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TABLE OF CONTENTS

[Intervention Review]

Steroid avoidance or withdrawal for kidney transplant recipients

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ABSTRACT

Background

Steroid-sparing strategies have been attempted in recent decades to avoid morbidity from long-term steroid intake among kidney transplant recipients. Previous systematic reviews of steroid withdrawal after kidney transplantation have shown a significant increase in acute rejection. There are various protocols to withdraw steroids after kidney transplantation and their possible benefits or harms are subject to systematic review. This is an update of a review first published in 2009.

Objectives

To evaluate the benefits and harms of steroid withdrawal or avoidance for kidney transplant recipients.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 15 February 2016 through contact with the Information Specialist using search terms relevant to this review.

Selection criteria

All randomised and quasi-randomised controlled trials (RCTs) in which steroids were avoided or withdrawn at any time point after kidney transplantation were included.

Data collection and analysis

Assessment of risk of bias and data extraction was performed by two authors independently and disagreement resolved by discussion. Statistical analyses were performed using the random-effects model and dichotomous outcomes were reported as relative risk (RR) and continuous outcomes as mean difference (MD) with 95% confidence intervals.

Main results

We included 48 studies (224 reports) that involved 7803 randomised participants. Of these, three studies were conducted in children (346 participants). The 2009 review included 30 studies (94 reports, 5949 participants). Risk of bias was assessed as low for sequence generation in 19 studies and allocation concealment in 14 studies. Incomplete outcome data were adequately addressed in 22 studies and 37 were free of selective reporting.

The 48 included studies evaluated three different comparisons: steroid avoidance or withdrawal compared with steroid maintenance, and steroid avoidance compared with steroid withdrawal. For the adult studies there was no significant difference in patient mortality either in studies comparing steroid withdrawal versus steroid maintenance (10 studies, 1913 participants, death at one year post transplantation: RR 0.68, 95% CI 0.36 to 1.30) or in studies comparing steroid avoidance versus steroid maintenance (10 studies, 1462 participants, death at one year after transplantation: RR 0.96, 95% CI 0.52 to 1.80). Similarly no significant difference in graft loss was found comparing steroid withdrawal versus steroid maintenance (8 studies, 1817 participants, graft loss excluding death with functioning graft at one year after transplantation: RR 1.17, 95% CI 0.72 to 1.92) and comparing steroid avoidance versus steroid maintenance (7 studies, 1211 participants, graft loss excluding death with functioning graft at one year after transplantation: RR 1.09, 95% CI 0.64 to 1.86). The risk of acute rejection significantly increased in patients treated with steroids for less than 14 days after transplantation (7 studies, 835 participants: RR 1.58, 95% CI 1.08 to 2.30) and in patients who were withdrawn from steroids at a later time point after transplantation (10 studies, 1913 participants, RR 1.77, 95% CI 1.20 to 2.61). There was no evidence to suggest a difference in harmful events, such as infection and malignancy, in adult kidney transplant recipients. The effect of steroid withdrawal in children is unclear.

Authors' conclusions

This updated review increases the evidence that steroid avoidance and withdrawal after kidney transplantation significantly increase the risk of acute rejection. There was no evidence to suggest a difference in patient mortality or graft loss up to five year after transplantation, but long-term consequences of steroid avoidance and withdrawal remain unclear until today, because prospective long-term studies have not been conducted.

PLAIN LANGUAGE SUMMARY

Steroid avoidance or withdrawal for kidney transplant recipients

What is the issue?

Each year more than 28,000 kidney transplants are performed globally. Kidney transplantation is the treatment of choice for eligible people who have lost kidney function. Most kidney transplant recipients receive corticosteroids as part of their immunosuppression treatment. Steroids are effective in preventing acute rejection, which is a major problem in the early period after kidney transplantation. However, steroids can also lead to serious side effects when taken long-term. This review looked at two strategies to reduce steroid administration after kidney transplantation: either discontinuing steroids soon after transplantation (within 14 days) or stopping steroid treatment later.

What did we do?

We searched the literature up to February 2016 and identified 48 studies (7803 patients) that were evaluated in this review. Only three studies included children. This is an update of a review that was last published in 2009.

What did we find?

Our review looked at data relating to 7803 kidney transplant recipients. We assessed the risk of bias in all studies and found that most were unblinded, about half did not report funding sources or how they randomised and allocated study participants.

We found that the risk of acute rejection significantly increased with both steroid-reducing treatments among adults who received kidney transplants. There was no little or no difference in the numbers of deaths or loss of transplanted kidneys for both steroid-

reducing strategies within five years after kidney transplantation. Side effects, such as infection, cancer or diabetes after transplantation did not differ between groups of patients whose steroids were discontinued compared with those who continued to take steroids. The effect of steroid withdrawal in children is unclear.

Conclusions

There was no evidence to suggest a difference in patient mortality or graft loss up to five year after transplantation, but longer-term consequences of steroid avoidance and withdrawal still remain unclear.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Steroid withdrawal versus steroid maintenance for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: steroid withdrawal
Comparison: steroid maintenance

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Steroid maintenance	Steroid withdrawal			
Mortality Follow-up: 1 year	**22 per 1000**	**15 per 1000** (8 to 29)	**RR 0.68** (0.36 to 1.3)	1913 (10)	⊕⊕◯◯ **low**[1,2]
Graft loss (excluding death) Follow-up: 1 year	**32 per 1000**	**38 per 1000** (23 to 62)	**RR 1.17** (0.72 to 1.92)	1817 (8)	⊕⊕◯◯ **low**[2,3]
Acute rejection Follow-up: 1 year	**152 per 1000**	**268 per 1000** (182 to 396)	**RR 1.77** (1.2 to 2.61)	1913 (10)	⊕⊕⊕◯ **moderate**[1]
NODAT Follow-up: 5 years	**57 per 1000**	**44 per 1000** (28 to 69)	**RR 0.77** (0.49 to 1.21)	1439 (6)	⊕⊕◯◯ **low**[2,4]
CMV infection Follow-up: 5 years	**100 per 1000**	**104 per 1000** (80 to 137)	**RR 1.04** (0.8 to 1.36)	1758 (5)	⊕⊕◯◯ **low**[2,5]

*The **assumed risk** is the baseline risk in the control group treated with steroid maintenance. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; NODAT: new-onset diabetes after transplantation; CMV - cytomegalovirus

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Most studies were unblinded (9 studies) and did not report details about random sequence generation or allocation concealment or both (8 studies). One study had inappropriate random sequence generation. Four studies were industry sponsored. ITT analysis was unclear in four.

[2] Total number of events were fewer than 300.

[3] Most studies were unblinded (7 studies) and did not report details about random sequence generation or allocation concealment or both (6 studies). One study had inappropriate random sequence generation. Four studies were industry sponsored. ITT analysis was unclear in two.

[4] Most studies were unblinded (5 studies) and did not report details about random sequence generation or allocation concealment or both (5 studies). Three studies were industry sponsored. ITT analysis was unclear in three studies. One study had selective outcome reporting.

[5] Most studies were unblinded (4 studies) and did not report details about random sequence generation or allocation concealment or both (4 studies). Three studies were industry sponsored. ITT analysis was unclear in two studies. One study had selective outcome reporting.

BACKGROUND

Description of the condition

Patients with end-stage kidney disease (ESKD) have to undergo renal replacement therapy which is available either as dialysis or kidney transplantation. Kidney transplantation is the preferred treatment for eligible patients with ESKD, because it offers a nearly normal life and is associated with better survival and quality of life compared to dialysis treatment. More than 16,000 kidney transplants are currently performed annually in the USA (OPTN/SRTR 2014) and more than 12,000 in Europe (ERA-EDTA 2013). Despite kidney transplants from live donors, organ demand exceeds organ availability worldwide and the number of patients wait listed for kidney transplantation continues to rise (ANZDATA 2012; ERA-EDTA 2013; OPTN/SRTR 2014). Although short-term outcomes of kidney transplantation have continuously improved since the 1980s, long-term results have only marginally improved until today. Death with a functioning graft and chronic allograft nephropathy are the most important causes of graft loss (Pascual 2002). Thus, strategies that prolong patient survival and graft patency have become a priority in kidney transplantation.

One of the key factors that influence transplant outcomes is immunosuppression which prohibits progressive immune mediated injury of the allograft. Standard immunosuppressive protocols nowadays consist of an initial induction treatment followed by a maintenance regimen. Immunosuppression is induced by an intensive treatment for the initial days after transplantation either with higher dosages of the immunosuppressive drugs or by adding an additional immunosuppressive agent, such as anti-T-cell antibodies or interleukin 2 receptor antibodies. Maintenance immunosuppression usually comprises a combination of three drug groups: calcineurin inhibitors, such as cyclosporin (CsA) or tacrolimus (TAC), anti-proliferative agents, such as azathioprine (AZA) or mycophenolate mofetil (MMF) and corticosteroids, such as prednisolone.

Corticosteroids are long known for their anti-inflammatory and immunosuppressive properties and have been used to prevent rejection since the early days of kidney transplantation. Although steroids are effective in preventing acute rejection, chronic steroid use may be an important cause of morbidity and mortality (Opelz 2005). Steroids exhibit a wide range of adverse effects, such as skin fragility, bodyweight gain, osteoporosis and cataracts, can adversely affect important cardiovascular and metabolic risk factors including hypertension, hyperglycaemia and dyslipidaemia and may contribute to an increased risk of infection (Coutinho 2011; Czock 2005; Matas 2005; Patel 2001). A literature review on the safety of low dose glucocorticoid treatment in rheumatoid arthritis suggested that the toxicity of steroids is overestimated, because adverse effects of chronic low dose steroid treatment ($\leq$ 10 mg/d prednisolone equivalent) were found to be modest and rarely statistically significantly different from placebo (Da Silva 2006).

Description of the intervention

With the aim to reduce the adverse effects of long-term corticosteroid therapy, there has been much effort to limit the exposure of kidney transplant recipients to steroids. Lessening exposure to steroids can be achieved by either steroid avoidance or steroid withdrawal. In steroid avoidance, steroids are either avoided completely or withdrawn within the first days after kidney transplantation and steroid withdrawal refers to discontinuation of steroids at a certain time point in the later post-transplant phase. This review evaluated all steroid avoidance or withdrawal strategies in kidney transplant recipients.

How the intervention might work

Steroids show adverse cardiovascular and metabolic effects and therefore discontinuing steroid treatment may take effect by a decrease in this accelerated cardiovascular risk. However, while steroid avoidance and withdrawal potentially reduces post-transplant atherosclerosis, ischaemic heart disease, post-transplant diabetes and death, it may significantly increase the risk of acute rejection. Acute rejection is associated with late graft loss, especially if rejection episodes are severe, followed by impaired kidney function, occur late and affect arteries (Basadonna 1993; Massy 1996). The new immunosuppressants TAC and MMF have led to important declines in the incidence of acute rejection and may provide a more potent substrate to attempt safe steroid-free immunosuppression or steroid withdrawal.

Why it is important to do this review

It is important to reduce the cardiovascular risk in kidney transplant recipients, who area population at increased cardiovascular risk, but at the same time it is important to avoid rejection and graft loss. Steroids have been associated with increased cardiovascular risk in kidney transplant recipients, but long-term benefits and harms of steroid discontinuation have not yet been established with controlled long-term data (Knight 2010). Prednisone was perceived as the least effective and least favoured immunosuppressive drug compared to calcineurin inhibitors, MMF and AZA in a survey among Canadian kidney transplant recipients and the majority of US transplant physicians and surgeons stated that steroid-free immunosuppression was a goal for future organ transplant recipients (Hricik 2002; Prasad 2003). Steroid use varies largely in clinical practice around the globe. While steroids are discontinued in many centres worldwide, they are at the same time frequently used for long-term treatment in kidney transplant recipients to protect the allograft. There is no consensus whether

discontinuation of steroids is safe, what type of patients benefit from steroid discontinuation and at what time point after transplantation steroids are best stopped. A number of RCTs evaluating steroid avoidance or withdrawal at various time-points after kidney transplantation with different immunosuppressive regimes have been performed during the last decades and were first systematically reviewed in 2009 (Pascual 2009). Steroid avoidance and steroid withdrawal strategies in kidney transplantation were not associated with increased patient mortality or graft loss, despite an overall higher incidence of acute rejection for steroid withdrawal strategies compared with steroid maintenance. The aim of this review was to update the benefits and harms of steroid withdrawal and avoidance in kidney transplant recipients with new evidence from RCTs.

OBJECTIVES

To evaluate the benefits and harms of steroid withdrawal or avoidance for kidney transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs or quasi-RCTs (in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods), whether published or unpublished, in which steroids were avoided or withdrawn at any time point after kidney transplantation were eligible for inclusion. RCTs evaluating any other steroid-sparing strategy (i.e. dose reduction) or attempting other interventions in addition to steroid withdrawal (i.e. switch from AZA to MMF, induction treatment in addition to steroid withdrawal) were excluded in this review.

Types of participants

Adult and paediatric recipients of a first or subsequent kidney transplant from a cadaveric or living donor. Recipients of multiorgan transplants (kidney-pancreas, kidney-liver, kidney-heart) were excluded.

Types of interventions

- Steroid avoidance, defined as steroid use during less than 14 days after kidney transplantation versus steroid maintenance
- Steroid withdrawal, defined as steroid use for more than 14 days after transplantation versus steroid maintenance
- Steroid avoidance versus steroid withdrawal.

Types of outcome measures

Outcome measures used by transplant registries to report patient and graft survival were selected for this review. Outcome events were assessed within the first year and up to five years after kidney transplantation. A secondary outcome looking at infection has been amended for this update to specify cytomegalovirus (CMV) infection.

Primary outcomes

1. All-cause mortality
2. Graft loss or death with a functioning graft; and graft loss censored for death with a functioning graft (loss of graft function resulting in either return to dialysis or retransplantation)
3. Acute rejection (clinically suspected and treated) and biopsy-proven acute rejection.

Secondary outcomes

1. Cardiovascular events
2. New-onset diabetes after transplantation (NODAT)
3. Malignancy
4. Infection and CMV infection
5. Kidney function measures (serum creatinine (mg/dL); creatinine clearance (mL/min)).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 15 February 2016 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference

proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.
See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategies described was used to obtain title and abstracts of studies relevant to this review. Three authors independently screened titles and abstracts, and discarded reports that were not applicable. Studies and reviews that might include relevant data or information on studies were retained initially and two authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third author.

Data extraction and management

Two authors independently carried out data extraction using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one report of a study existed, reports were grouped together and the publication with the most complete data was used in the analyses. We examined any prior or subsequent report for supplementary outcomes or data to ensure the inclusion of all relevant information. If data were unclear, ambiguous or missing, authors were contacted for further information and any provided additional data was included in the review. Whenever necessary, disagreements were resolved by discussion.

Assessment of risk of bias in included studies

Two authors independently assessed the following items using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used.

Unit of analysis issues

The unit of analysis was the study participant and not the events; that is the number of study participants with an acute rejection rather than the number of episodes of acute rejection.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained in this manner was to be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011). If standard deviation was not available, it was estimated using standard error (if provided) (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 (on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance) and with the I^2 statistic, calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

We assessed publication bias by constructing funnel plots for primary outcomes if there was sufficient data available to enable this analysis (at least 10 included studies in the meta-analysis).

Data synthesis

Data were pooled for summary estimates using the random-effects model but the fixed-effect model was also to be used to ensure robustness of the model chosen and susceptibility to outliers. Results reported used the random-effects model because this is more conservative in the presence of known or unknown heterogeneity (Deeks 2001).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were used to explore possible sources of heterogeneity and potential effect modifiers were defined a priori. The main source of heterogeneity among participants could be related to age, therefore adults and children who were kidney transplant recipients were analysed separately. Heterogeneity in treatments could be related to duration of steroid therapy and concomitant immunosuppressants. Therefore subgroup analysis was undertaken using stratified meta-analysis for type of calcineurin inhibitor, type of antimetabolite and whether an induction treatment was administered.

Sensitivity analysis

Sensitivity analysis was performed to demonstrate that final results did not vary where low quality studies were included or excluded. Low quality studies were defined based on publication type (conference abstract or peer reviewed journal) and methodological conduct (whether intention-to-treat analysis was assessed as adequate or inadequate/unclear).

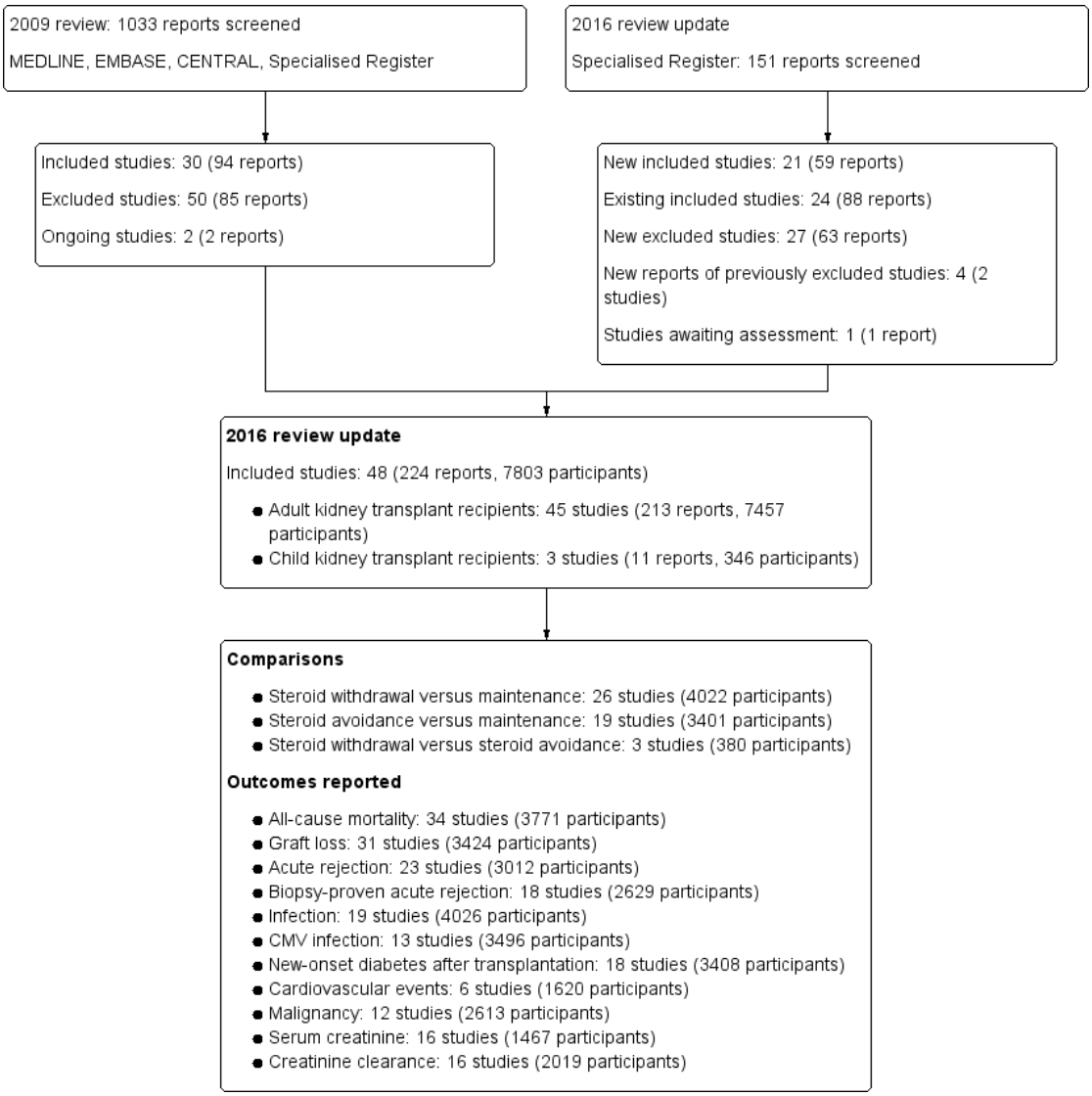
RESULTS

Description of studies

Results of the search

A search in 15 February 2016 identified 151 reports. Additionally three previously excluded studies were re-evaluated and included; these had been incorrectly excluded for reasons of insufficient data (Aswad 1998; Kacar 2004; Pisani 2001). All three are published as abstract only. Pisani 2001 contributed data for the meta-analysis. We also re-evaluated three previously included studies and excluded them because they had been incorrectly included despite a wrong co-intervention (CARMEN Study 2005; Tarantino 1991; ter Meulen 2002). In CARMEN Study 2005 and ter Meulen 2002 induction treatment with daclizumab was only given to patients in the steroid withdrawal group and in Tarantino 1991 AZA was given solely to patients in the steroid maintenance group. We included 21 new studies (59 reports) that involved 1854 participants, two of these new studies (seven reports) concerned children. We found that 88 new reports were additional reports of previously included studies. This update includes 48 studies (224 reports) that involved 7803 participants, including three studies (11 reports) that involved 346 children. See Figure 1.

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies.

The 48 included studies were published in 22 different journals and seven had preliminary abstract data only available (Aswad 1998; Burke 2000; del Castillo 2005; INFINITY Study 2013; Kacar 2004; Kim 2002; Pisani 2001).The effect of steroid withdrawal compared versus steroid maintenance was investigated in 26 studies (4022 participants) and the effect of steroid avoidance compared versus steroid maintenance was investigated in 19 studies (3401 participants). We identified three studies (380 participants) that evaluated the effect of steroid avoidance compared versus steroid withdrawal. Numbers of participants per study varied from 21 (Aswad 1998) to 560 patients (THOMAS Study 2002). It is noteworthy that 25 studies randomised fewer than 100 participants, 15 studies included between 100 and 300 participants, and eight studies randomised more than 300 participants.

Trials in adult kidney transplant recipients

This update included 45 studies (208 reports, 7457 participants) of steroid withdrawal or avoidance in adult kidney transplant re-

cipients.

Participants

Trials recruited participants who were older than 18 years of age, except two studies which recruited participants older than 12 years (Stiller 1983) or between five and 62 years (Nagib 2015). In 14 studies the age range was not further specified (Albert 1985; Aswad 1998; Gulanikar 1991; INFINITY Study 2013; Isoniemi 1990; Johnson 1989a; Kacar 2004; Kim 2002; Ratcliffe 1993; Schulak 1989; Smak Gregoor 1999; Sola 2002; THOMAS Study 2002; Zhu 2008a).The majority of studies included cadaveric and living kidney transplant recipients (25 studies: Ahsan 1999; ATLAS Study 2005; Boletis 2001; Boots 2002; Burke 2000; DOMINOS Study 2012; EVIDENCE Study 2014; Farmer 2006; FREEDOM Study 2008; Gulanikar 1991; Jankowska-Gan 2009; Kim 2002; Kumar 2005; Laftavi 2005; Lebranchu 1999; Matl 2000; Montagnino 2005; Nott 1985; Pelletier 2006; Schulak 1989; Stiller 1983; Smak Gregoor 1999; THOMAS Study 2002; Vincenti 2003a; Woodle 2005). Kidney transplantation was limited to cadaveric donor sources in 11 studies (Bouma 1996; De Vecchi 1986; FRANCIA Study 2007; Isoniemi 1990; Johnson 1989a; Maiorca 1988; Ponticelli 1997; Ratcliffe 1993; Sandrini 2009; Sola 2002; Zhu 2008a) and to living donors in four studies (Aswad 1998; Nagib 2015; Nematalla 2007; Park 1994) In 17 studies first or subsequent kidney transplant recipients were eligible (Boots 2002; Bouma 1996; DOMINOS Study 2012; EVIDENCE Study 2014; Farmer 2006; Gulanikar 1991; Johnson 1989a; Lebranchu 1999; Montagnino 2005; Nott 1985; Pisani 2001; Ponticelli 1997; Ratcliffe 1993; Schulak 1989; Stiller 1983; THOMAS Study 2002; Woodle 2005), while in 19 studies limited participants to recipients of first kidney transplants (Ahsan 1999; ATLAS Study 2005; Boletis 2001; Burke 2000; del Castillo 2005; FRANCIA Study 2007; FREEDOM Study 2008; INFINITY Study 2013; Isoniemi 1990; Kumar 2005; Laftavi 2005; Maiorca 1988; Matl 2000; Nagib 2015; Nematalla 2007; Park 1994; Pelletier 2006; Sandrini 2009; Vincenti 2003a).

Study comparisons

The 45 included studies evaluated three different comparisons in adults.

- Steroid withdrawal compared versus steroid maintenance was investigated in 24/45 studies in adult patients (Ahsan 1999; Albert 1985; Aswad 1998; Boletis 2001; Bouma 1996; Burke 2000; del Castillo 2005; EVIDENCE Study 2014; Farmer 2006; Gulanikar 1991; Isoniemi 1990; Jankowska-Gan 2009; Kacar 2004; Lebranchu 1999; Maiorca 1988; Matl 2000; Park 1994; Pelletier 2006; Pisani 2001; Ratcliffe 1993; Smak Gregoor 1999; Sola 2002; THOMAS Study 2002; Zhu 2008a). Steroids were withdrawn three months after transplantation in eight studies (Ahsan 1999; EVIDENCE Study 2014; Gulanikar 1991; Isoniemi 1990; Lebranchu 1999; Park 1994; Sola 2002; THOMAS Study 2002); six months after transplantation in eight studies (Albert 1985; Aswad 1998; Boletis 2001; Burke 2000; del Castillo 2005; Pisani 2001; Smak Gregoor 1999; Zhu 2008a); one year after transplantation in one study (Matl 2000), and beyond one year after transplantation in six studies (Bouma 1996; Farmer 2006; Jankowska-Gan 2009; Kacar 2004; Maiorca 1988; Ratcliffe 1993). In one study, steroids were withdrawn at different time points after transplantation and the time point of withdrawal was not reported, but all patients had steroids for more than 14 days (Pelletier 2006).
- Steroid avoidance compared versus steroid maintenance was investigated in 18/45 studies in adult kidney transplant recipients (ATLAS Study 2005; De Vecchi 1986; FRANCIA Study 2007; FREEDOM Study 2008; Nott 1985; INFINITY Study 2013; Johnson 1989a; Kim 2002; Kumar 2005; Laftavi 2005; Stiller 1983; Montagnino 2005; Nagib 2015; Nematalla 2007; Ponticelli 1997; Schulak 1989; Vincenti 2003a; Woodle 2005). In two studies steroids were not given at any time point before, during or after transplantation (FREEDOM Study 2008; Stiller 1983). Steroids were withdrawn until day seven after transplantation in 12 studies (ATLAS Study 2005; De Vecchi 1986; FRANCIA Study 2007; Nott 1985; Johnson 1989a; Kim 2002; Kumar 2005; Laftavi 2005; Montagnino 2005; Nematalla 2007; Ponticelli 1997; Vincenti 2003a) and between day 8 and day 14 in two studies (Schulak 1989; Woodle 2005).
- Steroid avoidance was compared versus steroid withdrawal in 3/45 studies with adults (Boots 2002; DOMINOS Study 2012; Sandrini 2009). In all of these three studies, steroids were withdrawn until day seven after transplantation in the avoidance group and between three to six months after transplantation in the withdrawal group.

Immunosuppression

CsA was used in 34 studies evaluating steroid withdrawal or steroid avoidance (Ahsan 1999; Albert 1985; Boletis 2001; Bouma 1996; Burke 2000; del Castillo 2005; De Vecchi 1986; DOMINOS Study 2012; EVIDENCE Study 2014; Farmer 2006; FRANCIA Study 2007; FREEDOM Study 2008; Gulanikar 1991; INFINITY Study 2013; Isoniemi 1990; Jankowska-Gan 2009; Johnson 1989a; Kim 2002; Kumar 2005; Lebranchu 1999; Maiorca 1988; Matl 2000; Montagnino 2005; Nott 1985; Park 1994; Pelletier 2006; Pisani 2001; Ponticelli 1997; Ratcliffe 1993; Sandrini 2009; Schulak 1989; Smak Gregoor 1999; Vincenti 2003a). TAC was used in 10 studies investigating steroid withdrawal or steroid avoidance (Aswad 1998; ATLAS Study 2005; Boots 2002; Laftavi 2005; Nagib 2015; Nematalla 2007; Sola 2002; THOMAS Study 2002; Woodle 2005; Zhu 2008a). One study provided no information about the baseline immunosuppression used (Kacar 2004). Of the three studies comparing steroid avoidance with steroid withdrawal, two used a CsA-based im-

munosuppression (DOMINOS Study 2012; Sandrini 2009) and one used a TAC-based immunosuppression (Boots 2002).

Five studies investigated steroid withdrawal compared versus steroid maintenance in patients without an additional antiproliferative immunosuppressant (either MMF or enteric-coated mycophenolate sodium or AZA or mTOR-inhibitor) (Albert 1985; Bouma 1996; Gulanikar 1991; Maiorca 1988; Park 1994) and five studies investigated steroid avoidance compared versus steroid maintenance without an additional antiproliferative (De Vecchi 1986; Johnson 1989a; Nott 1985; Stiller 1983; Ponticelli 1997). Steroid avoidance compared versus steroid withdrawal in patients without an antiproliferative was investigated in Boots 2002. An immunosuppressive regimen including an additional antiproliferative agent was used in 18 studies that investigated steroid withdrawal compared versus steroid maintenance (Ahsan 1999; Aswad 1998; Boletis 2001; Burke 2000; del Castillo 2005; EVIDENCE Study 2014; Farmer 2006; Isoniemi 1990; Jankowska-Gan 2009; Lebranchu 1999; Matl 2000; Pelletier 2006; Pisani 2001; Ratcliffe 1993; Smak Gregoor 1999; Sola 2002; THOMAS Study 2002; Zhu 2008a). Of these 18 studies, 12 used MMF (Ahsan 1999; Boletis 2001; del Castillo 2005; Burke 2000; Jankowska-Gan 2009; Pelletier 2006; Pisani 2001; Smak Gregoor 1999; Sola 2002; THOMAS Study 2002; Lebranchu 1999; Zhu 2008a), five used AZA (Aswad 1998; Farmer 2006; Isoniemi 1990; Matl 2000; Ratcliffe 1993), and one used Everolimus (EVIDENCE Study 2014). Steroid avoidance compared versus steroid maintenance using an additional antiproliferative immunosuppressant was used in 13 studies (ATLAS Study 2005; FRANCIA Study 2007; FREEDOM Study 2008; INFINITY Study 2013; Kim 2002; Kumar 2005; Laftavi 2005; Montagnino 2005; Nagib 2015; Nematalla 2007; Schulak 1989; Vincenti 2003a; Woodle 2005). Of these, nine used MMF (ATLAS Study 2005; FRANCIA Study 2007; Kim 2002; Kumar 2005; Laftavi 2005; Nagib 2015 Nematalla 2007; Vincenti 2003a; Woodle 2005), two used enteric-coated mycophenolate sodium (FREEDOM Study 2008; INFINITY Study 2013), one used AZA (Schulak 1989), and one used everolimus (Montagnino 2005). Steroid avoidance compared versus steroid withdrawal in patients treated with an additional antiproliferative was investigated in two studies (DOMINOS Study 2012; Sandrini 2009). One study used enteric-coated mycophenolate sodium (DOMINOS Study 2012) and one used sirolimus (Sandrini 2009) as the third immunosuppressant.

Induction treatment was administered in 17 studies with adult kidney transplant recipients in three studies comparing steroid withdrawal with steroid maintenance (EVIDENCE Study 2014; Pelletier 2006; Pisani 2001), in 12 studies comparing steroid avoidance with steroid maintenance (FRANCIA Study 2007; FREEDOM Study 2008; INFINITY Study 2013; Kim 2002; Kumar 2005; Laftavi 2005; Montagnino 2005; Nagib 2015; Nematalla 2007; Schulak 1989; Vincenti 2003a; Woodle 2005), and in two studies comparing steroid avoidance with steroid withdrawal (DOMINOS Study 2012; Sandrini 2009). In 12 studies an IL-2 receptor antagonist was used for induction treatment (DOMINOS Study 2012; EVIDENCE Study 2014; FREEDOM Study 2008; INFINITY Study 2013; Kim 2002; Kumar 2005; Montagnino 2005; Nagib 2015; Nematalla 2007; Pisani 2001; Sandrini 2009; Vincenti 2003a), in three studies an anti-lymphocytic depleting antibodies was used (FRANCIA Study 2007; Laftavi 2005; Schulak 1989) and two studies allowed the type of induction treatment to be chosen by the investigator (Pelletier 2006; Woodle 2005).

