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[Intervention Review]

Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients

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ABSTRACT

Background

Modern immunosuppressive regimens after kidney transplantation usually use a combination of two or three agents of different classes to prevent rejection and maintain graft function. Most frequently, calcineurin-inhibitors (CNI) are combined with corticosteroids and a proliferation-inhibitor, either azathioprine (AZA) or mycophenolic acid (MPA). MPA has largely replaced AZA as a first line agent in primary immunosuppression, as MPA is believed to be of stronger immunosuppressive potency than AZA. However, treatment with MPA is more costly, which calls for a comprehensive assessment of the comparative effects of the two drugs.

Objectives

This review of randomised controlled trials (RCTs) aimed to look at the benefits and harms of MPA versus AZA in primary immunosuppressive regimens after kidney transplantation. Both agents were compared regarding their efficacy for maintaining graft and patient survival, prevention of acute rejection, maintaining graft function, and their safety, including infections, malignancies and other adverse events. Furthermore, we investigated potential effect modifiers, such as transplantation era and the concomitant immunosuppressive regimen in detail.

Search methods

We searched Cochrane Kidney and Transplant's Specialised Register (to 21 September 2015) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

All RCTs about MPA versus AZA in primary immunosuppression after kidney transplantation were included, without restriction on language or publication type.

Data collection and analysis

Two authors independently determined study eligibility, assessed risk of bias and extracted data from each study. Statistical analyses were performed using the random-effects model and the results were expressed as risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes with 95% confidence intervals (CI).

Main results

We included 23 studies (94 reports) that involved 3301 participants. All studies tested mycophenolate mofetil (MMF), an MPA, and 22 studies reported at least one outcome relevant for this review. Assessment of methodological quality indicated that important information on factors used to judge susceptibility for bias was infrequently and inconsistently reported.

MMF treatment reduced the risk for graft loss including death (RR 0.82, 95% CI 0.67 to 1.0) and for death-censored graft loss (RR 0.78, 95% CI 0.62 to 0.99, P < 0.05). No statistically significant difference for MMF versus AZA treatment was found for all-cause mortality (16 studies, 2987 participants: RR 0.95, 95% CI 0.70 to 1.29). The risk for any acute rejection (22 studies, 3301 participants: RR 0.65, 95% CI 0.57 to 0.73, P < 0.01), biopsy-proven acute rejection (12 studies, 2696 participants: RR 0.59, 95% CI 0.52 to 0.68) and antibody-treated acute rejection (15 studies, 2914 participants: RR 0.48, 95% CI 0.36 to 0.65, P < 0.01) were reduced in MMF treated patients. Meta-regression analyses suggested that the magnitude of risk reduction of acute rejection may be dependent on the control rate (relative risk reduction (RRR) 0.34, 95% CI 0.10 to 1.09, P = 0.08), AZA dose (RRR 1.01, 95% CI 1.00 to 1.01, P = 0.10) and the use of cyclosporin A micro-emulsion (RRR 1.27, 95% CI 0.98 to 1.65, P = 0.07). Pooled analyses failed to show a significant and meaningful difference between MMF and AZA in kidney function measures.

Data on malignancies and infections were sparse, except for cytomegalovirus (CMV) infections. The risk for CMV viraemia/syndrome (13 studies, 2880 participants: RR 1.06, 95% CI 0.85 to 1.32) was not statistically significantly different between MMF and AZA treated patients, whereas the likelihood of tissue-invasive CMV disease was greater with MMF therapy (7 studies, 1510 participants: RR 1.70, 95% CI 1.10 to 2.61). Adverse event profiles varied: gastrointestinal symptoms were more likely in MMF treated patients and thrombocytopenia and elevated liver enzymes were more common in AZA treatment.

Authors' conclusions

MMF was superior to AZA for improvement of graft survival and prevention of acute rejection after kidney transplantation. These benefits must be weighed against potential harms such as tissue-invasive CMV disease. However, assessment of the evidence on safety outcomes was limited due to rare events in the observation periods of the studies (e.g. malignancies) and inconsistent reporting and definitions (e.g. infections, adverse events). Thus, balancing benefits and harms of the two drugs remains a major task of the transplant physician to decide which agent the individual patient should be started on.

PLAIN LANGUAGE SUMMARY

Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients

After kidney transplantation, patients receive a combination of immunosuppressive medications to prevent rejection of the transplanted kidney. These regimens usually contain a calcineurin-inhibitor (tacrolimus or cyclosporin A), corticosteroids and an antiproliferative agent (mycophenolic acid (MPA), e.g. mycophenolate mofetil (MMF), or azathioprine (AZA)). MPA is considered to be of stronger immunosuppressive potency than AZA, but the benefits on survival of the graft and its safe use over a long period of time are insufficiently understood.

In this systematic review, we compared the efficacy and safety of MPA versus AZA in randomised controlled trials (RCTs) when given as part of the immunosuppressive regimen immediately after kidney transplantation.

Searches to 21 September 2015 identified 23 studies in which 3301 patients were treated with MPA (all studies used MMF) or AZA. Methodological quality of the studies was limited, e.g. only in two RCTs was the study medication administered in a blinded fashion.

MMF was more effective than AZA for reducing the risk of graft loss (by approximately 20%) and acute rejection (by approximately 30%). No difference in mortality was observed. Moreover, graft function appeared to be similar in both treatments.

When drugs are given to suppress the immune system, this can result in serious side effects such as infections and malignancies. The data on adverse events was limited by relatively short follow up in the studies as some of these side effects occur after several years of treatment. Furthermore, the studies did not focus on these harms and did not use harmonised diagnostic criteria. The incidence of cytomegalovirus infections did not differ between MMF and AZA, but there was a 1.7-fold increased risk for the more severe, tissue-invasive cytomegalovirus disease in MMF-treated patients. Information on malignancies was reported only in five studies; therefore no robust conclusions can be drawn. Gastrointestinal side effects (e.g. nausea, diarrhoea) were more common with MMF-treatment, whereas bone marrow suppression (e.g. thrombocytopenia) and elevated liver enzymes were observed more frequently in AZA treated patients.

In general, evidence for efficacy outcomes is of high quality and can be seen as considerably robust, but there is less certainty on aspects of safety. Therefore, caregivers should balance potential benefits and harms of MMF and AZA according to individual patient's risks and preferences. Physicians need to individualise the decision between these agents as components of the immunosuppressive regimen.

Summary of findings for the main comparison. Mycophenolate mofetil (MMF) versus azathioprine (AZA) for primary immunosuppression in kidney transplant recipients

MMF compared to AZA for primary immunosuppression in kidney transplant recipients

Patient or population: patients with kidney transplant recipients
Settings: primary immunosuppressive regimens (RCTs)
Intervention: MMF
Comparison: AZA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	AZA	MMF				
Death, all cause Follow-up: 0.5 to 5 years	**49 per 1000**	**47 per 1000** (34 to 63)	**RR 0.95** (0.7 to 1.29)	2987 (16)	⊕⊕⊕⊖ **moderate** [1]	No evidence for difference due to low precision
Graft loss, censored for death Follow-up: 0.5 to 6 years	**11 per 100**	**9 per 100** (7 to 11)	**RR 0.78** (0.61 to 0.98)	2540 (17)	⊕⊕⊕⊕ **high** [2]	Statistically significant risk reduction of meaningful magnitude (˜20%) with MMF treatment
Malignancy, any Follow-up: 1 to 6 years	**10 per 100**	**8 per 100** (6 to 11)	**RR 0.81** (0.6 to 1.09)	1735 (5)	⊕⊖⊖⊖ **very low** [3,4,5]	Statistically not significant favourable point estimate (˜20%) with MMF treatment, but very low quality evidence
Acute rejection, steroid resistant/antibody treated As reported in the articles Follow-up: 0.5 to 3 years	**11 per 100**	**5 per 100** (4 to 7)	**RR 0.48** (0.36 to 0.65)	2914 (15)	⊕⊕⊕⊕ **high**	Statistically significant risk reduction of meaningful magnitude (˜50%) with MMF treatment
Infection, CMV tissue invasive As reported in the articles Follow-up: 0.5 to 3 years	**4 per 100**	**7 per 100** (5 to 11)	**RR 1.7** (1.1 to 2.61)	1510 (7)	⊕⊕⊕⊕ **high** [3,6]	Statistically significantly increased risk of meaningful magnitude (1.7 fold) with MMF treatment
Acute rejection, total Any treated acute rejection, including biopsy-proven Follow-up: 0.5 to 5 years	**35 per 100**	**23 per 100** (20 to 26)	**RR 0.65** (0.57 to 0.73)	3301 (22)	⊕⊕⊕⊕ **high**	Statistically significant risk reduction of meaningful magnitude (˜35%) with MMF treatment

Chronic allograft nephropathy Biopsy required in 2 RCTs, one study with optional biopsy Follow-up: 1 to 6 years	**36 per 100**	**25 per 100** (17 to 36)	**RR 0.69** (0.48 to 0.99)	203 (3)	⊕⊕⊝⊝ **low** [3,4]	Statistically significant risk reduction of meaningful magnitude (30%) with MMF treatment, but low quality evidence due to sparse data

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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

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.

AZA - azathioprine; CMV - cytomegalovirus; MMF - mycophenolate mofetil; RCT - randomised controlled trial
[1] Insufficient statistical power to detect a small effect of either treatment on the outcome
[2] Large beneficial effect of MMF treatment
[3] Considerable risk of reporting bias as data were provided by a limited number of studies only
[4] Study populations in which the outcome were reported are a subset not representative for patients enrolled in all trials identified for the review
[5] Insufficient statistical power due to sparse data on a potential beneficial effect on the incidence of malignancies with MMF treatment
[6] Substantial harm caused by MMF

BACKGROUND

Description of the condition

While there are several immunosuppressive drugs available, usually a combination of two or three agents of different classes is used to prevent rejection and maintain graft function after kidney transplantation. In most regimens, calcineurin inhibitors (CNI) (cyclosporin A (CsA) or tacrolimus (Tac)), form the cornerstone of treatment and are combined with corticosteroids and a proliferation-inhibitor with its representatives azathioprine (AZA) and mycophenolic acid (MPA). There are currently two formulations available for MPA, mycophenolate mofetil (MMF) and the more recently approved enteric-coated mycophenolate sodium (ec-MPS) (Hardinger 2013; Marcen 2009)

Description of the intervention

MMF was approved by the US Food and Drug Administration (FDA) in 1995 for the prevention of acute rejection in kidney transplant recipients. This was based on the results of three randomised controlled trials (RCT), the pivotal trials, where a total of 1493 patients in North America, Europe and Australia were enrolled. MMF was compared to AZA (MMF TRI Study 1996; MMF US Study 1995) or placebo (European MMF Study Group 1995) in a regimen with concomitant use of CsA (original formulation) and steroids. In all three studies, MMF showed superior ability to prevent acute rejection within the first six months after transplantation.

In the past decade, MPA was tested against AZA in various immunosuppressive regimens in kidney transplantation as a variety of new drugs have been developed, including mammalian target of rapamycin (mTOR) inhibitors (Webster 2006), Tac and a micro-emulsion formulation of CsA (CsA-ME) (Webster 2005).

How the intervention might work

Both proliferation inhibitors, MPA and AZA, reduce purine synthesis either through direct inhibition of the cell cycle (AZA) or on the level of nucleotide synthesis (MPA) (Staatz 2007). AZA was one of the first drugs used for immunosuppression in kidney transplantation in the 1960s (Mowbray 1965). Following the results of the pivotal trials, AZA was widely replaced by MPA, particularly MMF, as a component of primary immunosuppressive regimens in most of the developed countries (Halloran 2004; Hardinger 2013), since acute rejection has been shown to be a strong predictor for diminished graft function and reduced graft survival (Pascual 2002).

Why it is important to do this review

Despite MMF being considered to be more effective than AZA in the prevention of acute rejection, its superior effect on long-term graft function and graft survival has not been shown in RCTs (Srinivas 2005). Instead, similar kidney function and graft survival was found in long-term follow-up data of two of the pivotal trials (MMF TRI Study 1996; MMF US Study 1995). The lack of statistical power within the single studies is a crucial aspect that needs to be considered for this phenomenon. Calculations have shown that a sample size of 8 to 10 times the number actually enrolled in the pivotal trials would have been needed to prove a benefit on graft survival (Ekberg 2003). Meta-analyses are the tool of choice to address the limitation of under-powered studies.

Observational evidence also highlighted that the use of considerably strong immunosuppressive regimens in recent years has led to acute rejection rates as low as 10% to 15%, sometimes even lower; but that this reduced acute rejection rate has not translated into similar prolongation of long-term graft survival (Tantravahi 2007). This may be due to side effects directly related to the level of immunosuppression, such as (opportunistic) infections (e.g. Polyoma BK/JC virus or cytomegalovirus (CMV) (Marcen 2009; Staatz 2007) and malignancies (Domhan 2009; Johnston 2010). These complications not only impact patient survival. For example, MMF was reported to be associated with the incidence of the very rare but life threatening progressive multifocal leukoencephalopathy which is caused by JC-virus activation (FDA 2008). In addition, these complications have been shown to directly impair graft function, e.g. polyomavirus-associated nephropathy (PVAN). Finally, one of the major causes for death in patients with a functioning graft is cardiovascular disease (CVD) (Israni 2010). Side effects of immunosuppressive agents, particularly CNI and mTOR-inhibitors, further aggravate classical CVD risk factors, such as hypertension, diabetes and dyslipidaemia (Webster 2005; Webster 2006).

Aside from safety issues due to the general level of immunosuppression, specific adverse events vary for both proliferation-inhibitors. AZA often provokes leucopenia and may increase the risk of cancer through accumulation of mutagenic metabolites (Domhan 2009). MPA causes more gastrointestinal problems like nausea and diarrhoea and is also contraindicated in pregnancy because of negative effects on foetal development (Sifontis 2006).

The relative efficacy of MMF versus AZA in the prevention of rejection and their impact on long-term graft survival might also be modulated by the concomitant immunosuppressive therapy and by the overall level of modern transplant therapy. The MYSS Study 2004 compared both drugs in a CsA-ME based regimen and showed similar acute rejection rates, graft function and survival in both groups up to seven years of follow-up.

OBJECTIVES

This review of RCTs aimed to look at the benefits and harms of MPA versus AZA in primary immunosuppressive regimens after kidney transplantation. Both agents were compared regarding their efficacy for maintaining graft and patient survival, prevention of acute rejection, maintaining graft function, and their safety, including infections, malignancies and other adverse events. Furthermore, we investigated potential effect modifiers, such as transplantation era and the concomitant immunosuppressive regimen in detail.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs and quasi-RCTs (RCTs in which allocation to treatment was performed by somewhat predictable methods) looking at the direct comparison of MPA versus AZA in primary immunosuppressive regimens in kidney transplantation, without restriction on language or publication type.

Types of participants

Inclusion criteria

We included studies investigating children (< 18 years) and adult kidney transplant recipients with any duration of follow-up in the review, regardless of donor type (living or deceased) or previous transplantation status.

Exclusion criteria

We excluded studies that involved multi-organ transplantation (e.g. kidney-pancreas, kidney-liver) as well as studies in which the intervention was performed in secondary regimens (when the immunosuppressive therapy was changed due to acute rejection, chronic allograft nephropathy (CAN), CNI toxicity or in stable graft function status).

Types of interventions

We included studies in the review in which MPA, namely MMF or ec-MPS, was tested against AZA in primary immunosuppressive regimens along with any concomitant immunosuppressive therapy (e.g. use of induction antibody treatment, any formulation of CNI (CsA original formulation, CsA-ME, Tac), various CNI target levels, treatment with or without steroids or mTOR inhibitors). Concomitant immunosuppression regimens needed to be identical in both the intervention and control groups (e.g. studies investigating MMF/CsA versus AZA/Tac were excluded).

Types of outcome measures

Primary outcomes

Graft loss and all-cause mortality were considered primary outcomes of interest in terms of efficacy and safety, respectively.

Secondary outcomes

Secondary outcomes were acute rejection, CAN, graft function measures (e.g. serum creatinine (SCr), creatinine clearance (CrCl), proteinuria), immunosuppression related (malignancies, infections) and drug specific (e.g. new onset diabetes after transplantation (NODAT), haematological disorders, such as leucopenia, anaemia, elevated liver enzymes) side effects.

Following the suggestions of the GRADE working group (Atkins 2004) we classified outcomes of interest according to clinical importance (critical – high – moderate).

Critical importance

- Death and death with a functioning graft
- Graft loss, and graft loss censored for death
- Malignancies (except non-melanoma skin cancer).

High importance

- Acute rejection, biopsy-confirmed acute rejection, and steroid resistant/antibody-treated acute rejection
- CAN
- Infections of any type, including CMV infection, tissue invasive CMV disease, PVAN
- Non-melanoma skin cancer.

Moderate importance

- Kidney function measures: absolute values of measured glomerular filtration rate (GFR), estimated GFR, CrCl, SCr, and proteinuria (in any measurement and metric)
- Adverse events, including hypertension, hyperlipidaemia, NODAT, leucopenia, anaemia, nausea, diarrhoea, elevation of liver enzymes or bilirubin.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register (to 21 September 2015) through contact with the Trials' Search Co-ordinator using search terms relevant to this review (Appendix 1). The Specialised Register contains studies identified from the following sources.

1. Quarterly 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 and transplant 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 the Cochrane Kidney and Transplant.

Searching other resources

We also checked the reference lists of nephrology textbooks, review articles, and identified studies for this review. In particular, we reconciled the studies included in previous systematic reviews addressing MMF versus AZA (Knight 2009; Wang 2004a; Wang 2004b; Wang 2005; Zhang 2004).

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts potentially relevant to the review. All titles and abstracts were screened by at least two authors. Studies not applicable to the review were discarded. Those references that might include relevant data or information on studies were retrieved in full text and the described authors determined if the studies satisfied the inclusion criteria.

Data extraction and management

All articles of eligible studies were retrieved in full text and data relevant for the review were extracted into standardized forms in duplicate independently by two authors.

- Data about study design, inclusion and exclusion criteria, items of quality assessment, definitions of primary and

secondary study endpoints, etc. were extracted into an Excel file. Information from multiple publications of the same study were reconciled and condensed accordingly
- Data on outcomes of interest were extracted in a separate Excel file. Results for dichotomous outcomes were extracted as actual numbers of patients achieving the respective outcome. If only proportions were reported in the studies, we calculated the numbers based on intention-to-treat (ITT) population or on-treatment population as specified in the article.
- Studies reported in non-English language were translatedand data were assessed respectively

Disagreements were resolved via discussion among authors. All data were entered into Review Manager 5 and checked twice.

Assessment of risk of bias in included studies

The following items were assessed 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

Dichotomous outcome results (e.g. death, graft loss, acute rejection) are expressed as risk ratio (RR) with 95% confidence intervals (CI). For treatment effects on continuous scales of measurement (e.g. SCr, CrCl, GFR), the mean difference (MD) was used. The proportion of events per treatment arm at the desired time-points were extracted from Kaplan Meier curve graphs using planimetric (digitising) software, such as the Engauge Digitizer program (http://digitizer.sourceforge.net/), assuming no censoring. The mean and the standard error (SE)/standard deviation (SD) of continuous outcomes were assessed at the respective time-points along with the number of patients at risk for the given outcome. If the SD was missing for continuous outcomes, it was imputed based on the median SD of studies in which the relevant outcome was reported.

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 was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as ITT, as-treated and per-protocol population was 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 information about covariates that were further investigated in meta-regression analyses (see below) was missing, we imputed the year of transplantation from the year of first publication minus duration of follow-up minus two years, to account for lag between study completion and publication. If the AZA dose was reported to be body-weight-adjusted (mg/kg/d) it was transformed into mg/d using the mean body weight as reported in the study, and by using 70 kg (60 kg in exclusively Asian populations) if information on body weight was missing. Looking at the year of transplantation, it was likely that the original oil-based formulation of CsA was used in many studies not providing detailed information on which kind of CsA drug was tested, and thus CsA original formulation and studies without this information were grouped and compared to studies reporting the use of CsA-ME. Studies in which more than one MMF dose was tested, i.e. 3 g versus 2 g (MMF TRI Study 1996; MMF US Study 1995), 2 g versus 1.5 g (Ling 1998) and 2 g versus 1 g (Mendez 1998), were split into two independent studies and each compared to half of the group and events of the patients treated with AZA. In the case of uneven numbers, the nearest integer was used.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity. Considerable clinical heterogeneity was assumed due to a multitude of concomitant immunosuppressive regimens in studies of a long era of kidney transplantation, and over a variety of different study populations and clinical settings.

Assessment of reporting biases

We planned to construct funnel plots to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Review Manager 5 was used for all meta-analyses, using Der Simonian and Laird random-effects models by default because of clinical heterogeneity rather than fixed-effects models although we frequently found no evidence for statistical heterogeneity. Summary results, i.e. RR and MD, are presented in forest-plots according to subgroups of clinically relevant time intervals (≤ 6 months, 6 to 12 months or ≤ 1 year, 1 to 4 years, ≥ 4 years). Moreover, a subgroup longest duration of follow-up was defined that included data on the longest time interval of each study for the primary study population, i.e. we used six months data provided for the entire study population, rather than 24 months data of only a subgroup of the original study. These study data were further used for meta-regression analyses (adjusted for duration of follow-up, see below).

Subgroup analysis and investigation of heterogeneity

Meta-regression

We performed random effects meta-regression analyses (Meta-Analyst for Windows *7*, version December 2013, Brown University, Providence, RI, USA; Wallace 2009) to explore possible sources of heterogeneity on the following outcomes: mortality, death-censored graft loss, malignancy (any), acute rejection (any), CMV viraemia/syndrome, tissue-invasive CMV disease, SCr, diarrhoea and leucopenia. The logarithmic form of the RR was analysed and back-transformed regression coefficients are presented as relative risk ratio (RRR) with 95% CI. For continuous outcomes, the MD was

modelled and the coefficient with 95% CI is displayed in the table. Furthermore, bubble plots with the size of the bubble reflecting weight of the study in the meta-regression, visualise the direction of the association between the covariate and the logarithmic RR of MMF versus AZA. Tested covariates included study level factors (year of transplantation, donor type, previous transplantation, dose of the study drugs, antibody induction therapy, maintenance CNI (Tac versus CsA), CsA formulation) and items of study quality and risk of bias (blinding, publication type, industry funding).

The fact that we tested a multitude of factors on a variety of outcomes on a dataset with limited sample size (22 studies) provided a high chance that associations were found or even missed only by chance. Our primary interest was the direction of any effect modification rather than the magnitude of the relative effect. Therefore, and also with our concern about type II error, we have used a threshold of $P \leq 0.10$ and presented these results in the respective sections (and highlighted these results accordingly in the table).

Subgroup analyses

To further investigate heterogeneity, subgroup analyses were performed (using Review Manager 5) on the following strata: RCT versus quasi-RCT, inclusion of children, ITT analysis, publication type and source of funding.

Sensitivity analysis

Sensitivity analyses (performed in Meta-Analyst) were used to test the robustness of findings. Results from studies were sequentially included or excluded from the analysis with a particular focus on the largest or most dominant studies.

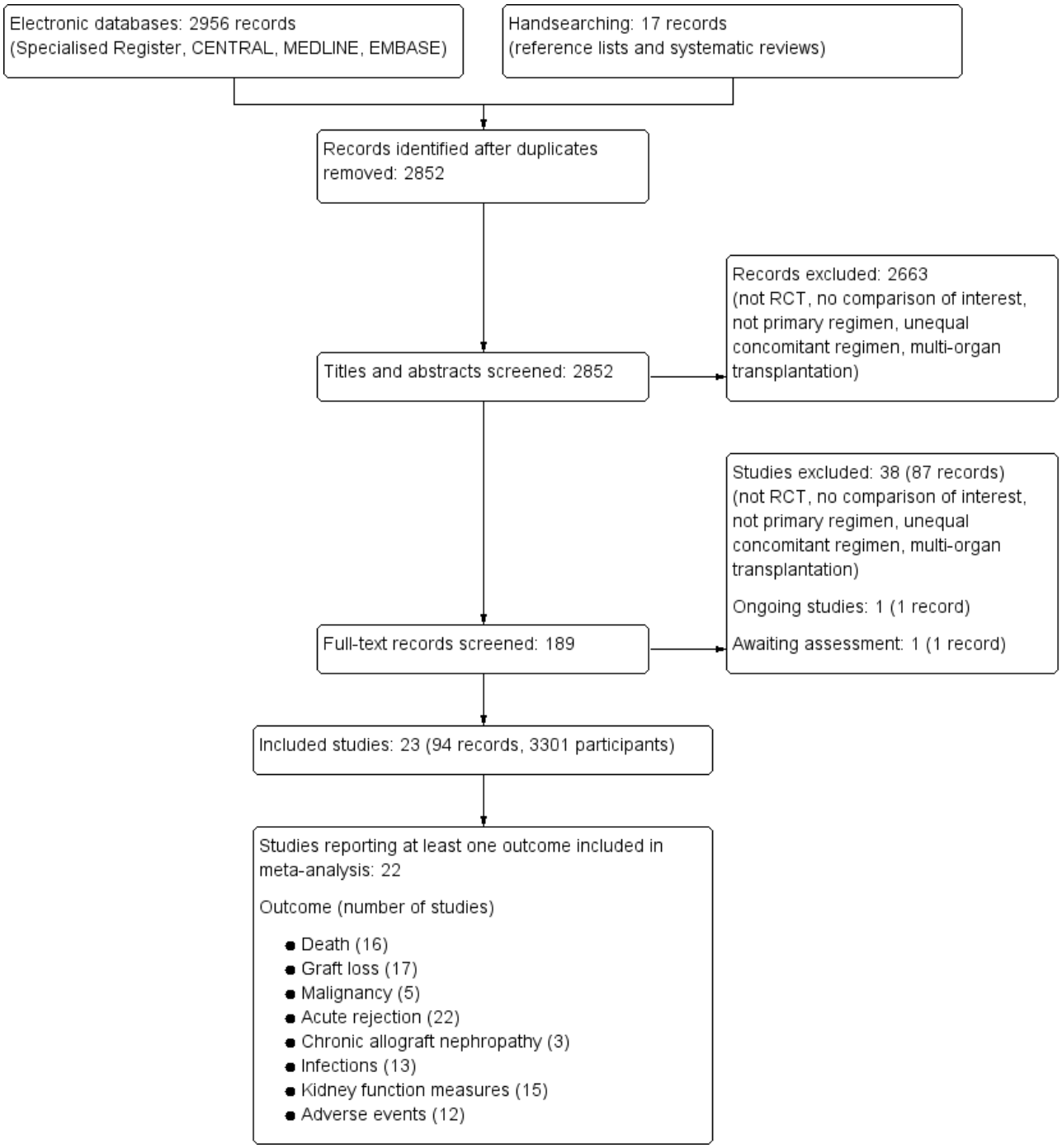
RESULTS

Description of studies

Results of the search

The literature search yielded a total of 2852 citations (Figure 1), including handsearching of the reference lists of included studies and previously published systematic reviews on MMF versus AZA in kidney transplantation. Notably, the reference lists of two Chinese systematic reviews about MMF versus AZA (Wang 2004a; Wang 2004b; Wang 2005; Zhang 2004) were reconciled with the search results of the current review which led to the addition of two eligible studies not identified by the electronic searches.

Figure 1. Literature search and identification of studies



In total, 94 reports of 23 studies (Army Hospital 2002; Baltar 2002; Busque 2001; COSTAMP Study 2002; Egfjord 1999; Folkmane 2001; Isbel 1997; Ji 2001; Joh 2005; Johnson 2000; Keven 2003; Ling 1998; Merville 2004; Miladipour 2002; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Sun 2002b; Tuncer 2002; Weimer 2002) enrolling 3301 patients were included (see Characteristics of included studies). In addition, one ongoing Italian study that aims to investigate MMF versus AZA as sole immunosuppressive treatment after antibody (IL-2, ATG) induction and CsA-ME based regimen for one year, was identified (ATHENA Study 2012, see Characteristics of ongoing studies). While 15 studies were reported at least once as full article in a peer reviewed journal (Baltar 2002; COSTAMP Study 2002; Ji 2001; Joh 2005; Johnson 2000; Keven 2003; Merville 2004; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Sun 2002b; Tuncer 2002; Weimer 2002), five studies (Busque 2001; Folkmane 2001; Miladipour 2002; Suhail 2000; Tuncer 2002) were published in *Transplantation Proceedings* only, and three studies (Army Hospital 2002; Egfjord 1999; Isbel 1997) were presented solely as conference abstracts. Nineteen studies published at least one article in English, three studies were published exclusively in Chinese (Ji 2001; Ling 1998; Sun 2002b) and one study was in

Spanish language (Baltar 2002). Of the identified 23 studies, one (Isbel 1997) did not provide any information on outcomes relevant for the review.

Prior to publication an additional report was identified (Do 2001a). This appears to be a report of Joh 2005. Details will be assessed in a future update of this review

Included studies

All studies investigated MMF versus AZA, whereas no study used ec-MPS. Doses of study drugs were reported in 19 studies (Busque 2001; COSTAMP Study 2002; Egfjord 1999; Folkmane 2001; Ji 2001; Joh 2005; Johnson 2000; Keven 2003; Ling 1998; Merville 2004; Miladipour 2002; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Sun 2002b; Tuncer 2002) and ranged from 1 to 3 g/d for MMF, and 50 to 175 mg/d for AZA. Patients were enrolled in the studies between 1992 and 2002 and 78% (2575 participants) were studied in nine multicentre studies (Busque 2001; COSTAMP Study 2002; Johnson 2000; Merville 2004; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002).

Participants

In 14 studies (Baltar 2002; Busque 2001; Egfjord 1999; Folkmane 2001; Ji 2001; Joh 2005; Johnson 2000; Ling 1998; Merville 2004; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Suhail 2000), only deceased donor transplantation was performed; one study exclusively investigated living donor transplantation (Army Hospital 2002); five studies included both deceased and living (COSTAMP Study 2002; Keven 2003; Sadek 2002; Tuncer 2002; Weimer 2002); and three studies did not report the type of graft donation (Isbel 1997; Miladipour 2002; Sun 2002b). Two studies included children (Johnson 2000; Mendez 1998), eight exclusively enrolled adult recipients (Busque 2001; COSTAMP Study 2002; Keven 2003; Merville 2004; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002) and no information was provided in the remaining 13 studies (Army Hospital 2002; Baltar 2002; Egfjord 1999; Folkmane 2001; Isbel 1997; Ji 2001; Joh 2005; Ling 1998; Miladipour 2002; Suhail 2000; Sun 2002b; Tuncer 2002; Weimer 2002). The inclusion of patients that previously lost a kidney graft and the values of panel reactive antibodies (PRA) are widely considered measures of baseline immunological risk of the study population; however, this information was limited in the studies.

Patients with previous kidney transplants were included in seven studies (COSTAMP Study 2002; Egfjord 1999; Folkmane 2001; Miladipour 2002; Mendez 1998; MMF TRI Study 1996; Weimer 2002) (ranging from 5.3% to 14.3% of participants), excluded in 10 studies (Army Hospital 2002; Baltar 2002; Busque 2001; Johnson 2000; Merville 2004; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Tuncer 2002), and not reported in six studies (Isbel 1997; Ji 2001; Joh 2005; Keven 2003; Ling 1998; Sun 2002b). In only eight studies (Ji 2001; Joh 2005; Johnson 2000; Merville 2004; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; Weimer 2002), information about PRA was provided, however this information was not described consistently (e.g. as proportion above a certain cut-off (> 10% or > 20%), or maximum PRA level). Overall, most studies enrolled patients with considerably low to moderate immunological risk.

Concomitant Immunosuppression

A depleting antibody induction therapy (ATG, ALG or OKT3) was used in five studies (Egfjord 1999; Ji 2001; Merville 2004; Mendez 1998; MMF US Study 1995) as initiating immunosuppressive agent in all patients. This therapy was only used in a subset of patients in five studies (e.g. those with higher immunological baseline risk, or patients experiencing delayed graft function) (Busque 2001; Johnson 2000; Keven 2003; Tuncer 2002; Weimer 2002). The remaining 13 studies (Army Hospital 2002; Baltar 2002; COSTAMP Study 2002; Folkmane 2001; Isbel 1997; Joh 2005; Ling 1998; Miladipour 2002; MMF TRI Study 1996; MYSS Study 2004; Sadek 2002; Suhail 2000; Sun 2002b) did not use any antibody induction therapy. All maintenance immunosuppressive regimens were CNI based, while 18 studies used CsA (Army Hospital 2002; Baltar 2002; Egfjord 1999; Folkmane 2001; Isbel 1997; Ji 2001; Joh 2005; Ling 1998; Merville 2004; Miladipour 2002; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Sun 2002b; Tuncer 2002; Weimer 2002), four studies used Tac (Busque 2001; COSTAMP Study 2002; Johnson 2000; Mendez 1998) and one study (Keven 2003) reported the use of either CsA or Tac. Of those using CsA, six studies (Egfjord 1999; Merville 2004; MYSS Study 2004; Sadek 2002; Suhail 2000; Weimer 2002) reported treatment with CsA-ME, two studies (MMF TRI Study 1996; MMF US Study 1995) clearly stated the use of the original CsA solution, one study used both CsA and CsA-ME (Tuncer 2002), and 10 studies (Army Hospital 2002; Baltar 2002; Folkmane 2001; Isbel 1997; Ji 2001; Joh 2005; Keven 2003; Ling 1998; Miladipour 2002; Sun 2002b) did not clearly specify the CsA formulation.

Target CNI trough levels were reported for all four studies using Tac (C_0 levels at month 3: 5 to 15 ng/mL), but in only six studies using CsA (C_0levels at month 3: 100 to 500 ng/mL) (Folkmane 2001; Ji 2001; Ling 1998; Merville 2004; MYSS Study 2004; Sadek 2002). Two CsA studies reported the dosage of CsA as being delivered “according to local practice” (MMF TRI Study 1996; MMF US Study 1995) and no information was provided in 11 studies (Army Hospital 2002; Baltar 2002; Egfjord 1999; Isbel 1997; Joh 2005; Keven 2003; Miladipour 2002; Suhail 2000; Sun 2002b; Tuncer 2002; Weimer 2002). Corticosteroids completed the concomitant immunosuppressive regimen in all studies, while in one study (MYSS Study 2004) steroid therapy was withdrawn according to protocol. Notably, IL-2 receptor antibody induction or mTOR-inhibitor therapy was not used in the studies identified for the review.

Excluded studies

A total of 87 records (38 studies) were excluded as they did not fulfil the inclusion criteria (see Characteristics of excluded studies). The reasons for exclusion were as follows.

- Study design not RCT or quasi-RCT (nine studies)
- Not solely kidney transplantation (two studies); studies enrolling patients undergoing multiorgan transplantation, e.g. simultaneous kidney-pancreas transplantation were excluded.
- Not primary immunosuppressive regimen (18 studies), i.e. the randomisation to MPA versus AZA was not performed at the time of transplantation, but subsequently during the maintenance phase (e.g. due to previous acute rejection, CAN, CNI-toxicity or in stable graft function status)

- Randomised intervention not of interest for the review (eight studies), i.e. not MPA versus AZA
- Unequal concomitant regimen (four studies), i.e. different immunosuppressive regimens were administered to patients randomised to treatment and control group (e.g. MMF/CsA versus AZA/Tac.

Risk of bias in included studies

Details of the risk of bias assessment tool (Appendix 2) can be found for each study in Characteristics of included studies and are displayed in Figure 2, Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

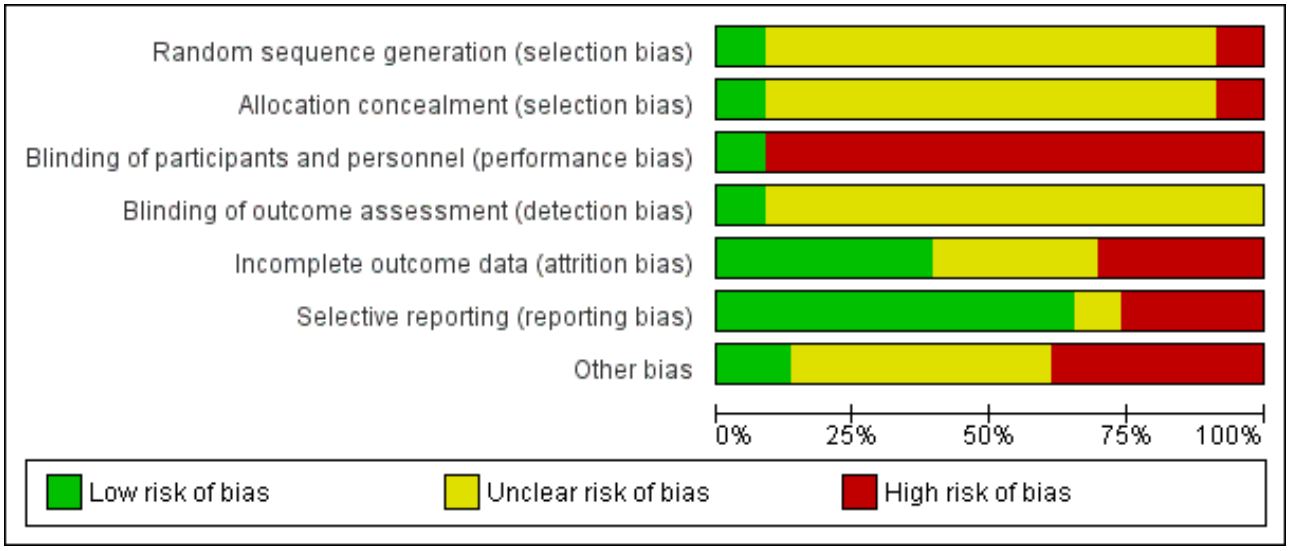


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

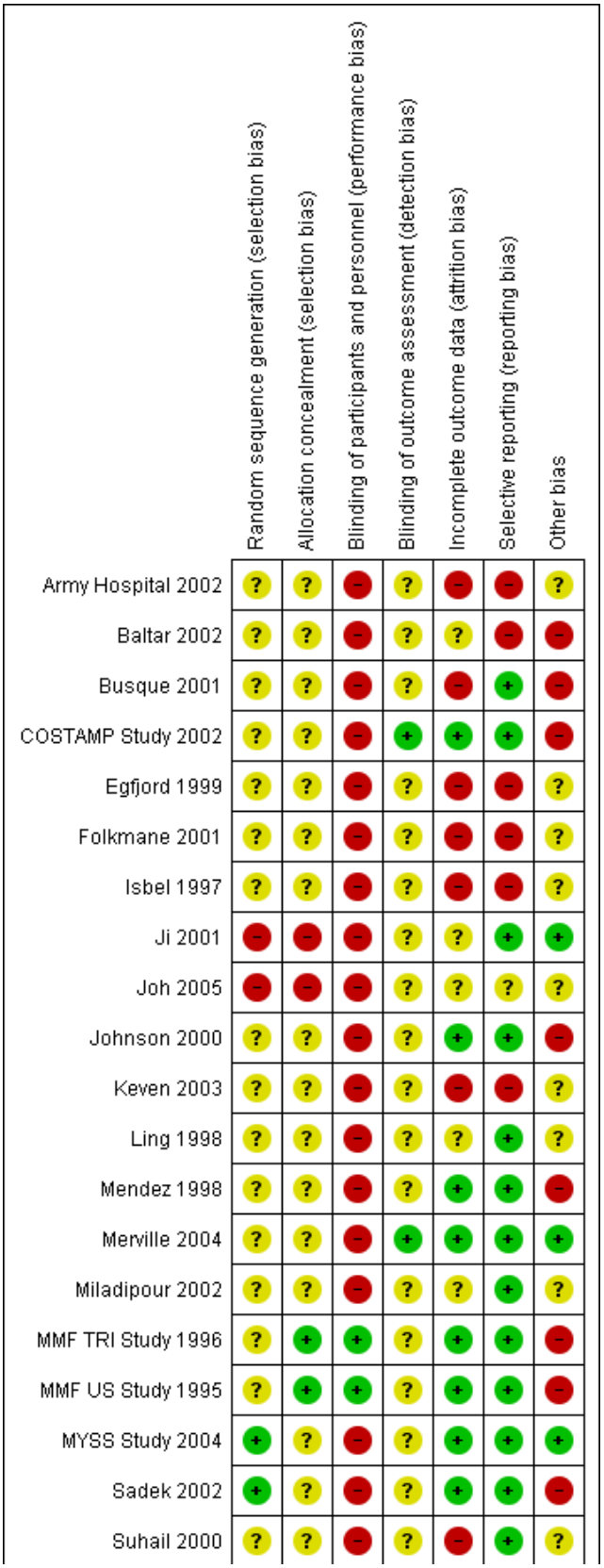
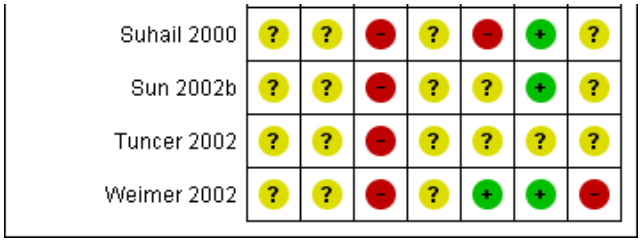


Figure 3. (Continued)



Allocation

Details about the methodology of studies were generally limited. Of the included 23 studies, 21 were considered RCTs, while two studies reported allocation methods that classified them as quasi-RCT (studies in which the method of allocation to the respective treatments was somewhat predictable) (Ji 2001; Joh 2005). In most studies, no detailed information was provided on allocation concealment (19 studies) or the procedure for randomisation (21 studies).

Blinding

Only two studies blinded the intervention of the study drug to patients and study personnel using placebo (MMF TRI Study 1996; MMF US Study 1995).

Incomplete outcome data

Broad descriptions of the course of patients in the study and drop-out rates were reported in 14 studies (COSTAMP Study 2002; Ji 2001; Joh 2005; Johnson 2000; Keven 2003; Ling 1998; Merville 2004; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Weimer 2002), while very detailed information about patients (e.g. information about cross-over treatments, MMF to AZA and *vice versa*) was available in four studies (Johnson 2000; Mendez 1998; Suhail 2000; Weimer 2002).

