRL: 2/19 Mouth ulcers SRL: 6/19 Gum hypertrophy CNI: 5/19 Vomiting CNI: 2/19 SRL: 2/19

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Bakker et al. 2003[79] Followup to Hollander 1995	Conversion from CsA to AZA	NR	Skin cancer CsA 15.2% vs AZA 16%; p=0.5	NR	Cardiovascular mortality 15 year followup CsA: 21.2%; AZA: 23.3%, no significant difference 42.2% in the CsA group and 36.2% in the AZA group had at least one vascular event (p=0.57)	Proteinuria (<1g/day), after 15 years CsA: 14 AZA: 15 Proteinuria (>1g/day), after 15 years CsA: 1 AZA: 2	Hypertension AZA: 1 No significant differences in total cholesterol and blood pressure.	Gout (n=1) and hypertension (n=1) led authors to convert one patient's medication to AZA and "accept lower cyclosporine trough levels in another" During follow-up, 15 patients in the cyclosporine group had their medications changed; in 13 of them (87%), the reason for this change was cyclosporine nephrotoxicity.
MacPhee et al. 1998[80]	Conversion from CsA to AZA	NR	Total malignancies AZA: 2 (2%) CsA: 2 (1.8%)	CMV AZA: 1 Serious infections requiring hospitalization were lower in AZA group. CsA: 42 AZA: 31 Total infections AZA: 5 (4.9%) CsA: 3 (2.6%)	Cardiovascular events CsA: 19 AZA: 21; no significant difference	NR	No significant differences in total cholesterol and blood pressure.	NR

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Hilbrands et al. 1996[81]	Conversion from CsA to AZA	NR	NR	NR	NR	NR	Antihyper-tensive therapy CsA: 19 (56%) AZA: 29 (64%)	<u>6 months post-transplant</u> Excessive hair growth CsA: 59; AZA-Pred: 24; p<0.01 Swollen face CsA: 12; AZA-Pred: 33 Stiff or painful muscles CsA: 74; AZA-Pred: 36; p<0.01 Tingling in hands CsA: 15; AZA-Pred: 16 Headache CsA: 18; AZA-Pred: 31 Swollen ankles CsA: 26; AZA-Pred: 16 Shortness of breath CsA: 18; AZA-Pred: 31 Difficulty sleeping CsA: 24; AZA-Pred: 22 Bruises CsA: 15; AZA-Pred: 29 Heartburn CsA: 6; AZA-Pred: 20 Dizziness CsA: 0; AZA-Pred: 20; p<0.05 <u>12 months post-transplant</u> Excessive hair growth CsA: 32; AZA-Pred: 7; p<0.01 Swollen face CsA: 9; AZA-Pred: 20 Stiff or painful muscles CsA: 35; AZA-Pred: 31 Tingling in hands CsA: 2; AZA-Pred: 9

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
								Headache CsA: 18; AZA-Pred: 18 Swollen ankles CsA: 15; AZA-Pred: 13 Shortness of breath CsA: 15; AZA-Pred: 16 Difficulty sleeping CsA: 21; AZA-Pred: 16 Bruises CsA: 9; AZA-Pred: 33; p<0.05 Heartburn CsA: 9; AZA-Pred: 22 Dizziness CsA: 6; AZA-Pred: 13

AZA=azathioprine; BK=polyomavirus; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; GI=gastrointestinal; IFTA=interstitial fibrosis and tubular atrophy on kidney allograft biopsy; LDL=low density lipoprotein; MMF=mycophenolate mofetil group; MPS=mycophenolate sodium; NR=not reported; Pred=prednisone; SRL=sirolimus; STER=steroid; TAC=tacrolimus; UTI=urinary tract infection

Table E-9. Study design characteristics of withdrawal studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Chadban et al. 2014[19]	Withdrawal of CsA	CsA and EC-MPS withdrawn + EVR (8-12 ng/mL) + STER	CsA (C2 target 500–700 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	2 months	Excluded age >65, PRA >50%, retransplants
Asberg et al. 2012[82]	Withdrawal of CsA	CsA withdrawn "in steps over a four-wk period") + MMF (≥2,000 mg) + STER (prednisolone)	CsA (75–125 ng/mL) + MMF withdrawn + STER (prednisolone)	NR	NR	>1 year	Excluded PRA >20%
Mourer et al. 2012[83]	Withdrawal of CNI	CsA (C2 target 600–800 ng/mL) or TAC (100–140 µg·hr/mL) withdrawn by 50% reduction followed after 2 weeks by elimination + MMF (MPA-AUC_{0-12} target 60–90 µg·hr/mL) + STER (prednisolone 5–10 mg)	CsA (C2 target 600–800 ng/mL) or TAC (100–140 µg·hr/mL) + MMF withdrawn by 50% reduction followed after 2 weeks by elimination + STER (prednisolone 5-10 mg)	NR	NR	Minimum 6 months	Excluded PRA >60%
Flechner et al. 2011[84]	Withdrawal of TAC	TAC (6–15 ng/mL) withdrawn by 25% reduction weekly until elimination + SRL (8-15 ng/mL before, 12-20 ng/mL after TAC withdrawal) + STER (5 mg)	TAC (5-15 ng/mL) + MMF (1,000-2,000 mg) + STER (5 mg)	IA	Daclizumab	13 weeks	NR
Freitas et al. 2011[85]	Withdrawal of TAC	TAC (5–8 ng/mL) withdrawn over 4 weeks + SRL (12–20 ng/mL) + STER (prednisone 10 mg)	TAC (5–8 ng/mL) + SRL (12–20 ng/mL) + STER (prednisone 10 mg) withdrawn over 4 weeks	NR	None	3 months	Excluded PRA >50%
Pascual et al. 2008[86]	Withdrawal of CNI	TAC (5–10 ng/mL) or CsA (100–200 ng/mL) withdrawn by 25–50% reduction on day of randomization, followed by elimination 7–14 days after + MMF (1,000–2,000 mg) or EC-MPS (720–1,440 mg) + STER (methylprednisolone 5–7.5 mg)	TAC (5–10 ng/mL) or CsA (100–200 ng/mL) + MMF (1,000–2,000 mg) or EC-MPS (720–1,440 mg) + STER (methylprednisolone 5–7.5 mg)	NR	Alemtuzumab	Between 2 and 16 months	Excluded PRA >10%

Table E-9. Study design characteristics of withdrawal studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Ekberg et al. 2007a[42]	Withdrawal of CsA	CsA withdrawn by 33% reduction each month + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	NR	Daclizumab in intervention group	4 months	Excluded PRA >20%, retransplants
Hazzan et al. 2006[87] (1 year follow up to Hazzan et al. 2005[88])	Withdrawal of CsA	CsA (100–300 ng/mL) withdrawn by 25% reduction weekly until elimination + MMF (2,000 mg) + STER (prednisone 0.10–0.15 mg/kg)	CsA (100–300 ng/mL) + MMF (2,000 mg) withdrawn by 25% reduction weekly until elimination + STER (prednisone 0.10–0.15 mg/kg)	NR	ATG	3 months	Excluded PRA >30%
Suwelack et al. 2004[89]	Withdrawal of CNI	CsA (80–120 ng/mL) or TAC (4–7 ng/mL) withdrawn by 33% reduction every 2 weeks until elimination + MMF (2,000 mg) + STER (prednisone ≥5 mg)	CsA (80–120 ng/mL) or TAC (4–7 ng/mL) + MMF (2,000 mg) + STER (prednisone ≥5 mg)	NR	NR	Minimum 1 year	All patients had chronic allograft dysfunction
Stallone et al. 2003[90]	Withdrawal of CsA	CsA (150–250 ng/mL) withdrawn + SRL (10–15 ng/mL) + STER (prednisone 5 mg)	CsA (150–250 ng/mL) + SRL (10–15 ng/mL) + STER (prednisone 5 mg)	NR	NR	3 months	NR
Abramowicz et al. 2002[91]	Withdrawal of CsA	CsA (100–200 ng/mL) withdrawn by 33% reduction every 6 weeks until elimination + MMF (2,000 mg) + STER (mean dose 13 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg)+ STER (mean dose 7.5 mg)	NR	NR	Between 12 and 30 months	Excluded PRA >50%
Gonwa et al. 2002[92]	Withdrawal of CsA	CsA (100–150- ng/mL) withdrawn by 25% reduction weekly until elimination + SRL (10–20 ng/mL) + STER (0.15 mg/kg)	CsA (150–250 ng/mL) + SRL (fixed dose 2 mg) + STER (0.15 mg/kg)	IA HPLC, Mass Spectrometry	NR	2 months	NR
Schnuelle et al. 2002[93]	Withdrawal of CsA	CsA (150–250 ng/mL) withdrawn by 33% reduction every 3 weeks until elimination + MMF (2,000 mg) + STER (7.5–10 mg)	CsA (100–250 ng/mL) + MMF withdrawn by 500 mg reduction every 2 weeks until elimination + STER (7.5–10 mg)	IA	None used	3 months	Excluded PRA >50%

Table E-9. Study design characteristics of withdrawal studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Smak Gregoor et al. 2002[94] Roodnat et al. 2014[95]	Withdrawal of CsA	CsA (125–175 ng/mL) withdrawn by 50% reduction followed after 2 weeks by elimination + MMF (2,000 mg) + STER (prednisone)	CsA (125–175 ng/mL) + MMF (2,000 mg) + STER (prednisone) maintained or withdrawn over 10 weeks	IA	None used	Minimum 6 months	NR
Johnson et al. 2001[96]	Withdrawal of CsA	CsA (150–300 ng/mL) withdrawn "over the course of 4–6 weeks" + SRL (20–30 ng/mL) + STER (5–10 mg)	CsA (75–200 ng/mL) + SRL (>5 ng/mL) + STER (5–10 mg)	IA	NR	3 months	NR

AUC_{0-12}=area under the curve 0-12 hours; CNI=calcineurin inhibitors; CsA=cyclosporine; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; mg/kg=milligram per kilogram; MMF=mycophenolate mofetil group; MPA=medroxyprogesterone acetate; MPS=mycophenolate sodium; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; SRL=sirolimus; STER=steroid; TAC=tacrolimus; μg·hr/mL=micrograms per hour per milliliter

Table E-10. Study population characteristics of withdrawal studies

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Chadban et al. 2014[19]	Withdrawal of CsA	Asia Australia New Zealand	49	47	Deceased: 52 Living related: 51 Living unrelated: 21	48 vs. 46	71%	51%	NR
Asberg et al. 2012[82]	Withdrawal of CsA	Norway	20	19	Deceased: 21 Living: 18	63 vs. 54	67%	NR	NR
Mourer et al. 2012[83]	Withdrawal of CNI	Netherlands	79	79	Deceased: 95 Living: 63	52 vs. 53	70%	NR	34% vs. 34%
Flechner et al. 2011[84]	Withdrawal of TAC	Worldwide	152	139	Deceased: 181 Living related: 67 Living unrelated: 43	48 vs. 48	65%	74%	13% vs. 15%
Freitas et al. 2011[85]	Withdrawal of TAC	Brazil	23	24	Living related and unrelated	35 vs. 35	57%	55%	NR
Pascual et al. 2008[86]	Withdrawal of CNI	USA	20	20	Deceased: 23 Living related: 11 Living unrelated: 6	55 vs. 54	80%	100%	20% vs. 20%

Table E-10. Study population characteristics of withdrawal studies (continued)

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Ekberg et al. 2007a[42]	Withdrawal of CsA	Worldwide	179	173	Deceased: 273 Living related: 56 Living unrelated: 23	47 vs. 49	62%	82%	17% vs. 22%
Hazzan et al. 2006[87] Hazzan et al. 2005[88])	Withdrawal of CsA	France	54	54	Deceased	45 vs. 42	63%	NR	NR
Suwelack et al. 2004[89]	Withdrawal of CNI	Germany	18	20	NR	48 vs. 49	74%	100%	NR
Stallone et al. 2003[90]	Withdrawal of CsA	Italy	20	20	Deceased	40 vs. 47	NR	100%	40% vs. 45%
Abramowicz et al. 2002[91]	Withdrawal of CsA	Worldwide	85	85	Deceased: 154 Living: 16	45 vs. 48	59%	96%	NR
Gonwa et al. 2002[92]	Withdrawal of CsA	USA Europe	100	97	Deceased	45 vs. 45	57%	77%	NR
Schnuelle et al. 2002[93]	Withdrawal of CsA	Germany	44	40	NR	45 vs. 51, p=0.02	64%	NR	18% vs. 20%
Smak Gregoor et al. 2002[94] Roodnat et al. 2014[95]	Withdrawal of CsA	Netherlands	63	149	Deceased: 160 Living: 52	52 vs. 51	66%	NR	NR
Johnson et al. 2001[96]	Withdrawal of CsA	Australia Canada Europe	215	215	Deceased: 370 Living related: 37 Living unrelated: 14	45 vs. 46	64%	94%	19% vs. 22%

CNI=calcineurin inhibitors; CsA=cyclosporine; NR=not reported; TAC=tacrolimus

Table E-11. Clinical outcomes of withdrawal studies

Reference	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Chadban et al. 2014[19]	1 year	15/49 vs. 6/47, p<0.05 Banff (year not reported): Grade 1A: 7 vs. 3 Grade 1B: 5 vs. 4 Grade 2A: 6 vs. 0 Grade 2B: 1 vs. 1 Grade 3: 0 vs. 1 Unspecified: 0 vs. 2	0 vs. 2	0 vs. 1	65.1±15.4 vs. 67.1±18.2, p<0.05 (Nankivell)	NR	24 vs. 8
Asberg et al. 2012[82]	7 years	6/20 vs. 0/19, p=0.02	5 vs. 1, p=NS	6 vs. 6	NR	1 year: 120±59 vs. 104±23, p=NS 7 years: 87±24 vs. 116±24, p=0.01	7 vs. 4
Mourer et al. 2012[83]	3 years	6 months: 3/79 vs. 1/79 1 year: 4 vs. 1 3 years: 4 vs. 2	1 vs. 1	4 vs. 6	1 year: 61.1±1.8 vs. 52.9±1.8, p<0.01 3 years: 59.5±2.1 vs. 51.1±2.1, p<0.01 (MDRD)	NR	11 vs. 7, p=NS
Flechner et al. 2011[84]	2 years	1 year: 23/152 vs. 11/139 2 years: 26 vs. 17	17 vs. 7, p=NS	8 vs. 5	1 year: 59.1±23.9 vs. 62.0±22.1, p=NS 2 years: 58.3 vs. 62.2, p=NS (Nankivell)	No difference	52 vs. 31
Freitas et al. 2011[85]	1 year	2/21 vs. 1/24 Banff 97: Grade 1A: 1 vs. 0 Grade 2A: 1 vs. 1	0	1 vs 1	63.4±10.5 vs. 60.0±11.5, p=NS (Nankivell)	114.92±30.94 vs. 129.95±22.98, p=NS	5 vs. 3
Pascual et al. 2008[86]	1 year	2/20 vs. 0/20 Banff 97: Grade 1A: 1 Grade 2A: 1	0	0	72.1±11.6 vs. 68.0±12.1, p=NS Change from baseline: 3.9±9.7 vs. 4.3±11.5, p=NS	1.52±0.64 vs. 1.45±0.30, p=NS	NR
Ekberg et al. 2007a[42]	1 year	68/179 vs. 48/173, p<0.05	12 vs. 9	8 vs. 5	50.9±6.4 vs. 48.6±6.9	1.7 mg/dL vs. 1.6 mg/dL	NR

Table E-11. Clinical outcomes of withdrawal studies (continued)

Reference	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Hazzan et al. 2006[87] Hazzan et al. 2005[88]	2 years	1 year: 10/54 vs. 3/54, p<0.05 2 years: 12/54 vs. 3/54 Banff 97: Grade 1: 9 vs. 2 Grade 2: 1 vs. 1 NR: 2	1 year: 0 2 year: 4 vs. 1, p=NS	0	1 year: 49.1±17.8 vs. 40.1±11.1, p<0.05 2 years: 45.6±21.6 vs. 37.7±11.0, p<0.05 (aMDRD)	NR	12 vs. 18, p=NS
Suwelack et al. 2004[89]	9 months	0	0 vs. 3	NR	NR	As measured by the slope of the reciprocal of serum creatinine, renal function significantly improved in the intervention group and deteriorated in the control group: 0.00585±0.01122 vs. -0.00728±0.01105, p<0.01	NR
Stallone et al. 2003[90]	1 year	2/20 vs. 2/20	0	0	3 months: 57.1±16.3 vs. 57.8±18.9 (Nankivell) 1 year: 66±17 vs. 54±14, p<0.01	3 months: 1.6±0.4 vs. 1.9±0.4 1 year: 1.3±0.3 vs. 2.0±0.3, p<0.01	NR
Abramowicz et al. 2002[91]	9 months	9/85 vs. 2/85, p<0.05 Grade 1: 5 vs. 1 Grade 2: 1 vs. 1 Grade 3: 1 vs. 0 Fine needle aspirate: 2 vs. 0	0	1 vs. 0	Intervention group 2.3 mL/min higher than control, p=NS (Nankivell) Intervention group 4.5 mL/min higher than control, p=NS (Cockcroft-Gault)	Change from baseline: -1 vs. 4, p=NS	NR
Gonwa et al. 2002[92]	1 year	6 months: 18/100 vs. 15/97, p=NS 1 year: 22 vs. 18, p=NS	5 vs. 7	4 vs. 3	6 months: 64.2 vs. 55.9, p<0.01 1 year: 65.3 vs. 56.4, p<0.01 (Nankivell)	6 months: 1.59±0.07 vs. 1.93±0.12, p<0.01 1 year: 1.64±0.12 vs. 1.99±0.15, p=NS	NR
Schnuelle et al. 2002[93]	1 year	5/44 vs. 2/40 Banff 93: Grade 1: 2 vs. 2 Grade 2: 3 vs. 0	1 vs. 0	0	6 months: 76.4±16.9 vs. 66.1±12.2, p<0.01 1 year: 73.2±14.9 vs. 61.9±11.8, p<0.01 (Nankivell)	6 months: 115.4±33.3 vs. 127.8±30.8, p=NS 1 year: 120.7±32.5 vs. 138.3±30.8, p<0.05	NR

Table E-11. Clinical outcomes of withdrawal studies (continued)

Reference	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Smak Gregoor et al. 2002[94] Roodnat et al. 2014[95]	15 years	18 months: 14/63 vs. 4/149, p<0.01 Banff 93: Grade 1: 5 vs. 3 Grade ≥2: 9 vs. 1	18 months: 2 vs. 3 15 years: 17 vs. 26, p=NS	18 months: 0 vs. 4 15 years: 31 vs. 61, p=NS	Median, 6 months: 66 vs. 63 vs. 58 (CsA withdrawal + MMF + STER vs. CsA + MMF + STER vs. CsA + MMF + withdrawal of STER) 18 months: 64 vs. 65 vs. 58 (Cockcroft-Gault)	Median, 6 months: 117 vs. 124 vs. 137 18 months: 123 vs. 125 vs. 137	18 months: 18 vs. 12, p<0.05 15 years: 20 vs. 69
Johnson et al. 2001[96]	1 year	21/215 vs. 9/215, p<0.05	6 vs. 9	4 vs. 6	62.7±1.5 vs. 56.6±1.3, p<0.01	141.6±5.3 vs. 158.1±4.2, p<0.01	58 vs. 39, p<0.05

aMDRD=abbreviated modification of diet in renal disease; MDRD=modification of diet in renal disease; NR=not reported; NS=not significant

Table E-12. Adverse events reported in withdrawal studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Chadban et al. 2014[19]	Withdrawal of CsA	18 vs. 13	2 vs. 1	CMV: 2 vs. 4 All infections: 33 vs. 34	NR	1 vs. 1	No difference between groups for cholesterol	No difference between groups for GI, anemia
Asberg et al. 2012[82]	Withdrawal of CsA	NR	4/20 vs 1/19	Sepsis: 0 vs. 2	Cardiovascular cause of death: 1 vs. 2	NR	NR	NR
Mourer et al. 2012[83]	Withdrawal of CNI	4 vs. 5	4 vs. 6	34 vs. 25, p=NS	NR	NR	No difference in BP, cholesterol	Anemia: 18 vs. 9, p=0.06
Flechner et al. 2011[84]	Withdrawal of TAC	27/120 vs. 12/110, p<0.05	7/152 vs. 5/139	All infections: 61.2% vs. 66.9%	NR	17 vs. 9	Cholesterol and triglycerides higher in intervention group	Intervention group had higher incidence of edema, hyperlipidemia, tremor, hyperkalemia, lymphoceles, thrombocytopenia, acne Control group had higher incidence of diarrhea; no difference for anemia, hypertension

Table E-12. Adverse events reported in withdrawal studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Freitas et al. 2011[85]	Withdrawal of TAC	"similar between groups"	0	"similar between groups"	NR	3 vs. 2	No difference in BP, triglycerides, dyslipidemia; total cholesterol higher in intervention group, p=0.02	Intervention group: higher incidence (NS) of lymphocele or lymphorrhea, stomatitis, headache, leucopenia, thrombocytopenia, dyslipidemia Control group: higher incidence (NS) of diarrhea, anemia, cramps; 1 case of nephrotoxicity in control group
Pascual et al. 2008[86]	Withdrawal of CNI	0/20 vs. 2/20	NR	CMV: 3 vs. 2 Herpes zoster: 0 vs. 1 Gastroenteritis: 0 vs. 1 UTI: 2 vs. 0 Sinusitis: 1 vs. 0	NR	Increased in both groups, difference NS	No difference	2 cases of nephrotoxicity in control group
Ekberg et al. 2007a[42]	Withdrawal of CsA	NR	4 (including 2 posttransplant lymphopro-liferative disorder) vs. 1	CMV: 23 vs. 24 Candida: 8 vs. 16 Herpes simplex: 14 vs. 11 Herpes zoster: 3 vs. 9	NR	NR	No difference	No difference for lymphocele, hypertension
Hazzan et al. 2006[87] Hazzan et al. 2005[88]	Withdrawal of CsA	NR	NR	NR	NR	No difference	NR	15 cases of nephrotoxicity in control group
Suwelack et al. 2004[89]	Withdrawal of CNI	NR	0	CMV: 1 vs. 6 Herpes zoster: 0 vs. 2	2 vs. 0	0.50±0.55 vs. 1.50±0.48, p=0.01	BP lower in intervention group	Lower incidence of GI, anemia in intervention group
Stallone et al. 2003[90]	Withdrawal of CsA	5/20 vs. 5/20	NR	NR	NR	NR	No difference	NR