Studies in child kidney transplant recipients

This update included three studies (11 reports, 346 participants) of steroid withdrawal or avoidance in child kidney transplant recipients (Benfield 2005; Höcker 2009; Mericq 2013).

Participants

Studies recruited participants who were younger than 20 years of age. All three studies included cadaveric and living kidney transplant recipients. In Benfield 2005 and Mericq 2013 only first kidney transplant recipients were eligible; in Höcker 2009 first or subsequent kidney transplantation was included.

Study comparisons

The three studies evaluated two different comparisons in children. Benfield 2005 and Höcker 2009 investigated steroid withdrawal versus steroid maintenance; Mericq 2013 investigated steroid avoidance versus steroid withdrawal.

Immunosuppression

All three studies used a calcineurin inhibitor-based immunosuppressive regimen including an additional antiproliferative agent. Höcker 2009 used CsA and MMF, Benfield 2005 allowed either CsA or TAC to be used with sirolimus and Mericq 2013 used TAC in combination with MMF. Benfield 2005 and Mericq 2013 also used basiliximab for induction treatment, but Benfield 2005 was terminated early when the Data Safety Monitoring Board noted an excess risk of post-transplant lymphoproliferative disease in both treatment groups.

Reported outcome measures

The reporting of outcome measures varied across studies. Of the 45 included studies, 34 reported patient mortality and 23 reported acute rejection (see Figure 1). Reporting of harms was more limited and inconsistent among studies (six studies reported cardiovascular events with varying definitions of cardiovascular events or definitions not reported). Frequently, studies reported incomplete data for harm outcomes or expressed their results as 'episodes',

which complicated meaningful use of such data in the meta-analysis.

Excluded studies

We excluded a total of 48 studies because studies: were not randomised (12), concerned ineligible populations (3), involved ineligible interventions (11) or ineligible co-interventions (22).

Risk of bias in included studies

Reporting of details of study methodology regarding design and conduct of the study was incomplete in most studies. The assessment of risk of bias is shown in Figure 2 and Figure 3. Figure 2 shows the risk of bias indicators for individual studies. Figure 3 shows the proportion of studies assessed as low, high or unclear risk of bias for each risk of bias indicator.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

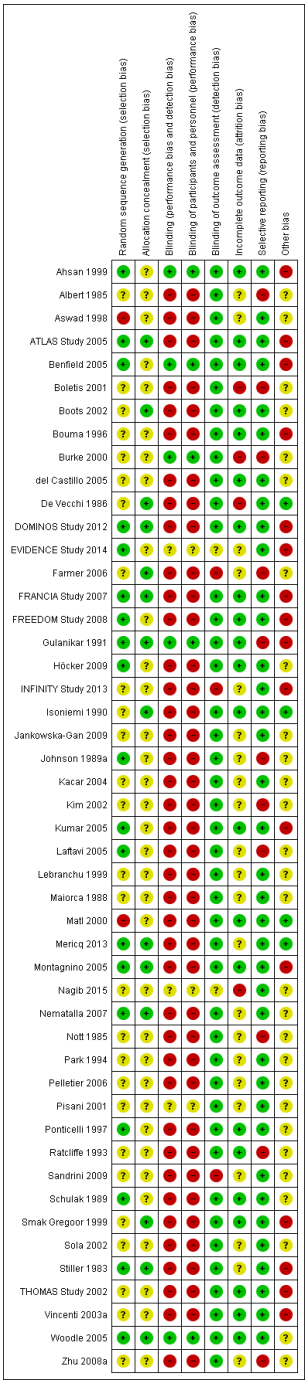
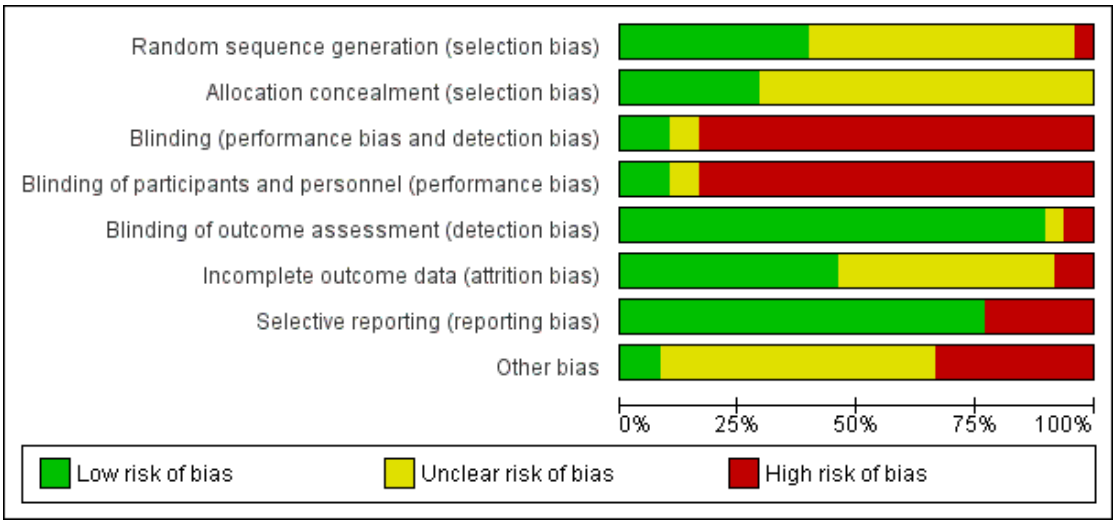


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

Random sequence generation was judged to be at low risk of bias in 19 studies (Ahsan 1999; ATLAS Study 2005; Benfield 2005; DOMINOS Study 2012; EVIDENCE Study 2014; FRANCIA Study 2007; FREEDOM Study 2008; Gulanikar 1991; Höcker 2009; Johnson 1989a; Kumar 2005; Laftavi 2005; Mericq 2013; Montagnino 2005; Nematalla 2007; Ponticelli 1997; Schulak 1989; Stiller 1983; Woodle 2005) and considered at high risk in two studies (Aswad 1998; Matl 2000). Randomisation methods were not reported in 27 studies (Albert 1985; Boletis 2001; Boots 2002; Bouma 1996; Burke 2000; del Castillo 2005; De Vecchi 1986; Farmer 2006; INFINITY Study 2013; Isoniemi 1990; Jankowska-Gan 2009; Kacar 2004; Kim 2002; Lebranchu 1999; Maiorca 1988; Nagib 2015; Nott 1985; Park 1994; Pelletier 2006; Pisani 2001; Ratcliffe 1993; Sandrini 2009; Smak Gregoor 1999; Sola 2002; THOMAS Study 2002; Vincenti 2003a; Zhu 2008a).

Allocation concealment was assessed to be at low risk of bias in 14 studies (ATLAS Study 2005; Boots 2002; De Vecchi 1986; DOMINOS Study 2012; Farmer 2006; FRANCIA Study 2007; Gulanikar 1991; Isoniemi 1990; Mericq 2013; Montagnino 2005; Nematalla 2007; Smak Gregoor 1999; Stiller 1983; Woodle 2005); no study was judged to be at high risk of bias. Methods used for allocation concealment were unclear in the remaining 34 studies (Ahsan 1999; Albert 1985; Aswad 1998; Benfield 2005; Boletis 2001; Bouma 1996; Burke 2000; del Castillo 2005; EVIDENCE Study 2014; FREEDOM Study 2008; Höcker 2009; INFINITY Study 2013; Jankowska-Gan 2009; Johnson 1989a; Kacar 2004; Kim 2002; Kumar 2005; Laftavi 2005; Lebranchu 1999; Maiorca 1988; Matl 2000; Nagib 2015; Nott 1985; Park 1994; Pelletier 2006; Pisani 2001; Ponticelli 1997; Ratcliffe 1993; Sandrini 2009; Schulak 1989; Sola 2002; THOMAS Study 2002; Vincenti 2003a; Zhu 2008a).

Blinding

Participants and investigators were blinded in only five studies (Ahsan 1999; Benfield 2005; Burke 2000; Gulanikar 1991; Woodle 2005). The absence of blinding was judged as high risk of bias because clinical management could be influenced by knowledge of treatment group. Blinding of outcome assessment was considered as low risk of bias because outcomes were objective and therefore more robust against influence by knowledge of treatment group (e.g. death, graft loss, serum creatinine).

Incomplete outcome data

Incomplete outcome data was judged to be at low risk of bias in 22 studies (Ahsan 1999; ATLAS Study 2005; Benfield 2005; Boots 2002; Bouma 1996; del Castillo 2005; DOMINOS Study 2012;

FRANCIA Study 2007; FREEDOM Study 2008; Gulanikar 1991; Höcker 2009; Isoniemi 1990; Kumar 2005; Matl 2000; Montagnino 2005; Ponticelli 1997; Ratcliffe 1993; Schulak 1989; Smak Gregoor 1999; THOMAS Study 2002; Vincenti 2003a; Woodle 2005). Exclusion of participants after randomisation and attrition were considered at high risk in four studies (Boletis 2001; Burke 2000; De Vecchi 1986; Nagib 2015). Methods for addressing incomplete outcome data remained unclear in 22 studies (Albert 1985; Aswad 1998; EVIDENCE Study 2014; Farmer 2006; INFINITY Study 2013; Jankowska-Gan 2009; Johnson 1989a; Kacar 2004; Kim 2002; Laftavi 2005; Lebranchu 1999; Maiorca 1988; Mericq 2013; Nematalla 2007; Nott 1985; Park 1994; Pelletier 2006; Pisani 2001; Sandrini 2009; Sola 2002; Stiller 1983; Zhu 2008a).

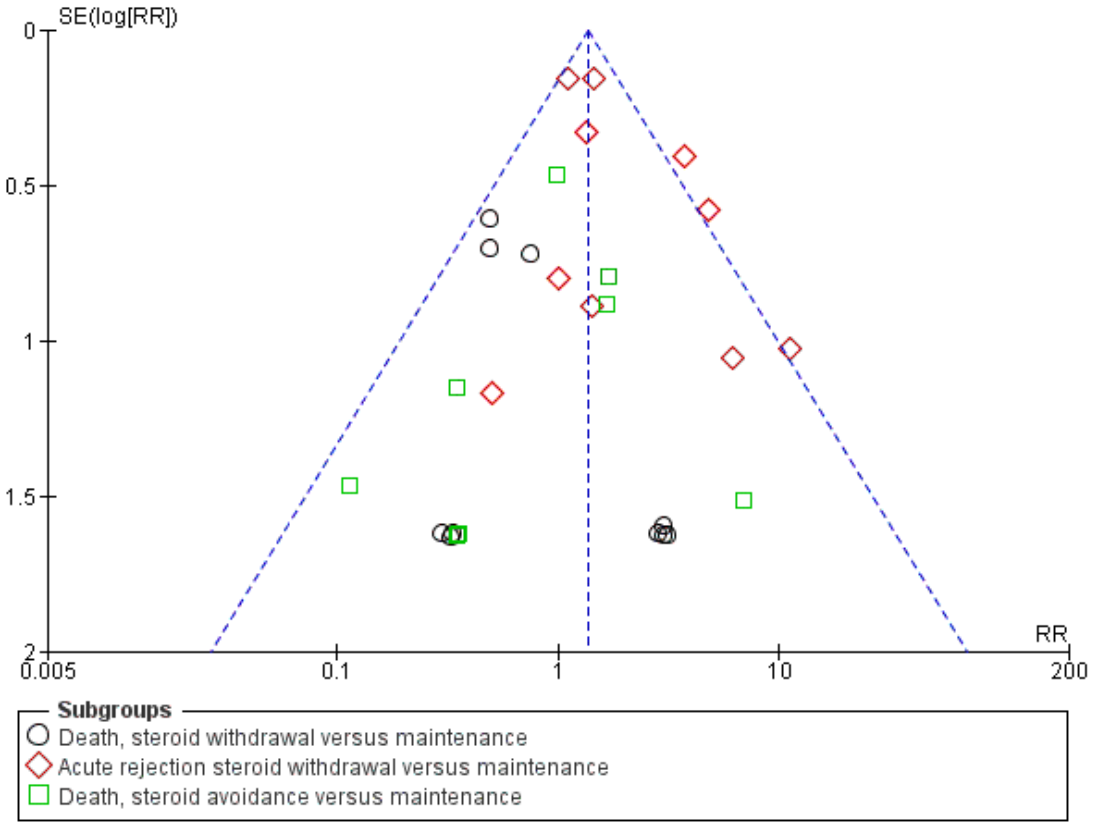
Selective reporting

Selective outcome reporting was judged as low risk in 37 studies (Ahsan 1999; Aswad 1998; ATLAS Study 2005; Benfield 2005; Boots 2002; Bouma 1996; del Castillo 2005; De Vecchi 1986; DOMINOS Study 2012; EVIDENCE Study 2014; FRANCIA Study 2007; FREEDOM Study 2008; Höcker 2009; INFINITY Study 2013; Isoniemi 1990; Jankowska-Gan 2009; Kacar 2004; Kumar 2005; Lebranchu 1999; Maiorca 1988; Matl 2000; Mericq 2013; Montagnino 2005; Nagib 2015; Nematalla 2007; Park 1994; Pelletier 2006; Pisani 2001; Ponticelli 1997; Sandrini 2009; Schulak 1989; Smak Gregoor 1999; Sola 2002; Stiller 1983; THOMAS Study 2002; Vincenti 2003a; Woodle 2005). Eleven studies did not report all hard clinical outcomes that were considered primary outcomes for this review and were assessed as high risk of bias for selective outcome reporting (Albert 1985; Boletis 2001; Burke 2000; Farmer 2006; Gulanikar 1991; Nott 1985; Johnson 1989a; Kim 2002; Laftavi 2005; Ratcliffe 1993; Zhu 2008a).

Other potential sources of bias

Funding from academic independent sources was considered as low risk of bias in four studies (De Vecchi 1986; Isoniemi 1990; Matl 2000; Mericq 2013). In 16 studies a pharmaceutical company was reported as funding source, which was judged as high risk of bias (Ahsan 1999; ATLAS Study 2005; Benfield 2005; Bouma 1996; DOMINOS Study 2012; FRANCIA Study 2007; FREEDOM Study 2008; Kumar 2005; Montagnino 2005; Gulanikar 1991; Smak Gregoor 1999; Stiller 1983; THOMAS Study 2002; Vincenti 2003a). In 27 studies funding sources were not disclosed (Albert 1985; Aswad 1998; Boletis 2001; Boots 2002; Burke 2000; del Castillo 2005; EVIDENCE Study 2014; Farmer 2006; Höcker 2009; INFINITY Study 2013; Jankowska-Gan 2009; Johnson 1989a; Kacar 2004; Kim 2002; Laftavi 2005; Lebranchu 1999; Maiorca 1988; Nematalla 2007; Nott 1985; Park 1994; Pelletier 2006; Pisani 2001; Ponticelli 1997; Ratcliffe 1993; Sandrini 2009; Schulak 1989; Sola 2002; Woodle 2005; Zhu 2008a). Publication bias was assessed by constructing funnel plots for three comparisons that included at least 10 studies in the meta-analysis (death and acute rejection for steroid withdrawal versus steroid maintenance and acute rejection for steroid avoidance versus steroid maintenance). All funnel plots are symmetric and do not indicate publication bias (see Figure 4).

Figure 4. Funnel plot of comparisons that included at least 10 studies in the meta-analysis



Effects of interventions

See: **Summary of findings for the main comparison** Steroid withdrawal versus steroid maintenance for kidney transplant recipients; **Summary of findings 2** Steroid avoidance versus steroid maintenance for kidney transplant recipients

Studies in adults with kidney transplant recipients

Steroid withdrawal versus steroid maintenance

Steroid withdrawal may lead to little of no difference in patient mortality at either one year (Analysis 1.1.1 (10 studies, 1913 participants): RR 0.68, 95% CI 0.36 to 1.30; I^2 = 0%) or one to five years post transplantation (Analysis 1.1.2 (7 studies, 1118 participants): RR 1.26, 95% CI 0.73 to 2.17; I^2 = 0%). Likewise steroid withdrawal may lead to little or no difference in graft loss excluding death at either one year (Analysis 1.1.5 (8 studies, 1817 participants): RR 1.17, 95% CI 0.72 to 1.92; I^2 = 0%) or one to five years post transplantation (Analysis 1.1.6 (7 studies, 1092 participants): RR 1.61, 95% CI 0.98 to 2.64; I^2 = 0%).

The risk of acute rejection significantly increased by 77% in patients withdrawn from steroids compared versus patients maintained on steroids within the first year after transplantation (Analysis 1.2.1 (10 studies, 1913 participants): RR 1.77, 95% CI 1.20 to 2.61; I^2 = 54%), but there was no difference in the incidence of biopsy-proven acute rejection (Analysis 1.2.2 (5 studies, 1292 participants): RR 1.32, 95% CI 0.78 to 2.22; I^2 = 65%).

The incidence of NODAT (Analysis 1.3.1 (6 studies, 1439 participants): RR 0.77, 95% CI 0.49 to 1.21; I^2 = 0%) as well as the incidence of cardiovascular events (Analysis 1.3.2 (2 studies, 607 participants): RR 0.98, 95% CI 0.42 to 2.33; I^2 = 0%) up to five years after transplantation were not significantly different between groups, mainly because of the low number of studies reporting these rarely occurring outcomes. Likewise data was sparse for harmful events, such as infection (Analysis 1.4.1 (5 studies, 1819 participants): RR 1.02, 95% CI 0.84 to 1.22; I^2 = 30%), CMV infection (Analysis 1.4.2 (RR 1.04, 95% CI 0.80 to 1.36; partic-

ipants = 1758; studies = 5; I^2 = 0%), and malignancy (Analysis 1.4.3 (3 studies, 756 participants): RR 0.77, 95% CI 0.41 to 1.46; I^2 = 0%) and a difference in these outcomes could not be demonstrated up to five years after transplantation. There was also no evidence of difference in kidney function as determined by measurement of serum creatinine and creatinine clearance up to one as well as up to five years after transplantation (Analysis 1.5) (See also Summary of findings for the main comparison).

Sensitivity and subgroup analyses for steroid withdrawal versus steroid maintenance studies

Results of the sensitivity and subgroup analyses are summarised in Table 1.

We have performed sensitivity analysis to assess the impact of publication status and use of intention-to-treat-analysis on primary endpoints (mortality, death censored graft loss, acute rejection and biopsy-proven acute rejection) using data from studies reporting these outcomes at any time point within the first year after transplantation. There was no evidence to suggest a difference in effect estimates of mortality, graft loss and biopsy-proven acute rejection for studies depending on whether they have performed intention-to-treat analysis or whether the study was published in a peer-reviewed journal. The significant increase in risk for acute rejection in patients withdrawn from steroids compared versus those maintained on steroids was further increased in studies published in a peer-reviewed journal (8 studies, 1741 participants: RR 2.02, 95% CI 1.26 to 3.23) and in studies that applied intention-to-treat analysis (6 studies, 1199 participants: RR 2.07, 95% CI 1.10 to 3.91), but was lost in studies published as abstract-only and in studies where intention-to-treat analysis was either not used or unclear.

We performed subgroup analysis stratified by calcineurin-inhibitor type, type of antimetabolite and induction treatment on primary endpoints (mortality, death censored graft loss, acute rejection and biopsy-proven acute rejection) using data from studies reporting these outcomes at any time point within the first year after transplantation. There was no difference in mortality and graft loss in any of the subgroups. The risk of acute rejection after steroid withdrawal was further increased in patients treated with CsA (9 studies, 1357 participants: RR 2.08, 95% 1.29 to 3.35), especially among those who did not receive an additional antimetabolite (2 studies, 150 participants: RR 5.80, 95% CI 2.16 to 15.57) and in patients who did not receive induction treatment (8 studies, 1765 participants: RR 1.93, 95% CI 1.26 to 2.94), but was decreased in patients who received either MMF or enteric-coated mycophenolate sodium (6 studies, 1612 participants: RR 1.41, 95% CI 1.02 to 1.94) or any type of antimetabolite (8 studies, 1763 participants: RR 1.46, 95% CI 1.07 to 1.98).

Steroid avoidance versus steroid maintenance

Results are summarised in Summary of findings 2.

Steroid avoidance did not show a significant effect on patient mortality at either one year (Analysis 2.1.1 (10 studies, 1462 participants): RR 0.96, 95% CI 0.52 to 1.80; I^2 = 0%) or one to five years post transplantation (Analysis 2.1.2 (7 studies, 1201 participants): RR 0.57, 95% CI 0.32 to 1.01; I^2 = 0%). Likewise steroid avoidance did not show any significant effects on graft loss excluding death at either one year (Analysis 2.1.5 (7 studies, 1211 participants): RR 1.09, 95% CI 0.64 to 1.86; I^2 = 0%) or one to five years post transplantation (Analysis 2.1.6 (7 studies, 1245 participants): RR 0.98, 95% CI 0.66 to 1.45; I^2 = 0%).

Steroid avoidance significantly increased the risk of acute rejection within the first year after transplantation by 58% compared versus patients maintained on steroids (Analysis 2.2.1 (7 studies, 835 participants): RR 1.58, 95% CI 1.08 to 2.30; I^2 = 63%). This effect of steroid avoidance was also demonstrated for biopsy-proven acute rejection with a risk increase of 94% within the first year after transplantation (Analysis 2.2.2 (6 studies, 1073 participants): RR 1.94, 95% CI 1.26 to 2.98; I^2 = 45%).

There was no evidence of difference in the occurrence of NODAT, cardiovascular events, infection, CMV infection and malignancy between groups up to five years after transplantation (Analysis 2.3; Analysis 2.4). Kidney function determined as serum creatinine and creatinine clearance up to one year as well as up to five years after transplantation was not different for patients treated with steroids for less than 14 days compared versus patients maintained on steroids (Analysis 2.5).

Sensitivity and subgroup analysis for steroid avoidance versus steroid maintenance - studies

We performed sensitivity analysis to assess the impact of use of intention-to-treat-analysis on primary endpoints (mortality, death censored graft loss, acute rejection and biopsy-proven acute rejection) using data from studies reporting these outcomes at any time point within the first year after transplantation. There was no study investigating steroid avoidance compared versus steroid maintenance that was published as abstract only, consequently the influence of publication status on the effect estimates could not be tested. There was no evidence to suggest a difference in effect estimates of mortality and graft loss for studies depending on whether they have performed intention-to-treat analysis. The increased risk for acute rejection and biopsy-proven acute rejection in patients treated with steroids for less than 14 days after kidney transplantation compared versus those maintained on steroids was further increased in studies that applied intention-to-treat analysis (acute rejection: 4 studies, 655 participants: RR 1.92, 95% CI 1.18 to 3.14; biopsy-proven acute rejection: 4 studies, 918 participants: RR 2.31, 95% CI 1.47 to 3.63), but lost significance in studies where intention-to-treat analysis was either not used or unclear.

We have performed subgroup analysis stratified by type of calcineurin inhibitor, type of antimetabolite and induction treatment

on primary endpoints (mortality, death censored graft loss, acute rejection and biopsy-proven acute rejection) using data from studies reporting these outcomes at any time point within the first year after transplantation. Stratified analysis did not reveal any difference in patient mortality and graft loss. The significant increase in risk for biopsy-proven acute rejection persisted in patients treated with CsA (3 studies, 615 participants: RR 1.89, 95% CI 1.29 to 2.79), while patients treated with TAC did not have an increased risk for biopsy-proven acute rejection (See Table 2).

Steroid avoidance versus steroid withdrawal

Only three studies investigating the effect of steroid avoidance compared versus steroid withdrawal were identified, wherefore data is specifically sparse for this comparison. There is no evidence to suggest a difference in any outcome (death: Analysis 3.1; rejection: Analysis 3.2; NODAT, infection, malignancy: Analysis 3.3; kidney function: Analysis 3.4). Sensitivity and subgroup analysis could not be performed due to the small number of studies identified.

Studies in children with kidney transplant recipients

Steroid withdrawal versus steroid maintenance

We identified only two studies that investigated the effect of steroid withdrawal compared versus steroid maintenance in children (Benfield 2005; Höcker 2009). Death and graft loss at five years were significantly lower for children withdrawn from steroids, but these results were drawn from Benfield 2005 only, since neither death nor graft loss were observed in Höcker 2009 (Analysis 4.1.2: RR 0.16, 95% CI 0.02 to 1.35). The effect of steroid withdrawal on acute rejection is unclear due to the small number of studies and wide confidence intervals (Analysis 4.2). Kidney function was reported in Höcker 2009 only and was not significantly different between groups (Analysis 4.3).

Benfield 2005 was terminated early due to an unanticipated high incidence of post-transplant lymphoproliferative disease. Of the 274 enrolled participants, 19 developed post-transplant lymphoproliferative disease, 10 before randomisation. Sensitivity and subgroup analysis could not be performed due to the small number of studies identified.

Steroid avoidance versus steroid maintenance

Only Mericq 2013 investigated the effect of steroid avoidance compared versus steroid maintenance in children. Neither death nor graft loss was observed in this study, and due to sparse data, a difference in biopsy-proven acute rejection could not be demonstrated. Kidney function was not reported. Sensitivity and subgroup analysis could not be performed on a single study.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Steroid avoidance versus steroid maintenance for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: steroid avoidance
Comparison: steroid maintenance

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Steroid avoidance versus steroid maintenance				
Mortality Follow-up: 1 year	**31 per 1000**	**30 per 1000** (16 to 56)	**RR 0.96** (0.52 to 1.8)	1462 (10)	⊕⊕◯◯ **low**[1,2]	
Graft loss (excluding death) Follow-up: 1 year	**42 per 1000**	**46 per 1000** (27 to 79)	**RR 1.09** (0.64 to 1.86)	1211 (7)	⊕⊕◯◯ **low**[2,3]	
Acute rejection Follow-up: 1 year	**204 per 1000**	**323 per 1000** (221 to 470)	**RR 1.58** (1.08 to 2.3)	835 (7)	⊕⊕⊕◯ **moderate**[4]	
NODAT Follow-up: 5 years	**107 per 1000**	**80 per 1000** (54 to 117)	**RR 0.75** (0.51 to 1.1)	1618 (9)	⊕⊕◯◯ **low**[2,5]	
CMV Infection Follow-up: 5 years	**106 per 1000**	**101 per 1000** (74 to 138)	**RR 0.96** (0.7 to 1.31)	1454 (6)	⊕⊕◯◯ **low**[2,6]	

*The **assumed risk** is the baseline risk in the control group treated with steroid maintenance. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; NODAT: new-onset diabetes after transplantation; CMV - cytomegalovirus

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate

[1] All studies were unblinded. Six studies were industry sponsored. In six studies random sequence generation or allocation concealment or both was unclear. In two studies ITT was either not performed or unclear. One study had selective outcome reporting

[2] Total number of events was fewer than 300

[3] All studies were unblinded. Five studies were industry sponsored. In four studies random sequence generation or allocation concealment or both was unclear. ITT was unclear in one study. One study had selective outcome reporting

[4] All studies were unblinded. Five studies were industry sponsored. In four studies random sequence generation or allocation concealment or both was unclear. In three studies ITT was either not performed or unclear. One study had selective outcome reporting

[5] Most studies were unblinded (8 studies). Five studies were industry sponsored. In four studies random sequence generation or allocation concealment or both was unclear. One study had selective outcome reporting

[6] Most studies were unblinded (5 studies). Four studies were industry sponsored. One study had unclear ITT

DISCUSSION

Summary of main results

The aim of this review was to provide updated evidence addressing the benefits and harms of steroid avoidance and withdrawal in kidney transplant recipients. All identified studies concerned one of the three comparisons defined for this review. The majority of studies compared steroid withdrawal versus steroid maintenance (24 adult studies, 2 studies in children). Steroid avoidance was compared versus steroid maintenance in 19 studies, one of which was conducted in child kidney transplantation. Of the three studies that compared steroid avoidance versus steroid withdrawal, none involved children. In adult kidney transplantation meta-analysis could be carried out for all three comparisons, but data was particularly scarce for the comparison of steroid avoidance with steroid withdrawal. The low number of studies with child kidney transplant recipients did not enable data synthesis through meta-analysis.

We were unable to demonstrate clear beneficial effects, such as a reduction in mortality or NODAT within five years after transplantation for steroids withdrawal or avoidance in adult kidney transplant recipients. Both steroid withdrawal and steroid avoidance showed little or no effect on mortality, graft loss, and CMV infection. The risk of acute rejection did significantly increase by 77% after steroid withdrawal and by 58% after steroid avoidance compared to steroid maintenance (see Summary of findings for the main comparison, Summary of findings 2).

The effect of steroid withdrawal in children is uncertain. The available data allowed only one meta-analysis for acute rejection in children, which found no significant difference. Death and graft loss had not been observed in one of the two studies in children and outcomes such as biopsy-proven acute rejection and malignancy were only reported in one of the two studies which further reduced the quantity of the available data. Only one study investigated the effect of steroid avoidance compared versus steroid maintenance in children, thus a meta-analysis was not possible.

Overall completeness and applicability of evidence

An extensive literature review was performed to identify studies that assessed the benefits and harms of steroid withdrawal or avoidance in kidney transplant recipients. In general, two parameters are particularly relevant for assessing benefits and harms of steroid withdrawal in kidney transplant recipients: firstly, the time-point of steroid withdrawal after kidney transplantation and secondly, the duration of follow-up to observe outcome events in kidney transplant patients.

Steroids are withdrawn at various time points after kidney transplantation in clinical practice and this fact was reflected by the variety of time points used to investigate the effects of steroid withdrawal in clinical studies. We used a cut-off of 14 days after transplantation to discriminate between steroid withdrawal and steroid avoidance. With this approach we were able to combine different time points for steroid withdrawal within these clinically relevant time frames. The majority of steroid avoidance studies used steroids for seven days or less, and the majority of the steroid withdrawal studies withdrew steroids between three to six months after transplantation. Thus, our findings may not be applicable for patients who are withdrawn from steroids at other time-points after transplantation.

Most studies had between one and three years of follow-up after either steroid avoidance or withdrawal which constitutes a major limitation for conclusions regarding long-term consequences for patient and graft survival. Acute rejection is a major risk factor for reduced long-term graft survival and typically occurs within the first year after transplantation. The impact of acute rejection on long-term graft outcomes depends on the severity, recurrence and treatment of the acute rejection. While particularly severe and recurrent rejections increase the risk of graft loss, a single early acute rejection with complete functional recovery after treatment appears to be less harmful for long-term graft outcomes. Most of the acute rejections reported in the included studies occurred early after transplantation and were mild and easily controlled with steroids which could be an argument to conclude that an increased risk of long-term graft loss after steroid withdrawal is unlikely. However, recognizing that potential harms arising from steroid withdrawal may remain hidden for up to five years after steroid withdrawal (Gulanikar 1991); follow-up periods of the included studies were too short to determine long-term graft survival. Furthermore, it is important to stress that only half of the studies reported acute rejection. Consequently, potential harmful effects of steroid withdrawal on long-term graft survival cannot be ruled out with this review with sufficient confidence.

Reporting of harmful events was especially limited and inconsistent. More than half of the studies did not report adverse events such as infection and CMV infection and less than a third of the studies reported malignancy and cardiovascular events. Even though we did not find evidence to suggest a difference in harmful events, it is important to point out that the absence of evidence does not mean there is evidence for absence of effect. It is unclear which outcomes occurred in the studies that provided no data. Although we believe this is the most comprehensive evidence summary on this topic, interpretation of our findings must consider the limitations of available data from this cohort. The value of increasing available evidence of potential harms associated with interventions has been widely recognised and is also not a problem peculiar to this review, but is common to many randomised studies and systematic reviews (Cuervo 2003; Tunis 2003).