Selective reporting

Outcome reporting and outcome details varied substantially among studies (see Figure 1). One study did not report any outcome information relevant for the review (Isbel 1997). Graft-related outcomes were available for the majority of studies. All 22 studies provided information on acute rejection, 17 reported graft loss (Busque 2001; Egfjord 1999; Folkmane 2001; Ji 2001; Joh 2005; Johnson 2000; Ling 1998; Merville 2004; Miladipour 2002; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Tuncer 2002; Weimer 2002) and 15 reported a measure of graft function (Army Hospital 2002; Busque 2001; COSTAMP Study 2002; Egfjord 1999; Johnson 2000; Ling 1998; Merville 2004; Miladipour 2002; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Sun 2002b; Weimer 2002). Mortality rates were also reported in 16 studies (Busque 2001;COSTAMP Study 2002; Egfjord 1999; Ji 2001; Joh 2005; Johnson 2000; Ling 1998; Mendez 1998; Merville 2004; MMF US Study 1995; MMF TRI Study 1996; MYSS Study 2004; Sadek 2002; Suhail 2000; Tuncer 2002; Weimer 2002). Data on CAN were sparse (three studies, Merville 2004; Tuncer 2002; Weimer 2002). Complications of immunosuppressive therapy were reported much less frequently than efficacy outcomes: any malignancy was reported in five studies (Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002) and infections such as *Herpes* was reported in four studies (COSTAMP Study 2002; Johnson 2000; MMF TRI Study 1996; MMF US Study 1995), and *pneumocystis* in five studies (Johnson 2000; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004). Events and details of CMV viraemia/syndrome were reported in 13 studies (COSTAMP Study 2002; Ji 2001; Joh 2005; Johnson 2000; Keven 2003; Merville 2004; Mendez 1998; Miladipour 2002; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Weimer 2002), and CMV tissue-invasive disease in seven studies (Folkmane 2001; Ji 2001; Johnson 2000; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; Suhail 2000). Only one study provided information on PVAN (Weimer 2002). Aside from diarrhoea (11 studies) (COSTAMP Study 2002; Ji 2001; Ling 1998; Mendez 1998; Miladipour 2002; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Sun 2002b), and leucopenia (12 studies) (Army Hospital 2002; COSTAMP Study 2002; Ji 2001; Ling 1998; Mendez 1998; Miladipour 2002; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Suhail 2000; Sun 2002b), the occurrence of adverse events was inconsistently and rarely reported, and most often not defined in detail.

Other potential sources of bias

Analysis of outcomes by ITT was stated by the authors and supported by details of the presented results in 12 studies (COSTAMP Study 2002; Egfjord 1999; Ji 2001; Johnson 2000; Ling 1998; Mendez 1998; Merville 2004; MMF TRI Study 1996; MMF US Study 1995; MYSS Study 2004; Sadek 2002; Weimer 2002). The type of analysis was unclear in an additional nine studies (Baltar 2002; Busque 2001; Folkmane 2001; Isbel 1997; Joh 2005; Miladipour 2002; Suhail 2000; Sun 2002b; Tuncer 2002) and not performed by ITT in two studies (Army Hospital 2002; Keven 2003). Only two studies (Merville 2004; MYSS Study 2004) clearly stated funding independent from pharmaceutical companies (407 patients, 12%), while nine studies (2252 patients, 68%) reported industry support (Baltar 2002; Busque 2001; COSTAMP Study 2002; Johnson 2000; Mendez 1998; MMF TRI Study 1996; MMF US Study 1995; Sadek 2002; Weimer 2002). For the remaining 11 studies the funding source was unclear (Army Hospital 2002; Egfjord 1999; Folkmane 2001; Isbel 1997; Ji 2001; Joh 2005; Keven 2003; Ling 1998; Miladipour 2002; Suhail 2000; Sun 2002b; Tuncer 2002).

Effects of interventions

See: **Summary of findings for the main comparison** Mycophenolate mofetil (MMF) versus azathioprine (AZA) for primary immunosuppression in kidney transplant recipients

Summary analyses of the comparative efficacy and safety of MMF versus AZA can be found in the section *Analyses 1*. Outcomes of interest for the review were frequently reported at multiple time points, thus subgroups of clinically meaningful time intervals are

displayed. Summary results reported in the text represent longest duration of follow-up unless stated otherwise.

Primary outcomes

Death

No statistically significant difference for MMF versus AZA treatment was found for all-cause mortality at any time interval (Analysis 1.1.4 (16 studies, 2987 participants): RR 0.95, 95% CI 0.70 to 1.29; I^2 = 0%). Disease-specific mortality was reported less frequently; therefore no robust conclusions can be drawn. While being clearly not statistically significant, the point estimate for death due to cardio-, cerebrovascular disease favoured MMF (11 studies: RR 0.66, 95% CI 0.37 to 1.18, P = 0.16), and the point estimate for death due to infectious causes suggested reduced risk in AZA patients (11 studies: RR 1.28, 95% CI 0.57 to 2.91, P = 0.55) (detailed data not shown).

Graft loss

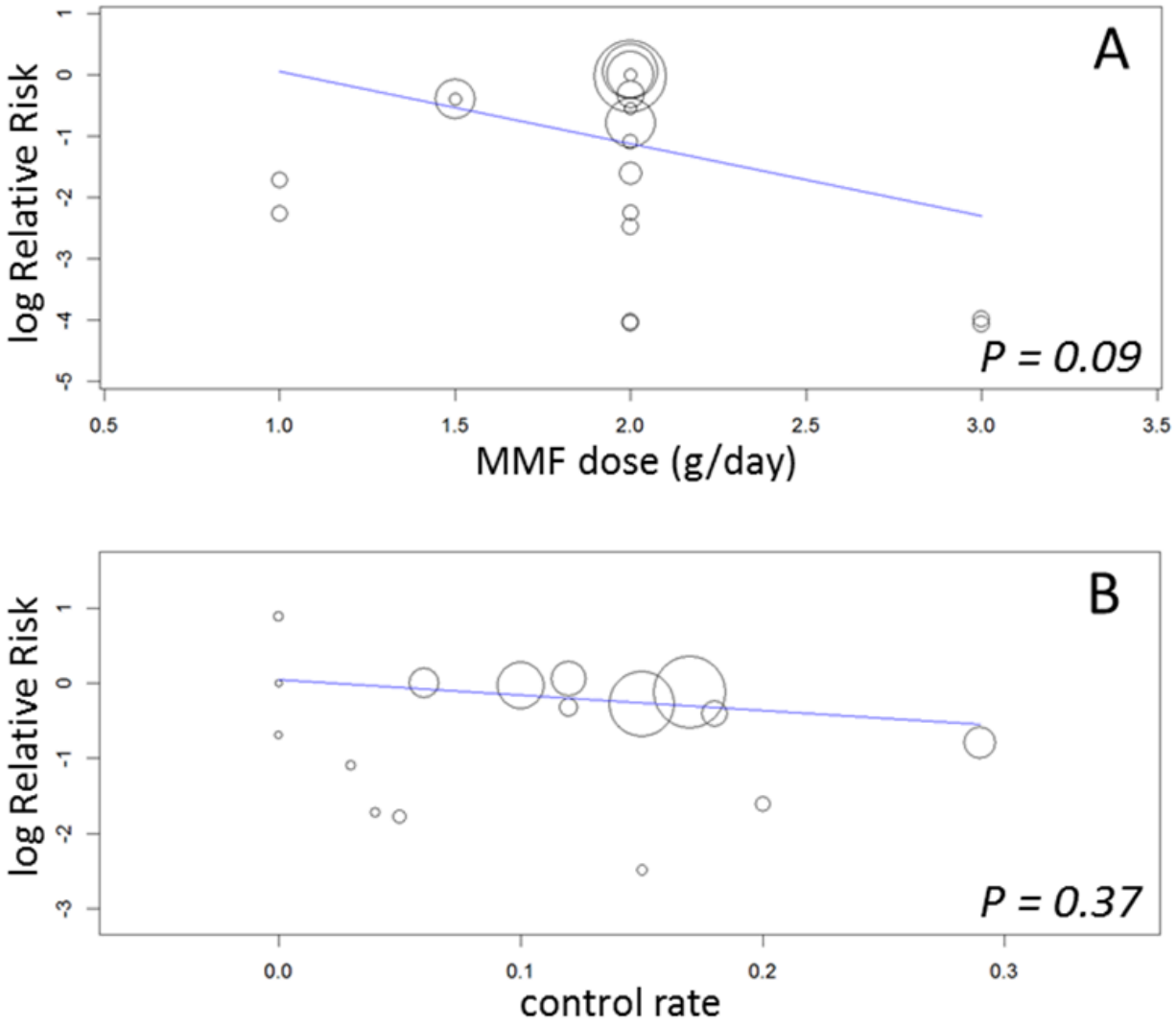
Consistently across all time-intervals, MMF treatment significantly reduced the risk for graft loss including death (Analysis 1.2.4 (15 studies, 2653 participants): RR 0.82, 95% CI 0.67 to 1.00; I^2 = 0%) as well as for death-censored graft loss (Analysis 1.3.4 (17 studies, 2540 participants): RR 0.78, 95% CI 0.62 to 0.99; I^2 = 0%). In particular, the risk of graft loss due to rejection was markedly reduced in MMF treated patients (13 studies, RR 0.59, 95% CI 0.41 to 0.86, P < 0.01), while data on graft loss because of any other specific cause was rarely reported (detailed data not shown).

Non-functioning graft

Information regarding primary non-function of the graft was provided by 11 studies, however, only 18 events were observed by four studies investigating a total of 1601 patients indicating no significant difference between the treatments (Analysis 1.4: RR 0.47, 95% CI 0.19 to 1.18; I^2 = 0%).

Statistical heterogeneity was not observed for these primary outcomes. Meta-regression analyses (See Table 1: Meta-regression analyses) suggested a more pronounced risk for death-censored graft loss in AZA patients, if higher doses of MMF were used (RRR 0.26, 95%CI 0.06 to 1.24, P = 0.09; Figure 4, panel A). Neither of the remaining study level factors indicated any modification of the treatment effect. In particular, varying baseline risk for death censored graft loss as indicated by the control rate (i.e. the incidence of death censored graft loss in AZA treated patients) was not related to the magnitude of the treatment effect of MMF versus AZA (RRR 0.13, 95% CI 0.01 to 10.70, P = 0.37, Figure 4, panel B).

Figure 4. Meta-regression of logarithmic relative risk of death censored graft loss by MMF dose (panel A) and by control rate (panel B)



Secondary outcomes

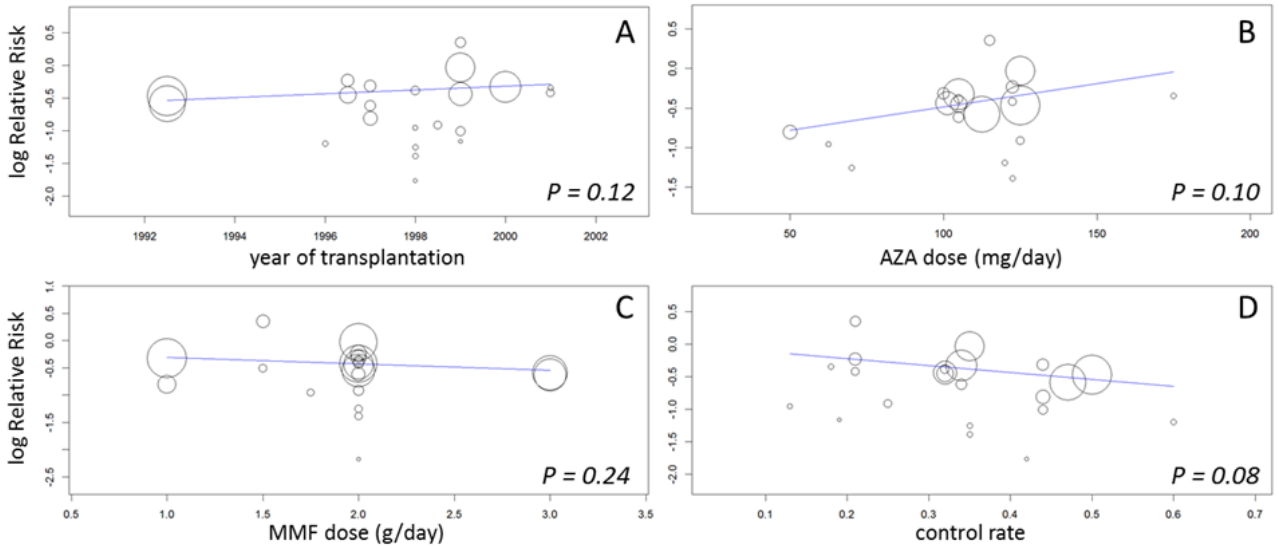
Malignancy

The summary effect for any malignancy indicated a reduced risk in MMF-treated patients (Analysis 1.5.1 (5 studies, 1734 participants): RR 0.81, 95% CI 0.60 to 1.09; I^2 = 0%), but this finding was not statistically significant. Similarly, the risk for non-melanoma skin cancer tended to be reduced by approximately 20% in MMF treated patients, but the association did not reach statistical significance due to the limited number of studies and events (Analysis 1.5.3 (4 studies, 1416 participants): RR 0.78, 95% CI 0.46 to 1.34; I^2 = 19%).

Acute rejection

A consistent risk reduction for any acute rejection (about 35%) was observed with MMF-treatment across all time intervals (Analysis 1.6.4 (22 studies, 3301 participants): RR 0.65, 95% CI 0.57 to 0.73; I^2 = 9%). The effect was approximately 40% for biopsy-proven acute rejection (Analysis 1.7.4 (12 studies, 2696 participants): RR 0.59, 95% CI 0.52 to 0.68; I^2 = 0%) and approximately 50% in steroid-resistant/antibody-treated acute rejection (Analysis 1.8.4 (15 studies, 2914 participants): RR 0.48, 95% CI 0.36 to 0.65; I^2 = 14%) both with low statistical heterogeneity. In meta-regression analyses (see Table 1), a higher AZA dose (RRR 1.01, 95% CI 1.00 to 1.01, P = 0.10, Figure 5, panel B) and the use of CsA-ME rather than the original CsA solution (RRR 1.27, 95% CI 0.98 to 1.65, P = 0.07) tended to attenuate the benefit of MMF versus AZA for acute rejection (i.e. a RR closer to 1, but still favouring MMF treatment). No clear signal was observed for transplantation in the most recent era (RRR 1.03, 95% CI 0.99 to 1.06, P = 0.12, Figure 5, panel A) and a higher MMF dose (RRR 0.90, 95% CI 0.74 to 1.08, P = 0.24, Figure 5, panel C). Moreover, the benefit of MMF over AZA treatment on the reduction of acute rejection was more pronounced with an increased control rate, indicating elevated immunological baseline risk of the study population (RRR 0.34, 95% CI 0.10 to 1.09, P = 0.08, Figure 5, panel D).

Figure 5. Meta-regression of logarithmic relative risk of any acute rejection by year of transplantation (panel A), AZA-dose (panel B), MMF-dose (panel C) and by control rate (panel D)



Chronic allograft nephropathy

Meta-analysis showed a significant reduction of the risk for CAN with MMF treatment (Analysis 1.9.4 (3 studies, 203 participants): RR 0.69, 95% CI 0.48 to 0.99; I^2 = 0%). Two studies required diagnosis by biopsy (Merville 2004; Weimer 2002) and in one study biopsy was optional (Tuncer 2002).

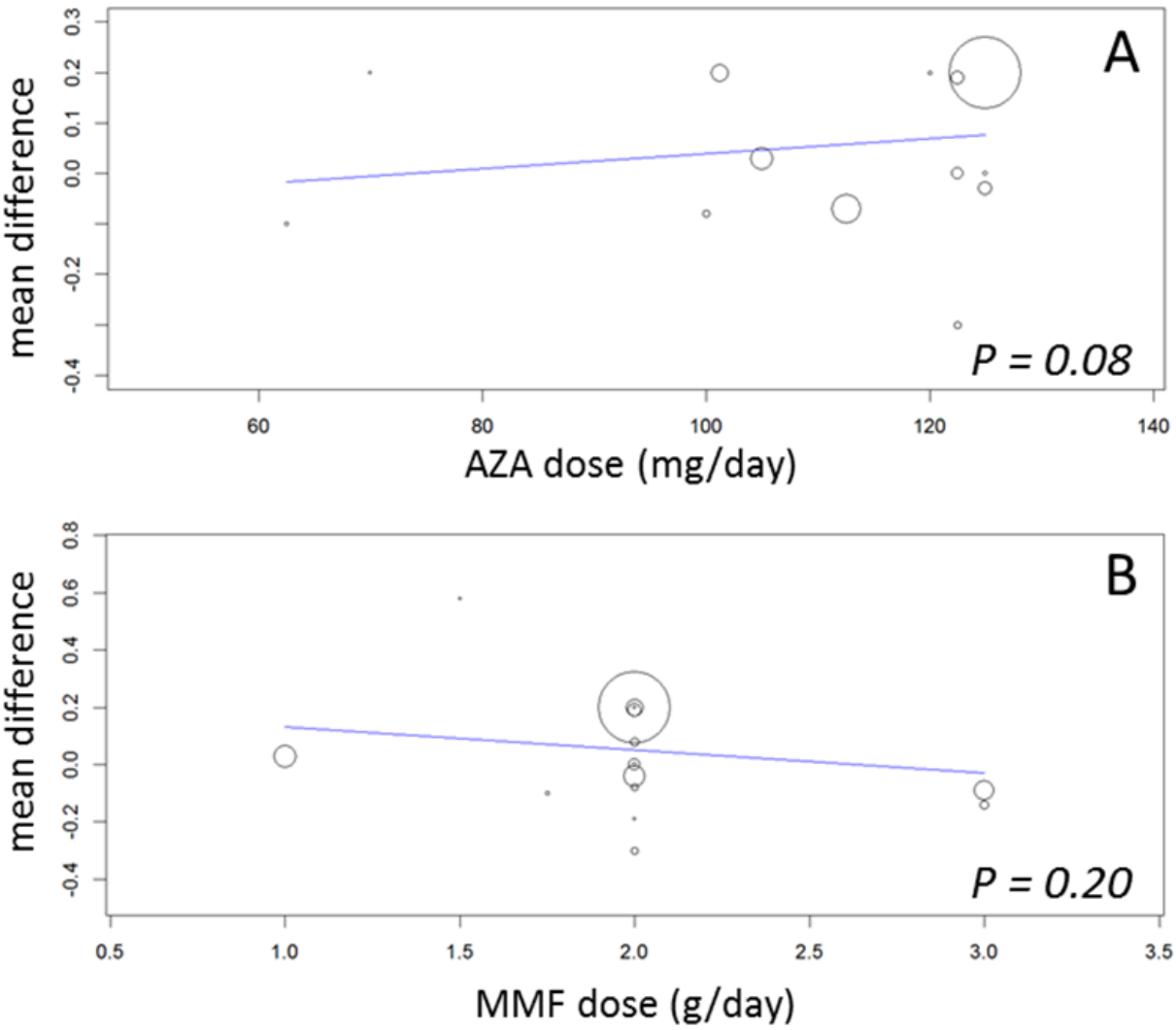
Infection

Evidence on infections such as urinary tract infection/cystitis, *Herpes zoster*, *Candida* and *Aspergillus* infections, is limited due to inconsistent and sparse reporting (Analysis 1.10). Only CMV viraemia/syndrome was reported by a substantial number of studies and no clear signal of a benefit for any treatment was found (Analysis 1.11.3 (13 studies, 2880 participants): RR 1.06, 95% CI 0.85 to 1.32; I^2 = 24%). However, in seven studies the risk of tissue-invasive CMV disease was significantly elevated with MMF treatment (Analysis 1.12.3 (7 studies, 1510 participants): (RR 1.70, 95% CI 1.10 to 2.61; I^2 = 0%). None of the tested study level factors indicated treatment effect modification in meta-regression analyses on either CMV viraemia/syndrome or tissue-invasive CMV disease (See Table 1). Only one study reported no observed events of PVAN (Weimer 2002). Although *Pneumocystis carinii/jiroveci* pneumonia (PCP) were generally rare diseases in the studies (5 studies, 9 events in 1650 patients), eight of these events occurred in AZA-treated patients, thus resulting in a statistically significant result favouring MMF treatment (Analysis 1.10: RR 0.19, 95% CI 0.05 to 0.69; I^2 = 0%).

Graft function

While 15 studies reported a measure of graft function, the vast majority did not provide detailed information on either the number of patients in whom these measurements were performed (those with a functioning graft at the various time points) or the standard error/deviation of the reported mean. In general, graft function did not differ substantially at the various time intervals as indicated by point estimates between 0.01 and 0.05 mg/dL. Still, numerically, slightly lower mean values of SCr were observed in AZA treated patients (Analysis 1.13.3 (15 studies, 2233 participants): MD 0.05 mg/dL, 95% CI -0.05 to 0.15; I^2 = 60%). Substantial heterogeneity was observed. Meta-regression on study level factors (See Table 1) suggested even greater benefit for AZA treatment if exclusively patients receiving their first graft were studied (MD coefficient -0.13, 95% CI -0.25 to -0.02; P = 0.03). While higher doses of AZA tended to further enhance the benefit for AZA treatment on graft function (MD coefficient 0.004, 95% CI -0.001 to 0.009, P = 0.08, Figure 6, panel A), yet no such trend was found for higher doses of MMF although the point estimate of the coefficient suggested possible effect modification (MD coefficient 0.08, 95% CI -0.04 to 0.19, P = 0.20, Figure 6, panel B). Further measures of graft function (CrCl or GFR) were less frequently reported but demonstrated similar results (Analysis 1.14). Data on proteinuria were provided by only three studies (Merville 2004; MMF TRI Study 1996; MYSS Study 2004) and no reliable conclusions could be drawn (Analysis 1.15).

Figure 6. Meta-regression of mean difference in serum creatinine (mg/dL) by AZA dose (panel A), and by MMF dose (panel B)



Adverse events

Adverse events and side effects were very inconsistently reported.

Gastrointestinal disorders were more common under MMF therapy with a statistically significant difference for diarrhoea (Analysis 1.17.1 (11 studies, 2638 participants): RR 1.55, 95% CI 1.32 to 1.83; I^2 = 0%) and trends for both abdominal pain (Analysis 1.17.2 (3 studies, 1311 participants): RR 1.18, 95% CI 0.97 to 1.44; I^2 = 0%) and vomiting (Analysis 1.17.3 (4 studies, 1587 participants): RR 1.27, 95% CI 0.83 to 1.94; I^2 = 67%). The only two studies reporting gastrointestinal bleeding suggest a significantly elevated risk in MMF treated patients (Analysis 1.17.4 (575 participants): RR 3.99, 95% CI 1.07 to 14.86; I^2 = 0%).

Insulin-treated NODAT was reported in four studies where the maintenance regimen was based on Tac, which itself is a known risk factor for the occurrence of NODAT (Webster 2005). The risk for NODAT was further significantly enhanced by AZA treatment, vice versa reduced by MMF (Analysis 1.18.1 (4 studies, 445 participants): RR 0.57, 95% CI 0.34 to 0.95; I^2 = 0%). No clear effect of either treatment on anaemia, leucopenia, or dyslipidaemia was observed. The risk of thrombocytopenia tended to be reduced by MMF treatment (Analysis 1.19.5 (5 studies, 1492 participants): RR 0.73, 95% CI 0.52 to 1.03; I^2 = 0%), as well as the risk of elevated liver enzymes (Analysis 1.18.4 (3 studies, 272 participants): RR 0.50, 95% CI 0.21 to 1.23; I^2 = 50%).

Investigation of confounding, small study bias and sensitivity analyses

We performed meta-regression analysis (Table 1) and subgroup-analyses (Analyses 2 to 6) to investigate potential confounding by various factors (e.g. study quality factors, data-analysis, publication type) regarding their association with the effect size of MMF versus AZA.

Confounding by study design and data analysis

Blinding of the intervention, which was only performed by the two pivotal trials (MMF TRI Study 1996; MMF US Study 1995), indicated a possible effect modification towards a greater difference in acute

rejection favouring MMF treatment (RRR 0.87, 95% CI 0.70 to 1.07, P = 0.19) and a reduced risk for tissue-invasive CMV disease (RRR 0.42, 95% CI 0.12 to 1.50, P = 0.18), but both results were not statistically significant. The two studies classified as quasi-RCTs (Ji 2001; Joh 2005) reported a lower risk for CMV viraemia/syndrome as compared to true RCTs (Analysis 2.3). No effects on graft loss, acute rejection, or SCr were found. Stronger effects favouring MMF treatment were reported in studies where ITT analysis was unclear or certainly not performed for graft loss (Analysis 3.1) and acute rejection (Analysis 3.2). In these studies, superior graft function in MMF-treated patients was reported (Analysis 3.4). No substantial heterogeneity of the results was observed if studies enrolling adults only were compared to studies that also enrolled children (Analysis 4).

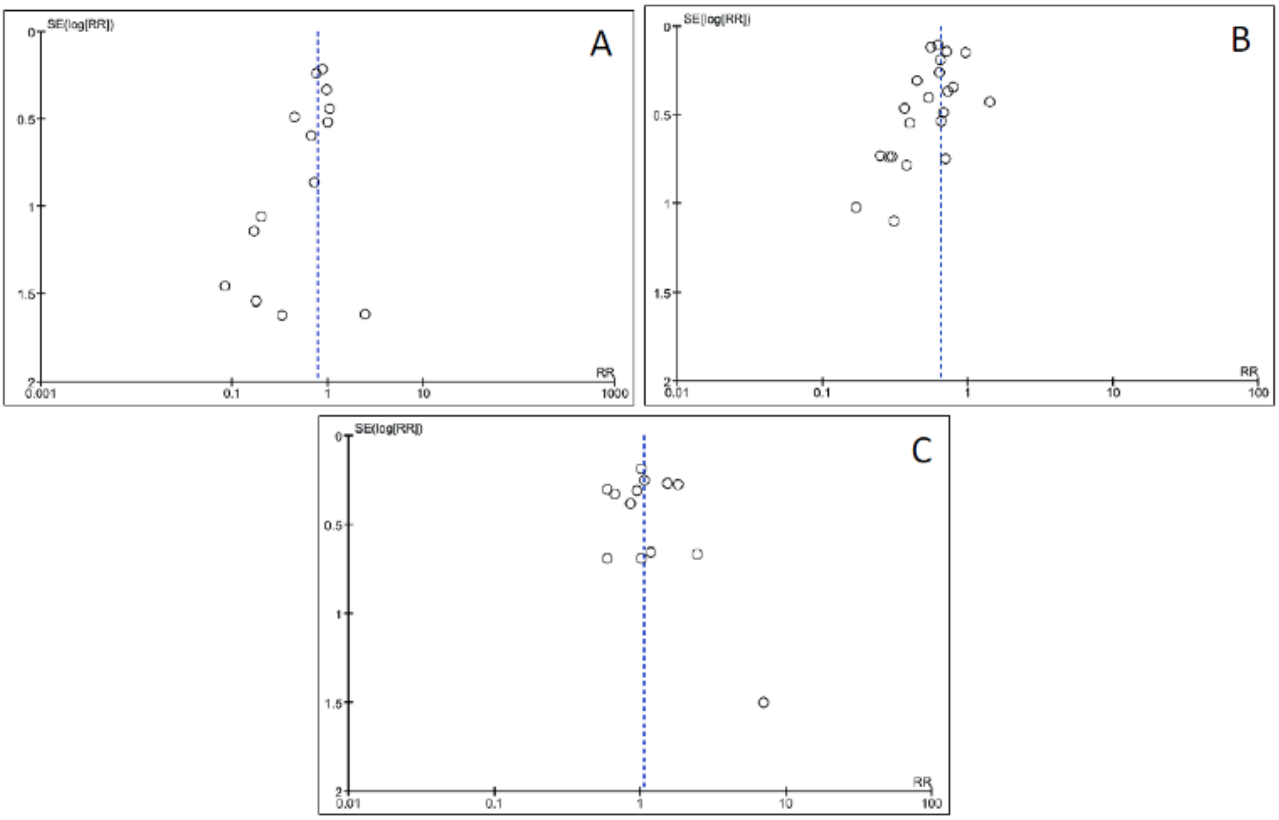
Confounding by funding source and publication type

Studies clearly reporting industry funding demonstrated a potentially higher risk for CMV viraemia/syndrome in AZA treated patients (Analysis 5.3; meta-regression RRR 1.53, 95% CI 0.96 to 2.41, P = 0.07). Studies that were explicitly not supported by industry (Merville 2004; MYSS Study 2004) reported a smaller non-significant benefit in the reduction of acute rejection in MMF treated patients (Analysis 5.2; RRR 0.84, 95% CI 0.66 to 1.07, P = 0.17) and a significant greater mean difference in SCr favouring AZA treatment (Analysis 5.4; meta-regression MD coefficient -0.14, 95% CI -0.25 to -0.02, P = 0.02). Studies published at least once as a full manuscript in a peer reviewed journal reported a somewhat attenuated risk for death-censored graft loss (Analysis 6.1; RRR 1.82, 95% CI 0.84 to 3.95, P = 0.13). No other differences were found for the other tested outcomes.

Small study bias and sensitivity analyses

Investigation of funnel plots did not indicate strong signals for asymmetry (Figure 7). However, there are many explanations for why an inverted funnel plot may be asymmetric, including chance, heterogeneity, publication and reporting bias (Sterne 2011). Visual judgment of funnel plots has been shown to be misleading in empirical research (Lau 2006; Terrin 2005).

Figure 7. Funnel plots of outcomes. Graft loss: censored for death (panel A, Analysis 1.3); acute rejection: total (panel B, Analysis 1.6); Infection: cytomegalovirus viraemia/syndrome (panel C, Analysis 1.11)



Finally, in sensitivity analyses, the robustness of effect estimates and potential influence of single studies was tested by sequential inclusion and exclusion of each study. In general, the point estimates of all tested outcomes (mortality, death-censored graft loss, any acute rejection, CMV viraemia/syndrome, tissue-invasive CMV disease, SCr, diarrhoea and leucopenia) remained fairly stable in each exclusion/inclusion step. Only two studies resulted in an attenuation of significance for death-censored graft loss (MMF TRI Study 1996: RR 0.79, 95% CI 0.60 to 1.03, P = 0.08; Egfjord 1999: RR 0.79, 95% CI 0.62 to 1.003, P = 0.053, respectively), but did not affect the magnitude of the summary effect. Similarly, by leaving out MMF US Study 1995 in tissue-invasive CMV disease, the effect estimate did not change markedly, but the association lost significance (RR 1.76, 95% CI 0.89 to 3.48, P = 0.11). No significant changes in the mean difference for SCr were observed which would not make the difference in SCr clinically meaningful (all MD < 0.09 mg/dL).

DISCUSSION

Summary of main results

Summarising the evidence from 23 RCTs identified for this review, MMF was superior over AZA in efficacy outcomes after kidney transplantation. In particular, MMF demonstrated a statistically significant risk reduction of about 20% for any graft loss as well as death-censored graft loss compared to AZA. A stronger beneficial effect, although not statistically significant, was suggested in studies using higher doses of MMF. The risk of acute rejection was significantly reduced by about 35%, 40% if the rejection was proven by biopsy and 50% for more severe rejection episodes that required antibody treatment. This finding was more pronounced in studies of enhanced overall baseline risk (as indicated by a higher control rate). On the other hand, higher AZA dose and the concomitant use of CsA-ME rather than CsA suggested an attenuated benefit from MMF over AZA treatment. Although based on sparse data, MMF treatment was related to lower rates of CAN. Graft function did not differ between the two drugs and the observed trend towards slightly lower creatinine levels of 0.05 mg/dL in AZA treated patients may not yield a clinically relevant benefit.

Evidence regarding safety outcomes was more limited since a smaller number of studies reported these. Also definitions of adverse events were rarely provided and likely varied across studies. The non-significant summary effect for towards lower rates of malignancies in MMF-treated patients was supported by five studies only. One study reported no events of PVAN and nine events reported in five studies showed the significantly reduced risk for PCP in MMF-treated patients. Data on CMV viraemia/syndrome were provided by a substantial number of studies (n = 13) showing no difference between the two drugs, however tissue-invasive CMV disease was significantly less likely in AZA-treated patients based on seven studies only. The incidence of insulin-dependent NODAT was reported exclusively in studies investigating Tac-based regimens and was significantly higher in AZA-treated patients. Gastrointestinal side effects were more common in MMF-treated patients, while no significant differences were found for elevated liver enzymes and hematologic disturbances such as leucopenia, anaemia or thrombocytopenia.

Applying current standards to assess methodological quality of the studies (Higgins 2011) indicated that important information on factors used to judge susceptibility for bias were infrequently and inconsistently reported.

Overall completeness and applicability of evidence

Based on an exhaustive search process, we tried to comprehensively collect any published evidence for our research objectives. A large number of published abstracts were screened and many abstracts from conferences in the early and mid-1990s were retrieved and assessed for eligibility. In total, we included 23 studies enrolling 3301 patients in our review. Study populations varied across continents and patients were treated in a multitude of different health care systems including not only the USA, Canada, various western European countries and Australia, but also China, Singapore, Korea, India, Latvia, Hungary, Turkey, Brazil and Iran. When this information was available, it appeared that studies included patients who were at low to moderate immunological baseline risk as frequently patients received their first kidney graft of a deceased donor. Further details on known markers of immunological risk, such as PRA level, HLA mismatch, or the proportion of patients of African American ancestry were inconsistently and rarely reported.

Quality of the evidence

Items of study quality such as blinding, ITT analysis, allocation concealment can help assess the risk of bias and thus judge the validity of the results. Based on the criteria defined for Cochrane reviews (Higgins 2011), most of the studies of this review lacked sufficient information on methodological items. Many of the studies were sponsored by industry, in particular by the company that held the patent on MMF. Most studies were published at least once as a full manuscript in a peer reviewed journal but a substantial number (eight studies) were conference abstracts or *Transplantation Proceedings* articles only and thus underwent an abbreviated peer review process. These factors (low methodological quality, industry sponsorship, and publication in non-peer-reviewed journals) have the potential to being associated with modification of treatment effects of over- or underestimation (Moher 1998; Pittler 2000; Ridker 2006). Overall, although we found evidence suggestive for the effect estimates being associated with study quality/risk of bias factors, we would not claim clinically relevant impact on the summary effects. Studies of lower quality and with unclear ITT analysis tended to overestimate efficacy results as did publications in non-peer reviewed journals and those sponsored by industry. These studies were also more likely to report attenuated risks for tissue invasive CMV disease and MMF-specific side effects such as diarrhoea. The most important limitation of our data is the lack of evidence and a considerably large reporting bias in particular for safety outcomes and conditional outcomes, such as graft function which naturally can be measured only in those with a functioning graft. However, numbers of patients at risk or those with a functioning graft were rarely provided.

Potential biases in the review process

We followed high standards to reduce risk of bias in the methodology of this review, such as a comprehensive literature search that was not restricted to publications in English language, article selection and data extraction performed independently by two or more authors and the collection of all potentially relevant outcomes from the included studies. However, the main limitations of the current review are two-fold: First, while the body of evidence is fairly robust for efficacy outcomes, any conclusion on safety lacks certainty. Only few studies reported data on malignancies, and only CMV-related diseases/infections were commonly presented. Second, most of the studies did not report outcome data with enough follow-up to be able to detect development of specific diseases, in particular malignancies, with long induction and latent periods. Finally, most of the studies that investigated MMF versus AZA were performed in the late 1990s and early 2000, a certainly different era of kidney transplantation as we are in nowadays. During the time of these studies, outcomes of interest differed from what we judge important today: CAN or more specifically IF/TA (interstitial fibrosis/tubular atrophy in graft biopsies) and *Polyoma BK/JC virus* reactivation and PVAN are considered as of higher long-term importance than acute rejection episodes, which are frequently mild and if diagnosed early can be treated and cured.

Agreements and disagreements with other studies or reviews

Our results are consistent with a systematic review by Knight 2009 who also investigated the comparative efficacy and safety of MMF versus AZA. This review used fixed-effects models if no statistical heterogeneity was detected while we chose the more conservative random-effects model by default given the clinical heterogeneity. Moreover, we tried to investigate potential effect modification in detail by a number of a priori defined study level and study quality factors. Another existing systematic review by Wang *et al.* included studies of secondary regimens (Wang 2004a; Wang 2004b; Wang 2005; Zhang 2004) and is thus not directly comparable.

Observational data can help to understand the findings of the review, in particular how benefits of MMF regarding lower rates of rejection and improved graft survival are balanced against the potential for harm such as infections and malignancies associated with stronger immunosuppressive regimens. Temporal trends in cohort studies have reported diminishing acute rejection rates but higher incidence of Polyoma BK/JC virus infections/reactivations and PVAN during the last decade (Ramos 2009), likely to be caused by the use of stronger immunosuppressive regimens, rather than by a specific agent (Brennan 2005; Snyder 2009). Polyoma BK/JC virus infections/reactivations and PVAN are characterised by impaired graft function and an aggravated risk of graft loss and the rare but life-threatening progressive multifocal leukoencephalopathy (FDA 2008). The total burden of PVAN especially in the setting of RCTs so far has probably been underestimated since these outcomes were only rarely reported in RCTs in the past.

An about 3- to 4-fold increased risk for cancer in kidney transplant recipients was described when compared to the general population (Domhan 2009). As with infections, the risk is associated with the overall level of immunosuppression rather than a specific drug (Wimmer 2007). We found a non-significant point estimate suggesting higher risk for PTLD/lymphomas, but also trends towards fewer malignancies in general with MMF treatment, although being of stronger immunosuppressive potency. These findings could be explained by AZA directly causing accumulation of mutagenic metabolites (Domhan 2009), but data are conflicting (Kauffman 2006; Meier-Kriesche 2003; Morath 2004; Schold 2009).

AUTHORS' CONCLUSIONS

Implications for practice

We found that while the risks for graft loss and acute rejection were reduced by MMF treatment, graft function did not differ in a clinically relevant magnitude and evidence regarding safety outcomes was limited. Thus, it is still a major task of the transplant physician to balance benefits and harms of the two drugs and to decide which agent the individual patient should be started on. Patient's risks and preferences should be considered to individualise this decision.

In this context it should be mentioned, that although none of the included studies tested ec-MPS against AZA, it is unlikely that ec-MPS treatment would have considerably changed the evidence derived from MMF-studies. MPA is the active agent of both, MMF and ec-MPS, but the latter was developed to limit gastrointestinal disorders since it is absorbed in the gut rather than in the stomach. Studies that have directly compared MMF versus ec-MPS showed similar efficacy and adverse event profiles including gastrointestinal adverse events (Budde 2004; Salvadori 2004).

Another important aspect is the fact that MPA is contraindicated in pregnancy (Sifontis 2006) and frequently MMF gets replaced by AZA in transplant patients before pregnancy is attempted. The current review did not address the comparison of MPA versus AZA in secondary regimens, including the change of the immunosuppressive regimen in patients with stable graft function. However, Sadek 2002 found that replacement of MMF by AZA three months post-transplant overall was safe and effective up to 12 months follow-up in this study.

Finally, a general limitation of how results from meta-analyses can be applied to the individual patient should briefly be mentioned. Patients enrolled in RCTs (which subsequently get summarised in meta-analyses) typically differ from each other in their baseline risk for achieving the outcome of interest. Although being equally distributed between treatment and control group, frequently a higher risk group of patients may experience most of the events that drive the main results of the intervention (Kent 2007). The phenomenon of varying treatment effects dependent on baseline risk is likely to be relevant in the setting of kidney transplantation (Wagner 2009). Meta-analyses and meta-regression analyses are not helpful to identify the benefits and harms of a particular treatment to the individual patient (Schmid 2004).

Implications for research

Our review highlights the need for consistent ascertainment and reporting of adverse events in kidney transplant intervention studies (Ioannidis 2004), including infections (e.g. Polyoma BK virus) and malignancies. Further, the deficiencies in the reporting of study quality items point to the need for editors to hold kidney transplant trialists to universal reporting guidelines, such as the CONSORT statement (Moher 2001).

As most of the evidence about MMF versus AZA is based on the late 1990s and early 2000s, it will be interesting how the two drugs compare in the current era. The ongoing ATHENA Study 2012 will provide insights about the two proliferation-inhibitors in a low-dose CNI regimen with scheduled CNI withdrawal on CAN and PVAN.