Table E-12. Adverse events reported in withdrawal studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Abramowicz et al. 2002[91]	Withdrawal of CsA	NR	1/85 vs. 4/85	8 vs. 11 Includes CMV, herpes, zoster, herpes simplex, candida (specific data not reported)	NR	NR	No difference for BP, triglycerides; improved LDL and total cholesterol for intervention group	Higher incidence of diarrhea in intervention group
Gonwa et al. 2002[92]	Withdrawal of CsA	No difference	4/100 vs. 0/97 (2 skin carcinomas, 1 lymphopro-liferative disease, 1 renal cell carcinoma)	"no significant differences in the rates of clinically important infections"	NR	NR	Systolic BP lower in intervention group ($p<0.05$) but no difference in diastolic BP; total cholesterol higher in intervention group ($p<0.05$); no difference in triglycerides	Intervention group: higher incidence of atrial fibrillation, diarrhea, abnormal liver function, thrombocytopenia, hypokalemia Control group: significantly higher incidence of edema, dyspnea, hypertension, hypervolemia, hypomagnesemia, hirsutism
Schnuelle et al. 2002[93]	Withdrawal of CsA	4/44 vs. 6/40	NR	CMV: 3 vs. 1 Herpes simplex: 1 vs. 1 Herpes zoster: 1 vs. 0 Oral candidiasis: 1 vs. 0 PCP: 0 vs. 1 UTI: 4 vs. 13 Upper respiratory tract: 2 vs. 1 Pneumonia: 3 vs. 3 Septicemia: 0 vs. 3 Other: 1 vs. 1	NR	NR	Lower BP and improved lipids in intervention group	No difference in GI, hirsutism; 1 case of nephrotoxicity in control group

Table E-12. Adverse events reported in withdrawal studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Smak Gregoor et al. 2002[94] Roodnat et al. 2014[95]	Withdrawal of CsA	NR	2 skin carcinomas, 1 lymphoma	18 months: CMV: 4 vs. 3 Herpes simplex: 5 vs. 13 Herpes zoster: 2 vs. 3 Candida stomatitis: 3 vs. 4 Oesofagitis: 0 vs. 2 Pneumonia: 3 vs. 8 Bronchitis: 2 vs. 18 UTI: 36 vs. 64 Upper respiratory tract: 13 vs. 32 Gastrointestinal: 4 vs. 6 Skin: 7 vs. 9 Other: 1 vs. 5 Sepsis: 3 vs. 2	NR	No difference between groups, or vs. baseline	Triglycerides lower in intervention group at 18 months, p<0.05	Nephrotoxicity: 1 vs. 7
Johnson et al. 2001[96]	Withdrawal of CsA	9 vs. 7	2 (lymphoma and “other”) vs. 7 (4 skin cancer, 1 lymphoma, 2 “other”)	CMV: 8 vs. 7 Sepsis: 4 vs. 8 Pneumonia: 15 vs. 9 Herpes simplex: 13 vs. 10 Herpes zoster: 1 vs. 11 Oral moniliasis: 5 vs. 7	NR	NR	No difference in BP, cholesterol, triglycerides	Hypertension lower in intervention group; thrombocytopenia and hypokalemia higher in intervention group Nephrotoxicity: 5 vs. 15, p<0.05

BP=blood pressure; CMV=cytomegalovirus=CNI=calcineurin inhibitors; CsA=cyclosporine; GI=gastrointestinal; NR=not reported; NS=not significant; PCP=pneumocystis carinii pneumonia; UTI=urinary tract infection; TAC=tacrolimus

Table E-13. Study design characteristics of avoidance studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Asher et al. 2013[97]	Avoidance of TAC	SRL (8-10 mg/day) + MMF (1,000 mg) + STER (prednisolone)	TAC (5-10 ng/mL) + MMF (1,000 mg) + STER (prednisolone)	NR	Daclizumab	Immediate	NR
Vincenti et al. 2010[98] BENEFIT Follow-ups: Larsen et al. 2010[99] Vincenti et al. 2012[100] Rostaing et al. 2013[101] Dobbels et al. 2014[102]	Avoidance of CsA	Belatacept (5 mg/kg) in more intensive or less intensive schedule of administration + MMF (2,000 mg) + STER (≥2.5 mg)	CsA (100–250 ng/mL) + MMF (2,000 mg) + STER (≥2.5 mg)	NR	Basiliximab	Immediate	Excluded PRA >50%, or PRA >30% for retransplants
Durrbach et al. 2010[103] BENEFIT-EXT Follow-ups: Larsen et al. 2010[99] Pestana et al. 2012[104] Charpentier et al. 2013[105] Dobbels et al. 2014[102]	Avoidance of CsA	Belatacept (5 mg/kg) in more intensive or less intensive schedule of administration + MMF (2,000 mg) + STER (≥2.5 mg)	CsA (100–250 ng/mL) + MMF (2,000 mg) + STER (≥2.5 mg)	NR	Basiliximab	Immediate	Extended criteria donors: Age ≥60 years; or age ≥50 years with at least 2 risk factors (cerebro-vascular accident, hypertension or serum creatinine >1.5 mg/dL); or anticipated cold ischemia time ≥24 hours; or donation after cardiac death
Refaie et al. 2011[106]	Avoidance of TAC	SRL (10–15 ng/mL)	TAC (4–8 ng/mL)	NR	Alemtuzumab	Immediate	Excluded retransplants
Glotz et al. 2010[107]	Avoidance of TAC	rATG induction (1.25–1.5 mg/kg) + SRL (12–20 ng/mL) + MMF (1,500 mg) + STER (prednisolone 0.1 mg/kg)	TAC (5-9 ng/mL) + MMF (1,500 mg) + STER (prednisolone 0.1 mg/kg)	HPLC	rATG for intervention group only	Immediate	Excluded age>65, PRA >50%

Table E-13. Study design characteristics of avoidance studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Ekberg et al. 2007b[43]	Avoidance of CsA	SRL (4–8 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	IA (CNI) HPLC (SRL)	Daclizumab in intervention group	Immediate	Excluded age>75, PRA >20%
Schaefer et al. 2006[108]	Avoidance of TAC	SRL (8–12 ng/mL) + MMF (2,000 mg) + STER (prednisone 10 mg)	TAC (8–12 ng/mL) + MMF (2,000 mg) + STER (prednisone 5–10 mg) or withdrawal of STER	NR	ATG	Immediate	NR
Flechner et al. 2002[109]	Avoidance of CsA	SRL (5–10 ng/mL) + MMF (2,000 mg) + STER (prednisone 7.5 mg)	CsA (200–250 ng/mL) + MMF (2,000 mg) + STER (prednisone 7.5 mg)	IA (CsA) HPLC-MS (SRL)	Basiliximab	Immediate	Excluded age>70, retransplants
Groth et al. 1999[110]	Avoidance of CsA	SRL (15 ng/mL) + AZA (2 mg/kg) + STER (prednisone or prednisolone 10 mg)	CsA (100–200 ng/mL) + AZA (2 mg/kg) + STER (prednisone or prednisolone 10 mg)	IA (CsA) HPLC (SRL)	Not used	Immediate	Excluded age>60, PRA >70%

ATG/rATG=antithymocyte globulin/rabbit antithymocyte globulin; AZA=azathioprine; CNI=calcineurin inhibitors; CsA=cyclosporine; HPLC=high performance liquid chromatography; IA=immunoassay; mg/kg=milligram per kilogram; mg/mL=milligram per milliliter; MMF=mycophenolate mofetil group; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; SRL=sirolimus; TAC=tacrolimus

Table E-14. Study population characteristics of avoidance studies

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Asher et al. 2013[97]	Avoidance of TAC	United Kingdom	19	19	Deceased	49 vs. 49	NR	NR	NR
Vincenti et al. 2010[98] BENEFIT Follow-ups: Larsen 2010[99] Vincenti et al. 2012[100] Rostaing et al. 2013[101] Dobbels et al. 2014[102]	Avoidance of CsA	Worldwide	445	221	Deceased: 280 Living related: 280 Living unrelated: 106	44 vs. 43	70%	61%	15% vs. 18%
Durrbach et al. 2010[103] BENEFIT-EXT Follow-ups: Larsen et al. 2010[99] Pestana et al. 2012[104] Charpentier et al. 2013[105] Dobbels et al. 2014[102]	Avoidance of CsA	Worldwide	359	184	NR	57 vs. 56	68%	76%	47% vs. 49%
Refaie et al. 2011[106]	Avoidance of TAC	Egypt	10	11	Living related	30 vs. 34	75%	NR	NR
Glotz et al. 2010[107]	Avoidance of TAC	France Belgium	71	70	Deceased	48 vs. 47	62%	84%	NR
Ekberg et al. 2007b[43]	Avoidance of CNI	Worldwide	399	390	Deceased: 512 Living related: 231 Living unrelated: 46	45 vs. 46	65%	93%	NR
Schaefer et al. 2006[108]	Avoidance of TAC	USA	41	78	Deceased Living	NR	NR	NR	NR

Table E-14. Study population characteristics of avoidance studies (continued)

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Flechner et al. 2002[109]	Avoidance of CsA	USA	31	30	Deceased: 40 Living related: 14 Living unrelated: 7	48 vs. 47	66%	67%	13% vs. 17%
Groth et al. 1999[110]	Avoidance of CsA	Europe	41	42	Deceased	48 vs. 42, p=0.02	65%	93%	17% vs. 7%

BENEFIT=Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial; CNI=calcineurin inhibitors; CsA=cyclosporine; NR=not reported; TAC=tacrolimus

Table E-15. Clinical outcomes of avoidance studies

Reference	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Asher et al. 2013[97]	Avoidance of TAC	5/19 vs. 2/19	0	1 vs. 0	3 months eGFR: 56.7 vs. 58.0, p=NS (Cockcroft-Gault) 6 months eGFR: 67.1 vs. 55.8, p=NS 9 months eGFR: 49.9 vs. 61.9, p=NS 1 year eGFR: 51.1 vs. 59.1	3 months: 128±1.45 vs. 141±1.59, p=NS 6 months: 130±1.47 vs. 134±1.52, p=NS 9 months: 153±1.73 vs. 153±1.73, p=NS 1 year: 143±1.62 vs. 142±1.62, p=NS	10/19 SRL switched to TAC within 3 months

Table E-15. Clinical outcomes of avoidance studies (continued)

Reference	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Vincenti et al. 2010[98] BENEFIT Follow-ups: Larsen et al. 2010[99] Vincenti et al. 2012[100] Rostaing et al. 2013[101] Dobbels et al. 2014[102]	5 years	1 year: 88/445 vs. 16/221 Banff 97: Grade 1A: 11 vs. 3 Grade 1 B: 11 vs. 5 Grade 2A: 33 vs. 6 Grade 2B: 30 vs. 2 Grade 3: 3 vs. 0 2 years: 92 vs. 20 3 years: 92 vs. 21 5 years: 93 vs. 22	1 year: 9 vs. 8 2 years: 12 vs. 8 3 years: 19 vs. 10 5 years: 19 vs. 13	1 year: 10 vs. 7 2 years: 15 vs. 13 3 years: 19 vs. 15 5 years: 24 vs. 22	1 year measured GFR: 65.0±30.0 vs. 63.4±27.7 vs. 50.4±18.7, p<0.01 2 years measured GFR: 65.0±27.2 vs. 67.9±29.9 vs. 50.5±20.5 3 years eGFR (MDRD): 65.2±26.3 vs. 65.8±27.0 vs. 44.4±23.6 5 years eGFR (MDRD): 74.1±18.9 vs. 76.4±19.0 vs. 53.0±17.2, p<0.01	NR	1 year: 133 overall 2 years: 167 overall
Durrbach et al. 2010[103] BENEFIT-EXT Follow-ups: Larsen et al. 2010[99] Pestana et al. 2012[104] Charpentier et al. 2013[105] Dobbels et al. 2014[102]	5 years	1 year: 64/359 vs. 26/184 Banff 97: Grade 1A: 4 vs. 2 Grade 1B: 9 vs. 2 Grade 2A: 27 vs. 17 Grade 2B: 24 vs. 5 2 years: 64 vs. 28 3 years: 66 vs. 29 5 years: 69 vs. 29	1 year: 33 vs. 20 2 years: 38 vs. 22 3 years: 39 vs. 23 5 years: 42 vs. 28	1 year: 12 vs. 8 2 years: 24 vs. 12 3 years: 37 vs. 17 5 years: 51 vs. 23	1 year measured GFR: 52.1±21.9 vs. 49.5±25.4 vs. 45.2±21.1, p<0.01 for more intensive vs. CsA 2 years measured GFR: 51.5±22.2 vs. 49.7±23.7 vs. 45.0±27.2 5 years eGFR: 55.9 vs. 59.0 vs. 44.6	NR	1 year: 149 overall 2 years: 189 overall
Refaie et al. 2011[106]	4 years	2/10 vs. 5/11 Antibody-mediated rejection: 2 vs. 2 Borderline: 0 vs. 2 Grade 1A: 0 vs. 1	2 vs. 1	0 vs. 1	1.83±0.88 mL/second vs. 1.38±0.48 mL/second, p<0.05	114.9±17.7 vs. 114.9±26.4, p=NS	2 vs. 8
Glotz et al. 2010[107]	1 year	12/71 vs. 9/70 Banff 97: Grade 1A: 6 vs. 4 Grade 1B: 2 vs. 3 Grade 2A: 3 vs. 1 Grade 2B: 1 vs. 0 Grade 3: 0 vs. 1	10 vs. 3, p<0.05	3 vs. 2	6 months eGFR: 72.7 vs. 65.2, p<0.05 (Nankivell) 1 year eGFR: 68 vs. 62, p=NS 6 months CrCl: 68.8±21.6 vs. 57.5 ±19.4, p<0.05 (Cockcroft-Gault)	NR	33 vs. 7, p<0.001

Table E-15. Clinical outcomes of avoidance studies (continued)

Reference	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Ekberg et al. 2007b[43]	1 year	6 months: 141/399 vs. 94/390 12 months: 160 vs. 117	33 vs. 32	12 vs. 13	56.7±26.9 vs. 57.1±25.1 (Cockcroft-Gault) 47.5±26.1 vs. 46.2±23.1 (MDRD)	NR	NR
Schaefer et al. 2006[108]	1 year	5/41 vs. 5/78	3 vs. 1	2 vs. 0	NR	3 months: 1.3±0.4 vs. 1.5±0.4 (with STER) vs. 1.4±0.4 (without STER) p=0.01 for intervention group vs. control group with STER	NR
Flechner et al. 2002[109]	1 year	2/31 vs. 5/30 Borderline: 1 vs. 2 Grade 1A: 1 vs. 2 Grade 2A: 1	1 vs. 1	1 vs. 0	6 months: 77.8±21.0 vs. 64.1±19.1, p<0.01 1 year: 81.1±23.9 vs. 61.1±14.6, p<0.01 (Cockcroft-Gault)	6 months: 1.29±0.30 vs. 1.74±0.81 mg/dL, p<0.01 1 year: 1.32±0.33 vs. 1.78±0.76 mg/dL, p<0.01	0 vs. 3
Groth et al. 1999[110]	1 year	6 months: 17/41 vs. 16/42 Banff 93: Grade 1: 6 vs. 9 Grade 2: 9 vs. 6 Grade 3: 2 vs. 1	1 vs. 4	0 vs. 1	3 months: 66.1±3.3 vs. 54.2±3.3, p<0.05 6 months: 66.7±3.6 vs. 59.0±3.4, p=NS 1 year: 69.5±4.1 vs. 58.7±3.6, p=NS (Nankivell)	3 months: 126.2±11.4 vs. 159.2±11.2, p<0.05 6 months: 126.2±8.7 vs. 135.4±8.2, p=NS 1 year: 115.8±8.9 vs. 133.5±7.7, p=NS	24 vs. 19

CrCl=creatinine clearance; CsA=cyclosporine; GFR/eGFR=glomerular filtration rate/estimated glomerular filtration rate; MDRD=modification of diet in renal disease; mg/dL=milligrams per deciliter; NS=not significant; STER=steroids

Table E-16. Adverse events reported in avoidance studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Asher et al. 2013[97]	Avoidance of TAC	NR	NR	NR	NR	NR	NR	2 cases of edema, 1 case of arthralgia, 1 case of sepsis, 1 case of graft dysfunction, all in intervention group
Vincenti et al. 2010[98] BENEFIT Follow-ups: Larsen et al. 2010[99] Vincenti et al. 2012[100] Rostaing et al. 2013[101] Dobbels et al. 2014[102]	Avoidance of CsA	1 year: 18 vs. 16, p=NS 2 years: no change	1 year: 9 vs. 1 2 years: 27 vs. 11 3 years: 28 vs. 12 Post-transplant lymphoproliferative disorder: 5 vs. 1 5 years: 20 vs. 12 (neoplasms included)	1 year: CMV: 30 vs. 19 BK: 13 vs. 9 Pneumonia: 5 vs. 5 Sepsis: 3 vs. 4 UTI: 117 vs. 50 Upper respiratory tract: 46 vs. 26 Nasopharyngitis: 20 vs. 20 Influenza: 32 vs. 10 Oral candidiasis: 18 vs. 13 Bronchitis: 16 vs. 5 Gastroenteritis: 13 vs. 7 2 years: CMV: 24 vs. 7 Pneumonia: 9 vs. 9 UTI: 26 vs. 23 3 years: CMV: 48 vs. 25 BK: 28 vs. 18 Herpes simplex: 6 vs. 2 Herpes zoster: 18 vs. 11 Oral candidiasis: 26 vs. 14 Onchomycosis: 19 vs. 6 Candidiasis: 14 vs. 2 Body tinea: 8 vs. 1 5 years: Pneumonia: 7 vs. 3 UTI: 11 vs. 5 Pyelonephritis: 5 vs. 3	5 years: 8 vs. 4	NR	BP, cholesterol, triglycerides better in intervention group at 1, 2, and 5 years	No difference in GI, lymphocele, pyrexia at 1, 2, and 5 years No difference in metabolic, vascular, nervous system disorders at 5 years

Table E-16. Adverse events reported in avoidance studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Durrbach et al. 2010[103] BENEFIT-EXT Follow-ups: Larsen et al. 2010[99] Pestana et al. 2012[104] Charpentier et al. 2013[105] Dobbels et al. 2014[102]	Avoidance of CsA	1 year: 8 vs. 11, p<0.05 for less intensive belatacept vs. CsA	1 year: 8 vs. 6 Post-transplant lymphoproliferative disorder: 3 vs. 0 2 years: 27 vs. 17 3 years: 31 vs. 19 Post-transplant lymphoproliferative disorder: 5 vs. 0 5 years: 40 vs. 22 Post-transplant lymphoproliferative disorder: 8 vs. 1	1 year: CMV: 45 vs. 24 Pneumonia: 15 vs. 5 UTI: 112 vs. 62 Upper respiratory tract: 22 vs. 14 Nasopharyngitis: 33 vs. 13 Oral candidiasis: 12 vs. 12 Bronchitis: 27 vs. 11 Gastroenteritis: 11 vs. 10 2 years: CMV: 33 vs. 12 Pneumonia: 14 vs. 6 UTI: 38 vs. 17 Pyelonephritis: 10 vs. 8 3 years: CMV: 59 vs. 31 BK: 19 vs. 9 Herpes simplex: 5 vs. 3 Herpes zoster: 32 vs. 9 Oral candidiasis: 18 vs. 12 Onchomycosis: 9 vs. 3 Candidiasis: 9 vs. 6 Body tinea: 5 vs. 7 5 years: CMV: 8 vs. 3 BK: 5 vs. 1 Herpes (all): 18 vs. 10 Pneumonia: 7 vs. 3 Sepsis: 4 vs. 4 UTI: 10 vs. 5 Pyelonephritis: 5 vs. 6 Central nervous system infections: 3 vs. 0 Fungal infections: 31 vs. 12	NR	NR	1 year: BP, triglycerides, non-HDL cholesterol better in intervention group; no difference for LDL and HDL cholesterol 3 years: BP lower in intervention group; no difference in cholesterol or triglycerides 5 years: BP lower in intervention group; total and non-HDL cholesterol lower in intervention group; no difference in HDL cholesterol; triglycerides lower in intervention group	No difference in GI, anemia, leukopenia, hyperkalemia, pyrexia at 1 and 3 years
Refaie et al. 2011[106]	Avoidance of TAC	3/10 vs. 2/11	0 vs. 1 (Kaposi sarcoma)	1 (tuberculosis) vs. 1 (hepatitis B)	NR	7/9 vs. 3/6, p=0.2	No difference in cholesterol	NR

Table E-16. Adverse events reported in avoidance studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Glotz et al. 2010[107]	Avoidance of TAC	11 vs. 14	2 vs. 1 (all lympho-proliferative disorder)	CMV: 1 vs. 14, p<0.001 Herpes: 9 vs. 5, p=NS BK: 2 vs. 0 Pneumonia: 5 vs. 1	NR	No difference in mean values; but 36% of intervention vs. 14% of control have proteinuria (p<0.05)	No difference in hypertension or hyperlipidemia Hypercholester-olemia higher in intervention group	Higher incidence of edema, hypokalemia, anemia, thrombocytopenia in intervention group Higher incidence of hyperkalemia, leukopenia in control group No difference in stomatitis
Ekberg et al. 2007b[43]	Avoidance of CNI	25 vs. 23	10 vs. 5 Post-transplant lymphoproliferative disorder, oral mucosa, renal-cell, non-small-cell lung, small-cell lung, breast, colon, T-cell non-Hodgkin's, B-cell non-Hodgkin's, ovarian vs. 2 basal-cell, squamous-cell, oral mucosa, Kaposi's sarcoma	All "opportunistic infections" (per study designation): 77 vs. 100 CMV: 23 vs. 55 Candida: 19 vs. 29 Herpes simplex: 23 vs. 21 All other infections: 200 vs. 208 UTI: 88 vs. 109 Pneumonia: 19 vs. 18 Nasopharyngitis: 15 vs. 22	11 vs. 15	20 vs. 9	No differences	No difference for anemia, leukopenia, edema, pyrexia, disorders of the nervous system, respiratory system, or vascular system Higher incidence of lymphoceles and serious GI events in low dose SRL group
Schaefer et al. 2006[108]	Avoidance of TAC	6/41 vs. 5/78, p<0.05	NR	Viral infections (CMV, BK): 0 vs. 2	NR	NR	Cholesterol, lipids, triglycerides higher in intervention group compared with steroid-free control group	NR

Table E-16. Adverse events reported in avoidance studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Flechner et al. 2002[109]	Avoidance of CsA	NR	NR	CMV: 3 vs. 2	NR	NR	No difference in BP; cholesterol and triglycerides higher in both groups compared with baseline, but no difference between groups	NR
Groth et al. 1999[110]	Avoidance of CsA	1/41 vs. 1/42	0 vs. 2 (stomach carcinoid, basal cell carcinoma)	CMV: 6 vs. 5 Herpes simplex: 10 vs. 4 Herpes zoster: 0 vs. 1 Oral candida 3 vs. 0 PCP: 0 vs. 1 UTI: 17 vs. 12 Septicemia: 6 vs. 1 Pneumonia: 7 vs. 1	NR	NR	Hypercholester-olemia and hypertriglycer-idemia higher in intervention group ($p<0.01$, both); no difference in hypertension	Hypokalemia, thrombocytopenia, leukopenia, arthralgia higher in intervention group; no difference in anemia