Only one study investigating steroid avoidance included an mTOR-inhibitor as baseline immunosuppression. Consequently, we cannot extrapolate the safety of steroid avoidance or withdrawal

to protocols including mTOR-inhibitors.

The inclusion and exclusion criteria for participation in the included studies may mean that our findings are not generalizable to all kidney transplant recipients. Eight studies did not specify any exclusion criteria, of which four did not specify any inclusion criteria. In three studies only recipients of a living kidney transplant were included and 11 studies included solely recipients of a cadaveric kidney transplant. Seventeen studies limited participation for patients who received their first kidney transplant and 16 studies excluded kidney transplant recipients who had experienced previous acute rejection. Kidney transplant recipients with a PRA > 50% were excluded in 13 studies. It is unclear whether the findings of this review apply to kidney transplant recipients with a higher immunologic transplant risk.

Although almost all studies included participants of a wide range of adult ages, none of the studies reported results for different age groups. Therefore we were unable to determine whether there is any difference in results depending on age. Due to the low number of studies in child kidney transplantation, our findings need to be interpreted with great caution in the light of a clear lack of evidence in children.

Quality of the evidence

The quality of the included studies was rather variable. The main limitations in the quality of the studies were allocation concealment, incomplete outcome data, blinding of participants and personnel and disclosure of funding. Of the 48 included studies only five studies blinded participants and personnel. This was considered a high risk of bias because clinical decision making could be influenced by knowledge of the treatment, such as for example that patients withdrawn from steroids were more closely monitored for signs of acute rejection. Adequate allocation concealment was reported in 14 studies and 19 studies demonstrated adequate sequence generation. The lack of adequate sequence generation and allocation concealment can lead to biased estimates of treatment effects in the original study and thus in a systematic review (Hollis 1999; Juni 1999; Moher 1998; Schulz 1995). All hard clinical outcomes (mortality, graft loss, acute rejection) were reported in 37 studies, but incomplete reporting of relevant data for a meta-analysis in many studies hampered use of the provided data in our analysis. Comparison of kidney function was only possible in a limited number of studies because frequently either the number of participants in whom kidney function was measured or a measure of variability of the effect estimate were not provided. It might be more informative to compare the number of patients at risk of graft loss with a low creatinine clearance rather than assessing mean data. However, these data were not provided in any of the studies. Similarly dichotomous outcomes, especially infection and acute rejection were frequently reported as rates or episodes which complicated the use of such data for meta-analysis. For disclosure of funding sources, 16 studies reported receiving of funding from pharmaceutical companies and 28 studies did not disclose their sponsor. We found that blinding of outcome assessors was adequate in 43 studies where the primary outcome were hard-clinical endpoints (mortality, graft loss, acute rejection) and considered unlikely to be influenced by lack of blinding.

Potential biases in the review process

We searched multiple databases without language restriction in attempt to reduce publication bias. The Cochrane Kidney and Transplant's Specialised Register contains handsearched reports of studies presented at conferences and meetings, but there is a possibility that we missed unpublished data presented at smaller conferences or studies published in foreign language journals and low impact journals. Studies may have been added since our last search of the register. Not all included studies reported all outcomes which may have affected the results of the meta-analysis.

Agreements and disagreements with other studies or reviews

Several previous systematic reviews have addressed steroid avoidance and withdrawal after kidney transplantation. The first review included three steroid withdrawal and four steroid avoidance studies in patients on CsA with or without AZA and showed a significant increase in acute rejection with an incidence of acute rejection of 48% in those withdrawn from steroids versus 30% in those maintained on steroids (P = 0.012) (Hricik 1993). The review published seven years later (Kasiske 2000) included 10 studies and showed an increased proportion of patients with acute rejection by 0.14 (95% CI 0.10 to 0.17; P < 0.001) and an increase in graft failure after steroid withdrawal by 40% (RR 1.40, 95% CI 1.09 to 1.70; P = 0.012). Most studies included in this meta-analysis used CsA-based immunosuppression with either no anti-metabolite added or in combination with AZA. Only two studies with MMF were included and subgroup analysis showed similar results for these studies compared versus those that did not include MMF. A review of six studies of steroid withdrawal in kidney transplant recipients on triple therapy with calcineurin inhibitors and MMF showed an increase in acute rejection and no difference in graft failure (Pascual 2004). Due to the relative short follow-up in these six studies long-term consequences for graft survival given the observed increase in acute rejection after steroid withdrawal is unclear. A meta-analysis published in 2012 by Knight 2010 found an increased risk of acute rejection and a reduced cardiovascular risk after steroid withdrawal or avoidance, but these findings resulted from a combined analysis of all steroid withdrawal or avoidance time points and were based on surrogate outcomes such as hypercholesterolaemia, hypertension and NODAT. Another review (Pascual 2012) with nine studies comparing steroid avoidance to steroid maintenance in kidney transplant re-

cipients who received an immunosuppressive regimen consisting of antibody induction, either CsA or TAC and MMF reported that the increased risk of acute rejection in steroid avoidance was lost when patients received TAC-based immunosuppression.

AUTHORS' CONCLUSIONS

Implications for practice

Steroid avoidance and steroid withdrawal after kidney transplantation significantly increased the risk of acute rejection. We found no evidence to suggest a difference in patient and graft survival up to five years after transplantation, but the data to support the absence of harm is limited due to the low number of events observed in rather small studies. Follow-up periods were too short to draw any conclusions on long-term outcomes in kidney transplant recipients after steroid withdrawal or avoidance. In child kidney transplant recipients data is very limited and does not allow any conclusions about steroid withdrawal, but caution is warranted with induction treatment that may increase the risk of post-transplant lymphoproliferative disease in children.

Implications for research

Proving that steroid avoidance or withdrawal after kidney transplantation is safe and beneficial requires demonstration of beneficial effects, such as a reduction in patient mortality or cardiovascular events while at the same time graft survival is not reduced in the long-term. Until now, only short-term data exist that demonstrate an increased risk of acute rejection and the absence of evidence of harm, but there is no long-term data to draw any conclusions about the harms and benefits of steroid avoidance or withdrawal beyond five years after transplantation. Long-term RCTs are needed to determine whether steroid withdrawal and avoidance after kidney transplantation are safe and beneficial. Child kidney transplant recipients constitute a target population in a clear need of well-conducted steroid withdrawal studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahsan 1999

Methods	• Study design: parallel RCT • Study duration: not reported • Follow-up period: 1 year • Primary endpoint: biopsy-proven or presumptive acute rejection episode or treatment failure within 1 year post-transplant
Participants	• Country: USA • Setting: multicentre (21 centres) • Health status: first cadaveric or living kidney transplant; > 18 years; SCr < 2.4 mg/dL or CrCl > 50 mL/min • Number: withdrawal group (134); maintenance group (132) • Median age, range (years): withdrawal group: (50, 20 to 71); maintenance group (50, 18 to 74) • Sex (female): withdrawal group (34%); maintenance group (45%) • Donor source (living donor): withdrawal group (45%); maintenance group (41%) • Exclusion criteria: acute rejection; proteinuria > 2 g/d; significant gastrointestinal disorder; WCC < 2500/mm^3, Hb < 6.5 g/dL; immunosuppression other than CsA + MMF + steroids
Interventions	Withdrawal group • Steroid withdrawal (prednisone) 3 months after transplantation • Prednisone 10 to 15 mg/d before randomisation, after randomisation: days 1 to 21: 15 mg/d, days 22 to 28: 12.5 mg/d, days 29 to 35: 10 mg/d, days 36 to 42: 7.5 mg/d, days 43 to 49: 5 mg/d, days 50 to 56: 2.5 mg/day, then withdrawn Maintenance group • Steroid maintenance (prednisone) • Prednisone: days 1 to 21: 15 mg/d; days 22 to 42: 12.5 mg/d; days 43 to 365: 10 mg/d Baseline immunosuppression • CsA: 5 to 15 mg/kg/d • MMF: months 1 to 3: 2000 mg/d, adjusted to centre practice
Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • Infection • Kidney function measures: SCr (mg/dL), CrCl (mL/min)
Notes	• Did not report number screened for eligibility • The study was stopped on 22 July 1998 due to statistically significant difference in the incidence of acute rejection • Funding source: Roche Laboratories • Contact with study authors for additional information: authors contacted 28

Ahsan 1999 (*Continued*)

	August 2013; response received 28 August 2013	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomization was stratified by centre and was done centrally to maintain a 1:1 ratio at each centre'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind placebo controlled. Stated 'After randomisation, recipients received blister packs containing tablets for their 'prednisone' dose. Neither recipients nor physicians knew whether a randomised patient was in the withdrawal group'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo controlled. Stated 'After randomisation, recipients received blister packs containing tablets for their 'prednisone' dose. Neither recipients nor physicians knew whether a randomised patient was in the withdrawal group'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind placebo controlled. Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all participants were followed for the primary endpoint until study closure on 22 July 1998
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	The study was supported by Roche Laboratories

Albert 1985

Methods	• Study design: parallel RCT • Time frame: 1983 to 1984 • Follow-up period: 13 (2 to 23) months • Primary endpoint: not reported

Albert 1985 (*Continued*)

Participants	• Country: Germany • Setting: single centre • Inclusion criteria: not reported • Number analysed: avoidance group (25); withdrawal group (25) • Mean age, range (years): avoidance group (38, 10 to 51); withdrawal group (36, 21 to 54) • Sex (female): avoidance group (44%); withdrawal group (32%) • Exclusion criteria: not reported
Interventions	Avoidance group • CsA monotherapy Withdrawal group • Steroid withdrawal 3 to 6 months after transplantation Baseline immunosuppression • CsA ○ Started with 15 mg/kg, divided into two daily doses, adjusted to trough levels 250 to 700 ng/mL • Steroids ○ Steroid avoidance group: no steroids ○ Steroid withdrawal group: oral fluocortolone: 0.5 mg/kg, withdrawn 3 to 6 months after transplantation
Outcomes	• Mortality • Graft loss
Notes	• Did not report the number screened for eligibility or randomised • Number of patients discontinued treatment ○ Switched from avoidance group to withdrawal group: 13 ○ Switched from withdrawal group to avoidance group: 1 ○ 4 patients in avoidance group and 5 patients in withdrawal group switched to AZA and steroids

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

Albert 1985 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed, total number of patients by group analysed not reported, results presented as percentages/rates
Selective reporting (reporting bias)	High risk	Acute rejection not reported
Other bias	Unclear risk	Funding sources not reported

Aswad 1998

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: not reported • Primary endpoint: not reported
Participants	• Country: USA • Setting: single centre • Living kidney transplant, no further inclusion criteria provided • Number analysed: withdrawal group (11); maintenance group (10) • Mean age ± SD (years): not reported • Sex: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Steroid withdrawal 6 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • TAC: adjusted to trough levels month 1: 10 to 15 ng/mL; thereafter: 5 to 10 ng/mL • AZA: no further information provided • Prednisone: no further information provided
Outcomes	• Mortality • Graft loss • Acute rejection • SCr
Notes	• Did not report the number screened for eligibility or randomised
Risk of bias	

Aswad 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Stated 'randomly assigned' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients by group not reported for outcomes; unclear if ITT analysis performed
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported Abstract-only publication

ATLAS Study 2005

Methods	• Study design: parallel RCT • Time frame: not reported, but before 2005 • Follow-up period: 3 years • Primary endpoint: incidence of and time to first biopsy-proven acute rejection within 6 months after transplantation
Participants	• Country: 10 European countries • Setting: multicentre (21 centres) • First cadaveric or living kidney transplant; aged 18 to 65 years • Number (randomised/analysed): withdrawal group (152/147); maintenance group (151/151) • Mean age ± SD (years): withdrawal group (44 ± 12); maintenance group (43 ± 13) • Sex (female): withdrawal group (35%); maintenance group (40%) • Donor source (living donor): withdrawal group (13%); maintenance group (12%) • Exclusion criteria: PRA ≥ 50% in previous 6 months; previous organ transplant; non-heart beating kidney donor; requiring any other immunosuppression; HIV infection; uncontrolled infection; significant liver disease; malignancy; severe diarrhoea; vomiting; active peptic ulcer

ATLAS Study 2005 (*Continued*)

Interventions	Treatment group • Steroid withdrawal day 1 after transplantation Control group • Steroid maintenance Baseline immunosuppression • TAC: started within 12 hours before transplantation with 0.2 mg/kg divided in two doses, adjusted to trough levels day 28: 10 to 20 ng/mL, thereafter: 5 to 15 ng/mL • MMF: day 0: 1000 mg, day 1 to 14: 2000 mg, thereafter: 1000 mg • Steroids ○ IV methylprednisone: day 0: 500 mg or less ○ Withdrawal group: no further steroids ○ Maintenance group: IV methylprednisone day 1: 125 mg, or prednisone day 2 to 14: 20 mg; day 15 to 28: 15 mg; day 29 to 42: 10 mg; thereafter: 5 mg
Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • NODAT • Infection • CMV infection • Malignancy • Cardiovascular events • SCr (μM) • CrCl (mL/min)
Notes	• This study had a third arm with basiliximab induction followed by TAC monotherapy (154 patients) • Did not report number screened for eligibility • Number of patients excluded from analysis ○ Withdrawal group: 1 (either did not receive study drug or did not undergo transplantation) ○ Maintenance group: 4 (either did not receive study drug or did not undergo transplantation) • Number of patients discontinued study ○ Withdrawal group: 8 (primarily because of protocol violation) within the first year ○ Maintenance group: 13 (primarily because of protocol violation) within the first year • 3-year follow-up: data of 278 patients available (139/139)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated 'Randomization was performed with a 1:1 ratio stratified by centre. The randomization list was generated by the Data Operation Department of Fujisawa

ATLAS Study 2005 (*Continued*)

		GmbH. Each centre received a unique sequence of patient numbers and a set of sealed envelopes.'
Allocation concealment (selection bias)	Low risk	Stated 'sealed envelopes'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review have been reported
Other bias	High risk	Sponsored by a grant from Fujisawa GmbH The investigator-initiated 1-year follow-up was supported by an unrestricted grant from Astellas, Munich, Germany

Benfield 2005

Methods	• Study design: parallel RCT • Time frame: 2001 to 2004 • Follow-up period: 3 years • Primary endpoint: change in standardised height z score
Participants	• Country: Mexico, USA • Setting: multicentre (17 centres) • Age: 0 to 20 years • First cadaveric or living kidney transplant; enrolment at transplantation; randomisation 6 months after transplantation of participants without previous rejection if clinical or histologic evidence of rejection in protocol biopsy absent • Number: withdrawal group (73); maintenance group (59) • Mean age ±SD (years): withdrawal group (11 ± 5); maintenance group (12 ± 6) • Sex (female): withdrawal group (44%); maintenance group (37%) • Donor source (living donors): withdrawal group (64%); maintenance group (69%) • Exclusion criteria: not reported

Interventions	Treatment group • Steroid withdrawal 6 to 12 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: day 0 and 4 • CsA or TAC ○ CsA trough level: weeks 1 to 2: 175 to 400 ng/mL; week 3 to month 3: 175 to 300 ng/mL; thereafter: 50 to 250 ng/mL; ○ TAC trough level: weeks 1 to 4: 10 to 15 ng/mL; thereafter: 5 to 10 ng/mL • SRL: starting on day 1 with 6 mg/m^2/d adjusted to trough level: 10 to 20 ng/mL • Steroids ○ IV methylprednisone: day 0 and 1: 10 mg/kg ○ Oral prednisone: starting on day 2 with 2 mg/kg/d, tapered to 0.15 mg/kg/d by day 74 ◇ Withdrawal group: withdrawal by end of month 12 after transplantation ◇ Maintenance group: maintained on 0.15 mg/kg/d
Outcomes	• Mortality • Graft loss • Acute rejection • CrCl (mL/min) • Malignancy (PTLD)
Notes	• The study was terminated on 13 August 2004 due to an unanticipated high incidence of post-transplant lymphoproliferative disease; 19 patients developed PTLD (before randomisation: 10) • Did not report number screened for eligibility • 142/274 enrolled participants were not randomised (52% drop out before randomisation), because of rejection (40), graft loss (9), death (2), had not yet reached 6 month protocol biopsy when study was stopped (35), adverse events (16). protocol violation (4), lost to follow-up/withdrawal of consent (5), other reasons (31) • Contact with study authors for additional information: authors contacted 8 July 2013; no response received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated 'centrally randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated 'in a placebo controlled double-blinded fashion' but no further information provided

Benfield 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated 'in a placebo controlled double-blinded fashion' but no further information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated 'in a placebo controlled double-blinded fashion' but no further information provided. Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total number of patients by group not reported for outcomes; ITT analysis performed
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review have been reported
Other bias	High risk	High drop-out rate before randomisation (52%) Choice of calcineurin inhibitor was centre specific (TAC or CsA) Support provided by NIH UO1-A1-46135 and Wyeth Pharmaceuticals The study was terminated early due to an unanticipated high incidence of PTLD

Boletis 2001

Methods	• Study design: parallel RCT • Time frame: 1996 to 1998 • Follow-up period: 1 year • Primary endpoint: not reported
Participants	• Country: Greece • Setting: single centre • First cadaveric or living kidney transplant ○ CsA $\geq$ 3 mg/kg with C_0 levels of > 150 ng/mL and C_2 levels > 600 ng/mL without signs of nephrotoxicity ○ MMF 2 g or 1.5 g if body weight < 50 kg • Number randomised: withdrawal group (34); maintenance group (/32) • Mean age ±SD (years): withdrawal group (43 ± 11); maintenance group (38 ± 11) • Sex (female): withdrawal group (41%); maintenance group (19%) • Donor source (living donors): withdrawal group (53%); maintenance group (38%) • Exclusion criteria: previous acute rejection; SCr > 2 mg/dL; proteinuria > 0.5 g/24 h

Boletis 2001 (*Continued*)

Interventions	Treatment group • Steroid withdrawal 6 months after transplantation Control group • Steroid maintenance with alternate day steroid Baseline immunosuppression • CsA: no further information provided. • MMF: no further information provided. • Methylprednisone: no further information provided
Outcomes	• Mortality • Graft loss • Acute rejection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomly assigned' but no further information provided
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of patients in whom the outcome were measured is ambiguous (two reports with different number of patients in each group); 14% failed to comply with follow-up protocol; unclear if ITT analysis performed
Selective reporting (reporting bias)	High risk	Death and graft loss are only reported in one of the two published reports, but number of participants in each group vary between reports

Boletis 2001 (*Continued*)

Other bias	Unclear risk	Unclear whether informative censoring is present, because the two published reports are different in regard to number of participants and time period of study Funding source not reported

Boots 2002

Methods	• Study design: parallel RCT • Time frame: 1997 to 2000, excluding October 1998 to October 1999 (a different multicentre study during that period) • Follow-up period: 2.7 years (range 0.9 to 3.4) years • Primary endpoints: patient survival, graft survival, incidence of first acute rejection in first 6 months after transplantation
Participants	• Country: The Netherlands • Setting: multicentre (number of centres not reported) • First and second cadaveric or living kidney transplant; Previous graft loss not because of immunological causes; PRA < 50%; 18 to 65 years • Number (randomised/analysed): avoidance group (28/28); withdrawal group (34/34) • Mean age ± SD (years): avoidance group (54 ±14); withdrawal group (48 ± 13) • Sex (female): avoidance group (61%); withdrawal group (35%) • Donor source (living donors): avoidance group (14%); withdrawal group (12%) • Exclusion criteria: HLA identical living donor; mismatch on HLA-B or HLA-DR locus

Interventions	Avoidance group
	• Steroid withdrawal 7 days after transplantation or after TAC levels > 15 ng/mL
	Withdrawal group
	• Steroid withdrawal 3 to 5 months after transplantation
	Baseline immunosuppression
	• TAC: started within 12 hours before transplantation with 0.1 to 0.15 mg/kg twice daily adjusted to trough levels: week 1 to 2: 15 to 20 ng/mL; week 3 to 4: 10 to 15 ng/mL; thereafter: reduced to 5 to 7 ng/mL 6 months after transplantation
	• Steroids
	  ○ IV methylprednisone: day 0: 125 mg
	  ○ Avoidance group: oral prednisone: day 1 to 8: 10 mg, then stopped
	  ○ Withdrawal group: oral prednisone: month 1: 10 mg; month 2: 7.5 mg; month 3: 5 mg; then withdrawn within 1 to 3 months

Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • SCr (mg/dL) • CrCl (mL/min) • NODAT

Boots 2002 (*Continued*)

	• Infection
Notes	• Number screened for eligibility: 76

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed by opening a closed opaque numbered envelope
Allocation concealment (selection bias)	Low risk	Stated 'closed opaque envelopes'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up or accounted for; ITT analysis performed ('Analyses were made on an ITT basis.'
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review have been reported
Other bias	Unclear risk	Funding source not reported

Bouma 1996

Methods	• Study design: parallel RCT • Time frame: 1993 to 1995 • Follow-up period: 1 year • Primary endpoint: proportion of successful steroid withdrawal defined as lack of prednisone reinstitution for any reason
Participants	• Country: The Netherlands • Setting: multicentre (2 centres) • First and second cadaveric kidney transplant 1 year after transplantation on CsA + steroids • Number (analysed): withdrawal group (42); maintenance group (42) • Mean age ± SD (years): withdrawal group (48 ± 13); maintenance group (54 ± 12)

Bouma 1996 (*Continued*)

	• Sex (female): withdrawal group (31%); maintenance group (31%) • Exclusion criteria: CrCl < 40 mL/min; immunosuppression with AZA; steroid requirement for other disease; PRA > 50%; previous graft loss within 3 months after transplantation because of irreversible rejection; > 2 acute rejections of current transplant
Interventions	Treatment group • Steroid withdrawal at least 1 year after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: twice daily, adjusted to whole blood level 80 to 150 µg/mL • Steroids ○ Oral prednisone: 10 mg/d ◇ Withdrawal group: week 1 to 2: 7.5 mg/d; week 3 to 5: 5 mg/d; week 6 to 8: 2.5 mg/d; then withdrawn ◇ Maintenance group: unchanged
Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • NODAT • Infection • Malignancy • Cardiovascular event • CrCl (mL/min)
Notes	• Did not report number screened for eligibility; 86 randomised; 84 analysed • 28/42 patients in treatment group had successful steroid withdrawal • Contact with study authors for additional information: authors contacted: 21 June 2013; response received: 4 July 2013

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

Bouma 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	This study was supported by a grant from Sandoz, The Netherlands

Burke 2000

Methods	• Study design: parallel RCT • Time frame: not reported, but before 2000 • Follow-up period: 3 years • Primary endpoint: not reported
Participants	• Country: USA • Setting: single centre • First cadaveric or living kidney transplant; aged 18 to 65 years • Number (randomised/analysed): withdrawal group (26/14); maintenance group (25/15) • Mean age (years): withdrawal group (46.5); maintenance group (47.1) • Sex: not reported • Donor source (living donors): withdrawal group (42%); maintenance group (28%) • Exclusion criteria: > 1 acute rejection during the first 3 months; previous graft loss because of immunological causes; PRA > 50%
Interventions	Treatment group • Steroid withdrawal 3 months after transplantation (completed 6 months after transplantation) Control group • Steroid maintenance Baseline immunosuppression • CsA: 8 to 10 mg/kg/d adjusted to blood levels 250 to 350 ng/mL • MMF: 2 to 3 g/d • Steroids ○ Prednisone: day 0: 200 mg; day 1 to 5: tapered to 20 mg/d; day 6 to 90: 20 mg/d ○ Withdrawal group: month 4 to 6: reduced by 5 mg/mo until complete withdrawal at month 6 ○ Maintenance group: month 4 to 6: reduced to 10 mg/d at month 6; month 7 to 12: reduced to 15 mg every other day at month 12
Outcomes	• SCr (mg/dL)

Burke 2000 (*Continued*)

Notes	• Did not report number screened for eligibility • Number of patients discontinued study: 22 patients were withdrawn from the study because of noncompliance (6), MMF intolerance (2), patient request for steroid withdrawal (4), pulmonary disease requiring steroids (3), second acute rejection (2), PTLD (1), hepatitis B (1), death (3)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'all patients were randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind placebo controlled, but partially unblinded for interim analysis
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo controlled, but partially unblinded for interim analysis
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind placebo controlled, outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	High risk	43% of patients were withdrawn from the study for various reasons; patients who died/lost their graft were excluded from the study; unclear if ITT analysis performed
Selective reporting (reporting bias)	High risk	Primary endpoints for this review not reported, primarily surrogate outcomes reported
Other bias	Unclear risk	Abstract data only available Funding source not reported

De Vecchi 1986

Methods	• Study design: parallel RCT • Time frame: not reported but before 1986 • Follow-up period: 2 years • Primary endpoint: not reported

De Vecchi 1986 (*Continued*)

Participants	• Country: Italy • Setting: single centre • Cadaveric kidney transplantation, no further inclusion criteria provided • Number (randomised/analysed): withdrawal group (25/25); maintenance group 26/26) • Mean age ± SD (years): withdrawal group (36 ± 12); maintenance group (36 ± 10) • Sex (female): withdrawal group (48%); maintenance group (35%) • Exclusion criteria: not reported
Interventions	Treatment group • Steroid withdrawal day 1 after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: day 0 to 3: 5 mg/kg/d IV; from day 4: 15 mg/kg/d PO; tapered by 2 mg/kg every 16 days until maintenance dose of 5 mg/kg/d at month 4, given as single morning dose • Steroids ○ IV methylprednisone: 500 mg during transplantation ○ Withdrawal group: no further steroids. ○ Maintenance group: methylprednisone: day 1: 160 mg IV; day 2: 120 mg IV; day 3: 16 mg; reduced by 4 mg every 2 months until maintenance dose of 8 mg/d by the end of month 6
Outcomes	• Mortality • Graft loss • Acute rejection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment ○ 18 patients in the withdrawal group had steroids added ○ 6 patients in withdrawal group switched to AZA or triple immunosuppression and were excluded ○ 5 patients in maintenance group switched to AZA or triple immunosuppression and were excluded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomly assigned' but no further information provided
Allocation concealment (selection bias)	Low risk	Stated 'assigned by sealed envelopes'

De Vecchi 1986 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis not performed; 6 patients in treatment group and 5 patients in control group excluded because of switch to different immunosuppression
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Low risk	Funded by grant of the Consiglio Nazionale delle Richerche

del Castillo 2005

Methods	• Study design: parallel RCT • Time frame: 2002 to 2004 • Follow-up period: 1 year • Primary endpoint: not reported
Participants	• Country: Spain, Portugal • Setting: multicentre (16 centres) • First kidney transplant, no further inclusion criteria provided • Number (randomised/analysed): withdrawal group (70/70); maintenance group (72/72) • Mean age ± SD (years): withdrawal group (47 ± 11); maintenance group (47 ± 11) • Sex (female): withdrawal group (53%); maintenance group (26%) • Exclusion criteria: not reported
Interventions	Treatment group • Steroid withdrawal 6 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: not reported • MMF: not reported • Prednisone: not reported

Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • SCr (mg/dL) • CrCl (mL/min)
Notes	• Did not report number screened for eligibility • 4 patients were excluded post randomisation but pre-intervention because they did not fulfil the inclusion criteria • 2 control patients lost to follow-up during the 12 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed-up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported; abstract data only

DOMINOS Study 2012

Methods	• Study design: parallel RCT • Time frame: 2007 to 2009 • Follow-up period: 6 months • Primary endpoint: incidence of treatment failure month 6, defined as clinical biopsy-proven acute rejection, graft loss, death or loss to follow-up
Participants	• Country: France • Setting: multicentre (14 centres) • First or second cadaveric or living kidney transplant; PRA < 20%; 18 to 70 years • Number (randomised/analysed): avoidance group (112/112); withdrawal group (110/110) • Mean age ± SD (years): avoidance group (51 ± 10); withdrawal group (51 ± 12) • Sex (female): avoidance group (32%); withdrawal group (36%) • Donor source (living donor): avoidance group (0%); withdrawal group (2%) • Exclusion criteria: multi-organ transplant; previous non-kidney transplant; cold ischaemia time > 36 hours; non-heart beating donor

Interventions	Treatment group
	• Avoidance group
	  ○ Steroid withdrawal day 1 after transplantation
	Control group
	• Withdrawal group
	  ○ Steroid withdrawal 4 to 6 months after transplantation
	Baseline immunosuppression
	• IL-2RA: according to centre protocol
	• CsA: started within 24 hours of transplantation with 8mg/kg/d, divided into 2 single doses, adjusted to C_2 levels: month 1: 1100 to 1300 ng/mL; month 2 to 3: 800 to 1000 ng/mL; month 4 to 6: 600 to 800 ng/mL
	• EC-MPS: week 1 to 6: 2160 mg/d divided in two doses; after week 6: 1440 mg/d divided in two doses
	• Steroids
	  ○ IV methyl prednisone: day -1 and 0: 250 mg
	  ○ Avoidance group: no further steroids unless 'clinically mandated'
	  ○ Withdrawal group: prednisone: week 1: 1 mg/kg/d (max 80 mg/d); week 2: 0.5 mg/kg/d (max 40 mg/d); decreased by 5 mg/wk until dose 20 mg/d; decreased by 2.5 mg/wk until dose 10 mg/d; 10 mg/d maintained for 4 weeks and at least until month 3, biopsy at month 3: with rejection continued at 10 mg/d, without rejection decreased by 2.5 mg/15 days until stopped

Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • SCr (µmol/L) • CrCl (mL/min) • eGFR (mL/min)
Notes	• Did not report number screened for eligibility • Number of patients discontinued study ○ Avoidance group (20); adverse events (9); unsatisfactory therapeutic effect

	(11) ○ Withdrawal group (20); adverse events (11); unsatisfactory therapeutic effect (9)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Patients were randomised using a block size of 4 with no stratification by the contract research organization using a validated automated system.'
Allocation concealment (selection bias)	Low risk	'With sealed envelopes distributed to the participating centers...opened after randomization by the investigator.'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed, all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	The study was funded by Novartis Pharma SAS, Rueil-Malmaison, France The manuscript was prepared with editorial support from a freelance medical writer funded by Novartis Pharma SAS

EVIDENCE Study 2014

Methods	• Study design: parallel RCT • Time frame: 2009 to 2012 • Follow-up period: 9 months • Primary endpoint: treatment failure rate (mortality, graft loss, biopsy-proven acute rejection, loss to follow-up) between randomisation (month 3) and month 12 after transplantation
Participants	• Country: Italy • Setting: multicentre (number of centres not reported) • First or second kidney transplant from a donor aged > 14 years; aged > 18 years • Number: withdrawal group (68); maintenance group (71) • Mean age ± SD (years): withdrawal group (48 ± 12); maintenance group (49 ± 13) • Sex (female): withdrawal group (32%); maintenance group (28%) • Donor source (living donor): withdrawal group (4%); maintenance group (1%) • Exclusion criteria: > 25% PRA, severe thrombocytopenia; leucopenia or anaemia; history of malignancy within 5 years; viral hepatitis; pregnancy; severe adverse events including active infections requiring hospitalisation • Enrolled patients were not randomised if CrCl < 40 mL/min, proteinuria > 0.8 g/24 h; severe adverse events or infections; poor adherence; withdrawal of consent; development of anti-HLA antibodies

Interventions	Treatment group
	• Steroid withdrawal 3 months after transplantation, tapered by 1 mg/wk until stopped within 5 to 6 weeks
	• CsA: dose adjusted to C_2 levels 300 to 500 ng/mL
	• EVL: dose adjusted to C_0 levels 6 to 10 ng/mL
	Control group
	• Steroid maintenance with oral prednisone 5 mg/d
	• CsA: dose adjusted to C_2 levels 200 to 450 ng/mL
	• EVL: dose adjusted to C_0 levels 6 to 10 ng/mL
	Baseline immunosuppression
	• Basiliximab: day 0 and 4
	• CsA: within 48 hours of graft reperfusion at 4mg/kg/d twice daily; dose adjusted to C_2 levels: until day 30: 500 to 700 ng/mL; day 30 to 90: 300 to 500 ng/mL
	• EVL: within 48 hours of graft reperfusion at 1.5 mg/d twice daily; dose adjusted to C_0 levels: day 3 to 7: 3 to 8 ng/mL; after day 7: 8 to 12 ng/mL
	• Steroids
	  ○ IV methyl prednisone: day 0: 500 mg; day 1: 40 mg
	  ○ Oral prednisone: day 2 to 7: 20 mg; day 8 to 15: 15 mg; day 16 to 22: 12.5 mg; day 23 to 30: 10 mg; day 30 to 45: 7.5 mg; day 46 to 90: 5 mg

Outcomes	• Treatment failure rate (mortality, graft loss, biopsy-proven acute rejection, loss to follow-up) • Mortality • Graft loss • Biopsy-proven acute rejection • Change in CrCl (mL/min) • Change in eGFR (mL/min) • NODAT

Notes	• Screened for eligibility (332), randomised (184), analysed in ITT population (184); PP population (135)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'...eligible patients were randomised 1:1 to 1 of the treatment arms. Randomization was stratified according to centre, recipient age at transplantation (<60 and 60 years) and creatinine clearance at month 3 (55 and >55 mL/min), according to a biased coin design.'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis for primary analysis, but total number of patients by group for outcomes not reported
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	Difference in CsA levels between groups (higher levels in treatment group) The study was sponsored by Novartis according to ClinicalTrials.gov. 'Editorial assistance was provided by Mary Hines, Springer Healthcare Communications, and funded by Novartis Farma, Italy.'