Support for the every-day decision on which agent (MMF or AZA) a kidney transplant recipient should be started on could be addressed by decision analyses in which the benefits and harms are weighted against each other in various settings. Another approach could be to stratify patients in RCTs at baseline according to immunological risk. The benefits and harms of certain therapies (e.g. MMF versus AZA) could then be investigated across all as well as within subgroups of lower, moderate, and higher risk patients (Wagner 2009). With these endeavours, research in kidney transplantation can make one important step forward to individualise medical therapy and towards choosing the best immunosuppressive regimen for a particular patient.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year of study]

MMF US Study 1995

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: July 1992 to September 1993 • Duration of follow-up: 3 years

Participants	• Country: USA
	• Setting: multicentre (14)
	• Patients ≥18 years of age receiving a cadaveric kidney allograft as their first transplant; no contraindication for CsA, prednisone, AZA or ALG; able to receive oral medication; negative T cell crossmatch; women were to have a negative pregnancy test at time of entry; both men and women were instructed to utilize an adequate method of contraception
	  ○ Deceased donor: 100%
	  ○ Previous transplantation: 0%
	  ○ PRA > 20%: 4.7%
	  ○ HLA mismatch (mean): 3.4
	  ○ Cold ischaemia time (mean): 22 h
	  ○ Delayed graft function: not reported
	• Number (randomised/analysed): treatment group 1 (167/165); treatment group 2 (166/166); control group (166/164)
	• Mean age ± SD (years): treatment group 1 (45.1 ± 13.2); treatment group 2 (46.1 ± 12.6); control group (45.9 ± 12.2)
	• Sex (M/F): treatment group 1 (59/41); treatment group 2 (57/43); control group (57/43)
	• Exclusion criteria: WCC < 2.5 x 10^3/µL, platelet count < 100 x 10^3/ µL, Hb < 6 g/dL; serologic evidence of infection with HIV-I or HTLV-I or the presence of HBsAg; active peptic ulcer disease, severe diarrhoea, or other GI disorder that might interfere with their ability to absorb oral medications; pregnancy or lactation; malignancy or history of malignancy other than adequately treated non-melanoma skin carcinoma

Interventions	Treatment group 1 • MMF • 2 g/d, orally Treatment group 2 • MMF • 3 g/d, orally Control group • AZA • 1 to 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: ATG/ALG, all patients • CsA (original formulation), target C_0 (month 3): according to local practice • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function

MMF US Study 1995 *(Continued)*

	• Malignancy (except non-melanoma skin cancer) • Acute rejection • Infections • Non-melanoma skin cancer • Kidney function measures (SCr, CrCl) • Adverse events (diarrhoea, abdominal pain, nausea, vomiting, GI bleeding, anaemia, leucopenia, thrombocytopenia)
Notes	• Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Low risk	The study was double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind. Investigators and patients were blinded until all patients had been in the study for 1 year
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported; four patients never received study drug and were excluded from some of the analysis; all patients followed-up or accounted for
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes regarding efficacy and safety
Other bias	High risk	This study was sponsored by a grant from Syntex (U.S.A.), Inc., Palo Alto, CA. Syntex (funder) was unblinded to provide the results of the efficacy analysis for all patients as of 6 months after transplant and the results of the analyses of safety data collected for patients as of the data cut-off date of March 4, 1994

MMF TRI Study 1996

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: August 1992 to September 1994 • Duration of follow-up: 3 years

Participants	• Countries: Canada, Australia, Finland, United Kingdom, Germany, France, Switzerland, Ireland, Italy
	• Setting: international multicentre study (21 centres)
	• Patients ≥ 18 years of age receiving their first or second cadaveric kidney transplantable to receive oral medication
	  ◦ Deceased donor: 100%
	  ◦ Previous transplantation: 11.9%
	  ◦ PRA > 20%: 8%

MMF TRI Study 1996 *(Continued)*

- HLA mismatch: not reported
- Cold ischaemia time (mean): 20 h
- Delayed graft function: 18%

- Number (randomised/analysed): treatment group 1 (173/171); treatment group 2 (164/164); control group (166/162)
- Mean age ± SD (years): treatment group 1 (46 ± 13); treatment group 2 (46 ± 13); control group (47 ± 13)
- Sex (M/F): treatment group 1 (93/79); treatment group 2 (98/66); control group (111/55)
- Exclusion criteria: history of malignancy, except successfully treated nonmetastatic basal or squamous cell carcinoma of the skin; serologic evidence of HIV of HBV; systemic infections requiring continued antibiotic therapy at the time of entry; severe diarrhoea, GI disorders or active peptic ulcer disease; pregnant women, nursing mothers and patients who did not agree to use of adequate contraception

Interventions	Treatment group 1 • MMF • 2 g/d, orally Treatment group 2 • MMF • 3 g/d, orally Control group • AZA • 100 mg/d if body weight < 75 kg, 150 mg/d if ≥ 75 kg Concomitant immunosuppression • Induction antibody: none • CsA (original formulation), target C_0 (month 3): according to local practice • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function • Malignancy (except non-melanoma skin cancer) • Acute rejection • Infections • Non-melanoma skin cancer • Kidney function measures (SCr, proteinuria) • Adverse events (diarrhoea, abdominal pain, nausea, vomiting, anaemia, leucopenia, thrombocytopenia)
Notes	• Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Low risk	The study was double-blind

MMF TRI Study 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding of investigators and patients continued throughout the 3 years of this study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported, six patients never received study drug and were excluded from some of the analysis; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes regarding efficacy and safety
Other bias	High risk	This study was supported by Roche Pharmaceuticals

Isbel 1997

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported • Duration of follow-up: 4 to 6 weeks
Participants	• Country: Australia • Setting: single centre • Kidney transplant recipients; patient characteristics not reported • Number: treatment group (13); control group (25) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • MMF • Dose and administration: not reported Control group • AZA • Dose and administration: not reported Concomitant immunosuppression • Induction antibody: none • CsA (formulation: not reported), target C_0 (month 3): not reported • Corticosteroids
Outcomes	• No relevant outcomes reported
Notes	• Publication: conference abstract only • Language: English
Risk of bias	

Isbel 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, presumably open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis unclear; number randomised or number of patients at the end of the study not reported, data only available from conference abstract
Selective reporting (reporting bias)	High risk	No relevant data for this review - data only available from conference abstract
Other bias	Unclear risk	Funding source not reported

Mendez 1998

Methods	• Study type: parallel RCT • Study time frame/year of transplant: 1996 to 1997 • Duration of follow-up: 1 year

Participants	• Country: USA
	• Setting: multicentre (13)
	• Patients ≥ 12 years old weighing ≥ 40 kg and receiving a cadaveric kidney transplant (primary or re-transplant)
	  ○ Deceased donor: 100%
	  ○ Previous transplantation: 8%
	  ○ PRA > 10%: 11.4%
	  ○ HLA mismatch (mean): 3.4
	  ○ Cold ischaemia time: not reported
	  ○ Delayed graft function: 14%
	• Number: treatment group 1 (59); treatment group 2 (58); control group (59)
	• Mean age ± SD (years): treatment group 1 (44.0 ± 11.9); treatment group 2 (44.4 ± 12.4); control group (45.5 ± 11.2)
	• Sex (M/F): treatment group 1 (24/36); treatment group 2 (22/36); control group (25/34)
	• Exclusion criteria: recipient of a living donor kidney transplant; recipient of other solid organ transplants and receiving immunosuppressive medication; listed for any other solid organ transplant; recipient of an ABO-incompatible transplant; pregnant or nursing women; patients with known sensitivity to Tac, AZA, MMF; carriers of HIV

Interventions	Treatment group 1 • MMF

Mendez 1998 *(Continued)*

- 1 g/d, orally

Treatment group 2

- MMF
- 2 g/d, orally

Control group

- AZA
- 1.5 mg/kg body weight/d, orally

Concomitant immunosuppression

- Induction antibody: ATG/OKT3, all patients
- Tac, target C_0 (month 3): 5 to 15 ng/mL
- Corticosteroids

Outcomes

- Death
- Graft loss
- Primary non-function
- Malignancy (except non-melanoma skin cancer)
- Acute rejection
- Infections
- NODAT
- Non-melanoma skin cancer
- Adverse events (diarrhoea, nausea, vomiting, anaemia, leucopenia, hyperlipidaemia)

Notes

- Publication: full journal article
- Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported; eleven patients never received study drug or kidney graft and were excluded from the analyses; all patients followed up or accounted for. 11 patients in the AZA group discontinued AZA and crossed over to the MMF group
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes regarding efficacy and safety

Mendez 1998 *(Continued)*

Other bias	High risk	This study was supported by a grant from Fujisawa Healthcare, Inc, Deerfield, IL.

Ling 1998

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported: • Duration of follow-up: 6 months

Participants	• Country: China
	• Setting: single centre
	• Kidney transplant recipients
	  ○ Deceased donor: 100%
	  ○ Previous transplantation: not reported
	  ○ PRA level: not reported
	  ○ HLA mismatch: not reported
	  ○ Cold ischaemia time: not reported
	  ○ Delayed graft function: not reported
	• Number: treatment group 1 (5); treatment group 2 (6); control group (5)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: not reported

Interventions	Treatment group 1 • MMF • 1.5 g/d, orally Treatment group 2 • MMF • 2 g/d, orally Control group • AZA • 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: none • CsA (formulation not reported), target C_0 (month 3): 100 to 200 ng/mL • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function • Acute rejection • Kidney function measures (SCr) • Adverse events (diarrhoea, leucopenia)
Notes	• Publication: full journal article • Language: Chinese

Ling 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding available (no blinding assumed)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear; all patients followed-up
Selective reporting (reporting bias)	Low risk	The published report included most expected outcomes regarding efficacy and safety
Other bias	Unclear risk	Funding source not reported

Egfjord 1999

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1996 to 1998 • Duration of follow-up: 1 year

Participants	• Country: Denmark
	• Setting: single centre
	• patients receiving first or second cadaveric kidney transplant
	  ○ Deceased donor: 100%
	  ○ Previous transplantation: not reported
	  ○ PRA level: not reported
	  ○ HLA mismatch: not reported
	  ○ Cold ischaemia time: not reported
	  ○ Delayed graft function: 38%
	• Number: treatment group (25); control group (25)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: not reported

Interventions	Treatment group • MMF • 2 g/d, orally Control group

Egfjord 1999 *(Continued)*

	• AZA • 100 mg/d, orally Concomitant immunosuppression • Induction antibody: ATG, all patients • CsA-ME, target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function • Acute rejection • Kidney function measures (SCr)
Notes	• Publication: conference abstract only • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis unclear; number randomised or number of patients at the end of the study was not reported. (data only available from conference abstract)
Selective reporting (reporting bias)	High risk	The published report included few outcomes regarding efficacy and safety. (data only available from conference abstract)
Other bias	Unclear risk	Funding source not reported

Johnson 2000

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1996 to 1997 • Duration of follow-up: 3 years
Participants	• Country: Canada, USA • Setting: international multicentre (15)

Johnson 2000 *(Continued)*

- Patients ≥ 12 years old weighing ≥ 40 kg body weight and receiving their first cadaveric kidney transplant; female patients of child-bearing potential were to have a negative pregnancy test and agreed to practice effective birth control during the study and for 6 weeks after discontinuation of MMF
  - Deceased donor: 100%
  - Previous transplantation: 0%
  - PRA > 20 %: 9.5%; PRA > 10%: 12.2%
  - HLA mismatch (mean): 3.4
  - Cold ischaemia time (mean): 18 h
  - Delayed graft function: 32%
- Number: treatment group (72); control group (76)
- Mean age ± SD (years): treatment group (49.9 ± 12.6); control group (46.5 ± 12.4)
- Sex (M/F): treatment group (29/43); control group (44/32)
- Exclusion criteria: recipient of a paediatric en bloc kidneys; recipient of a kidney from a non-heart beating donor; recipient of a previous organ transplant; currently receiving multiorgan transplant; recipient of a living donor kidney transplant or ABO incompatible with their donor; known carrier of HIV; lactating female; known to have hypersensitivity to Tac, CsA, MMF, or castor oil; receiving investigational prophylactic immunosuppressants

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 1.5 to 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: ATG/ OKT3, if delayed graft function within the first day post-transplantation • Tac, target C_0 (month 3): 5 to 15 ng/mL • Corticosteroids
Outcomes	• Death • Graft loss • Malignancy (except non-melanoma skin cancer) • Acute rejection • Infections • NODAT • Kidney function measures (SCr, CrCl) • Adverse events (hyperlipidaemia, serum cholesterol)
Notes	• Additional intervention arm (CsA/MMF) • Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on method used is available

Johnson 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported; all patients followed up or accounted for; twelve patients discontinued study drug
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes regarding efficacy and safety. Relevant outcomes (efficacy and safety) for this review have been reported
Other bias	High risk	This study was supported by a grant from Fujisawa Healthcare, Inc, Deerfield, IL

Suhail 2000

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1997 to 1999 • Duration of follow-up: 6 months

Participants	• Country: Singapore
	• Setting: single centre
	• Patients undergoing cadaveric kidney transplant
	  ◦ Deceased donor: 100%
	  ◦ Previous transplantation: 0%
	  ◦ PRA level: not reported
	  ◦ HLA mismatch: not reported
	  ◦ Cold ischaemia time: not reported
	  ◦ Delayed graft function: not reported
	• Number: treatment group (20); control group (20)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: seropositivity to hepatitis B surface antigen or hepatitis C; hematologic abnormalities; need for antilymphocyte preparations for prophylaxis; abnormal perfusion scan within the first 24 hours post-kidney transplant

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 1 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: none

Suhail 2000 *(Continued)*

	• CsA-ME, target C_0(month 3): not reported • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function • Acute rejection • Infections • Kidney function measures (SCr) • Adverse events (diarrhoea, leucopenia)
Notes	• Publication: Transplantation Proceedings • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis unclear; number randomised or number of patients at the end of the study was not reported
Selective reporting (reporting bias)	Low risk	The published report included most expected outcomes regarding efficacy and safety
Other bias	Unclear risk	Funding source not reported

Folkmane 2001

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1997 to 1999 • Duration of follow-up: 1 year

Participants	• Country: Latvia
	• Setting: single centre
	• Patients receiving their first cadaveric kidney transplant
	  ○ deceased donor: 100%
	  ○ Previous transplantation: 0%
	  ○ PRA level: not reported

Folkmane 2001 *(Continued)*

- HLA mismatch: not reported
- Cold ischaemia time: not reported
- Delayed graft function: not reported

- Number: treatment group (23); control group (25)
- Median age ± SD: 42.6 ± 13.2 years
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 1 to 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: none • CsA (formulation not reported), target C_0 (month 3): 150 to 250 ng/mL • Corticosteroids
Outcomes	• Graft loss • Primary non-function • Acute rejection • Infections
Notes	• Additional intervention arm (basiliximab/CsA/AZA) • Funding: not reported • Publication: Transplantation Proceedings • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis unclear; number randomised or number of patients at the end of the study was not reported

Folkmane 2001 *(Continued)*

Selective reporting (reporting bias)	High risk	The published report included few outcomes regarding efficacy and safety
Other bias	Unclear risk	Funding source not reported

Busque 2001

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported • Duration of follow-up: 6 months

Participants	• Country: Canada
	• Setting: multicentre (6)
	• Adult recipients receiving their first cadaveric kidney transplant
	  ○ Deceased donor: 100%
	  ○ previous transplantation: 0%
	  ○ PRA level: not reported
	  ○ HLA mismatch (median): 3
	  ○ Cold ischaemia time (mean): 15 h
	  ○ Delayed graft function: 22%
	• Number: treatment group (23); control group (23)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: not reported

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 1.5 to 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: agent unclear, if delayed graft function • Tac target C_0 (month 3): 5 to 15 ng/mL • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function • Acute rejection • NODAT • Kidney function measures (SCr)
Notes	• Additional intervention arm (CsA/MMF) • Publication: Transplantation Proceedings • Language: English

Risk of bias

Busque 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis unclear; number randomised or number of patients at the end of the study was not reported
Selective reporting (reporting bias)	Low risk	The published report included most expected outcomes regarding efficacy and safety
Other bias	High risk	The study was supported by Fujisawa Canada Inc.

Ji 2001

Methods	• Study type: quasi-RCT • Study time frame/year of transplantation: 1996 to 1998 • Duration of follow-up: 6 months

Participants	• Country: China
	• Setting: single centre
	• Primary deceased donor kidney transplantation; PRA negative; negative cross-match
	  ◦ Deceased donor: 100%
	  ◦ Previous transplantation: not reported
	  ◦ PRA level: max. 6%
	  ◦ HLA mismatch (mean): 3
	  ◦ Cold ischaemia time: not reported
	  ◦ Delayed graft function: not reported
	• Number: treatment group (56); control group (50)
	• Mean age: 39
	• Sex (M/F): not reported
	• Exclusion criteria: HLA (A, B, DR) > 3 mismatches; contraindication against CsA, steroids, AZA, MMF; contraindication against oral medication

Interventions	Treatment group • MMF • 1 g/d, orally Control group • AZA

Ji 2001 *(Continued)*

	• 50 mg/d, orally Concomitant immunosuppression • Induction antibody: ATG/ALG, all patients • CsA (formulation not reported), target C_0 (month 3): 500 ng/mL • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function • Acute rejection • Infections • Adverse events (diarrhoea, leucopenia, elevated liver enzymes)
Notes	• Publication: full journal article • Language: Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-RCT, patients allocated in alternating sequence
Allocation concealment (selection bias)	High risk	Patients were consecutively enrolled and were allocated to the treatment arms in alternating sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear; all patients followed-up
Selective reporting (reporting bias)	Low risk	The published report included most expected outcomes regarding efficacy and safety
Other bias	Low risk	The study was funded by a university grant

Weimer 2002

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1998 to 2000 • Duration of follow-up: 2 years
Participants	• Country: Germany • Setting: single centre • Patients receiving a kidney allograft (deceased or living donor)

Weimer 2002 *(Continued)*

- Deceased donor: 75%
- Previous transplantation: 14.3%
- PRA level: max 8%
- HLA mismatch (mean): 2.6
- Cold ischaemia time (mean): 13 h
- Delayed graft function: 16 %

- Number: treatment group (31); control group (25)
- Mean age: 47 years
- Sex: 39% male
- Exclusion criteria: not reported

Interventions	Treatment group • MMF • Dose unclear Control group • AZA • Dose unclear Concomitant immunosuppression • Induction antibody: ATG if previous transplantation, or PRA > 5 %, or delayed graft function • CsA-ME, target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Death • Graft loss • Primary non-function • Acute rejection • CAN • Infections • Kidney function measures (SCr, CrCl)
Notes	• Additional intervention arm (Tac/AZA) • Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgment

Weimer 2002 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	The published report included most expected outcomes regarding efficacy and safety
Other bias	High risk	The study was supported in part by the Fujisawa, Roche, Novartis, Biotest and Fresenius companies

Sun 2002b

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported • Duration of follow-up: 1 year

Participants	• Country: China
	• Setting: single centre
	• Deceased donor transplantation; cause of ESRD chronic glomerulonephritis; ABO compatible; negative cross-match
	  ◦ Deceased donor: 100%
	  ◦ Previous transplantation: not reported
	  ◦ age (mean): 35 years, gender: 80 % male
	  ◦ PRA level: not reported
	  ◦ HLA mismatch: not reported
	  ◦ Cold ischaemia time: not reported
	  ◦ Delayed graft function: not reported
	• Number: treatment group (40); control group (46)
	• Mean age: 35 years
	• Sex: 80% male
	• Exclusion criteria: not reported

Interventions	Treatment group • MMF • 1.5 to 2 g/d, orally Control group • AZA • 50 to 75 mg/d, orally Concomitant immunosuppression • Induction antibody: none • CsA (formulation not reported), target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Graft loss • Acute rejection • Infections • Kidney function measures (SCr)

Sun 2002b *(Continued)*

	• Adverse events (diarrhoea, leucopenia, thrombocytopenia, elevated liver enzymes)
Notes	• Publication: full journal article • Language: Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear; all patients followed-up.
Selective reporting (reporting bias)	Low risk	The published report included most expected outcomes regarding efficacy and safety.
Other bias	Unclear risk	Funding source not reported

Tuncer 2002

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1995 to 1999 • Duration of follow-up: 5 years

Participants	• Country: Turkey
	• Setting: single centre
	• Patients receiving their first-graft cadaveric or living donor kidney transplant
	  ◦ Deceased donor: 19.7%
	  ◦ Previous transplantation: 0%
	  ◦ PRA level: not reported
	  ◦ HLA mismatch (mean): 2.6
	  ◦ Cold ischaemia time: not reported
	  ◦ Delayed graft function: not reported
	• Number: treatment group (38); control group (38)
	• Mean age ± SE (years): treatment group (34.8 ± 2.3); control group (41.4 ± 3.0)
	• Sex (M/F): treatment group (27/11); control group (28/10)
	• Exclusion criteria: not reported

Interventions	Treatment group

Tuncer 2002 *(Continued)*

	• MMF • 2 g/d, orally Control group • AZA • 1.5 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: ATG, if deceased donor transplantation • CsA/CsA-ME, target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Death • Graft loss • Acute rejection • CAN
Notes	• Publication: Transplantation Proceedings • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	"non-blinded study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear; all patients were followed up
Selective reporting (reporting bias)	Unclear risk	The published report included few outcomes regarding efficacy and safety
Other bias	Unclear risk	Funding source not reported

Army Hospital 2002

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported • Duration of follow-up: unclear

Army Hospital 2002 *(Continued)*

Participants	• Country: India
	• Setting: single centre
	• Kidney transplant recipients; living graft donation
	  ○ deceased donor: 0%
	  ○ previous transplantation: 0%
	  ○ PRA level: not reported
	  ○ HLA mismatch: not reported
	  ○ Cold ischaemia time: not reported
	  ○ Delayed graft function: not reported
	• Number: treatment group (17); control group (16)
	• Mean age: 34 years
	• Sex: 82% male
	• Exclusion criteria: not reported

Interventions	Treatment group • MMF • Dose and administration unclear Control group • AZA • Dose and administration unclear Concomitant immunosuppression • Induction antibody: none • CsA (formulation not reported), target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Acute rejection • Infections • Kidney function measures (SCr) • Adverse events (anaemia, leucopenia)
Notes	• Publication: conference abstract only • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment.
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment

Army Hospital 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis unclear; number randomised and number of patients at the end of the study not reported. (data only available from conference abstract)
Selective reporting (reporting bias)	High risk	The published report included few outcomes regarding efficacy and safety. (data only available from conference abstract)
Other bias	Unclear risk	Funding source not reported

Sadek 2002

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported • Duration of follow-up: 1 year

Participants	• Country: Belgium, Brazil, Canada, Italy, Norway, Spain, Switzerland, UK
	• Setting: international multicentre (28)
	• Patients between 18 to 70 years old receiving a first cadaveric or living donor kidney transplant; female patients of childbearing age required a negative pregnancy test
	  ◦ Deceased donor: 86.5%
	  ◦ Previous transplantation: 0 %
	  ◦ PRA level: not reported
	  ◦ HLA mismatch: not reported
	  ◦ Cold ischaemia time: not reported
	  ◦ Delayed graft function: not reported
	• Number: treatment group (162); control group 157()
	• Mean age ± SD (years): treatment group (43.9 ± 12.8); control group (43.9 ± 13.0)
	• Sex (M): treatment group (71.0%); control group (59.9%)
	• Exclusion criteria: graft originated from an asystolic donor; previous kidney transplant or other transplanted organ; induction therapy with any antilymphocytic antibody preparation, positive T-cell crossmatch, and ABO incompatibility against the donor; positive HIV status; malignancy (other than local basal or squamous cell carcinoma of the skin) within the last 5 years; pre-existing gout treated with allopurinol; use of any other investigational drug within 30 days of study entry; female patients of childbearing potential who were unwilling to use an effective for of contraception for 12 months

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 1 to 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: none • CsA-ME, target C_0 (month 3): 150 to 250 ng/mL • Corticosteroids
Outcomes	• Death • Graft loss • Malignancy (except non-melanoma skin cancer)

Sadek 2002 *(Continued)*

	• Acute rejection • Infections • Kidney function measures (SCr) • Adverse events (diarrhoea, abdominal pain, nausea, vomiting, anaemia, leucopenia, hypertension)
Notes	• Additional intervention arm (MMF replaced by AZA, 3 months post-transplantation) • Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomization was [...] performed with the Almedica Drug Labeling System (Almedica Service Corp., Allendale, New Jersey). The numbers assigned to each center were sequential within each stratum."
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported, all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes regarding efficacy and safety
Other bias	High risk	This study was supported by a grant from Novartis Pharma AG, Basel, Switzerland

Miladipour 2002

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1997 to 2000 • Duration of follow-up: 6 months
Participants	• Country: Iran • Setting: single centre • Kidney transplant recipients; primary or secondary transplantation; patient characteristics not reported • Number: treatment group (40); control group (40) • Mean age, range: 39, 20 to 68 years • Sex (M/F): 21/22 • Exclusion criteria: not reported

Miladipour 2002 *(Continued)*

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 100 to 150 mg/d, orally Concomitant immunosuppression • Induction antibody: none • CsA (formulation not reported), target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Graft loss • Acute rejection • Infections • Kidney function measures (SCr) • Adverse events (diarrhoea, GI bleeding, leucopenia, thrombocytopenia, elevated liver enzymes)
Notes	• Publication: Transplantation proceedings • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear; all patients followed up
Selective reporting (reporting bias)	Low risk	The published report included most outcomes regarding efficacy and safety
Other bias	Unclear risk	Funding source not reported

COSTAMP Study 2002

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1999 to 2001 • Duration of follow-up: 6 months

Participants	• Countries: Poland, Hungary, Czech Republic, Ireland
	• Setting: international multicentre
	• Patients ≥18 years old and candidates for primary kidney transplantation or re-transplantation; female patients were to maintain effective birth control during the study
	  ◦ Deceased donor: 96%
	  ◦ Previous transplantation: 5.3%
	  ◦ PRA level: not reported
	  ◦ HLA mismatch (mean): 2.7
	  ◦ Cold ischaemia time (mean): 21 h
	  ◦ Delayed graft function: not reported
	• Number: treatment group (243); control group (246)
	• Mean age (years): treatment group (43.8); control group (42.1)
	• Sex (M/F): treatment group (156/87); control group (157/89)
	• Exclusion criteria: PRA grade > 50%; loss of a previous graft within <1 year due to immunological reasons; intolerance to any of the study drugs, HCO-60, or macrolide antibiotics; requiring systemic immunosuppressive medication for other reasons that transplantation; significant liver disease; severe diarrhoea; history of malignancy, uncontrolled infections or HIV; unlikely to comply or had a history of substance abuse

Interventions	Treatment group • MMF • 1 g/d, orally Control group • AZA • 1 to 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: none • Tac, target C_0 (month 3): 5 to 10 ng/mL • Corticosteroids, withdrawal planned by study protocol at month 3
Outcomes	• Death • Graft loss • Acute rejection • Infections • NODAT • Kidney function measures (SCr) • Adverse events (diarrhoea, leucopenia, hyperlipidaemia)
Notes	• Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement

COSTAMP Study 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The histological evaluation of the biopsy was performed by the local histopathologist who was blinded towards the patient's treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported, all patients followed up or accounted for. The majority of patients (452 patients; 92 %) completed the study
Selective reporting (reporting bias)	Low risk	The published report included most expected outcomes regarding efficacy and safety
Other bias	High risk	This study was supported by Fujisawa GmbH, Munich, Germany

Baltar 2002

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported • Duration of follow-up: 1 year

Participants	• Country: Spain
	• Setting: single centre
	• Primary deceased donor kidney transplantation
	  ◦ Deceased donor: 100%
	  ◦ Previous transplantation: 0%
	  ◦ PRA level: not reported
	  ◦ HLA mismatch (mean): 2.2
	  ◦ Cold ischaemia time (mean): 17 h
	  ◦ Delayed graft function: 35%
	• Number: treatment group (14); control group (12)
	• Median age, range: 41, 32 to 47 years
	• Sex (M/F): 69%/31%
	• Exclusion criteria: not reported

Interventions	Treatment group • MMF • dose and administration unclear Control group • AZA • dose and administration unclear Concomitant immunosuppression

Baltar 2002 *(Continued)*

	• Induction antibody: none • CsA (formulation not reported), target C_0 (month 3): not reported • Corticosteroids
Outcomes	• acute rejection
Notes	• Publication: full journal article • Language: Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear; all patients followed up
Selective reporting (reporting bias)	High risk	The published report included very few outcomes regarding efficacy
Other bias	High risk	The study was supported by Roche

Keven 2003

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 2000 to 2002 • Duration of follow-up: 6 months

Participants	• Country: Turkey
	• Setting: single centre
	• Patients 18 to 60 years old receiving cadaveric or living related kidney transplant
	  ○ Deceased donor: 24.4%
	  ○ Previous transplantation: not reported
	  ○ PRA level: not reported
	  ○ HLA mismatch: not reported
	  ○ Cold ischaemia time: not reported
	  ○ Delayed graft function: not reported
	• Number: treatment group (24); control group (17)
	• Mean age ± SD (years): treatment group (32.9 ± 9.9); control group (32.1 ± 11.2)

Keven 2003 *(Continued)*

- Sex (M/F): treatment group (15/7); control group (10/7)
- Exclusion criteria: ascites; chronic diarrhoea (for longer than 3 weeks); significant proteinuria before or after transplantation (> 1 g/d); stopping or interruption of their MMF or AZA for 15 days; as least one low immunoglobulin level before transplantation

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 2 to 3 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: ATG, if delayed graft function in deceased donor transplantation • Tac or CsA (formulation not reported): "randomly selected", target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Acute rejection • Infections
Notes	• Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT analysis: eight patients not analysed due to reported reasons (e.g. diarrhoea, proteinuria, etc.); however, all patients followed up
Selective reporting (reporting bias)	High risk	The published report included very few outcomes regarding efficacy and safety
Other bias	Unclear risk	Funding source not reported

Merville 2004

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: not reported • Duration of follow-up: 1 year

Participants	• Country: France
	• Setting: multicentre (3)
	• Men and women, 18 to 70 years of age; first ABO-compatible cadaver kidney transplant
	  ○ Deceased donor: 100%
	  ○ Previous transplantation: 0%
	  ○ PRA > 20%: 8.5%
	  ○ HLA mismatch (mean): 2.8
	  ○ Cold ischaemia time (mean): 22 h
	  ○ Delayed graft function: 42%
	• Number: treatment group (37); control group (34)
	• Mean age ± SD (years): treatment group (41 ± 16); control group (42 ± 14)
	• Sex (M/F): treatment group (26/11); control group (23/11)
	• Exclusion criteria: previous organ transplant; receiving a multiorgan transplant; high immunological risk (PRA ≥ 80%); donor age ≥ 65 years; currently receiving immunosuppressants; patients were excluded after randomisation if the randomised drug therapy was discontinued for more than 14 days

Interventions	Treatment group • MMF • 2 g/d, orally Control group • AZA • 1.5 to 2 mg/kg body weight/d, orally Concomitant immunosuppression • Induction antibody: ATG, all patients • CsA-ME, target C_0 (month 3): 100 to 150 ng/mL • Corticosteroids
Outcomes	• Death • Graft loss • Acute rejection • CAN • Infections • Kidney function measures (SCr, CrCl, proteinuria) • Adverse events (total cholesterol)
Notes	• Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment

Merville 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All biopsies (from donors and recipients) were blindly and centrally examined by the same pathologist (CD)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported; all patients followed up or accounted for; 3 patients, 2 in the MMF group and one in the AZA group, were excluded after randomisation for discontinuation of the randomised drug and a total of 71 individuals was finally available for analysis
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes regarding efficacy and safety
Other bias	Low risk	The study was financially supported partly by the Association Promotion Transplantation Renale and the Centre Hospitalier Universitaire de Bordeaux (non-industry)

MYSS Study 2004

Methods	• Study type: parallel RCT • Study time frame/year of transplantation: 1997 to 2001 • Duration of follow-up: 18 months, follow-up study up to 7 years

Participants	• Countries: Italy, France, Belgium
	• Setting: international multicentre (11)
	• Patients 18 to 70 years old receiving their first kidney transplant from a cadaver donor
	  ◦ Deceased donor: 100%
	  ◦ Previous transplantation: 0%
	  ◦ age (mean): 45 years, gender: 66 % male
	  ◦ PRA level: not reported
	  ◦ HLA mismatch (mean): 1.9
	  ◦ Cold ischaemia time (mean): 16 h
	  ◦ Delayed graft function: 33%
	• Number (randomised/analysed): treatment group (168/167); control group (168/167)
	• Mean age ± SD (years): treatment group (43.3 ± 12.9); control group (45.9 ± 11.5)
	• Sex (M/F): treatment group (119/49); control group (101/67)
	• Exclusion criteria: history of malignant disorders (apart from successfully treated non-metastatic basal or squamous cell carcinoma of the skin); serological evidence of infection with HIV or hepatitis B virus; systemic infections requiring continued antibiotic therapy; haematological abnormalities (WCC < 3 x10^9/L, platelet count < 1 x10^9/L, or Hb < 50 g/L); severe GI disorders, active peptic ulcer disease; inability to take oral medication long term; pregnant women, nursing mothers, women who did not agree to use adequate contraception; not fully understanding the purposes of the study or already involved in other studies

Interventions	Treatment group • MMF

MYSS Study 2004 *(Continued)*

	• 2 g/d, orally Control group • AZA • 100 mg/d if body weight < 75 kg, 150 mg/d if body weight ≥ 75 kg, orally Concomitant immunosuppression • Induction antibody: none • CsA-ME, target C_0 (month 3): 150 to 250 ng/mL • Corticosteroids, withdrawal planned by study protocol at month 6
Outcomes	• Death • Graft loss • Primary non-function • Malignancy (except non-melanoma skin cancer) • Acute rejection • Infections • Non-melanoma skin cancer • Kidney function measures (SCr, CrCl, GFR, proteinuria) • Adverse events (diarrhoea, anaemia, leucopenia)
Notes	• Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was centralised at the Laboratory of Biostatistics of the Clinical Research Centre for Rare Diseases Aldo e Cele Daccò of the Mario Negri Institute for Pharmacological Research, under the responsibility of an independent investigator who was not involved in design or performance of the study."
Allocation concealment (selection bias)	Unclear risk	Randomisation stated, but no information on allocation method used is available
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported, two patients did not receive study drug or kidney graft and were excluded from the analyses; all patients followed up or accounted for
Selective reporting (reporting bias)	Low risk	The published report included all expected outcomes regarding efficacy and safety
Other bias	Low risk	No conflicts of interest declared. The study was supported by non-industry funding

Joh 2005

Methods	• Study type: quasi-RCT • Study time frame/year of transplantation: 1998 to 2000 • Duration of follow-up: 5 years

Participants	• Country: Korea
	• Setting: single centre
	• Patients receiving cadaveric kidney transplant
	  ○ Deceased donor: 100%
	  ○ Previous transplantation: not reported
	  ○ PRA > 20%: 2.9%
	  ○ HLA mismatch: not reported
	  ○ Cold ischaemia time (mean): 6.6 h
	  ○ Delayed graft function: not reported
	• Number: treatment group (34); control group (34)
	• Mean age: 39 years
	• Sex: 53% male
	• Exclusion criteria: not reported

Interventions	Treatment group • MMF • 1.5 g/d, orally Control group • AZA • 100 to 130 mg/d, orally Concomitant immunosuppression • Induction antibody: none • CsA (formulation not reported), target C_0 (month 3): not reported • Corticosteroids
Outcomes	• Death • Graft loss • Acute rejection • Infections
Notes	• Publication: full journal article • Language: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-RCT: "When two cases of kidney transplantation took place from the same cadaveric donor in our hospital, transplantation was performed on a first come first serve base. MMF was administered to the early-transplanted patient and AZA to the following patient and vice versa in the next case"
Allocation concealment (selection bias)	High risk	Patients were consecutively enrolled and were allocated to the treatment arms in alternating sequence

Joh 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis unclear; all patients were followed up
Selective reporting (reporting bias)	Unclear risk	The published report included few outcomes regarding efficacy and safety
Other bias	Unclear risk	Funding source not reported

ALG - antilymphocyte globulin; ATG - antithymocyte globulin; AZA - azathioprine; CAN - chronic allograft nephropathy; CrCl - creatinine clearance; CsA - cyclosporin A, CsA-ME - cyclosporin A microemulsion; GI - gastrointestinal; Hb - haemoglobin; HBV - hepatitis B virus; HIV - human immunodeficiency virus; HLA - human leucocyte antigen; HTLV - human T-lymphotropic virus; ITT - intention-to-treat; MMF - mycophenolate mofetil; NODAT - new onset diabetes after transplantation; PRA - panel reactive antibody; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; SE - standard error; Tac - tacrolimus; WCC - white cell count

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

Study	Reason for exclusion
Araujo 1999	Not primary regimen
Asci 2002	Not primary regimen
Baek 2004	Not RCT
Bataille 2010	Unequal concomitant regimen
Benfield 1999	Randomised to OKT3 and CsA (not AZA and MMF)
Boletis 1999b	Not RCT
Brennan 2005	Not comparison of interest
Cransberg 2007	Not primary regimen, no comparison of interest
El-Agroudy 2009	Not primary regimen
Ettenger 1995	Not comparison of interest
Griffin 2003	Not primary regimen
Ha 2004	Not primary regimen
Hernandez 2007	No comparison of interest
Jain 2001	Not primary regimen

Study	Reason for exclusion
Jirasiritham 2000	Not primary regimen
Kasiske 1997	Not RCT
Khosroshahi 2006a	not RCT
Kim 1999	not RCT
Langman 1996	Not primary regimen
Lezaic 2005	Not primary regimen
Lison 2004	Not comparison of interest
Makhdoomi 2005	Not RCT
Mandelbaum 1998	not RCT
Merion 2000	Multi-organ transplantation
Metcalfe 2002	Not primary regimen
MMF 1998	Not primary regimen
MO2ART Study 2003	Not comparison of interest
Nowacka-Cieciur 2000	Not primary regimen, no comparison of interest
Oliveira 1999	No RCT
Schurter 1997	Not primary regimen
Smak Gregoor 2000	Not primary regimen
Touchard 2005	Not primary regimen
Tsinalis 2000	Unequal concomitant regimen
Vacher-Coponat 2006	Unequal concomitant regimen
van der Mast 2000	Not primary regimen
Vanrenterghem 1998	Not comparison of interest
Woeste 2002	Multi-organ transplantation, unequal concomitant regimen
Wuthrich 2000	Not primary regimen

AZA - azathioprine; CsA - cyclosporin A; MMF - mycophenolate mofetil; RCT - randomised controlled trial
Legend: no RCT: study design not RCT or quasi-RCT; **multi-organ transplantation**: not solely kidney transplantation, exclusion of studies enrolling patients undergoing multi-organ transplantation, e.g. simultaneous kidney-pancreas transplantation; **not primary regimen:** the randomisation to MMF versus AZA was not performed at the time of transplantation, but subsequently during the maintenance phase (e.g. due to previous acute rejection, chronic allograft nephropathy, calcineurin-inhibitor-toxicity or in stable graft function status); **no comparison of interest:** randomised intervention not of interest for the review, i.e. not MMF versus AZA; **unequal concomitant regimen**,

i.e. patients randomised to intervention and control were treated with different immunosuppressive regimens (e.g. MMF/cyclosporin A versus AZA/tacrolimus)

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

ATHENA Study 2012

Trial name or title	A randomized, prospective, multicenter trial to compare the effect on chronic allograft nephropathy prevention of mycophenolate mofetil versus azathioprine as the sole immunosuppressive therapy for kidney transplant recipients (ATHENA)
Methods	RCT, multicentre (6) Year of transplantation: 2007 to 2012 Study duration: 4 years
Participants	Estimated enrolment: 224 Country: Italy Deceased donor: 100% Previous transplantation: 0% Inclusion criteria • Patients 18 to 75 years, receiving their first single or double kidney transplant from deceased donors Exclusion criteria • WCC < 2000/µl • "high immunological risk" (previous transplantation, PRA level > 10%) • History of malignancy • Evidence of active Hepatitis C, Hepatitis B or HIV • Pregnancy or lactation • Women of childbearing potential without following a scientifically accepted form of contraception • Legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequence of the trial • Evidence of an uncooperative attitude • Any evidence that the patient will not be able to complete the trial follow-up
Interventions	Treatment group • MMF • 1.5 g/d, orally Control group • AZA • 75 mg/d if body weight < 75 kg, 125 mg/d if body weight ≥ 75 kg, orally Concomitant regimen • Induction therapy: IL-2 receptor antibody (20 mg basiliximab twice) and RATG (0.5 mg/kg for 7 days) and IV steroids (6 days) • CsA-ME, withdrawn after 1 year, if rejection-free and no evidence of tubulitis in graft biopsy
Outcomes	Primary endpoint

ATHENA Study 2012 *(Continued)*	• Biopsy proven CAN 3 years post-transplant in patients completing CsA withdrawal Secondary endpoints • overall incidence of acute rejections at 1 and 2 years • overall incidence of CAN at 3 years • graft and patient survival at 4 years
Starting date	May 2007
Contact information	Norberto Perico, MD; Mario Negri Institute for Pharmacological Research; Milano, Italy
Notes	The study was registered at clinicaltrials.gov (#NCT00494741) on June 29, 2007 This study is ongoing, but not recruiting participants (last update February 24, 2014) Estimated completion date: September 2016

AZA - azathioprine; CAN - chronic allograft nephropathy; CsA-ME - cyclosporin A emulsion; HIV - human immunodeficiency virus; IL-2 - interleukin 2; IV - intravenous; MMF - mycophenolate mofetil; PRA - panel reactive antibody; RATG - rabbit antithymocyte globulin; WCC - white cell count

DATA AND ANALYSES

Comparison 1. Mycophenolate mofetil versus azathioprine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death: all cause	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Follow-up ≤ 1 year	16	2987	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.76, 1.68]
1.2 Follow-up 1 to 4 years	7	1595	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
1.3 Follow-up > 4 years	3	457	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.59, 1.07]
1.4 Longest duration of follow-up	16	2987	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.29]
2 Graft loss: including death	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Follow-up ≤ 1 year	15	2653	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.02]
2.2 Follow-up 1 to 4 years	6	1347	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.04]
2.3 Follow-up > 4 years	2	209	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.29, 1.66]
2.4 Longest duration of follow-up	15	2653	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.00]
3 Graft loss: censored for death	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Follow-up ≤ 1 year	15	2384	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.49, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Follow-up 1 to 4 years	6	1512	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.13]
3.3 Follow-up > 4 years	4	525	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.60, 1.25]
3.4 Longest duration of follow-up	17	2540	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.99]
4 Primary non-function	11	1864	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.19, 1.18]
5 Malignancy: longest duration of follow-up	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Any malignancy	5	1735	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.60, 1.09]
5.2 Lymphoma/PTLD	5	1564	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.43, 3.66]
5.3 Non-melanoma skin cancer	4	1416	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.46, 1.34]
6 Acute rejection: total	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Follow-up ≤ 6 months	19	3128	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.55, 0.75]
6.2 Follow-up 6 to 12 months	10	2086	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.58, 0.74]
6.3 Follow-up > 12 months	5	603	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.61, 0.99]
6.4 Longest duration of follow-up	22	3301	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.57, 0.73]
7 Acute rejection: confirmed by biopsy	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Follow-up ≤ 6 months	10	2306	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.50, 0.69]
7.2 Follow-up 6 to 12 months	4	714	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.49, 0.88]
7.3 Follow-up > 12 months	1	148	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.40, 1.56]
7.4 Longest duration of follow-up	12	2696	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.52, 0.68]
8 Acute rejection: steroid resistant/antibody treated	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Follow-up ≤ 6 months	11	2350	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.80]
8.2 Follow-up 6 to 12 months	5	740	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.29, 0.81]
8.3 Follow-up > 12 months	2	223	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.11, 2.44]
8.4 Longest duration of follow-up	15	2914	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.36, 0.65]