BENEFIT=Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial; BP=blood pressure; BK=BK polyomavirus; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporine; GI=gastrointestinal; HDL=high density lipoprotein; LDL=low density lipoprotein; NR=not reported; NS=not significant; PCP=pneumocystis carinii pneumonia; SRL=sirolimus; TAC=tacrolimus; UTI=urinary tract infection

Table E-17. Study design characteristics of studies comparing two regimens

Reference	Type of Intervention	Minimization Regimen	Comparator Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Rivelli et al. 2015[111]	Minimization of TAC Withdrawal of TAC	Minimization: TAC (3-7 ng/mL) + SRL (6-12 ng/mL) + STER (prednisone 500 mg)	Withdrawal: Withdrawal of TAC + SRL (8-15 ng/mL) + STER (prednisone 500 mg)	HPLC	rATG for deceased donor recipients	3 months	Excluded age >65 and PRA >25%
Burkhalter et al. 2012[112]	Minimization of TAC Withdrawal of TAC	Minimization: TAC (4–8 ng/mL) + SRL (4–8 ng/mL) + EC-MPS (>2 mg/mL)	Withdrawal: Withdrawal of TAC by 50% reduction and then elimination over 2 weeks + SRL (8–12 ng/mL) + EC-MPS (>2 mg/mL)	NR	Basiliximab	3 months	NR

Table E-17. Study design characteristics of studies comparing two regimens (continued)

Reference	Type of Intervention	Minimization Regimen	Comparator Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Han et al. 2011[113]	Minimization of CsA Conversion from CsA to SRL	Minimization: CsA (150–200 ng/mL if 6 months–1 year post-transplant; 100-150 ng/mL if 1–2 years post-transplant, and 50–100 ng/mL if >2 years post-transplant) + MMF + STER	Conversion: Conversion from CsA to SRL (5–8 ng/mL) + MMF + STER	NR	NR	Minimum 6 months	All patients had chronic allograft dysfunction; Excluded retransplants
Pankewycz et al. 2011[114]	Minimization of TAC Conversion from TAC to SRL	Minimization: TAC (4–6 ng/mL) + MMF (1,440 mg) + STER (prednisone 5 mg)	Conversion: Conversion from TAC to SRL (5–10 ng/mL) + MMF (1,440 mg) + STER (prednisone 5 mg)	NR	rATG	3 months	Excluded PRA >30%, retransplants
Cataneo-Davila et al. 2009[115]	Minimization of CNI Conversion from CNI to EVR	Minimization: CNI (CsA or TAC) at 80% reduction from baseline + EVR (3–8 ng/dL) + STER (prednisone 5–10 mg)	Conversion: Conversion from CNI to EVR (5–10 ng/dL) + STER (prednisone 5–10 mg) + either MMF or AZA	NR	NR	Minimum 6 months	All patients had chronic allograft dysfunction
Liu et al. 2007[116]	Minimization of CsA Conversion from CsA to SRL	Minimization: CsA (dose 1.5–2 mg/kg) + MMF (1,500 mg) + STER (prednisone 5 mg)	Conversion: Conversion from CsA to SRL (5–10 ng/mL) + MMF (1,500 mg) + STER (prednisone 5 mg)	FPLA (CsA) HPLC (SRL)	NR	Minimum 1 year	All patients had chronic allograft dysfunction; excluded age>60, PRA >10%
Hamdy et al. 2005[117]	Minimization of TAC Avoidance	Minimization: TAC (3–7 ng/mL) + SRL (6–12 ng/mL) + STER (prednisolone 0.1 mg/kg)	Avoidance: SRL (10–15 ng/mL) + MMF (2,000 mg) + STER (prednisolone 0.1 mg/kg)	NR	Basiliximab	Within 24 hours	Excluded retransplants

Table E-17. Study design characteristics of studies comparing two regimens (continued)

Reference	Type of Intervention	Minimization Regimen	Comparator Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/ Exclusion Criteria
Stallone et al. 2005[118]	Minimization of CNI Conversion from CNI to SRL	Minimization: CsA (C2 target 400–500 ng/mL) or TAC (4–6 ng/mL) + MMF (1,000 mg) + STER (prednisone 5 mg)	Conversion: Conversion from CNI to SRL (6–10 ng/mL) + STER (prednisone 5 mg)	IA (CNI) HPLC (SRL)	NR	1–3 years	All patients had chronic allograft dysfunction
Lo et al. 2004[119]	Minimization of TAC Avoidance	Avoidance: SRL (12–15 ng/mL) + MMF (2,000 mg) + STER (5 mg)	Minimization: TAC (3–6 ng/mL) + SRL (10–15 ng/mL) + STER (5 mg)	HPLC-MS	rATG	Within 2 days	High risk population: 71% African-American; 30% age >50 years; 47% with delayed graft function; all donors deceased

CNI=calcineurin inhibitors; CsA=cyclosporine; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; FPIA=fluorescence polarization immunoassay; HPLC=high performance liquid chromatography; IA=immunoassay; mg/kg=milligram per kilogram; mg/mL=milligram per milliliter; MS=mass spectrometry; MMF=mycophenolate mofetil group; MPS=mycophenolate sodium; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; rATG=rabbit antithymocyte globulin; SRL=sirolimus; STER=steroid; TAC=tacrolimus

Table E-18. Study population characteristics in studies comparing regimens

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Rivelli et al. 2015[111]	Minimization of TAC Withdrawal of TAC	Brazil	Minimization: 23 Withdrawal: 22	NR	Deceased: 29 Living: 16	Minimization: 46 Withdrawal: 45	56%	51%	Minimization: 53% Withdrawal: 29%
Burkhalter et al. 2012[112]	Minimization of TAC Withdrawal of TAC	Switzerland	Minimization: 19 Withdrawal: 18	NR	Deceased: 9 Living: 28	Minimization: 55 Withdrawal: 43 p<0.05	86%	NR	NR
Han et al. 2011[113]	Minimization of CsA Conversion from CsA to SRL	China	Minimization: 29 Conversion: 22	NR	Deceased	Minimization: 44 Conversion: 45	75%	100% Asian	NR

Table E-18. Study population characteristics in studies comparing regimens (continued)

Reference	Type of Intervention	Country/ Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Pankewycz et al. 2011[114]	Minimization of TAC Conversion from TAC to SRL	USA	Minimization: 29 Conversion: 23	NR	Deceased: 24 Living: 28	Minimization: 57 Conversion: 51	69%	13% African-American	Minimization: 17% Conversion: 4%
Cataneo-Davila et al. 2009[115]	Minimization of CNI Conversion from CNI to EVR	Mexico	Minimization: 10 Conversion: 10	NR	Deceased: 5 Living: 15	Minimization: 29 Conversion: 39	45%	NR	NR
Liu et al. 2007[116]	Minimization of CsA Conversion from CsA to SRL	China	Minimization: 64 Conversion: 56	NR	Deceased	Minimization: 36 Conversion: 35	75%	100% Asian	NR
Hamdy et al. 2005[117]	Minimization of TAC Avoidance	Egypt	Minimization: 65 Avoidance: 67	NR	Living	Minimization: 32 Avoidance: 32	75%	NR	NR
Stallone et al. 2005[118]	Minimization of CNI Conversion from CNI to SRL	Italy	Minimization: 50 Conversion: 34	NR	NR	Minimization: 43 Conversion: 49	NR	NR	Minimization: 24% Conversion: 29%
Lo et al. 2004[119]	Minimization of TAC Avoidance	USA	Minimization: 41 Avoidance: 29	NR	Deceased	Minimization: 44 Avoidance: 42	57%	71% African-American	Minimization: 56% Avoidance: 34%

CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; NR=not reported; SRL=sirolimus; TAC=tacrolimus

Table E-19. Clinical outcomes of studies comparing regimens

Reference	Type of Intervention	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Rivelli et al. 2015[111]	Minimization of TAC Withdrawal of TAC	1 year	Minimization: 5 Withdrawal: 5	Minimization: 2 Withdrawal: 3	Minimization: 2 Withdrawal: 1	CrCl, 3 months Minimization: 54.9±14.6 Withdrawal: 57.8±14.7; p=NS CrCL, 1 year Minimization: 57.0±16.6 Withdrawal: 68.1±9.1; p<0.05	3 months Minimization: 1.4±0.3 Withdrawal: 1.4±0.4; p=NS 1 year Minimization: 1.4±0.4 Withdrawal: 1.2±0.4; p<0.05	NR
Burkhalter et al. 2012[112]	Minimization of TAC Withdrawal of TAC	6 months	Minimization: 1 Withdrawal: 2	NR	NR	Minimization: 52 Withdrawal: 45 (Median)	NR	Minimization: NR Withdrawal: 4
Han et al. 2011[113]	Minimization of CsA Conversion from CsA to SRL	4 years	Minimization: 2 Conversion: 2	"graft survival estimate": Minimization: 55% Conversion: 77%	NR	eGFR declined in minimization group over baseline, p<0.05; eGFR higher in conversion group compared with minimization group, p<0.05	NR	NR
Pankewycz et al. 2011[114]	Minimization of TAC Conversion from TAC to SRL	1 year	Minimization: 0 Conversion: 1	Minimization: 0 Conversion: 1	NR	Minimization: 74±15 Conversion: 66±18	NR	Minimization: 1 Conversion: 4
Cataneo-Davila et al. 2009[115]	Minimization of CNI Conversion from CNI to EVR	1 year	Minimization: 1 Conversion: 0	Minimization: 0 Conversion: 0	Minimization: 0 Conversion: 0	Minimization: 76.2±22.6 Conversion: 66.2±13.7	Minimization: 1.24±0.4 Conversion: 1.25±0.3	Minimization: 1 Conversion: 0
Liu et al. 2007[116]	Minimization of CsA Conversion from CsA to SRL	2 years	NR	"graft survival ratio was markedly higher in conversion group"	NR	Minimization: 37±9.7 Conversion: 50±12.3 p<0.05	Minimization: 210.2±66.9 Conversion: 150.4±54.8 p<0.05	NR

Table E-19. Clinical outcomes of studies comparing regimens (continued)

Reference	Type of Intervention	Length of Followup	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Hamdy et al. 2005[117]	Minimization of TAC Avoidance	2 years	Minimization: 12 Avoidance: 9	Minimization: 4 Avoidance: 3	Minimization: 2 Avoidance: 0	Minimization: 79.6±25.5 Avoidance: 94.9±28.9 p<0.05	Minimization: 1.43±0.40 Avoidance: 1.25±0.39 p<0.05	Minimization: 20 Avoidance: 6
Stallone et al. 2005[118]	Minimization of CsA Conversion from CsA to SRL	2 years	Minimization: 0 Conversion: 0	Minimization: 8 Conversion: 1	Minimization: 0 Conversion: 0	Minimization: 47.8±17.6 Conversion: 53.1±21.5	Minimization: 1.99±0.59 Conversion: 1.86±0.60	NR
Lo et al. 2004[119]	Minimization of TAC Avoidance	1 year	Minimization: 4 Avoidance: 2	Minimization: 8 Avoidance: 3	Minimization: 1 Avoidance: 0	Minimization: 52.9±22.8 Avoidance: 72.4±20.0 p<0.05	NR	Minimization: 5 Avoidance: 8

CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; eGFR=estimated glomerular filtration rate; mL/min=milliliter per minute; NR=not reported; SRL=sirolimus; TAC=tacrolimus; µmol/L=micromoles per liter

Table E-20. Adverse events reported in studies comparing regimens

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Rivelli et al. 2015[111]	Minimization of TAC Withdrawal of TAC	NR	NR	NR	NR	NR	NR	Polyomavirus-associated nephropathy: Minimization 0 vs. Withdrawal 2 Acute pyelonephritis: Minimization 1 vs. Withdrawal 1
Burkhalter et al. 2012[112]	Minimization of TAC Withdrawal of TAC	NR	NR	NR	NR	NR	Triglycerides higher in withdrawal group; no difference for cholesterol	NR
Han et al. 2011[113]	Minimization of CsA Conversion from CsA to SRL	NR	NR	1 pneumonia in conversion group	NR	NR	Cholesterol and triglycerides increased in conversion group	NR
Pankewycz et al. 2011[114]	Minimization of TAC Conversion from TAC to SRL	NR	NR	Minimization: 1 BK Conversion: 1 pneumonia, 1 pyelonephritis	NR	1 severe case in conversion group	1 patient in conversion group changed regimen due to elevated triglycerides	NR
Cataneo-Davila et al. 2009[115]	Minimization of CNI Conversion from CNI to EVR	NR	NR	"no severe infections"	NR	NR	Cholesterol and triglycerides higher than baseline in conversion group; no difference in minimization group	NR
Liu et al. 2007[116]	Minimization of CsA Conversion from CsA to SRL	NR	NR	NR	NR	Higher than baseline in both groups, but no difference between groups	Cholesterol and triglycerides higher in conversion group than minimization group; no difference for BP	NR

Table E-20. Adverse events reported in studies comparing regimens (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Hamdy et al. 2005[117]	Minimization of TAC Avoidance	Minimization: 18 Avoidance: 13	NR	Minimization: 14 UTI, 3 tuberculosis, 4 fungal Avoidance: 5 herpes zoster, 23 UTI, 1 tuberculosis, 2 fungal	NR	Minimization: 9 Avoidance: 20	Cholesterol and hyperlipidemia higher in avoidance group	Higher incidence of GI in minimization group; no difference for leukopenia
Stallone et al. 2005[118]	Minimization of CNI Conversion from CNI to SRL	No difference	NR	"no major infections occurred"	NR	Minimization: 0.92±0.52 Conversion: 1.2±0.69	No differences	NR
Lo et al. 2004[119]	Minimization of TAC Avoidance	Minimization: 10 Avoidance: 5	Minimization: 1 post-transplant lymphopro-liferative disorder Avoidance: 1 prostate cancer	No CMV in either group Minimization: 1 sepsis, 4 pneumonia, 2 UTI Avoidance: 4 pneumonia, 2 UTI	NR	NR	Cholesterol, triglycerides, hyperlipidemia increased in both groups over baseline, but no significant differences between groups	No difference for GI, anemia, thrombocytopenia. 28 patients in minimization group and 17 patients in avoidance group were readmitted to hospital

BP=blood pressure; BK=polyomavirus; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; GI=gastrointestinal; NR=not reported; SRL=sirolimus; TAC=tacrolimus; UTI=urinary tract infection

Table E-21. Risk of bias assessment for studies addressing Key Question 3

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Cai et al. 2014[18]	Yes	NR	Yes	NR	NR	NR	Yes	NR	Yes	No	High
Muhlbacher et al. 2014[20]	Yes	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Oh et al. 2014[21]	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	No	Low
Bechstein et al. 2013[22]	NR	NR	Yes	NR	NR	Yes	Yes	Yes	Yes	No	High
Chadban et al. 2013[23]	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Cibrik et al. 2013[24]	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	No	Moderate
Takahashi et al. 2013[25]	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	No	Moderate
Chan et al. 2012[26]	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Kamar et al. 2012[27]	Yes	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	Moderate
Langer et al. 2012[28]	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Paoletti et al. 2012[29]	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Low
Bertoni et al. 2011[30]	NR	NR	Yes	NR	NR	NR	Yes	NR	Yes	Yes	High

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Xu et al. 2011[32]	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	High
Etienne et al. 2010[33]	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Low
Fangmann et al. 2010[34]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	NR	Moderate
Gaston et al. 2009[35]	Yes	NR	Yes	NR	No	NR	Yes	Yes	Yes	No	High
Salvadori et al. 2009[36]	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Spagnoletti et al. 2009[37]	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	High
Bolin et al. 2008[38]	Yes	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Chan et al. 2008[39]	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	No	Moderate
Budde et al. 2007[40]	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Cibrik et al. 2007[41]	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	No	Moderate
Ghafari et al. 2007[44]	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	NR	NR	High
Hernandez et al. 2007[45]	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Moderate

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Frimat et al. 2006[46] Frimat et al. 2010[47]	Yes	NR	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Tang et al. 2006[48]	Yes	NR	Yes	Yes	NR	Yes	Yes	Yes	NR	No	High
Vathsala et al. 2005[49]	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Lo et al. 2004[50]	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	High
Nashan et al. 2004[51]	NR	NR	Yes	NR	NR	NR	Yes	Yes	No	No	High
Stoves et al. 2004[52]	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	No	Moderate
Pascual et al. 2003[53]	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
de Sevaux et al. 2001[54]	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	NR	No	High
Budde et al. 2015[56] Budde et al. 2015[55]	Yes	NR	Yes	Yes	NR	No	Yes	Yes	No	No	High
Rostaing et al. 2015[57]	NR	NR	Yes	NR	No	NR	Yes	Yes	No	No	High
Bensal et al. 2013[58]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Chhabra et al. 2013[59]	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	High
Silva et al. 2013[60]	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Moderate
Budde et al. 2015[61] Budde et al. 2012[62] Budde et al. 2011[63]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Mjornstedt et al. 2012[65]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	No	Moderate
Nafar et al. 2012[66]	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	High
Heilman et al. 2011[67]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	No	Moderate
Rostaing et al. 2011[68]	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	High
Weir et al. 2011[69]	Yes	NR	Yes	NR	Yes	NR	Yes	Yes	No	No	High
Guba et al. 2010[70]	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	No	No	Moderate
Bemelman et al. 2009[71]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	No	Moderate
Schena et al. 2009[72]	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	No	No	Moderate

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Lebranchu et al. 2011[73] Lebranchu 2009[74]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Durrbach et al. 2008[75]	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	No	No	High
Barsoum et al. 2007[76]	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	High
Dudley et al. 2005[77]	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	No	No	Moderate
Watson et al. 2005[78]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Bakker et al. 2003[79]	NR	NR	Yes	Yes	No	NR	Yes	Yes	Yes	NR	High
MacPhee et al. 1998[80]	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	High
Hilbrands et al. 1996[81] Quality of Life	NR	NR	Yes	Yes	Yes	Yes	No	Yes	No	No	High
Hilbrands et al. 1996[81] Renal function, BPAR	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	No	No	High
Asberg et al. 2012[82]	NR	NR	NR	NR	Yes	NR	Yes	NR	Yes	No	High

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Mourer et al. 2012[83]	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Flechner et al. 2011[84]	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	High
Freitas et al. 2011[85]	Yes	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Pascual et al. 2008[86]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Hazzan et al. 2006[87,88])	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	High
Suwelack et al. 2004[89]	NR	NR	Yes	NR	NR	NR	Yes	Yes	No	No	High
Stallone et al. 2003[90]	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	NR	High
Abramowicz et al. 2002[91]	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Moderate
Gonwa et al. 2002[92]	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	High
Schnuelle et al. 2002[93]	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	High
Smak Gregoor et al. 2002[94] Roodnat et al. 2014[95]	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Johnson et al. 2001[96]	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	No	High

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Asher et al. 2013[97]	NR	NR	Yes	NR	No	NR	Yes	Yes	No	NR	High
Vincenti et al. 2010[98-101]	Yes	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	No	Moderate
Durrbach et al. 2010[99,103-105]	Yes	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	No	Moderate
Refaie et al. 2011[106]	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	High
Glotz et al. 2010[107]	NR	NR	Yes	Yes	No	NR	Yes	Yes	Yes	No	High
Schaefer et al. 2006[108]	NR	NR	Yes	NR	NR	NR	Yes	Yes	NR	NR	High
Flechner et al. 2002[109]	Yes	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	Moderate
Groth et al. 1999[110]	Yes	Yes	Yes	NR	No	NR	Yes	Yes	Yes	No	Moderate
Chadban et al. 2014[19]	Yes	Yes	Yes	NR	No	No	Yes	Yes	No	No	High
Holdaas et al. 2011[31]	Yes	NR	Yes	NR	No	NR	Yes	Yes	Yes	No	High
Ekberg et al. 2007a[42]	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Ekberg et al. 2007b[43]	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	No	No	Moderate
Rivelli et al. 2015[111]	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Low

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

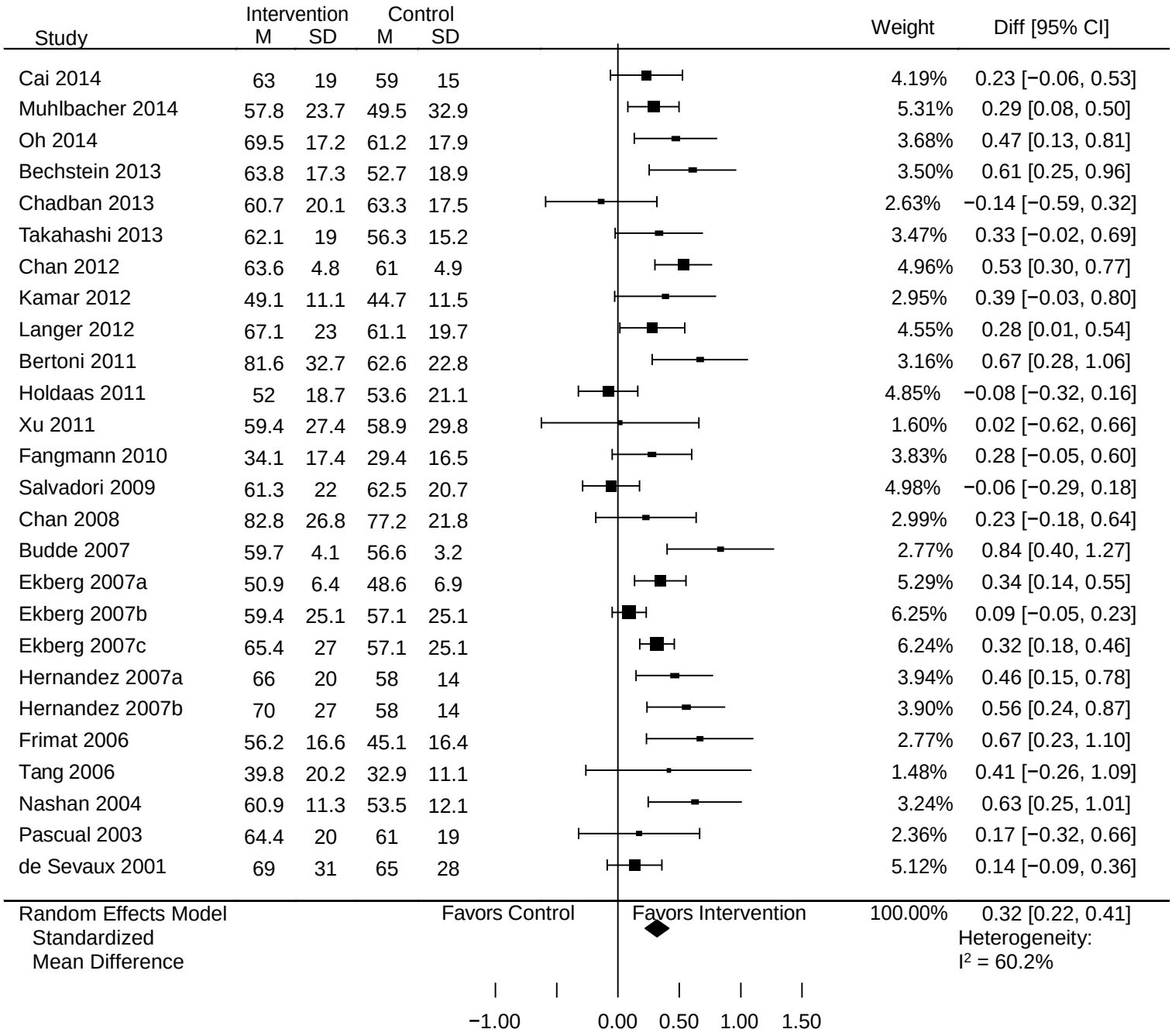
Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Burkhalter et al. 2012[112]	Yes	Yes	Yes	NR	No	NR	Yes	Yes	Yes	NR	Moderate
Han et al. 2011[113]	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	High
Pankewycz et al. 2011[114]	NR	NR	Yes	NR	No	NR	Yes	Yes	No	No	High
Cataneo-Davila et al. 2009[115]	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	High
Liu et al. 2007[116]	NR	NR	Yes	NR	NR	NR	Yes	Yes	NR	NR	High
Hamdy et al. 2005[117]	NR	NR	Yes	NR	No	NR	Yes	Yes	Yes	NR	High
Stallone et al. 2005[118]	NR	NR	Yes	Yes	NR	Yes	Yes	Yes	NR	Yes	High
Lo et al. 2004[119]	NR	NR	Yes	NR	No	NR	Yes	Yes	No	No	High