Farmer 2006

Methods	• Study design: parallel RCT • Time frame: not reported but before 2006 • Follow-up period: 1 year • Primary endpoint: incidence of biopsy-proven acute cellular rejection 1 year following steroid withdrawal
Participants	• Country: UK • Setting: single centre • First or second cadaveric or living kidney transplant with functioning graft > 1 year; < 10% rise in SCr within preceding 6 months; SCr < 200 µmol/L; < 15% variability in CsA levels; CsA levels between 80 to 120 µg/L; aged 18 to 80 years • Number: withdrawal group (44); maintenance group (48) • Mean age ± SD (years): withdrawal group (44 ± 15); maintenance group (45 ± 13) • Sex (female): withdrawal group (32%); maintenance group (40%) • Donor source (living donor): withdrawal group (28%); maintenance group (25%) • Exclusion criteria: malignancy; previous rejection on steroid withdrawal; history of Addison's disease; bilateral adrenalectomy; multi-organ transplant; recurrence of focal and segmental glomerulosclerosis; treatment with Sandimmun; ischaemic heart disease; malnutrition; recent severe infection

Interventions	Treatment group
	• Steroid withdrawal > 1 year after transplantation
	Control group
	• Steroid maintenance
	Baseline immunosuppression
	• CsA: no further information provided
	• AZA: no further information provided
	• Steroids:
	  ○ Withdrawal group: steroids withdrawn at a rate of 1 mg/mo
	  ○ Maintenance group: prednisolone unchanged

Outcomes	• Biopsy-proven acute cellular rejection • SCr (µmol/L)
Notes	• Screened for eligibility (572); randomised (92); did not reported number analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided.
Allocation concealment (selection bias)	Low risk	'Using sealed envelopes'.
Blinding (performance bias and detection bias) All outcomes	High risk	'Patients were informed to which arm of the trial they had been allocated.'

Farmer 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	"The patients randomised to the withdrawal group were followed with more frequent serum creatinine estimation." A rise in serum creatinine prompted kidney biopsy to detect biopsy proven acute cellular rejection which is the primary endpoint of this study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Total number of patients by group for outcomes not reported. Number of patients who were lost to follow up is unclear
Selective reporting (reporting bias)	High risk	Patient and graft survival are not reported
Other bias	Unclear risk	Time lead bias, because follow up started with date steroids were completely withdrawn in treatment group but with randomisation for control group Funding source not reported

FRANCIA Study 2007

Methods	• Study design: parallel RCT • Time frame: 2001 to 2005 • Follow-up period: 1 year • Primary endpoint: acute rejection during first year after transplantation
Participants	• Country: France • Setting: multicentre (6 centres) • First cadaveric kidney transplantation; aged 18 to 65 years • Number (randomised/analysed): withdrawal group (98/103); maintenance group 103/99) • Mean age, range (years): withdrawal group (48, 19 to 65); maintenance group (48, 17 to 65) • Sex (female): withdrawal group (28%); maintenance group (35%) • Exclusion criteria: PRA > 20%; cold ischaemia time > 36 hours; malignancy; immunosuppressive therapy before transplantation; wait listed for another transplant; leucocytes < 2000/mm^3; platelets < 50000/mm^3; underlying kidney disease; focal and segmental glomerular sclerosis
Interventions	Treatment group • Steroid withdrawal day 1 after transplantation Control group • Steroid maintenance until at least 6 months after transplantation, thereafter

FRANCIA Study 2007 (*Continued*)

	according to centre practice Baseline immunosuppression • ATG: day 0: 9 mg/kg; day 1, 3, 5, 7: 3 mg/kg • CsA: starting on day 5 with 8 mg/kg/d, divided into 2 single doses, adjusted to trough levels 150 to 200 ng/mL • MMF: 1000 mg/d twice daily, adjusted to centre practice • Steroids ○ IV methylprednisone day 0: 500 mg ○ Withdrawal group: no further steroids ○ Maintenance group: prednisone: day 0 to 5: 1 mg/kg/d; day 6 to 10: 0.5 mg/kg/d; day 11 to 15: 0.25 mg/kg/d; day 16 to 30: 0.2 mg/kg/d; day 31 to 180: 0.1 mg/kg/d; after day 180 according to centre practice
Outcomes	• Mortality • Graft loss • Acute rejection • SCr (µmol/L)
Notes	• Did not report number screened for eligibility • Number of patients excluded from analysis: maintenance group (4) because of substantial deviations from the immunosuppressant therapy protocol • Number of patients discontinued study: 3 patients were excluded after randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Eligible patients were assigned to CS or non-CS treatment at a 1:1 ratio using block randomization with stratification according to the recipient's age and cold ischaemia time.'
Allocation concealment (selection bias)	Low risk	'Treatment codes were provided in sealed envelopes'.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints.

FRANCIA Study 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; 4 patients in control group excluded from analysis for acute rejection but included for patient and graft survival analysis
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported.
Other bias	High risk	TAC, SRL, EVL, AZA could be introduced according to centre practice Steroid dosing after 6 months according to centre practice, unclear whether patients were withdrawn from steroids or maintained on steroids Study was sponsored by the Nantes University Hospital Statistical analysis of study data was supported by Fresenius Biotech GmbH, Germany

FREEDOM Study 2008

Methods	• Study design: parallel RCT • Time frame: 2001 to 2005 • Follow-up period: 1 year • Primary endpoint: eGFR at 1 year post-transplant
Participants	• Country: North America, South Africa, Europe, Australia, Asia • Setting: multicentre (40 centres) • First cadaveric or living kidney transplantation; aged 18 to 75 years • Number (randomised/analysed): treatment group 1 (112/111); treatment group 2 (116/115); control group (109/109) • Mean age ± SD (years): treatment group 1 (43 ± 13); treatment group 2 (46 ± 12) ; control group (47 ± 13) • Sex (female): treatment group 1 (35%); treatment group 2 (27%); control group (36%) • Donor source (living donor) • Treatment group 1 (48%); treatment group 2 (30%); control group (41%) • Exclusion criteria: donor age > 60 years; non heart beating donor; previous organ transplant; current PRA > 20%; cold ischaemia time > 24 h
Interventions	Treatment group 1 • No steroids at any time Treatment group 2 • Steroid withdrawal day 7 after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: day 0 and 4: 20 mg

FREEDOM Study 2008 (*Continued*)

	• CsA: starting within 24 h of transplantation with 10 mg/kg/d adjusted to C_2 levels month 1: 1500 to 2000 ng/mL; month 2: 1300 to 1700 ng/mL; month 3: 1100 to 1500 ng/mL; month 4 to 6: 900 to 1300 ng/mL; thereafter: 800 to 1000 ng/mL • EC-MPS: day 0: 720 to 1440 mg; thereafter 1440 mg/day divided in two doses • Steroids (for treatment group 2 and control group) ○ IV methyl prednisone: day 0: 500 mg; day 1: 250 mg; day 2: 125 mg ○ Oral prednisolone: day 3: 60 mg; day 4: 40 mg; day 5: 30 mg; day 6: 20 mg ○ Treatment group 2: no further steroids ○ Control group: month 1: 10 to 30 mg; month 2: 10 to 20 mg; thereafter: 5 to 10 mg
Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • NODAT • Infection • CMV infection • Malignancy • CrCl (mL/min) • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Number of patients excluded from analysis ○ Did not undergo transplantation: treatment group 1 (1); treatment group 2 (1); control group (0) • Number of patients discontinued treatment: treatment group 1 (38, 25%); treatment group 2 (34, 34%); 20 patients in control group (20, 20%) • Number of patients discontinued study ○ Treatment group 1 (8%): loss to follow-up (2), withdrawal of consent (2), death (5) ○ Treatment group 2 (10%):loss to follow-up (4), withdrawal of consent (5), death (2) ○ Control group (9%): loss to follow-up (3), withdrawal of consent (5), death (2)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated 'Randomization was undertaken in a 1:1:1 ratio using a validated system that automates the random assignment of treatment groups to randomization numbers.'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label

FREEDOM Study 2008 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary endpoints for this review reported
Other bias	High risk	The study was funded by Novartis Pharma AG

Gulanikar 1991

Methods	• Study design: parallel RCT • Time frame: 1982 to 1992 • Follow-up period: 5 years
Participants	• Country: Canada • Setting: multicentre (14) • First and subsequent cadaveric or living kidney transplant; functioning graft 90 days after transplantation, with SCr < 2.5 mg/d • Number (randomised/analysed): withdrawal group (260/260); maintenance group (263/263) • Mean age ± SD (years): withdrawal group (39 ± 1); maintenance group (40 ± 1) • Sex (female): withdrawal group (35%); maintenance group (41%) • Donor source (% living donors): not reported • Exclusion criteria: acute rejection in previous 2 weeks; malignancy
Interventions	Treatment group • Steroid withdrawal after at least 90 days Control group • Steroid maintenance Baseline Immunosuppression • CsA: twice daily adjusted to 12-h trough levels between 75 to 200 ng/mL • Steroids ○ Prednisone: from day 1 after transplantation 1 mg/kg on alternate days, reduced by 5 mg (when clinical conditions allowed) until a dosage of 0.3 mg/kg
Outcomes	• Mortality • Graft loss • NODAT • Infection • CMV infection

Gulanikar 1991 (*Continued*)

	• Malignancy • Cardiovascular event • SCr (mg/dL) • CrCl (mL/min)
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment ○ Withdrawal group: 143 patients; cessation by physician (45), decoded on request (34), no test drug given (33), CsA stopped (15), noncompliance (15), technical withdrawal (1) ○ Maintenance group: 123 patients; because of cessation by physician (33), decoded on request (32), no test drug given (25), CsA stopped (18), noncompliance (14), technical withdrawal (1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated 'randomised blocks of various sizes were generated and used to attain a balanced, restricted randomization according to treatment centre. The order of randomization did not have a repeating sequence'
Allocation concealment (selection bias)	Low risk	Stated 'Physicians did not know the randomization number until the patient was enrolled, and the code was not broken until the analysis'
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated '...the code was not broken until the analysis. Patients were randomly assigned at 90 days to receive either a placebo or prednisone by means of a process that prevented prior knowledge of their treatment group'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated 'The study was doubly blinded. The placebo and prednisone were prepared in an indistinguishable form and dispensed as coded therapy'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded placebo controlled, outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stated 'No patients were excluded after entry (as distinct from withdrawals in the survival analysis) or lost to follow-up.'; ITT analysis performed

Gulanikar 1991 (*Continued*)

Selective reporting (reporting bias)	High risk	Acute rejection not reported
Other bias	High risk	This work was supported by Sandoz Ltd. , Basel, Switzerland, Sandoz Canada Inc. , Dorval, Que., Upjohn Ltd., Kalamazoo, Mich., the Richard and Jean Ivey Fund, London, Ont., the Michael Fung Endowment Fund, London, Ont., the Claudine Keown Endowment Fund, London, Ont. , the University Hospital Transplant Research Fund, London, Ont., Robarts Research Institute endowment funds and the City of London, Ont

Höcker 2009

Methods	• Study design: parallel RCT • Time frame: 2000 to 2006 • Follow-up period: 2 years • Primary endpoint: standardised longitudinal growth
Participants	• Country: Germany • Setting: multicentre (8 centres) • Aged < 18 years; 12 to 24 months after first or second cadaveric or living kidney transplant; triple immunosuppression at study entry with CsA, MMF and steroids • Number (analysed/randomised): withdrawal group (23/23); maintenance group (19/17) • Mean age ± SD (years): withdrawal group (10 ± 1); maintenance group (11 ± 1) • Sex (female): withdrawal group (35%); maintenance group (32%) • Donor source (living donors): withdrawal group (22%); maintenance group (32%) • Exclusion criteria: irreversible acute rejection of a previous graft; PRA > 80% within 12 months before study entry; any previous steroid-resistant acute rejection; > 2 acute rejections; biopsy-proven acute rejection; GFR < 40 mL/min; SCr increase > 20% within the last 6 months before study entry; growth hormone therapy
Interventions	Treatment group • Steroid withdrawal 12 to 24 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: 5 to 10 mg/kg/d divided into 2 or 3 single doses adjusted to trough level 70 to 140 µg/L • MMF: 1200 mg/m^2 body surface area/d, divided into two single doses • Steroids ○ Either prednisone 5 mg/m^2/d or methylprednisolone 4 mg/m^2/d ◇ Withdrawal group: tapered over 12 weeks by either 0.35 mg/m^2/wk or by 0.7 mg/m^2/2 wk until withdrawal

	◇ Maintenance group: unchanged
Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • Infection • CrCl (mL/min)
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment ○ Withdrawal group: switched to different immunosuppression (mTOR-inhibitor (2), TAC (2), MMF withdrawal (1)) ○ Maintenance group: withdrew MMF (1) • Number of patients discontinued study ○ Withdrawal group: were lost to follow-up (2) ○ Maintenance group: withdrew consent after randomisation (2); received growth hormone (1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated 'central randomization by the principal investigator', stated 'block randomization stratified by pubertal status'
Allocation concealment (selection bias)	Unclear risk	Stated 'concealed allocation' but not further information provided
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported

Other bias	Unclear risk	'Because recruitment of patients for this study was more difficult than anticipated (because some patient's parents and covering physicians had a strong bias pro or con steroid withdrawal, we performed an interim analysis, which revealed a significant difference in growth between both groups. Hence, the study was finished prematurely. ' Funding source not reported

INFINITY Study 2013

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 6 month • Primary endpoint: Treatment failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up)
Participants	• Country: France • Setting: multicentre (number of centres not reported) • De novo kidney transplant recipients at low immunological risk (PRA < 20%, cold ischaemia time < 36 h) • Number: 131 analysed, no further data available • Age: not reported • Mean age ± SD (years): not reported • Sex (% female): not reported • Donor source (% living donor): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Steroid avoidance, no further information provided Control group • Steroid maintenance, no further information provided Baseline immunosuppression • IL-2RA: no further information provided • CsA: no further information provided • Intensified enteric-coated mycophenolate sodium: 2160 mg/d to week 6; 1440 mg/d thereafter • Steroids: no further information provided
Outcomes	• Treatment failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up) • Mortality • Graft loss • Biopsy-proven acute rejection • CrCl (mL/min)

INFINITY Study 2013 (*Continued*)

Notes	• Did not report number screened for eligibility or randomised • Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if ITT analysis conducted
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	Funding source not reported but authors disclose 'Grant/Research Support, Novartis (Myfortic)', Co-authors affiliated with Novartis Pharma SAS, Rueil-Malmaison, France Abstract data only Lack of important information regarding design and conduct of study

Isoniemi 1990

Methods	• Study design: parallel RCT • Time frame: 1986 to 1987 • Follow-up period: 4 years • Primary endpoint: not reported
Participants	• Country: Finland • Setting: single centre • First cadaveric kidney transplant

Isoniemi 1990 (*Continued*)

	• Number (randomised/analysed): withdrawal group (32/32); /maintenance group (32/29) • Mean age ± SD (years): withdrawal group (49 ± 13); maintenance group (47 ± 11) • Sex (female): withdrawal group (53%); maintenance group (38%) • Exclusion criteria: living donor kidney transplants; ineligibility for triple immunosuppression with CsA + AZA + steroids
Interventions	Treatment group • Steroid withdrawal 10 weeks after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: day 0: 5 mg/kg; thereafter: 10 mg/kg/d adjusted to trough levels, but no further information provided • AZA: day 0 to 14: 2mg/kg/d ◇ Withdrawal group: from day 15: 1 mg/kg/d but temporarily increased to 2 mg/kg/d during steroid withdrawal and thereafter adjusted to WCC ◇ Maintenance group: from day 15: 1 mg/kg/d • Steroids: ○ Methylprednisone: day 0: 1 mg/kg/d tapered in 3-day intervals to 0.25 mg/kg by day 10 ◇ Withdrawal group: withdrawal over 1 to 2 weeks ◇ Maintenance group: tapered to 4 to 12 mg/d during the first year
Outcomes	• Mortality • Graft loss • Acute rejection • Infection • SCr (μmol/L)
Notes	• Screened for eligibility: 184 • This had two additional arms (in total 128 patients randomised) ○ Arm 3 with withdrawal of CsA (32 patients) ○ Arm 4 with withdrawal of AZA (32 patients) • Number of patients discontinued treatment ○ Withdrawal group: switched immunosuppression within 2 year follow-up; AZA withdrawn (7), CsA withdrawn (3), steroids reinitiated (3) ○ Maintenance group: switched immunosuppression within 2 year follow-up; AZA withdrawn (6), CsA withdrawn (3), steroids withdrawn (1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided.
Allocation concealment (selection bias)	Low risk	Stated 'using the sealed envelope method'

Isoniemi 1990 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Low risk	'The study was supported by a grant from the Sigrid Juselius Foundation.' AZA dose was increased during and after steroid withdrawal in treatment group while it remained unchanged in maintenance group

Jankowska-Gan 2009

Methods	• Study design: parallel RCT • Time frame: 2002 • Follow-up period: 3 years • Primary endpoint: incidence of allograft rejection (original primary endpoint: graft function)
Participants	• Country: USA • Setting: single centre RCT • Aged ≥ 55 years; living or cadaveric kidney transplantation > 1 year ago; CNI + MMF + prednisone since transplantation; SCr < 1.8 mg/dL or CrCl > 55 mL/min; stable cardiovascular function; HCT ≥ 32%; WCC ≥ 3.0 K/μL • Number (randomised/analysed): withdrawal group (32/32); maintenance group (10/10) • Mean age (± SD): not reported • Sex (female): withdrawal group (36%); maintenance group (10%) • Donor source (% living donors): withdrawal group (60%); maintenance group (60%) • Exclusion criteria: acute rejection within past 12 months; > 1 rejection episode; steroid dependency due to pre-existing disease; African-American

Jankowska-Gan 2009 (*Continued*)

Interventions	Treatment group • Steroid withdrawal > 1 year after transplantation Control group • Steroid maintenance Baseline immunosuppression • CNI: no further information provided • MMF: no further information provided • Steroids ○ Steroid withdrawal group: slow withdrawal during 3 months, then stopped
Outcomes	• Mortality • Graft loss • Acute rejection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Enrolment lagged due to difficulty in enrolling older transplant patients and was terminated at 32 (target was 75) • Contact with study authors for additional information: authors contacted 4 July 2013; response received 5 September 2013

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed; number of patients by group not reported for outcomes
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported

Jankowska-Gan 2009 (*Continued*)

Other bias	Unclear risk	Funding source not reported Patients in treatment group were enrolled later after transplantation compared to control group

Johnson 1989a

Methods	• Study design: parallel RCT • Time frame: started in 1981 • Follow-up period: 7 years • Primary endpoint: not reported
Participants	• Country: UK • Setting: single centre RCT • First or second cadaveric kidney transplantation • Number (randomised): withdrawal group (376); maintenance group (182) • Mean age ± SD (years): not reported • Sex (female): not reported • Exclusion criteria: diabetes mellitus, urine output < 50 mL/h within the first 6 hours after transplantation
Interventions	Treatment group • Steroid withdrawal day 1 after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: started with 6 mg/kg IV over 12 hours until oral administration accepted; oral: 15mg/kg/d in divided doses; reduced after 2 weeks or if signs of toxicity to achieve target levels between 80 to 500 ng/mL before the end of the first month • Steroids ○ IV methylprednisone: during transplantation: 500 mg ○ Withdrawal group: no further steroids ○ Maintenance group: oral prednisone: 0.25 mg/kg, maximum 30 mg/d
Outcomes	• Mortality • Graft loss • CMV infection
Notes	• Screened for eligibility (700); did not report the number analysed • This study had a third arm with AZA + steroids (112 patients) • Number of patients discontinued treatment ○ Withdrawal group: received steroids permanently (125); switched to AZA + steroids (19); AZA added (27)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Johnson 1989a (*Continued*)

Random sequence generation (selection bias)	Low risk	'The recipient was entered into the trial by drawing a card to determine immunosuppressive therapy.'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if ITT analysis performed; total number of patients by group not reported for outcomes, results presented as rates and percentages
Selective reporting (reporting bias)	High risk	Acute rejection not reported
Other bias	Unclear risk	Funding sources not reported 465 patients included in first publication (1989), 700 patients included in second publication in (1990). Patients in third arm (AZA + steroids) remained equal in size, while the treatment group (steroid avoidance = CsA monotherapy) gained most of the additional patients, which was the group with the better outcomes in first publication Immunosuppressive protocol differs between these two publications with lower CsA target levels and more steroids in 2nd publication

Kacar 2004

Methods	• Study design: parallel RCT • Time frame: not reported, but before 2004 • Follow-up period: not reported • Primary endpoint: not reported
Participants	• Country: Turkey • Setting: single centre • Kidney transplantation > 2 years ago; stable kidney function • Number (randomised/analysed): withdrawal group (31/31); maintenance group (30/30) • Mean age ± SD (years): not reported • Sex (female): not reported • Exclusion criteria: acute rejection within last 6 months
Interventions	Treatment group • Steroid withdrawal > 2 years after transplantation Control group • Steroid maintenance Baseline immunosuppression • No further information provided
Outcomes	• Mortality • Graft loss • Acute rejection • SCr
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment ○ Withdrawal group: reintroduced steroids because of discontinuation of AZA, increase of SCr or acute rejection (7)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

Kacar 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed; total number of patients by group for outcomes not reported
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported Abstract-only publication

Kim 2002

Methods	• Study design: parallel RCT • Time frame: 1998 to 1999 • Follow-up period: 2 years • Primary endpoint: not reported
Participants	• Setting: multicentre (2 centres) • Country: USA • Cadaveric or living kidney transplant • Number (randomised/analysed): withdrawal group (12/11); maintenance group (12/12) • Mean age (years): withdrawal group (48); maintenance group: (48) • Sex (% female): not reported • Donor source (% living donors): not reported • Exclusion criteria: PRA > 5%
Interventions	Treatment group • Steroid withdrawal 4 days after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: day 0, 4: 20 mg • CsA: 8 to 10 mg/kg/d • MMF: 2 to 3 g/d • Steroids ○ IV methylprednisone: day 0: 500 mg; day 1: 250 mg; day 2: 125mg ○ Withdrawal group: day 3: 60 mg; day 4: 30 mg ○ maintenance group: day 3 to 21: tapered to 20 to 30 mg/d; day 22 to 91: tapered to 5 to 10 mg/d
Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection

Kim 2002 (*Continued*)

	• SCr (mg/dL)
Notes	• Did not report number screened for eligibility • 54% in withdrawal group (6/11 patients) off steroids at 2 years • Loss to follow-up: withdrawal group (1/12)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised 1:1 ratio' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One patient lost to follow up in withdrawal group (8%), unlikely to affect results; unclear if ITT analysis performed
Selective reporting (reporting bias)	High risk	Graft loss not reported
Other bias	Unclear risk	Funding source not reported Abstract-only publication

Kumar 2005

Methods	• Study design: parallel RCT • Time frame: 2000 to 2002 • Follow-up period: 1 year • Primary endpoint: not reported
Participants	• Country: USA • Setting single centre • Age > 20 years; first cadaveric or living kidney transplant • Number (randomised/analysed): withdrawal group (45/45); maintenance group (32/32)

	• Mean age ± SD (years): withdrawal group (50 ± 13); maintenance group (54 ± 13) • Sex (female): withdrawal group (28%); maintenance group (28%) • Donor source (living donors): withdrawal group (18%); maintenance group (9%) • Exclusion criteria: PRA > 10%; HIV seropositivity; HBsAG seropositivity
Interventions	Treatment group • Steroid withdrawal 7 days after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: days 0, 4: 20 mg ○ Withdrawal group: the first 17 patients received additionally 20 mg on day 60 and 64 • CsA: starting day 1 with 2 to 5 mg/kg twice daily, adjusted to trough blood levels: day 1 to 100: 250 to 300 ng/mL; day 101 to 365: 200 to 250ng/mL; thereafter: 150 to 200 ng/mL • MMF: 2 to 3 g/d ○ MMF intolerance: SRL: started with 5 mg/d adjusted to blood level 6 to 10 ng/mL • Steroids: ○ IV methylprednisone: day 0: 250 mg; day 1: 125 mg ○ Oral prednisone ◇ Withdrawal group: first 17 patients: day 2: 30 mg, tapered by 5 mg/d until withdrawal on day 7; remaining 28 patients: no further steroids ◇ Maintenance group: day 2: 30 mg; tapered to 5 mg/d at month 1
Outcomes	• Mortality • Graft loss • Acute rejection • NODAT • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Study was closed after 77 patients were randomised, because patients refused to be randomised in the maintenance group. Nevertheless 300 patients were enrolled through patient's choice. This systematic review only includes data on the randomised first 77 patients • 7 patients in withdrawal group and 3 patients in maintenance group received SRL because of MMF intolerance • Contact with study authors for additional information: authors contacted 5 July 2013; no response received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomization was completed using the first generator plan from randomization.com.'

Kumar 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	First 17 patients (38%) in withdrawal group received steroids until day 7 and two additional doses of basiliximab, the remaining 28 patients (62%) received steroids until day 2 and no additional basiliximab 'The study was funded internally by clinical revenue. The manuscript was support by an unrestricted educational grant from Novartis Pharm. Corp.'

Laftavi 2005

Methods	• Study design: parallel RCT • Time frame: 2002 to 2004 • Follow-up period: 1 year • Primary endpoint: not reported
Participants	• Country: USA • Setting: single centre • First cadaveric or living kidney transplant • Number (randomised): withdrawal group (32); maintenance group (28) • Mean age (± SD): withdrawal group (50 ± 13); maintenance group (51 ± 12) • Sex (female): withdrawal group (35%); maintenance group (36%) • Donor source (living donor): withdrawal group (16%); maintenance group (21%) • Exclusion criteria: PRA > 30%
Interventions	Treatment group • Steroid withdrawal day 7 after transplantation Control group

	• Steroid maintenance Baseline immunosuppression • Rabbit ALG: 1mg/kg per day for 3 to 5 doses • TAC: day 0: 0.5 to 1 mg twice daily adjusted to whole blood level: by day 7 to 10: 10 ng/mL; month 1 to 6: 10 to 15 ng/mL; thereafter: 8 to 10 ng/mL • MMF: starting on day 0: 2 g/d divided in 2 to 4 doses. • Steroids ○ IV methylprednisone: day 0: 250 mg; day 1: 125mg ○ Withdrawal group: prednisone: day 2: 30 mg/d; rapidly titrated down to a dose of 5 mg/d and withdrawn on day 7 ○ Maintenance group: prednisone: day 2: 30 mg/d, rapidly titrated down to a dose of 5 mg/d by end of month 1 and thereafter maintained at 5 mg/d
Outcomes	• Acute rejection • Biopsy-proven acute rejection • CrCl (mL/min)
Notes	• Did not report number screened for eligibility or number analysed • Number of patients discontinued study ○ Clinical adverse events, biopsy findings or subsequent pancreas transplantation: withdrawal group (10); maintenance group (6)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Patients were randomised by a blinded nurse coordinator according to random numbers.'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'A single pathologist who was blinded to the treatment arms, evaluated biopsy specimens for severity of rejection and fibrosis.'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed. In treatment group 16 of 32 patients and in control group 14 of 28 patients completed 1 year follow-up

Laftavi 2005 (*Continued*)

Selective reporting (reporting bias)	High risk	Mortality and graft loss are not reported
Other bias	Unclear risk	Funding source not reported Unclear whether groups were similar at baseline, because 'steroid withdrawal patients were at greater risk for rejection, having a higher average number of HLA mismatches and a greater number of African American patients'

Lebranchu 1999

Methods	• Study design: parallel RCT • Time frame: 1996 to 1997 • Follow-up period: 12 months • Primary endpoint: biopsy-proven acute rejection 6 months after transplantation
Participants	• Country: Europe, Australia, South Africa • Setting: multicentre (75 centres) • First or second cadaveric or living kidney transplant; > 18 years • Number (randomised/analysed): withdrawal group (252/252); maintenance group (248/248) • Mean age, range (years): withdrawal group (45, 18 to 69); maintenance group (46, 18 to 71) • Sex (female): withdrawal group (43%); maintenance group (41%) • Donor source (living donor): withdrawal group (10%); maintenance group (8%) • Exclusion criteria: immunosuppression other than CsA + MMF + steroids (induction with OKT 3 and ATG was allowed); historical PRA $\geq$ 80%; seropositivity for HTLV-1/HIV/HBsAG; WCC < 2.5 x 10^9/L; Hb < 5 g/dL; malignancy; systemic infection; severe gastrointestinal disorders; psychiatric problems; substance use
Interventions	Treatment group • Steroid withdrawal 3 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: started with 5 to 15 mg/kg/d adjusted to normal trough levels for participating centres • MMF: 1000 mg twice daily • Steroids ○ IV prednisolone: preoperative and postoperative dose: 500 mg ○ Withdrawal group: day 1 to 14: 15 mg; day 15 to 70: 10 mg; day 71 to 84: 5 mg; then no further steroids ○ Maintenance group: day 1 to 14: 30 mg; day 15 to 56: 20 mg; day 57 to 70: 15 mg; beyond day 71: 10 mg

Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • Infection • CMV infection • SCr (µmol/L)
Notes	• Did not report number screened for eligibility • Number of patients discontinued study (at 12 months) ○ Withdrawal group (25%): adverse events (35), unsatisfactory response to study treatment (6), required prohibited medication (4), death (4), other reasons (14) ○ Maintenance group (17%): adverse events (17), unsatisfactory response to study treatment (3), required prohibited medication (1), death (5), other reasons (15) • Completed 6 months follow-up double-blind period according to protocol: withdrawal group (174); maintenance group (193)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'Patients were randomly assigned to one of two treatment groups in a 1:1 ratio, with stratification by cadaveric/ living related donor transplant recipient and by type of cyclosporine' but random sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Stated 'Treatment continued in a blinded fashion for 6 months, after which the study was to be unblinded during a further 6 months, for a total study length of 1 year'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Stated 'Treatment continued in a blinded fashion for 6 months, after which the study was to be unblinded during a further 6 months, for a total study length of 1 year'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed; stated 'At 12 months 17% in the control group and 25% in the treatment group were prematurely withdrawn from