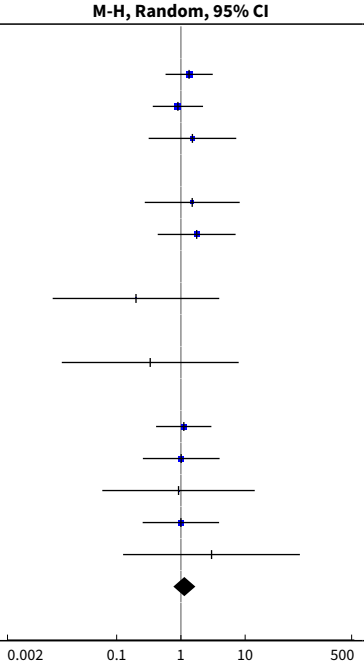
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Chronic allograft nephropathy	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Follow-up ≤ 1 year	1	71	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.43, 0.98]
9.2 Follow-up > 1 year	2	132	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.39, 1.87]
9.3 Longest duration of follow-up	3	203	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.48, 0.99]
10 Infection: other (longest duration of follow-up)	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Aspergillus	4	1316	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.65, 10.58]
10.2 BK-virus	1	56	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Candida	4	1316	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.77, 1.31]
10.4 Candida tissue invasive	4	1502	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.34, 2.31]
10.5 Herpes zoster	4	1629	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.80, 2.04]
10.6 Pneumocystis carinii/jiroveci	5	1650	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.05, 0.69]
10.7 Urinary tract/cystitis	6	1553	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.42]
11 Infection: CMV viraemia/syndrome	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Follow-up ≤ 1 year	13	2880	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.20]
11.2 Follow-up > 1 year	3	1240	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.77, 1.50]
11.3 Longest duration of follow-up	13	2880	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
12 Infection: CMV tissue invasive	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Follow-up ≤ 1 year	7	1510	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.12, 2.69]
12.2 Follow-up > 1 year	2	992	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.95, 2.40]
12.3 Longest duration of follow-up	7	1510	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.10, 2.61]
13 Graft function: serum creatinine	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 Follow-up ≤ 1 year	15	2457	Mean Difference (IV, Random, 95% CI)	0.03 [-0.07, 0.14]

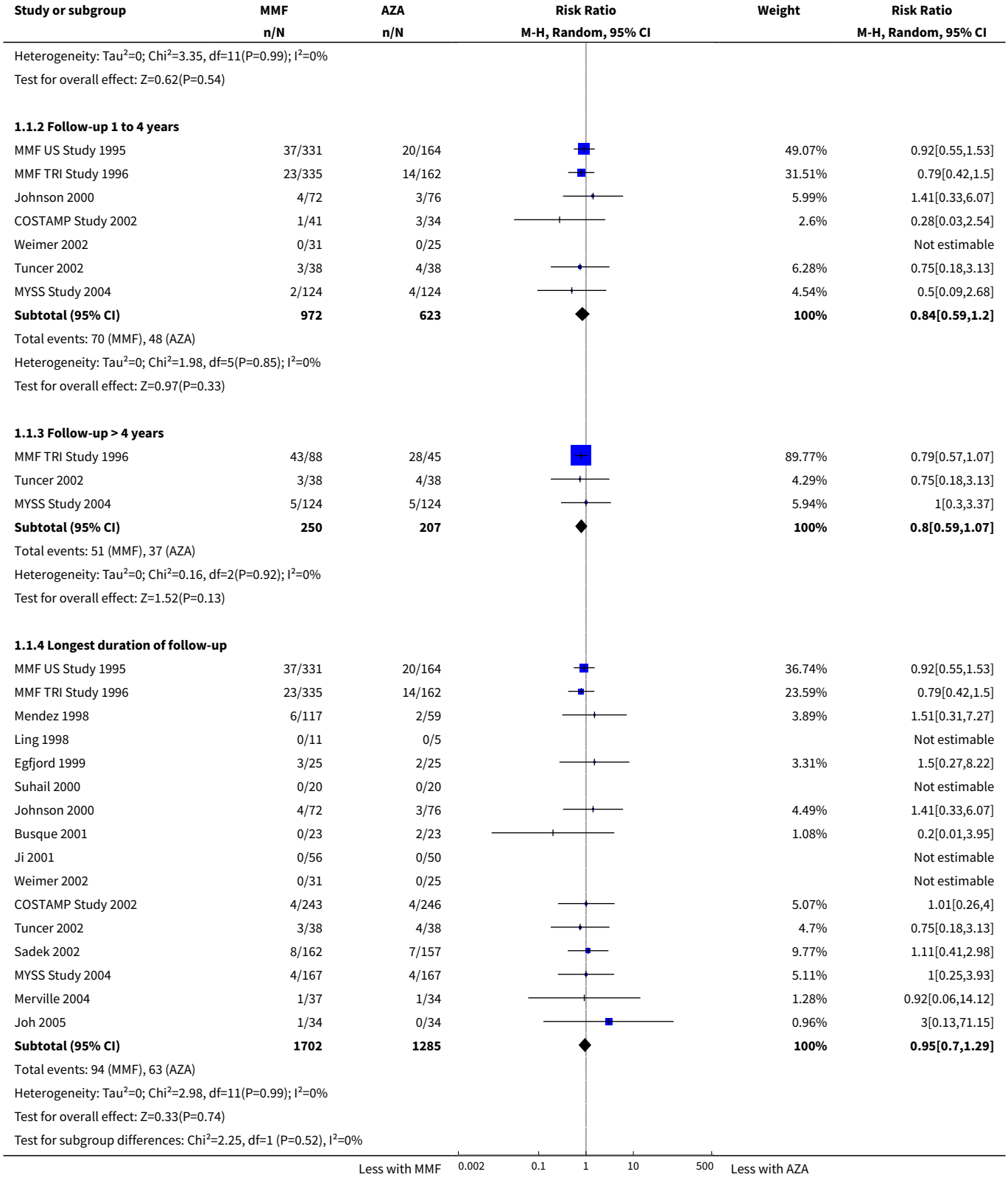
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Follow-up 1 to 4 years	4	712	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.14, 0.03]
13.3 Longest duration of follow-up	15	2233	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
14 Graft function: CrCl/GFR	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Follow-up ≤ 1 year	5	970	Mean Difference (IV, Random, 95% CI)	1.74 [-1.77, 5.25]
14.2 Follow-up 1 to 4 years	3	376	Mean Difference (IV, Random, 95% CI)	1.44 [-3.05, 5.94]
14.3 Follow-up > 4 years	2	120	Mean Difference (IV, Random, 95% CI)	0.56 [-3.48, 4.60]
14.4 Longest duration of follow-up	6	976	Mean Difference (IV, Random, 95% CI)	1.56 [-1.15, 4.27]
15 Graft function: proteinuria	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Follow-up 2 to 5 years	2	745	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.70, 1.43]
16 Graft function: proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16.1 Follow-up ≤ 1 year	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17 Adverse events: gastrointestinal (longest duration of follow-up)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 Diarrhoea	11	2638	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.32, 1.83]
17.2 Abdominal pain	3	1311	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.97, 1.44]
17.3 Vomiting	4	1487	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.83, 1.94]
17.4 Gastrointestinal bleeding	2	575	Risk Ratio (M-H, Random, 95% CI)	3.99 [1.07, 14.86]
17.5 Nausea	5	1573	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.20]
18 Adverse events: other (longest duration of follow-up)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 New onset diabetes in patients without diabetes at baseline, insulin-treated	4	445	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.34, 0.95]
18.2 Hypertension	1	319	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.64, 1.47]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.3 Hyperlipidaemia	3	813	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.59, 3.39]
18.4 Elevated liver enzymes	3	272	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.21, 1.23]
19 Adverse events: haematological (longest duration of follow-up)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 Anaemia	5	1821	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.87, 1.31]
19.2 Severe anaemia	2	528	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.61, 3.28]
19.3 Leucopenia	12	2671	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.78, 1.39]
19.4 Severe leucopenia	3	1025	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.33, 6.19]
19.5 Thrombocytopenia	5	1492	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.52, 1.03]
19.6 Severe thrombocytopenia	2	992	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.11, 3.21]
20 Total cholesterol	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 Follow-up ≤ 1 year	2	219	Mean Difference (IV, Random, 95% CI)	-2.57 [-15.65, 10.51]

Analysis 1.1. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 1 Death: all cause.

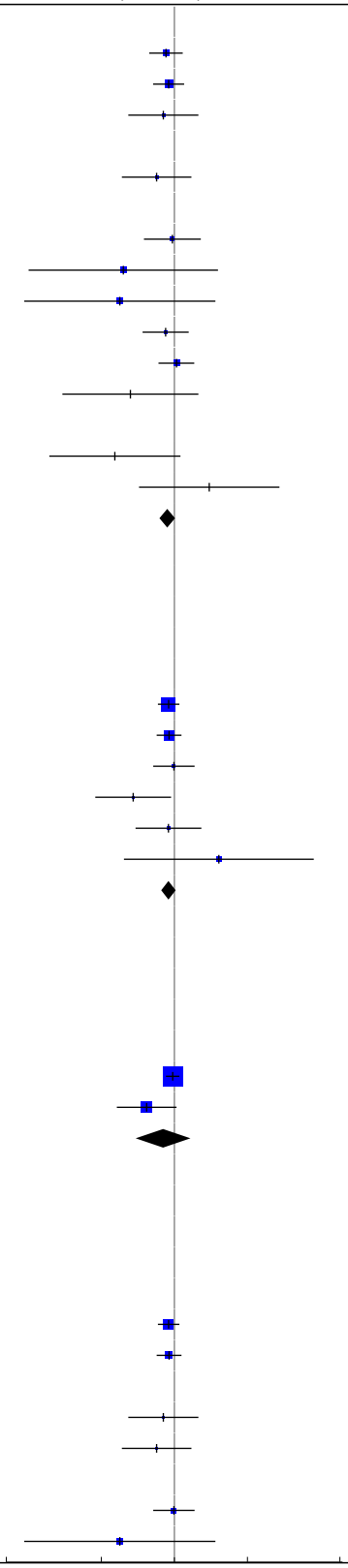
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Follow-up ≤ 1 year					
MMF US Study 1995	19/331	7/164		21.74%	1.34[0.58,3.13]
MMF TRI Study 1996	13/335	7/162		19.23%	0.9[0.37,2.21]
Mendez 1998	6/117	2/59		6.32%	1.51[0.31,7.27]
Ling 1998	0/11	0/5			Not estimable
Egfjord 1999	3/25	2/25		5.38%	1.5[0.27,8.22]
Johnson 2000	5/72	3/76		8%	1.76[0.44,7.1]
Suhail 2000	0/20	0/20			Not estimable
Busque 2001	0/23	2/23		1.75%	0.2[0.01,3.95]
Ji 2001	0/56	0/50			Not estimable
Tuncer 2002	0/38	1/38		1.55%	0.33[0.01,7.93]
Weimer 2002	0/31	0/25			Not estimable
Sadek 2002	8/162	7/157		15.87%	1.11[0.41,2.98]
COSTAMP Study 2002	4/243	4/246		8.24%	1.01[0.26,4]
Merville 2004	1/37	1/34		2.08%	0.92[0.06,14.12]
MYSS Study 2004	4/167	4/167		8.3%	1[0.25,3.93]
Joh 2005	1/34	0/34		1.55%	3[0.13,71.15]
Subtotal (95% CI)	**1702**	**1285**		**100%**	**1.13[0.76,1.68]**
Total events: 64 (MMF), 40 (AZA)					



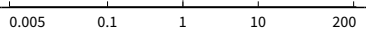


Analysis 1.2. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 2 Graft loss: including death.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Follow-up ≤ 1 year					
MMF US Study 1995	31/331	20/164		21.54%	0.77[0.45,1.3]
MMF TRI Study 1996	38/335	22/162		25.16%	0.84[0.51,1.36]
Mendez 1998	7/117	5/59		4.96%	0.71[0.23,2.13]
Ling 1998	0/11	0/5			Not estimable
Egfjord 1999	4/25	7/25		5.04%	0.57[0.19,1.71]
Suhail 2000	0/20	0/20			Not estimable
Johnson 2000	8/72	9/76		7.54%	0.94[0.38,2.3]
Busque 2001	0/23	2/23		0.68%	0.2[0.01,3.95]
Ji 2001	0/56	2/50		0.67%	0.18[0.01,3.64]
COSTAMP Study 2002	12/243	16/246		11.44%	0.76[0.37,1.57]
Sadek 2002	22/162	20/157		19%	1.07[0.61,1.87]
Tuncer 2002	1/38	4/38		1.32%	0.25[0.03,2.13]
Weimer 2002	0/31	0/25			Not estimable
Merville 2004	1/37	6/34		1.42%	0.15[0.02,1.21]
Joh 2005	3/34	1/34		1.24%	3[0.33,27.42]
Subtotal (95% CI)	**1535**	**1118**		**100%**	**0.8[0.62,1.02]**
Total events: 127 (MMF), 114 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=8.39, df=11(P=0.68); I^2=0%					
Test for overall effect: Z=1.8(P=0.07)					
1.2.2 Follow-up 1 to 4 years					
MMF US Study 1995	69/331	41/164		45.2%	0.83[0.59,1.17]
MMF TRI Study 1996	56/335	32/162		33.68%	0.85[0.57,1.25]
Johnson 2000	14/72	15/76		12.11%	0.99[0.51,1.89]
Tuncer 2002	3/38	11/38		3.62%	0.27[0.08,0.9]
COSTAMP Study 2002	6/41	6/34		4.81%	0.83[0.29,2.34]
Weimer 2002	2/31	0/25		0.58%	4.06[0.2,80.94]
Subtotal (95% CI)	**848**	**499**		**100%**	**0.83[0.66,1.04]**
Total events: 150 (MMF), 105 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=4.7, df=5(P=0.45); I^2=0%					
Test for overall effect: Z=1.62(P=0.1)					
1.2.3 Follow-up > 4 years					
MMF TRI Study 1996	63/88	34/45		63.11%	0.95[0.77,1.17]
Tuncer 2002	5/38	12/38		36.89%	0.42[0.16,1.07]
Subtotal (95% CI)	**126**	**83**		**100%**	**0.7[0.29,1.66]**
Total events: 68 (MMF), 46 (AZA)					
Heterogeneity: Tau^2=0.3; Chi^2=3.45, df=1(P=0.06); I^2=70.99%					
Test for overall effect: Z=0.81(P=0.42)					
1.2.4 Longest duration of follow-up					
MMF US Study 1995	69/331	41/164		33.39%	0.83[0.59,1.17]
MMF TRI Study 1996	56/335	32/162		24.88%	0.85[0.57,1.25]
Ling 1998	0/11	0/5			Not estimable
Mendez 1998	7/117	5/59		3.13%	0.71[0.23,2.13]
Egfjord 1999	4/25	7/25		3.18%	0.57[0.19,1.71]
Suhail 2000	0/20	0/20			Not estimable
Johnson 2000	14/72	15/76		8.95%	0.99[0.51,1.89]
Ji 2001	0/56	2/50		0.42%	0.18[0.01,3.64]

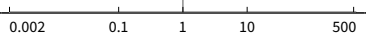


Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Busque 2001	0/23	2/23		0.43%	0.2[0.01,3.95]
Tuncer 2002	5/38	12/38		4.31%	0.42[0.16,1.07]
COSTAMP Study 2002	12/243	16/246		7.22%	0.76[0.37,1.57]
Sadek 2002	22/162	20/157		11.99%	1.07[0.61,1.87]
Weimer 2002	2/31	0/25		0.43%	4.06[0.2,80.94]
Merville 2004	1/37	6/34		0.9%	0.15[0.02,1.21]
Joh 2005	3/34	1/34		0.78%	3[0.33,27.42]
Subtotal (95% CI)	**1535**	**1118**		**100%**	**0.82[0.67,1]**
Total events: 195 (MMF), 159 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=10.51, df=12(P=0.57); I^2=0%					
Test for overall effect: Z=1.99(P=0.05)					
Test for subgroup differences: Chi^2=0.17, df=1 (P=0.98), I^2=0%					

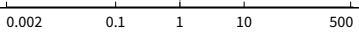


Analysis 1.3. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 3 Graft loss: censored for death.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Follow-up ≤ 1 year					
MMF US Study 1995	14/331	14/164		21.38%	0.5[0.24,1.01]
MMF TRI Study 1996	28/335	18/162		34.83%	0.75[0.43,1.32]
Mendez 1998	1/117	3/59		2.19%	0.17[0.02,1.58]
Ling 1998	0/11	0/5			Not estimable
Egfjord 1999	1/25	5/25		2.55%	0.2[0.03,1.59]
Suhail 2000	0/20	0/20			Not estimable
Ji 2001	0/56	2/50		1.21%	0.18[0.01,3.64]
Folkmane 2001	2/23	3/25		3.81%	0.72[0.13,3.96]
Busque 2001	0/23	0/23			Not estimable
Weimer 2002	0/31	0/25			Not estimable
Miladipour 2002	0/40	1/40		1.09%	0.33[0.01,7.95]
Sadek 2002	16/162	16/157		25.43%	0.97[0.5,1.87]
MYSS Study 2004	1/124	2/124		1.93%	0.5[0.05,5.44]
Merville 2004	0/37	5/34		1.34%	0.08[0,1.46]
Joh 2005	3/34	1/34		2.24%	3[0.33,27.42]
Joh 2005	2/34	1/34		1.98%	2[0.19,21.03]
Subtotal (95% CI)	**1403**	**981**		**100%**	**0.68[0.49,0.94]**
Total events: 68 (MMF), 71 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=10.54, df=11(P=0.48); I^2=0%					
Test for overall effect: Z=2.31(P=0.02)					
1.3.2 Follow-up 1 to 4 years					
MMF US Study 1995	50/331	28/164		44.4%	0.88[0.58,1.35]
MMF TRI Study 1996	39/335	25/162		36.63%	0.75[0.47,1.2]
Johnson 2000	9/72	9/76		10.6%	1.06[0.44,2.51]
Weimer 2002	2/31	0/25		0.89%	4.06[0.2,80.94]
MYSS Study 2004	3/124	7/124		4.5%	0.43[0.11,1.62]
Joh 2005	4/34	2/34		2.99%	2[0.39,10.2]
Subtotal (95% CI)	**927**	**585**		**100%**	**0.85[0.64,1.13]**
Total events: 107 (MMF), 71 (AZA)					

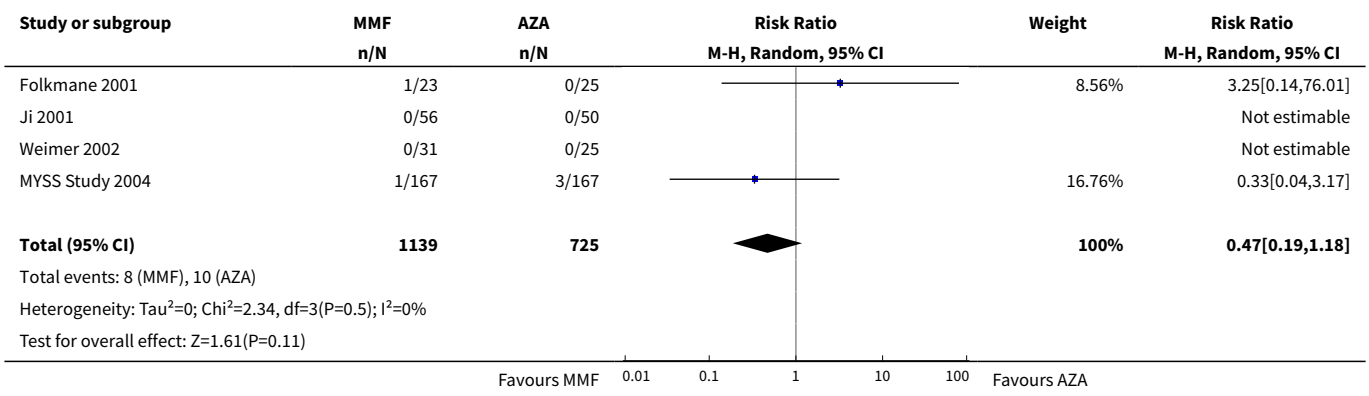


Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=3.66, df=5(P=0.6); I²=0%					
Test for overall effect: Z=1.09(P=0.28)					
1.3.3 Follow-up > 4 years					
MMF TRI Study 1996	34/88	17/45		63.1%	1.02[0.65,1.62]
Tuncer 2002	5/38	11/38		14.47%	0.45[0.17,1.18]
MYSS Study 2004	7/124	7/124		12.79%	1[0.36,2.77]
Joh 2005	4/34	6/34		9.64%	0.67[0.21,2.15]
Subtotal (95% CI)	**284**	**241**		**100%**	**0.87[0.6,1.25]**
Total events: 50 (MMF), 41 (AZA)					
Heterogeneity: Tau²=0; Chi²=2.56, df=3(P=0.47); I²=0%					
Test for overall effect: Z=0.75(P=0.45)					
1.3.4 Longest duration of follow-up					
MMF US Study 1995	50/331	28/164		31.29%	0.88[0.58,1.35]
MMF TRI Study 1996	39/335	25/162		25.82%	0.75[0.47,1.2]
Ling 1998	0/11	0/5			Not estimable
Mendez 1998	1/117	3/59		1.11%	0.17[0.02,1.58]
Egfjord 1999	1/25	5/25		1.3%	0.2[0.03,1.59]
Suhail 2000	0/20	0/20			Not estimable
Johnson 2000	9/72	9/76		7.47%	1.06[0.44,2.51]
Ji 2001	0/56	2/50		0.62%	0.18[0.01,3.64]
Busque 2001	0/23	0/23			Not estimable
Folkmane 2001	2/23	3/25		1.94%	0.72[0.13,3.96]
Weimer 2002	2/31	0/25		0.63%	4.06[0.2,80.94]
Sadek 2002	16/162	16/157		12.97%	0.97[0.5,1.87]
Miladipour 2002	0/40	1/40		0.56%	0.33[0.01,7.95]
Tuncer 2002	5/38	11/38		6.12%	0.45[0.17,1.18]
Merville 2004	0/37	5/34		0.69%	0.08[0,1.46]
MYSS Study 2004	7/124	7/124		5.41%	1[0.36,2.77]
Joh 2005	4/34	6/34		4.07%	0.67[0.21,2.15]
Subtotal (95% CI)	**1479**	**1061**		**100%**	**0.78[0.62,0.99]**
Total events: 136 (MMF), 121 (AZA)					
Heterogeneity: Tau²=0; Chi²=11.04, df=13(P=0.61); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi²=1.42, df=1 (P=0.7), I²=0%					

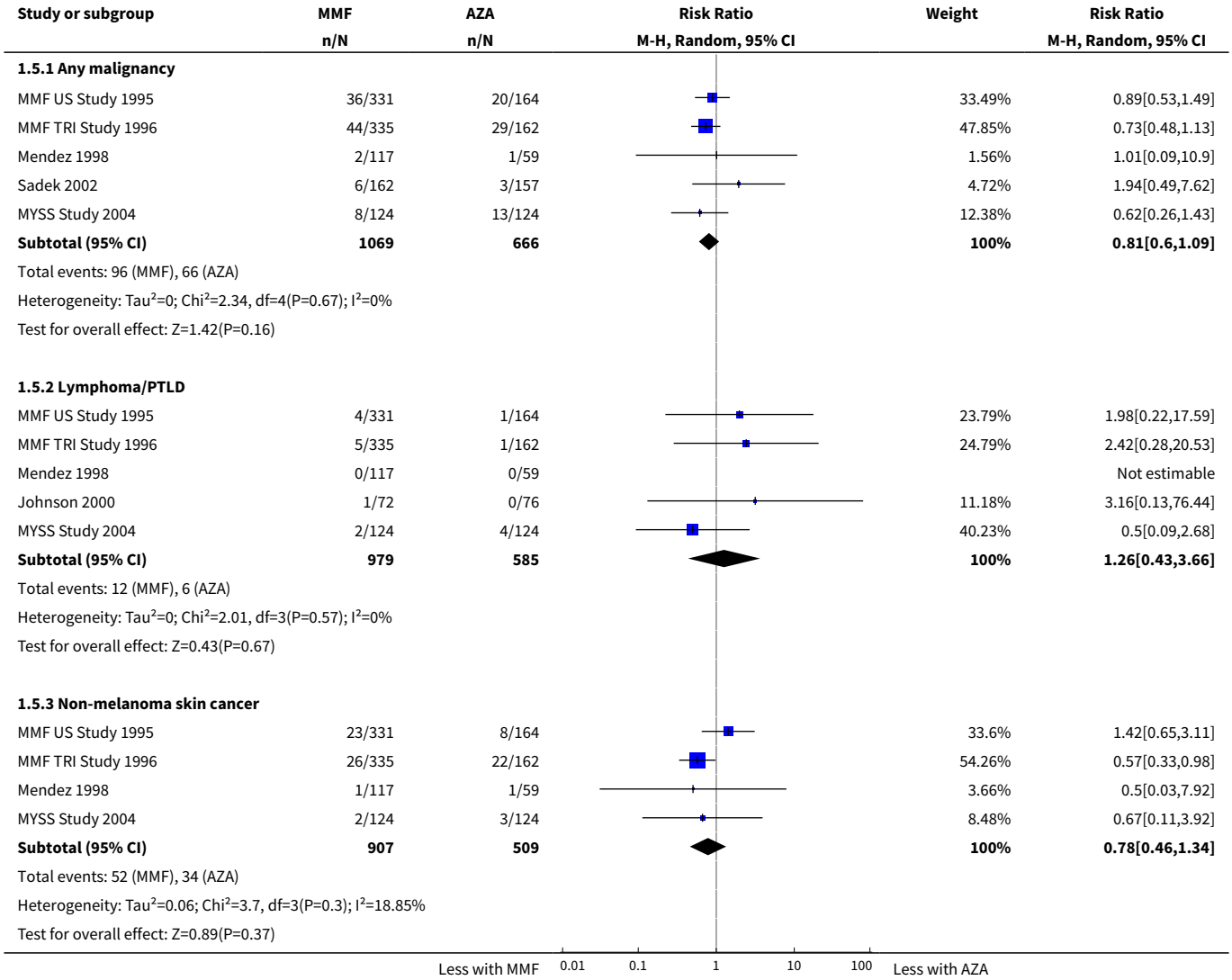


Analysis 1.4. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 4 Primary non-function.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MMF US Study 1995	1/331	0/164		8.33%	1.49[0.06,36.4]
MMF TRI Study 1996	5/335	7/162		66.35%	0.35[0.11,1.07]
Mendez 1998	0/117	0/59			Not estimable
Ling 1998	0/11	0/5			Not estimable
Egfjord 1999	0/25	0/25			Not estimable
Suhail 2000	0/20	0/20			Not estimable
Busque 2001	0/23	0/23			Not estimable

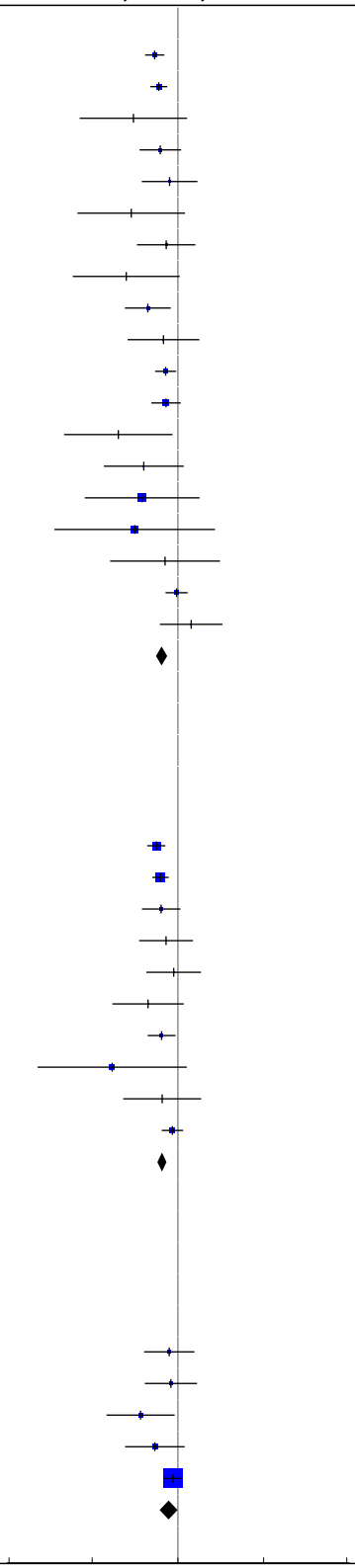


Analysis 1.5. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 5 Malignancy: longest duration of follow-up.

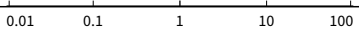


Analysis 1.6. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 6 Acute rejection: total.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Follow-up ≤ 6 months					
MMF US Study 1995	79/331	73/164		15.27%	0.54[0.41,0.69]
MMF TRI Study 1996	99/335	80/162		16.93%	0.6[0.48,0.75]
Ling 1998	2/11	3/5		1.05%	0.3[0.07,1.28]
Mendez 1998	21/117	17/59		5.77%	0.62[0.36,1.09]
Egfjord 1999	8/25	10/25		3.55%	0.8[0.38,1.69]
Suhail 2000	2/20	7/20		1.05%	0.29[0.07,1.21]
Johnson 2000	9/72	13/76		3.24%	0.73[0.33,1.6]
Busque 2001	2/23	8/23		1.06%	0.25[0.06,1.05]
Ji 2001	11/56	22/50		4.93%	0.45[0.24,0.83]
Folkmane 2001	5/23	8/25		2.25%	0.68[0.26,1.78]
COSTAMP Study 2002	59/243	83/246		13.97%	0.72[0.54,0.95]
Sadek 2002	33/162	44/157		9.54%	0.73[0.49,1.08]
Weimer 2002	2/31	8/25		1.03%	0.2[0.05,0.87]
Miladipour 2002	4/40	10/40		1.84%	0.4[0.14,1.17]
Sun 2002b	2/40	6/46		0.92%	0.38[0.08,1.79]
Army Hospital 2002	1/17	3/16		0.48%	0.31[0.04,2.71]
Keven 2003	3/24	3/17		1.01%	0.71[0.16,3.1]
MYSS Study 2004	56/167	58/167		13.25%	0.97[0.72,1.3]
Joh 2005	10/34	7/34		2.88%	1.43[0.62,3.31]
Subtotal (95% CI)	**1771**	**1357**		**100%**	**0.65[0.55,0.75]**
Total events: 408 (MMF), 463 (AZA)					
Heterogeneity: Tau^2=0.02; Chi^2=23.65, df=18(P=0.17); I^2=23.87%					
Test for overall effect: Z=5.7(P<0.0001)					
1.6.2 Follow-up 6 to 12 months					
MMF US Study 1995	87/331	77/164		25.41%	0.56[0.44,0.71]
MMF TRI Study 1996	105/335	81/162		30.71%	0.63[0.5,0.78]
Mendez 1998	24/117	19/59		5.67%	0.64[0.38,1.07]
Egfjord 1999	8/25	11/25		2.87%	0.73[0.35,1.5]
Johnson 2000	11/72	13/76		2.77%	0.89[0.43,1.86]
Weimer 2002	5/31	9/25		1.63%	0.45[0.17,1.17]
Sadek 2002	34/162	51/157		10.7%	0.65[0.44,0.94]
Baltar 2002	1/14	5/12		0.37%	0.17[0.02,1.27]
Merville 2004	5/37	7/34		1.36%	0.66[0.23,1.87]
MYSS Study 2004	50/124	58/124		18.49%	0.86[0.65,1.15]
Subtotal (95% CI)	**1248**	**838**		**100%**	**0.65[0.58,0.74]**
Total events: 330 (MMF), 331 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=8.43, df=9(P=0.49); I^2=0%					
Test for overall effect: Z=6.86(P<0.0001)					
1.6.3 Follow-up > 12 months					
Johnson 2000	12/72	16/76		11.96%	0.79[0.4,1.56]
COSTAMP Study 2002	11/41	11/34		11.15%	0.83[0.41,1.67]
Weimer 2002	5/31	11/25		6.68%	0.37[0.15,0.92]
Tuncer 2002	7/38	13/38		8.65%	0.54[0.24,1.2]
MYSS Study 2004	57/124	65/124		61.56%	0.88[0.68,1.13]
Subtotal (95% CI)	**306**	**297**		**100%**	**0.78[0.61,0.99]**
Total events: 92 (MMF), 116 (AZA)					



Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.01; Chi²=4.34, df=4(P=0.36); I²=7.74%					
Test for overall effect: Z=2.03(P=0.04)					
1.6.4 Longest duration of follow-up					
MMF US Study 1995	87/331	77/164		16.96%	0.56[0.44,0.71]
MMF TRI Study 1996	105/335	81/162		19.18%	0.63[0.5,0.78]
Mendez 1998	24/117	19/59		5.08%	0.64[0.38,1.07]
Ling 1998	2/11	3/5		0.7%	0.3[0.07,1.28]
Egfjord 1999	8/25	11/25		2.7%	0.73[0.35,1.5]
Suhail 2000	2/20	7/20		0.7%	0.29[0.07,1.21]
Johnson 2000	12/72	16/76		3.07%	0.79[0.4,1.56]
Busque 2001	2/23	8/23		0.71%	0.25[0.06,1.05]
Folkmane 2001	5/23	8/25		1.56%	0.68[0.26,1.78]
Ji 2001	11/56	22/50		3.66%	0.45[0.24,0.83]
Sadek 2002	34/162	51/157		8.81%	0.65[0.44,0.94]
COSTAMP Study 2002	59/243	83/246		13.69%	0.72[0.54,0.95]
Tuncer 2002	7/38	13/38		2.22%	0.54[0.24,1.2]
Weimer 2002	5/31	11/25		1.71%	0.37[0.15,0.92]
Army Hospital 2002	1/17	3/16		0.32%	0.31[0.04,2.71]
Sun 2002b	2/40	6/46		0.62%	0.38[0.08,1.79]
Baltar 2002	1/14	5/12		0.37%	0.17[0.02,1.27]
Miladipour 2002	4/40	10/40		1.26%	0.4[0.14,1.17]
Keven 2003	3/24	3/17		0.68%	0.71[0.16,3.1]
Merville 2004	5/37	7/34		1.32%	0.66[0.23,1.87]
MYSS Study 2004	56/167	58/167		12.66%	0.97[0.72,1.3]
Joh 2005	10/34	7/34		2.02%	1.43[0.62,3.31]
Subtotal (95% CI)	**1860**	**1441**		**100%**	**0.65[0.57,0.73]**
Total events: 445 (MMF), 509 (AZA)					
Heterogeneity: Tau²=0.01; Chi²=23.2, df=21(P=0.33); I²=9.48%					
Test for overall effect: Z=7.01(P<0.0001)					

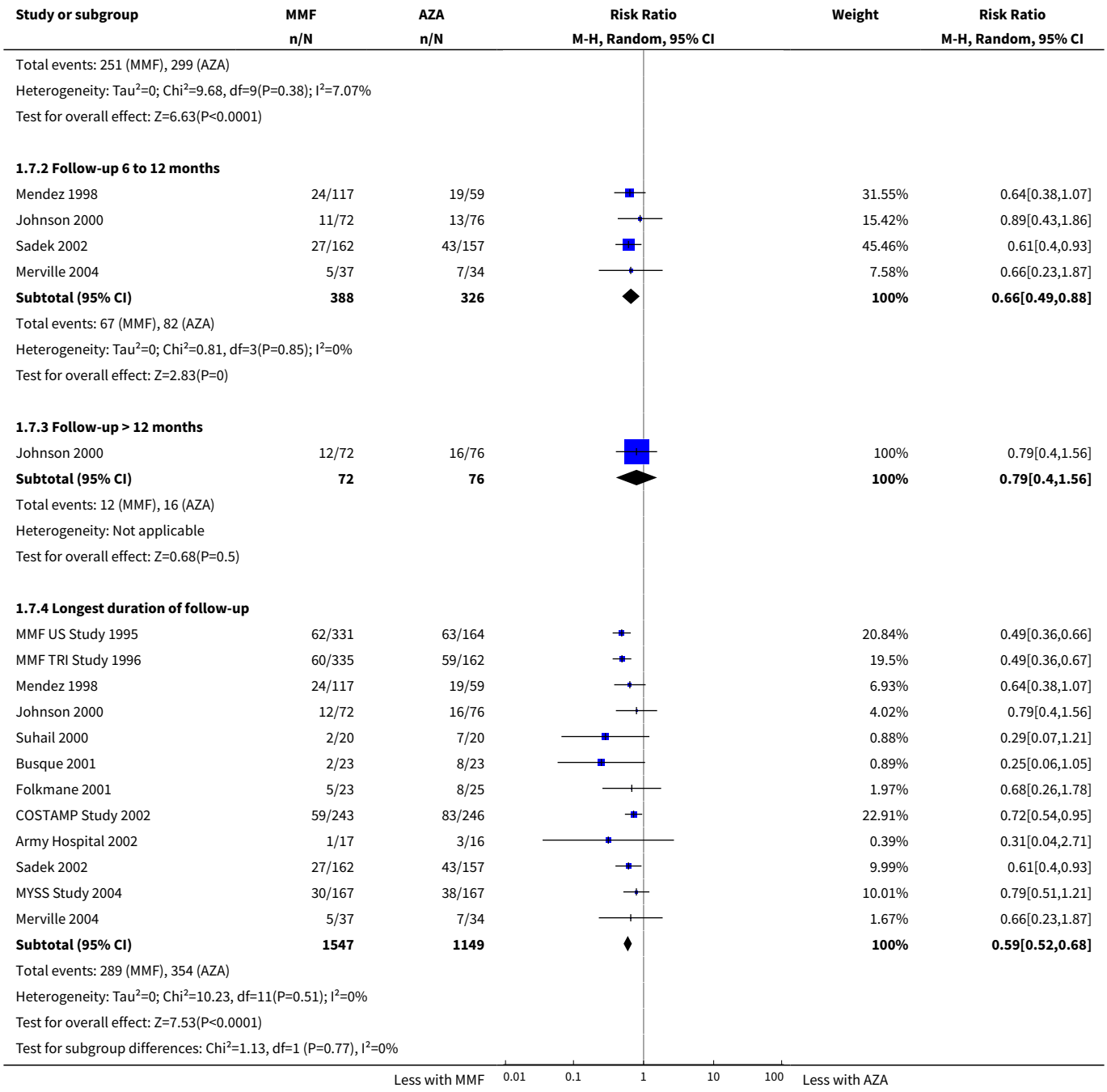


Less with MMF — Less with AZA

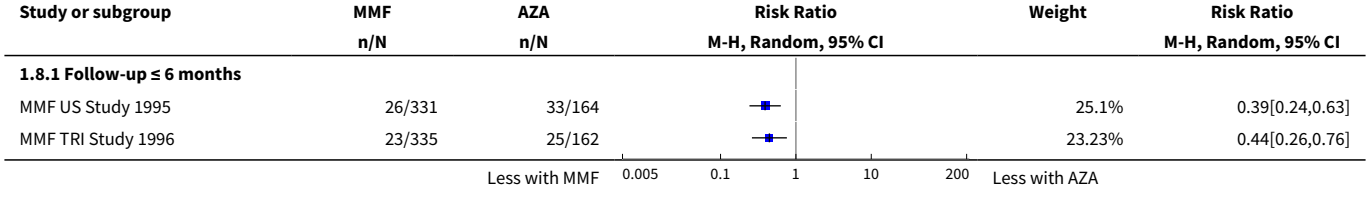
Analysis 1.7. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 7 Acute rejection: confirmed by biopsy.