BPAR=Biopsy proven acute rejection; NR=not reported

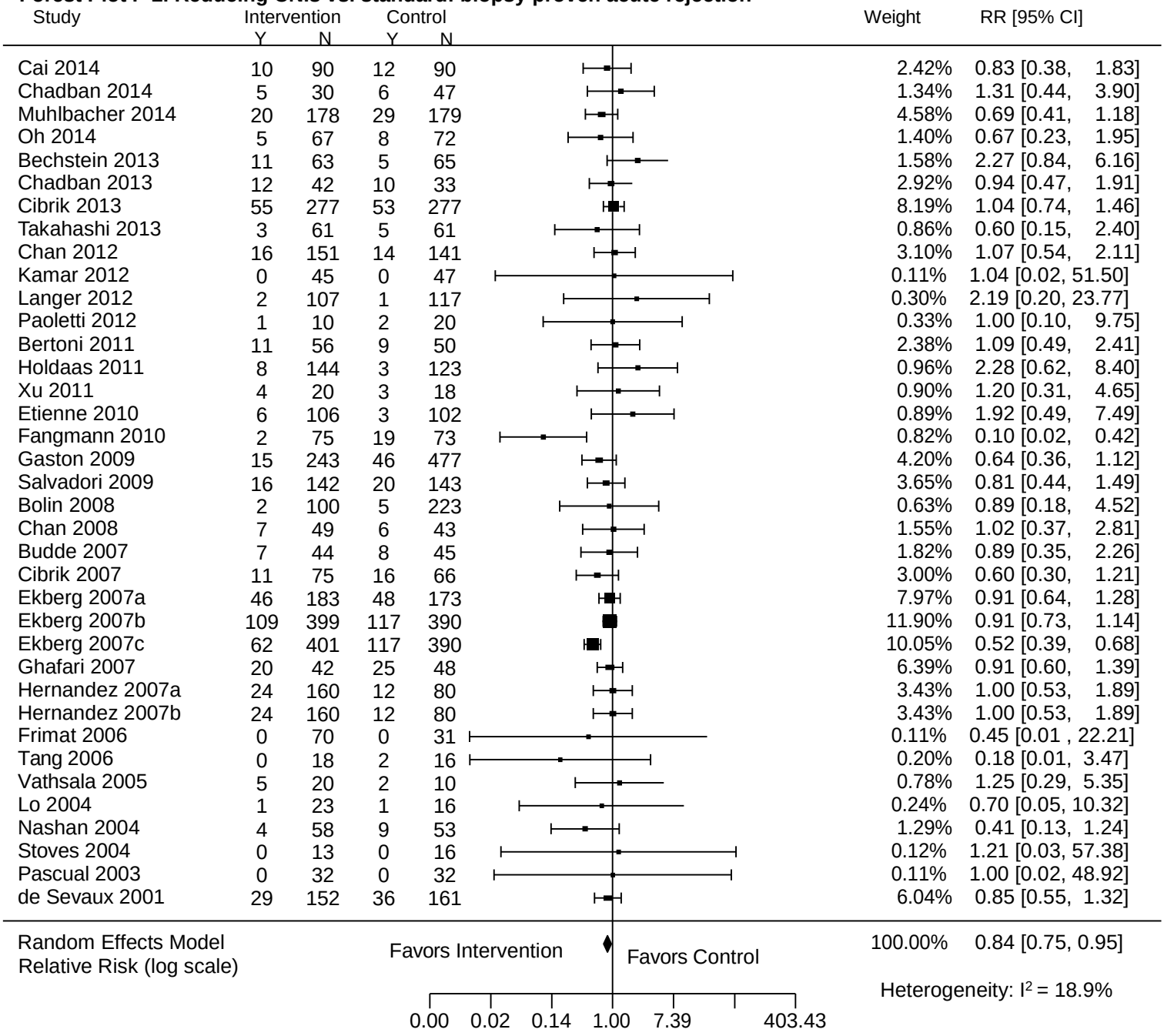
Appendix F. Forest Plots for Key Questions 3a and 3b

This Appendix includes 30 forest plots of data that were analyzed for Key Question 3a and 3b. Forest plots were generated and evaluated for every comparison and outcome that was meta-analyzed and included in the Strength of Evidence tables. For this Appendix, however, we included select comparisons and outcomes that correspond to our major findings and Key Points, and that are likely to be of greatest clinical interest.

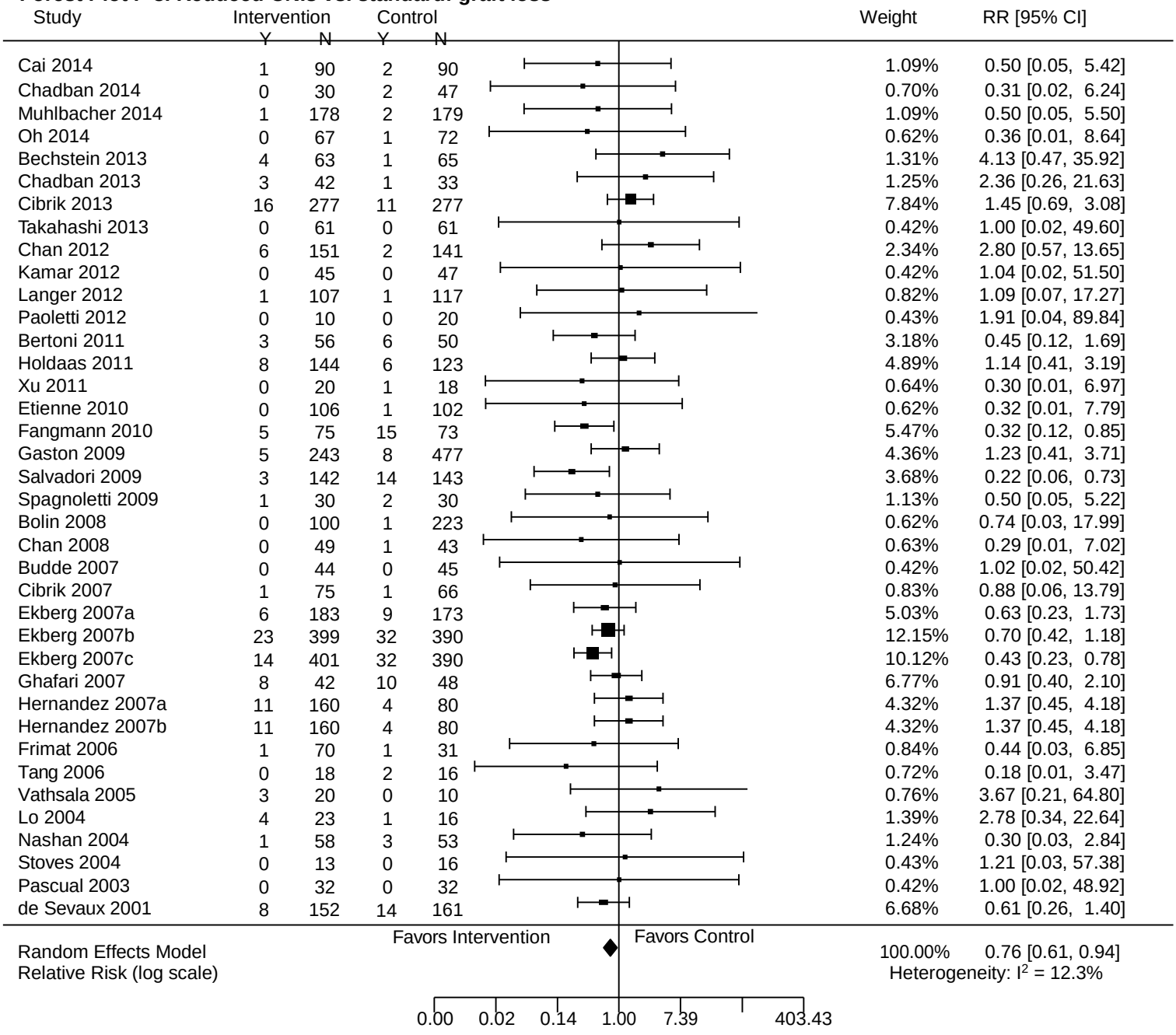
Forest Plot F-1. Reduced CNIs vs. standard: renal function



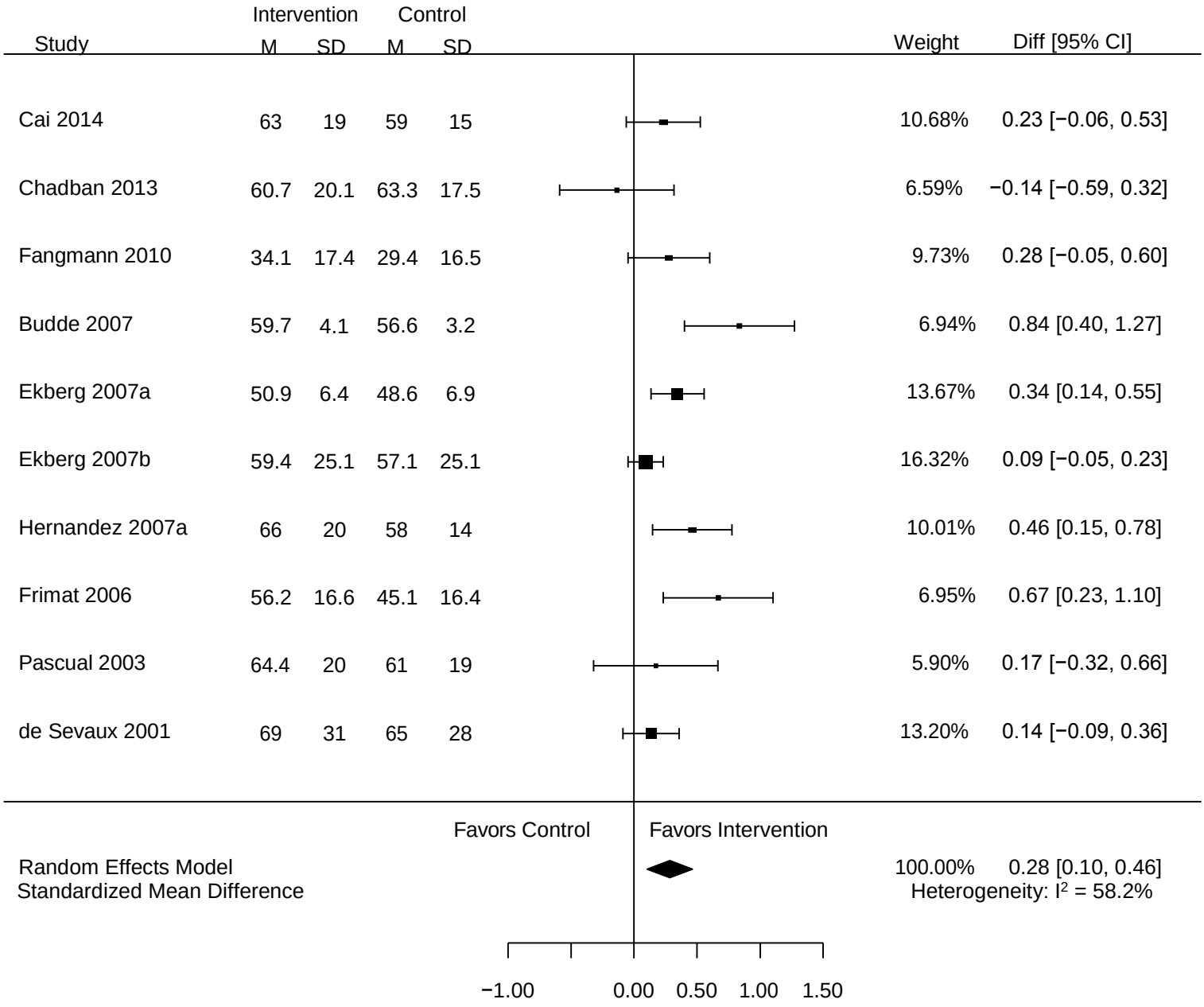
Forest Plot F-2. Reducing CNIs vs. standard: biopsy proven acute rejection



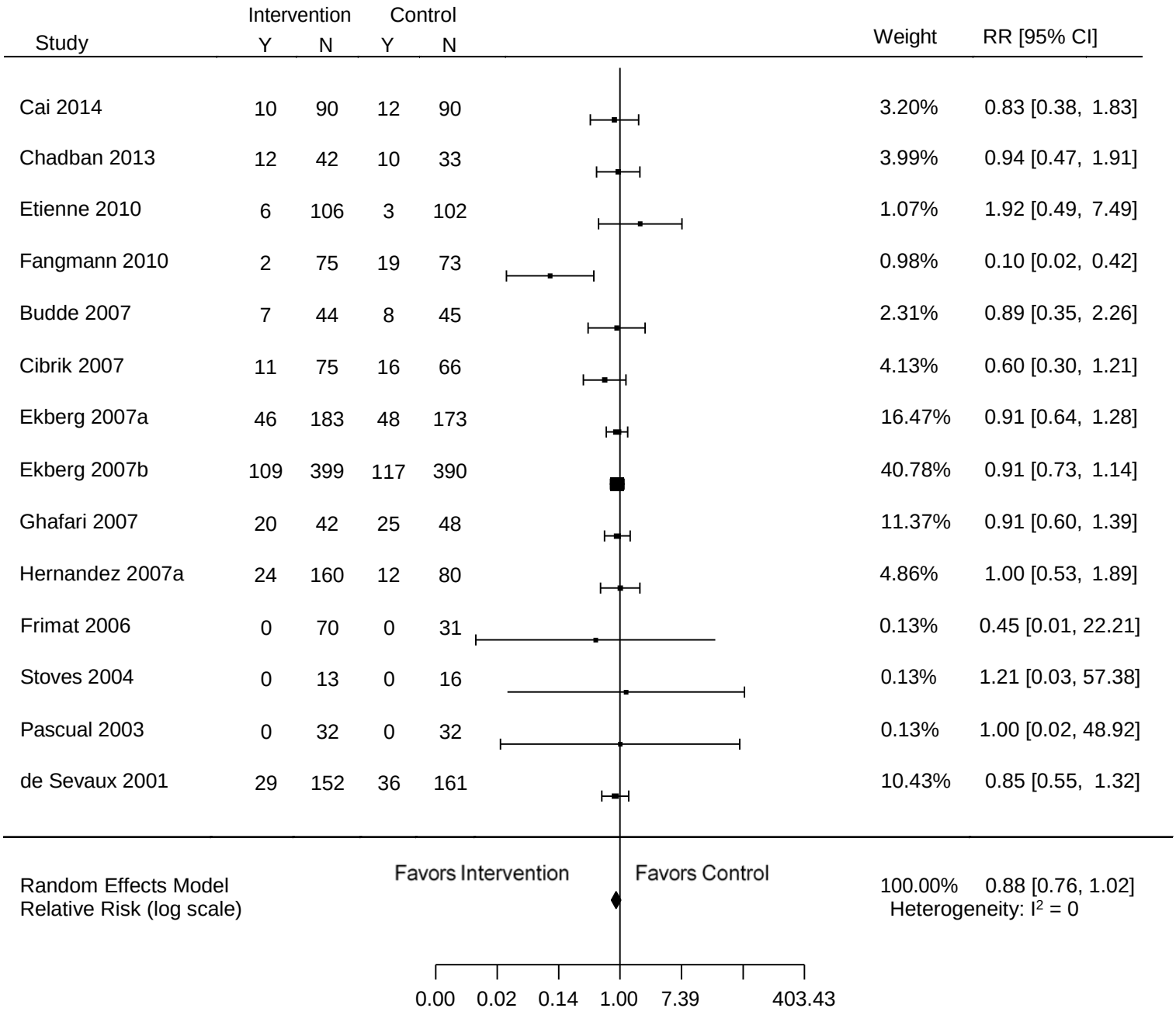
Forest Plot F-3. Reduced CNIs vs. standard: graft loss



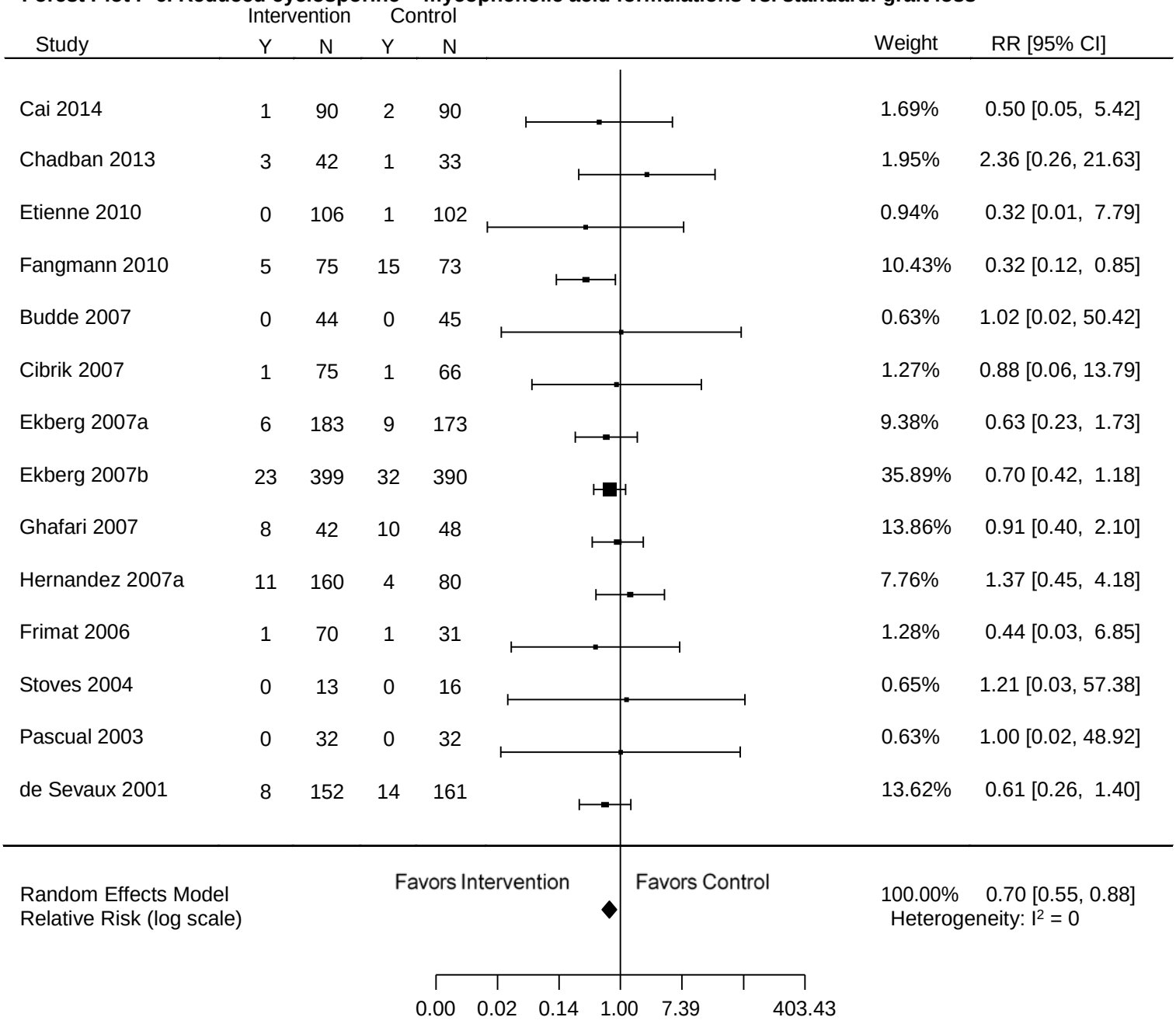
Forest Plot F-4. Reduced cyclosporine + mycophenolic acid formulations vs. standard: renal function