Lebranchu 1999 (*Continued*)

		the study'
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported

Maiorca 1988

Methods	• Study design: parallel RCT • Time frame: 1983 to 1986 • Follow-up period: 27 ± 9 months • Primary endpoint: not reported
Participants	• Country: Italy • Setting: single centre • First cadaveric kidney transplant; functioning graft 6 months after transplantation • Number (randomised/analysed): withdrawal group (35/35): maintenance group (31/31) • Mean age ± SD (years): withdrawal group (33 ± 10); maintenance group (35 ± 9) • Sex (female): withdrawal group (30%); maintenance group (29%) • Exclusion criteria: not reported
Interventions	Treatment group • Steroid withdrawal 6 months after transplantation (completed 13 months after transplantation) Control group • Steroid maintenance Baseline immunosuppression • CsA: no further information provided • Steroids ○ Withdrawal group: prednisone: reduced by 2 mg/wk until complete withdrawal 13 months after transplantation ○ Maintenance group: prednisone: continued 8 mg/d
Outcomes	• Mortality • Graft loss • Acute rejection • NODAT
Notes	• Did not report number screened for eligibility

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated' randomised' but no further information provided

Maiorca 1988 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients followed up or accounted for; unclear if ITT analysis performed
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported

Matl 2000

Methods	• Study design: parallel RCT • Time frame: not reported, but before 2000 • Follow-up period: 1 year • Primary endpoint: not reported
Participants	• Country: Czech Republic • Setting: single centre • First cadaveric or living kidney transplant; stable graft function one year after transplantation; 18 to 65 years • Number (randomised/analysed): withdrawal group (46/45); maintenance group (42/42) • Mean age ± SD (years): withdrawal group (50 ± 9); maintenance group (47 ± 13) • Sex (female): withdrawal group (45%); maintenance group (26%) • Donor source (% living donors): not reported • Exclusion criteria: SCr > 1.8 mg/dL
Interventions	Treatment group • Steroid withdrawal 1 year after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: adjusted to blood levels in the upper half of the therapeutic range • AZA: minimum of 1.5 mg/kg/d • Steroids ○ Withdrawal group: gradually withdrawn over a period of 6 months

	○ Maintenance group: unchanged, no further information provided
Outcomes	• Mortality • Graft loss • Acute rejection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Number of patients discontinued study ○ Withdrawal group: excluded after randomisation before steroid withdrawal (1) • Number of patients discontinued treatment ○ Withdrawal group: did not withdraw steroids because of rejection (3), leucopenia (1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Patients were randomised according to the month of birth
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up or accounted for; ITT analysis performed
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Low risk	The study was supported by grant N°3631-3 awarded by the Internal Grant Agency of the Ministry of Health of the Czech Republic

Mericq 2013

Methods	• Study design: parallel RCT • Time frame: 2008 to 2009 • Follow-up period: 1 year • Primary endpoint: stimulation of growth after 12 months
Participants	• Country: Chile • Setting: multicentre RCT (2 centres) • First cadaveric or living kidney transplant; < 16 years with a bone age ≤ 15 years in boys and ≤ 13 years in girls • Number (randomised/analysed): withdrawal group (14/12); maintenance group (16/12) • Mean age ± SD (years) (only reported for prepubertal patients); withdrawal group (6 ± 3); maintenance group (6 ± 4) • Sex (female) (only for prepubertal patients reported): withdrawal group (50%); maintenance group (42%) • Donor source (% living donor) not reported • Exclusion criteria: treatment with recombinant human growth hormone or bisphosphonate
Interventions	Treatment group • Steroid withdrawal 6 days after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: days 0, 4: 20 mg/m^2 • TAC: started with 0.15 mg/kg twice daily when creatinine < 2 mg/dL; adjusted to basal levels until day 30: 10 to 15 ng/mL; thereafter: 5 to 7 ng/mL • MMF: until day 30: 800 mg/m^2/d; day 31 to month 3: 600 mg/m^2/d; thereafter: 400 mg/m^2/d • Steroids ○ Withdrawal group: methylprednisone: day 0 to 2: 2 mg/kg/d; prednisone: day 3: 2 mg/kg/d; day 4: 1 mg/kg/d; day 5: 0.5 mg/kg/d; day 6: 0.25 mg/kg/d; then no further steroids ○ Maintenance group: methylprednisone: day 0 to 2: 2 mg/kg/d; prednisone: day 3 and 4: 2 mg/kg/d; day 5 to month 1: 1.5 mg/kg/d; reduced to 0.12 mg/kg/d until study end
Outcomes	• Mortality • Graft loss • Acute rejection
Notes	• Did not report number screened for eligibility

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated 'central randomization by the principle investigator'

Mericq 2013 (*Continued*)

Allocation concealment (selection bias)	Low risk	Stated 'stratified treatment allocation on the basis of block randomization carried out by a statistician who was not participating in this study using numbered containers by a computerized statistical program'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed; outcomes for prepubertal patients only reported. Number of events and per group not reported
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Low risk	This study was supported by Fondecyt 1080166 (National Fund for Scientific and Technological Development)

Montagnino 2005

Methods	• Study design: parallel RCT • Time frame: not reported, but before 2005 • Follow-up period: 3 years • Primary endpoint: graft survival
Participants	• Country: Italy • Setting: multicentre (number of centres not reported) • First and second cadaveric or living kidney transplant; 18 to 65 years • Number (randomised/analysed): withdrawal group (65/65); maintenance group (68/68) • Mean age ± SD (years): withdrawal group (44 ± 10); maintenance group (46 ± 12) • Sex (female): withdrawal group (31%); maintenance group (38%) • Donor source (living donors): withdrawal group (5%); maintenance group (6%) • Exclusion criteria: ischaemia time > 40 hours; PRA > 50%

Montagnino 2005 (*Continued*)

Interventions	Treatment group • Steroid withdrawal 7 days after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: days 0 and 4: 20 mg • CsA: twice daily 3 to 5 mg/kg adjusted to trough levels; week 1 to 4: 150 to 300 ng/mL; month 2 to 6: 100 to 250 ng/mL; thereafter: 100 to 200ng/mL ○ Amendment to study protocol after availability of new evidence: CsA levels < 100 ng/mL • EVL: 1.5 mg twice daily • Steroids ○ Withdrawal group: prednisone: day 1 to 5: 20 mg/d; day 6: 5 mg; day 7: 5 mg; then stopped ○ Maintenance group: prednisone: week 1 to 2: 20 mg/d; week 3 to 4: 15 mg/d; week 5 to 6: 10 mg/d; week 7 to month 12: 5 to 10 mg/day; thereafter: 2.5 to 5 mg/d
Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • NODAT • Malignancy • Infection • CMV infection • SCr (mg/dL) • CrCl (mL/min)
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment ○ Withdrawal group: reintroduced steroids (28) • Contact with study authors for additional information: authors contacted 2 September 2013; no response received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised randomisation by a randomisation list, stratified within centres using an interactive voice-response system
Allocation concealment (selection bias)	Low risk	'The sequence was concealed until interventions were assigned.'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label

Montagnino 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up or accounted for; ITT analysis performed ('All the analyses considered all the randomised patients, grouped originally by randomised treatment as per ITT concept.')
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	Supported by grant from Novartis

Nagib 2015

Methods	• Study design: parallel RCT • Time frame: 2003 to 2014 • Follow-up period: median follow-up was 66 ± 41 months • Primary endpoint: incidence of a first biopsy-proven acute rejection (Banff type 1 or higher) within 36 months after transplantation
Participants	• Country: Egypt • Setting: single centre • Primary kidney transplantation from living donors between 21 and 60 years of age with compatible ABO blood groups • Number (randomised): avoidance group (214); maintenance group (214) • Age range: 5 to 62 years • Mean age ± SD (years): avoidance group (30 ± 12); maintenance group (24 ± 13) • Sex (female): avoidance group (24%); maintenance group (26%) • Exclusion criteria: lost follow-up; pretransplantation diabetes mellitus; other immunosuppressive protocols

Interventions	Treatment group
	• Steroid avoidance on day 4
	Control group
	• Steroid maintenance
	Baseline immunosuppression
	• Basiliximab: days 0 and 4
	• TAC: no further information provided
	• MMF: no further information provided
	• Steroids
	  ○ IV methylprednisone: days 0 and 1: 500 mg; day 2: 250 mg; day 3: 100 mg
	  ○ Avoidance group: steroids stopped at day 4 provided that an acceptable TAC

Nagib 2015 (*Continued*)

	level was achieved ○ Maintenance group: 1.5 mg/kg/d methylprednisolone days tapered gradually to 0.15 mg/kg/d by the 9 months post-transplantation
Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • SCr (μmol/L)
Notes	• Did not report number screened for eligibility or analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'...patients were randomised to receive...' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear if ITT analysis performed; total number of patients by group for outcomes not reported
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported

Nematalla 2007

Methods	• Study design: parallel RCT • Time frame: 2004 to 2005 • Follow-up period: 1 year • Primary endpoint: incidence of biopsy-proven acute rejection within 12 months after transplantation
Participants	• Country: Egypt • Setting: single centre • First living kidney transplant; recipient age 22 to 56 years; donor age 21 to 60 years • Number (randomised/analysed): withdrawal group (50/50); maintenance group (50/50) • Mean age ± SD (years): withdrawal group (30 ± 11); maintenance group (29 ± 10) • Sex (female): withdrawal group (20%); maintenance group (36%) • Exclusion criteria: mismatch at HLA-DR locus

Interventions	Treatment group
	• Steroid withdrawal day 4 after transplantation (if TAC levels in target range)
	Control group
	• Steroid maintenance
	Baseline immunosuppression
	• Basiliximab: day 0 and 4: 20 mg
	• TAC: starting on day -2 with 0.1 mg/kg/d adjusted to trough levels week 1 to 2: 10-15 ng/mL; thereafter: 5 to 10 ng/mL
	• MMF: week 1 to 2: 1000 mg twice daily; thereafter 750 mg twice daily
	• Steroids
	  ○ IV methylprednisone: day 0: 500 mg
	  ○ Withdrawal group: methylprednisone: day 1: 500 mg; day 2: 250 mg; day 3: 100 mg; thereafter no further steroids
	  ○ Maintenance group: methylprednisone: day 1, 3, 7, 14: 3.5 mg/kg/d; followed by gradual tapering to 0.15 mg/kg/d by month 9

Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • NODAT • Infection • CMV infection • SCr (μmol/L) • eGFR (mL/min)
Notes	• Did not report number screened for eligibility • Contact with study authors for additional information: authors contacted 9 July 2013; no response received

Risk of bias

Bias	Authors' judgement	Support for judgement

Nematalla 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	'100 similar closed opaque envelopes were made, each containing a slip of opaque paper with the type of maintenance immunosuppression. Therefore, 50 envelopes were with steroid and the rest were without. All envelopes were kept closed until the morning of the transplant day, when one envelope was selected for each patient'
Allocation concealment (selection bias)	Low risk	'Similar closed opaque envelopes, each containing a slip of opaque paper'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed; number of patients in groups varies slightly between reports
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Different protocol between groups for steroid dosing before withdrawal Funding source not reported

Nott 1985

Methods	• Study design: parallel RCT • Time frame: 1982 • Follow-up period: 14 to 39 months • Primary endpoint: not reported
Participants	• Country: UK • Setting: single centre • All ages; first or subsequent cadaveric or living kidney transplant • Number (randomised): withdrawal group (59); maintenance group (58) • Mean age (± SD): not reported • Sex (% female): not reported • Donor source (% living donors): 0.05%

	• Exclusion criteria: none
Interventions	Treatment group • Steroid withdrawal day 1 after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: 17 mg/kg/d divided in 2 doses, reduced by 2 mg/kg every 2 weeks adjusted to whole blood level 250 to 700 ng/mL. Dose reduction to 15 mg/kg after the first 20 patients due to nephrotoxicity • Steroids ○ IV methylprednisone: day 0: 500 mg ○ Oral prednisolone: starting on day 2 with 2 mg/kg/d; tapered to 0.15 mg/kg/d by day 74 ◇ Withdrawal group: no further steroids ◇ Maintenance group: from day 1: 0.3 mg/kg/d as divided dose; reduced by 5 mg/mo to a maintenance dose of 10 to 15 mg/d
Outcomes	• Mortality • Graft loss • Cardiovascular event • Infection • SCr (mmol/L)
Notes	• Did not report number screened for eligibility or analysed • Number of patients discontinued treatment ○ Withdrawal group: switched to different immunosuppression (steroid added (13), converted to AZA + steroids (19))

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was achieved by drawing a card
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints

Nott 1985 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Total number of patients by group not reported for outcomes; ITT analysis performed
Selective reporting (reporting bias)	High risk	Acute rejection not reported
Other bias	Unclear risk	Immunosuppressive protocol differs between publications No patient characteristics shown, unclear whether the groups were similar at baseline Funding source not reported

Park 1994

Methods	• Study design: parallel RCT • Time frame: not reported, but before 1994 • Follow-up period: 1 year (6 years for 68 patients) • Primary endpoint: patient and graft survival rates
Participants	• Country: Korea • Setting: multicentre (number of centres not reported) • First living kidney transplant; 18 to 65 years • Number (randomised): withdrawal group (141); maintenance group (153) • Mean age ± SD (years): not reported • Sex (% female): not reported • Exclusion criteria: SCr > 1.5 mg/dL 3 months after transplantation; active hepatitis; HBsAG seropositivity
Interventions	Treatment group • Steroid withdrawal 3 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: day 0 to 2: 3 mg/kg IV; day 3: 10 mg/kg PO; reduced to 3 to 5 mg/kg/d adjusted to trough levels: month 1 to 3: 200 to 400 ng/mL; thereafter: 100 to 200 ng/mL • Steroids ○ IV methylprednisone: day 0: 1000 mg; day 1: 200 mg; reduced to 60 mg by day 4 ○ Oral prednisone: day 5: 30 mg/d; reduced to 10 mg/d by end of month 3 ◇ Withdrawal group: prednisone reduced by 2.5 mg every 2 weeks until complete withdrawal 6 to 8 weeks after randomisation
Outcomes	• Mortality • Graft loss • Acute rejection • NODAT • Infection

	• SCr (mg/dL) • CrCl (mL/min)
Notes	• Did not report number screened for eligibility; randomised (294); analysed in 1998 (68) • Number of patients discontinued study ○ At 1 year 18 patients withdrawn from study because of regimen failure, death, graft loss, compliance, adverse events

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients in which the outcome was measured are not reported, survival only reported as rates; unclear if ITT analysis performed
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported There's a substantial difference between number of participants in first published report (1994) (294) and second report (1998) (68) which is not explained

Pelletier 2006

Methods	• Study design: parallel RCT • Time frame: 1997 to 2002 • Follow-up period: mean 3.7 years • Primary endpoints: incidence of acute rejection, chronic rejection and graft loss within 1 year of consent
Participants	• Country: USA • Setting: single centre • First cadaveric or living kidney transplant; > 18 years; MMF > 2 g (unless intolerant) and CsA > 2 mg/kg/d or trough levels > 150 ng/mL • Number (randomised/analysed): withdrawal group (60/59); maintenance group (60/59) • Mean age ± SD (years): withdrawal group (45 ± 14); maintenance group (45 ± 14) • Sex (female): withdrawal group (22%); maintenance group (31%) • Donor source (living donors): withdrawal group (36%); maintenance group (37%) • Exclusion criteria: SCr > 2.5 mg/dL; previous acute rejection; proteinuria > 600 mg/24 h; presence of steroid treated disease

Interventions	Treatment group
	• Steroid withdrawal at different time points after transplantation (exact time point of steroid withdrawal unclear, but all patients had steroids for > 14 days)
	Control group
	• Steroid maintenance
	Baseline immunosuppression
	• Basiliximab (54 patients): day 0 and 4: 20 mg
	• OKT3 (40 patients): day 3 to 5: 5 mg/d
	• Thymoglobulin (6 patients): day 3 to 5
	• No induction: 14 patients
	• CsA: starts with 5 to 6 mg/kg/d adjusted to trough levels: year 1: 250 ng/mL; thereafter: 150
	• MMF: 2 g/d
	• Steroids
	  ○ Prednisone: starts with 2 mg/kg, tapered to 0.2 mg/kg at month 1; tapered to 0.15 mg/kg at month 12
	  ○ Steroid withdrawal: reduced by 2.5 mg/2 wk

Outcomes	• Mortality • Graft loss • Acute rejection • SCr (mg/dL) • NODAT

Notes	• Did not report number screened for eligibility
	• Number of patients discontinued study
	  ○ Withdrawal group: 1 patient
	  ○ Maintenance group: 1 patients withdrawn from study shortly after consent because of proteinuria > 600 mg/24 h and non-compliance

Pelletier 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if ITT analysis performed
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported Steroids have been withdrawn at different time points after transplantation and the time point of steroid withdrawal is unclear Different induction treatments used, 14% of patients did not receive any induction treatment

Pisani 2001

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: not reported • Primary endpoint: incidence of acute rejection
Participants	• Country: Italy • Setting: single centre • First or second kidney transplant • Number (analysed): withdrawal group (15); maintenance group (15) • Mean age: withdrawal group (41 years); maintenance group (45 years) • Sex (female): withdrawal group (33%); maintenance group (30%) • Donor source (% living donors): not reported

Pisani 2001 (*Continued*)

	• Exclusion criteria: not reported
Interventions	Treatment group • Steroid withdrawal 6 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: day 0 and 4: 20 mg • CsA: started with 8 mg/kg/d adjusted to blood levels in month 1 to 2: 350 to 400 ng/mL; month 3: 250 to 300 ng/mL • MMF: 1500 mg/d • Steroids ○ IV methylprednisone day 0: 500 mg ○ Oral prednisone: month 1: 20 mg/d; tapered to 5 mg/day at month 3
Outcomes	• Mortality • Graft loss • Acute rejection • SCr (µmol/L) • NODAT • Infection • CMV infection
Notes	• Did not report number screened for eligibility; randomised (46); analysed (30) • Steroids withdrawn in 8/15 patients in withdrawal group at time of preliminary report • This study had a third arm with 'standard immunosuppression' CsA + MMF + steroids (17 patients) • Contact with study authors for additional information: authors contacted 9 July 2013; no response received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Pisani 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis was performed; number of patients per group and in total vary between reports
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported Abstract-only data Lack of important information regarding design and conduct of study

Ponticelli 1997

Methods	• Study design: parallel RCT • Time frame: 1990 to 1993 • Follow-up period: 9 years • Primary endpoint: not reported
Participants	• Country: Italy • Setting multicentre (number of centres not reported) • First or second cadaveric kidney transplant; 16 to 70 years • Number (randomised): withdrawal group (115); maintenance group (117) • Mean age ± SD (years): withdrawal group (41 ± 11); maintenance group (41 ± 11) • Sex (female): withdrawal group (39%); maintenance group (32%) • Exclusion criteria: PRA > 50%; acute rejection or need for dialysis within 5 days after transplantation
Interventions	Treatment group • Steroid withdrawal day 5 after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: day 0 and 1: 5 mg/kg IV; day 2 to 14: 12 mg/kg/d divided in two doses; day 15: 10 mg/kg then tapered every fortnight by 2 mg/kg to maintenance dose 4-5 mg/kg/d; adjusted to target level: month 1 to 3: 175 to 400 ng/mL; month 4 to 6: 125 to 300 ng/mL; month 7 to 12: 100 to 225 ng/mL; thereafter: 75 to 200 ng/mL • Steroids ○ IV methylprednisone day 0: 500 mg; day 1: 200 mg; day 2: 50 mg ○ Withdrawal group: day 3 and 4: 16 mg/d; then steroids withdrawn ○ Maintenance group: month 1 to3: 16 mg/d; then gradually tapered to 8 mg/d by end of month 6

Outcomes	• Mortality • Graft loss • Acute rejection • Cardiovascular events • NODAT • Malignancy • Infection • CrCl (mL/min)
Notes	• Number screened for eligibility: 547; did not report number analysed • This study had a third arm with CsA + AZA + steroids (122 patients) • Number of patients discontinued treatment ○ Withdrawal group: switched to different immunosuppression: steroids added (37), steroids + AZA added (20), AZA added (2), conversion to AZA + steroids (1) ○ Maintenance group: switched to different immunosuppression: AZA added (23), steroids withdrawn (1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Random assignments were made according to a randomization list balanced per centre through a telephone call to the coordinating centre.'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported Sandoz Prodotti Farmaceutici SpA provided logistic support for the SIMTRE

Ponticelli 1997 (*Continued*)

		group meetings

Ratcliffe 1993

Methods	• Study design: parallel RCT • Time frame: 1988 - 1991 • Follow-up period: 1 year (another 24 months uncontrolled)
Participants	• Country: UK • Setting: single centre • First and second cadaveric kidney transplant; stable kidney function 1 to 6 years after transplantation • Number (randomised/analysed): withdrawal group (49/49); maintenance group (51/51) • Mean age ± SD (years): withdrawal group (48 ± 14); maintenance group (48 ± 14) • Sex (female): withdrawal group (35%); maintenance group (31%) • Exclusion criteria: not on triple immunosuppression; history of steroid resistant rejection; rejection after the first year following transplantation or within 6 months of eligibility assessment; SCr > 2.8 mg/dL
Interventions	Treatment group • Steroid withdrawal 1 to 6 years after transplantation Control group • Steroid maintenance Baseline immunosuppression • CsA: no further information provided • AZA: no further information provided • Prednisone: no further information provided
Outcomes	• Mortality • Graft loss • SCr (mg/dL) • CrCl (mL/min)
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment ○ Withdrawal group: did not stop steroids because of increased SCr (3), severe myalgia (2), death (2)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided.
Allocation concealment (selection bias)	Unclear risk	Not reported

Ratcliffe 1993 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up or accounted for; ITT analysis performed ("Unless otherwise stated, data were analysed with groups assigned on the basis of "intention-to-treat")
Selective reporting (reporting bias)	High risk	Acute rejection is not reported
Other bias	Unclear risk	Funding source not reported

Sandrini 2009

Methods	• Study design: parallel RCT • Time frame: 2002 to 2004 • Follow-up period: 4 years • Primary endpoint: percentage of patients who could be successfully withdrawn from steroids at 12 and 48 months
Participants	• Country: Italy • Setting: single centre • First cadaveric kidney transplant; PRA < 50%; all ages • Number (randomised/analysed): avoidance group (49/44); /withdrawal group (47/46) • Mean age ± SD (years): avoidance group (50 ± 11); withdrawal group (51 ± 11) • Sex (% female): not reported • Exclusion criteria: underlying disease requiring steroids; HIV seropositivity
Interventions	Avoidance group • Steroid withdrawal day 5 after transplantation Withdrawal group • Steroid withdrawal 6 months after transplantation Baseline immunosuppression • Basiliximab: day 0 and 4: 20 mg • CsA: started on day 0 with 5 mg/kg/d divided into 2 doses, adjusted to C_2 levels month 1 to 6: 800 to 1000 g/L; month 7 to 12: 600 to 800 g/L; thereafter: 400 to 500 g/L • Sirolimus: started on day 2 with 6 mg/d, then 2 mg/d, adjusted to blood levels 5

Sandrini 2009 (*Continued*)

	to 10 ng/mL • Steroids ○ IV methylprednisone: day 0: 500 mg ○ Avoidance group: methylprednisone: day 1: 200 mg; day 2: 100 mg; day 3: 50 mg; day 4: 20 mg; then no further steroids ○ Withdrawal group: methylprednisone: day 1: 200 mg; day 2: 200 mg; day 3: 150 mg; day 4: 100 mg; day 5: 50 mg; day 6: 20 mg; day 7 to month 1: 16 mg; month 2: 12 mg; month 3 to 5: 8 mg; month 6: withdrawn but only in selected patients with stable kidney function (proteinuria < 1g/d, SCr < 2.0 mg/dL, < 3 acute rejections)
Outcomes	• Mortality • Graft loss • Acute rejection • NODAT • Malignancy • Infection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Number of patients excluded from analysis ○ Avoidance group protocol violation (continued to take steroids) (1) • Number of patients discontinued study ○ Avoidance group: lost to follow-up at 1 year (4) ○ Withdrawal group: lost to follow-up at 1 year (1) • Patients discontinued treatment ○ Avoidance group: 38% ○ Withdrawal group: not withdrawn from steroids at 1 year because of acute rejection, delayed graft function, patient 'unsuitability' (33%) • Contact with study authors for additional information: authors contacted 14 January 2013; no response received.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

Sandrini 2009 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label, primary study endpoint was the percentage of patients who could be successfully withdrawn from steroids at 1 and 4 years after transplantation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Stated ' The results were analyzed on an ITT basis' but patients were excluded from analysis due to protocol violation; reasons for loss to follow-up not reported
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported Lack of important information regarding design and conduct of study High percentage of protocol failure (38% in avoidance group and 33% in withdrawal group not withdrawn from steroids at 1 year after transplantation)

Schulak 1989

Methods	• Study design: parallel RCT • Time frame: 1987 to 1989 • Follow-up period: 2 years
Participants	• Country: USA • Setting: single centre • First and second cadaveric or living kidney transplant • Number (randomised/analysed): withdrawal group 32/32); maintenance group (35/35) • Mean age ± SD (years): withdrawal group (44 ± 13); maintenance group (43 ± 12) • Sex (female): withdrawal group (50%); maintenance group (34%) • Donor source (living donors): withdrawal group (16%); maintenance group (9%) • Exclusion criteria: previous graft lost due to rejection; ongoing steroid therapy for other diseases
Interventions	Treatment group • Steroid withdrawal after 6 to 20 days after transplantation (most had steroids < 14 days), steroids were withdrawn shortly after CsA initiation Control group • Steroid maintenance Baseline immunosuppression • ALG: 10 mg/kg day 1; 20 mg/kg day 5 to 12 depending on graft function • CsA: starting on last day of ALG administration with 10 mg/kg/d adjusted to blood levels between 100 to 250 ng/mL during first 3 months; tapered to 3 to 5 mg/kg/d by 6 months • AZA: 5 mg/kg once prior to transplantation; 1.5 to 2.0 mg/kg daily after

Schulak 1989 (*Continued*)

	transplantation
	• Steroids
	  ○ IV methylprednisone: day 0: 250 mg; day 1 to 3: tapered doses
	  ○ Oral prednisone: day 4: 1mg/kg/d; tapered to 30 mg/d by week 2; tapered to 15 mg/d at month 3 to 4

Outcomes	• Mortality • Graft loss • Acute rejection • Infection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment ○ Withdrawal group: returned to steroid maintenance (18)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Patients were randomised using a table of random numbers'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients followed up or accounted for; ITT analysis performed
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Groups at baseline were different regarding gender, race and causes of kidney failure with more females, less African-Americans, more diabetics in the steroid avoidance group Funding source not reported

Smak Gregoor 1999

Methods	• Study design: parallel RCT • Time frame: 1997 to 1999 • Follow-up period: 18 months • Primary endpoint: first biopsy-proven acute or chronic rejection between 6 months and 24 months after transplantation
Participants	• Country: The Netherlands • Setting: multicentre (3 centres) • Cadaveric or living kidney transplant with stable graft function 6 months after transplantation • Number (randomised/analysed): withdrawal group (76/76); maintenance group (73/73) • Mean age, range (years): withdrawal group (52, 19 to 68); maintenance group (51, 19 to 70) • Sex (female): withdrawal group (32%); maintenance group (37%) • Donor source (% living donor): not reported • Exclusion criteria: ≥ 2 acute rejections; biopsy-proven acute vascular rejection; proteinuria > 3 g/d; immunosuppression other than CsA + MMF + steroids

Interventions	Treatment group
	• Steroid withdrawal 6 months after transplantation
	Control group
	• Steroid maintenance
	Baseline immunosuppression
	• CsA: adjusted to trough levels: 125 to 175 ng/mL (from 3 months after transplantation)
	• MMF: 1000 mg twice daily
	• Steroid:
	  ○ Prednisone: 0.1 mg/kg/d
	  ○ Withdrawal group: steroids tapered over 10 weeks and then withdrawn
	  ○ Maintenance group: no further details provided

Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • Infection • CMV infection • Malignancy • SCr (mg/dL) • CrCl (mL/min)
Notes	• Number screened for eligibility: 313 • This study had a third arm with CsA withdrawal (63 patients) • Number of patients discontinued treatment ○ Withdrawal group: never stopped steroids (1); returned to steroids (4) • Contact with study authors for additional information: authors contacted 3 September 2013; no response received
Risk of bias	

Smak Gregoor 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'Patients were randomly assigned to one of the three treatment groups in a 1: 1:1 ratio, with stratification for cadaveric/ living related transplant, for centre, and for the number of acute rejections during the first 6 mo after transplantation' but random sequence generation not reported
Allocation concealment (selection bias)	Low risk	Stated 'Randomization was carried out by opening a sealed envelope with the lowest available study number'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	The study was supported by Roche Pharmaceuticals, Mijdrecht, the Netherlands

Sola 2002

Methods	• Study design: parallel RCT • Time frame: not reported, but before 2002 • Follow-up period: 2 years • Primary endpoint: acute rejection and kidney function 2 years after steroid withdrawal
Participants	• Country: Spain • Setting: single centre • Cadaver kidney transplant; stable kidney function 3 months after transplantation • number (randomised): withdrawal group (46); maintenance group (46) • Mean age (± SD): not reported • Sex (% female): not reported

	• Exclusion criteria: PRA > 50%; previous acute rejection
Interventions	Treatment group • Steroid withdrawal after 3 months Control group • Steroid maintenance Baseline Immunosuppression • TAC: day 0 to 15: 10 to 15 ng/mL; from day 16: 5 to 10 ng/mL • MMF: 1 g/d • Steroids ○ IV methylprednisone day 0: 500 mg; day 1: 125 mg ○ Oral prednisone: day 2 to month 2: 20 to 25 mg/d; month 2 to month 3: tapered to 5 mg/d
Outcomes	• Mortality • Graft loss • Acute rejection • NODAT • SCr (mg/dL) • CrCl (mL/min)
Notes	• Did not report number screened for eligibility or analysed • 28/120 were not randomised

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of events and number of patients analysed not reported; unclear if ITT analysis performed

Sola 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported

Stiller 1983

Methods	• Study design: parallel RCT • Time frame: 1982 to 1983 • Follow-up period: not reported • Primary endpoint: not reported
Participants	• Country: Canada • Setting: multicentre (9 centres) • First or subsequent cadaveric or living kidney transplant; > 12 years • Number (randomised): no steroids group (33); maintenance group (36) • Mean age: no steroids group (35 years); maintenance group (35 years) • Sex (female): no steroids group (33%); maintenance group (36%) • Donor source (living donor): no steroids group (18%); maintenance group (36%) • Exclusion criteria: acute or progressive liver disease; previous generalised or metastatic malignancy; localised malignancy within the previous year; disease requiring maintenance steroid
Interventions	Treatment group • No steroids at any time Control group • Steroid maintenance Baseline immunosuppression • CsA: prior to transplantation: 15 mg/kg, thereafter 7.5 mg/kg twice daily adjusted to trough levels: day 1 to 60: 100 to 300 ng/mL; thereafter: 50 to 200 ng/mL • Steroids ○ Maintenance group: prednisone: 1 mg/kg alternate day reduced by 5 mg every other day to 0.3 mg/kg/d
Outcomes	• Mortality • Graft loss • Acute rejection • Infection • CMV infection • Malignancy • SCr (mg/dL)
Notes	• Did not report number screened for eligibility or analysed • Number of patients discontinued treatment ○ No steroids group: switched to different immunosuppression: AZA + steroids (6), steroids added (12) ○ Maintenance group: switched to AZA + steroids (3)
Risk of bias	

Stiller 1983 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'A computer-derived randomised blocks of varying size was generated and noted in a series of opaque envelopes held by the research pharmacist at each participating centre.'
Allocation concealment (selection bias)	Low risk	Stated 'opaque envelopes'
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether ITT analysis performed and whether all patients have been followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	The study was supported by Medical Research Council of Canada; Richard and Jean Ivey Fund, London, Ontario; Sandoz Ltd, Basel; the Micheal Fung Endowment Fund, London, Ontario; the University Hospital Transplant Research Fund, London, Ontario

THOMAS Study 2002

Methods	• Study design: parallel RCT • Time frame: 1998 to 2000 • Follow-up period: 6 months • Primary endpoint: not reported
Participants	• Country: 11 European countries • Setting: multicentre (47 centres) • First or second cadaveric or living kidney transplant; adults • Number (randomised/analysed): withdrawal group (281/279); maintenance group (279/277)

	• Mean age: withdrawal group (46 years); maintenance group (47 years) • Sex (female): withdrawal group (33%): maintenance group (38%) • Donor source (living donor): withdrawal group (8%); maintenance group (8%) • Exclusion criteria to enter study: previous organ transplant other than kidney transplantation; loss of a previous kidney transplant due to early acute rejection; PRA ≥ 50%; requirement for immunosuppression besides kidney transplantation; HIV seropositivity; familial hypercholesterolaemia; malignancy; ongoing infection • Exclusion criteria to enter steroid withdrawal phase after 3 months: steroid resistant rejection; graft loss; dose of steroids or MMF modified > 10 consecutive days; stopped TAC < 1 day; protocol violation during the first 3 months
Interventions	Treatment group • Steroid withdrawal 3 months after transplantation Control group • Steroid maintenance Baseline immunosuppression • TAC: started with 0.2 mg/kg/d divided in two doses adjusted to trough levels day 0 to 14: 10 to 20 ng/mL; thereafter: 5 - 15 ng/mL • MMF: 1000 mg daily divided in two doses • Steroids ○ IV methylprednisone: day 0: 500 mg or less; day 1: 125 mg ○ Prednisone: day 2 to 14: 20 mg; day 15 to 28: 15 mg; day 29 to 92: 10 mg ○ Withdrawal group: steroids tapered over 2 weeks and then withdrawn ○ Maintenance group: steroids maintained with 10 mg
Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • NODAT • Infection • CMV infection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility; 446 entered steroid withdrawal phase (221/225) • This study had a third arm with MMF withdrawal (278 patients) • Number of patients excluded from analysis: 2 patients in withdrawal group and 2 patients in maintenance group because they did not undergo transplantation • Number of patients discontinued study (before the steroid withdrawal phase) ○ Withdrawal group: steroid resistant acute rejection (11), graft loss (13), protocol violation (14), other reasons (18); withdrawn from study in the steroid withdrawal phase because of protocol violation (10), other reasons (11) ○ Maintenance group: steroid resistant acute rejection (16), graft loss (6), protocol violation (13), other reasons (14); withdrawn from study in the steroid withdrawal phase because of protocol violation (6), other reasons (5)
Risk of bias	

THOMAS Study 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated 'Randomization (1:1:1) was stratified by centre and donor type' but random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Stated 'The investigators were blinded with respect to randomization until the month-3 visit.' which is the time before start of the intervention, but thereafter investigators were unblinded, thus this is an open-label study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Stated 'The investigators were blinded with respect to randomization until the month-3 visit.' which is the time before start of the intervention, but thereafter investigators were unblinded, thus this is an open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed-up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	Unclear whether the rather short follow-up period allows sufficient time for endpoints to occur This study was supported by Fujisawa GmbH, Munich, Germany

Vincenti 2003a

Methods	• Study design: parallel RCT • Time frame: not reported but before 2003 • Follow-up period: 12 months • Primary endpoint: incidence of biopsy-proven acute rejection episodes within the first 12 months
Participants	• Country: not reported • Setting: multicentre (5 centres) • First cadaveric or living kidney transplant; 18 to 70 years

	• Number (randomised/analysed) withdrawal group (40/40); maintenance group (43/43) • Mean age ± SD (years): withdrawal group (49 ± 11); maintenance group (49 ± 12) • Sex (female): withdrawal group (55%); maintenance group (28%) • Donor source (living donor): withdrawal group (55%); maintenance group (44%) • Exclusion criteria: previous or multiple organ transplant; non-heart beating cadaveric donor; PRA > 50%; planned induction with an antilymphocyte preparation; malignancy within five years; medical conditions likely to affect the safety of the subject
Interventions	Treatment group • Steroid withdrawal day 5 after transplantation Control group • Steroid maintenance Baseline immunosuppression • Basiliximab: day 0 and 4: 20mg • CsA: started on day 1 with 4 to 5 mg/kg twice daily adjusted to trough levels week 1 to 2: 150 - 450 ng/mL; week 3 to 12: 150 to 300 ng/mL; thereafter: 150 to 250 ng/mL (for patients with delayed graft function CsA was started with 3 mg/kg twice daily or delayed for up to 48 h) • MMF: 2000 mg daily divided in two doses (African-Americans and patients during delayed graft function received 3000 mg/d) • Steroids ○ IV methylprednisone: day 0: 500 mg; day 1: 250 mg; day 2: 125 mg ○ Withdrawal group: prednisone or methylprednisone: day 3: 60 mg; day 4 or until CsA levels in target range: 30 mg; then no further steroids (steroid withdrawal delayed in patients with delayed graft function until SCr < 50% of pretransplant value) ○ Maintenance group: prednisone: day 3 to 21: tapered to 20 to 30 mg; day 22 to 90: tapered to 5 to 20 mg day 91 to 180: 5 to 10 mg
Outcomes	• Mortality • Graft loss • Acute rejection • Biopsy-proven acute rejection • Infection • SCr (mg/dL)
Notes	• Did not report number screened for eligibility • Number of patients discontinued treatment: 28% of patients in withdrawal group were not withdrawn from steroids at 6 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported

Vincenti 2003a (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	High risk	The study was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ

Woodle 2005

Methods	• Study design: parallel RCT • Time frame: 1999 to 2007 • Follow-up period: 5 years • Primary endpoint: treatment failure defined as composite of death, graft loss or acute rejection at 5 years
Participants	• Country: USA • Setting: multicentre (26 centres) • First or subsequent cadaveric or living kidney transplant; during days 3 to 7 decrease in SCr $\geq$ 30% from pretransplant value; 18 to 70 years • Number (randomised/analysed): withdrawal group (197/191); maintenance group (200/195) • Mean age (± SD): withdrawal group (47 ± 12); maintenance group (46 ± 13) • Sex (female): withdrawal group (31%); maintenance group (36%) • Donor source (living donor): withdrawal group (57%); maintenance group (57%) • Exclusion criteria: acute rejection within the first 7 days after transplantation; current PRA $\geq$ 25%; peak PRA $\geq$ 50%; cold ischaemia time > 36 hours; multiple organ transplant; non heart beating donor; paediatric donor; dual kidney transplant; reasons for loss of previous kidney transplant other than technical reasons or recurrence of disease with low risk of recurrence; dialysis post-transplant; requirement for systematic steroids for other disease; HIV seropositivity
Interventions	Treatment group • Steroid withdrawal day 8 after transplantation Control group

	• Steroid maintenance Baseline immunosuppression • Antilymphocytic or anti-IL2 antibodies according to centre preference • TAC: started within 72 hours post-transplant with 0.15 to 0.2 mg/kg divided in two doses, adjusted to blood levels by day 7 to 90: 10 to 20 ng/mL; thereafter: 5 to 15 ng/mL • MMF: day 0: 1000 mg; day 1: 2000 mg, day 2 to 14: 3000 mg, thereafter: 2000 mg • Steroids ○ IV corticosteroid: day 0: 10 mg/kg (max 500 mg); day 1: 5 mg/kg (max 500 mg); day 2: 3 mg/kg (max 300 mg) ○ Corticosteroid: day 3: 2 mg/kg (max 200 mg); day 4: 1 mg/kg (max 100 mg) ; day 5: 0.7 mg/kg (max 70 mg); day 6: 0.5 mg/kg (max 50 mg); day 7: 0.4 mg/kg (max 40 mg) ○ Withdrawal group: no further steroids ○ maintenance group: day 8 to 14: 0.4 mg/kg; day 15 to 29: 0.3 mg; day 30 to 89: 0.2 mg/kg; day 90 to 119: 0.15 mg/kg; thereafter: 0.1 mg/kg
Outcomes	• Mortality • Graft loss • Biopsy-proven acute rejection • New-onset of diabetes after transplantation • Infection • CMV infection • Malignancy • Cardiovascular event • SCr (mg/dL) • CrCl (mL/min)
Notes	• Did not report number screened for eligibility • Induction treatment ○ Withdrawal group: thymoglobulin (65%); basiliximab (31%); daclizumab (3%) ○ Maintenance group: thymoglobulin (70%); basiliximab (27%); daclizumab (3%) • Number of patients excluded from analysis ○ Withdrawal group: rejection or dialysis within the first 7 days (3), withdrawal of consent (1), did not meet eligibility criteria (2) ○ Maintenance group : rejection or dialysis within the first 7 days (2), protocol violation (1), did not meet eligibility criteria (2) • Number of patients discontinued treatment ○ Withdrawal group: 67 patients (35%) ○ Maintenance group: 73 patients (37%) • Number of patients discontinued study ○ Withdrawal group: 25 patients were lost to follow-up or withdrew consent (13%) ○ Maintenance group: 31 patients were lost to follow-up or withdrew consent (16%)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated 'Randomization was based on a permuted block design with block sizes of 6 within each clinical site. Randomization was performed using a central randomization service at the EMMES Corporation (Potomac, Md, US). Patients were randomised 1:1 stratified by race and donor type'
Allocation concealment (selection bias)	Low risk	Stated 'The EMMES Corporation generated the allocation sequence and maintained the allocation code. The randomization order did not have a repeating sequence, and the randomization code was not broken or revealed to patients/investigators until subjects completed study'
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated 'Patients received a blinded study drug beginning on posttransplant day 8'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated 'Study subjects, investigators, study personnel, and those assessing outcomes remained blinded throughout 5-year duration of the study, unless medical necessity to unblind occurred'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated 'Study subjects, investigators, study personnel, and those assessing outcomes remained blinded throughout 5-year duration of the study, unless medical necessity to unblind occurred'
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	Primary outcomes for this review reported
Other bias	Unclear risk	Funding source not reported

Zhu 2008a

Methods	• Study design: parallel RCT • Time frame: 2003 to 2005 • Follow-up period: 2 years • Primary endpoint: not reported
Participants	• Country: China • Setting: single centre • Cadaveric kidney transplant • Number (randomised): 45 total • Median age (range): 44 (26 to 65) years • Sex (% female): not reported • Exclusion criteria: PRA > 10%; multi-organ transplantation; serious infections (e.g. AIDS); malignancy

Interventions	Treatment group
	• Steroid withdrawal 6 months after transplantation
	Control group
	• Steroid maintenance
	Baseline Immunosuppression
	• TAC: day 0 to 14: adjusted to blood levels between 10 to 20 ng/mL; thereafter: 5 to 15 ng/mL
	• MMF: 1.5 to 2.0 g/d
	• Steroids
	  ○ IV methylprednisone: day 0: 500 mg; day 1: 300mg; day 2: 200 mg
	  ○ Oral prednisone: day 3 to 14: 20 mg/d; day 15 to 28: 15 mg/d
	  ○ Withdrawal group: day 29 to 92: tapered to 5 mg/d; withdrawn on day 183
	  ○ Maintenance group: day 29 to study end: 10 mg/d

Outcomes	• Mortality • Acute rejection • NODAT • Infection • SCr (μmol/L)
Notes	• Did not report number screened for eligibility or analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'randomised' but no further information provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label

Zhu 2008a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective hard endpoints
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients and number of events per group not reported; unclear whether ITT analysis was performed. Number of patients lost to follow up not reported
Selective reporting (reporting bias)	High risk	Graft loss not reported
Other bias	Unclear risk	Funding source not reported It was not reported how many of the participants were randomised to either group, whether the timing of outcome assessment is similar in all groups, whether the groups were similar at baseline, whether co-interventions were avoided or similar Important information on design and conduct of study not reported

ALG - anti-lymphocyte globulin; ATG - anti-thymocyte globulin; AZA - azathioprine; CMV - cytomegalovirus; CNI - calcineurin inhibitor; CrCl - creatinine clearance; CsA - cyclosporin; EC-MPS - enteric-coated mycophenolate sodium; eGFR - estimated glomerular filtration rate; EVL - everolimus; GFR - glomerular filtration rate; HBsAG - hepatitis B surface antigen; HCT - haematocrit; HIV - human immunodeficiency virus; HLA - human leukocyte antigen; HTLV-1 - human T-lymphotropic virus type 1; IL-2RA - interleukin 2 receptor antagonist; ITT - intention-to-treat analysis; IV - intravenous; MMF - mycophenolate mofetil; NODAT - new-onset diabetes post transplant; PO - oral; PRA - panel reactive antibodies; PTLD - Post-transplant lymphoproliferative disease; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; SRL - sirolimus; TAC - tacrolimus; WCC - white cell count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alexander 2006	Wrong co-intervention
Anil Kumar 2005	Wrong co-intervention
Axelrod 2005	Not RCT

(*Continued*)

Berney 2004	Pancreatic islet transplantation
Birkeland 1998b	Not RCT
Birkeland 2002	Pancreatic islet transplantation
Budde 2001	**Wrong co-intervention** **PLEASE ADD REASON FOR EXCLUSION**
CAMPASIA Study 2005	Wrong co-intervention
CARMEN Study 2005	Wrong co-intervention
Citterio 2002	Wrong co-intervention
CORRETA Study 2008	No steroid withdrawal or avoidance
Curtis 1982	No steroid withdrawal or avoidance
Daniel 1985	No steroid withdrawal or avoidance
De Backer 1992	No steroid withdrawal or avoidance
de Sandes Freitas 2011	Wrong co-intervention
Delucchi 2006	Difference in co-intervention
ECSEL Study 2008	Wrong co-intervention
Hibbs 2010	Not RCT
Hilbrands 1993	Not RCT
Hodson 1989	Not RCT
Hricik 1993a	Not RCT
Hricik 1993b	Not RCT
John 2005	Not RCT
Juarez 2006	Not steroid withdrawal or avoidance
Kim 2004	Wrong co-intervention
Kim 2005	Not RCT
Lehmann 2004	Pancreatic islet transplantation

(*Continued*)

Li 2011a	Not steroid withdrawal or avoidance
Morris 1982	Not steroid withdrawal or avoidance
MYSS Study 2004	Wrong co-intervention
NCT00089947	Wrong co-intervention
Nori 2008	Wrong co-intervention
Paczek 2003a	Wrong co-intervention
Papadakis 1982	Not steroid withdrawal or avoidance
Reed 1991	Wrong co-intervention
Remport 2001	Not steroid withdrawal or avoidance
Robertson 1980	Not RCT
Sarwal 2012	Wrong co-intervention
SENIOR Study 2009	Wrong co-intervention
Shapiro 1993	Wrong co-intervention
Silverstein 2005	Not RCT
SOCRATES Study 2014	Not steroid withdrawal or avoidance
Tarantino 1991	Wrong co-intervention
Teplan 2003	Not RCT
ter Meulen 2002	Wrong co-intervention
TRIMS Study 2010	Wrong co-intervention
TWIST Study 2010	Wrong co-intervention
Weimert 2008	Wrong co-intervention

RCT - randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Newstead 1989

Methods	Unclear if this was a RCT
Participants	Kidney transplant recipients not further specified, unclear time frame, but before 1989
Interventions	Steroid withdrawal versus steroid maintenance plus CsA
Outcomes	Serum creatinine and acute rejection
Notes	Abstract-only data; unable to contact authors

CsA - cyclosporin; RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. Steroid withdrawal versus steroid maintenance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death and graft loss	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Death up to one year	10	1913	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.36, 1.30]
1.2 Death one to five years	7	1118	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.73, 2.17]
1.3 Graft loss including death up to one year	8	1817	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.64, 1.49]
1.4 Graft loss including death one to five years	7	1092	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.00, 2.01]
1.5 Graft loss excluding death up to one year	8	1817	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.72, 1.92]
1.6 Graft loss excluding death one to five years	7	1092	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.98, 2.64]
2 Rejection	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Acute rejection up to one year	10	1913	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.20, 2.61]
2.2 Biopsy-proven acute rejection up to one year	5	1292	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.78, 2.22]
3 New-onset diabetes after transplantation and cardiovascular events	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 New onset diabetes after transplantation up to five years	6	1439	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.49, 1.21]
3.2 Cardiovascular events up to five years	2	607	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.42, 2.33]
4 Infection and malignancy	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Infection (all) up to five years	5	1819	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.84, 1.22]
4.2 CMV infection up to five years	5	1758	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.80, 1.36]
4.3 Malignancy up to five years	3	756	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.41, 1.46]
5 Kidney function	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Serum creatinine (mg/dL) up to one year	4	644	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.21, 0.13]
5.2 Serum creatinine (mg/dL) one to five years	5	762	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.06, 0.23]
5.3 Creatinine clearance (mL/min) up to one year	2	215	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.35, 0.21]
5.4 Creatinine clearance (mL/min) one to five years	3	669	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.56, 0.13]

Comparison 2. Steroid avoidance versus steroid maintenance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death and graft loss	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Death up to one year	10	1462	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.52, 1.80]
1.2 Death one to five years	7	1201	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.32, 1.01]
1.3 Graft loss including death up to one year	7	1211	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.72, 1.62]
1.4 Graft loss including death one to five years	7	1245	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.53, 1.18]
1.5 Graft loss excluding death up to one year	7	1211	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.64, 1.86]
1.6 Graft loss excluding death one to five years	7	1245	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.66, 1.45]
2 Rejection	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Acute rejection up to one year	7	835	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.08, 2.30]
2.2 Biopsy-proven acute rejection up to one year	6	1073	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.26, 2.98]
3 New-onset diabetes after transplantation and cardiovascular events	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 New onset diabetes after transplantation up to five years	9	1618	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.51, 1.10]
3.2 Cardiovascular events up to five years	4	1013	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.30, 1.05]
4 Infection and malignancy	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Infection (all) up to five years	9	1833	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
4.2 CMV Infection up to five years	6	1454	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.31]
4.3 Malignancy up to five years	7	1635	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.61, 1.52]
5 Kidney function	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Serum creatinine (mg/dL) up to one year	5	735	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.12, 0.17]
5.2 Serum creatinine (mg/dL) one to five years	3	688	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.16, 0.14]
5.3 Creatinine clearance (mL/min) up to one year	6	1104	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.23, 0.08]
5.4 Creatinine clearance (mL/min) one to five years	3	563	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.25, 0.08]

Comparison 3. Steroid avoidance versus steroid withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death and graft loss	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Death up to one year	1	222	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.08, 1.98]
1.2 Death one to five years	2	152	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.63, 11.32]
1.3 Graft loss including death up to one year	1	222	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.32, 2.29]
1.4 Graft loss including death one to five years	2	152	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.89, 6.70]
1.5 Graft loss excluding death up to one year	1	222	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.40, 6.68]
1.6 Graft loss excluding death one to five years	2	152	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.48, 7.67]
2 Rejection	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Acute rejection up to one year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Biopsy-proven acute rejection up to one year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 New-onset diabetes after transplantation, infection, malignancy	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 New onset diabetes after transplantation up to five years	3	351	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.09]
3.2 Infection (all) up to five years	3	374	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.76, 1.50]
3.3 CMV Infection up to five years	2	284	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.30, 0.92]
3.4 Malignancy up to five years	1	90	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.28, 8.94]
4 Kidney function	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Serum creatinine (mg/dL) up to one year	2	88	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.47, 0.37]
4.2 Creatinine clearance (mL/min) up to one year	2	206	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.14]

Comparison 4. Steroid withdrawal versus maintenance in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death and graft loss	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Death up to five years	2	174	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.35]
1.2 Graft loss including death up to five years	2	174	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.69]

1.3 Graft loss excluding death up to five years	2	174	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.00, 1.64]
2 Rejection, malignancy	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Acute rejection up to one year	2	174	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.13, 1.02]
2.2 Biopsy-proven acute rejection up to one year	1	42	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 3.27]
2.3 Malignancy (PTLD) up to five years	1	132	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.51, 6.98]
3 Kidney function	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Creatinine clearance (mL/min) up to five years	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Publication bias

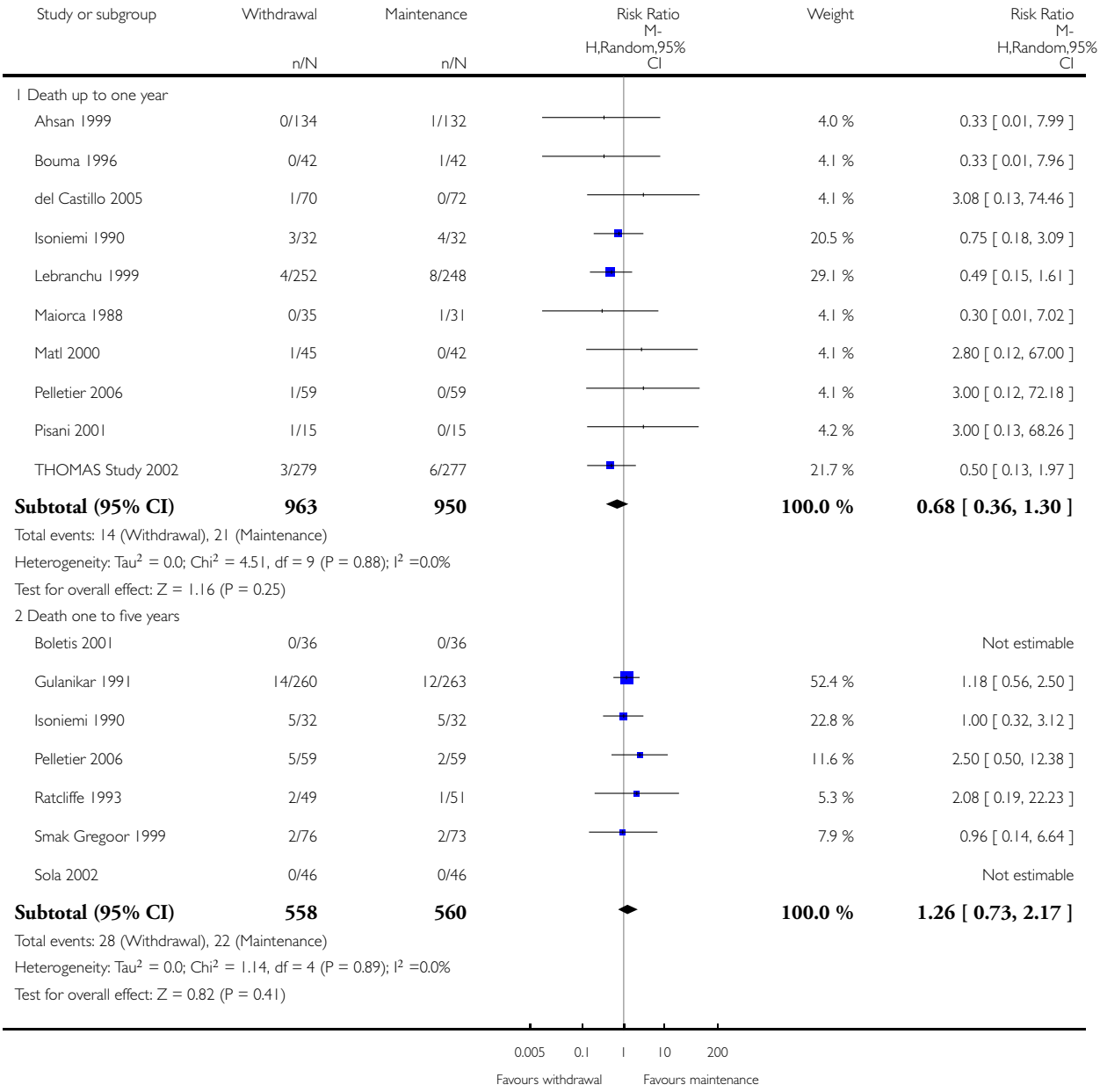
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Funnel plots	20	5288	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.15, 1.62]
1.1 Death, steroid withdrawal versus maintenance	10	1913	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.39, 1.29]
1.2 Acute rejection steroid withdrawal versus maintenance	10	1913	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.28, 1.87]
1.3 Death, steroid avoidance versus maintenance	10	1462	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.52, 1.63]

Analysis 1.1. Comparison 1 Steroid withdrawal versus steroid maintenance, Outcome 1 Death and graft loss.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 1 Steroid withdrawal versus steroid maintenance

Outcome: 1 Death and graft loss



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Study or subgroup	Withdrawal n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Graft loss including death up to one year					
Ahsan 1999	2/134	3/132		5.8 %	0.66 [0.11, 3.87]
Bouma 1996	1/42	1/42		2.4 %	1.00 [0.06, 15.47]
del Castillo 2005	5/70	5/72		12.8 %	1.03 [0.31, 3.40]
Isoniemi 1990	3/32	6/32		10.8 %	0.50 [0.14, 1.83]
Lebranchu 1999	14/252	18/248		39.9 %	0.77 [0.39, 1.50]
Matl 2000	1/45	1/42		2.4 %	0.93 [0.06, 14.45]
Pelletier 2006	1/59	1/59		2.4 %	1.00 [0.06, 15.61]
THOMAS Study 2002	15/279	7/277		23.4 %	2.13 [0.88, 5.14]
Subtotal (95% CI)	**913**	**904**		**100.0 %**	**0.97 [0.64, 1.49]**
Total events: 42 (Withdrawal), 42 (Maintenance)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.73$, df = 7 (P = 0.69); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.12 (P = 0.90)					
4 Graft loss including death one to five years					
Boletis 2001	0/36	0/36			Not estimable
Gulanikar 1991	45/260	29/263		65.0 %	1.57 [1.02, 2.42]
Isoniemi 1990	7/32	8/32		15.5 %	0.88 [0.36, 2.13]
Maiorca 1988	2/35	1/31		2.2 %	1.77 [0.17, 18.60]
Pelletier 2006	8/59	4/59		9.3 %	2.00 [0.64, 6.28]
Ratcliffe 1993	2/49	1/51		2.2 %	2.08 [0.19, 22.23]
Smak Gregoor 1999	3/76	4/73		5.7 %	0.72 [0.17, 3.11]
Subtotal (95% CI)	**547**	**545**		**100.0 %**	**1.41 [1.00, 2.01]**
Total events: 67 (Withdrawal), 47 (Maintenance)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.65$, df = 5 (P = 0.75); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.94 (P = 0.052)					
5 Graft loss excluding death up to one year					
Ahsan 1999	2/134	2/132		6.4 %	0.99 [0.14, 6.89]
Bouma 1996	1/42	0/42		2.4 %	3.00 [0.13, 71.61]
del Castillo 2005	4/70	5/72		14.9 %	0.82 [0.23, 2.94]
Isoniemi 1990	0/32	2/32		2.7 %	0.20 [0.01, 4.01]
Lebranchu 1999	12/252	11/248		37.8 %	1.07 [0.48, 2.39]
Matl 2000	0/45	1/42		2.4 %	0.31 [0.01, 7.44]
Pelletier 2006	0/59	1/59		2.4 %	0.33 [0.01, 8.02]
THOMAS Study 2002	15/279	7/277		31.1 %	2.13 [0.88, 5.14]

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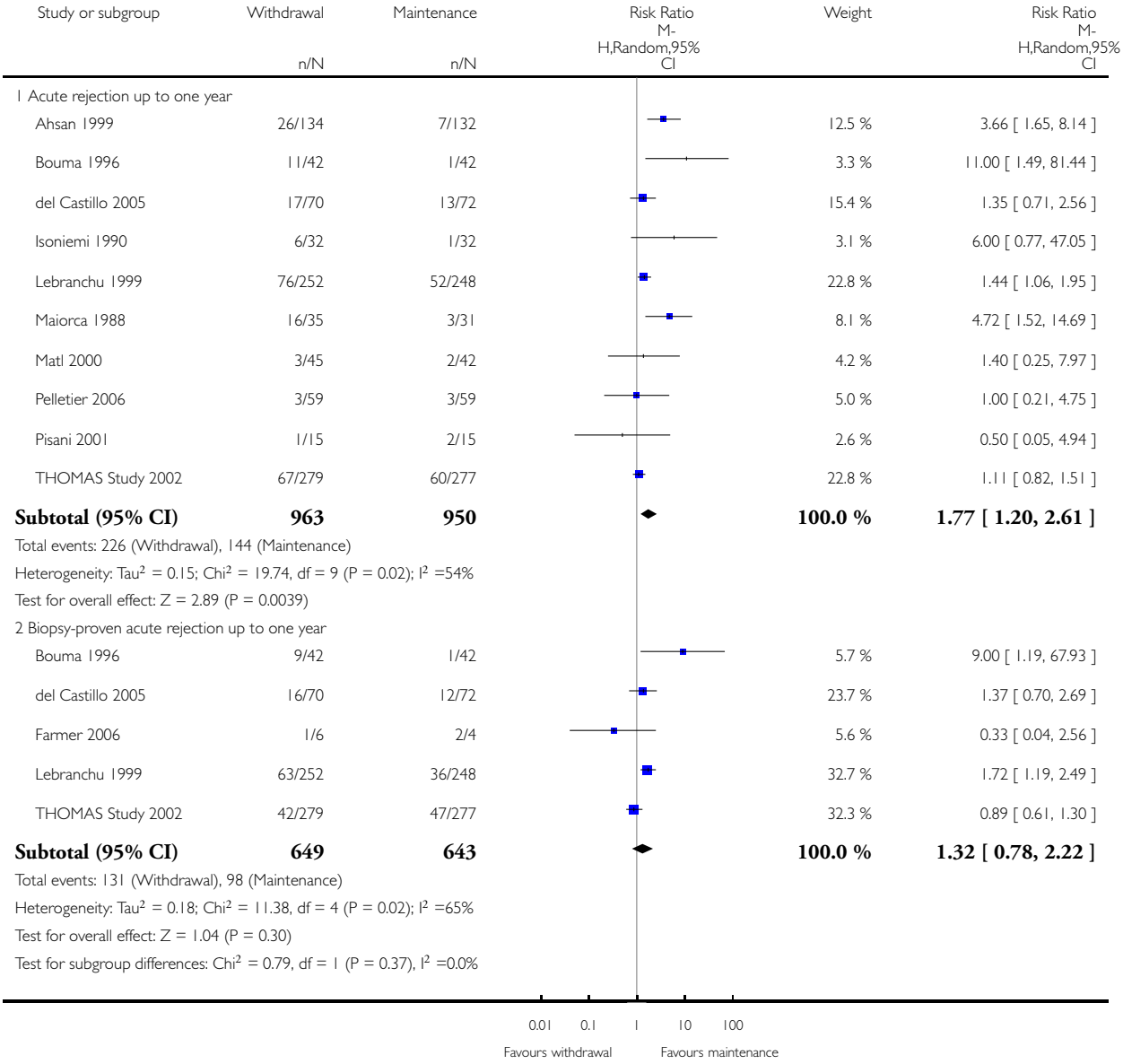
Study or subgroup	Withdrawal n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**913**	**904**		**100.0 %**	**1.17 [0.72, 1.92]**
Total events: 34 (Withdrawal), 29 (Maintenance)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.08$, df = 7 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.64 (P = 0.52)					
6 Graft loss excluding death one to five years					
Boletis 2001	0/36	0/36			Not estimable
Gulanikar 1991	31/260	17/263		76.6 %	1.84 [1.05, 3.25]
Isoniemi 1990	2/32	3/32		8.3 %	0.67 [0.12, 3.73]
Maiorca 1988	2/35	0/31		2.7 %	4.44 [0.22, 89.16]
Pelletier 2006	3/59	2/59		8.0 %	1.50 [0.26, 8.65]
Ratcliffe 1993	0/49	0/51			Not estimable
Smak Gregoor 1999	1/76	2/73		4.3 %	0.48 [0.04, 5.18]
Subtotal (95% CI)	**547**	**545**		**100.0 %**	**1.61 [0.98, 2.64]**
Total events: 39 (Withdrawal), 24 (Maintenance)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.67$, df = 4 (P = 0.61); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.89 (P = 0.059)					
Test for subgroup differences: $Chi^2 = 6.11$, df = 5 (P = 0.30), $I^2 = 18\%$					

Analysis 1.2. Comparison 1 Steroid withdrawal versus steroid maintenance, Outcome 2 Rejection.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 1 Steroid withdrawal versus steroid maintenance

Outcome: 2 Rejection

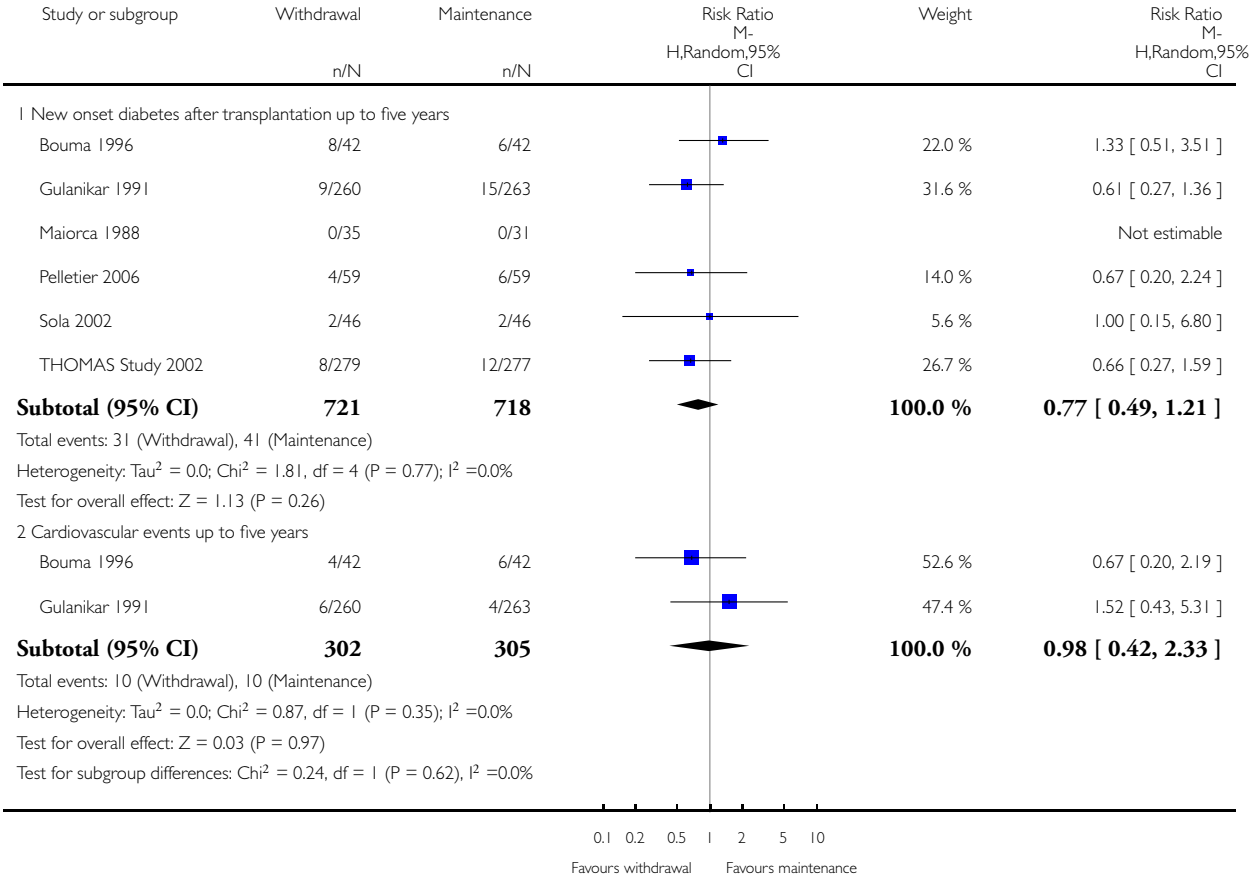


Analysis 1.3. Comparison 1 Steroid withdrawal versus steroid maintenance, Outcome 3 New-onset diabetes after transplantation and cardiovascular events.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 1 Steroid withdrawal versus steroid maintenance

Outcome: 3 New-onset diabetes after transplantation and cardiovascular events

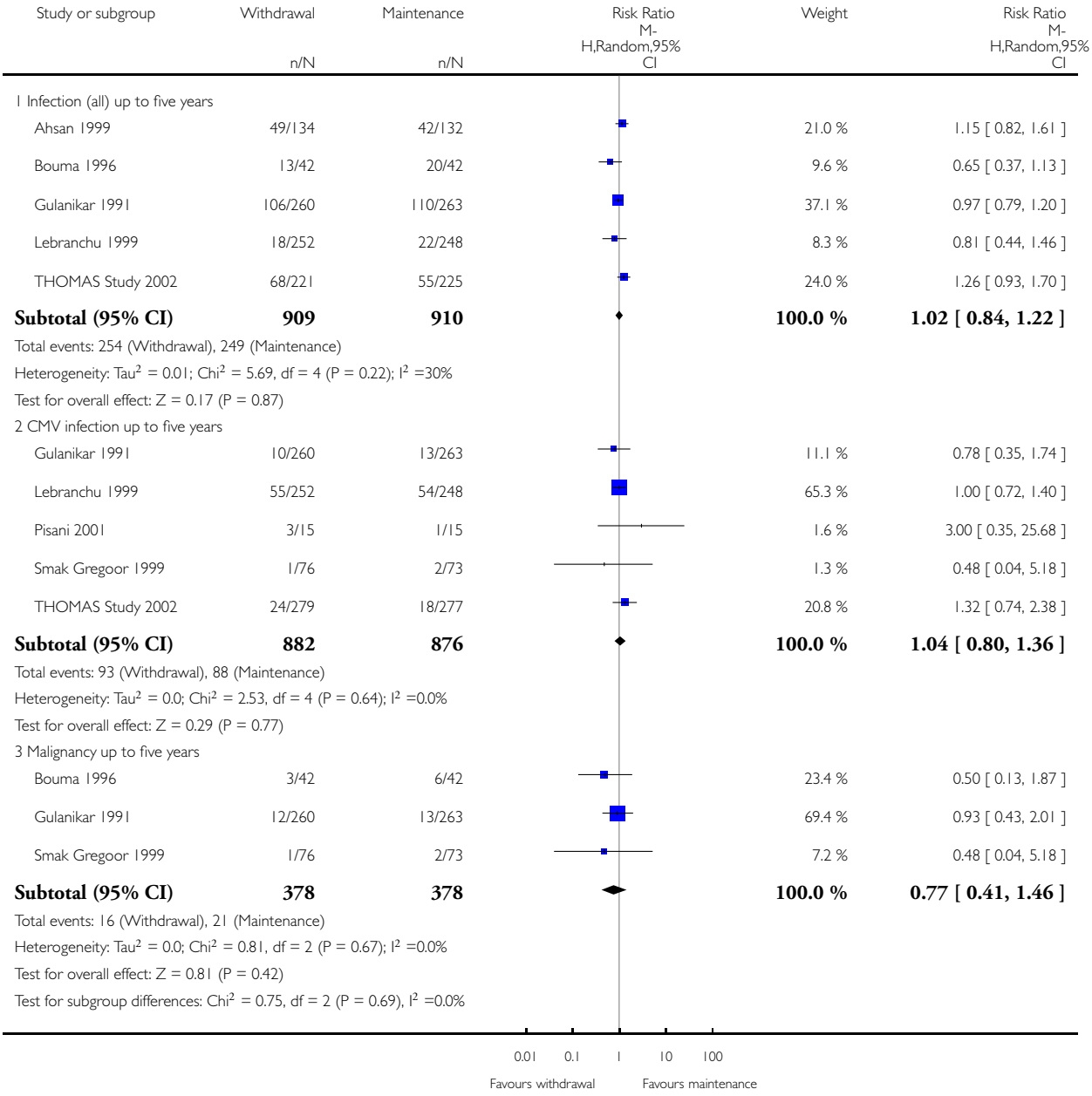


Analysis 1.4. Comparison 1 Steroid withdrawal versus steroid maintenance, Outcome 4 Infection and malignancy.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 1 Steroid withdrawal versus steroid maintenance

Outcome: 4 Infection and malignancy



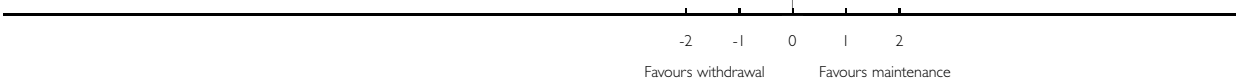
Analysis 1.5. Comparison 1 Steroid withdrawal versus steroid maintenance, Outcome 5 Kidney function.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 1 Steroid withdrawal versus steroid maintenance

Outcome: 5 Kidney function

Study or subgroup	Withdrawal N	Mean(SD)	Maintenance N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Serum creatinine (mg/dL) up to one year							
del Castillo 2005	65	1.7 (0.8)	67	1.6 (0.5)		22.0 %	0.15 [-0.19, 0.49]
Isoniemi 1990	28	1.6 (0.7)	26	1.5 (0.6)		9.6 %	0.15 [-0.38, 0.69]
Lebranchu 1999	162	1.5 (0.5)	180	1.6 (0.6)		48.8 %	-0.18 [-0.39, 0.03]
Pelletier 2006	57	1.6 (0.5)	59	1.6 (0.5)		19.6 %	0.0 [-0.36, 0.36]
Subtotal (95% CI)	**312**		**332**			**100.0 %**	**-0.04 [-0.21, 0.13]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.35, df = 3 (P = 0.34); I^2 =11%							
Test for overall effect: Z = 0.47 (P = 0.64)							
2 Serum creatinine (mg/dL) one to five years							
Burke 2000	14	1.7 (0.5)	15	1.5 (0.5)		3.7 %	0.39 [-0.35, 1.13]
Gulanikar 1991	260	2 (0.82)	263	2 (0.83)		68.9 %	0.0 [-0.17, 0.17]
Isoniemi 1990	25	1.5 (0.5)	24	1.4 (0.5)		6.4 %	0.20 [-0.36, 0.76]
Pelletier 2006	35	1.9 (0.5)	29	1.7 (0.6)		8.2 %	0.36 [-0.14, 0.86]
Ratcliffe 1993	47	1.7 (0.5)	50	1.6 (0.4)		12.7 %	0.22 [-0.18, 0.62]
Subtotal (95% CI)	**381**		**381**			**100.0 %**	**0.08 [-0.06, 0.23]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.38, df = 4 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 1.17 (P = 0.24)							
3 Creatinine clearance (mL/min) up to one year							
Bouma 1996	42	66 (33)	41	63 (20)		39.7 %	0.11 [-0.32, 0.54]
del Castillo 2005	65	59.1 (21.3)	67	62.9 (19.4)		60.3 %	-0.19 [-0.53, 0.16]
Subtotal (95% CI)	**107**		**108**			**100.0 %**	**-0.07 [-0.35, 0.21]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.10, df = 1 (P = 0.29); I^2 =9%							
Test for overall effect: Z = 0.48 (P = 0.63)							
4 Creatinine clearance (mL/min) one to five years							
Gulanikar 1991	260	54.5 (30.44)	263	54.6 (29.78)		47.2 %	0.00 [-0.17, 0.17]
Isoniemi 1990	25	57 (20)	24	62 (19)		22.0 %	-0.25 [-0.81, 0.31]
Ratcliffe 1993	47	47 (17)	50	56 (18)		30.7 %	-0.51 [-0.91, -0.10]



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Study or subgroup	Withdrawal N	Mean(SD)	Maintenance N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**332**		**337**			**100.0 %**	**-0.21 [-0.56, 0.13]**

Heterogeneity: Tau² = 0.06; Chi² = 5.43, df = 2 (P = 0.07); I² =63%

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Chi² = 3.29, df = 3 (P = 0.35), I² =9%

Analysis 2.1. Comparison 2 Steroid avoidance versus steroid maintenance, Outcome 1 Death and graft loss.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 2 Steroid avoidance versus steroid maintenance

Outcome: 1 Death and graft loss

Study or subgroup	Avoidance n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Death up to one year					
ATLAS Study 2005	3/151	0/147		4.4 %	6.82 [0.36, 130.81]
De Vecchi 1986	0/25	4/26		4.7 %	0.12 [0.01, 2.04]
FRANCIA Study 2007	1/98	3/103		7.7 %	0.35 [0.04, 3.31]
FREEDOM Study 2008	7/226	2/109		16.0 %	1.69 [0.36, 7.99]
Kumar 2005	0/45	0/32			Not estimable
Montagnino 2005	0/65	1/68		3.8 %	0.35 [0.01, 8.40]
Nematalla 2007	0/50	0/50			Not estimable
Nott 1985	8/59	8/58		46.6 %	0.98 [0.40, 2.44]
Schulak 1989	3/32	2/35		13.0 %	1.64 [0.29, 9.20]
Vincenti 2003a	0/40	1/43		3.8 %	0.36 [0.01, 8.54]
Subtotal (95% CI)	**791**	**671**		**100.0 %**	**0.96 [0.52, 1.80]**

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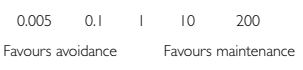
Study or subgroup	Avoidance n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 22 (Avoidance), 21 (Maintenance)					
Heterogeneity: Tau² = 0.0; Chi² = 6.22, df = 7 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 0.11 (P = 0.91)					
2 Death one to five years					
ATLAS Study 2005	3/139	5/139		16.2 %	0.60 [0.15, 2.46]
De Vecchi 1986	0/25	5/26		4.0 %	0.09 [0.01, 1.62]
Kim 2002	0/11	1/12		3.3 %	0.36 [0.02, 8.04]
Montagnino 2005	0/65	2/68		3.5 %	0.21 [0.01, 4.27]
Nematalla 2007	0/49	0/49			Not estimable
Ponticelli 1997	3/115	9/117		19.6 %	0.34 [0.09, 1.22]
Woodle 2005	11/191	13/195		53.3 %	0.86 [0.40, 1.88]
Subtotal (95% CI)	**595**	**606**		**100.0 %**	**0.57 [0.32, 1.01]**
Total events: 17 (Avoidance), 35 (Maintenance)					
Heterogeneity: Tau² = 0.0; Chi² = 3.90, df = 5 (P = 0.56); I² =0.0%					
Test for overall effect: Z = 1.92 (P = 0.055)					
3 Graft loss including death up to one year					
ATLAS Study 2005	9/151	6/147		16.3 %	1.46 [0.53, 4.00]
FRANCIA Study 2007	5/98	7/103		13.3 %	0.75 [0.25, 2.29]
FREEDOM Study 2008	13/226	5/109		16.4 %	1.25 [0.46, 3.43]
Kumar 2005	2/45	1/32		3.0 %	1.42 [0.13, 15.02]
Nematalla 2007	0/50	0/50			Not estimable
Nott 1985	17/59	16/58		49.4 %	1.04 [0.59, 1.86]
Vincenti 2003a	0/40	1/43		1.6 %	0.36 [0.01, 8.54]
Subtotal (95% CI)	**669**	**542**		**100.0 %**	**1.08 [0.72, 1.62]**
Total events: 46 (Avoidance), 36 (Maintenance)					
Heterogeneity: Tau² = 0.0; Chi² = 1.37, df = 5 (P = 0.93); I² =0.0%					
Test for overall effect: Z = 0.36 (P = 0.72)					
4 Graft loss including death one to five years					
ATLAS Study 2005	11/139	15/139		18.9 %	0.73 [0.35, 1.54]
De Vecchi 1986	1/25	7/26		3.7 %	0.15 [0.02, 1.12]
Montagnino 2005	3/65	10/68		8.7 %	0.31 [0.09, 1.09]
Nematalla 2007	0/49	0/49			Not estimable
Ponticelli 1997	18/115	24/117		26.5 %	0.76 [0.44, 1.33]
Schulak 1989	9/32	8/35		16.5 %	1.23 [0.54, 2.80]
Woodle 2005	22/191	20/195		25.7 %	1.12 [0.63, 1.99]



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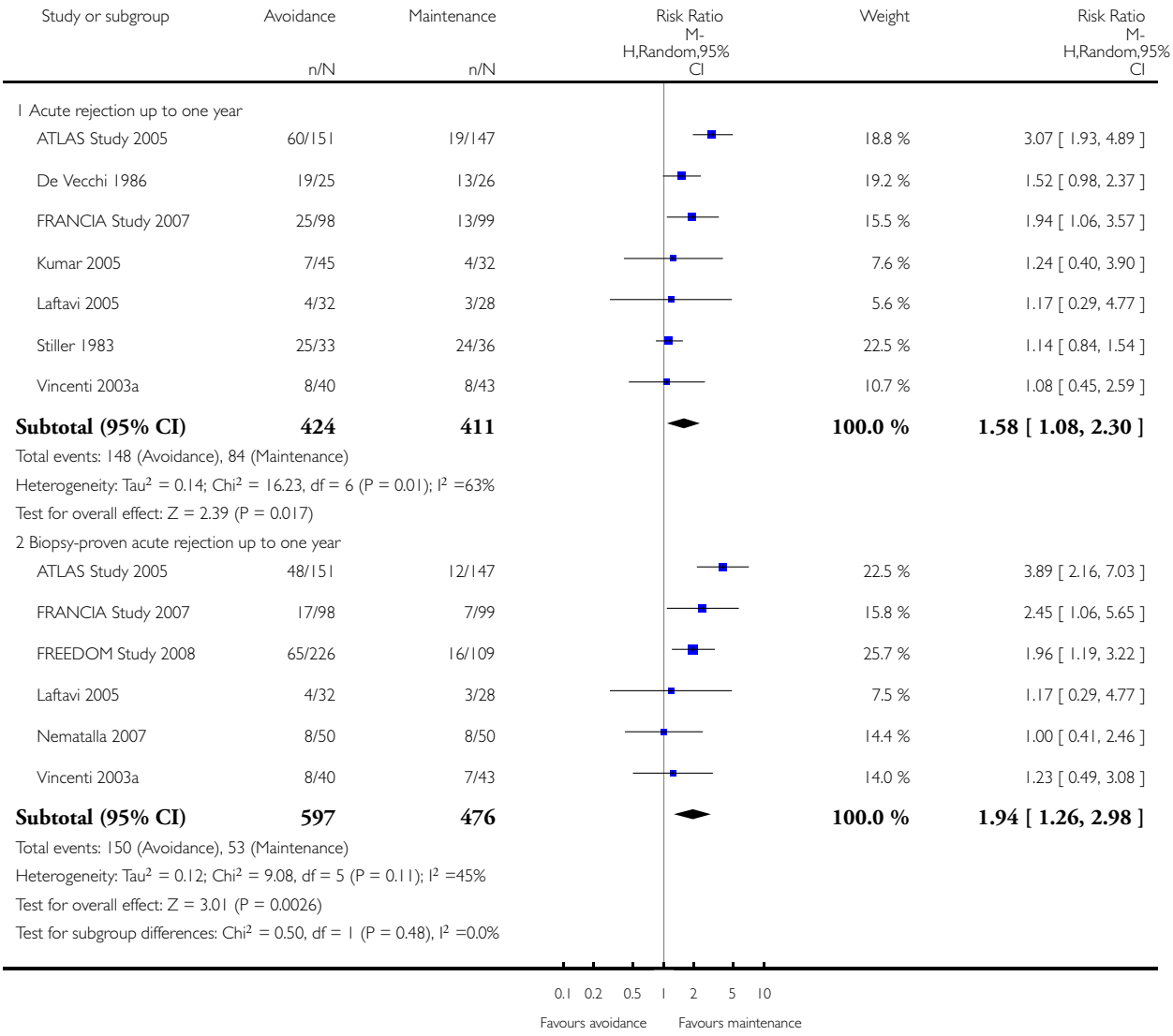
Study or subgroup	Avoidance n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**616**	**629**		**100.0 %**	**0.79 [0.53, 1.18]**
Total events: 64 (Avoidance), 84 (Maintenance)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 7.39, df = 5 (P = 0.19); I^2 =32%					
Test for overall effect: Z = 1.16 (P = 0.25)					
5 Graft loss excluding death up to one year					
ATLAS Study 2005	7/151	6/147		24.6 %	1.14 [0.39, 3.30]
FRANCIA Study 2007	5/98	5/103		19.2 %	1.05 [0.31, 3.52]
FREEDOM Study 2008	6/226	3/109		15.0 %	0.96 [0.25, 3.78]
Kumar 2005	2/45	1/32		5.0 %	1.42 [0.13, 15.02]
Nematalla 2007	0/50	0/50			Not estimable
Nott 1985	9/59	8/58		36.1 %	1.11 [0.46, 2.67]
Vincenti 2003a	0/40	0/43			Not estimable
Subtotal (95% CI)	**669**	**542**		**100.0 %**	**1.09 [0.64, 1.86]**
Total events: 29 (Avoidance), 23 (Maintenance)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 4 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.33 (P = 0.74)					
6 Graft loss excluding death one to five years					
ATLAS Study 2005	9/139	10/139		20.4 %	0.90 [0.38, 2.15]
De Vecchi 1986	1/25	2/26		2.8 %	0.52 [0.05, 5.38]
Montagnino 2005	3/65	8/68		9.4 %	0.39 [0.11, 1.41]
Nematalla 2007	0/49	0/49			Not estimable
Ponticelli 1997	15/115	15/117		34.6 %	1.02 [0.52, 1.98]
Schulak 1989	6/32	6/35		14.7 %	1.09 [0.39, 3.05]
Woodle 2005	11/191	7/195		18.0 %	1.60 [0.64, 4.05]
Subtotal (95% CI)	**616**	**629**		**100.0 %**	**0.98 [0.66, 1.45]**
Total events: 45 (Avoidance), 48 (Maintenance)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.42, df = 5 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.12 (P = 0.91)					
Test for subgroup differences: Chi^2 = 4.33, df = 5 (P = 0.50), I^2 =0.0%					

Analysis 2.2. Comparison 2 Steroid avoidance versus steroid maintenance, Outcome 2 Rejection.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 2 Steroid avoidance versus steroid maintenance

Outcome: 2 Rejection



Analysis 2.3. Comparison 2 Steroid avoidance versus steroid maintenance, Outcome 3 New-onset diabetes after transplantation and cardiovascular events.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 2 Steroid avoidance versus steroid maintenance

Outcome: 3 New-onset diabetes after transplantation and cardiovascular events

Study or subgroup	Avoidance n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 New onset diabetes after transplantation up to five years					
ATLAS Study 2005	6/127	4/126		8.1 %	1.49 [0.43, 5.15]
FRANCIA Study 2007	6/98	15/103		13.3 %	0.42 [0.17, 1.04]
FREEDOM Study 2008	19/227	16/109		21.6 %	0.57 [0.31, 1.06]
Kumar 2005	0/30	3/23		1.7 %	0.11 [0.01, 2.04]
Montagnino 2005	6/65	4/68		8.4 %	1.57 [0.46, 5.31]
Nematalla 2007	2/50	8/50		5.9 %	0.25 [0.06, 1.12]
Nott 1985	1/59	2/58		2.5 %	0.49 [0.05, 5.27]
Ponticelli 1997	9/115	9/117		13.7 %	1.02 [0.42, 2.47]
Woodle 2005	23/107	18/86		24.8 %	1.03 [0.59, 1.78]
Subtotal (95% CI)	**878**	**740**		**100.0 %**	**0.75 [0.51, 1.10]**
Total events: 72 (Avoidance), 79 (Maintenance)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 10.51$, df = 8 (P = 0.23); $I^2 = 24\%$					
Test for overall effect: Z = 1.49 (P = 0.14)					
2 Cardiovascular events up to five years					
ATLAS Study 2005	6/139	4/139		20.3 %	1.50 [0.43, 5.20]
Nott 1985	3/59	4/58		15.7 %	0.74 [0.17, 3.15]
Ponticelli 1997	6/115	18/117		33.1 %	0.34 [0.14, 0.82]
Woodle 2005	6/191	14/195		30.9 %	0.44 [0.17, 1.11]
Subtotal (95% CI)	**504**	**509**		**100.0 %**	**0.56 [0.30, 1.05]**
Total events: 21 (Avoidance), 40 (Maintenance)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 4.02$, df = 3 (P = 0.26); $I^2 = 25\%$					
Test for overall effect: Z = 1.81 (P = 0.071)					
Test for subgroup differences: $Chi^2 = 0.57$, df = 1 (P = 0.45), $I^2 = 0.0\%$					

Analysis 2.4. Comparison 2 Steroid avoidance versus steroid maintenance, Outcome 4 Infection and malignancy.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 2 Steroid avoidance versus steroid maintenance

Outcome: 4 Infection and malignancy

Study or subgroup	Avoidance n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Infection (all) up to five years					
ATLAS Study 2005	30/139	26/139		4.4 %	1.15 [0.72, 1.85]
FRANCIA Study 2007	66/98	75/103		29.5 %	0.92 [0.77, 1.11]
FREEDOM Study 2008	144/227	71/109		34.0 %	0.97 [0.82, 1.15]
Montagnino 2005	9/65	13/68		1.6 %	0.72 [0.33, 1.58]
Nott 1985	5/59	15/58		1.1 %	0.33 [0.13, 0.84]
Ponticelli 1997	39/115	47/117		8.5 %	0.84 [0.60, 1.18]
Schulak 1989	8/32	7/35		1.2 %	1.25 [0.51, 3.06]
Vincenti 2003a	13/40	12/43		2.3 %	1.16 [0.60, 2.24]
Woodle 2005	75/191	86/195		17.3 %	0.89 [0.70, 1.13]
Subtotal (95% CI)	**966**	**867**		**100.0 %**	**0.93 [0.84, 1.03]**
Total events: 389 (Avoidance), 352 (Maintenance)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.57, df = 8 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 1.42 (P = 0.16)					
2 CMV Infection up to five years					
ATLAS Study 2005	25/151	17/147		29.5 %	1.43 [0.81, 2.54]
FRANCIA Study 2007	16/98	20/103		27.2 %	0.84 [0.46, 1.53]
FREEDOM Study 2008	20/227	9/109		17.1 %	1.07 [0.50, 2.27]
Montagnino 2005	1/65	2/68		1.7 %	0.52 [0.05, 5.63]
Nematalla 2007	1/50	3/50		1.9 %	0.33 [0.04, 3.10]
Woodle 2005	14/191	20/195		22.7 %	0.71 [0.37, 1.37]
Subtotal (95% CI)	**782**	**672**		**100.0 %**	**0.96 [0.70, 1.31]**
Total events: 77 (Avoidance), 71 (Maintenance)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.04, df = 5 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.25 (P = 0.81)					
3 Malignancy up to five years					
ATLAS Study 2005	4/139	6/139		13.2 %	0.67 [0.19, 2.31]

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Study or subgroup	Avoidance n/N	Maintenance n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
FRANCIA Study 2007	0/98	5/103		2.5 %	0.10 [0.01, 1.70]
FREEDOM Study 2008	3/227	1/109		4.0 %	1.44 [0.15, 13.69]
Montagnino 2005	4/65	2/68		7.4 %	2.09 [0.40, 11.04]
Ponticelli 1997	5/115	3/117		10.3 %	1.70 [0.41, 6.93]
Stiller 1983	0/33	0/36			Not estimable
Woodle 2005	20/191	22/195		62.6 %	0.93 [0.52, 1.64]
Subtotal (95% CI)	**868**	**767**		**100.0 %**	**0.97 [0.61, 1.52]**
Total events: 36 (Avoidance), 39 (Maintenance)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.47$, df = 5 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.15 (P = 0.88)					
Test for subgroup differences: $Chi^2 = 0.06$, df = 2 (P = 0.97), $I^2 = 0.0\%$					

Analysis 2.5. Comparison 2 Steroid avoidance versus steroid maintenance, Outcome 5 Kidney function.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 2 Steroid avoidance versus steroid maintenance

Outcome: 5 Kidney function

Study or subgroup	Avoidance N	Avoidance Mean(SD)	Maintenance N	Maintenance Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Serum creatinine (mg/dL) up to one year							
ATLAS Study 2005	151	1.63 (0.93)	147	1.52 (0.81)		40.6 %	0.13 [-0.10, 0.35]
FRANCIA Study 2007	98	1.8 (1.4)	99	1.9 (1.5)		26.9 %	-0.07 [-0.35, 0.21]
Kumar 2005	45	2 (0.8)	32	2.1 (1)		10.2 %	-0.11 [-0.57, 0.34]
Nematalla 2007	50	1.22 (0.51)	50	1.22 (0.5)		13.7 %	0.0 [-0.39, 0.39]
Schulak 1989	30	1.8 (0.6)	33	1.8 (0.8)		8.6 %	0.0 [-0.49, 0.49]
Subtotal (95% CI)	**374**		**361**			**100.0 %**	**0.02 [-0.12, 0.17]**
Heterogeneity: Tau² = 0.0; Chi² = 1.56, df = 4 (P = 0.82); I² =0.0%							
Test for overall effect: Z = 0.29 (P = 0.77)							
2 Serum creatinine (mg/dL) one to five years							
ATLAS Study 2005	139	1.6 (0.9)	139	1.57 (0.79)		40.4 %	0.04 [-0.20, 0.27]
Montagnino 2005	53	1.8 (0.55)	49	1.95 (1.09)		14.8 %	-0.17 [-0.56, 0.21]
Woodle 2005	156	1.5 (0.6)	152	1.5 (0.7)		44.8 %	0.0 [-0.22, 0.22]
Subtotal (95% CI)	**348**		**340**			**100.0 %**	**-0.01 [-0.16, 0.14]**
Heterogeneity: Tau² = 0.0; Chi² = 0.84, df = 2 (P = 0.66); I² =0.0%							
Test for overall effect: Z = 0.15 (P = 0.88)							
3 Creatinine clearance (mL/min) up to one year							
ATLAS Study 2005	151	63.5 (21.7)	147	67.7 (24)		24.6 %	-0.18 [-0.41, 0.04]
FRANCIA Study 2007	98	58.19 (16.6)	99	57.84 (20.4)		19.5 %	0.02 [-0.26, 0.30]
FREEDOM Study 2008	226	55.6 (23.4)	109	58.8 (20.5)		24.5 %	-0.14 [-0.37, 0.09]
Laftavi 2005	10	80.7 (29.3)	11	61.5 (25.6)		2.9 %	0.67 [-0.21, 1.56]
Nematalla 2007	50	74.9 (23.1)	50	71.3 (10.9)		12.1 %	0.20 [-0.20, 0.59]
Ponticelli 1997	76	58.9 (16.1)	77	64 (21.3)		16.4 %	-0.27 [-0.59, 0.05]
Subtotal (95% CI)	**611**		**493**			**100.0 %**	**-0.08 [-0.23, 0.08]**
Heterogeneity: Tau² = 0.01; Chi² = 7.53, df = 5 (P = 0.18); I² =34%							
Test for overall effect: Z = 0.96 (P = 0.34)							
4 Creatinine clearance (mL/min) one to five years							
Montagnino 2005	53	52.3 (17.08)	49	52 (21.52)		18.1 %	0.02 [-0.37, 0.40]

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Study or subgroup	Avoidance N	Mean(SD)	Maintenance N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Ponticelli 1997	76	57.3 (16.3)	77	61.2 (23.3)		27.1 %	-0.19 [-0.51, 0.12]
Woodle 2005	156	58.6 (17.9)	152	59.8 (20.5)		54.8 %	-0.06 [-0.29, 0.16]
Subtotal (95% CI)	**285**		**278**			**100.0 %**	**-0.08 [-0.25, 0.08]**

Heterogeneity: Tau² = 0.0; Chi² = 0.74, df = 2 (P = 0.69); I² =0.0%

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Chi² = 1.28, df = 3 (P = 0.73), I² =0.0%

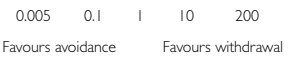
Analysis 3.1. Comparison 3 Steroid avoidance versus steroid withdrawal, Outcome 1 Death and graft loss.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 3 Steroid avoidance versus steroid withdrawal

Outcome: 1 Death and graft loss

Study or subgroup	Avoidance n/N	Withdrawal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Death up to one year					
DOMINOS Study 2012	2/112	5/110		100.0 %	0.39 [0.08, 1.98]
Subtotal (95% CI)	**112**	**110**		**100.0 %**	**0.39 [0.08, 1.98]**
Total events: 2 (Avoidance), 5 (Withdrawal)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					
2 Death one to five years					
Boots 2002	2/28	0/34		23.2 %	6.03 [0.30, 120.75]
Sandrini 2009	4/44	2/46		76.8 %	2.09 [0.40, 10.85]
Subtotal (95% CI)	**72**	**80**		**100.0 %**	**2.67 [0.63, 11.32]**
Total events: 6 (Avoidance), 2 (Withdrawal)					
Heterogeneity: Tau² = 0.0; Chi² = 0.38, df = 1 (P = 0.54); I² =0.0%					
Test for overall effect: Z = 1.34 (P = 0.18)					



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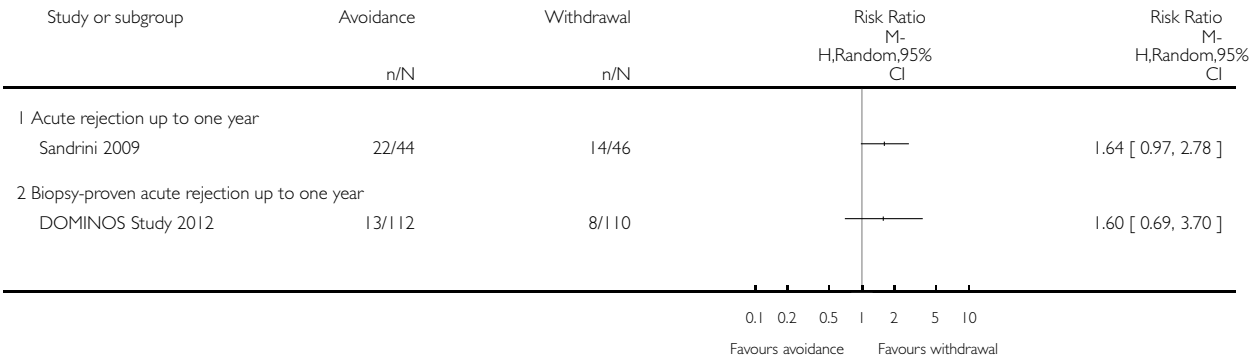
Study or subgroup	Avoidance n/N	Withdrawal n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Graft loss including death up to one year					
DOMINOS Study 2012	7/112	8/110		100.0 %	0.86 [0.32, 2.29]
Subtotal (95% CI)	**112**	**110**		**100.0 %**	**0.86 [0.32, 2.29]**
Total events: 7 (Avoidance), 8 (Withdrawal)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
4 Graft loss including death one to five years					
Boots 2002	5/28	2/34		41.8 %	3.04 [0.64, 14.47]
Sandrini 2009	6/44	3/46		58.2 %	2.09 [0.56, 7.85]
Subtotal (95% CI)	**72**	**80**		**100.0 %**	**2.44 [0.89, 6.70]**
Total events: 11 (Avoidance), 5 (Withdrawal)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 1.73 (P = 0.083)					
5 Graft loss excluding death up to one year					
DOMINOS Study 2012	5/112	3/110		100.0 %	1.64 [0.40, 6.68]
Subtotal (95% CI)	**112**	**110**		**100.0 %**	**1.64 [0.40, 6.68]**
Total events: 5 (Avoidance), 3 (Withdrawal)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
6 Graft loss excluding death one to five years					
Boots 2002	3/28	2/34		65.5 %	1.82 [0.33, 10.15]
Sandrini 2009	2/44	1/46		34.5 %	2.09 [0.20, 22.25]
Subtotal (95% CI)	**72**	**80**		**100.0 %**	**1.91 [0.48, 7.67]**
Total events: 5 (Avoidance), 3 (Withdrawal)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 0.91 (P = 0.36)					
Test for subgroup differences: Chi^2 = 5.49, df = 5 (P = 0.36), I^2 =9%					

Analysis 3.2. Comparison 3 Steroid avoidance versus steroid withdrawal, Outcome 2 Rejection.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 3 Steroid avoidance versus steroid withdrawal

Outcome: 2 Rejection

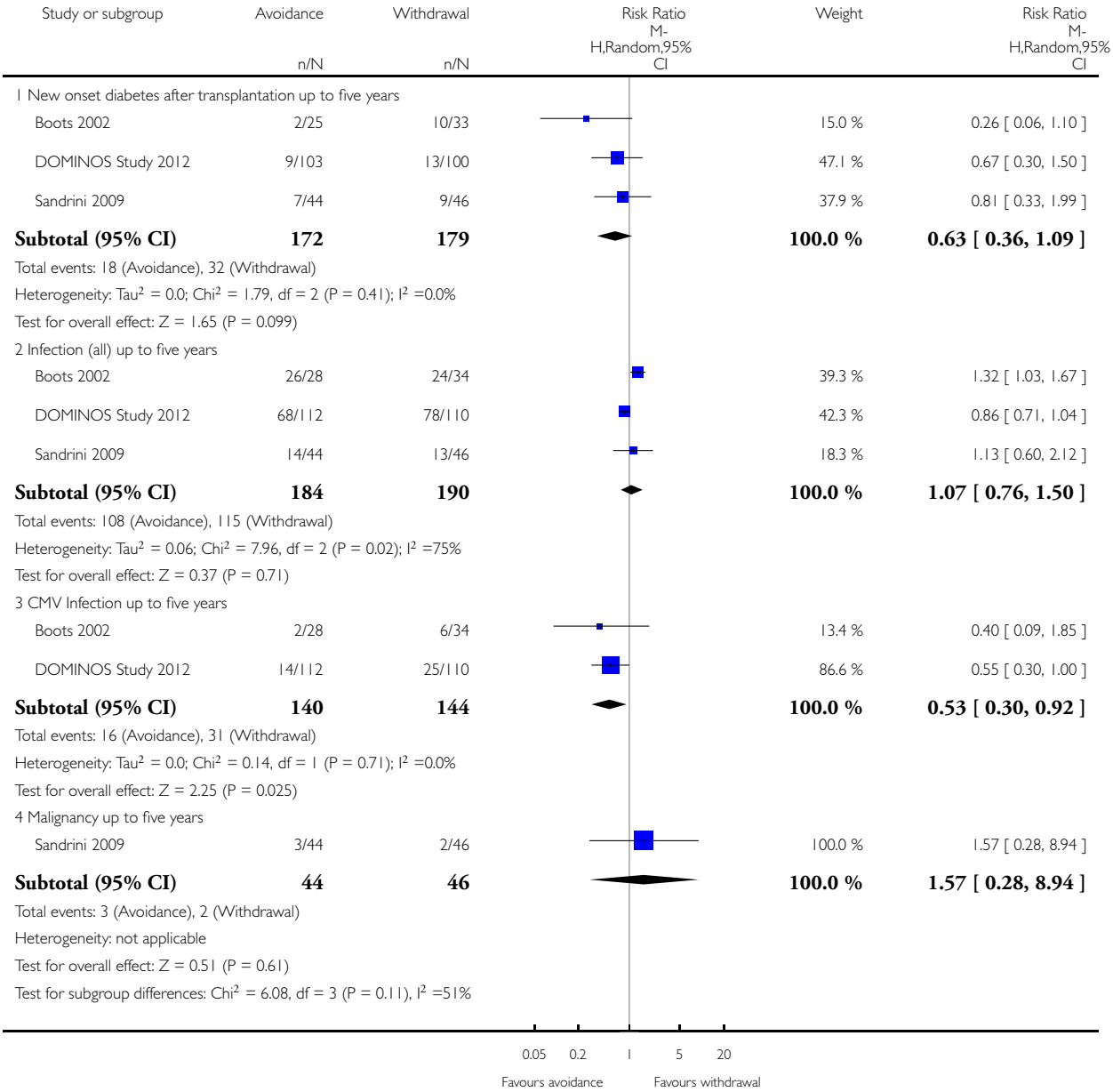


Analysis 3.3. Comparison 3 Steroid avoidance versus steroid withdrawal, Outcome 3 New-onset diabetes after transplantation, infection, malignancy.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 3 Steroid avoidance versus steroid withdrawal

Outcome: 3 New-onset diabetes after transplantation, infection, malignancy

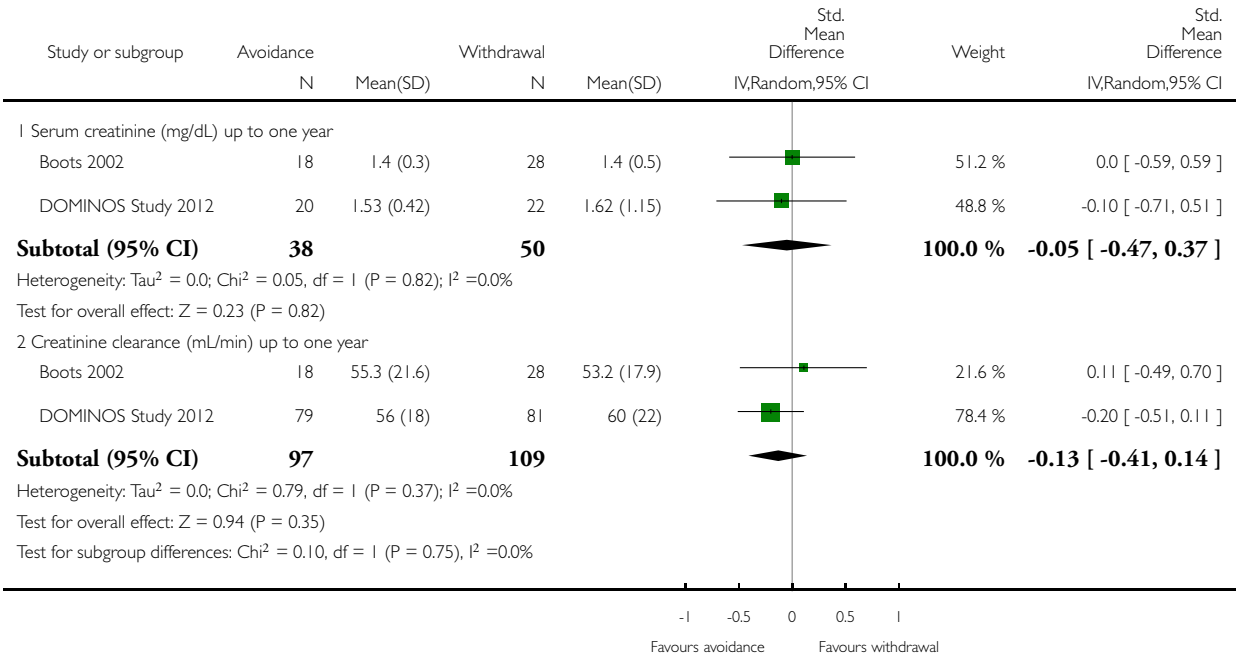


Analysis 3.4. Comparison 3 Steroid avoidance versus steroid withdrawal, Outcome 4 Kidney function.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 3 Steroid avoidance versus steroid withdrawal

Outcome: 4 Kidney function

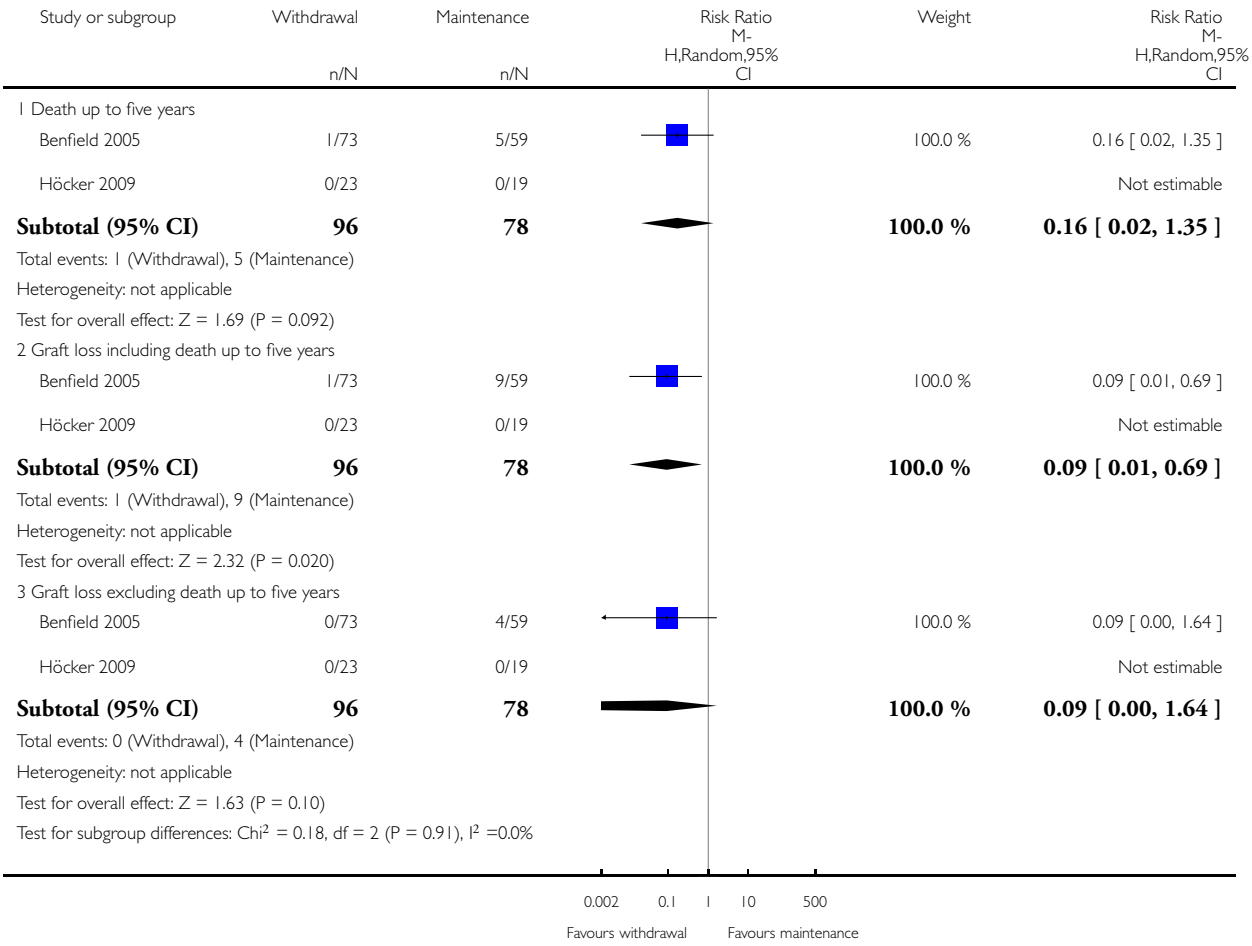


Analysis 4.1. Comparison 4 Steroid withdrawal versus maintenance in children, Outcome 1 Death and graft loss.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 4 Steroid withdrawal versus maintenance in children

Outcome: 1 Death and graft loss

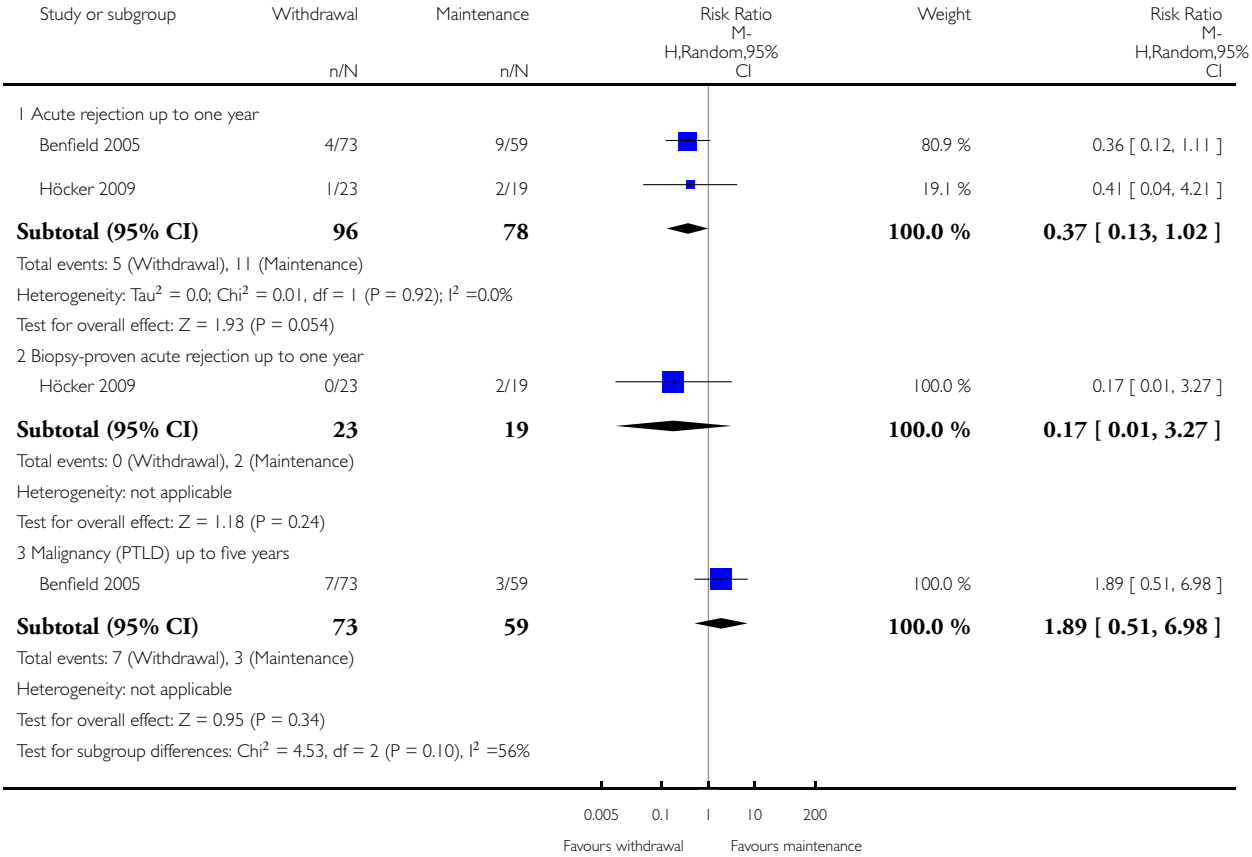


Analysis 4.2. Comparison 4 Steroid withdrawal versus maintenance in children, Outcome 2 Rejection, malignancy.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 4 Steroid withdrawal versus maintenance in children

Outcome: 2 Rejection, malignancy



Analysis 4.3. Comparison 4 Steroid withdrawal versus maintenance in children, Outcome 3 Kidney function.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 4 Steroid withdrawal versus maintenance in children

Outcome: 3 Kidney function

Study or subgroup	Withdrawal N	Mean(SD)	Maintenance N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Creatinine clearance (mL/min) up to five years						
Höcker 2009	23	95.5 (23.9792)	17	94.4 (28.4494)		1.10 [-15.60, 17.80]

Analysis 5.1. Comparison 5 Publication bias, Outcome 1 Funnel plots.

Review: Steroid avoidance or withdrawal for kidney transplant recipients

Comparison: 5 Publication bias

Outcome: 1 Funnel plots

Study or subgroup	Withdrawal n/N	Maintenance n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Death, steroid withdrawal versus maintenance					
Ahsan 1999	0/134	1/132		0.8 %	0.33 [0.01, 7.99]
Bouma 1996	0/42	1/42		0.8 %	0.33 [0.01, 7.96]
del Castillo 2005	1/70	0/72		0.3 %	3.08 [0.13, 74.46]
Isoniemi 1990	3/32	4/32		2.1 %	0.75 [0.18, 3.09]
Lebranchu 1999	4/252	8/248		4.2 %	0.49 [0.15, 1.61]
Maiorca 1988	0/35	1/31		0.8 %	0.30 [0.01, 7.02]
Matl 2000	1/45	0/42		0.3 %	2.80 [0.12, 67.00]
Pelletier 2006	1/59	0/59		0.3 %	3.00 [0.12, 72.18]
Pisani 2001	1/15	0/15		0.3 %	3.00 [0.13, 68.26]

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Study or subgroup	Withdrawal n/N	Maintenance n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
THOMAS Study 2002	3/279	6/277		3.1 %	0.50 [0.13, 1.97]
Subtotal (95% CI)	**963**	**950**		**12.8 %**	**0.70 [0.39, 1.29]**
Total events: 14 (Withdrawal), 21 (Maintenance)					
Heterogeneity: Chi^2 = 4.51, df = 9 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 1.14 (P = 0.25)					
2 Acute rejection steroid withdrawal versus maintenance					
Ahsan 1999	26/134	7/132		3.7 %	3.66 [1.65, 8.14]
Bouma 1996	11/42	1/42		0.5 %	11.00 [1.49, 81.44]
del Castillo 2005	17/70	13/72		6.6 %	1.35 [0.71, 2.56]
Isoniemi 1990	6/32	1/32		0.5 %	6.00 [0.77, 47.05]
Lebranchu 1999	76/252	52/248		27.2 %	1.44 [1.06, 1.95]
Maiorca 1988	16/35	3/31		1.6 %	4.72 [1.52, 14.69]
Matl 2000	3/45	2/42		1.1 %	1.40 [0.25, 7.97]
Pelletier 2006	3/59	3/59		1.6 %	1.00 [0.21, 4.75]
Pisani 2001	1/15	2/15		1.0 %	0.50 [0.05, 4.94]
THOMAS Study 2002	67/279	60/277		31.2 %	1.11 [0.82, 1.51]
Subtotal (95% CI)	**963**	**950**		**75.0 %**	**1.55 [1.28, 1.87]**
Total events: 226 (Withdrawal), 144 (Maintenance)					
Heterogeneity: Chi^2 = 19.74, df = 9 (P = 0.02); I^2 =54%					
Test for overall effect: Z = 4.58 (P < 0.00001)					
3 Death, steroid avoidance versus maintenance					
ATLAS Study 2005	3/151	0/147		0.3 %	6.82 [0.36, 130.81]
De Vecchi 1986	0/25	4/26		2.3 %	0.12 [0.01, 2.04]
FRANCIA Study 2007	1/98	3/103		1.5 %	0.35 [0.04, 3.31]
FREEDOM Study 2008	7/226	2/109		1.4 %	1.69 [0.36, 7.99]
Kumar 2005	0/45	0/32			Not estimable
Montagnino 2005	0/65	1/68		0.8 %	0.35 [0.01, 8.40]
Nematalla 2007	0/50	0/50			Not estimable
Nott 1985	8/59	8/58		4.2 %	0.98 [0.40, 2.44]
Schulak 1989	3/32	2/35		1.0 %	1.64 [0.29, 9.20]
Vincenti 2003a	0/40	1/43		0.8 %	0.36 [0.01, 8.54]
Subtotal (95% CI)	**791**	**671**		**12.2 %**	**0.92 [0.52, 1.63]**
Total events: 22 (Withdrawal), 21 (Maintenance)					
Heterogeneity: Chi^2 = 6.22, df = 7 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.27 (P = 0.78)					
Total (95% CI)	**2717**	**2571**		**100.0 %**	**1.36 [1.15, 1.62]**

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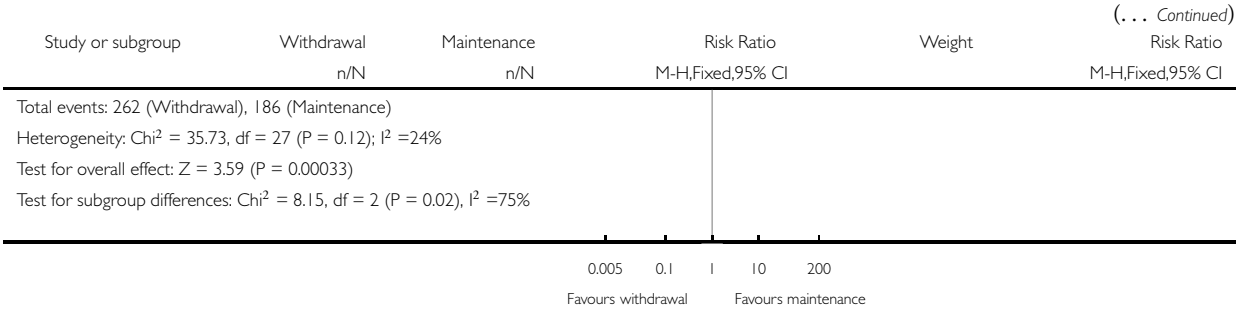

ADDITIONAL TABLES

Table 1. Steroid withdrawal versus steroid maintenance - stratified subgroup and sensitivity analysis for death, graft loss and acute rejection up to one year after transplantation

	Death			Graft loss			Acute rejection			Biopsy-proven acute rejection		
	Studies	**RR**	**95% CI**	**Studies**	**RR**	**95% CI**	**Studies**	**RR**	**95% CI**	**Studies**	**RR**	**95% CI**
Publication status												
Peer reviewed journal	8	0.60	0.31 to 1.17	7	1.25	0.73 to 2.13	8	2.02	1.23 to 3.23	4	1.32	0.66 to 2.66
Abstract only	2	3.04	0.33 to 28.29	1	0.82	0.23 to 2.94	2	1.25	0.67 to 2.32	1	1.37	0.70 to 2.69
ITT analysis												
ITT analysis used	6	0.69	0.30 to 1.61	6	1.31	0.69 to 2.46	6	2.07	1.10 to 3.91	3	1.37	0.64 to 2.94
ITT analysis not used/ unclear	4	0.67	0.25 to 1.81	2	1.00	0.46 to 2.17	4	1.65	0.81 to 3.36	2	1.04	0.24 to 4.59
Calcineurin inhibitor												
CsA	9	0.75	0.36 to 1.54	7	0.90	0.50 to 5.14	9	2.08	1.29 to 3.35	4	1.60	0.87 to 2.92

Table 1. Steroid withdrawal versus steroid maintenance - stratified subgroup and sensitivity analysis for death, graft loss and acute rejection up to one year after transplantation (*Continued*)

TAC	1	0.50	0.13 to 1.97	1	2.13	0.88 to 5.14	1	1.11	0.82 to 1.51	1	0.89	0.61 to 1.30
Antimetabolite												
MMF or EC-MPS	6	0.67	0.31 to 1.47	5	1.25	0.75 to 2.08	6	1.41	1.02 to 1.94	3	1.27	0.81 to 2.00
AZA	2	0.93	0.26 to 3.40	2	0.25	0.03 to 2.18	2	2.61	0.62 to 10.91	1	0.33	0.04 to 2.56
MMF or EC-MPS or AZA	8	0.73	0.38 to 1.43	7	1.15	0.70 to 1.89	8	1.46	1.07 to 1.98	4	1.19	0.75 to 1.90
none	2	0.31	0.03 to 2.95	1	3.00	0.13 to 71.61	2	5.80	2.16 to 15.57	1	9.00	1.19 to 67.93
Induction treatment												
Induction (yes)	2	3.00	0.32 to 27.87	1	0.33	0.01 to 8.02	2	0.80	0.22 to 2.91	NA	--	--
Induction (no)	8	0.60	0.31 to 1.17	7	1.21	0.74 to 1.99	8	1.93	1.26 to 2.94	NA	--	--

AZA - azathioprine; CI - confidence interval; CsA - cyclosporin A; EC-MPS - enteric-coated mycophenolate sodium; ITT - intention to treat; MMF - mycophenolate mofetil; NA - not available; RR - risk ratio; TAC - tacrolimus

Table 2. Steroid avoidance versus steroid maintenance - stratified subgroup and sensitivity analysis for death, graft loss and acute rejection up to one year after transplantation

	Death			**Graft loss**			**Acute rejection**			**Biopsy-proven acute rejection**		
	Studies	**RR**	**95% CI**	**Studies**	**RR**	**95% CI**	**Studies**	**RR**	**95% CI**	**Studies**	**RR**	**95% CI**
ITT analysis												
ITT analysis used	7	1.16	0.48 to 2.83	5	1.09	0.56 to 2.11	4	1.92	1.18 to 3.14	4	2.31	1.47 to 3.63

Table 2. Steroid avoidance versus steroid maintenance - stratified subgroup and sensitivity analysis for death, graft loss and acute rejection up to one year after transplantation (*Continued*)

ITT analysis not used/ unclear	3	0.51	0.07 to 3.83	2	1.11	0.46 to 2.67	3	1.24	0.97 to 1.59	2	1.05	0.49 to 2.23
Calcineurin inhibitor												
CsA	8	0.88	0.47 to 1.66	5	1.08	0.59 to 1.99	5	1.31	1.05 to 1.63	3	1.89	1.29 to 2.79
TAC	2	6.82	0.36 to 130.81	2	1.14	0.39 to 3.3	2	2.40	1.05 to 5.49	3	1.81	0.66 to 4.99
Antimetabolite												
MMF or EC-MPS	6	1.15	0.36 to 3.69	6	1.09	0.56 to 2.11	5	1.87	1.20 to 2.91	6	1.94	1.26 to 2.98
AZA	1	1.64	0.29 to 9.2	NA	--	--	NA	--	--	NA	--	--
MMF or EC-MPS or AZA	8	1.16	0.48 to 2.83	NA	--	--	NA	--	--	NA	--	--
None	2	0.51	0.07 to 3.83	1	1.11	0.46 to 2.67	2	1.26	0.95 to 1.65	NA	--	--
Induction treatment												
Induction (yes)	7	0.97	0.38 to 2.48	5	1.06	0.45 to 2.46	4	1.50	0.97 to 2.32	5	1.67	1.19 to 2.36
Induction (no)	3	0.92	0.17 to 5.01	2	1.12	0.57 to 2.2	3	1.72	0.89 to 3.32	1	3.89	2.16 to 7.03

AZA - azathioprine; CI - confidence interval; CsA - cyclosporin A; EC-MPS - enteric-coated mycophenolate sodium; ITT - intention to treat; MMF - mycophenolate mofetil; NA - not available; RR - risk ratio; TAC - tacrolimus

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. Kidney Transplantation [MESH] 2. kidney transplant* 3. 1 or 2 4. (avoid* or minim* or free* or withdraw* or spar* or discontinu* or taper* or conversion* or convert*) near25 (predniso* or corticosteroid* or steroid*) 5. 3 and 4
MEDLINE	1. Kidney Transplantation/ 2. ((avoid$ or minim$ or free$ or withdraw$ or spar$ or discontinu$ or taper$ or conversion$ or convert$) adj25 (predniso$ or corticosteroid$ or steroid$)).tw. 3. and/1-2
EMBASE	1. exp kidney transplantation/ 2. Drug Withdrawal/ 3. ((avoid$ or minim$ or free$ or withdraw$ or spar$ or discontinu$ or taper$ or conversion$ or convert$) adj25 (predniso$ or corticosteroid$ or steroid$)).tw. 4. or/2-3 5. and/1,4

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention

(*Continued*)

	group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome

(*Continued*)

	data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.

(*Continued*)

	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

WHAT'S NEW

Last assessed as up-to-date: 15 February 2016.

Date	Event	Description
15 February 2016	New search has been performed	New studies included (20)
15 February 2016	New citation required and conclusions have changed	New studies added; paediatric studies included

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 1, 2009

Date	Event	Description
14 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- MCH: performed study selection, data extraction, risk of bias assessment, data entry, data analyses and wrote the manuscript.
- AR: performed study selection, data extraction, risk of bias assessment, reviewed results and manuscript.
- EVN: performed study selection, resolved disagreement, reviewed results and manuscript and provided senior methodological support.
- JP: resolved disagreement, reviewed results and manuscript and provided senior expert support.
- ACW: resolved disagreement, reviewed results and manuscript and provided senior expert support.

DECLARATIONS OF INTEREST

- MCH: none known
- AR: none known
- EVN: none known
- JP: none known
- ACW: none known

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Internal sources

- No sources of support supplied

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the earlier version of this review (Pascual 2009), we did not specifically include CMV infection as an outcome. Recent publications include reporting of CMV infection as a specific outcome, and this has been translated to our review.

Since this review was last published (in 2009), the Cochrane risk of bias tool has been updated, and the current tool has been used in assessments for this update.

INDEX TERMS

Medical Subject Headings (MeSH)

Graft Rejection [immunology; *prevention & control]; Graft Survival [drug effects; immunology]; Immunosuppression; Immunosuppressive Agents [*administration & dosage; adverse effects]; Kidney Transplantation [*immunology; mortality]; Randomized Controlled Trials as Topic; Steroids [*administration & dosage; adverse effects]

MeSH check words

Humans