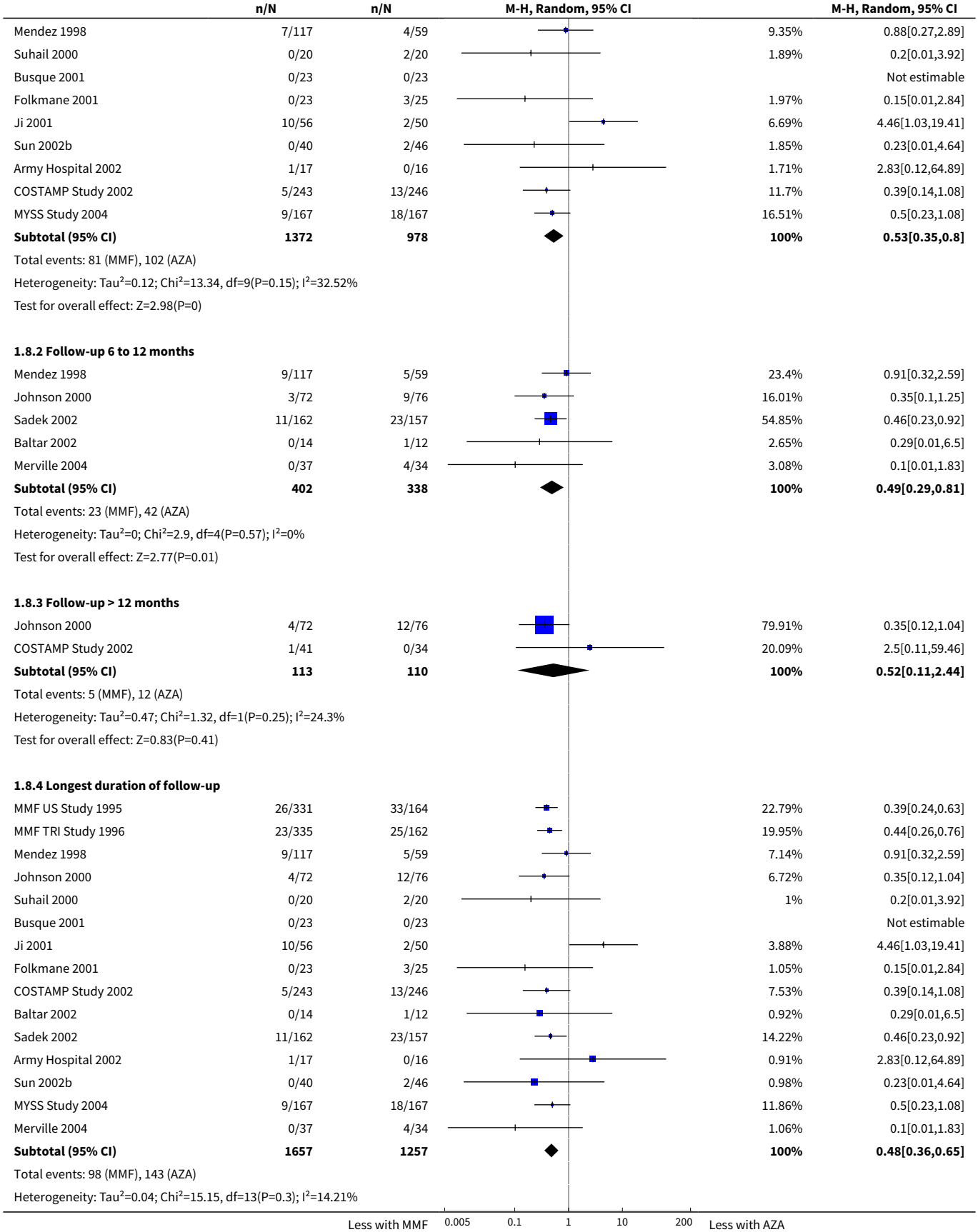
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Follow-up ≤ 6 months					
MMF US Study 1995	62/331	63/164		23.37%	0.49[0.36,0.66]
MMF TRI Study 1996	60/335	59/162		22.11%	0.49[0.36,0.67]
Mendez 1998	21/117	17/59		7.53%	0.62[0.36,1.09]
Suhail 2000	2/20	7/20		1.18%	0.29[0.07,1.21]
Johnson 2000	9/72	13/76		3.89%	0.73[0.33,1.6]
Folkmane 2001	5/23	8/25		2.62%	0.68[0.26,1.78]
Busque 2001	2/23	8/23		1.19%	0.25[0.06,1.05]
Army Hospital 2002	1/17	3/16		0.53%	0.31[0.04,2.71]
COSTAMP Study 2002	59/243	83/246		25.26%	0.72[0.54,0.95]
MYSS Study 2004	30/167	38/167		12.31%	0.79[0.51,1.21]
Subtotal (95% CI)	**1348**	**958**		**100%**	**0.59[0.5,0.69]**

Less with MMF — Less with AZA

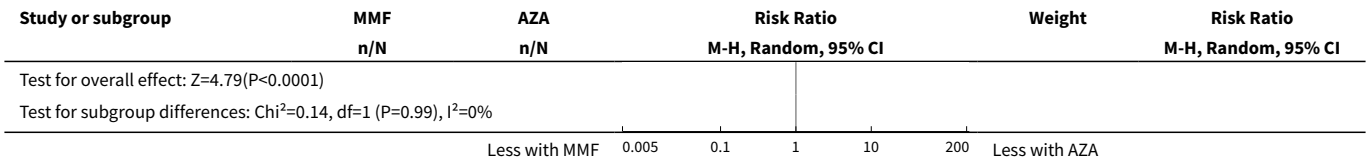


Analysis 1.8. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 8 Acute rejection: steroid resistant/antibody treated.

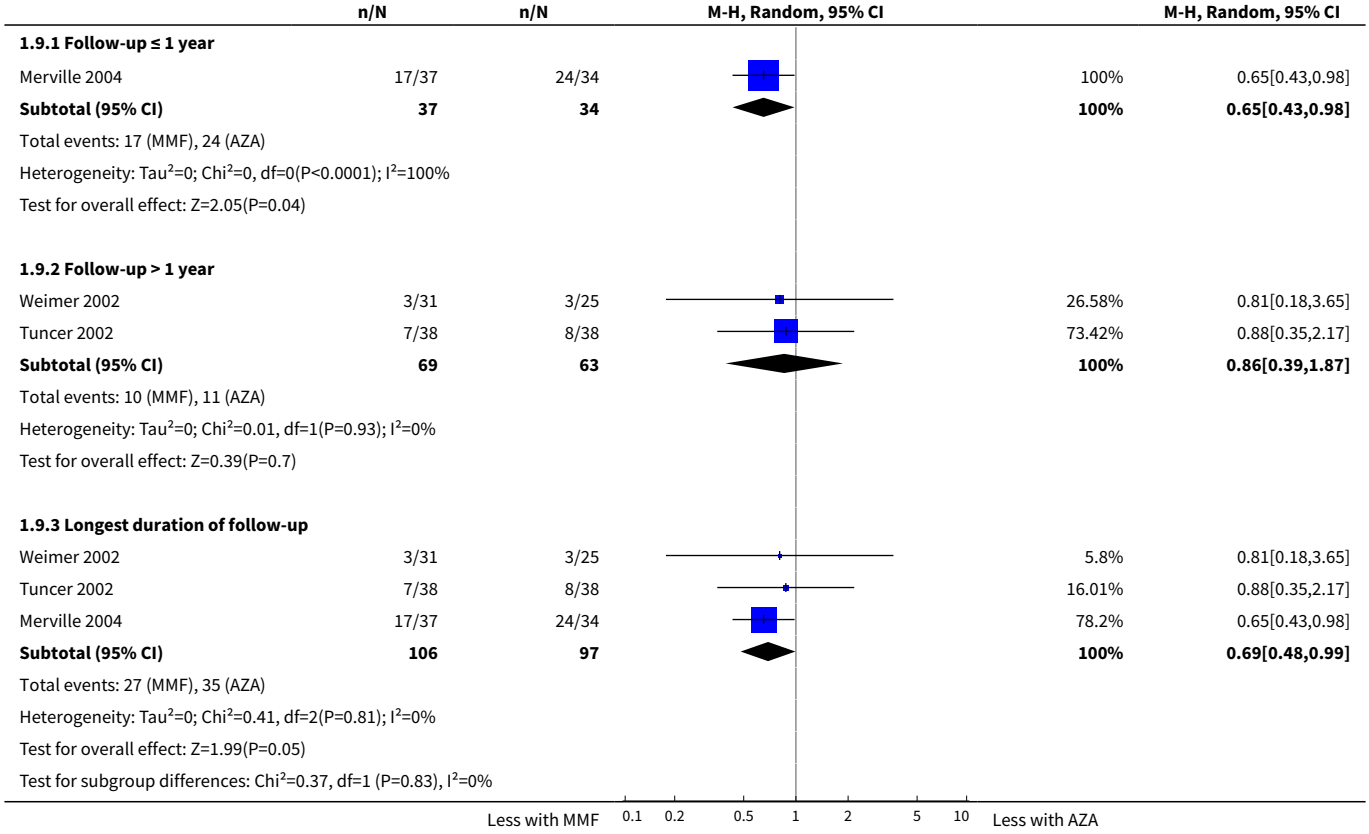




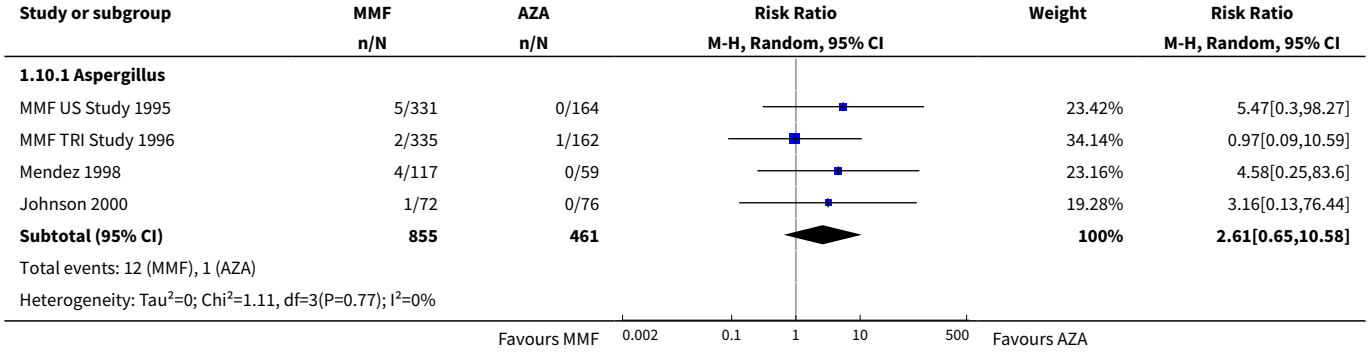
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mendez 1998	7/117	4/59		9.35%	0.88[0.27,2.89]
Suhail 2000	0/20	2/20		1.89%	0.2[0.01,3.92]
Busque 2001	0/23	0/23			Not estimable
Folkmane 2001	0/23	3/25		1.97%	0.15[0.01,2.84]
Ji 2001	10/56	2/50		6.69%	4.46[1.03,19.41]
Sun 2002b	0/40	2/46		1.85%	0.23[0.01,4.64]
Army Hospital 2002	1/17	0/16		1.71%	2.83[0.12,64.89]
COSTAMP Study 2002	5/243	13/246		11.7%	0.39[0.14,1.08]
MYSS Study 2004	9/167	18/167		16.51%	0.5[0.23,1.08]
Subtotal (95% CI)	**1372**	**978**		**100%**	**0.53[0.35,0.8]**
Total events: 81 (MMF), 102 (AZA)					
Heterogeneity: Tau²=0.12; Chi²=13.34, df=9(P=0.15); I²=32.52%					
Test for overall effect: Z=2.98(P=0)					
1.8.2 Follow-up 6 to 12 months					
Mendez 1998	9/117	5/59		23.4%	0.91[0.32,2.59]
Johnson 2000	3/72	9/76		16.01%	0.35[0.1,1.25]
Sadek 2002	11/162	23/157		54.85%	0.46[0.23,0.92]
Baltar 2002	0/14	1/12		2.65%	0.29[0.01,6.5]
Merville 2004	0/37	4/34		3.08%	0.1[0.01,1.83]
Subtotal (95% CI)	**402**	**338**		**100%**	**0.49[0.29,0.81]**
Total events: 23 (MMF), 42 (AZA)					
Heterogeneity: Tau²=0; Chi²=2.9, df=4(P=0.57); I²=0%					
Test for overall effect: Z=2.77(P=0.01)					
1.8.3 Follow-up > 12 months					
Johnson 2000	4/72	12/76		79.91%	0.35[0.12,1.04]
COSTAMP Study 2002	1/41	0/34		20.09%	2.5[0.11,59.46]
Subtotal (95% CI)	**113**	**110**		**100%**	**0.52[0.11,2.44]**
Total events: 5 (MMF), 12 (AZA)					
Heterogeneity: Tau²=0.47; Chi²=1.32, df=1(P=0.25); I²=24.3%					
Test for overall effect: Z=0.83(P=0.41)					
1.8.4 Longest duration of follow-up					
MMF US Study 1995	26/331	33/164		22.79%	0.39[0.24,0.63]
MMF TRI Study 1996	23/335	25/162		19.95%	0.44[0.26,0.76]
Mendez 1998	9/117	5/59		7.14%	0.91[0.32,2.59]
Johnson 2000	4/72	12/76		6.72%	0.35[0.12,1.04]
Suhail 2000	0/20	2/20		1%	0.2[0.01,3.92]
Busque 2001	0/23	0/23			Not estimable
Ji 2001	10/56	2/50		3.88%	4.46[1.03,19.41]
Folkmane 2001	0/23	3/25		1.05%	0.15[0.01,2.84]
COSTAMP Study 2002	5/243	13/246		7.53%	0.39[0.14,1.08]
Baltar 2002	0/14	1/12		0.92%	0.29[0.01,6.5]
Sadek 2002	11/162	23/157		14.22%	0.46[0.23,0.92]
Army Hospital 2002	1/17	0/16		0.91%	2.83[0.12,64.89]
Sun 2002b	0/40	2/46		0.98%	0.23[0.01,4.64]
MYSS Study 2004	9/167	18/167		11.86%	0.5[0.23,1.08]
Merville 2004	0/37	4/34		1.06%	0.1[0.01,1.83]
Subtotal (95% CI)	**1657**	**1257**		**100%**	**0.48[0.36,0.65]**
Total events: 98 (MMF), 143 (AZA)					
Heterogeneity: Tau²=0.04; Chi²=15.15, df=13(P=0.3); I²=14.21%					

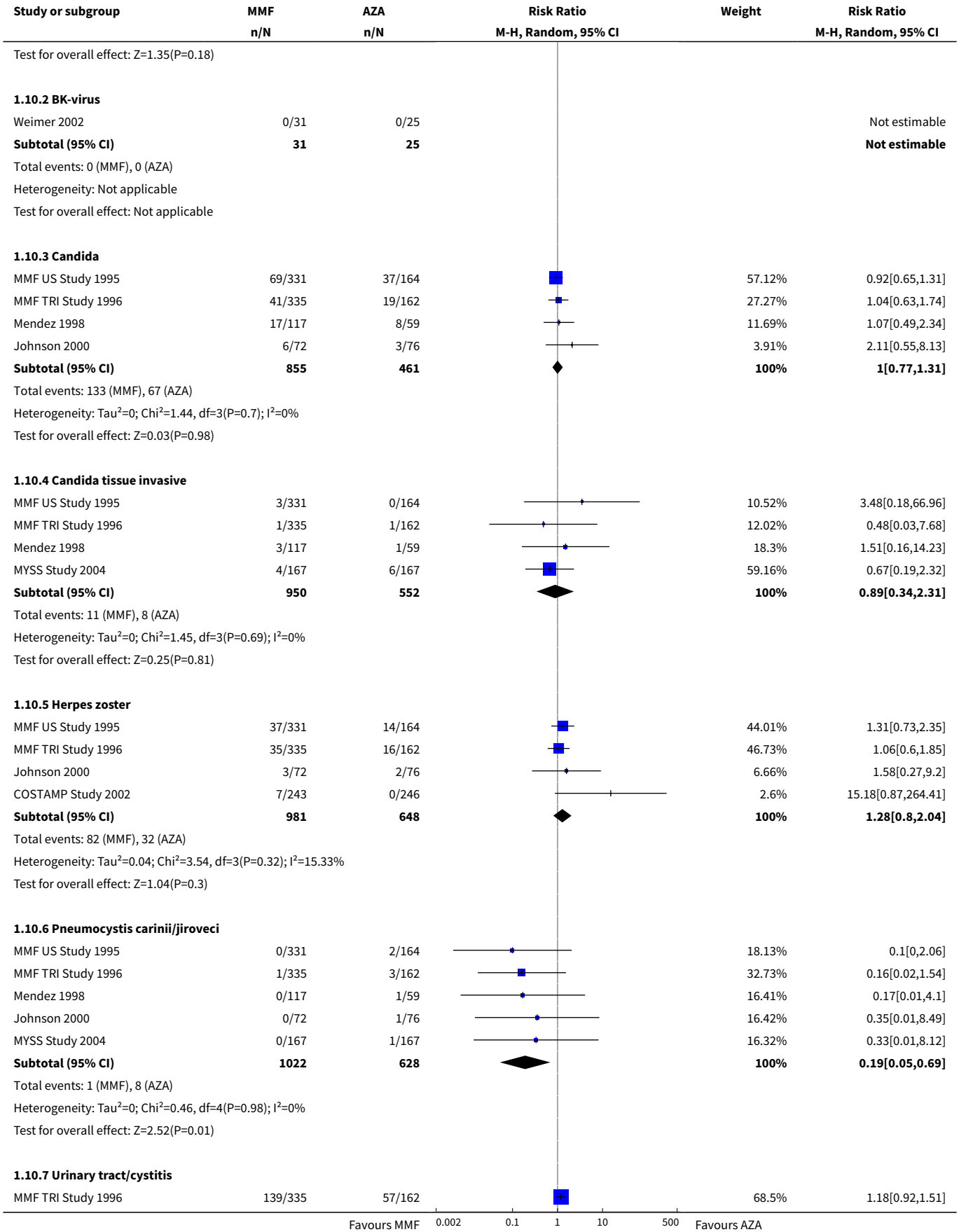


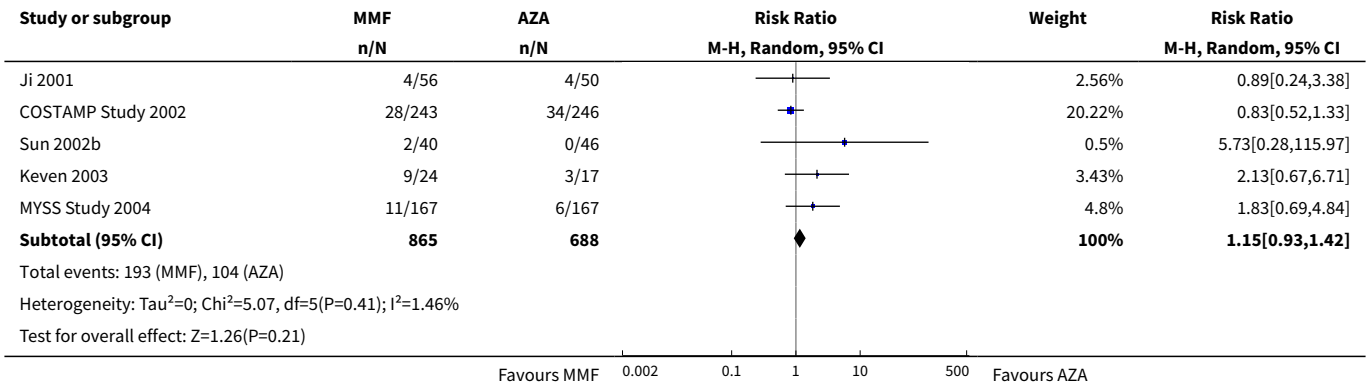
Analysis 1.9. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 9 Chronic allograft nephropathy.



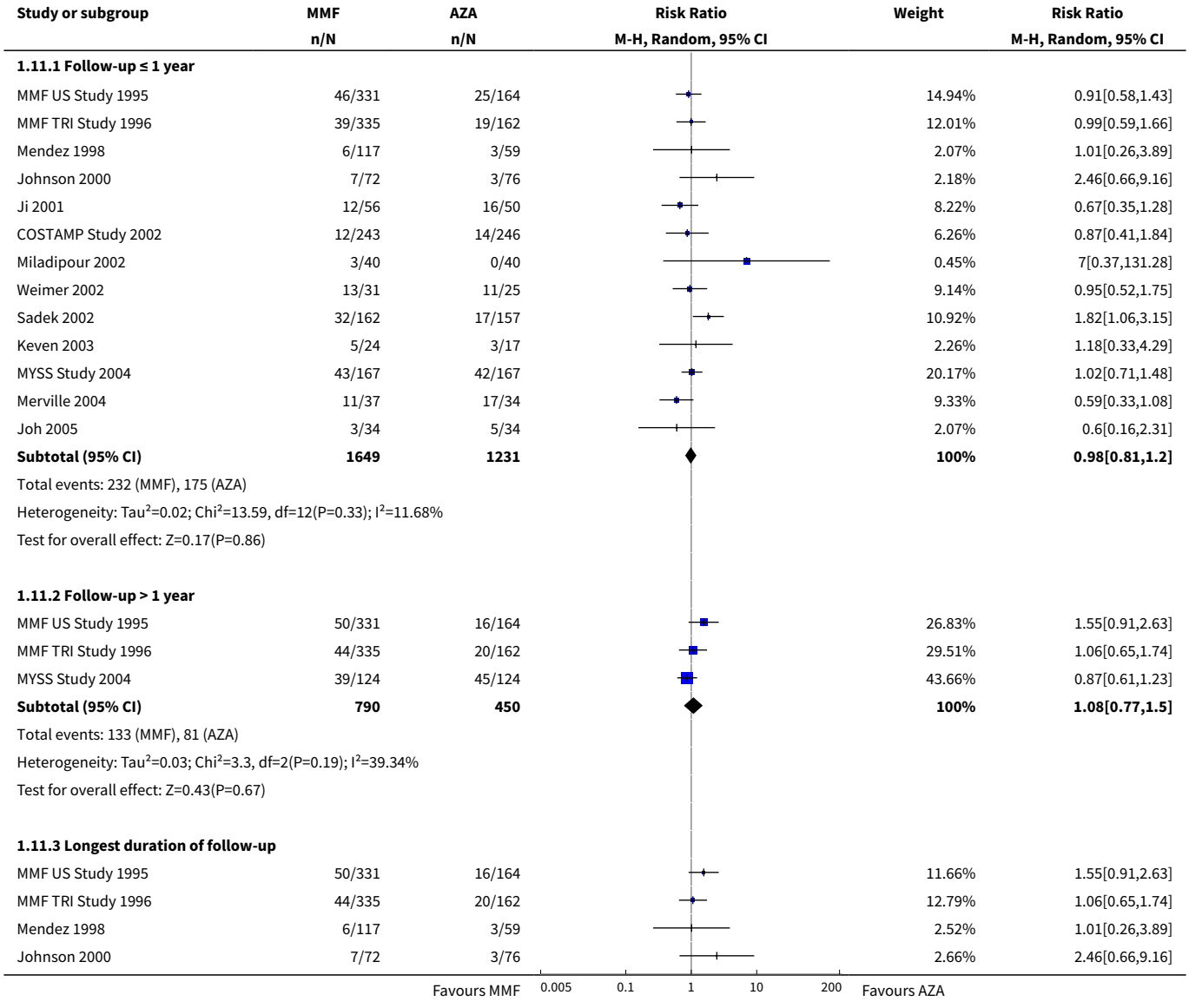
Analysis 1.10. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 10 Infection: other (longest duration of follow-up).

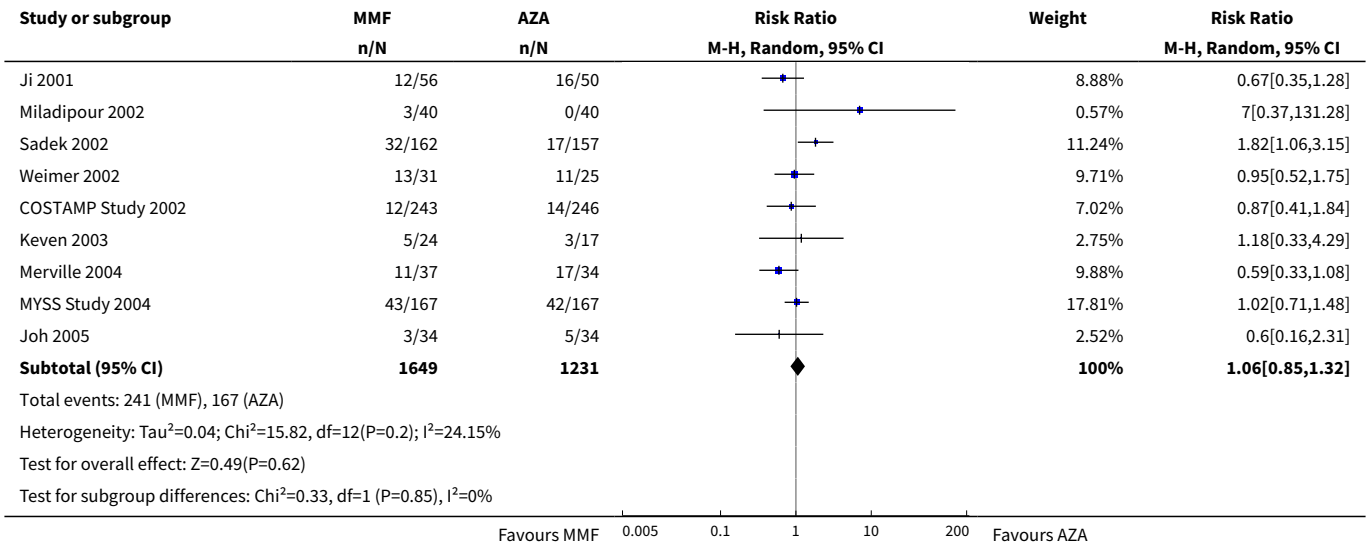




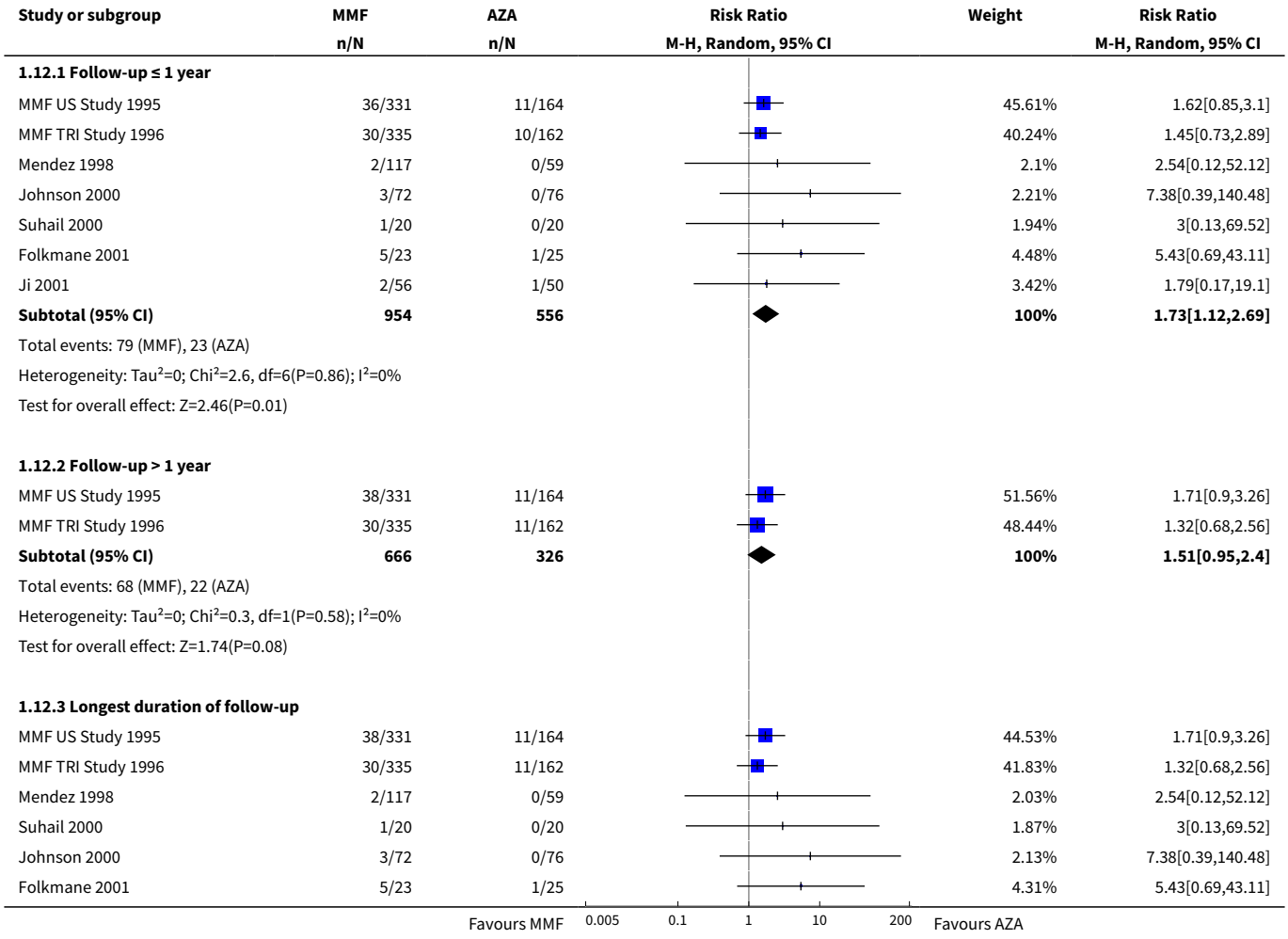


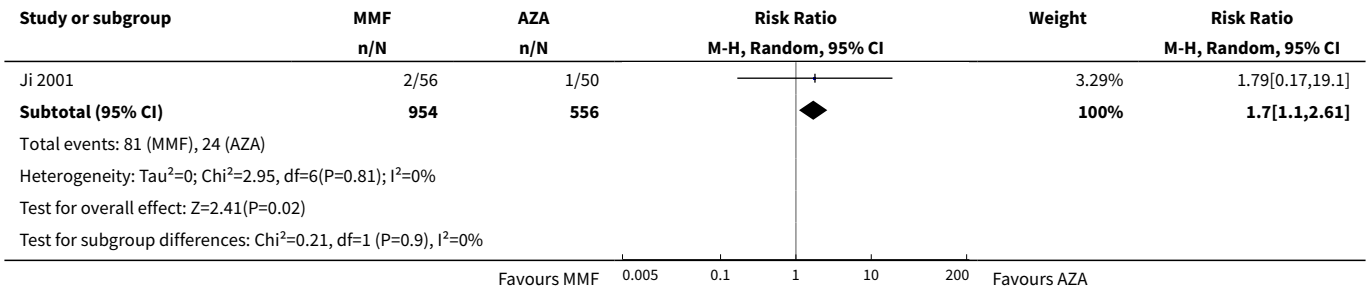
Analysis 1.11. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 11 Infection: CMV viraemia/syndrome.



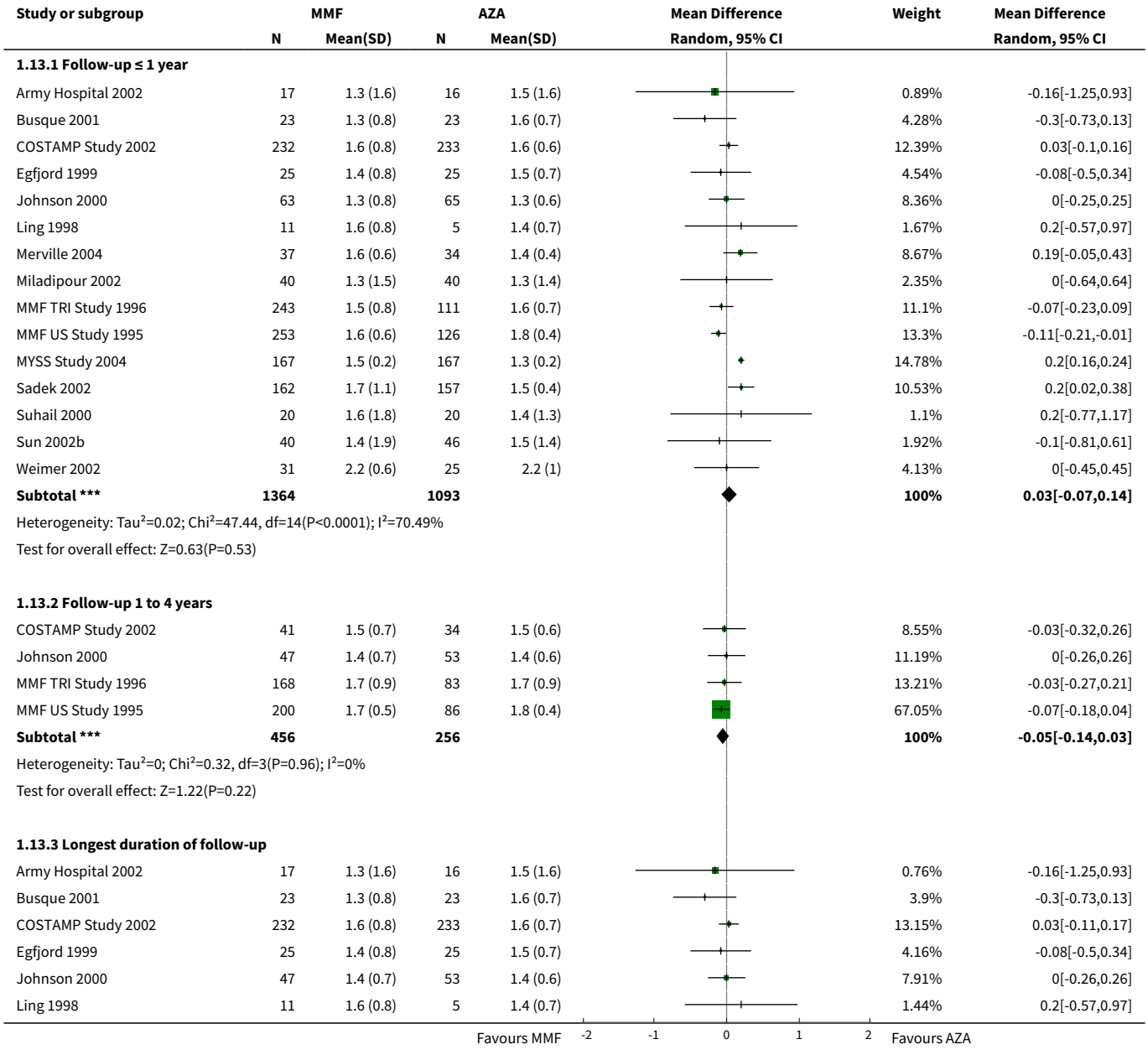


Analysis 1.12. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 12 Infection: CMV tissue invasive.

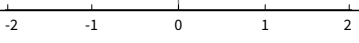




Analysis 1.13. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 13 Graft function: serum creatinine.

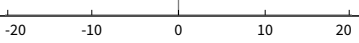


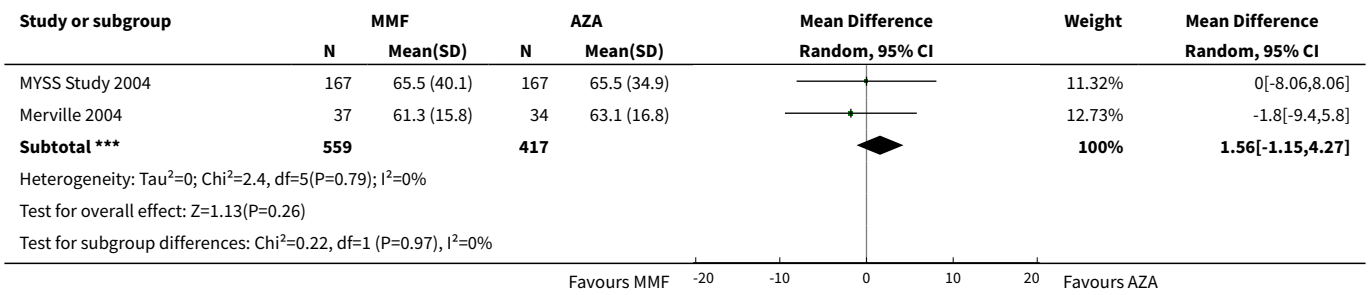
Study or subgroup	MMF N	MMF Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Merville 2004	37	1.6 (0.6)	34	1.4 (0.4)		8.69%	0.19[-0.05,0.43]
Miladipour 2002	40	1.3 (1.5)	40	1.3 (1.4)		2.06%	0[-0.64,0.64]
MMF TRI Study 1996	168	1.7 (0.9)	83	1.7 (0.9)		8.64%	-0.03[-0.27,0.21]
MMF US Study 1995	200	1.7 (0.5)	86	1.8 (0.4)		14.73%	-0.07[-0.18,0.04]
MYSS Study 2004	167	1.5 (0.2)	167	1.3 (0.2)		17.2%	0.2[0.16,0.24]
Sadek 2002	162	1.7 (1.1)	157	1.5 (0.4)		11.01%	0.2[0.02,0.38]
Suhail 2000	20	1.6 (1.8)	20	1.4 (1.3)		0.94%	0.2[-0.77,1.17]
Sun 2002b	40	1.4 (1.9)	46	1.5 (1.4)		1.67%	-0.1[-0.81,0.61]
Weimer 2002	31	2.2 (0.6)	25	2.2 (1)		3.75%	0[-0.45,0.45]
Subtotal * **	**1220**		**1013**			**100%**	**0.05[-0.05,0.15]**
Heterogeneity: Tau^2=0.01; Chi^2=35.41, df=14(P=0); I^2=60.46%							
Test for overall effect: Z=1.03(P=0.3)							
Test for subgroup differences: Chi^2=2.92, df=1 (P=0.23), I^2=31.51%							



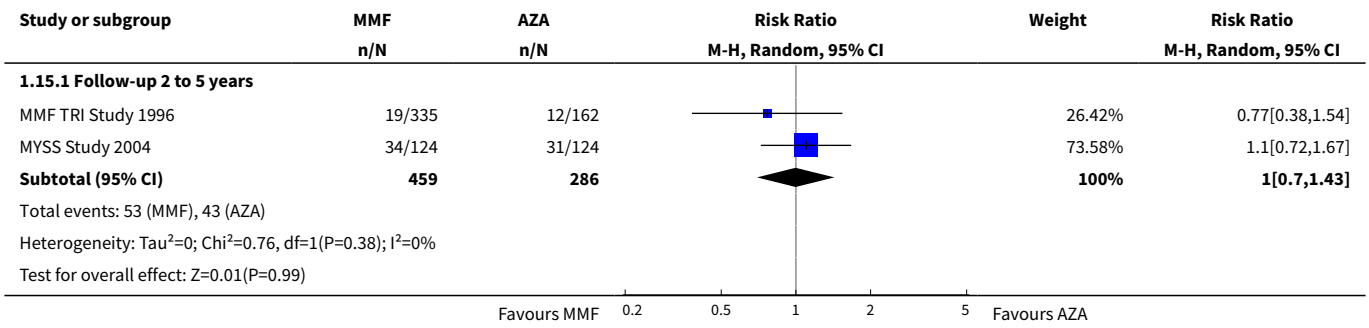
Analysis 1.14. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 14 Graft function: CrCl/GFR.

Study or subgroup	MMF N	MMF Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.14.1 Follow-up ≤ 1 year							
MMF US Study 1995	253	66.4 (32.3)	126	62.8 (28.3)		30.61%	3.6[-2.74,9.94]
Johnson 2000	65	61 (32.3)	65	63 (28.3)		11.3%	-2[-12.44,8.44]
Weimer 2002	31	46 (16.7)	25	39 (15)		17.82%	7[-1.31,15.31]
Merville 2004	37	61.3 (15.8)	34	63.1 (16.8)		21.31%	-1.8[-9.4,5.8]
MYSS Study 2004	167	65.5 (40.1)	167	65.5 (34.9)		18.95%	0[-8.06,8.06]
Subtotal * **	**553**		**417**			**100%**	**1.74[-1.77,5.25]**
Heterogeneity: Tau^2=0; Chi^2=3.37, df=4(P=0.5); I^2=0%							
Test for overall effect: Z=0.97(P=0.33)							
1.14.2 Follow-up 1 to 4 years							
Johnson 2000	47	59.3 (32.3)	53	62.3 (28.3)		14.11%	-3[-14.97,8.97]
Weimer 2002	29	48 (21.5)	25	42 (25)		12.86%	6[-6.54,18.54]
MYSS Study 2004	113	53.6 (20.2)	109	52.1 (19.8)		73.03%	1.5[-3.76,6.76]
Subtotal * **	**189**		**187**			**100%**	**1.44[-3.05,5.94]**
Heterogeneity: Tau^2=0; Chi^2=1.04, df=2(P=0.6); I^2=0%							
Test for overall effect: Z=0.63(P=0.53)							
1.14.3 Follow-up > 4 years							
MMF TRI Study 1996	26	48.2 (5.8)	12	46.1 (5.7)		64.14%	2.1[-1.82,6.02]
MYSS Study 2004	41	47.3 (14.1)	41	49.5 (13.4)		35.86%	-2.2[-8.15,3.75]
Subtotal * **	**67**		**53**			**100%**	**0.56[-3.48,4.6]**
Heterogeneity: Tau^2=2.63; Chi^2=1.4, df=1(P=0.24); I^2=28.45%							
Test for overall effect: Z=0.27(P=0.79)							
1.14.4 Longest duration of follow-up							
MMF US Study 1995	253	66.4 (32.3)	126	62.8 (28.3)		18.28%	3.6[-2.74,9.94]
MMF TRI Study 1996	26	48.2 (5.8)	12	46.1 (5.7)		47.87%	2.1[-1.82,6.02]
Johnson 2000	47	59.3 (32.3)	53	62.3 (28.3)		5.13%	-3[-14.97,8.97]
Weimer 2002	29	48 (21.5)	25	42 (25)		4.68%	6[-6.54,18.54]

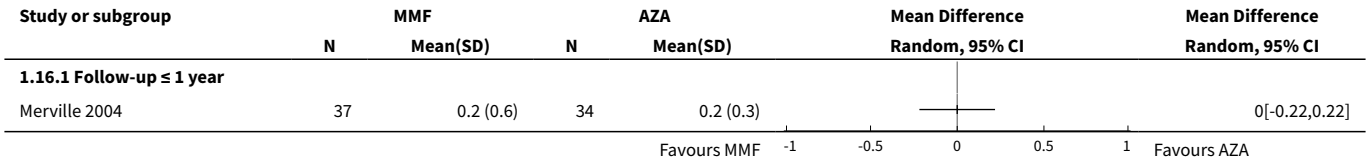




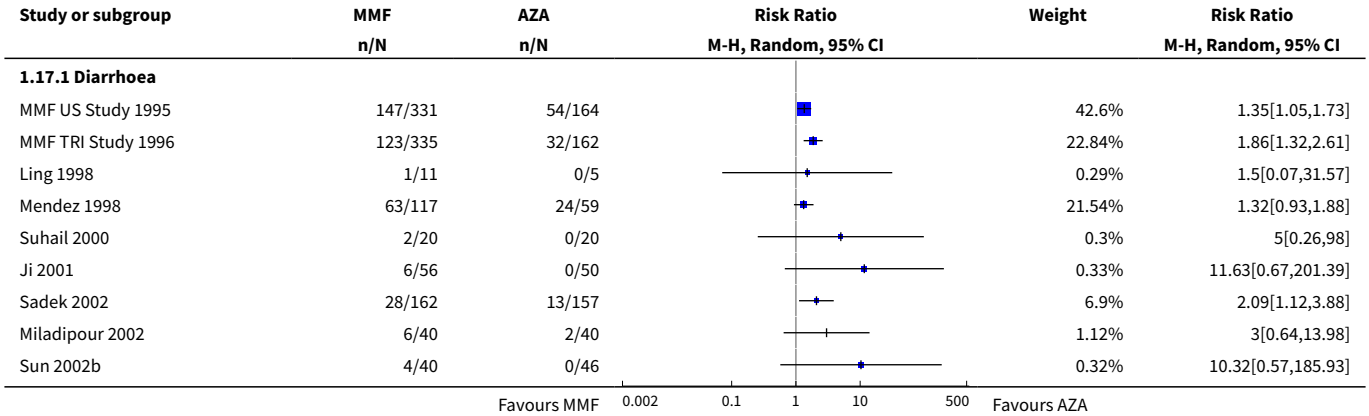
Analysis 1.15. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 15 Graft function: proteinuria.