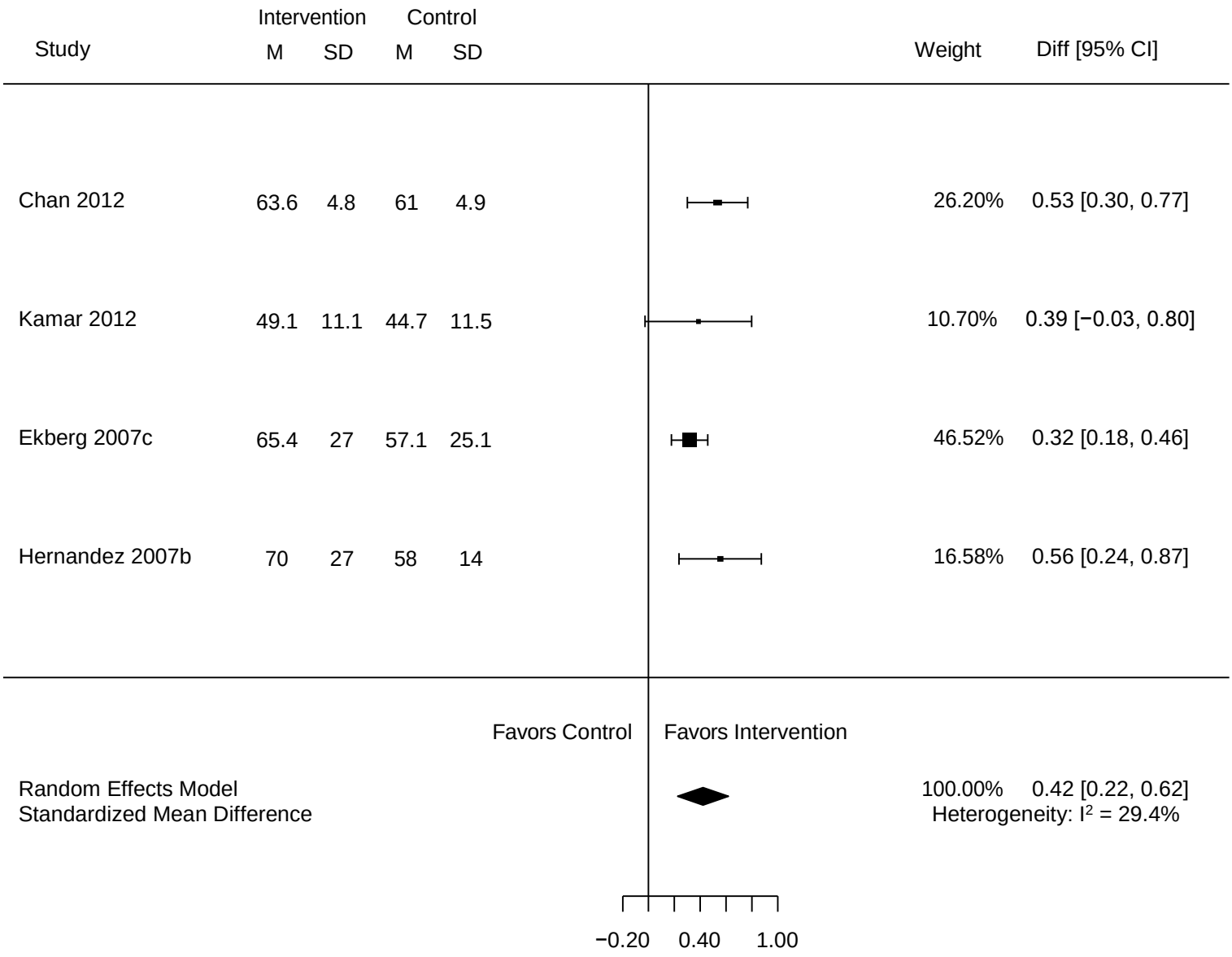
Forest Plot F-5. Reduced cyclosporine + mycophenolic acid formulations vs. standard: biopsy proven acute rejection



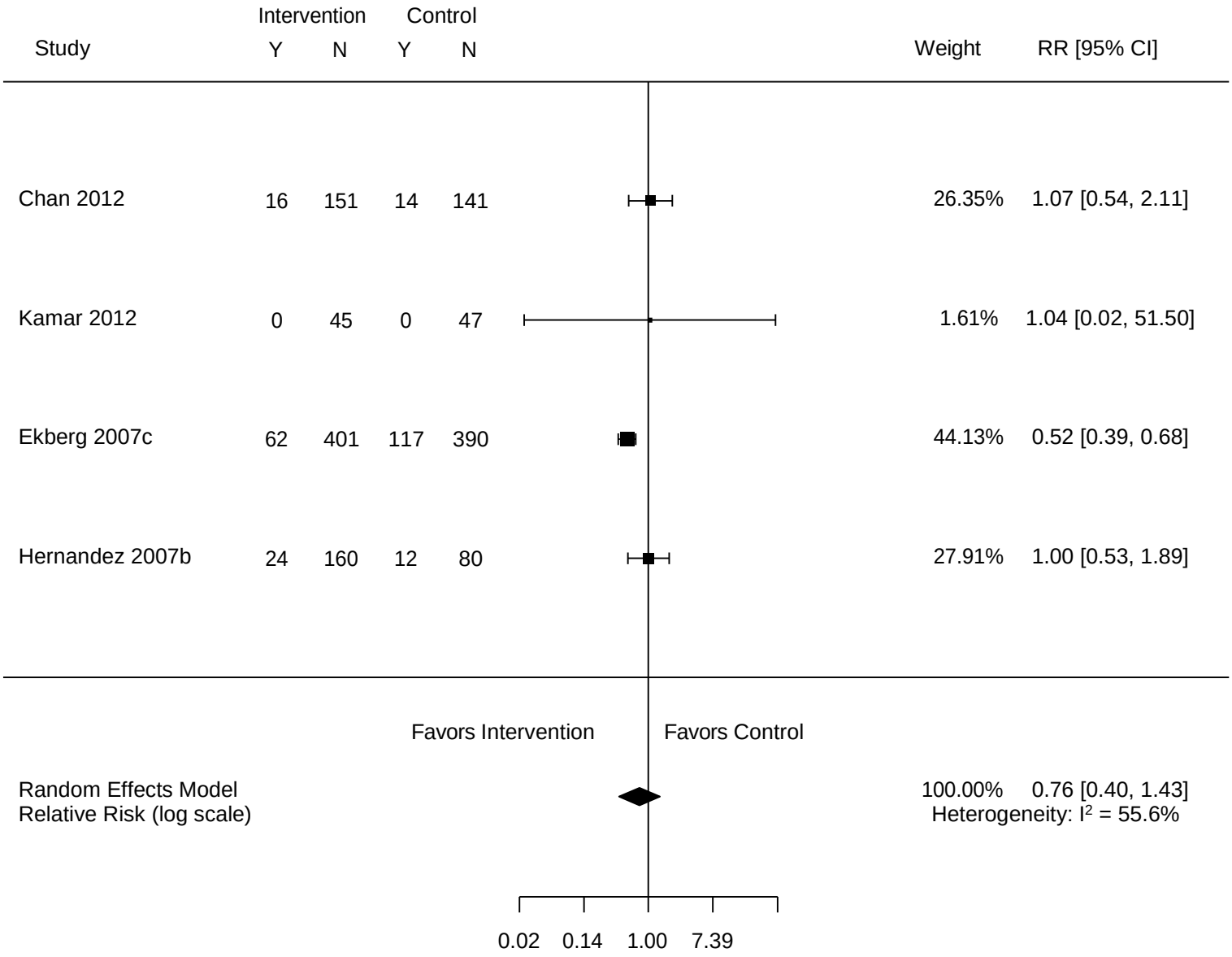
Forest Plot F-6. Reduced cyclosporine + mycophenolic acid formulations vs. standard: graft loss



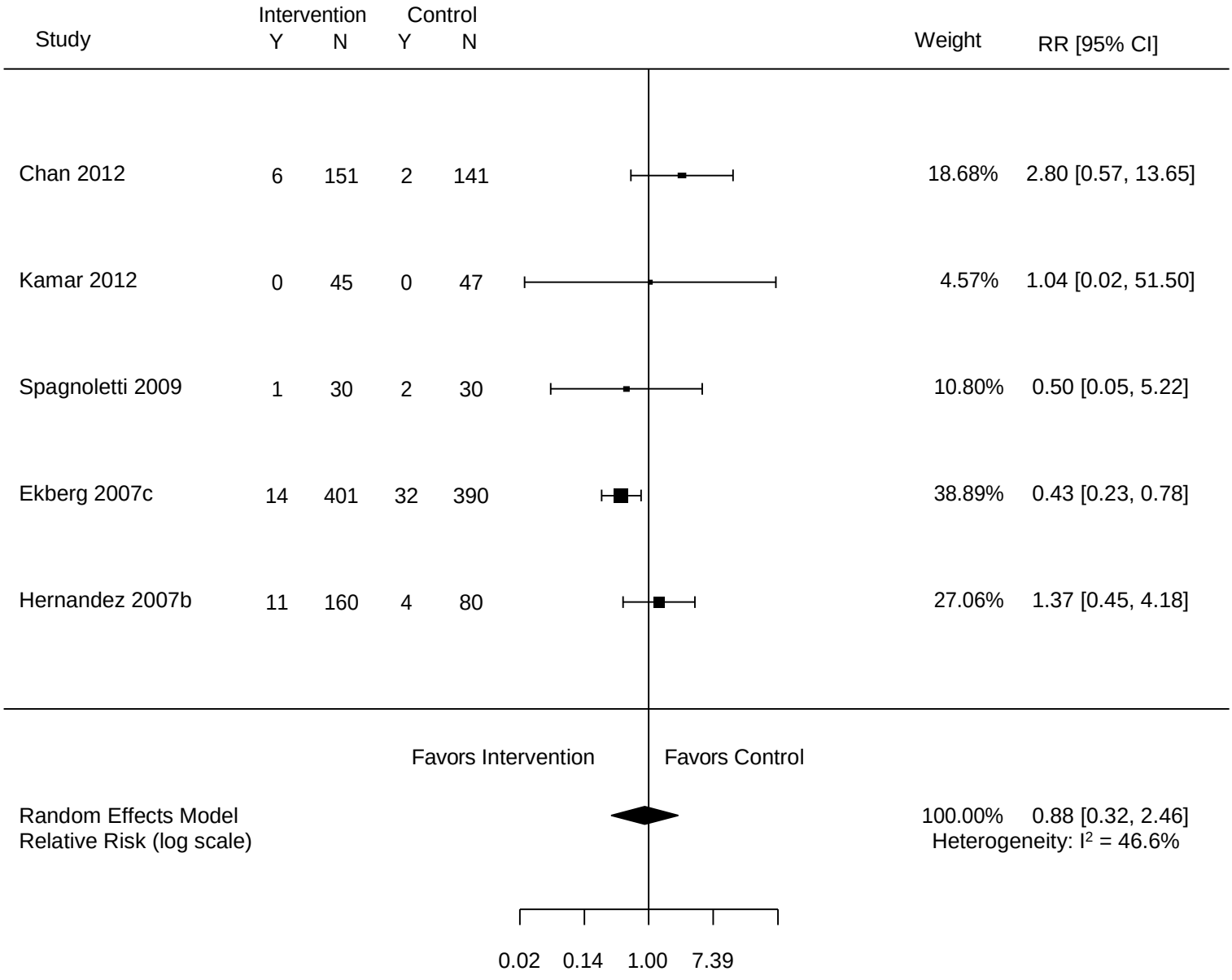
Forest Plot F-7. Reduced tacrolimus + mycophenolic acid formulations vs. standard: renal function



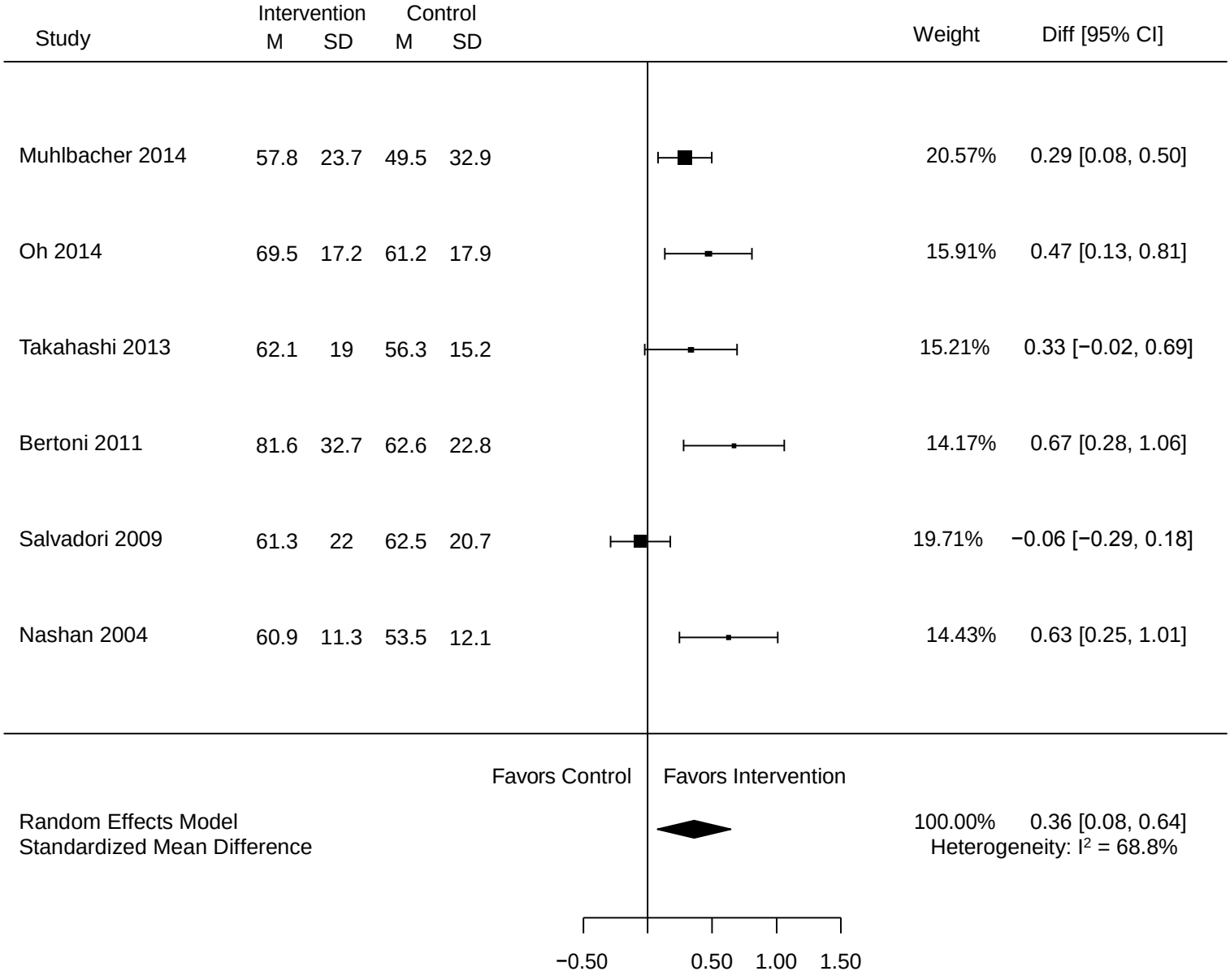
Forest Plot F-8. Reduced tacrolimus + mycophenolic acid formulations vs. standard: biopsy proven acute rejection



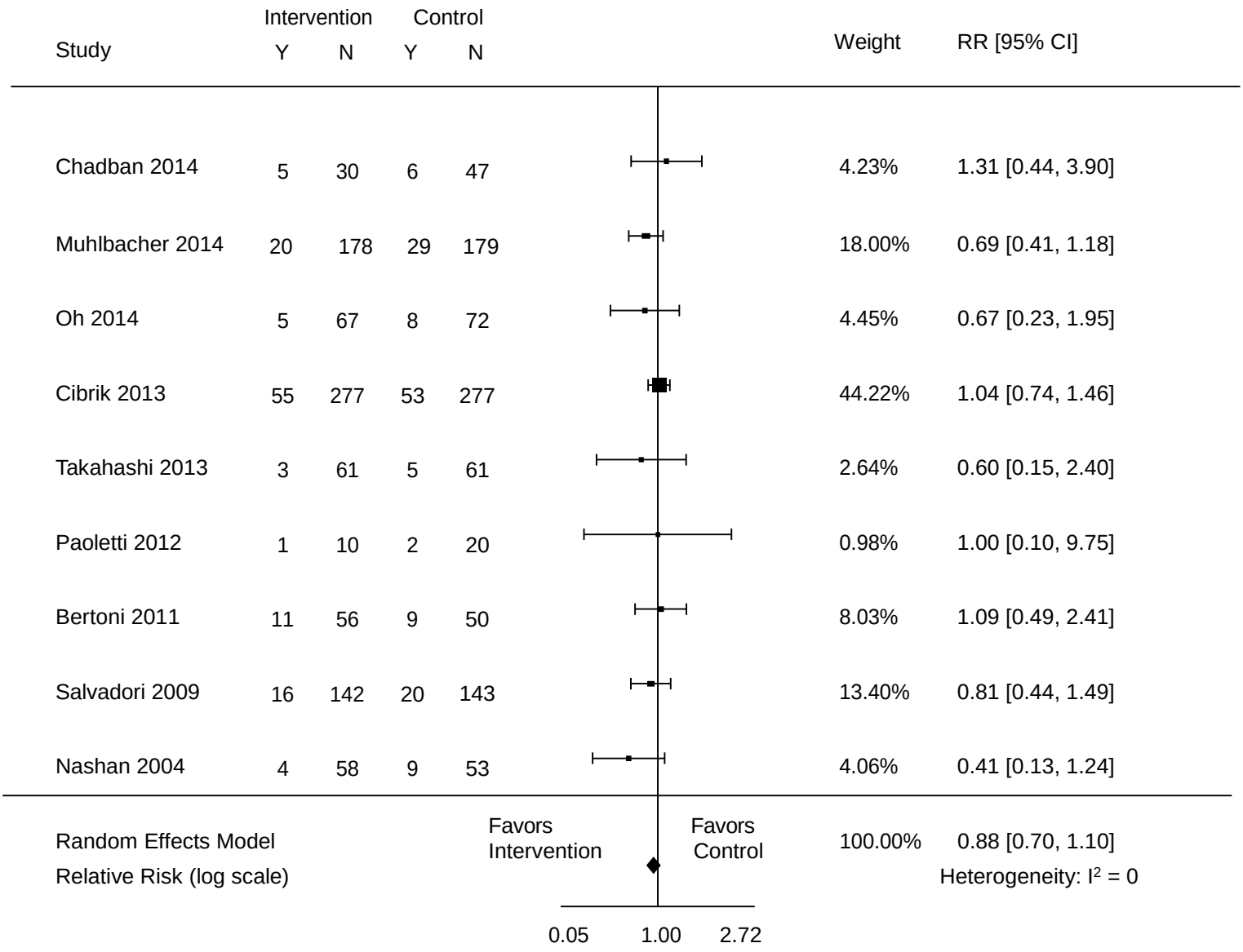
Forest Plot F-9. Reduced tacrolimus + mycophenolic acid formulations vs. standard: graft loss



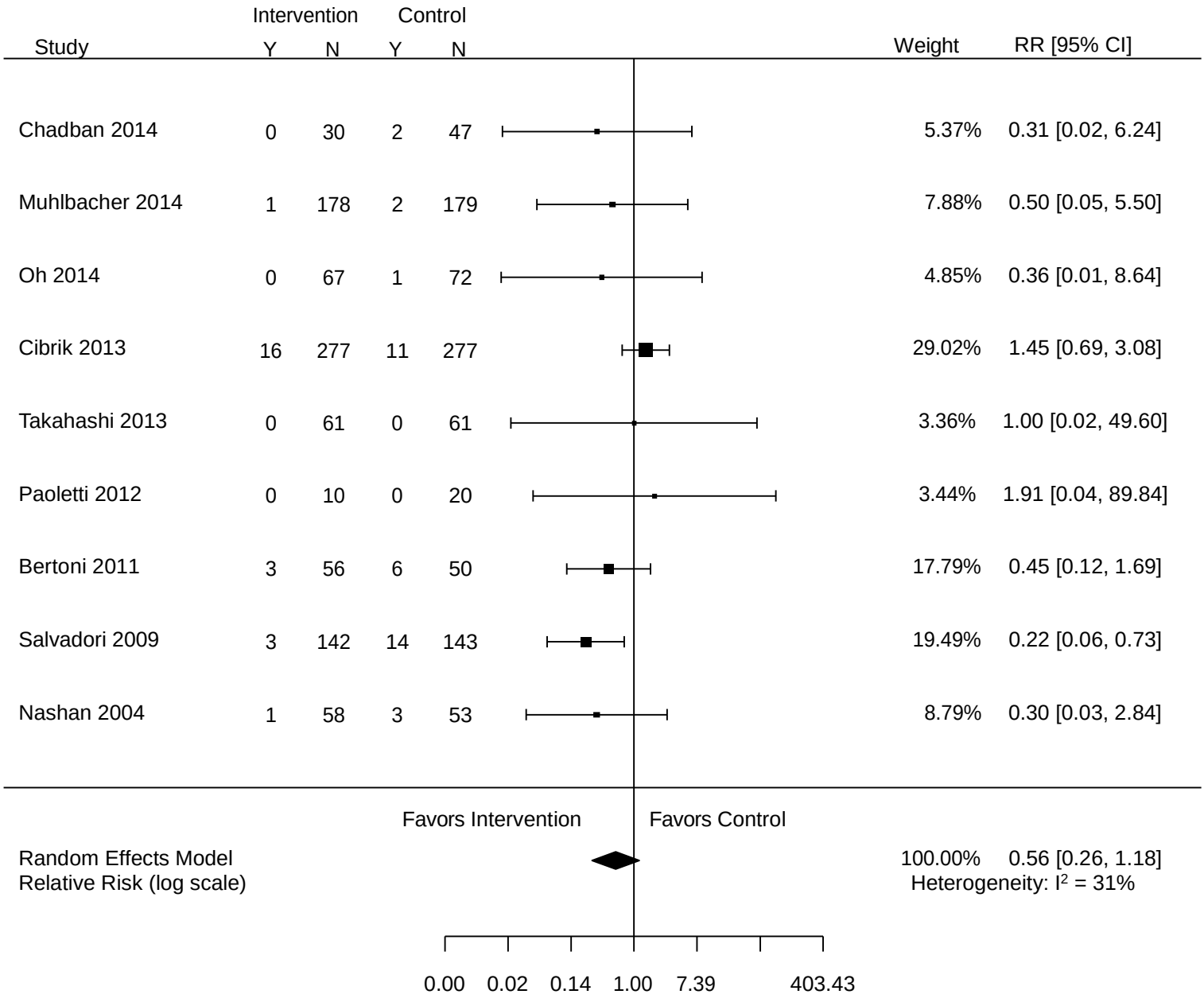
Forest Plot F-10. Reduced cyclosporine + mTOR inhibitors vs. standard: renal function



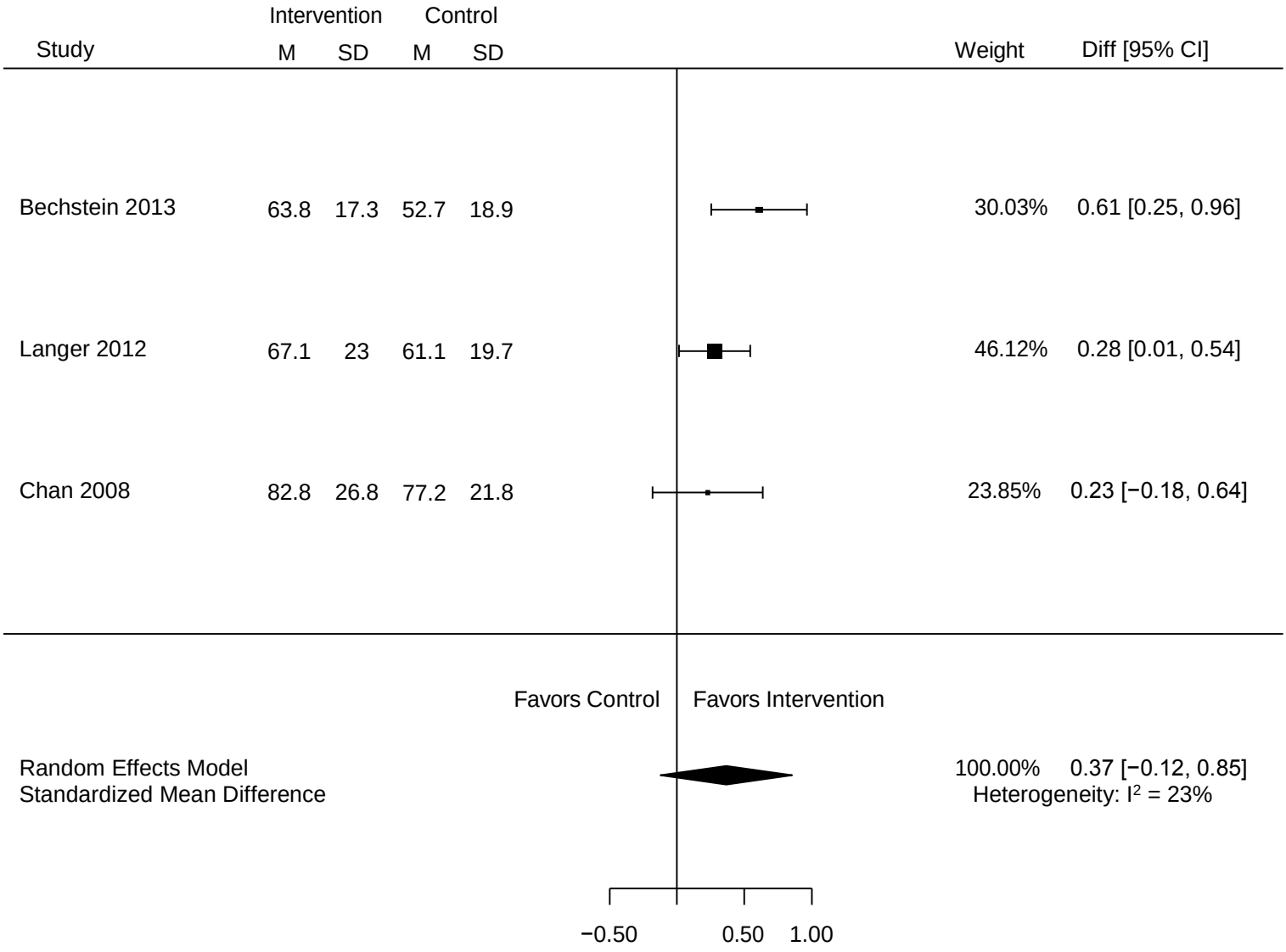
Forest Plot F-11. Reduced cyclosporine + mTOR inhibitors vs. standard: biopsy proven acute rejection



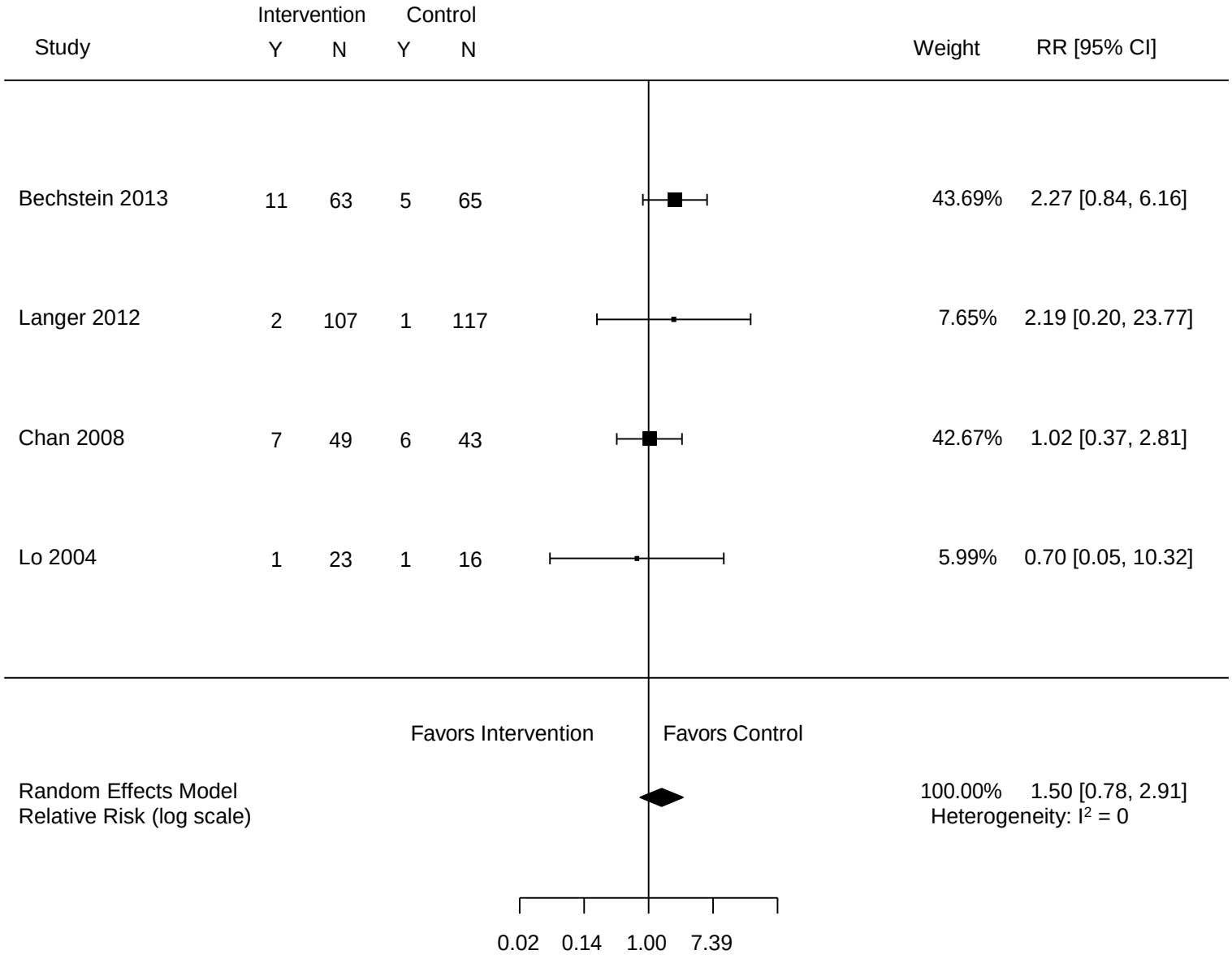
Forest Plot F-12. Reduced cyclosporine + mTOR inhibitors vs. standard: graft loss



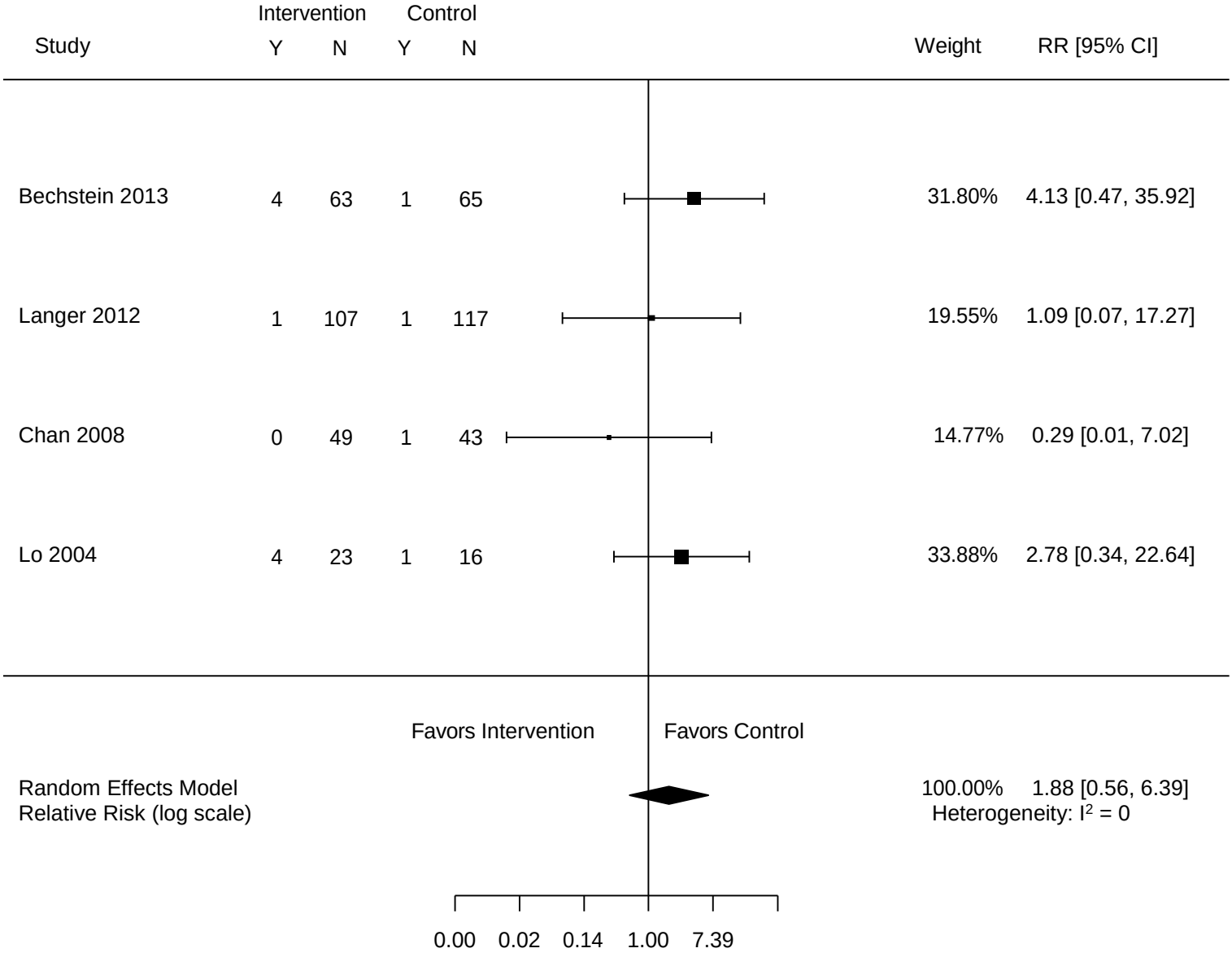
Forest Plot F-13. Reduced tacrolimus + mTOR inhibitors vs. standard: renal function



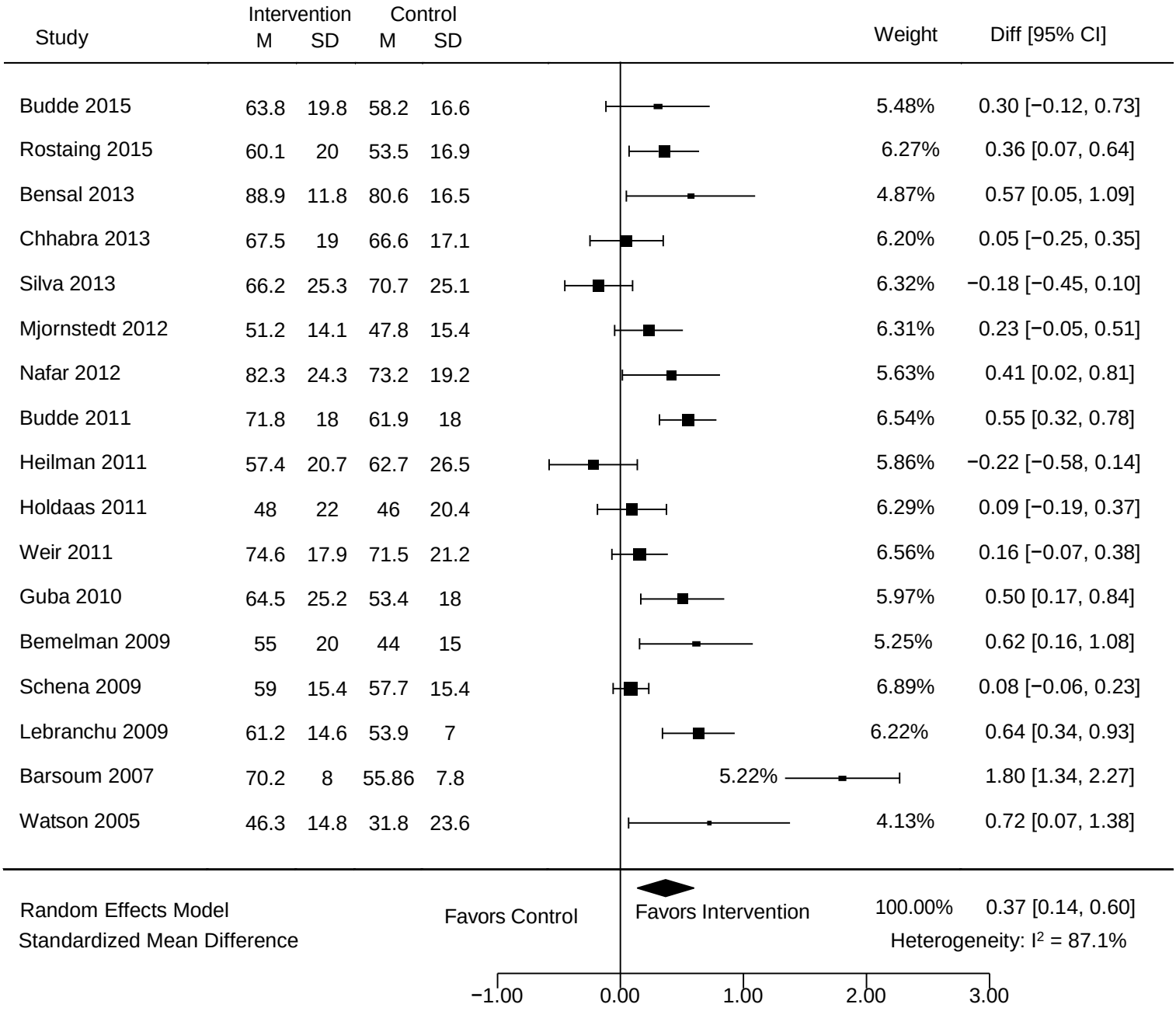
Forest Plot F-14. Reduced tacrolimus + mTOR inhibitors vs. standard: biopsy proven acute rejection



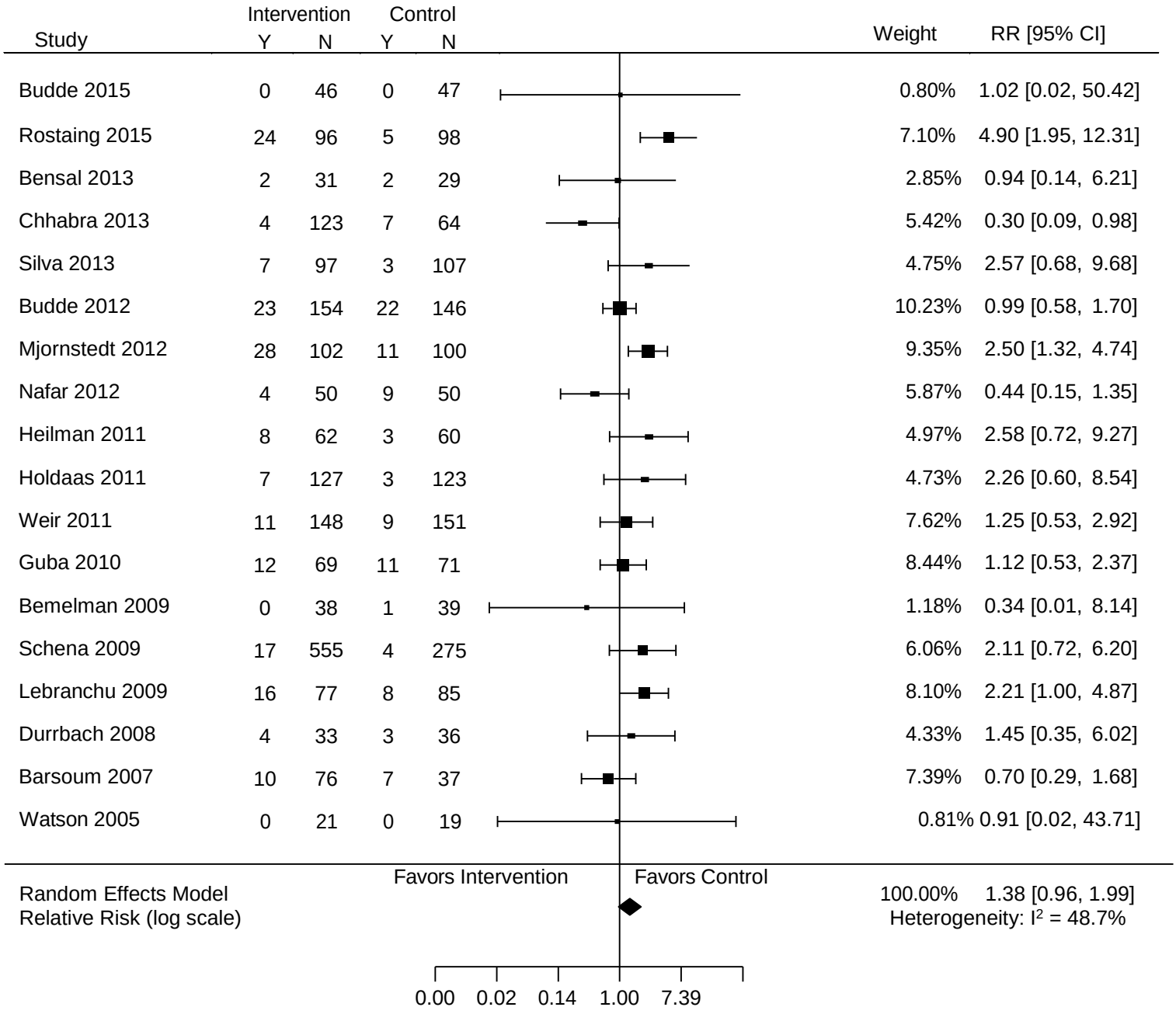
Forest Plot F-15. Reduced tacrolimus + mTOR inhibitors vs. standard: graft loss



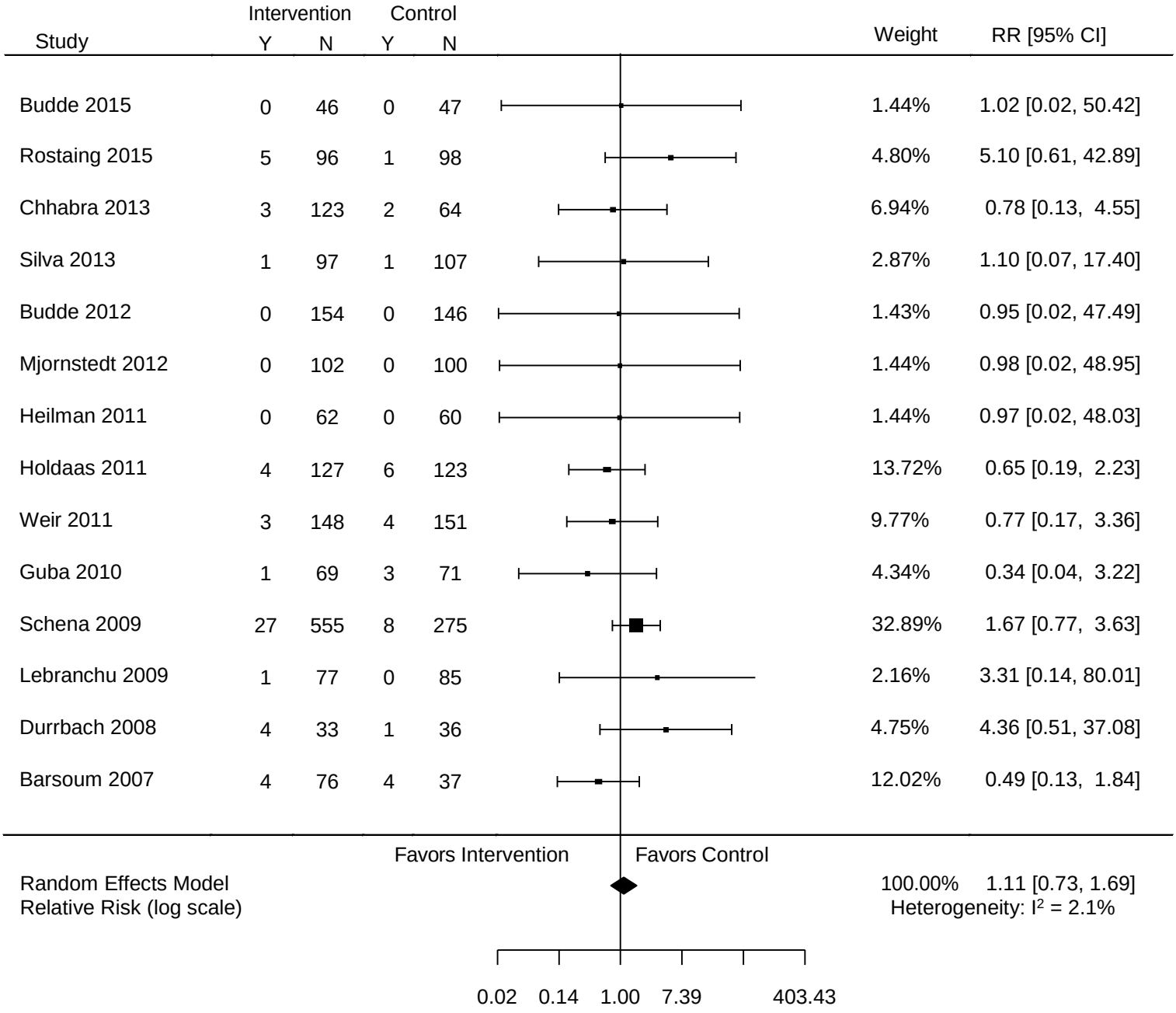
Forest Plot F-16. Conversion from CNIs to mTOR inhibitors: renal function



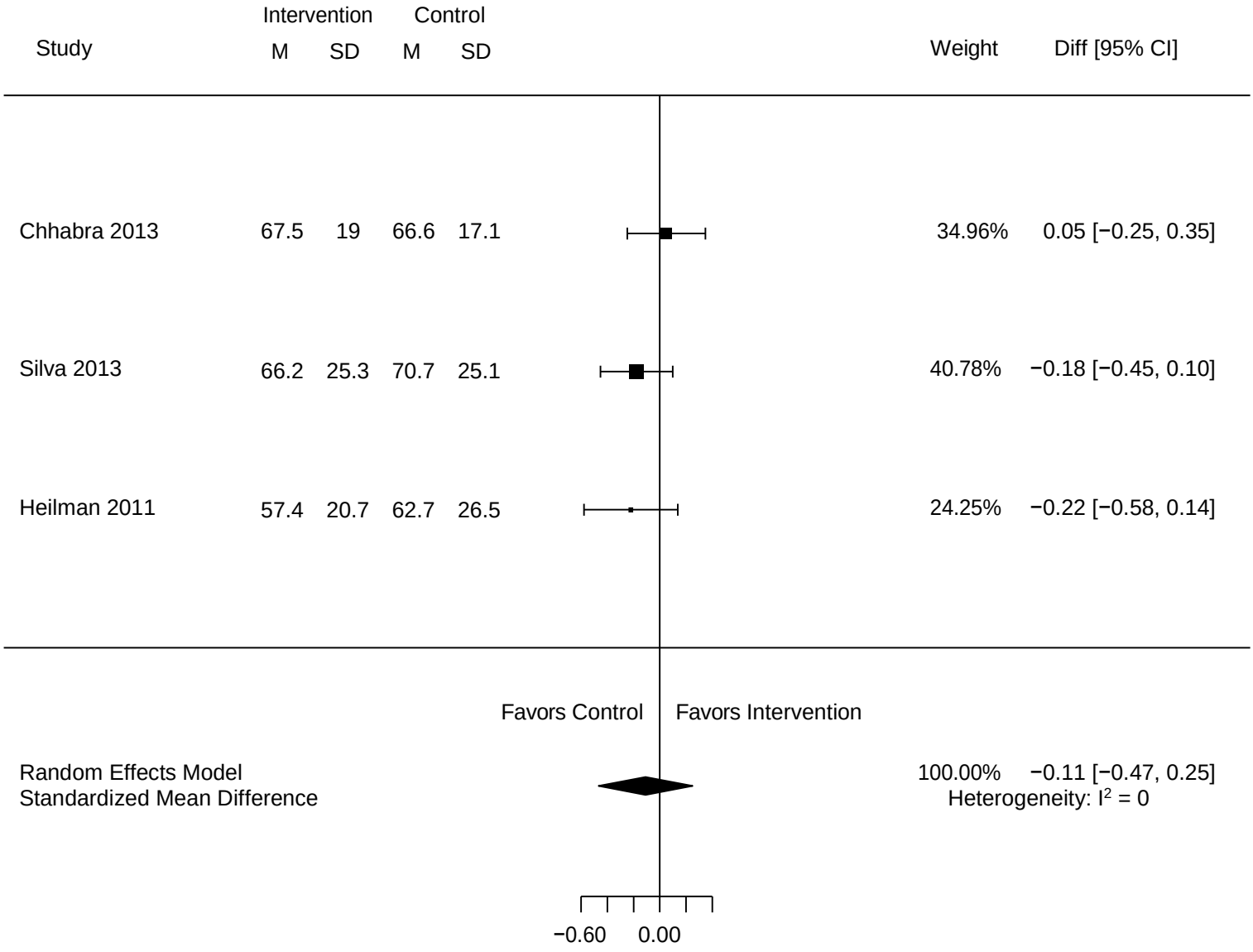
Forest Plot F-17. Conversion from CNIs to mTOR inhibitors: biopsy proven acute rejection



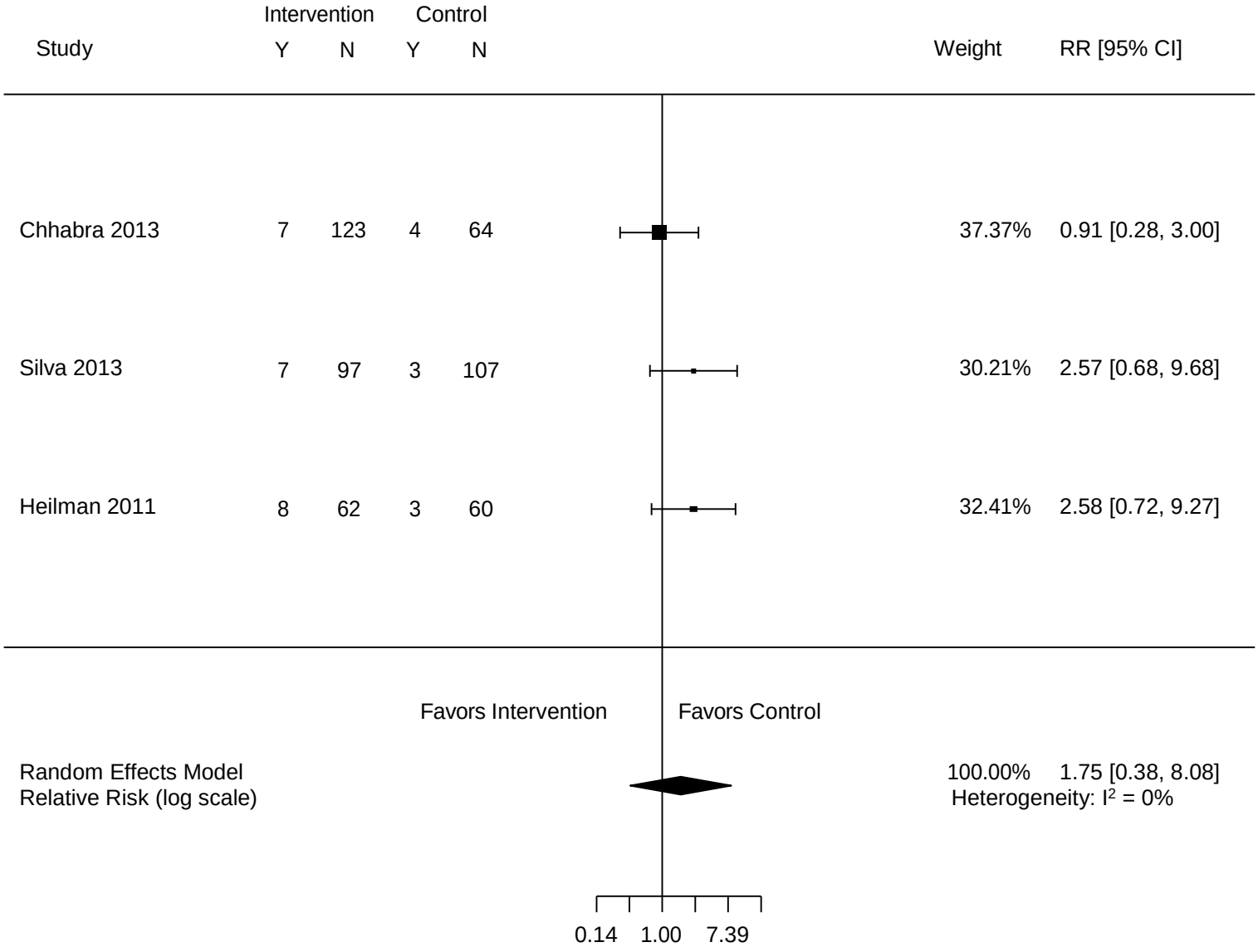
Forest Plot F-18. Conversion from CNIs to mTOR inhibitors: graft loss



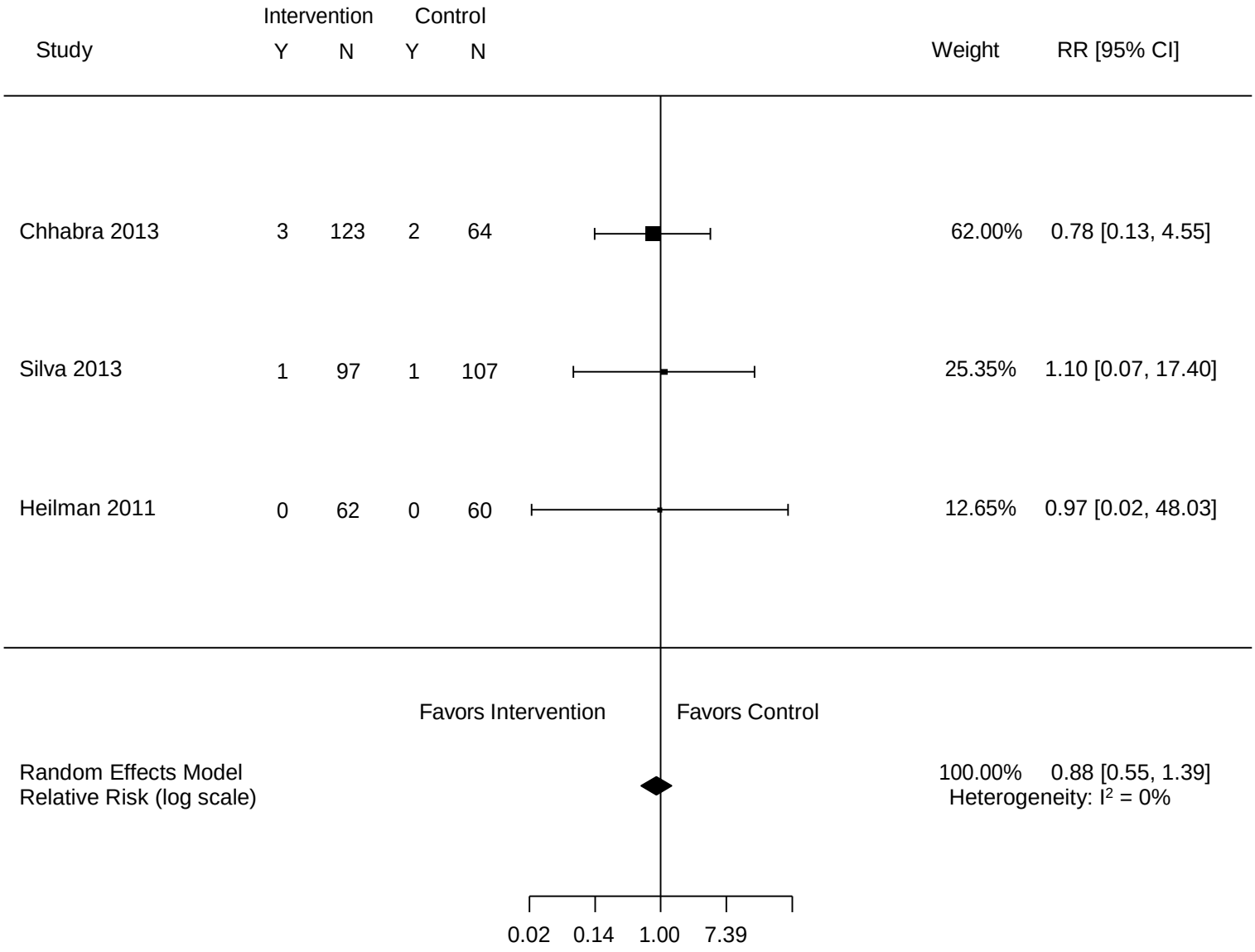
Forest Plot F-19. Conversion from tacrolimus to mTOR inhibitors: renal function



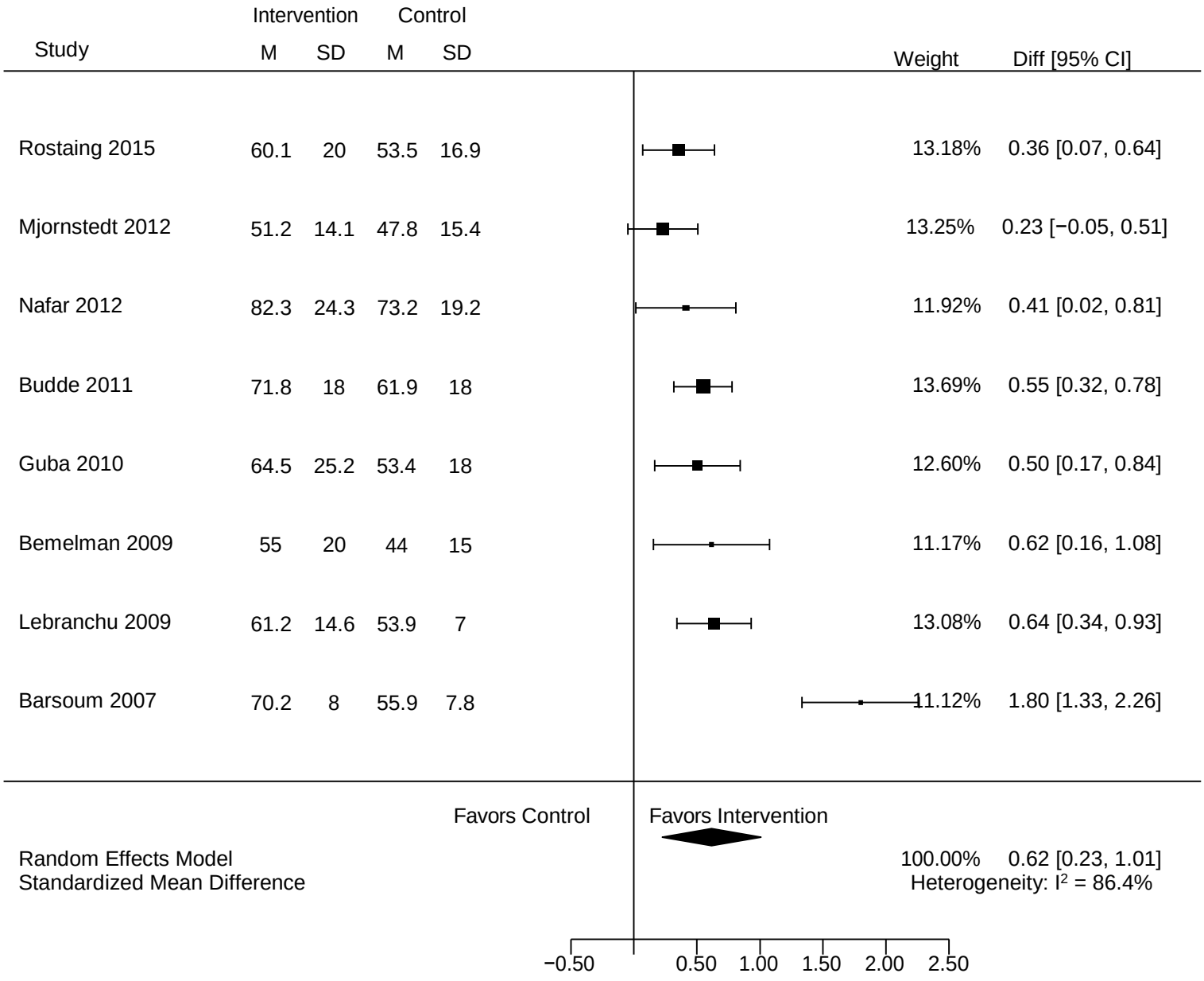
Forest Plot F-20. Conversion from tacrolimus to mTOR inhibitors: biopsy proven acute rejection



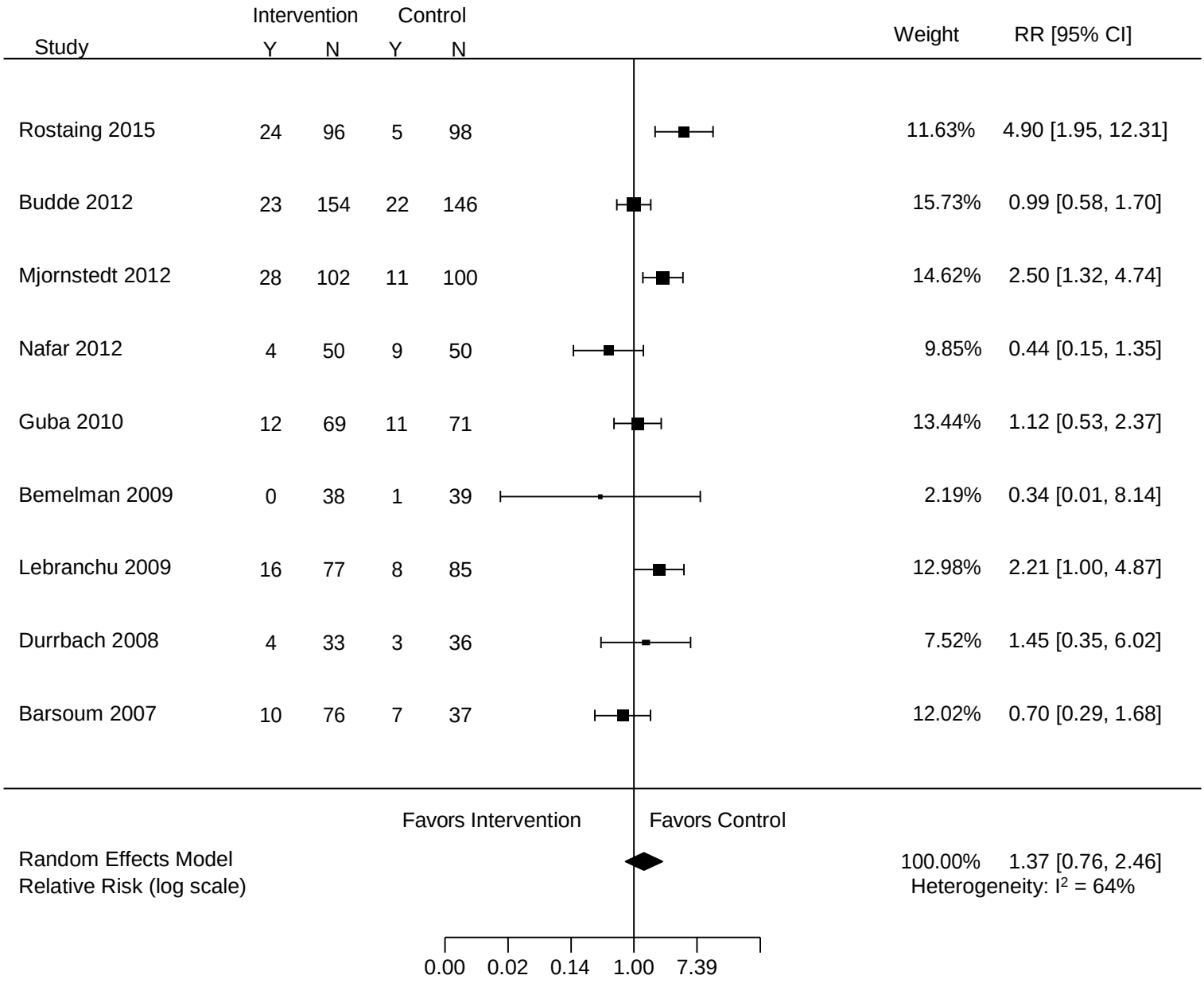
Forest Plot F-21. Conversion from tacrolimus to mTOR inhibitors: graft loss



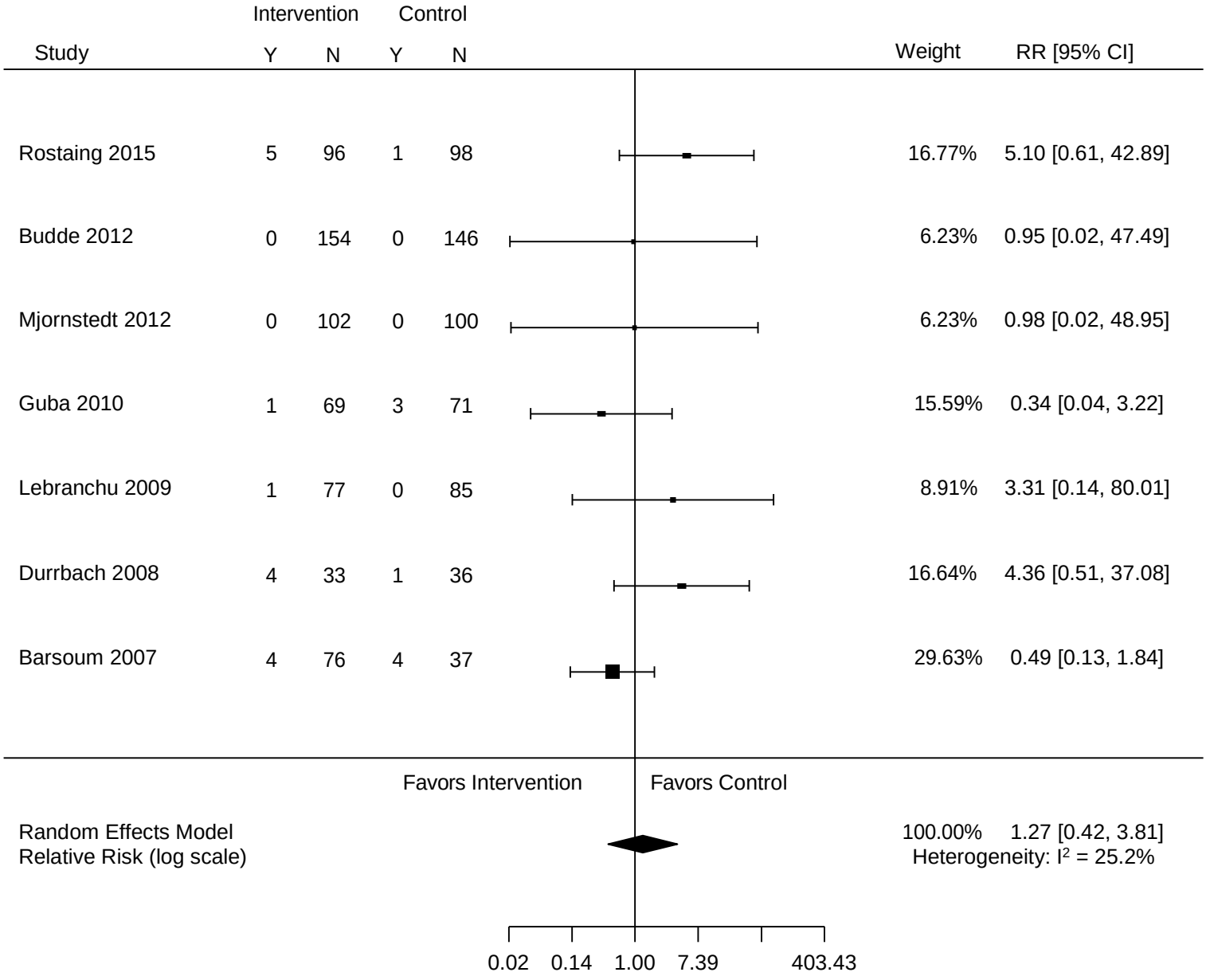
Forest Plot F-22. Conversion from cyclosporine to mTOR inhibitors: renal function