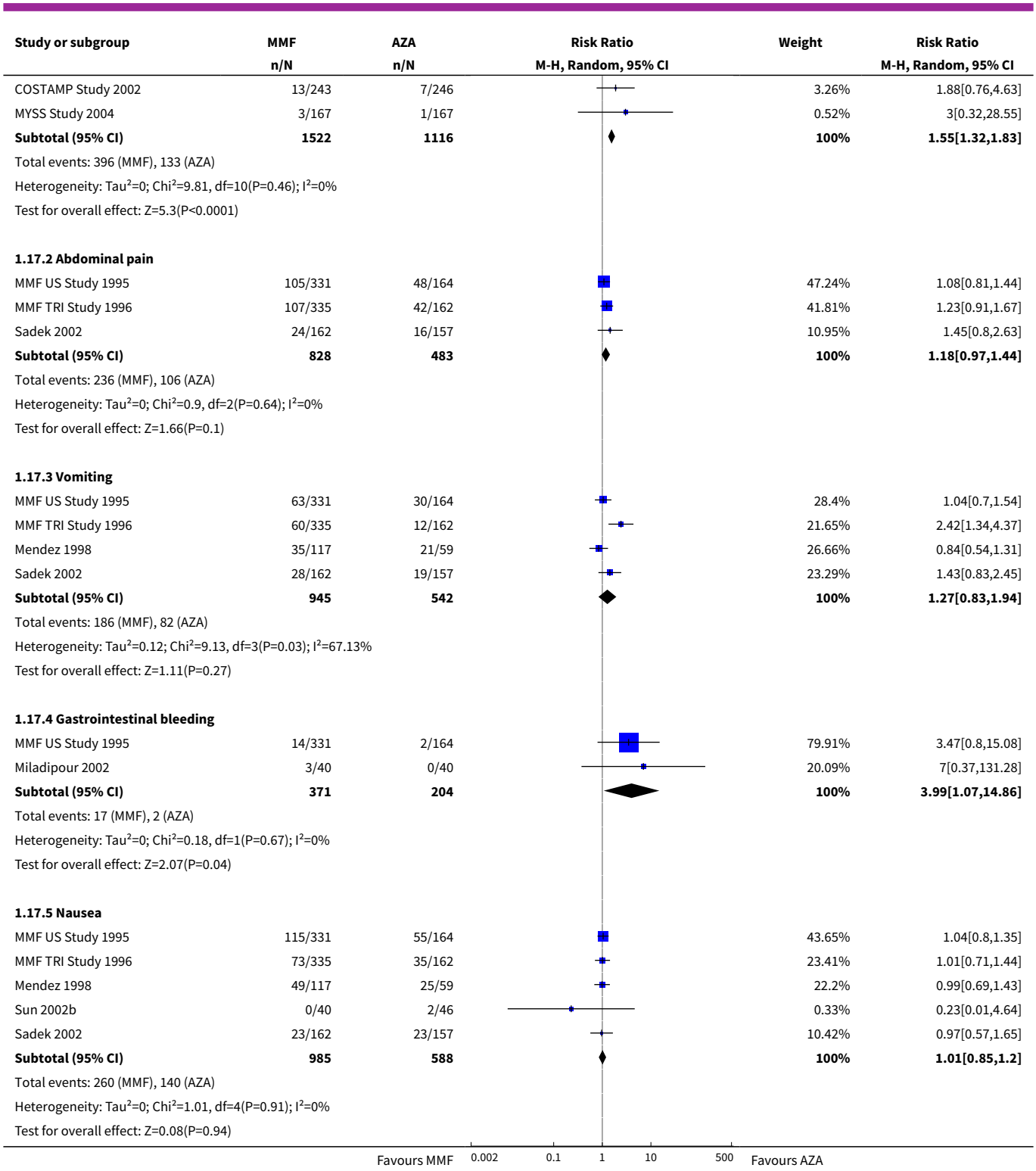


Analysis 1.16. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 16 Graft function: proteinuria.

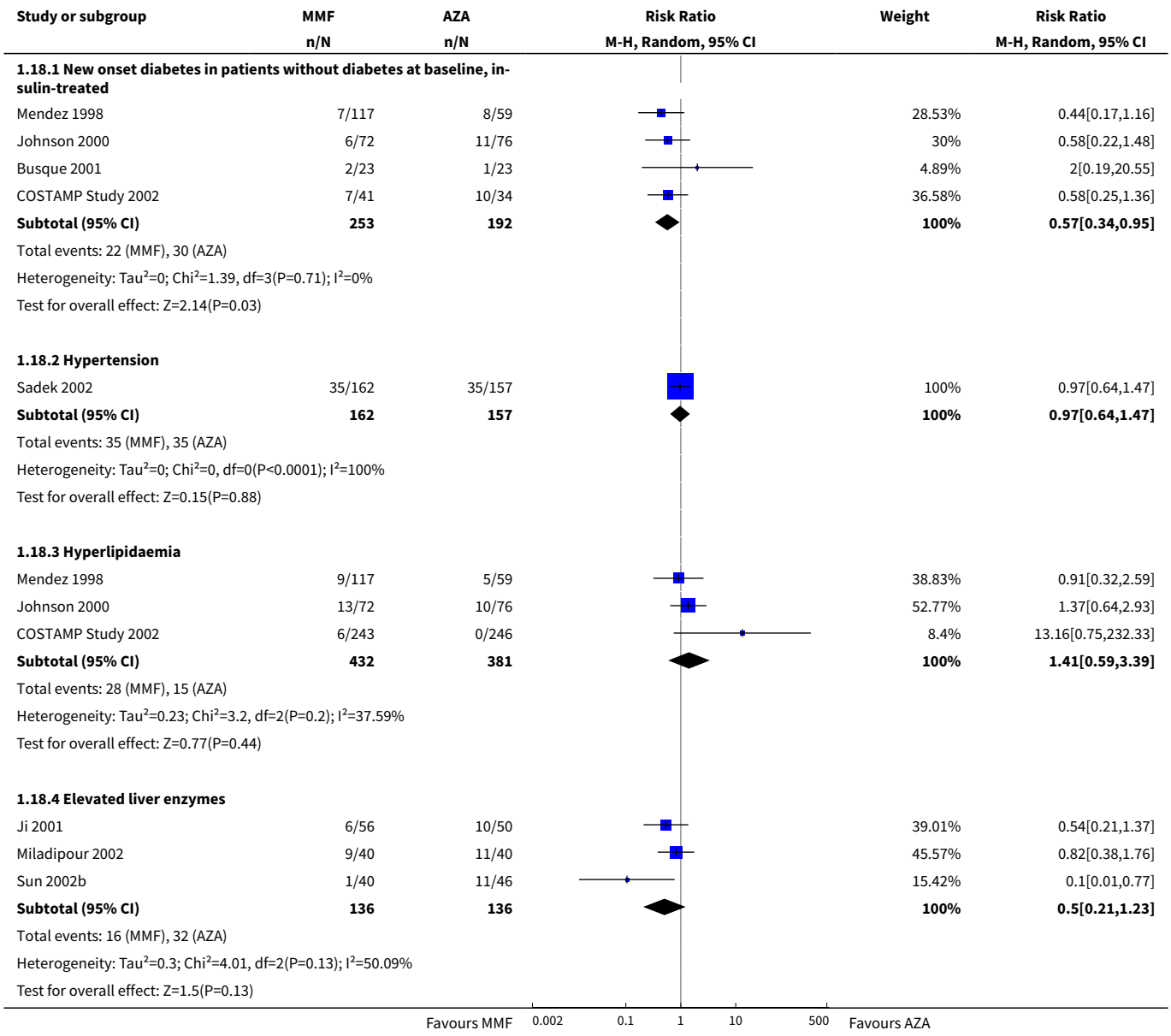


Analysis 1.17. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 17 Adverse events: gastrointestinal (longest duration of follow-up).



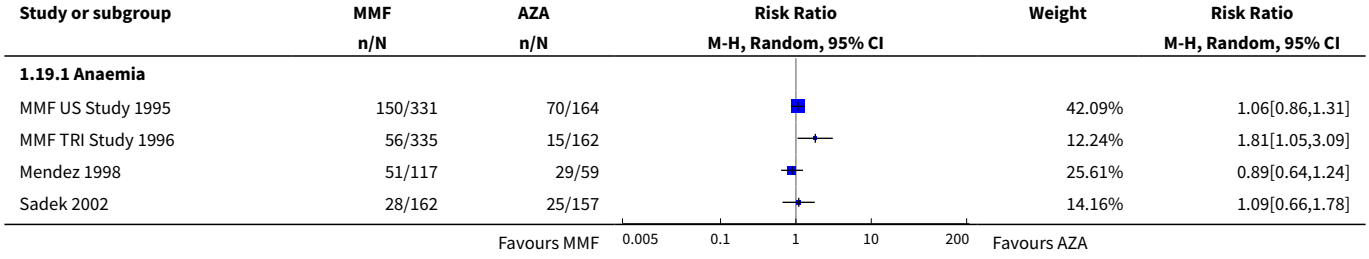


Analysis 1.18. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 18 Adverse events: other (longest duration of follow-up).

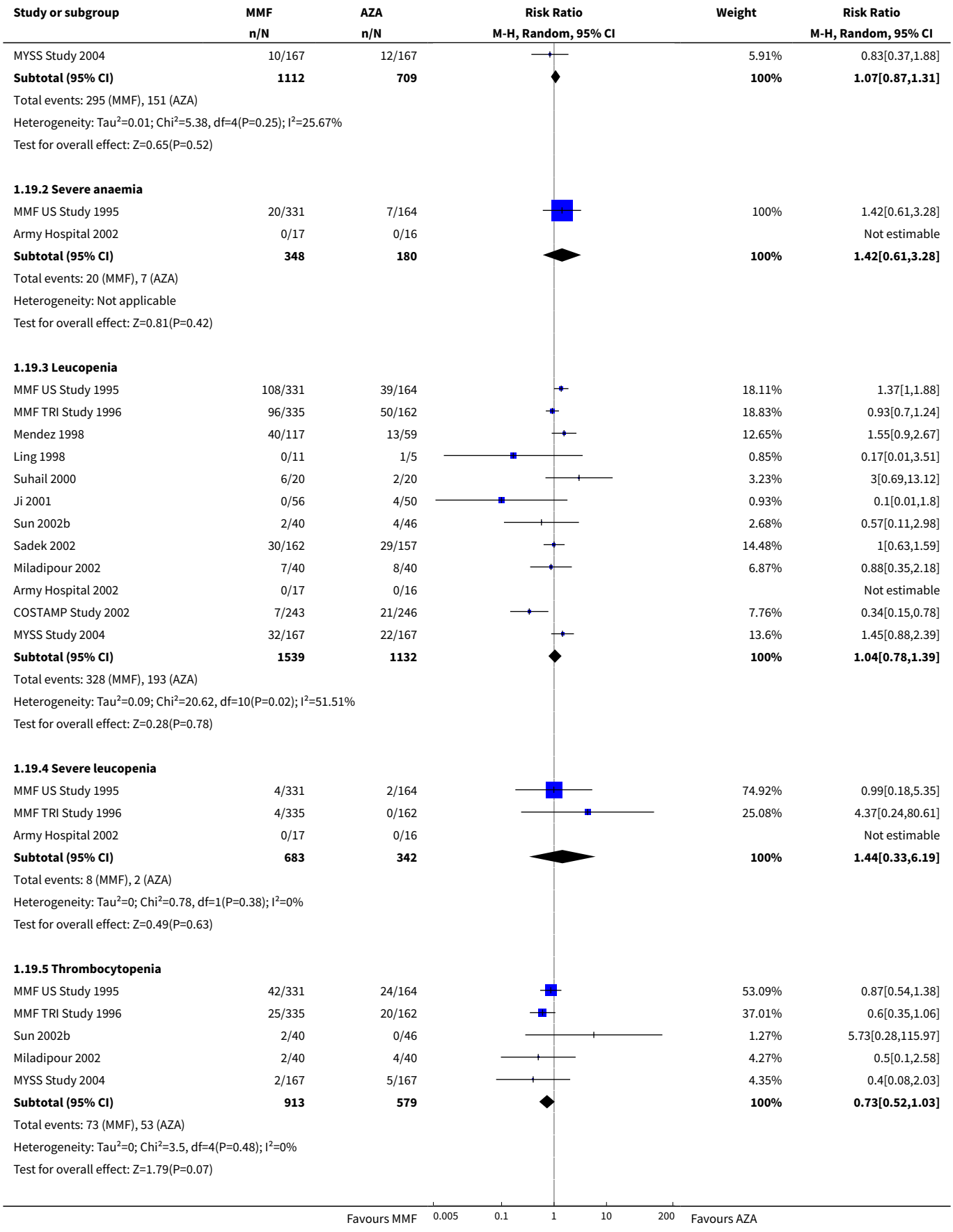


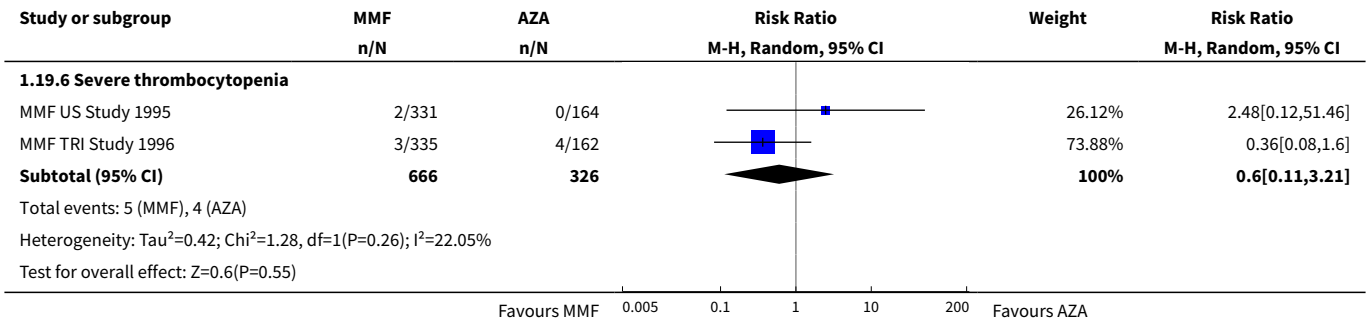
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 New onset diabetes in patients without diabetes at baseline, insulin-treated					
Mendez 1998	7/117	8/59		28.53%	0.44[0.17,1.16]
Johnson 2000	6/72	11/76		30%	0.58[0.22,1.48]
Busque 2001	2/23	1/23		4.89%	2[0.19,20.55]
COSTAMP Study 2002	7/41	10/34		36.58%	0.58[0.25,1.36]
Subtotal (95% CI)	**253**	**192**		**100%**	**0.57[0.34,0.95]**
Total events: 22 (MMF), 30 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=1.39, df=3(P=0.71); I^2=0%					
Test for overall effect: Z=2.14(P=0.03)					
1.18.2 Hypertension					
Sadek 2002	35/162	35/157		100%	0.97[0.64,1.47]
Subtotal (95% CI)	**162**	**157**		**100%**	**0.97[0.64,1.47]**
Total events: 35 (MMF), 35 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.15(P=0.88)					
1.18.3 Hyperlipidaemia					
Mendez 1998	9/117	5/59		38.83%	0.91[0.32,2.59]
Johnson 2000	13/72	10/76		52.77%	1.37[0.64,2.93]
COSTAMP Study 2002	6/243	0/246		8.4%	13.16[0.75,232.33]
Subtotal (95% CI)	**432**	**381**		**100%**	**1.41[0.59,3.39]**
Total events: 28 (MMF), 15 (AZA)					
Heterogeneity: Tau^2=0.23; Chi^2=3.2, df=2(P=0.2); I^2=37.59%					
Test for overall effect: Z=0.77(P=0.44)					
1.18.4 Elevated liver enzymes					
Ji 2001	6/56	10/50		39.01%	0.54[0.21,1.37]
Miladipour 2002	9/40	11/40		45.57%	0.82[0.38,1.76]
Sun 2002b	1/40	11/46		15.42%	0.1[0.01,0.77]
Subtotal (95% CI)	**136**	**136**		**100%**	**0.5[0.21,1.23]**
Total events: 16 (MMF), 32 (AZA)					
Heterogeneity: Tau^2=0.3; Chi^2=4.01, df=2(P=0.13); I^2=50.09%					
Test for overall effect: Z=1.5(P=0.13)					

Analysis 1.19. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 19 Adverse events: haematological (longest duration of follow-up).

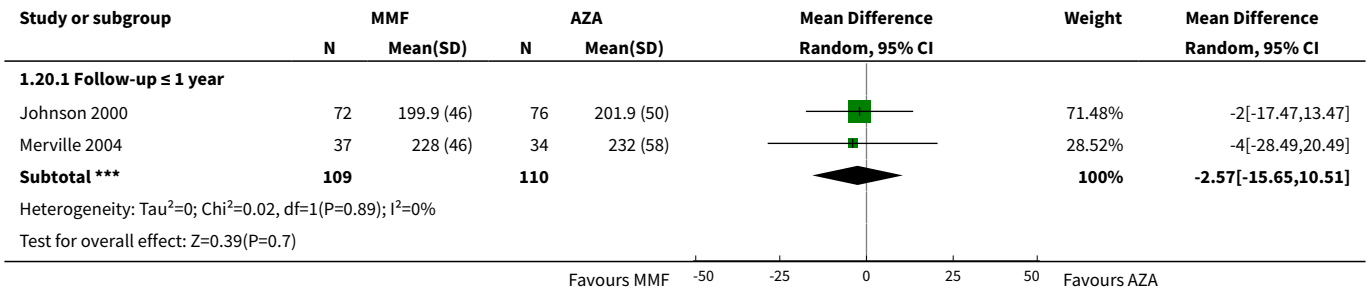


Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Anaemia					
MMF US Study 1995	150/331	70/164		42.09%	1.06[0.86,1.31]
MMF TRI Study 1996	56/335	15/162		12.24%	1.81[1.05,3.09]
Mendez 1998	51/117	29/59		25.61%	0.89[0.64,1.24]
Sadek 2002	28/162	25/157		14.16%	1.09[0.66,1.78]





Analysis 1.20. Comparison 1 Mycophenolate mofetil versus azathioprine, Outcome 20 Total cholesterol.



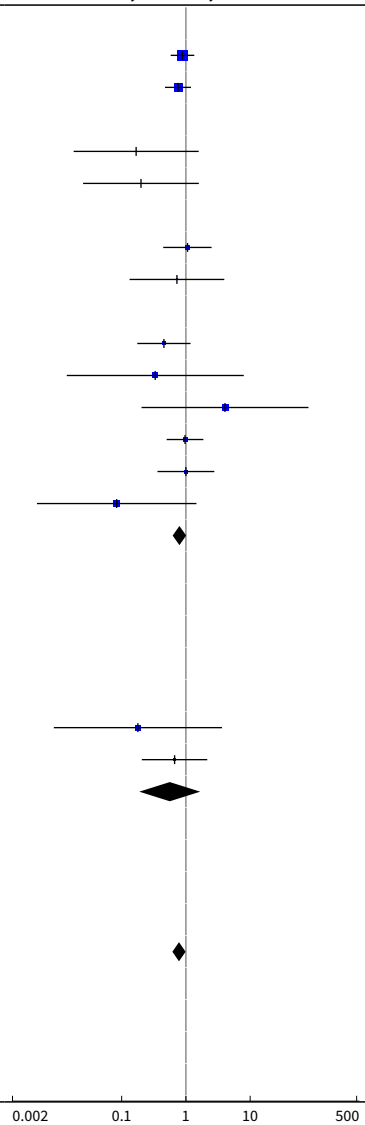
Comparison 2. Subgroup analyses: RCT versus quasi-RCT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss: censored for death	17	2540	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.99]
1.1 RCT	15	2366	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.62, 1.01]
1.2 quasi-RCT	2	174	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.19, 1.67]
2 Acute rejection (total)	22	3301	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.57, 0.73]
2.1 RCT	20	3127	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.58, 0.72]
2.2 quasi-RCT	2	174	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.25, 2.40]
3 Infection: CMV viraemia/syndrome	13	2880	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
3.1 RCT	11	2706	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.89, 1.42]
3.2 quasi-RCT	2	174	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.37, 1.17]
4 Graft function, serum creatinine	15	2233	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 RCT	15	2233	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
4.2 quasi-RCT	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

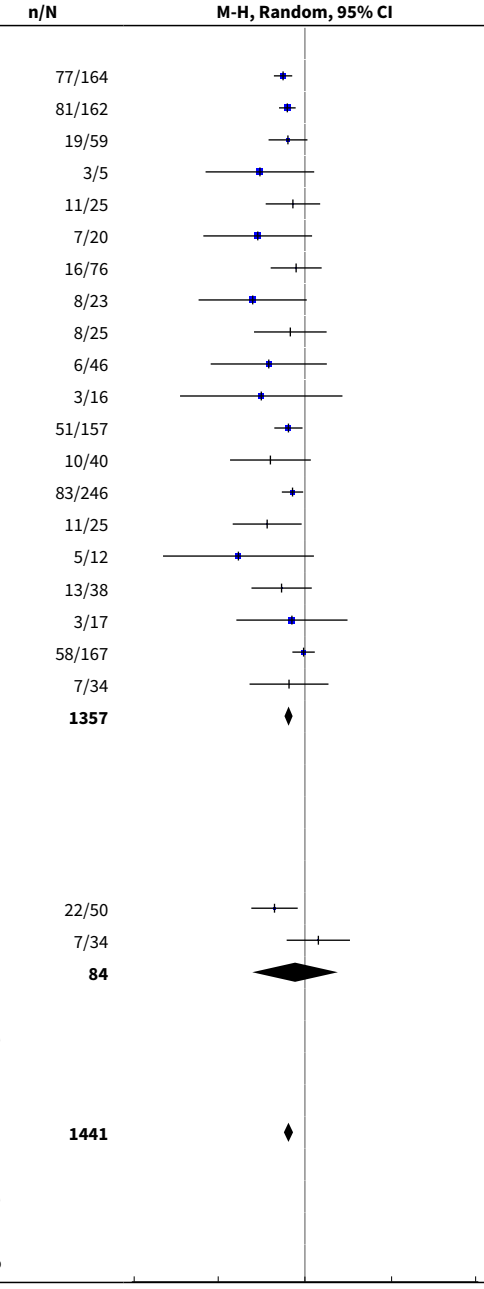
Analysis 2.1. Comparison 2 Subgroup analyses: RCT versus quasi-RCT, Outcome 1 Graft loss: censored for death.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 RCT					
MMF US Study 1995	50/331	28/164		31.29%	0.88[0.58,1.35]
MMF TRI Study 1996	39/335	25/162		25.82%	0.75[0.47,1.2]
Ling 1998	0/11	0/5			Not estimable
Mendez 1998	1/117	3/59		1.11%	0.17[0.02,1.58]
Egfjord 1999	1/25	5/25		1.3%	0.2[0.03,1.59]
Suhail 2000	0/20	0/20			Not estimable
Johnson 2000	9/72	9/76		7.47%	1.06[0.44,2.51]
Folkmane 2001	2/23	3/25		1.94%	0.72[0.13,3.96]
Busque 2001	0/23	0/23			Not estimable
Tuncer 2002	5/38	11/38		6.12%	0.45[0.17,1.18]
Miladipour 2002	0/40	1/40		0.56%	0.33[0.01,7.95]
Weimer 2002	2/31	0/25		0.63%	4.06[0.2,80.94]
Sadek 2002	16/162	16/157		12.97%	0.97[0.5,1.87]
MYSS Study 2004	7/124	7/124		5.41%	1[0.36,2.77]
Merville 2004	0/37	5/34		0.69%	0.08[0,1.46]
Subtotal (95% CI)	**1389**	**977**		**95.31%**	**0.79[0.62,1.01]**
Total events: 132 (MMF), 113 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=10.01, df=11(P=0.53); I^2=0%					
Test for overall effect: Z=1.87(P=0.06)					
2.1.2 quasi-RCT					
Ji 2001	0/56	2/50		0.62%	0.18[0.01,3.64]
Joh 2005	4/34	6/34		4.07%	0.67[0.21,2.15]
Subtotal (95% CI)	**90**	**84**		**4.69%**	**0.56[0.19,1.67]**
Total events: 4 (MMF), 8 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=0.66, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					
Total (95% CI)	**1479**	**1061**		**100%**	**0.78[0.62,0.99]**
Total events: 136 (MMF), 121 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=11.04, df=13(P=0.61); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi^2=0.37, df=1 (P=0.54), I^2=0%					



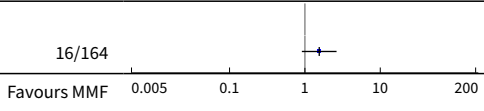
Analysis 2.2. Comparison 2 Subgroup analyses: RCT versus quasi-RCT, Outcome 2 Acute rejection (total).

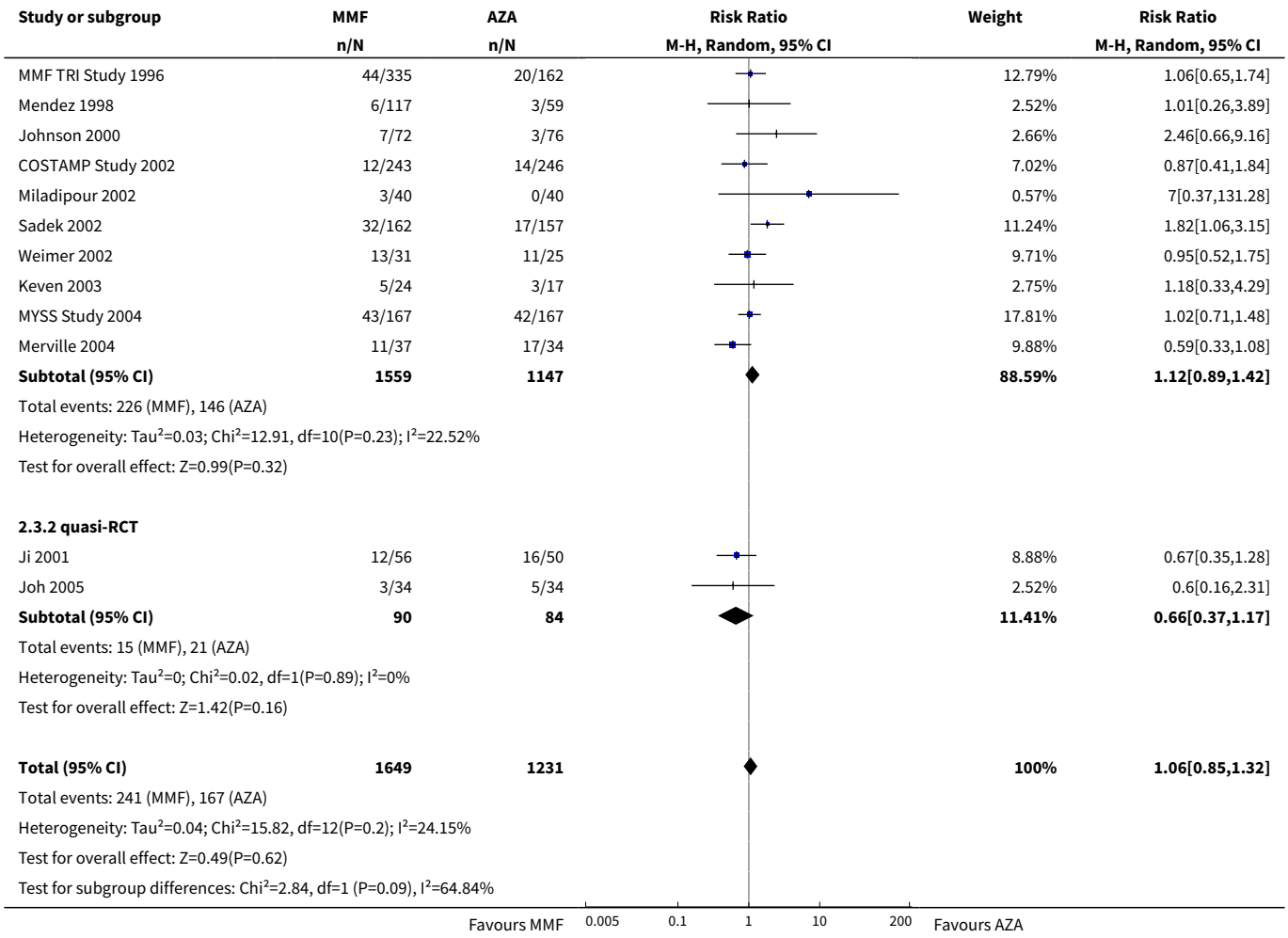
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 RCT					
MMF US Study 1995	87/331	77/164		16.96%	0.56[0.44,0.71]
MMF TRI Study 1996	105/335	81/162		19.18%	0.63[0.5,0.78]
Mendez 1998	24/117	19/59		5.08%	0.64[0.38,1.07]
Ling 1998	2/11	3/5		0.7%	0.3[0.07,1.28]
Egfjord 1999	8/25	11/25		2.7%	0.73[0.35,1.5]
Suhail 2000	2/20	7/20		0.7%	0.29[0.07,1.21]
Johnson 2000	12/72	16/76		3.07%	0.79[0.4,1.56]
Busque 2001	2/23	8/23		0.71%	0.25[0.06,1.05]
Folkmane 2001	5/23	8/25		1.56%	0.68[0.26,1.78]
Sun 2002b	2/40	6/46		0.62%	0.38[0.08,1.79]
Army Hospital 2002	1/17	3/16		0.32%	0.31[0.04,2.71]
Sadek 2002	34/162	51/157		8.81%	0.65[0.44,0.94]
Miladipour 2002	4/40	10/40		1.26%	0.4[0.14,1.17]
COSTAMP Study 2002	59/243	83/246		13.69%	0.72[0.54,0.95]
Weimer 2002	5/31	11/25		1.71%	0.37[0.15,0.92]
Baltar 2002	1/14	5/12		0.37%	0.17[0.02,1.27]
Tuncer 2002	7/38	13/38		2.22%	0.54[0.24,1.2]
Keven 2003	3/24	3/17		0.68%	0.71[0.16,3.1]
MYSS Study 2004	56/167	58/167		12.66%	0.97[0.72,1.3]
Merville 2004	5/37	7/34		1.32%	0.66[0.23,1.87]
Subtotal (95% CI)	**1770**	**1357**		**94.32%**	**0.65[0.58,0.72]**
Total events: 424 (MMF), 480 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=18.4, df=19(P=0.5); I^2=0%					
Test for overall effect: Z=7.82(P<0.0001)					
2.2.2 quasi-RCT					
Ji 2001	11/56	22/50		3.66%	0.45[0.24,0.83]
Joh 2005	10/34	7/34		2.02%	1.43[0.62,3.31]
Subtotal (95% CI)	**90**	**84**		**5.68%**	**0.77[0.25,2.4]**
Total events: 21 (MMF), 29 (AZA)					
Heterogeneity: Tau^2=0.54; Chi^2=4.79, df=1(P=0.03); I^2=79.12%					
Test for overall effect: Z=0.45(P=0.65)					
Total (95% CI)	**1860**	**1441**		**100%**	**0.65[0.57,0.73]**
Total events: 445 (MMF), 509 (AZA)					
Heterogeneity: Tau^2=0.01; Chi^2=23.2, df=21(P=0.33); I^2=9.48%					
Test for overall effect: Z=7.01(P<0.0001)					
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.77), I^2=0%					



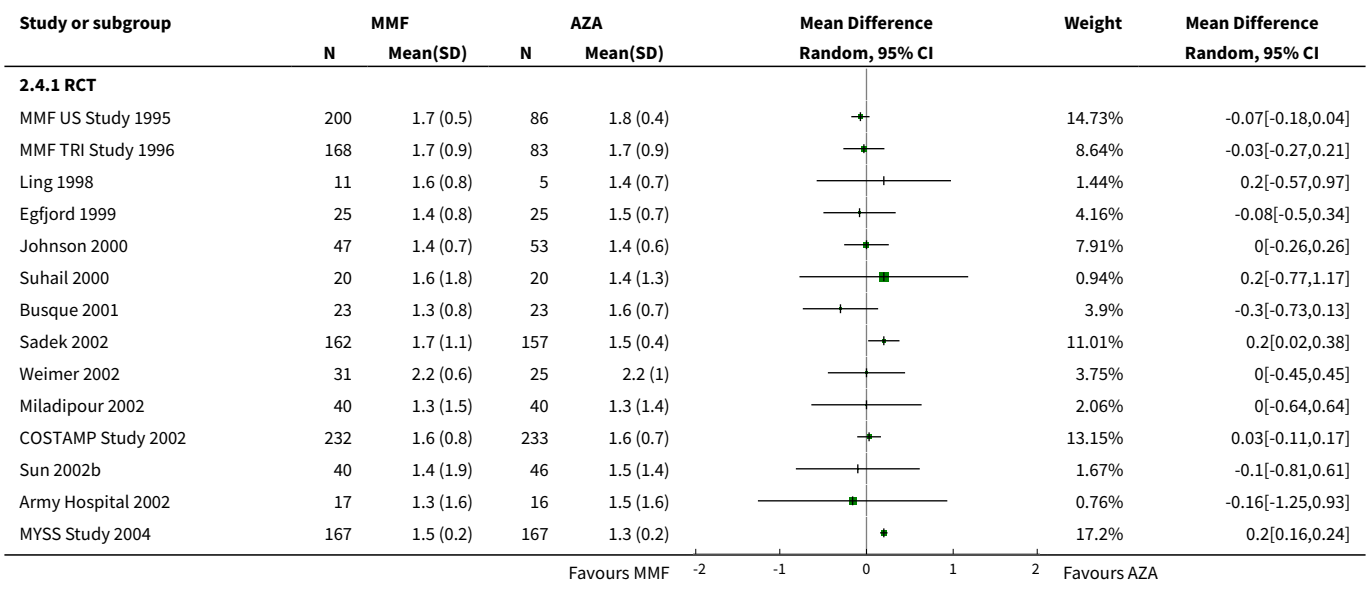
Analysis 2.3. Comparison 2 Subgroup analyses: RCT versus quasi-RCT, Outcome 3 Infection: CMV viraemia/syndrome.

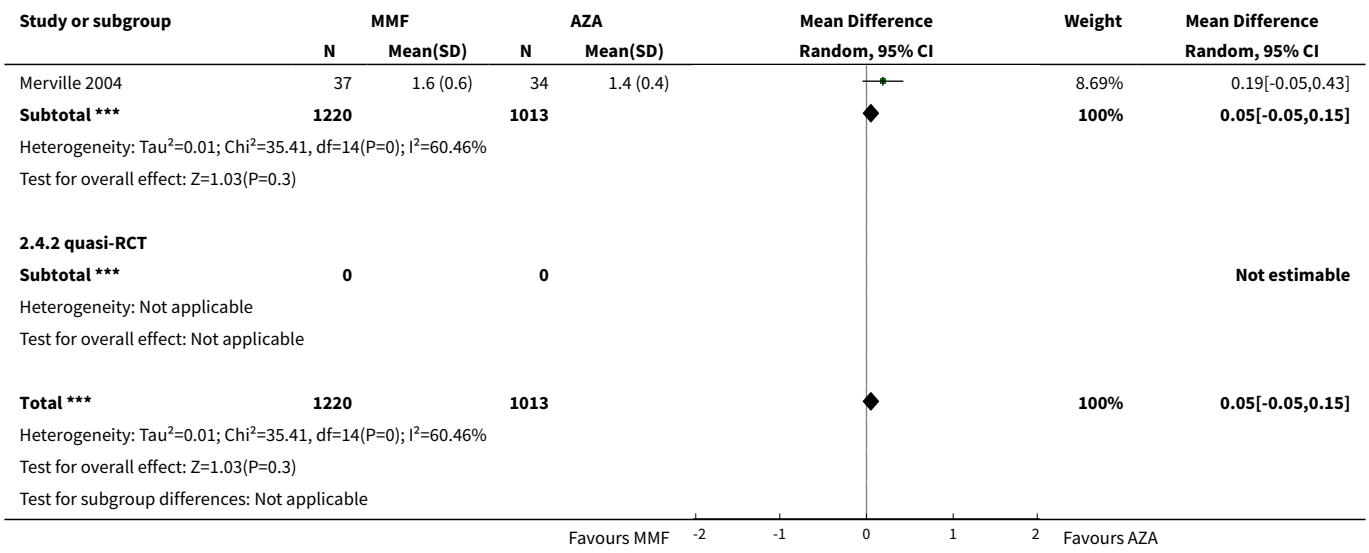
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 RCT					
MMF US Study 1995	50/331	16/164		11.66%	1.55[0.91,2.63]





Analysis 2.4. Comparison 2 Subgroup analyses: RCT versus quasi-RCT, Outcome 4 Graft function, serum creatinine.





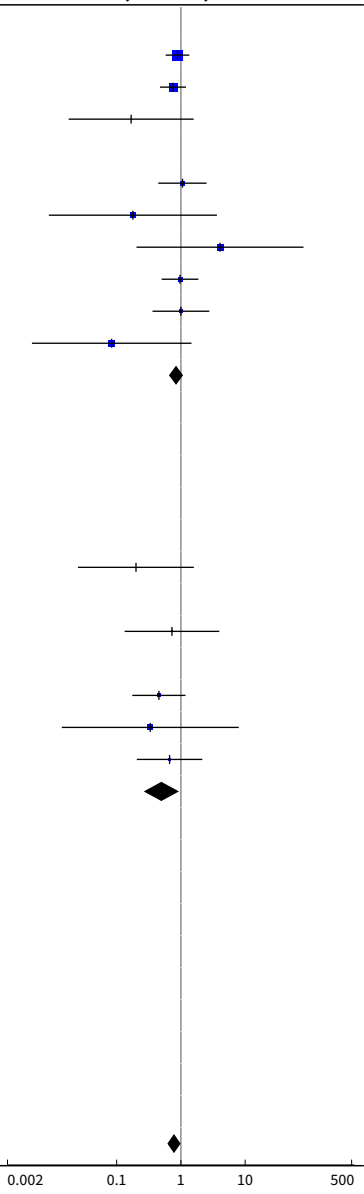
Comparison 3. Subgroup analyses: ITT analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss: censored for death	17	2540	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.99]
1.1 ITT analysis performed	10	2132	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.65, 1.08]
1.2 ITT analysis unclear	7	408	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.93]
1.3 ITT analysis not performed	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Acute rejection: total	22	3301	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.57, 0.73]
2.1 ITT analysis performed	12	2757	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.58, 0.75]
2.2 ITT analysis unclear	8	470	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.34, 0.84]
2.3 ITT analysis not performed	2	74	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.16, 1.85]
3 Infection: CMV viraemia/syndrome	13	2880	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
3.1 ITT analysis performed	10	2691	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.83, 1.34]
3.2 ITT analysis unclear	2	148	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.13, 16.10]
3.3 ITT analysis not performed	1	41	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.33, 4.29]
4 Graft function: serum creatinine	15	2233	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]

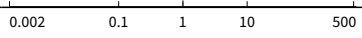
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 ITT performed	10	1948	Mean Difference (IV, Random, 95% CI)	0.07 [-0.03, 0.17]
4.2 ITT unclear	4	252	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.45, 0.16]
4.3 ITT not performed	1	33	Mean Difference (IV, Random, 95% CI)	-0.16 [-1.25, 0.93]

Analysis 3.1. Comparison 3 Subgroup analyses: ITT analysis, Outcome 1 Graft loss: censored for death.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 ITT analysis performed					
MMF US Study 1995	50/331	28/164		31.29%	0.88[0.58,1.35]
MMF TRI Study 1996	39/335	25/162		25.82%	0.75[0.47,1.2]
Mendez 1998	1/117	3/59		1.11%	0.17[0.02,1.58]
Ling 1998	0/11	0/5			Not estimable
Johnson 2000	9/72	9/76		7.47%	1.06[0.44,2.51]
Ji 2001	0/56	2/50		0.62%	0.18[0.01,3.64]
Weimer 2002	2/31	0/25		0.63%	4.06[0.2,80.94]
Sadek 2002	16/162	16/157		12.97%	0.97[0.5,1.87]
MYSS Study 2004	7/124	7/124		5.41%	1[0.36,2.77]
Merville 2004	0/37	5/34		0.69%	0.08[0,1.46]
Subtotal (95% CI)	**1276**	**856**		**86%**	**0.84[0.65,1.08]**
Total events: 124 (MMF), 95 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=7.44, df=8(P=0.49); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					
3.1.2 ITT analysis unclear					
Egfjord 1999	1/25	5/25		1.3%	0.2[0.03,1.59]
Suhail 2000	0/20	0/20			Not estimable
Folkmane 2001	2/23	3/25		1.94%	0.72[0.13,3.96]
Busque 2001	0/23	0/23			Not estimable
Tuncer 2002	5/38	11/38		6.12%	0.45[0.17,1.18]
Miladipour 2002	0/40	1/40		0.56%	0.33[0.01,7.95]
Joh 2005	4/34	6/34		4.07%	0.67[0.21,2.15]
Subtotal (95% CI)	**203**	**205**		**14%**	**0.5[0.26,0.93]**
Total events: 12 (MMF), 26 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=1.28, df=4(P=0.86); I^2=0%					
Test for overall effect: Z=2.17(P=0.03)					
3.1.3 ITT analysis not performed					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (MMF), 0 (AZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1479**	**1061**		**100%**	**0.78[0.62,0.99]**

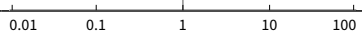


Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 136 (MMF), 121 (AZA)					
Heterogeneity: Tau²=0; Chi²=11.04, df=13(P=0.61); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi²=2.29, df=1 (P=0.13), I²=56.33%					

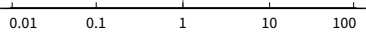


Analysis 3.2. Comparison 3 Subgroup analyses: ITT analysis, Outcome 2 Acute rejection: total.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 ITT analysis performed					
MMF US Study 1995	87/331	77/164		16.96%	0.56[0.44,0.71]
MMF TRI Study 1996	105/335	81/162		19.18%	0.63[0.5,0.78]
Ling 1998	2/11	3/5		0.7%	0.3[0.07,1.28]
Mendez 1998	24/117	19/59		5.08%	0.64[0.38,1.07]
Egfjord 1999	8/25	11/25		2.7%	0.73[0.35,1.5]
Johnson 2000	12/72	16/76		3.07%	0.79[0.4,1.56]
Ji 2001	11/56	22/50		3.66%	0.45[0.24,0.83]
Sadek 2002	34/162	51/157		8.81%	0.65[0.44,0.94]
Weimer 2002	5/31	11/25		1.71%	0.37[0.15,0.92]
COSTAMP Study 2002	59/243	83/246		13.69%	0.72[0.54,0.95]
MYSS Study 2004	56/167	58/167		12.66%	0.97[0.72,1.3]
Merville 2004	5/37	7/34		1.32%	0.66[0.23,1.87]
Subtotal (95% CI)	**1587**	**1170**		**89.55%**	**0.66[0.58,0.75]**
Total events: 408 (MMF), 439 (AZA)					
Heterogeneity: Tau²=0.01; Chi²=13.22, df=11(P=0.28); I²=16.8%					
Test for overall effect: Z=6.27(P<0.0001)					
3.2.2 ITT analysis unclear					
Suhail 2000	2/20	7/20		0.7%	0.29[0.07,1.21]
Folkmane 2001	5/23	8/25		1.56%	0.68[0.26,1.78]
Busque 2001	2/23	8/23		0.71%	0.25[0.06,1.05]
Tuncer 2002	7/38	13/38		2.22%	0.54[0.24,1.2]
Sun 2002b	2/40	6/46		0.62%	0.38[0.08,1.79]
Miladipour 2002	4/40	10/40		1.26%	0.4[0.14,1.17]
Baltar 2002	1/14	5/12		0.37%	0.17[0.02,1.27]
Joh 2005	10/34	7/34		2.02%	1.43[0.62,3.31]
Subtotal (95% CI)	**232**	**238**		**9.46%**	**0.53[0.34,0.84]**
Total events: 33 (MMF), 64 (AZA)					
Heterogeneity: Tau²=0.1; Chi²=9.05, df=7(P=0.25); I²=22.63%					
Test for overall effect: Z=2.7(P=0.01)					
3.2.3 ITT analysis not performed					
Army Hospital 2002	1/17	3/16		0.32%	0.31[0.04,2.71]
Keven 2003	3/24	3/17		0.68%	0.71[0.16,3.1]
Subtotal (95% CI)	**41**	**33**		**0.99%**	**0.55[0.16,1.85]**
Total events: 4 (MMF), 6 (AZA)					
Heterogeneity: Tau²=0; Chi²=0.38, df=1(P=0.54); I²=0%					
Test for overall effect: Z=0.97(P=0.33)					

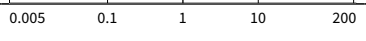


Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**1860**	**1441**		**100%**	**0.65[0.57,0.73]**
Total events: 445 (MMF), 509 (AZA)					
Heterogeneity: Tau^2=0.01; Chi^2=23.2, df=21(P=0.33); I^2=9.48%					
Test for overall effect: Z=7.01(P<0.0001)					
Test for subgroup differences: Chi^2=0.85, df=1 (P=0.65), I^2=0%					

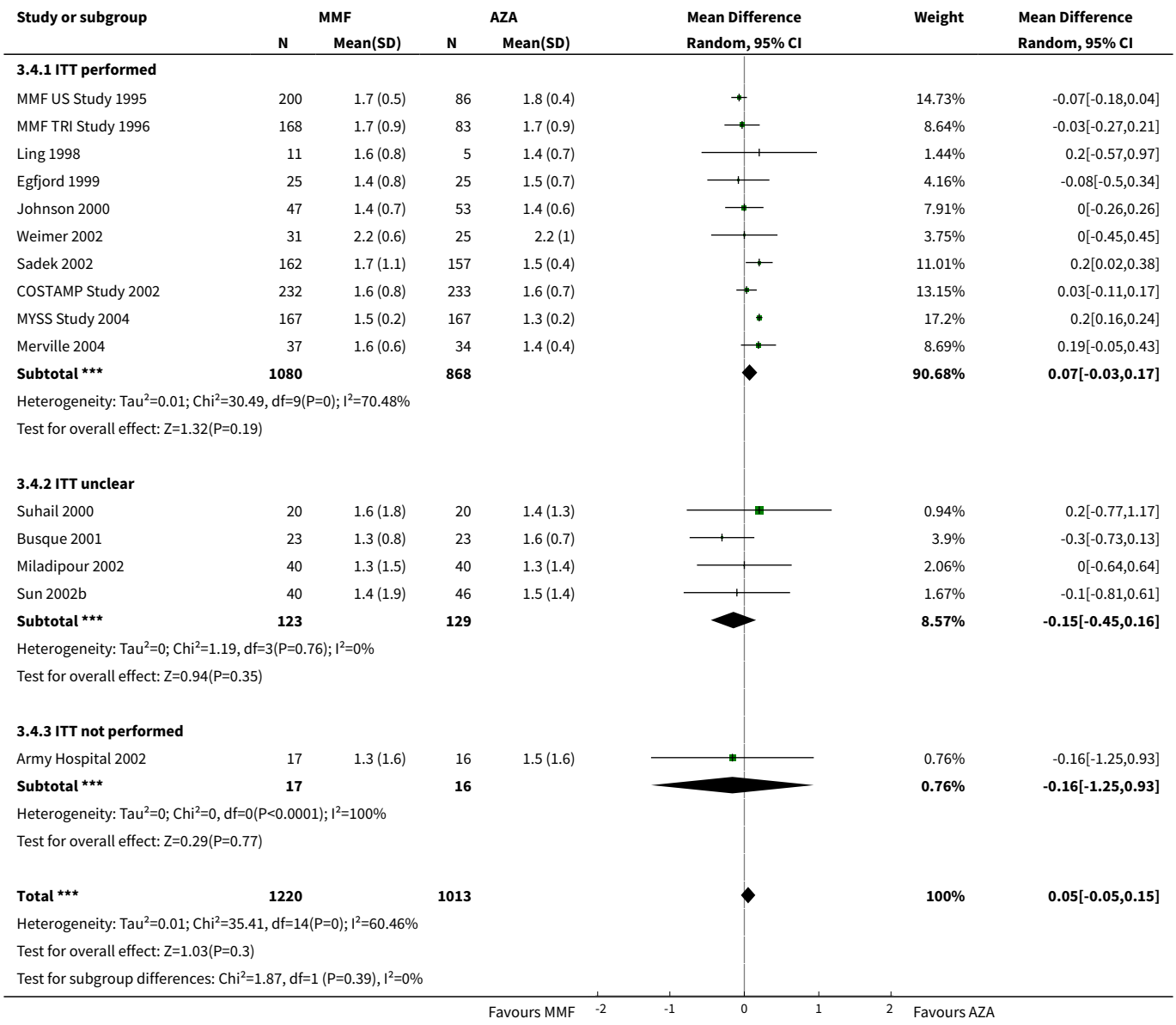


Analysis 3.3. Comparison 3 Subgroup analyses: ITT analysis, Outcome 3 Infection: CMV viraemia/syndrome.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 ITT analysis performed					
MMF US Study 1995	50/331	16/164		11.66%	1.55[0.91,2.63]
MMF TRI Study 1996	44/335	20/162		12.79%	1.06[0.65,1.74]
Mendez 1998	6/117	3/59		2.52%	1.01[0.26,3.89]
Johnson 2000	7/72	3/76		2.66%	2.46[0.66,9.16]
Ji 2001	12/56	16/50		8.88%	0.67[0.35,1.28]
COSTAMP Study 2002	12/243	14/246		7.02%	0.87[0.41,1.84]
Sadek 2002	32/162	17/157		11.24%	1.82[1.06,3.15]
Weimer 2002	13/31	11/25		9.71%	0.95[0.52,1.75]
Merville 2004	11/37	17/34		9.88%	0.59[0.33,1.08]
MYSS Study 2004	43/167	42/167		17.81%	1.02[0.71,1.48]
Subtotal (95% CI)	**1551**	**1140**		**94.16%**	**1.06[0.83,1.34]**
Total events: 230 (MMF), 159 (AZA)					
Heterogeneity: Tau^2=0.05; Chi^2=13.47, df=9(P=0.14); I^2=33.18%					
Test for overall effect: Z=0.46(P=0.64)					
3.3.2 ITT analysis unclear					
Miladipour 2002	3/40	0/40		0.57%	7[0.37,131.28]
Joh 2005	3/34	5/34		2.52%	0.6[0.16,2.31]
Subtotal (95% CI)	**74**	**74**		**3.09%**	**1.47[0.13,16.1]**
Total events: 6 (MMF), 5 (AZA)					
Heterogeneity: Tau^2=1.87; Chi^2=2.38, df=1(P=0.12); I^2=58.04%					
Test for overall effect: Z=0.31(P=0.75)					
3.3.3 ITT analysis not performed					
Keven 2003	5/24	3/17		2.75%	1.18[0.33,4.29]
Subtotal (95% CI)	**24**	**17**		**2.75%**	**1.18[0.33,4.29]**
Total events: 5 (MMF), 3 (AZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.8)					
Total (95% CI)	**1649**	**1231**		**100%**	**1.06[0.85,1.32]**
Total events: 241 (MMF), 167 (AZA)					
Heterogeneity: Tau^2=0.04; Chi^2=15.82, df=12(P=0.2); I^2=24.15%					
Test for overall effect: Z=0.49(P=0.62)					
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.95), I^2=0%					



Analysis 3.4. Comparison 3 Subgroup analyses: ITT analysis, Outcome 4 Graft function: serum creatinine.



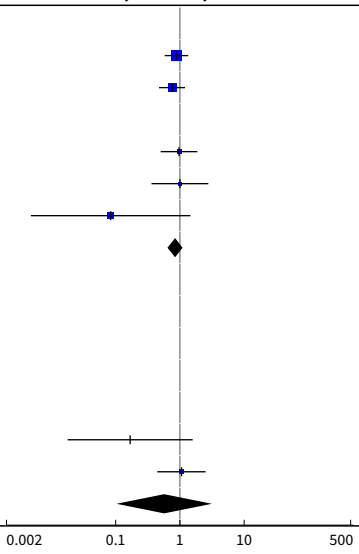
Comparison 4. Subgroup analyses: adults only versus children included

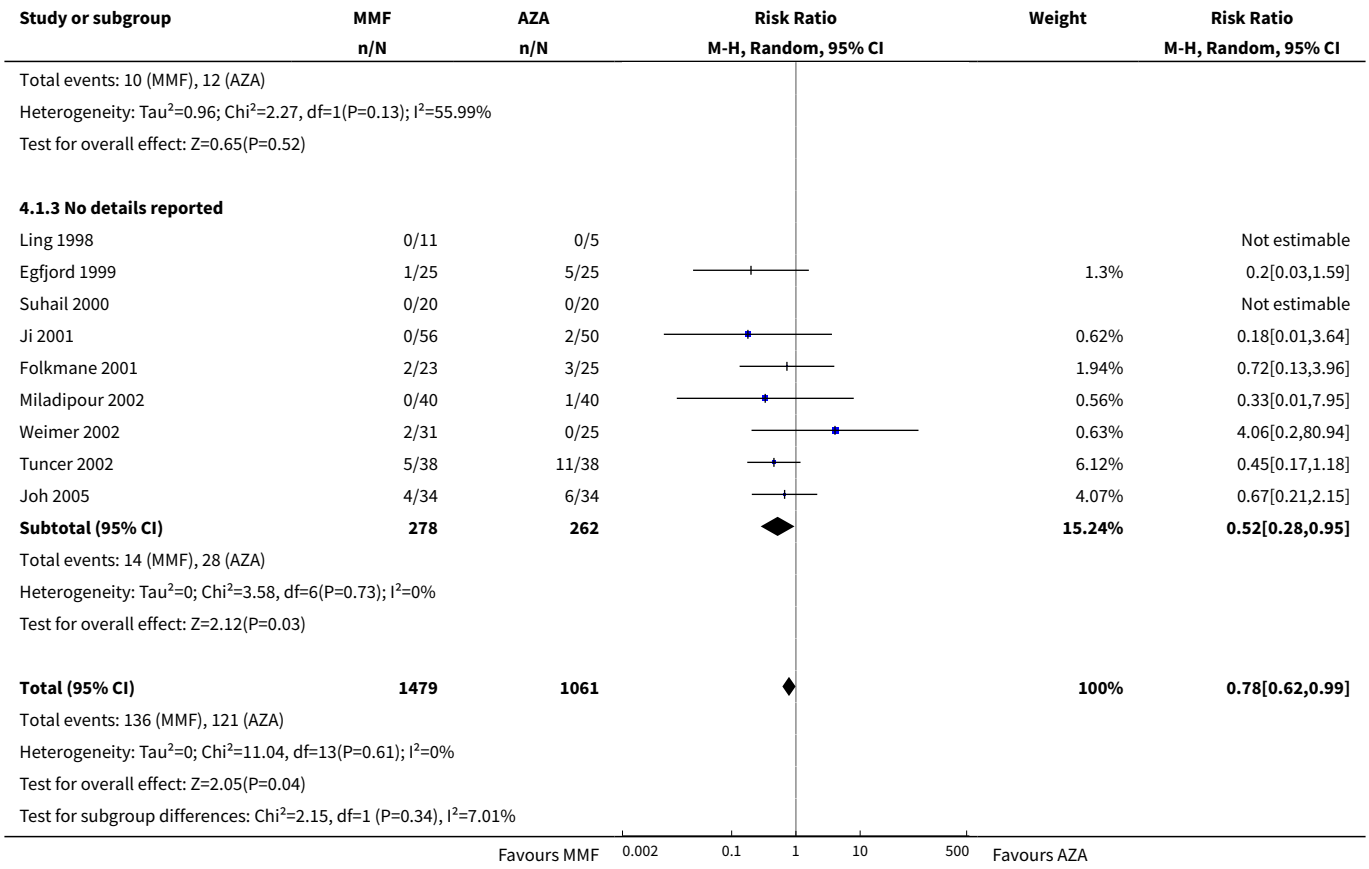
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss: censored for death	17	2540	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.99]
1.1 Adults only	6	1676	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.64, 1.10]
1.2 Children included	2	324	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.10, 3.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 No details reported	9	540	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.95]
2 Acute rejection: total	22	3301	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.57, 0.73]
2.1 Adults only	8	2292	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.57, 0.79]
2.2 Children included	2	324	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.04]
2.3 No details reported	12	685	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.40, 0.71]
3 Infection: CMV viraemia/syndrome	13	2880	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
3.1 Adults only	7	2246	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.84, 1.45]
3.2 Children included	2	324	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.62, 4.09]
3.3 No details reported	4	310	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.54, 1.24]
4 Graft function: serum creatinine	15	2233	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
4.1 Adults only	7	1772	Mean Difference (IV, Random, 95% CI)	0.06 [-0.06, 0.19]
4.2 Children included	1	100	Mean Difference (IV, Random, 95% CI)	0.0 [-0.26, 0.26]
4.3 No details reported	7	361	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.24, 0.22]

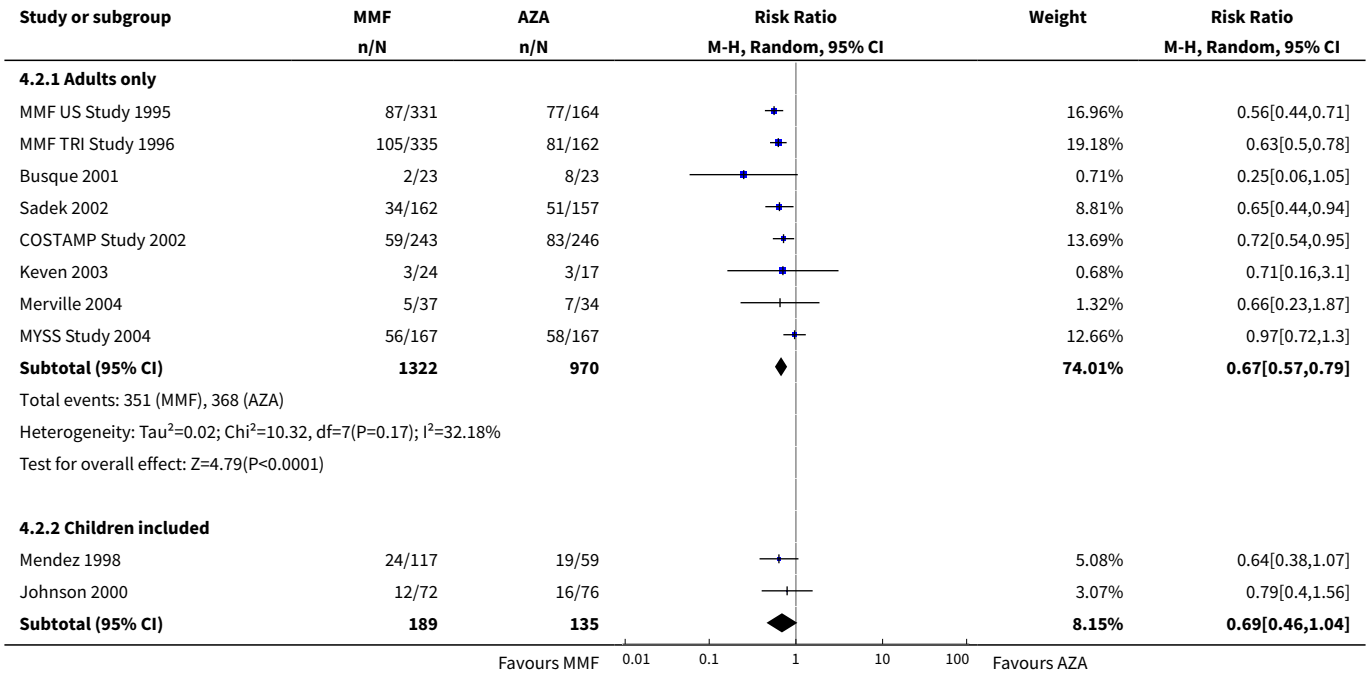
Analysis 4.1. Comparison 4 Subgroup analyses: adults only versus children included, Outcome 1 Graft loss: censored for death.

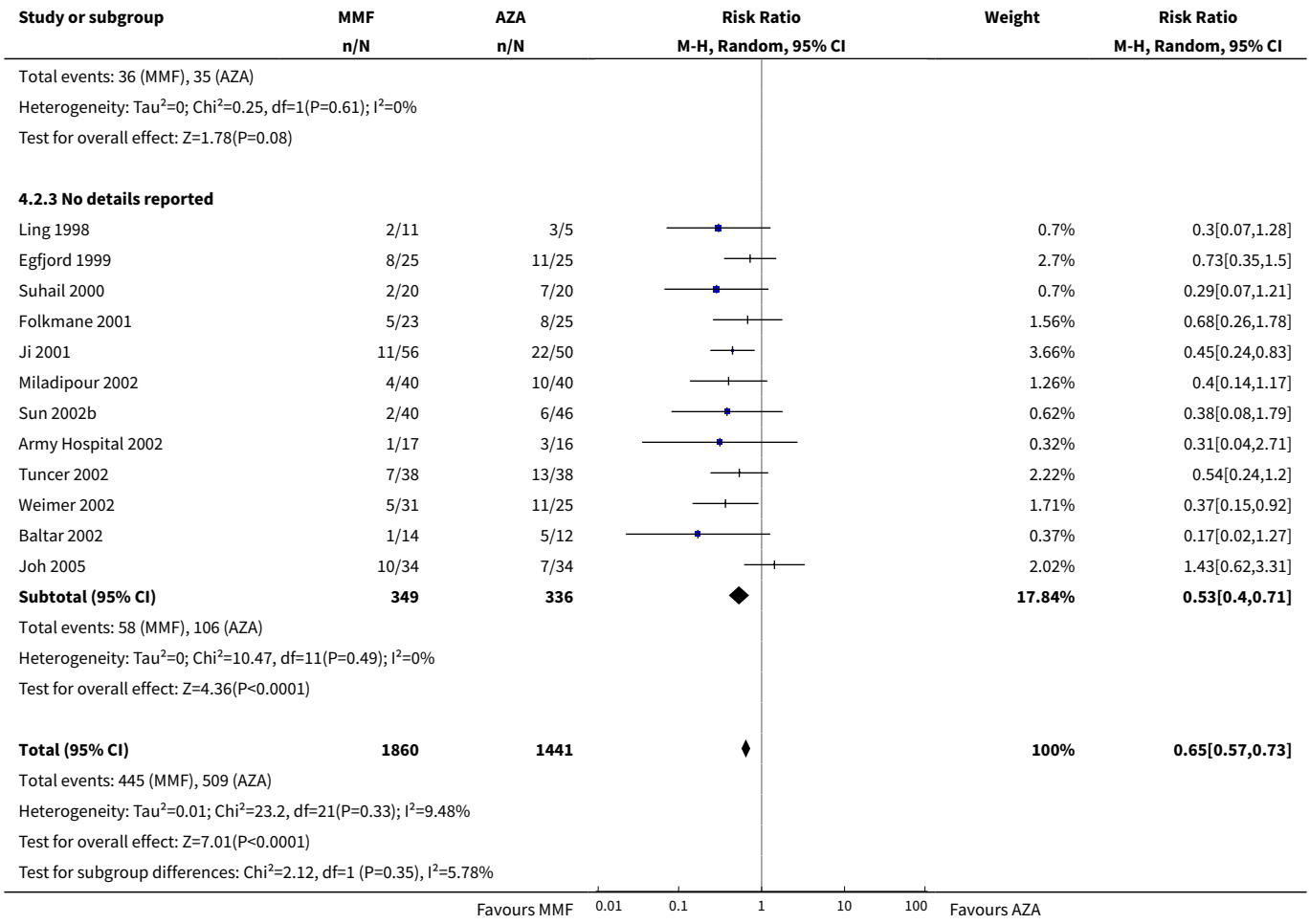
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Adults only					
MMF US Study 1995	50/331	28/164		31.29%	0.88[0.58,1.35]
MMF TRI Study 1996	39/335	25/162		25.82%	0.75[0.47,1.2]
Busque 2001	0/23	0/23			Not estimable
Sadek 2002	16/162	16/157		12.97%	0.97[0.5,1.87]
MYSS Study 2004	7/124	7/124		5.41%	1[0.36,2.77]
Merville 2004	0/37	5/34		0.69%	0.08[0,1.46]
Subtotal (95% CI)	**1012**	**664**		**76.17%**	**0.84[0.64,1.1]**
Total events: 112 (MMF), 81 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=3.1, df=4(P=0.54); I^2=0%					
Test for overall effect: Z=1.25(P=0.21)					
4.1.2 Children included					
Mendez 1998	1/117	3/59		1.11%	0.17[0.02,1.58]
Johnson 2000	9/72	9/76		7.47%	1.06[0.44,2.51]
Subtotal (95% CI)	**189**	**135**		**8.59%**	**0.57[0.1,3.15]**



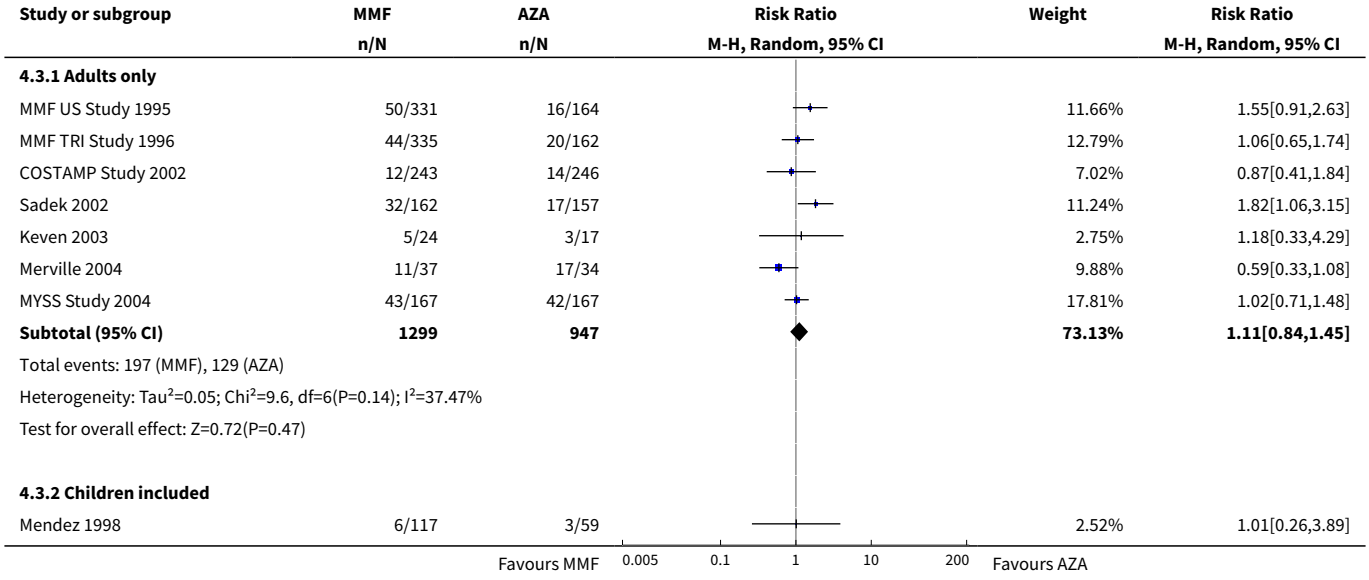


Analysis 4.2. Comparison 4 Subgroup analyses: adults only versus children included, Outcome 2 Acute rejection: total.

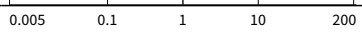




Analysis 4.3. Comparison 4 Subgroup analyses: adults only versus children included, Outcome 3 Infection: CMV viraemia/syndrome.

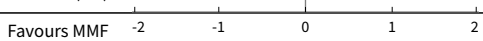


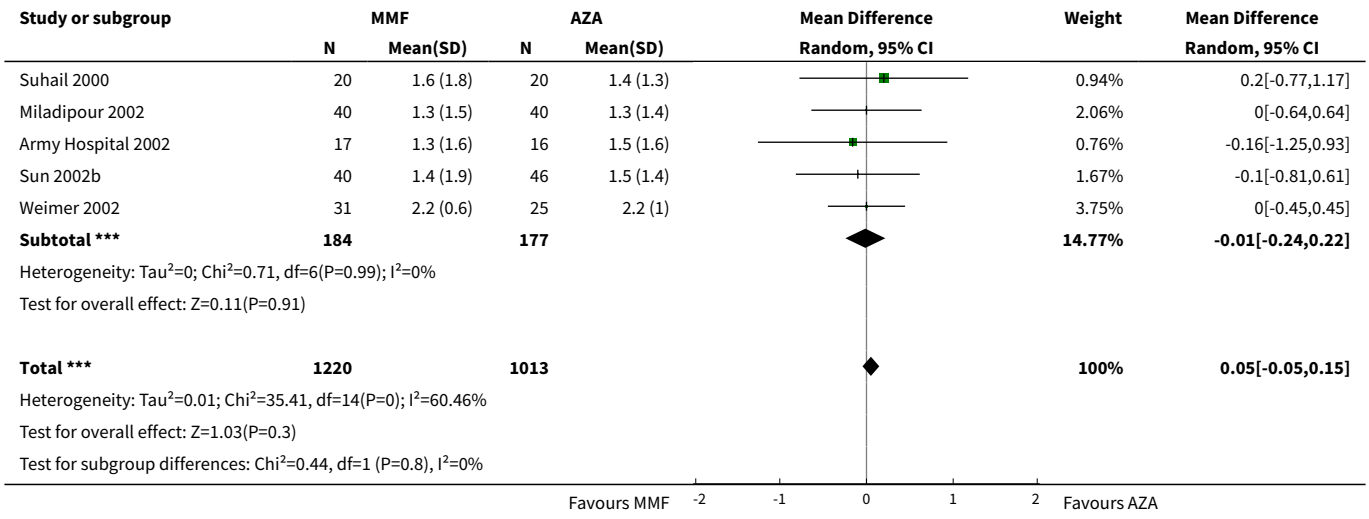
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Johnson 2000	7/72	3/76		2.66%	2.46[0.66,9.16]
Subtotal (95% CI)	**189**	**135**		**5.18%**	**1.6[0.62,4.09]**
Total events: 13 (MMF), 6 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=0.86, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
4.3.3 No details reported					
Ji 2001	12/56	16/50		8.88%	0.67[0.35,1.28]
Miladipour 2002	3/40	0/40		0.57%	7[0.37,131.28]
Weimer 2002	13/31	11/25		9.71%	0.95[0.52,1.75]
Joh 2005	3/34	5/34		2.52%	0.6[0.16,2.31]
Subtotal (95% CI)	**161**	**149**		**21.69%**	**0.82[0.54,1.24]**
Total events: 31 (MMF), 32 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=2.91, df=3(P=0.41); I^2=0%					
Test for overall effect: Z=0.94(P=0.35)					
Total (95% CI)	**1649**	**1231**		**100%**	**1.06[0.85,1.32]**
Total events: 241 (MMF), 167 (AZA)					
Heterogeneity: Tau^2=0.04; Chi^2=15.82, df=12(P=0.2); I^2=24.15%					
Test for overall effect: Z=0.49(P=0.62)					
Test for subgroup differences: Chi^2=2.24, df=1 (P=0.33), I^2=10.78%					



Analysis 4.4. Comparison 4 Subgroup analyses: adults only versus children included, Outcome 4 Graft function: serum creatinine.

Study or subgroup	MMF N	MMF Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.4.1 Adults only							
MMF US Study 1995	200	1.7 (0.5)	86	1.8 (0.4)		14.73%	-0.07[-0.18,0.04]
MMF TRI Study 1996	168	1.7 (0.9)	83	1.7 (0.9)		8.64%	-0.03[-0.27,0.21]
Busque 2001	23	1.3 (0.8)	23	1.6 (0.7)		3.9%	-0.3[-0.73,0.13]
Sadek 2002	162	1.7 (1.1)	157	1.5 (0.4)		11.01%	0.2[0.02,0.38]
COSTAMP Study 2002	232	1.6 (0.8)	233	1.6 (0.7)		13.15%	0.03[-0.11,0.17]
Merville 2004	37	1.6 (0.6)	34	1.4 (0.4)		8.69%	0.19[-0.05,0.43]
MYSS Study 2004	167	1.5 (0.2)	167	1.3 (0.2)		17.2%	0.2[0.16,0.24]
Subtotal ***	**989**		**783**			**77.32%**	**0.06[-0.06,0.19]**
Heterogeneity: Tau^2=0.02; Chi^2=31.74, df=6(P<0.0001); I^2=81.1%							
Test for overall effect: Z=1.01(P=0.31)							
4.4.2 Children included							
Johnson 2000	47	1.4 (0.7)	53	1.4 (0.6)		7.91%	0[-0.26,0.26]
Subtotal ***	**47**		**53**			**7.91%**	**0[-0.26,0.26]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
4.4.3 No details reported							
Ling 1998	11	1.6 (0.8)	5	1.4 (0.7)		1.44%	0.2[-0.57,0.97]
Egfjord 1999	25	1.4 (0.8)	25	1.5 (0.7)		4.16%	-0.08[-0.5,0.34]





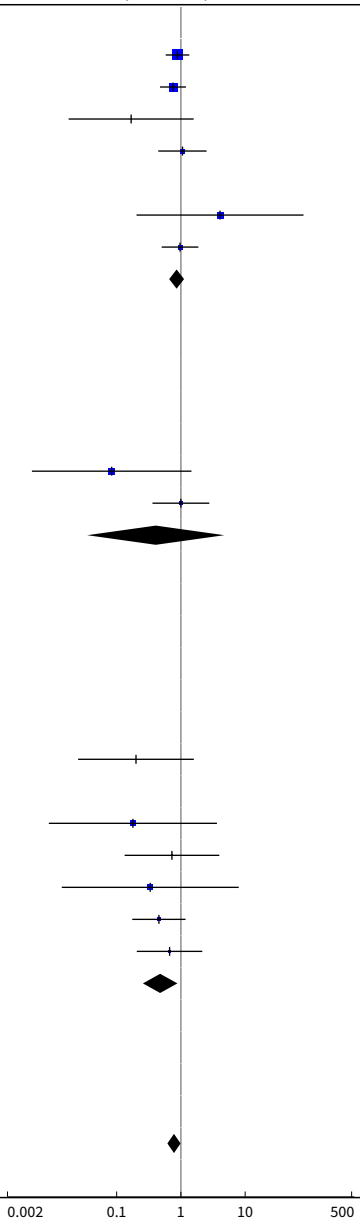
Comparison 5. Subgroup analyses: industry versus non-industry funding

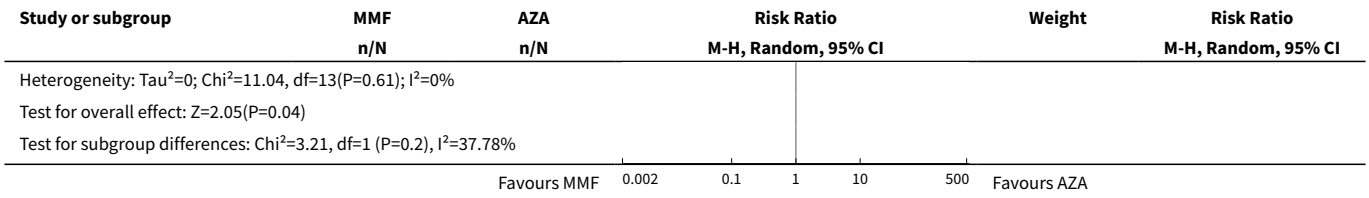
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss: censored for death	17	2540	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.99]
1.1 Industry funding	7	1737	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.66, 1.12]
1.2 Non-industry funding	2	319	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.03, 4.74]
1.3 No details reported	8	484	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.26, 0.88]
2 Acute rejection: total	22	3301	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.57, 0.73]
2.1 Industry funding	9	2252	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.55, 0.70]
2.2 Non-industry funding	2	405	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.25]
2.3 No details reported	11	644	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.43, 0.77]
3 Infection: CMV viraemia/syndrome	13	2880	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
3.1 Industry funding	7	2180	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.99, 1.62]
3.2 Non-industry funding	2	405	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.49, 1.39]
3.3 No details reported	4	295	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.46, 1.32]
4 Graft function: serum creatinine	15	2233	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
4.1 Industry funding	7	1523	Mean Difference (IV, Random, 95% CI)	0.00 [-0.09, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Non-industry funding	2	405	Mean Difference (IV, Random, 95% CI)	0.20 [0.16, 0.24]
4.3 No details reported	6	305	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.29, 0.25]

Analysis 5.1. Comparison 5 Subgroup analyses: industry versus non-industry funding, Outcome 1 Graft loss: censored for death.

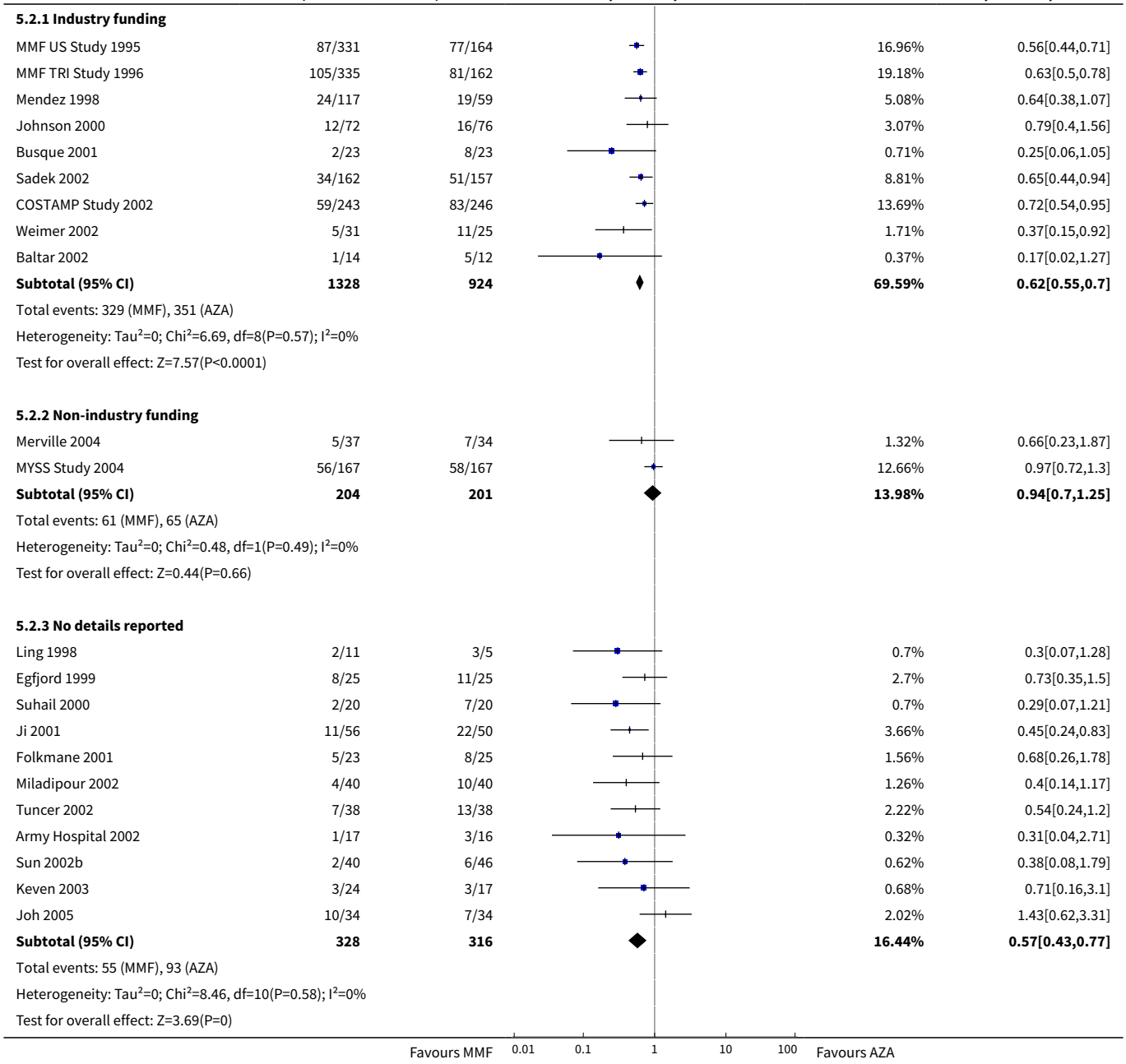
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Industry funding					
MMF US Study 1995	50/331	28/164		31.29%	0.88[0.58,1.35]
MMF TRI Study 1996	39/335	25/162		25.82%	0.75[0.47,1.2]
Mendez 1998	1/117	3/59		1.11%	0.17[0.02,1.58]
Johnson 2000	9/72	9/76		7.47%	1.06[0.44,2.51]
Busque 2001	0/23	0/23			Not estimable
Weimer 2002	2/31	0/25		0.63%	4.06[0.2,80.94]
Sadek 2002	16/162	16/157		12.97%	0.97[0.5,1.87]
Subtotal (95% CI)	**1071**	**666**		**79.29%**	**0.86[0.66,1.12]**
Total events: 117 (MMF), 81 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=3.73, df=5(P=0.59); I^2=0%					
Test for overall effect: Z=1.14(P=0.26)					
5.1.2 Non-industry funding					
Merville 2004	0/37	5/34		0.69%	0.08[0,1.46]
MYSS Study 2004	7/124	7/124		5.41%	1[0.36,2.77]
Subtotal (95% CI)	**161**	**158**		**6.09%**	**0.41[0.03,4.74]**
Total events: 7 (MMF), 12 (AZA)					
Heterogeneity: Tau^2=2.2; Chi^2=2.83, df=1(P=0.09); I^2=64.7%					
Test for overall effect: Z=0.72(P=0.47)					
5.1.3 No details reported					
Ling 1998	0/11	0/5			Not estimable
Egfjord 1999	1/25	5/25		1.3%	0.2[0.03,1.59]
Suhail 2000	0/20	0/20			Not estimable
Ji 2001	0/56	2/50		0.62%	0.18[0.01,3.64]
Folkmane 2001	2/23	3/25		1.94%	0.72[0.13,3.96]
Miladipour 2002	0/40	1/40		0.56%	0.33[0.01,7.95]
Tuncer 2002	5/38	11/38		6.12%	0.45[0.17,1.18]
Joh 2005	4/34	6/34		4.07%	0.67[0.21,2.15]
Subtotal (95% CI)	**247**	**237**		**14.62%**	**0.48[0.26,0.88]**
Total events: 12 (MMF), 28 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=1.72, df=5(P=0.89); I^2=0%					
Test for overall effect: Z=2.36(P=0.02)					
Total (95% CI)	**1479**	**1061**		**100%**	**0.78[0.62,0.99]**
Total events: 136 (MMF), 121 (AZA)					