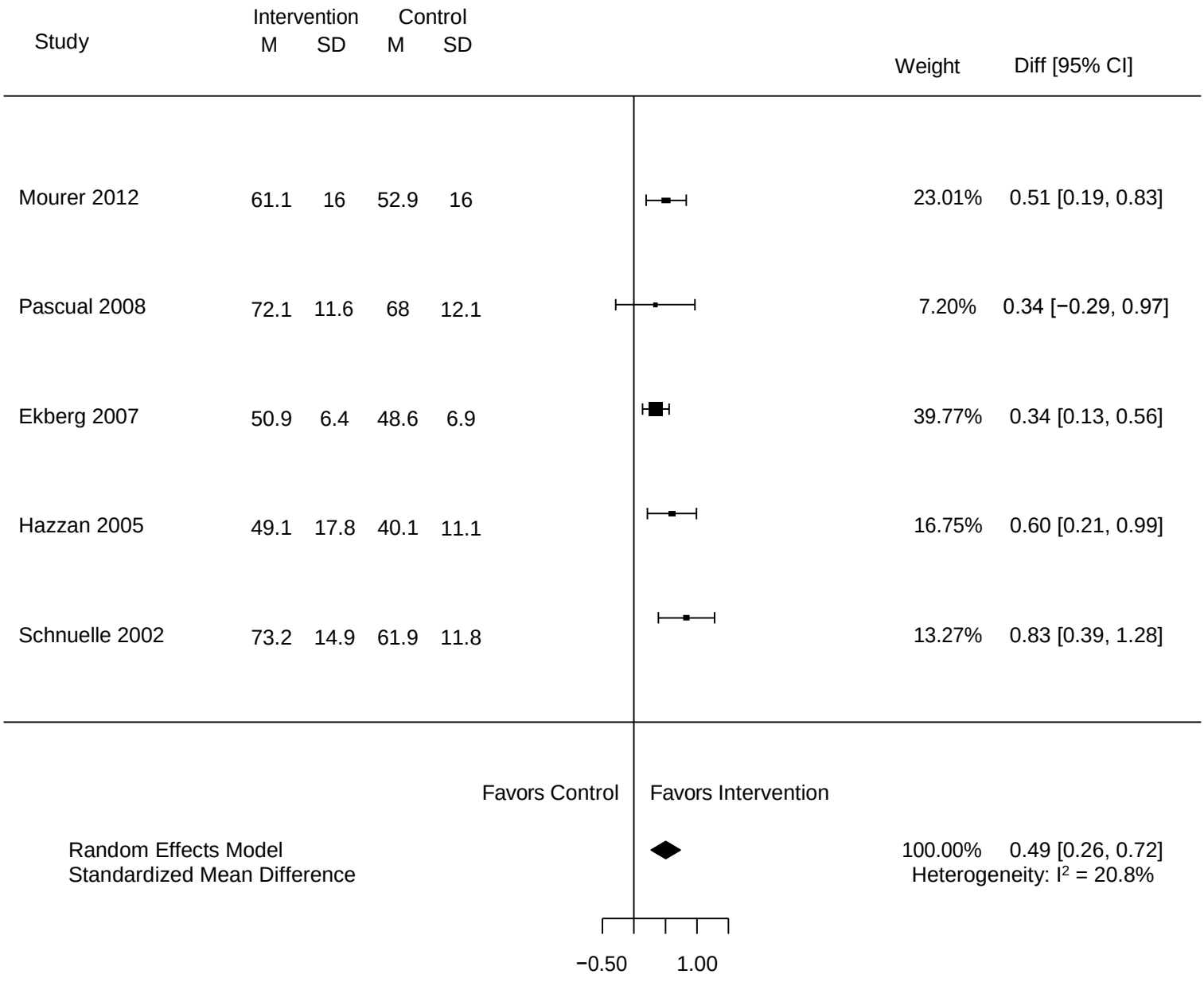
Forest Plot F-23. Conversion from cyclosporine to mTOR inhibitors: biopsy proven acute rejection



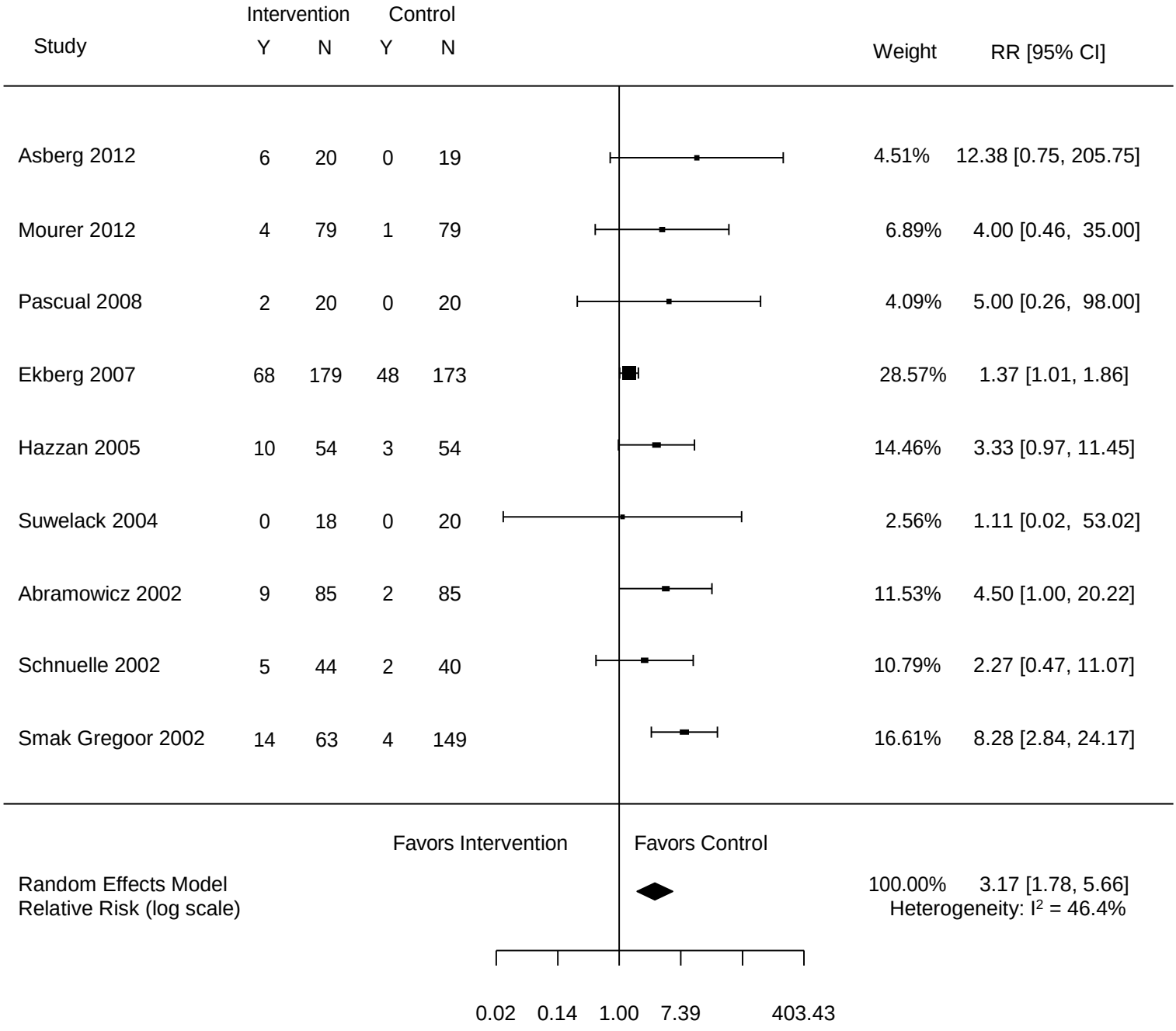
Forest Plot F-24. Conversion from cyclosporine to mTOR inhibitors: graft loss



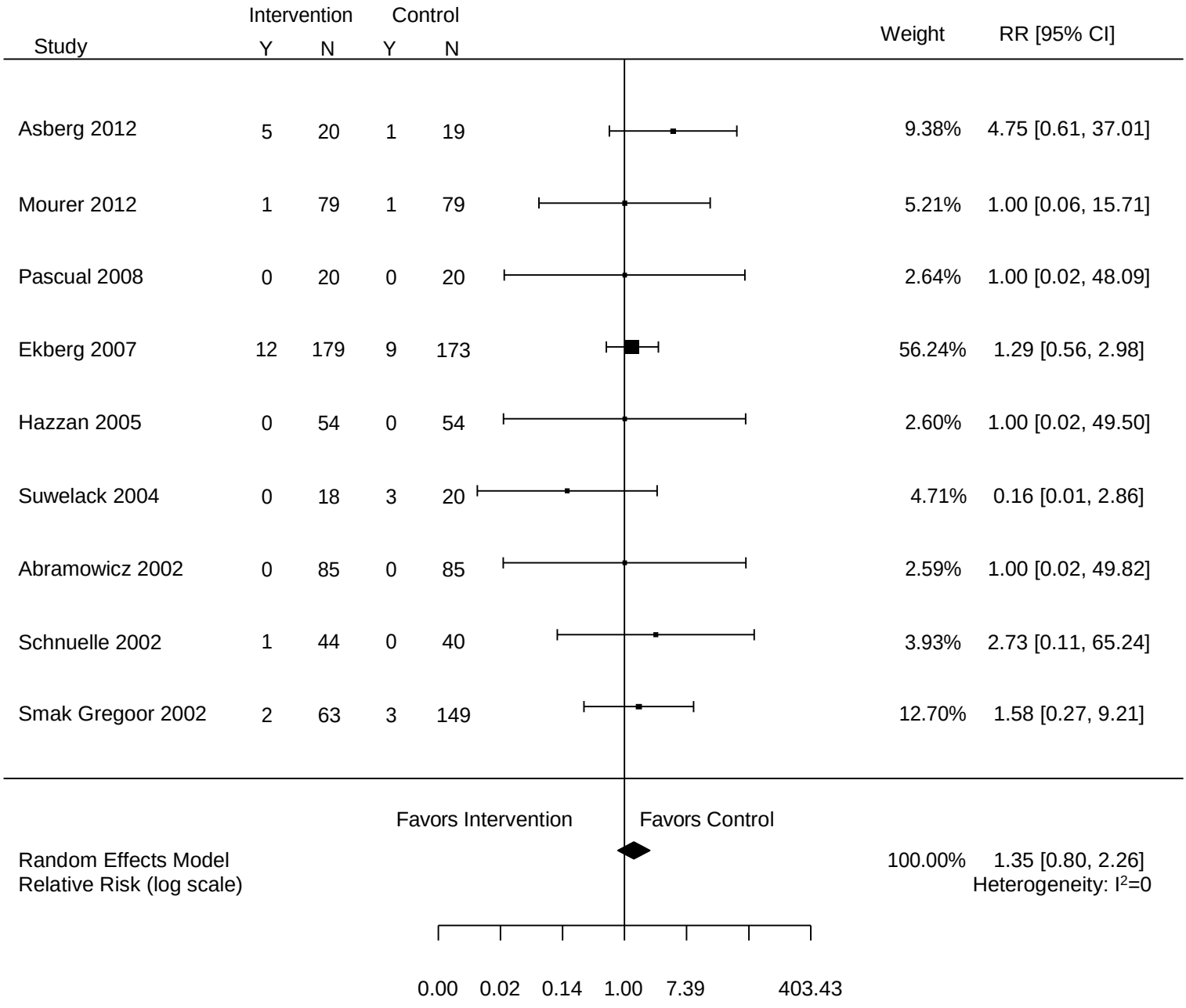
Forest Plot F-25. CNI withdrawal + mycophenolate: renal function



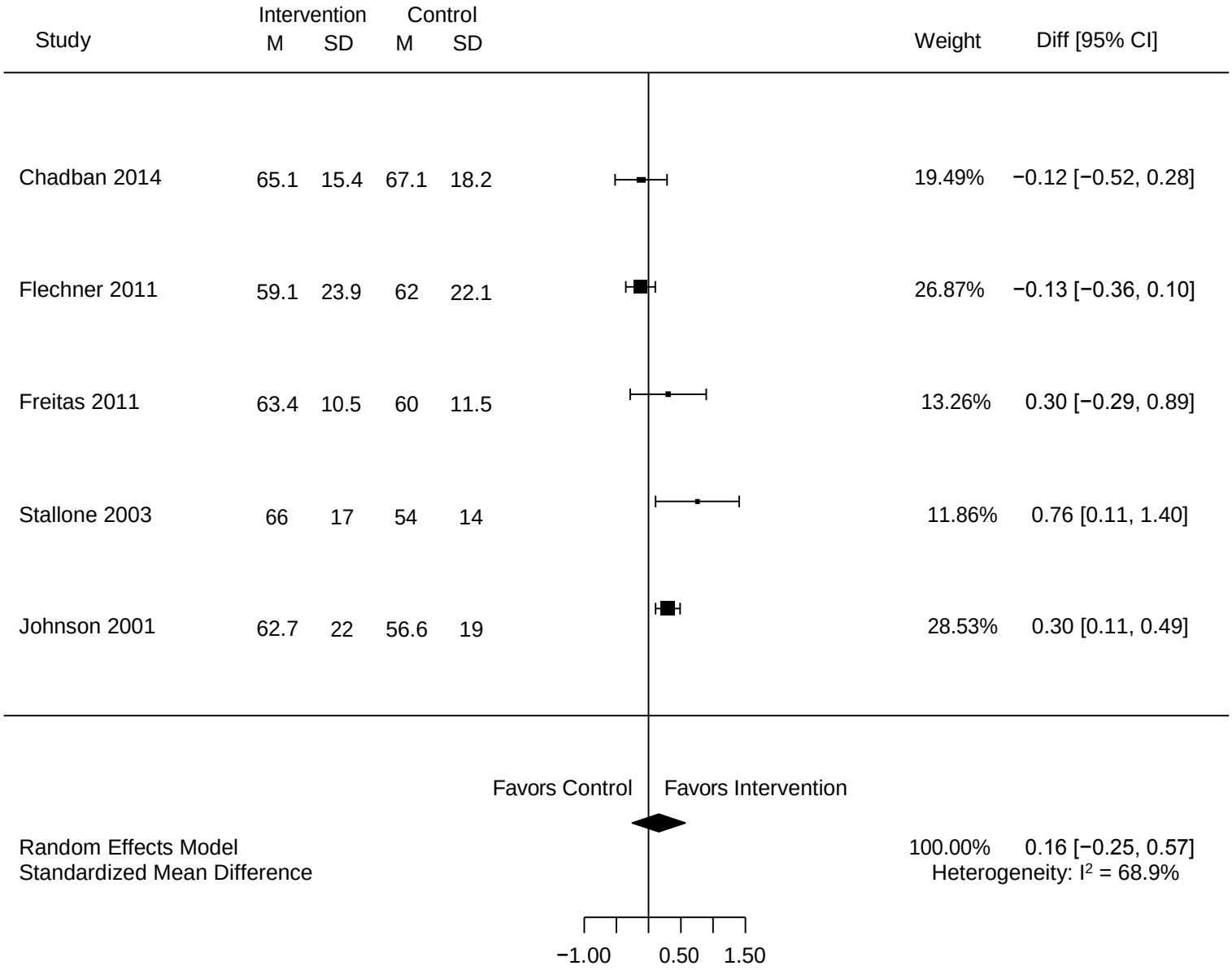
Forest Plot F-26. CNI withdrawal + mycophenolate: biopsy proven acute rejection



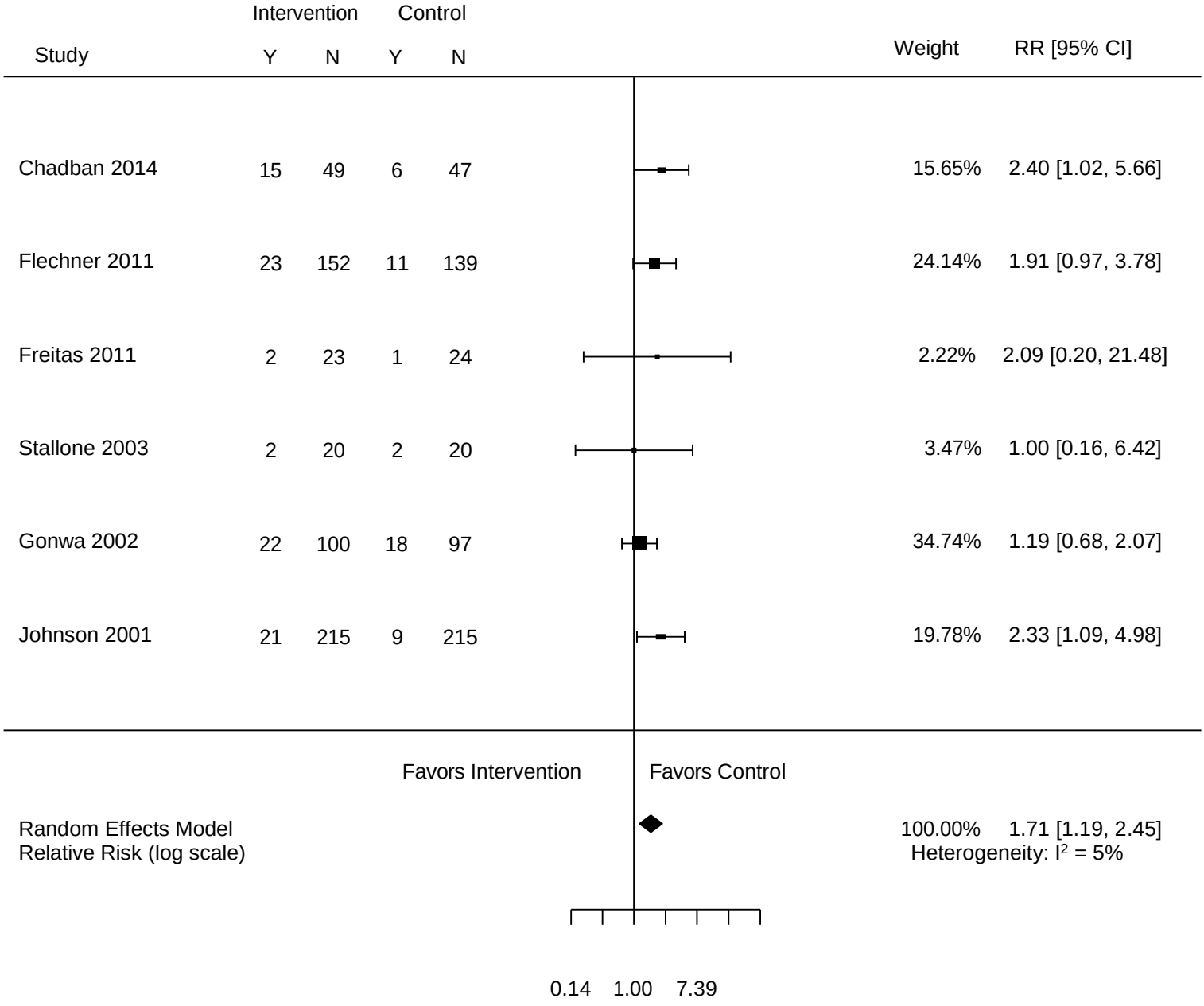
Forest Plot F-27. CNI withdrawal + mycophenolate: graft loss



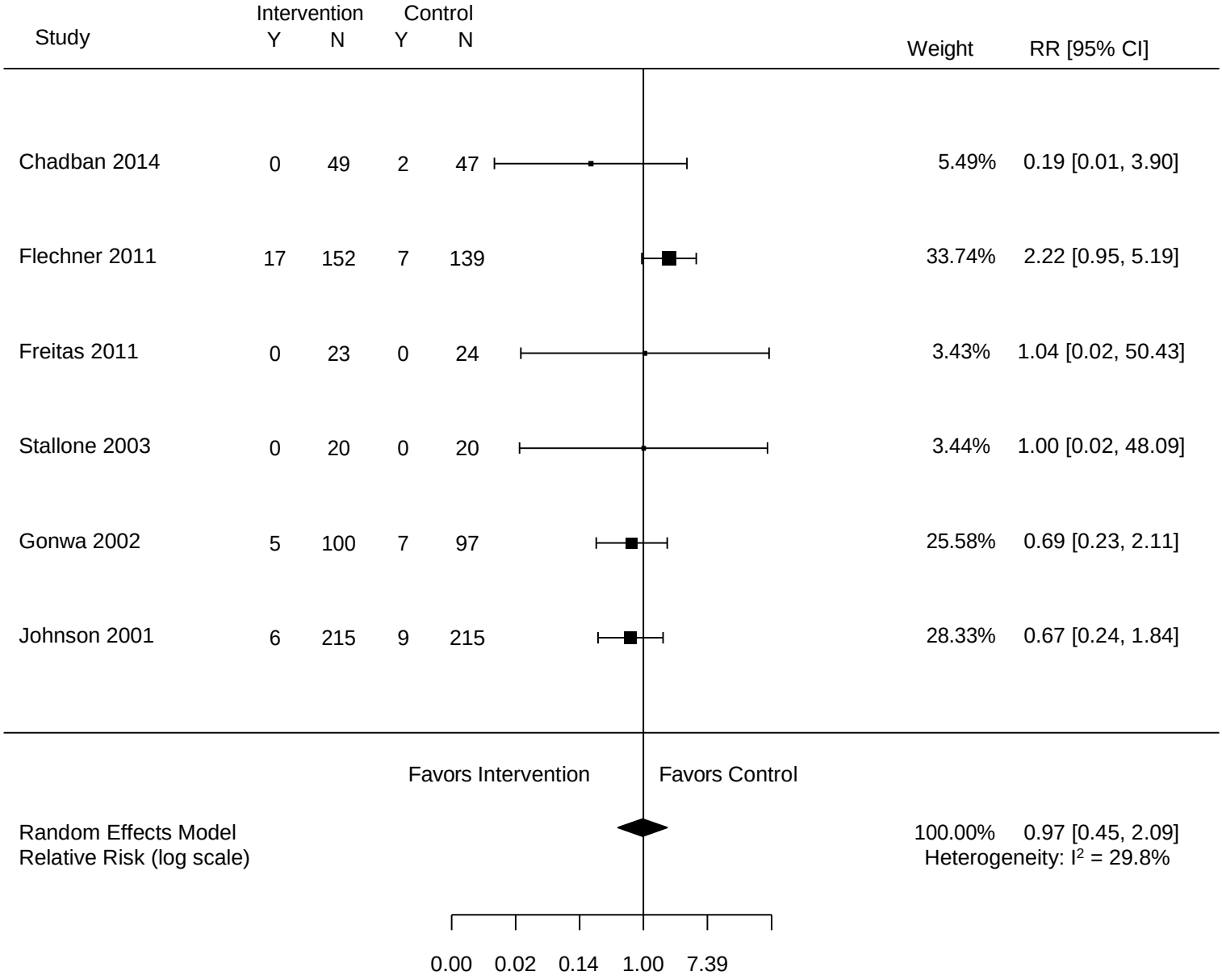
Forest Plot F-28. CNI withdrawal + mTOR inhibitors: renal function



Forest Plot F-29. CNI withdrawal + mTOR inhibitors: biopsy proven acute rejection



Forest Plot F-30. CNI withdrawal + mTOR inhibitors: graft loss



Appendix G. Appendix Reference List

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