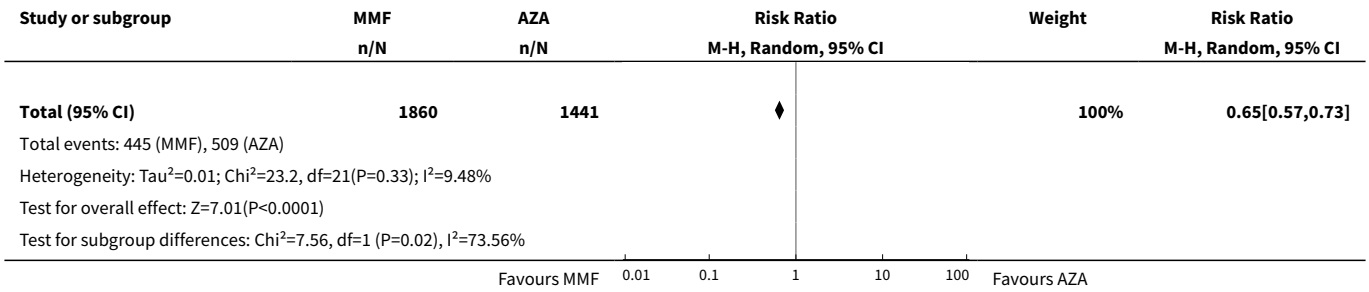




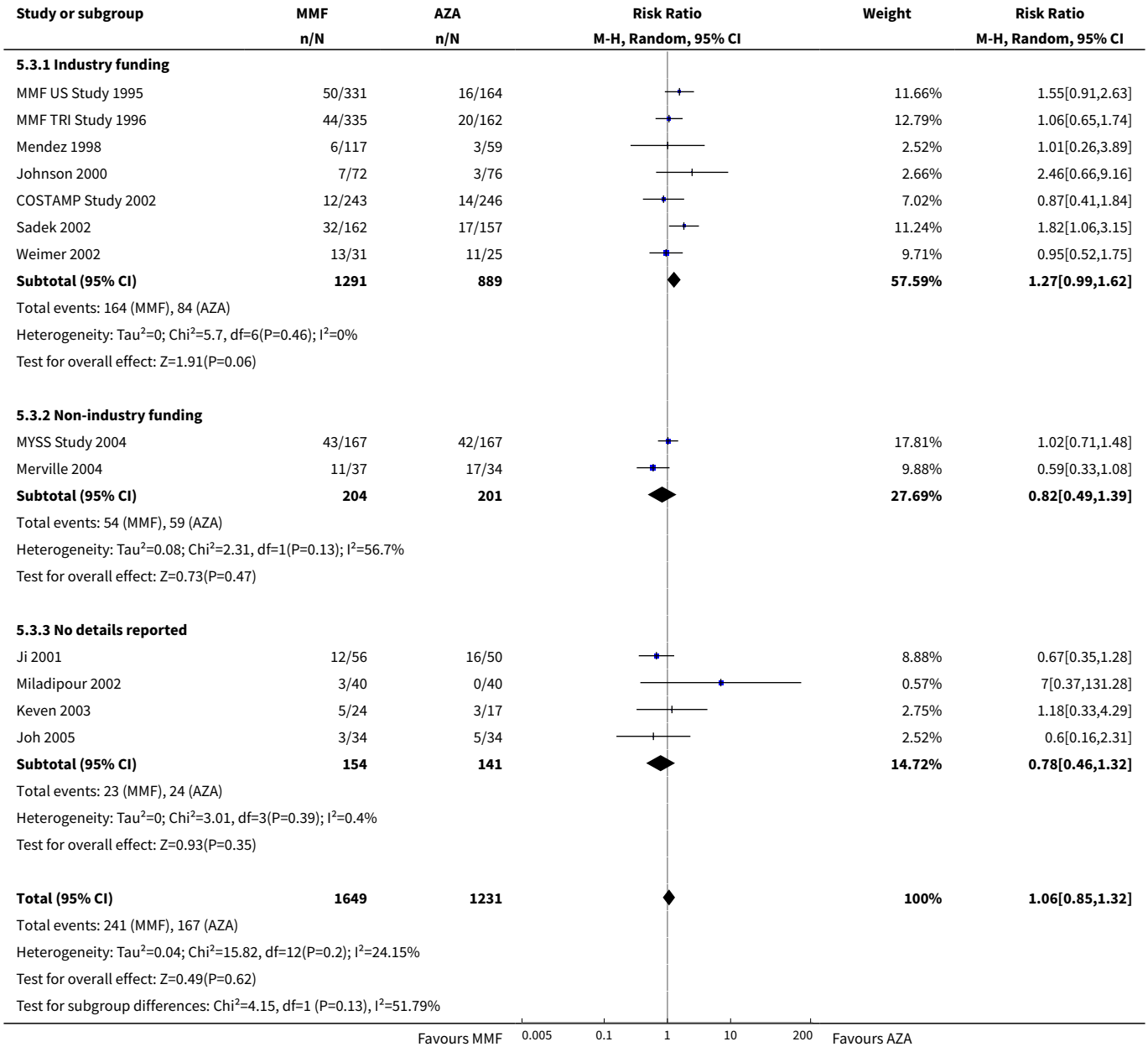
Analysis 5.2. Comparison 5 Subgroup analyses: industry versus non-industry funding, Outcome 2 Acute rejection: total.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Industry funding					
MMF US Study 1995	87/331	77/164		16.96%	0.56[0.44,0.71]
MMF TRI Study 1996	105/335	81/162		19.18%	0.63[0.5,0.78]
Mendez 1998	24/117	19/59		5.08%	0.64[0.38,1.07]
Johnson 2000	12/72	16/76		3.07%	0.79[0.4,1.56]
Busque 2001	2/23	8/23		0.71%	0.25[0.06,1.05]
Sadek 2002	34/162	51/157		8.81%	0.65[0.44,0.94]
COSTAMP Study 2002	59/243	83/246		13.69%	0.72[0.54,0.95]
Weimer 2002	5/31	11/25		1.71%	0.37[0.15,0.92]
Baltar 2002	1/14	5/12		0.37%	0.17[0.02,1.27]
Subtotal (95% CI)	**1328**	**924**		**69.59%**	**0.62[0.55,0.7]**
Total events: 329 (MMF), 351 (AZA)					
Heterogeneity: Tau²=0; Chi²=6.69, df=8(P=0.57); I²=0%					
Test for overall effect: Z=7.57(P<0.0001)					
5.2.2 Non-industry funding					
Merville 2004	5/37	7/34		1.32%	0.66[0.23,1.87]
MYSS Study 2004	56/167	58/167		12.66%	0.97[0.72,1.3]
Subtotal (95% CI)	**204**	**201**		**13.98%**	**0.94[0.7,1.25]**
Total events: 61 (MMF), 65 (AZA)					
Heterogeneity: Tau²=0; Chi²=0.48, df=1(P=0.49); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
5.2.3 No details reported					
Ling 1998	2/11	3/5		0.7%	0.3[0.07,1.28]
Egfjord 1999	8/25	11/25		2.7%	0.73[0.35,1.5]
Suhail 2000	2/20	7/20		0.7%	0.29[0.07,1.21]
Ji 2001	11/56	22/50		3.66%	0.45[0.24,0.83]
Folkmane 2001	5/23	8/25		1.56%	0.68[0.26,1.78]
Miladipour 2002	4/40	10/40		1.26%	0.4[0.14,1.17]
Tuncer 2002	7/38	13/38		2.22%	0.54[0.24,1.2]
Army Hospital 2002	1/17	3/16		0.32%	0.31[0.04,2.71]
Sun 2002b	2/40	6/46		0.62%	0.38[0.08,1.79]
Keven 2003	3/24	3/17		0.68%	0.71[0.16,3.1]
Joh 2005	10/34	7/34		2.02%	1.43[0.62,3.31]
Subtotal (95% CI)	**328**	**316**		**16.44%**	**0.57[0.43,0.77]**
Total events: 55 (MMF), 93 (AZA)					
Heterogeneity: Tau²=0; Chi²=8.46, df=10(P=0.58); I²=0%					
Test for overall effect: Z=3.69(P=0)					

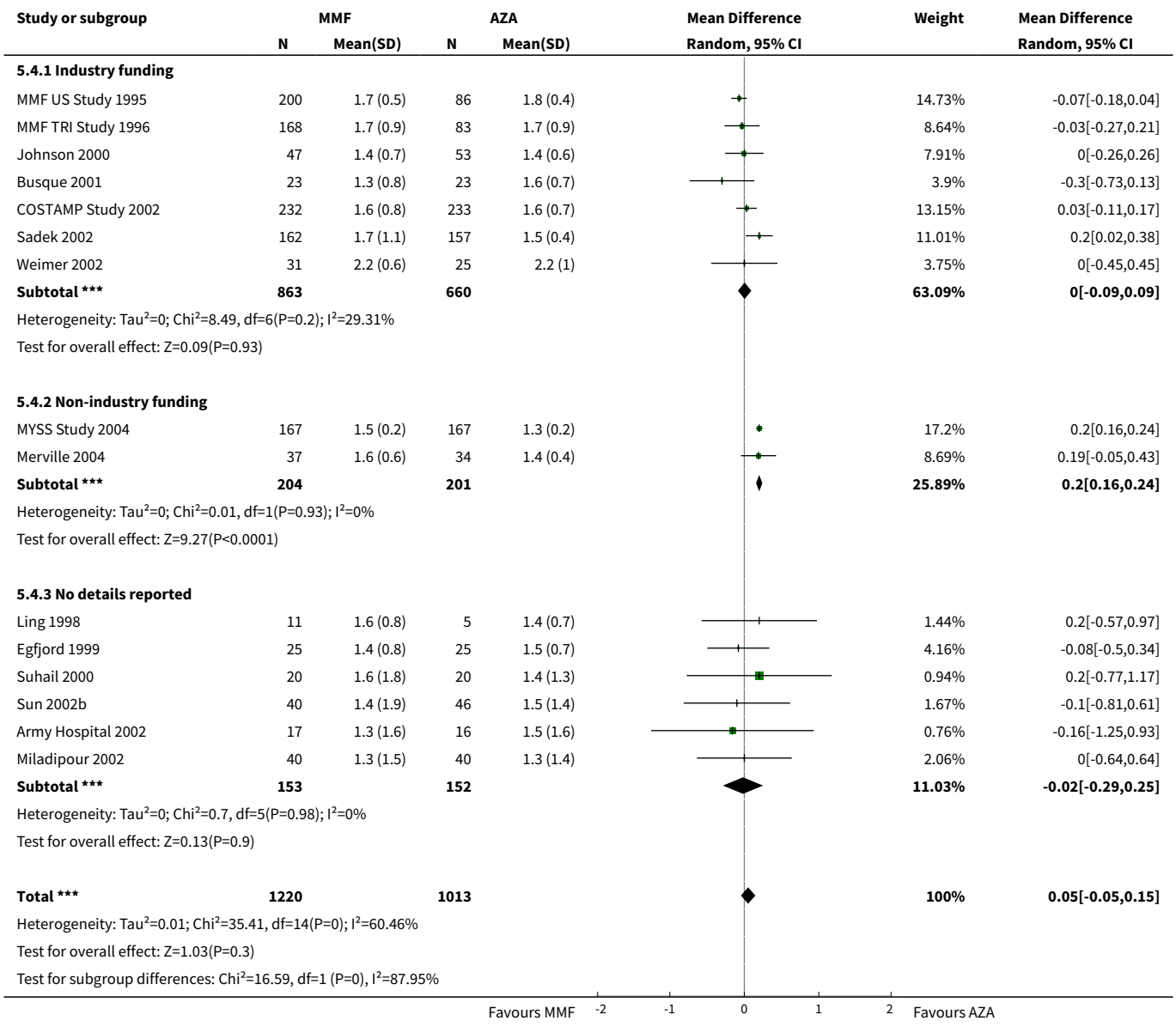




Analysis 5.3. Comparison 5 Subgroup analyses: industry versus non-industry funding, Outcome 3 Infection: CMV viraemia/syndrome.



Analysis 5.4. Comparison 5 Subgroup analyses: industry versus non-industry funding, Outcome 4 Graft function: serum creatinine.



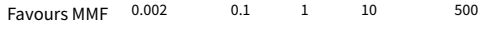
Comparison 6. Subgroup analyses: publication type

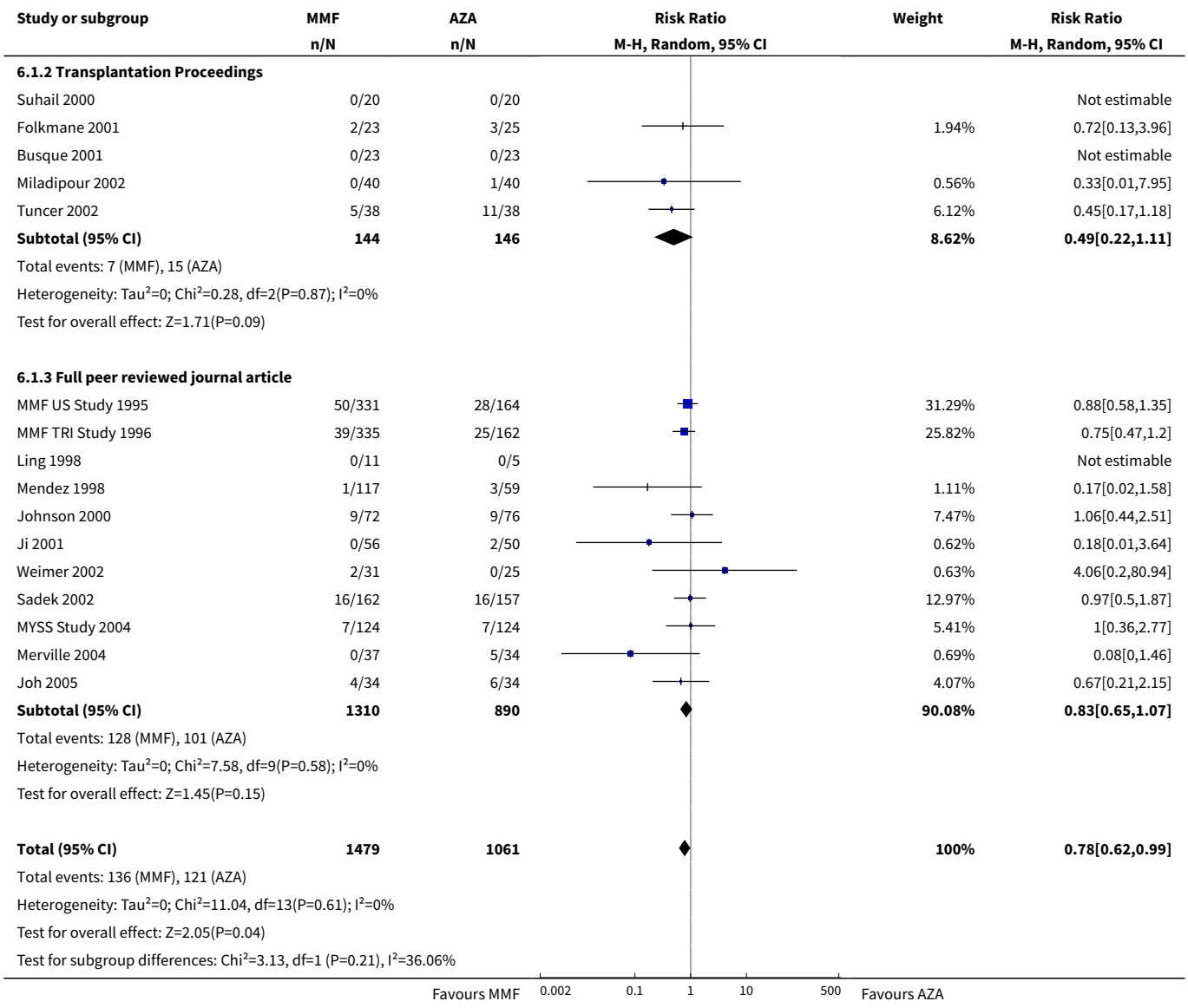
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss: censored for death	17	2540	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.99]
1.1 Conference abstract only	1	50	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.03, 1.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Transplantation Proceedings	5	290	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.22, 1.11]
1.3 Full peer reviewed journal article	11	2200	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.65, 1.07]
2 Acute rejection: total	22	3301	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.57, 0.73]
2.1 Conference abstract only	2	83	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.34, 1.33]
2.2 Transplantation Proceedings	5	290	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.29, 0.74]
2.3 Full peer reviewed journal article	15	2928	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.76]
3 Infection: CMV viraemia/syndrome	13	2880	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
3.1 Conference abstract only	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Transplantation Proceedings	1	80	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.37, 131.28]
3.3 Full peer reviewed journal article	12	2800	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.84, 1.30]
4 Graft function: serum creatinine	15	2233	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
4.1 Conference abstract only	2	83	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.48, 0.30]
4.2 Transplantation Proceedings	3	166	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.49, 0.18]
4.3 Full peer reviewed journal article	10	1984	Mean Difference (IV, Random, 95% CI)	0.07 [-0.03, 0.18]

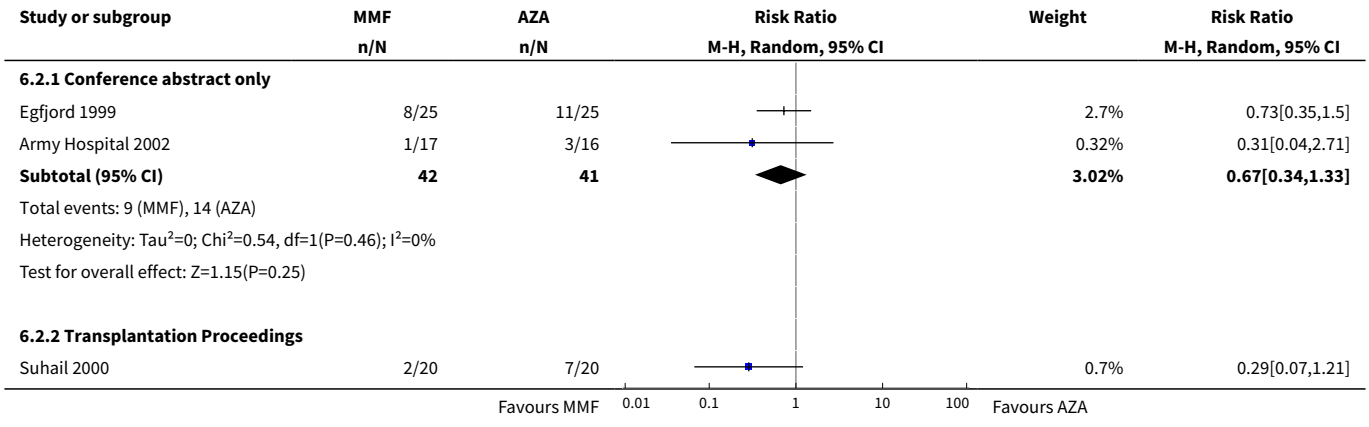
Analysis 6.1. Comparison 6 Subgroup analyses: publication type, Outcome 1 Graft loss: censored for death.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Conference abstract only					
Egfjord 1999	1/25	5/25		1.3%	0.2[0.03,1.59]
Subtotal (95% CI)	**25**	**25**		**1.3%**	**0.2[0.03,1.59]**
Total events: 1 (MMF), 5 (AZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					

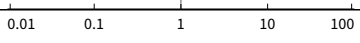




Analysis 6.2. Comparison 6 Subgroup analyses: publication type, Outcome 2 Acute rejection: total.

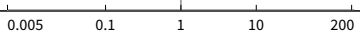


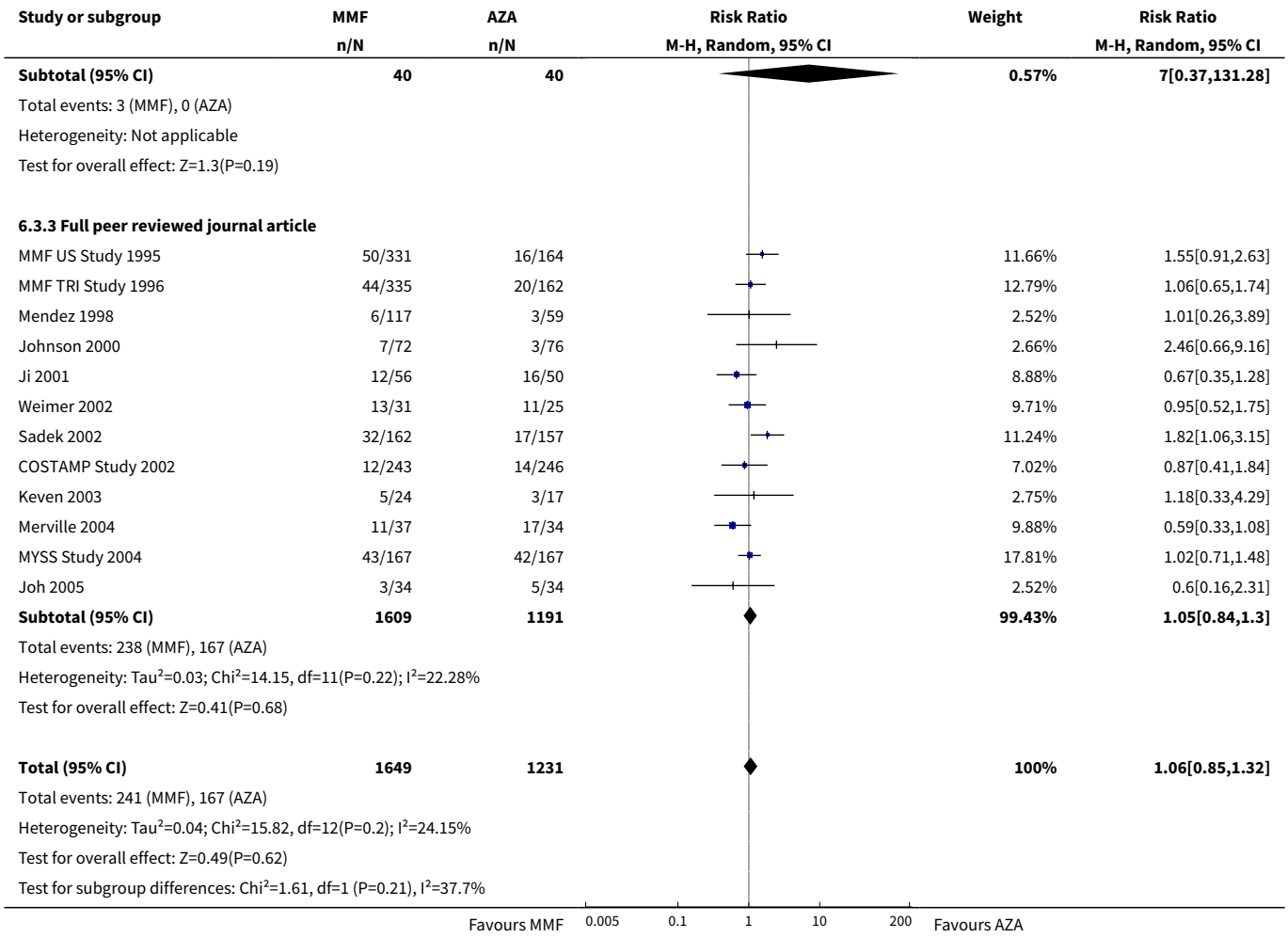
Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Busque 2001	2/23	8/23		0.71%	0.25[0.06,1.05]
Folkmane 2001	5/23	8/25		1.56%	0.68[0.26,1.78]
Miladipour 2002	4/40	10/40		1.26%	0.4[0.14,1.17]
Tuncer 2002	7/38	13/38		2.22%	0.54[0.24,1.2]
Subtotal (95% CI)	**144**	**146**		**6.45%**	**0.46[0.29,0.74]**
Total events: 20 (MMF), 46 (AZA)					
Heterogeneity: Tau^2=0; Chi^2=1.98, df=4(P=0.74); I^2=0%					
Test for overall effect: Z=3.2(P=0)					
6.2.3 Full peer reviewed journal article					
MMF US Study 1995	87/331	77/164		16.96%	0.56[0.44,0.71]
MMF TRI Study 1996	105/335	81/162		19.18%	0.63[0.5,0.78]
Mendez 1998	24/117	19/59		5.08%	0.64[0.38,1.07]
Ling 1998	2/11	3/5		0.7%	0.3[0.07,1.28]
Johnson 2000	12/72	16/76		3.07%	0.79[0.4,1.56]
Ji 2001	11/56	22/50		3.66%	0.45[0.24,0.83]
COSTAMP Study 2002	59/243	83/246		13.69%	0.72[0.54,0.95]
Sadek 2002	34/162	51/157		8.81%	0.65[0.44,0.94]
Sun 2002b	2/40	6/46		0.62%	0.38[0.08,1.79]
Weimer 2002	5/31	11/25		1.71%	0.37[0.15,0.92]
Baltar 2002	1/14	5/12		0.37%	0.17[0.02,1.27]
Keven 2003	3/24	3/17		0.68%	0.71[0.16,3.1]
MYSS Study 2004	56/167	58/167		12.66%	0.97[0.72,1.3]
Merville 2004	5/37	7/34		1.32%	0.66[0.23,1.87]
Joh 2005	10/34	7/34		2.02%	1.43[0.62,3.31]
Subtotal (95% CI)	**1674**	**1254**		**90.53%**	**0.66[0.57,0.76]**
Total events: 416 (MMF), 449 (AZA)					
Heterogeneity: Tau^2=0.02; Chi^2=18.61, df=14(P=0.18); I^2=24.79%					
Test for overall effect: Z=5.56(P<0.0001)					
Total (95% CI)	**1860**	**1441**		**100%**	**0.65[0.57,0.73]**
Total events: 445 (MMF), 509 (AZA)					
Heterogeneity: Tau^2=0.01; Chi^2=23.2, df=21(P=0.33); I^2=9.48%					
Test for overall effect: Z=7.01(P<0.0001)					
Test for subgroup differences: Chi^2=2, df=1 (P=0.37), I^2=0.16%					



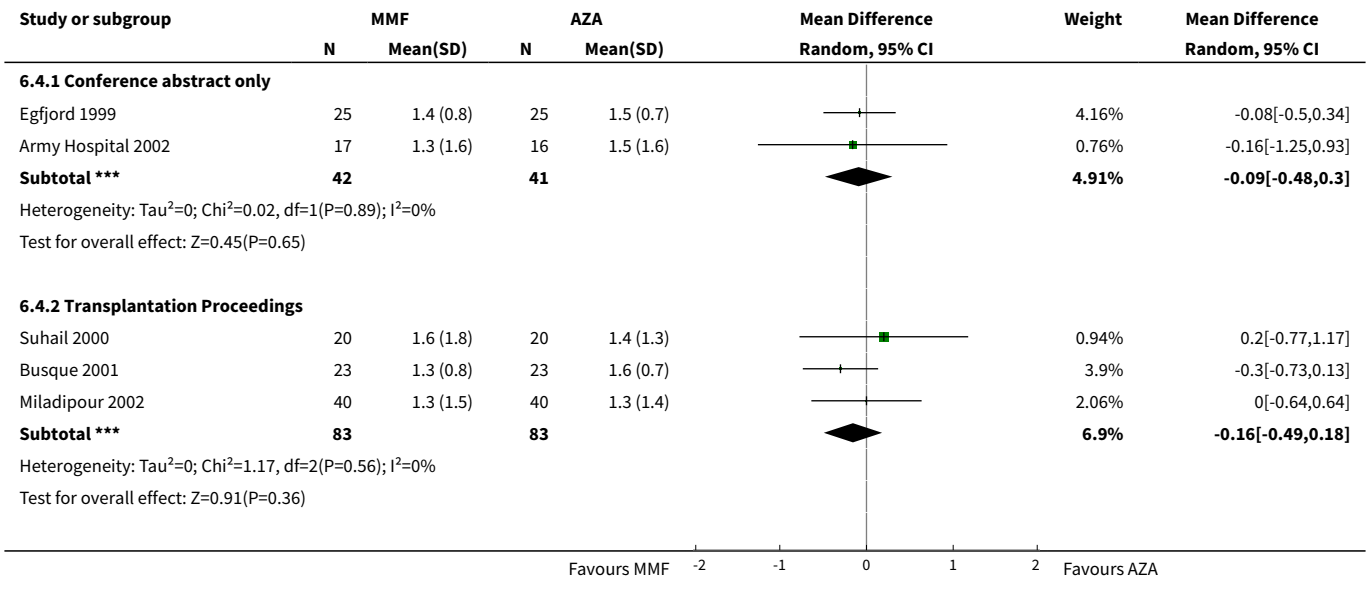
Analysis 6.3. Comparison 6 Subgroup analyses: publication type, Outcome 3 Infection: CMV viraemia/syndrome.

Study or subgroup	MMF n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Conference abstract only					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (MMF), 0 (AZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.3.2 Transplantation Proceedings					
Miladipour 2002	3/40	0/40		0.57%	7[0.37,131.28]

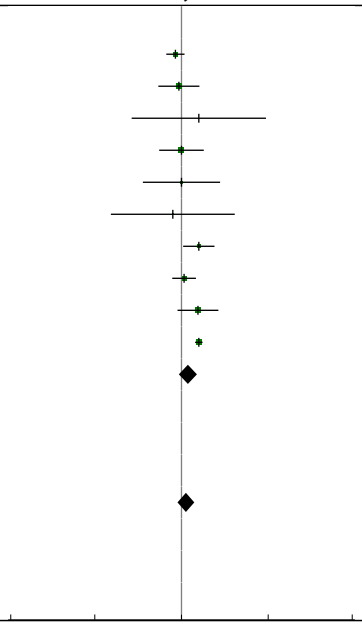




Analysis 6.4. Comparison 6 Subgroup analyses: publication type, Outcome 4 Graft function: serum creatinine.



Study or subgroup	MMF N	MMF Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.4.3 Full peer reviewed journal article							
MMF US Study 1995	200	1.7 (0.5)	86	1.8 (0.4)		14.73%	-0.07[-0.18,0.04]
MMF TRI Study 1996	168	1.7 (0.9)	83	1.7 (0.9)		8.64%	-0.03[-0.27,0.21]
Ling 1998	11	1.6 (0.8)	5	1.4 (0.7)		1.44%	0.2[-0.57,0.97]
Johnson 2000	47	1.4 (0.7)	53	1.4 (0.6)		7.91%	0[-0.26,0.26]
Weimer 2002	31	2.2 (0.6)	25	2.2 (1)		3.75%	0[-0.45,0.45]
Sun 2002b	40	1.4 (1.9)	46	1.5 (1.4)		1.67%	-0.1[-0.81,0.61]
Sadek 2002	162	1.7 (1.1)	157	1.5 (0.4)		11.01%	0.2[0.02,0.38]
COSTAMP Study 2002	232	1.6 (0.8)	233	1.6 (0.7)		13.15%	0.03[-0.11,0.17]
Merville 2004	37	1.6 (0.6)	34	1.4 (0.4)		8.69%	0.19[-0.05,0.43]
MYSS Study 2004	167	1.5 (0.2)	167	1.3 (0.2)		17.2%	0.2[0.16,0.24]
Subtotal * **	**1095**		**889**			**88.19%**	**0.07[-0.03,0.18]**
Heterogeneity: Tau^2=0.01; Chi^2=29.82, df=9(P=0); I^2=69.82%							
Test for overall effect: Z=1.38(P=0.17)							
Total * **	**1220**		**1013**			**100%**	**0.05[-0.05,0.15]**
Heterogeneity: Tau^2=0.01; Chi^2=35.41, df=14(P=0); I^2=60.46%							
Test for overall effect: Z=1.03(P=0.3)							
Test for subgroup differences: Chi^2=2.13, df=1 (P=0.35), I^2=5.93%							



ADDITIONAL TABLES

Table 1. Meta-regression analyses

	Death (all cause)	Graft loss (censored for death)	Malignancy (any)	Acute rejection (any)	CMV viraemia/syndrome	CMV tissue invasive	Serum creatinine [mg/dl]	Diarrhoea	Leukopenia
Number of studies	16	17	5	22	13	7	15	11	12
Study level factors									
Year of transplantation [a] per year	1.01 (0.86 to 1.18)	0.99 (0.91 to 1.08)	1.06 (0.92 to 1.22)	*1.03 (0.99 to 1.06)*	0.95 (0.83 to 1.10)	1.08 (0.14 to 8.30)	0.04 (-0.03 to 0.10)	1.16 (0.91 to 1.49)	0.84 (0.64 to 1.11)
Donor type [b] Both versus deceased only	1.02 (0.42 to 2.47)	1.04 (0.57 to 1.90)	2.04 (0.43 to 9.71)	1.01 (0.77 to 1.33)	*1.33 (0.87 to 2.02)*	-- (all studies deceased donor only)	*-0.08 (-0.20 to 0.03)*	1.35 (0.73 to 2.50)	***0.59 (0.34 to 1.02)***
Living only versus deceased only	(no living donor only studies)	(no living donor only studies)	(no living donor only studies)	0.46 (0.05 to 4.07)	(no living donor only studies)		-0.37 (-1.46 to 0.73)	(no living donor only studies)	*0.72 (0.01 to 35.2)*
Previous transplantation Yes versus 1st transplantation only	0.97 (0.51 to 1.85)	0.80 (0.48 to 1.34)	0.76 (0.41 to 1.41)	0.95 (0.74 to 1.22)	0.81 (0.53 to 1.24)	0.73 (0.27 to 1.97)	***-0.13 (-0.25 to -0.02)***	1.10 (0.77 to 1.57)	***0.71 (0.51 to 0.99)***
MMF dose [c] per g/d	1.20 (0.62 to 2.33)	0.26 (0.06 to 1.24)	0.92 (0.47 to 1.79)	0.90 (0.74 to 1.08)	1.31 (0.84 to 2.03)	1.40 (0.63 to 3.10)	0.08 (-0.04 to 0.19)	1.23 (0.88 to 1.72)	***1.60 (1.13 to 2.27)***
AZA dose [d] per mg/d	0.99 (0.96 to 1.03)	1.01 (0.98 to 1.03)	0.98 (0.93 to 1.03)	***1.01 (1.00 to 1.01)***	1.00 (0.99 to 1.01)	1.01 (0.97 to 1.05)	***0.004 (-0.001 to 0.009)***	1.00 (0.98 to 1.02)	1.00 (0.99 to 1.02)
Induction [e] Some versus no	1.06 (0.35 to 3.20)	0.87 (0.42 to 1.79)	(no studies with induction in some)	0.80 (0.41 to 1.58)	1.05 (0.60 to 1.85)	2.48 (0.10 to 64.07)	***-0.22 (-0.42 to -0.01)***	(no studies with induction in some)	(no studies with induction in some)
All versus no	1.16	0.91	1.10	*0.82*	*0.76*	1.21	-0.05	***0.68***	***1.46***

Table 1. Meta-regression analyses *(Continued)*

	(0.59 to 2.28)	(0.54 to 1.54)	(0.58 to 2.08)	*(0.64 to 1.04)*	*(0.50 to 1.15)*	(0.45 to 3.22)	(-0.23 to 0.12)	***(0.49 to 0.96)***	***(1.03 to 2.08)***
CNI	1.07	1.03	0.89	1.08	1.16	1.42	***-0.19***	***0.54***	0.85
Tac versus CsA	(0.40 to 2.82)	(0.46 to 2.32)	(0.08 to 10.63)	(0.81 to 1.44)	(0.60 to 2.24)	(0.12 to 16.53)	***(-0.31 to -0.06)***	***(0.30 to 0.99)***	(0.44 to 1.65)
CsA formulation	1.03	1.12	1.54	***1.27***	1.24	0.89	0.18	0.64	*1.69*
CsA-ME versus original or unclear	(0.26 to 4.10)	(0.62 to 2.04)	(0.60 to 3.97)	***(0.98 to 1.65)***	(0.73 to 2.11)	(0.03 to 29.84)	(-0.16 to 0.53)	(0.21 to 1.95)	*(0.79 to 3.63)*
Study quality/risk of bias factors									
Blinding	0.89	1.12	0.72	*0.87*	0.88	*0.42*	-0.23	7.16	0.38
Yes versus no or unclear	(0.39 to 2.06)	(0.69 to 1.83)	(0.30 to 1.68)	*(0.70 to 1.07)*	(0.11 to 7.13)	*(0.12 to 1.50)*	(-0.98 to 0.53)	(0.32 to 159.8)	(0.02 to 6.15)
Industry funding	0.96	1.60	0.43	*0.84*	***1.53***	1.58	***-0.14***	***0.39***	0.78
Yes versus no/unclear	(0.42 to 2.19)	(0.88 to 2.90)	(0.05 to 3.66)	*(0.66 to 1.07)*	***(0.96 to 2.41)***	(0.10 to 23.76)	***(-0.25 to -0.02)***	***(0.14 to 1.07)***	(0.40 to 1.49)
Publication	1.09	1.82	(all published as	1.25	*0.14*	0.68	***0.31***	0.49	0.75
Full manuscript versus abstract or *Transplantation Proceedings*	(0.38 to 3.12)	(0.84 to 3.95)	full manuscript)	(0.80 to 1.93)	*(0.01 to 2.61)*	(0.06 to 7.44)	***(0.06 to 0.57)***	(0.12 to 2.00)	(0.30 to 1.89)

Meta-regression was performed on the displayed outcomes, while data classified as "longest duration of follow-up" were used (see *Methods*). Displayed are Relative Risk Ratios (RRR), i.e. back-transformed values of the coefficient of the meta-regression, or the untransformed coefficient of the meta-regression for the mean difference (MD) for continuous outcome serum creatinine, along with 95% CI. All regression analyses were adjusted for duration of follow-up. Statistical significance values of $P < 0.20$ are highlighted as *Italic*, values of ***P < 0.10*** are ***bolded-Italic*** , respectively.

Abbreviations: MMF: mycophenolate mofetil, AZA: azathioprine; CNI: calcineurin-inhibitor; Tac: tacrolimus; CsA: cyclosporin A; CsA-ME: cyclosporin A microemulsion; CMV: cytomegalovirus

Interpretation

Summary effect for the outcome RR < 1 (e.g. acute rejection): RRR < 1 indicate a pronounced risk reduction for higher covariate values, while RRR > 1 indicate attenuated risk reduction.

Summary effect for the outcome RR > 1 (e.g. tissue invasive CMV disease): RRR < 1 indicate attenuated risk for higher covariate values, while RRR > 1 indicate increased risk.

Summary effect mean difference SCr: positive coefficients indicate greater difference in SCr, i.e. lower SCr values in AZA treated patients for higher covariate values, while negative coefficients indicate reduced difference or even negative difference in SCr, i.e. lower SCr values in MMF treated patients. Examples of various associations displayed in bubble-plots can be found in Figure 4; Figure 6; Figure 7.

[a] If missing, year of first publication minus duration of follow-up minus two years

[b] Both: living or deceased donor

[c] Studies in which more than one MMF dose was tested were split into two studies and each compared to half of the group of AZA-patients/ outcomes

[d] If reported to be body-weight-adjusted (mg/kg/d), transformation into mg/d using the mean body weight as reported in the study, and by using 70 kg (60 kg in exclusively Asian populations) if information on body weight was missing

[e] Some: antibody induction therapy used in selected patients, e.g. sensitised patients or those experiencing delayed graft function

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Kidney Transplantation, this term only 2. ((kidney or renal) NEXT transplant*):ti,ab,kw in Clinical Trials 3. (#1 OR #2) 4. MeSH descriptor Mycophenolic Acid, this term only 5. Mycophenolic Acid:ti,ab,kw in Clinical Trials 6. mmf:ti,ab,kw in Clinical Trials 7. mycophenolate mofetil:ti,ab,kw in Clinical Trials 8. Morpholinoethyl Ester:ti,ab,kw in Clinical Trials 9. cellcept:ti,ab,kw in Clinical Trials 10.myfortic:ti,ab,kw in Clinical Trials 11.MeSH descriptor Azathioprine, this term only 12.azathioprine:ti,ab,kw in Clinical Trials 13.aza:ti,ab,kw in Clinical Trials 14.azahexal:ti,ab,kw in Clinical Trials 15.azamun:ti,ab,kw in Clinical Trials 16.azapin:ti,ab,kw in Clinical Trials 17.imuran:ti,ab,kw in Clinical Trials 18.immuran:ti,ab,kw in Clinical Trials 19.imurel:ti,ab,kw in Clinical Trials 20.azasan:ti,ab,kw in Clinical Trials 21.(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20) 22.(#3 AND #21)
MEDLINE	1. Kidney Transplantation/ 2. Mycophenolic Acid/ 3. mmf.tw. 4. Mycophenolate mofetil.tw. 5. Morpholinoethyl Ester.tw. 6. cellcept.tw. 7. myfortic.tw. 8. Azathioprine/ 9. aza.tw. 10.azahexal.tw. 11.azamun.tw. 12.azapin.tw. 13.imuran.tw. 14.immuran.tw. 15.imurek.tw. 16.imurel.tw. 17.or/2-16
EMBASE	1. exp Kidney Transplantation/ 2. Mycophenolic Acid 2 Morpholinoethyl Ester/ 3. Mycophenolic Acid/

(Continued)

4. mycophenolate mofetil.tw.
5. mmf.tw.
6. Cellcept.tw.
7. myfortic.tw.
8. Azathioprine/
9. aza.tw.
10. azahexal/
11. azahexal.tw.
12. azamun.tw.
13. azapin.tw.
14. imuran.tw.
15. immuran.tw.
16. imurel.tw.
17. azasan.tw.
18. or/2-17
19. and/1,18

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 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.

(Continued)

	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 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.
	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.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: MW, EB, KU, AW
2. Study selection: MW, EB, AE
3. Data extraction from studies and entering into RevMan: MW, AE, IP
4. Study translation: JC and EB (Spanish); MC, CH and KH (Chinese)
5. Statistical analyses: MW, CS
6. Interpretation of results: MW, EB, KU, AW
7. Draft the final review: MW, AE, EB, KU, AW
8. Disagreement resolution: KU, EB, AW
9. Update the review: MW, AW

DECLARATIONS OF INTEREST

- In the past 5 years, MW received travel grants from Genzyme
- In the past 5 years, CS received grants from Blue Cross Blue Shield, TEVA Pharma and Glaxo Smith Kline
- AE, AW, EB and KU do not have any known conflicts of interest

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- No sources of support supplied

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- Agency for Healthcare Research and Quality, USA.

  (Grant # R01-HS018574)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the preparation of the review a few aspects were implemented in the current version of the review that was not pre-specified in the protocol.

Within the presentation of results according to primary and secondary outcomes, we highlighted the clinical importance of outcomes as suggested by the GRADE working group (Atkins 2004). We adopted the classification from the KDIGO workgroup of experts in the fields of kidney transplantation and methodology (KDIGO 2009).

We tested all covariates pre-specified in the protocol regarding confounding of the meta-analysis results and to investigate heterogeneity using meta-regression and subgroup-analyses. Herein, the effects of blinded administration of the study drug and studies excluding previous kidney transplantation were tested in meta-regression, rather than in subgroup-analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Kidney Transplantation [mortality]; Azathioprine [*therapeutic use]; Cyclosporine [therapeutic use]; Graft Rejection [mortality] [*prevention & control]; Immunosuppression Therapy [*methods]; Immunosuppressive Agents [*therapeutic use]; Mycophenolic Acid [*analogs & derivatives] [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans