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Webster AC, Taylor RRS, Chapman JR, Craig JC

Webster AC, Taylor RRS, Chapman JR, Craig JC.
Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients.
Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003961.
DOI: 10.1002/14651858.CD003961.pub2.

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[Intervention Review]

Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients

Angela C Webster[1], Rod RS Taylor[2], Jeremy R Chapman[3], Jonathan C Craig[4]

[1]School of Public Health, University of Sydney, Sydney, Australia. [2]PenTAG, Peninsula Medical School, Exeter, UK. [3]Renal Medicine, Westmead Hospital, Westmead, Australia. [4]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

Contact address: Angela C Webster, School of Public Health, University of Sydney, Edward Ford Building A27, Sydney, NSW, 2006, Australia. awebster@health.usyd.edu.au, angela.webster@gmail.com.

Editorial group: Cochrane Kidney and Transplant Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Webster AC, Taylor RRS, Chapman JR, Craig JC. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003961. DOI: 10.1002/14651858.CD003961.pub2.

ABSTRACT

Background

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Standard protocols in use typically involve three drug groups each directed to a site in the T-cell activation or proliferation cascade which are central to the rejection process: calcineurin inhibitors (e.g. cyclosporin, tacrolimus), anti-proliferative agents (e.g. azathioprine, mycophenolate mofetil) and steroids (prednisolone). It remains unclear whether new regimens are more specific or simply more potent immunosuppressants.

Objectives

To compare the effects of tacrolimus with cyclosporin as primary therapy for kidney transplant recipients.

Search methods

MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Renal Group's specialist register and conference proceedings were searched to identify relevant reports of randomised controlled trials (RCTs). Two reviewers assessed studies for eligibility, quality and extracted data independently.

Selection criteria

All RCTs where tacrolimus was compared with cyclosporin for the initial treatment of kidney transplant recipients

Data collection and analysis

Data were synthesised (random effects model) and results expressed as risk ratio (RR), values <1 favouring tacrolimus, with 95% confidence intervals (CI). Subgroup analysis and meta-regression were used to examine potential effect modification by differences in study design and immunosuppressive co-interventions.

Main results

123 reports from 30 studies (4102 patients) were included. At six months graft loss was significantly reduced in tacrolimus-treated recipients (RR 0.56, 95% CI 0.36 to 0.86), and this effect was persistent up to three years. Meta-regression showed that this benefit diminished as higher trough levels of tacrolimus were targeted (P = 0.04), after allowing for differences in cyclosporin formulation (P = 0.97) and cyclosporin target trough level (P = 0.38). At one year, tacrolimus patients suffered less acute rejection (RR 0.69, 95% CI 0.60 to 0.79), and less steroid-resistant rejection (RR 0.49, 95% CI 0.37 to 0.64), but more insulin-requiring diabetes mellitus (RR 1.86, 1.11 to 3.09), tremor, headache,

diarrhoea, dyspepsia and vomiting. Cyclosporin-treated recipients experienced significantly more constipation and cosmetic side-effects. We demonstrated no differences in infection or malignancy.

Authors' conclusions

Tacrolimus is superior to cyclosporin in improving graft survival and preventing acute rejection after kidney transplantation, but increases post-transplant diabetes, neurological and gastrointestinal side effects. Treating 100 recipients with tacrolimus instead of cyclosporin would avoid 12 suffering acute rejection, two losing their graft but cause an extra five to become insulin-requiring diabetics.

PLAIN LANGUAGE SUMMARY

Tacrolimus is superior to cyclosporin in improving graft survival and preventing acute rejection after kidney transplantation, but increases post-transplant diabetes and other side effects

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Strategies to increase donor organ availability and to prolong the transplanted kidney's survival have become priorities in kidney transplantation. Standard immunosuppressive therapy consists of initial treatment and maintenance regimes to prevent rejection and short courses of more intensive immunosuppressive therapy to treat episodes of acute rejection. This review compared tacrolimus and cyclosporin used as primary immunosuppression for kidney transplant recipients. Thirty studies (4102 patients) were included. Tacrolimus was shown to be superior to cyclosporin in improving graft survival and preventing acute rejection after kidney transplantation, but increases post-transplant diabetes, neurological and gastrointestinal side effects. There was insufficient information to assess the cost of tacrolimus versus cyclosporin, and there was a general failure to consider global quality of life (QOL) for transplant recipients which may inform our understanding of patient preference and compliance.

BACKGROUND

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). In the developed world there are approximately 280 patients/million population (pmp) with a functioning kidney transplant, a figure which has increased throughout the 1990s. The transplant rate is around 30 pmp and between 30% to 40% of transplanted organs come from living donors. Graft survival beyond five years has remained unchanged since the 1970s, with an average annual decline of 5% (Mathew 2001). Waiting lists for transplantation continue to grow because demand exceeds organ availability. Strategies to increase donor organ availability and to prolong kidney allograft survival have become priorities in kidney transplantation (ANZDATA 2001; UNOS 2000).

Transplant outcome is influenced by many factors. In the absence of effective immunosuppression, transplanted organs undergo progressive immune mediated injury (rejection). Standard immunosuppressive therapy consists of initial induction and maintenance regimes to prevent rejection and short courses of more intensive immunosuppressive therapy to treat episodes of acute rejection. Standard protocols in use typically involve three drug groups each directed to a site in the T-cell activation or proliferation cascade which are central to the rejection process: calcineurin inhibitors (e.g. cyclosporin, tacrolimus), anti-proliferative agents (e.g. azathioprine, mycophenolate mofetil) and steroids (prednisolone) (Hong 2000).

Short-term graft survival is related to control of the acute rejection process. The risk of graft rejection is greatest in the immediate post-transplant period, and immunosuppression is therefore initiated at high levels. This is achieved either by using higher doses of the agents used in maintenance therapy, or by adding either a polyclonal anti-lymphocyte antibody (e.g. anti-thymocyte globulin), or a monoclonal antibody (e.g. anti-CD3-muromonab), or by adding an interleukin 2 receptor antagonist (basiliximab, daclizumab).

The major cause of long-term graft loss is chronic allograft nephropathy, an ill-defined process characterised clinically by progressive deterioration in graft function, proteinuria and hypertension and pathologically by changes on biopsy. Chronic allograft nephropathy is a consequence of immunological and non-immunological injury. Immunological factors include HLA matching, episodes of acute rejection and suboptimal immunosuppression. Important non-immunological factors implicated are donor organ characteristics, delayed graft function, recipient related factors, hypertension and hyperlipidaemia. Recently the acute and chronic toxicity of calcineurin inhibitors has also been implicated (Pascual 2002).

Maintenance therapy aims to minimise the side effects of any single drug whilst maintaining adequate overall immunosuppression. The overall level of maintenance immunosuppression is mainly determined by the perceived risk of rejection. High-risk groups include young adults and children and 'sensitised' patients. Sensitised patients are those with high titres of pre-formed circulating anti-HLA antibodies, which may come about as a result of underlying illness, previous transplantation, previous pregnancy or multiple blood transfusions.

Both tacrolimus and cyclosporin inhibit the action of calcineurin, a pivotal enzyme, thus preventing the dephosphorylation reactions essential for lymphokine gene transcription. Tacrolimus is a macrolide derived from the fungus *Streptomyces tsukubaensis,* and was developed as an alternative to cyclosporin. Like cyclosporin, tacrolimus inhibits the first phase of T-cell activation. Tacrolimus binds to a cytoplasmic immunophilin to form a complex, which then binds to and inhibits the phosphatase activity of calcineurin, so preventing the critical dephosphorylation reactions necessary for early lymphokine (e.g. interleukin-2) gene transcription. Cyclosporin is structurally distinct and binds a different cytoplasmic receptor (cyclophilin A), but ultimately also inhibits the action of calcineurin in the same way (Denton 1999; Suthanthiran 1994).

Tacrolimus was first used in transplantation in 1989. It has been increasingly used world-wide since the mid-1990s, though its exact role in kidney transplantation remains incompletely defined. Tacrolimus is used for graft rejection prophylaxis, and for 'rescue' therapy (treatment of refractory or chronic graft rejection or for those not tolerating cyclosporin). Most immunosuppressants have been tested in combination with either tacrolimus or cyclosporin. Recently immunosuppressive regimens using tacrolimus have been favoured. It is widely perceived that tacrolimus offers an advantage with respect to the acute rejection rate (Denton 1999; Vanrenterghem 1999) Currently, there are pronounced global differences in the use of tacrolimus, with 59% of new renal transplant recipients in the USA but only 22% in Australia receiving tacrolimus as primary immunosuppression. At one year post-transplantation, 59% patients in the USA and 29% in Australia are on tacrolimus (ANZDATA 2001; UNOS 2000).

Known adverse reactions are similar for both calcineurin inhibitors (although the exact balance differs between the two). Tacrolimus has been associated with more diabetes and neurotoxic reactions, but with less hypertension, dyslipidaemia, hirsutism and gingival hyperplasia than cyclosporin. There is uncertainty about the equivalence of their nephrotoxic effects and how these adverse effects of therapy are related to patient and graft survival (Denton 1999). These distinct adverse side-effect profiles may impact on individual patient compliance and quality of life differently (Henry 1999; Kasiske 2000a).

There has been considerable variability in the use of immunosuppressive agents by clinicians, in combination and dosage regimen, both geographically and within patient groups. Currently in some countries, opinion favours minimising early graft injury by using induction therapy to prevent acute rejection, particularly in high-risk patients. However there is no direct proof that a decrease in early rejection rates translates into a uniform increase in long term graft survival for all. It remains unclear whether new regimens are more specific or simply more potent immunosuppressants. There is concern that newer drugs or combinations, whilst apparently improving early graft outcome, may in fact increase the risk of malignant or cardiovascular disease in the longer term, thereby curtailing patient survival (death with functioning allograft). In the absence of clear evidence, optimal maintenance therapy continues to be debated (Vanrenterghem 2001).

OBJECTIVES

The objective of this study was to systematically identify and summarise the evidence of transplant outcomes, toxicity and adverse effects when tacrolimus was compared directly with cyclosporin, in the treatment of kidney transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), where tacrolimus was compared with cyclosporin for the initial treatment of kidney transplant recipients were included, without language restriction. These broad criteria were deliberately chosen in order to allow investigation and specific analyses of potential differences in effect that might occur with variation in formulation or dosage of the 2 calcineurin inhibitors, or combinations of additional immunosuppressive agents used.

Types of participants

Inclusion criteria

Participants in eligible studies were children and adults, followed for any duration, and were recipients of a first or subsequent cadaveric or living donor renal transplant.

Exclusion criteria

Studies where participants received another solid organ in addition to a kidney transplant (e.g. kidney with pancreas) were excluded.

Types of interventions

We included studies comparing tacrolimus to cyclosporin solution (Sandimmune) or to cyclosporin microemulsion (neoral), used together with any combination of additional immunosuppressive therapies in the intervention and control arms.

Types of outcome measures

Outcome events were assessed up to five years post-transplantation. Where median or mean follow-up duration was quoted, and clarification from the authors was not forthcoming, data contributed to the analysis at the nearest time-point below the point estimate given.

- Graft loss censored for death
- Incidence of acute rejection diagnosed clinically or by biopsy
- Incidence of acute rejection diagnosed by biopsy
- Incidence of acute rejection not responsive to steroid therapy
- Graft loss including death with a functioning allograft.
- Patient all cause mortality
- Incidence of chronic allograft nephropathy (CAN) (biopsy proven or as specified by the authors)
- Graft function (measured as glomerular filtration rate (GFR), serum creatinine (SCr), or creatinine clearance)
- Incidence of all infectious complications
- Incidence of cytomegalovirus (CMV) infections (all definitions, then specifically invasive CMV disease)
- Incidence of new-onset diabetes mellitus in previously non-diabetic patients
- Incidence of treatment related adverse reactions (hyperkalaemia, neurotoxicity, hypertension, dyslipidaemia and gastrointestinal and haematological adverse reactions, cosmetic side effects)
- Incidence of malignancy (total malignancy, non melanocytic skin cancer and all other malignancy)
- Incidence of post-transplant lymphoproliferative disorder

Search methods for identification of studies

Relevant studies were obtained from the following sources(Additional Table 1 - *Electronic search strategies)*:-

1. Cochrane Renal Group's specialised register of RCTs
2. Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library* - issue 3 2003)
3. MEDLINE and Pre-MEDLINE (1966 - October 2003)
4. EMBASE (1980-October 2003)

These were combined with the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE (Dickersin 1994), and a similar strategy for EMBASE (Lefebvre 1996).

Unpublished studies were identified by hand-searching reference lists and abstracts of conference proceedings and nephrology scientific meetings (including, but not limited to, the American Society of Nephrology, the International Transplant Society, the American Society of Transplant Physicians, the American Society of Transplant Surgeons, the International society of Paediatric Nephrology, European Dialysis and Transplantation Society) from 1998-2003, reference lists of relevant studies, and by directly contacting study groups and pharmaceutical companies

Where duplicate reporting of the same study or patient group was suspected, authors were contacted for clarification. If duplication was confirmed the first complete publication was selected (the 'index' publication) and was the primary data source, and the study was 'named' using the primary author and year of the index publication. However, any other reports that included additional outcome data (such as longer-term follow-up) also contributed to the meta-analysis.

Data collection and analysis

The review was undertaken by five reviewers (AW, RW, RT, JRC, JCC).The literature search strategy described above was developed and performed to identify eligible studies (AW). The search results were combined and all titles, abstracts, or where necessary the full text, were independently screened by two reviewers (AW and RW or RT). Data extraction was performed independently by two reviewers (AW and RW or RT), using a standardised form. Any discrepancies were resolved by discussion (all). Data was entered into Cochrane meta-analytical software (RevMan 4.2) twice (AW).

Quality assessment

Quality of studies was assessed independently by two reviewers (AW and RW or RT) without blinding to journal or authorship using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by discussion (all). The quality items assessed were allocation concealment, intention to treat analysis, completeness of follow up and blinding of investigators, subjects

and outcomes assessment . Each item was assessed separately rather than combined in a scoring system.

Quality checklist

Allocation concealment

- Adequate - Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear - Randomisation stated but no information on method used is available
- Inadequate - Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/No/not stated
- Blinding of participants: Yes/No/not stated
- Blinding of outcome assessor: Yes/No/not stated
- Blinding of data analysis: Yes/No/not stated

In studies where no placebo is used, or where the intervention and comparison arms use drugs with different dosing schedules then unless otherwise clarified both the investigators and the participants were considered non-blinded.

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis (ITT) was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that ITT was undertaken
- Unclear. Reported but unable to confirm on study assessment, or not reported and unable to confirm by study assessment.
- No: Lack of intention-to-treat analysis confirmed on study assessment (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether ITT reported or not

Patients who were randomised but not transplanted were regarded as legitimate exclusions from the ITT population.

Completeness of follow-up

- Percentage of participants for whom data was complete at defined study end-point.
- Where interim analyses are reported 'not stated' was recorded.

Quantitative data synthesis and data analysis

Data was extracted first from individual studies and then pooled for summary estimates using a random effects model. Dichotomous outcome results were expressed as risk ratiostudy (RR), where values of <1 favoured tacrolimus treatment. Continuous outcomes were expressed as mean difference (MD), both with 95% confidence intervals (CI).

Heterogeneity amongst study results was analysed using a Cochran Q test (n -1 degrees of freedom), with P < 0·05 used to denote statistical significance, and with I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance (Higgins 2003). Subgroup analyses based on publication type, study methodological quality and baseline immunological risk of study population were undertaken, aiming to establish whether the estimated treatment effects were robust to reasonable assumptions of the influence of these potential biases. Analysis was undertaken using both random and fixed effects models, and no important differences were observed. Results reported here used the random effects model, as this is more conservative in the presence of heterogeneity (Deeks 2001). Publication bias was assessed for the primary outcomes, using funnel plots of the log odds ratio (OR) (Egger 1997).

Stratified meta-analysis and meta-regression were used to explore important clinical differences among the studies that might potentially be expected to alter the magnitude of treatment effect, using restricted maximum-likelihood to estimate the between study variance. Subgroups were defined *a priori* and included the cyclosporin formulation (solution or microemulsion), exposure levels to both tacrolimus and cyclosporin, the specific combination of additional baseline immunosuppressive agents and the dose of steroids used. Exposure to cyclosporin and tacrolimus was calculated using the midpoint of the declared intention-to-treat target range at the 12-hour post-dose nadir (trough), for all time points available, averaged over the first year post-transplantation.

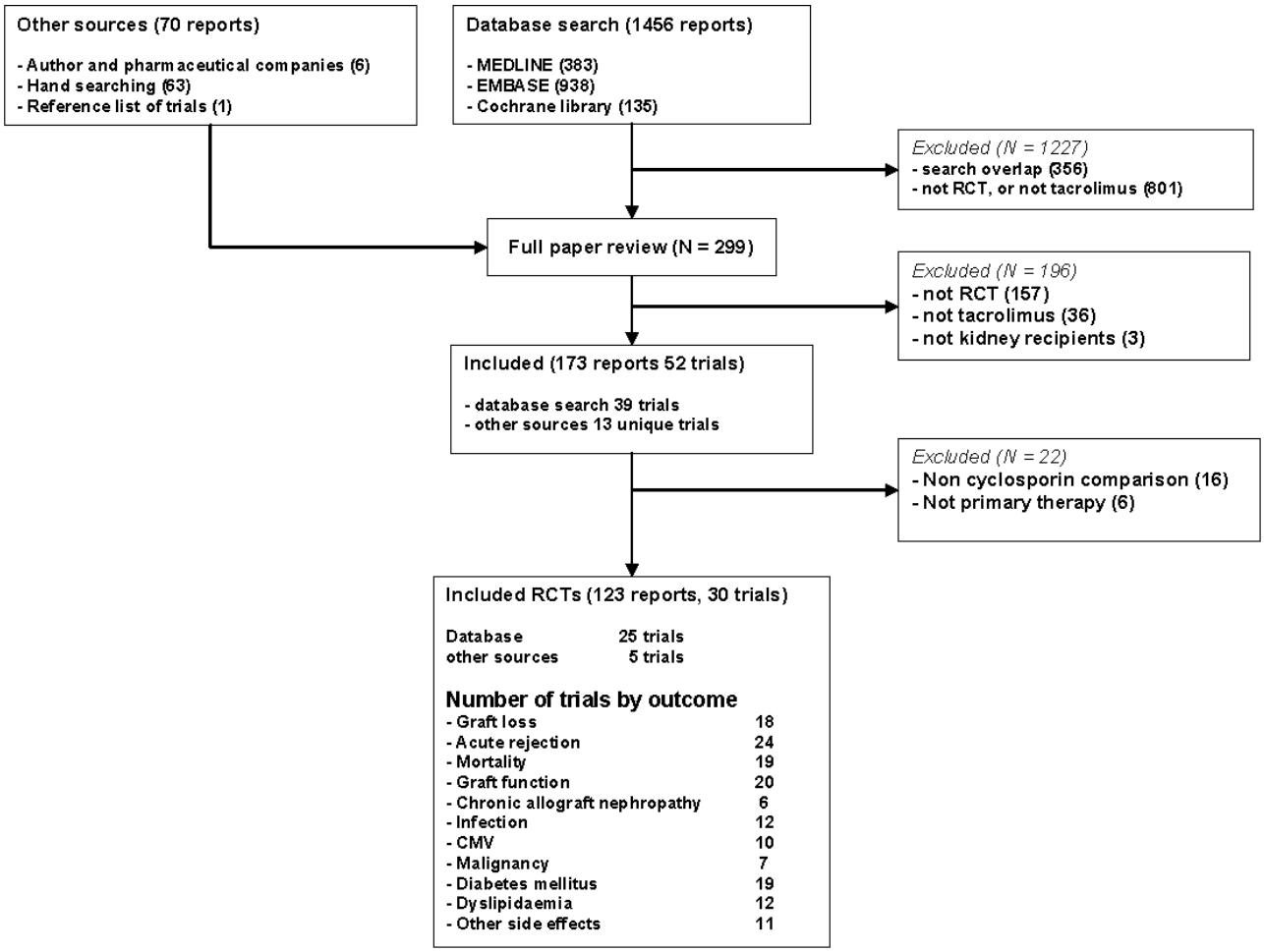
Meta-regression was performed for the primary outcomes of acute rejection and graft loss (death censored), and for the most commonly reported complication, diabetes mellitus requiring insulin treatment for >30 days in previously non-diabetic patients, using data up to the first year post-transplantation, with a priori subgroups as explanatory variables. Meta-regression was undertaken on the log RR scale using STATA software (Stata8, StataCorp LP, Texas, USA), each study weighting equal to the inverse of the variance of the estimate for that study, with between study variance estimated using the restricted maximum-likelihood method. Results were expressed as the ratio of the RR within each subgroup explanatory variable.

RESULTS

Description of studies

A total of 123 reports (publications and abstracts) of 30 studies were included in the review (Figure 1 - *Flow chart showing source and identification of* studies *for inclusion*). Combined, the 30 studies included a total of 4102 randomised participants. Five of these studies were available in abstract form only (239 participants), whilst the remaining 25 (3863 participants) were reported in 18 different journals. All index reports and the majority of additional reports of studies were in English; there were two additional reports in French and one in German.

Figure 1. Fig 1. Flow chart showing source and identification of studies for inclusion



Included studies

Six studies (1127 participants) compared tacrolimus with the original, oil based solution formulation of cyclosporin (Sandimmun®) (Ichimaru 2001; Laskow 1995; Mayer 1997; Pirsch 1997; Radermacher 1998; Shapiro 1991),19 studies (2744 participants) compared tacrolimus with the microemulsion formulation (Neoral®) and we were unable to clarify which formulation was used for the remaining five studies (231 participants) (Baskin 2002; Heering 1998; Liu 2003; van Duijnhoven 2002; Weimer 2002). Twenty studies (30.5% total participants) were single centre studies, the remaining 10 were multicentre studies.

Information on the study population demographics was limited for most studies. The majority of studies were restricted to unsensitized participants with low baseline risk for transplantation. Only two studies included participants with panel reactive antibodies (PRA) > 50% (Johnson 2000; Mayer 1997), and nine studies included a proportion (range 10-25%) of participants who had previously had a failed renal transplant (Campos 2002; Margreiter 2002; Mayer 1997; Morris-Stiff 1998; Pirsch 1997; Radermacher 1998; Trompeter 2002; van Duijnhoven 2002; White 2000). A further study was conducted exclusively in children (Trompeter 2002) and another in African-Americans (Raofi 1999), both populations widely perceived to be at greater risk of rejection and complications following renal transplantation (Cecka 1997; Ojo 1995).

Additional baseline immunosuppression varied both within studies (where three arms were investigated) and amongst studies. Three studies varied an antiproliferative agent across three study arms, investigating combinations of tacrolimus (Busque 2001; Johnson 2000), and cyclosporin (Weimer 2002) with mycophenolate (MMF) or azathioprine. Azathioprine was used in both tacrolimus and cyclosporin arms in 16 studies and MMF in eight studies. One study used sirolimus (Miller 2002), one used mirzoribine (Ichimaru 2001), one used no antiproliferative (White 2000) and one study did not state which antiproliferative was used (Shapiro 1991). Twelve studies used antibody induction agents. Seventeen studies reported their corticosteroid reducing regimen in detail, whereas the remaining 14 studies gave noted only that "local protocol" was followed, or that "a standard reducing schedule" was used (Agha 2001; Baskin 2002; Campos 2002; Egfjord 2002; El Haggan 2002; Heering 1998; Ichimaru 2001; Laskow 1995; Liu 2003; Shapiro 1991; Toz 2001; Tsinalis 2000; Weimer 2002).

The reporting of outcomes was variable (Figure 1) with transplant-focused outcomes reported far more frequently (e.g. acute rejection, 24 studies) than complications of immunosuppression or drug-specific adverse reactions (e.g. CMV infection, nine studies). For many adverse events there was wide variation in

the measures reported, and the time post-transplantation at which the data was collected. Although 12 studies (41%) reported dyslipidaemia, there was no consistent definition or measure used. Eleven studies reported hypercholesterolaemia, three reported the number of participants with elevated (level not consistently defined) cholesterol, and the remaining eight studies reported the summary average of the total cholesterol. Of these eight, two did not report the precision of these estimates (i.e. standard error or deviation) and so the information could not be combined, and the remaining six studies reported at five different time intervals post-transplantation, ranging from one month to three years, making meaningful meta-analysis difficult. Similar inconsistencies applied to reporting of measures of graft function and hypertension.

Risk of bias in included studies

Reporting of details of study methodology was incomplete for the majority of studies. Four studies reported adequate allocation concealment (Laskow 1995; Margreiter 2002; Trompeter 2002; White 2000) two used inadequate methods (Raofi 1999; van Duijnhoven 2002) and the remaining 24 studies were randomised but gave no indication of the allocation method used. There were no blinded studies, and ITT analysis was confirmed for 12 studies (Charpentier 2002; Heering 1998; Johnson 2000; Mayer 1997; Miller 2002; Morris-Stiff 1998; Pirsch 1997; Radermacher 1998; Raofi 1999; Wang 2000; Yang 1999; Yu 2000), not undertaken for eight (Campos 2002; El Haggan 2002; Laskow 1995; Margreiter 2002; Nichelle 2002; Shapiro 1991; Trompeter 2002; van Duijnhoven 2002), and unclear for the other 10 studies. Completeness of follow-up was neither reported nor could be deduced for 10 studies (Agha 2001; Busque 2001; Baskin 2002; Egfjord 2002; Liu 2003; Nichelle 2002; Raofi 1999; Shapiro 1991; van Duijnhoven 2002; Weimer 2002), and ranged between 77-100% for the remainder.

Effects of interventions

Transplant-focused outcomes

All primary outcomes favoured the use of tacrolimus over cyclosporin. Graft loss censored for death was reduced in tacrolimus treated recipients at all time points, and reached conventional thresholds of statistical significance at six months and three years post-transplantation, where graft loss was reduced by 44% and 29% respectively (Analysis 1.1.2: RR 0.56, 95% CI 0.36 to 0.86; Analysis 1.1.5: RR 0.71, 95% CI 0.52 to 0.96).

Whether diagnosed clinically or confirmed by biopsy, significantly fewer tacrolimus treated patients experienced acute rejection at any time point. The effect of tacrolimus in reducing the number of participants experiencing steroid-resistant rejection was even more marked, with a 55% reduction at six months (Analysis 1.4.2: RR 0.45, 95%CI 0.33 to 0.60). CAN was reported using biopsy criteria by only five studies (Margreiter 2002; Mayer 1997; Morris-Stiff 1998; Pirsch 1997; Raofi 1999) and changes of CAN appearing within the first year post-transplantation were significantly reduced (Analysis 1.7.3, three studies: RR 0.28, 95% CI 0.11 to 0.68) with no heterogeneity demonstrated (P = 0.75, I^2 = 0%).

The only consistently reported measure of graft function across studies was SCr. At six months, tacrolimus treated patients had a significantly lower SCr of 15.88 µmol/L less than cyclosporin treated patients (Analysis 1.22.3, seven studies: 95% CI -30.30 to -1.47), although there was significant heterogeneity of study results (P=0.04, I^2 = 54.8**%**). This heterogeneity was not explained by variations in study design, or methodology, but was partially explained by examining the clarity of reporting of the outcome. Three studies clearly reported the number of participants who contributed SCr measurements to the mean values (Analysis 7.2.2, Analysis 7.2.1), and showed a more profound difference in favour of tacrolimus (Analysis 7.2.2: MD SCr -41.63 µmol/L, 95% CI -71.89 to -11.36; heterogeneity P = 0.17, I^2 = 42%). In the remaining four studies the exact number of participants measured was not directly reported, but had to be calculated or inferred from other data; the summary result showed less difference (Analysis 7.2.1: SCr -5.47 µmol/L, 95% CI -13.71 to 2.76; heterogeneity P = 0.89, I^2 = 0%). At time points after six months post-transplantation, SCr remained favourable for tacrolimus treated patients, although the difference was less marked and not statistically significant, and showed increased heterogeneity (Analysis 1.22.4, one year, eight studies: SCr -13.07 µmol/L, 95% CI -37.27 to 11.12; heterogeneity P < 0.00001, I^2 = 91.3%).

Complications and side effects of immunosuppression

A limited number of studies sufficiently reported data on incidence of recipients with infection or malignancy, and no differences in treatment effects were demonstrated for these outcomes.

Studies reporting disturbance of glucose metabolism used variable definitions. The most consistent definition used was the development of new diabetes mellitus, defined as a requirement for insulin therapy for more than 30 days duration. The risk of new diabetes in previously non-diabetic recipients at six months, one and three years was significantly increased in tacrolimus treated recipients (Analysis 1.34.2: RR 2.56, 95% CI 1.37 to 4.78; Analysis 1.34.3: RR 1.86, 95% CI 1.11 to 3.09; Analysis 1.34.5: RR 3.86, 95%CI 2.01 to 7.41 respectively). The results at one year showed significant heterogeneity (P = 0.01, I^2 = 54.3%) which was largely due to Miller 2002 which reported very different rates of new diabetes; 9.0% in the tacrolimus arms compared to an average of 12.9% in the other studies, and 20% in the cyclosporin arm, compared to an average of 5.5% in the other studies. This was not explicable by differences in methodology or study population, but this was the only study to use sirolimus as a co-intervention. Sensitivity analysis (Analysis 7.4.2) showed a RR of 2.19 (95% CI 1.42 to 3.38), and much reduced heterogeneity (P = 0.18, I^2 = 27.5%) when this study was removed from the analysis. The proportion of new diabetics whose insulin requirement was sustained and on-going without recovery was similarly increased for tacrolimus patients at six months (Analysis 1.33.2: RR 2.61, 95% CI 1.16 to 5.85), one year (Analysis 1.22.3: RR 1.70, 95% CI 1.04 to 2.78) and three years (Analysis 1.33.5: RR 3.26, 95% CI 1.62 to 6.57).

Total cholesterol was significantly lower in tacrolimus treated patients at six months (Analysis 1.30.3, 3 studies: MD -0.58 mmol/L, 95% CI -0.77 to -0.39). Triglyceride levels were lower for tacrolimus treated patients, but the two studies (Margreiter 2002; Miller 2002) contributing data expressed their data differently (arithmetic versus geometric mean values) and so results could not be reliably combined.

Patients treated with tacrolimus were significantly more likely than those receiving cyclosporin to experience tremor and headache and to suffer dyspepsia, vomiting, diarrhoea and hypomagnesaemia. Patients treated with cyclosporin were significantly more likely to experience constipation, hirsutism and gingival hyperplasia.

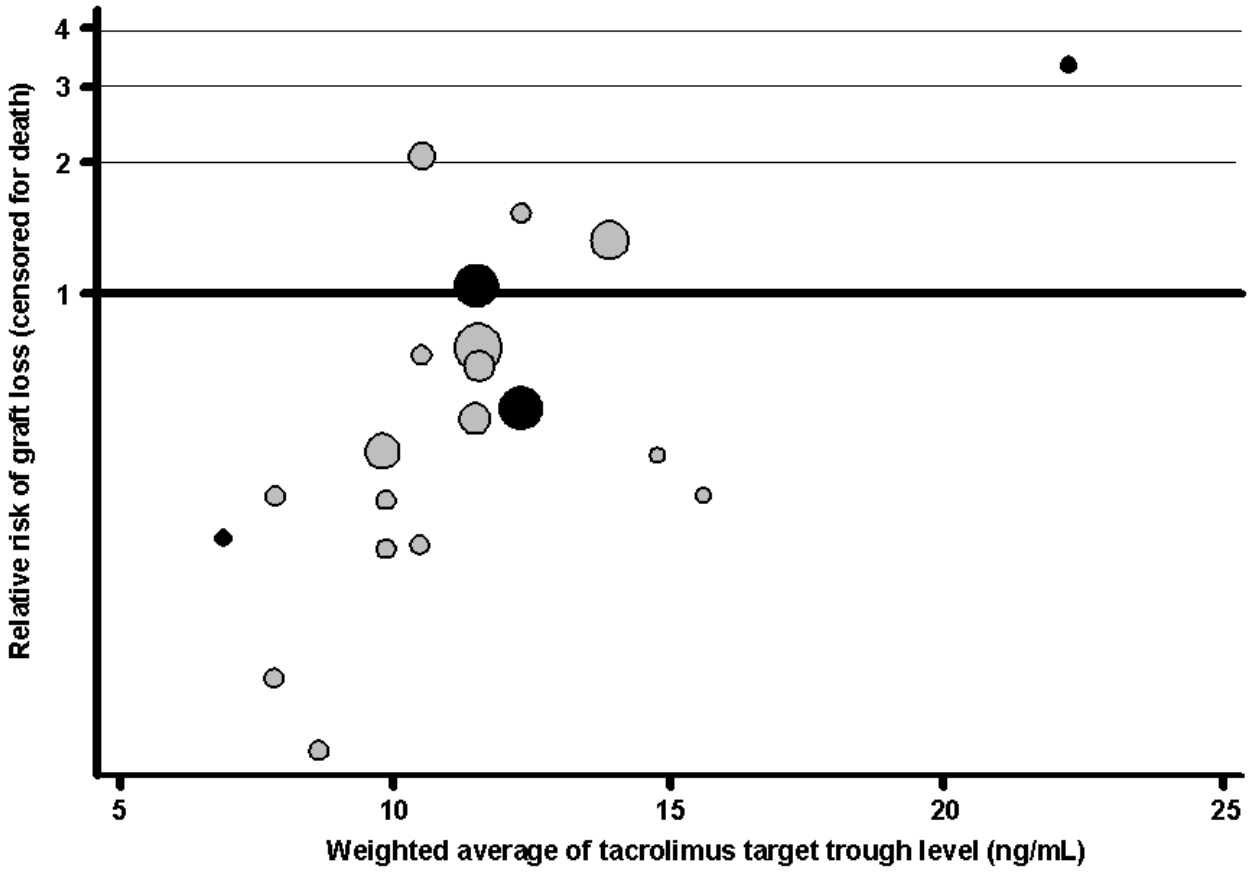
Subgroup analysis and meta-regression

Subgroup analysis was undertaken based on three study attributes; publication type, study methodological quality and baseline immunological risk of the study population. There was no evidence of any difference in the summary estimates of effect for graft loss. However, there was a significant difference (P = 0·01) between the estimate of effect for acute rejection dependent on publication status of studies. Studies published only in non peer-reviewed journals or abstract form showed no difference between tacrolimus and cyclosporin treated patients (Analysis 2.2.1, three studies: RR 1·02, 95% CI 0·57 to 1·82), whereas those published in peer reviewed journals demonstrated a significant reduction in patients experiencing acute rejection (Analysis 2.2.2, 11 studies: RR 0·64, 95% CI 0·57 to 0·72). We were unable to further determine whether this difference reflected publication bias, other reporting bias or true heterogeneity, as the funnel plot (not shown) for this outcome was uninformative, and study methodology details absent for some studies.

When studies conducted exclusively in adult recipients of primary cadaveric transplants (low immunological risk) were compared to studies containing a proportion of recipients of subsequent transplants, children or African-Americans (mixed and high immunological risk), there was no evidence of any difference demonstrated for new diabetes mellitus, acute rejection or graft loss between risk groups (Analysis 4; Table 2 - *Subgroup analyses).*

Univariate meta-regression (Table 3 - *Meta-regression and confounding*) showed no difference in graft loss (censored for death) for microemulsion (Neoral) over solution (Sandimmun) formulations of cyclosporin (P = 0·48), or for the target trough range of cyclosporin (P = 0·76), or for the use of MMF over azathioprine (P = 0·59). Most notably, higher tacrolimus doses were associated with an increased risk of graft loss compared with lower tacrolimus doses. This difference remained significant (P = 0·04), after allowing for differences in cyclosporin formulation and cyclosporin dosage. This relationship is demonstrated in Figure 2 (risk ratiostudy *of graft loss (censored for death) versus weighted average of target rough levels)* and suggests that when tacrolimus targets are ≤ 10 ng/mL, the benefit in graft survival is maximal.

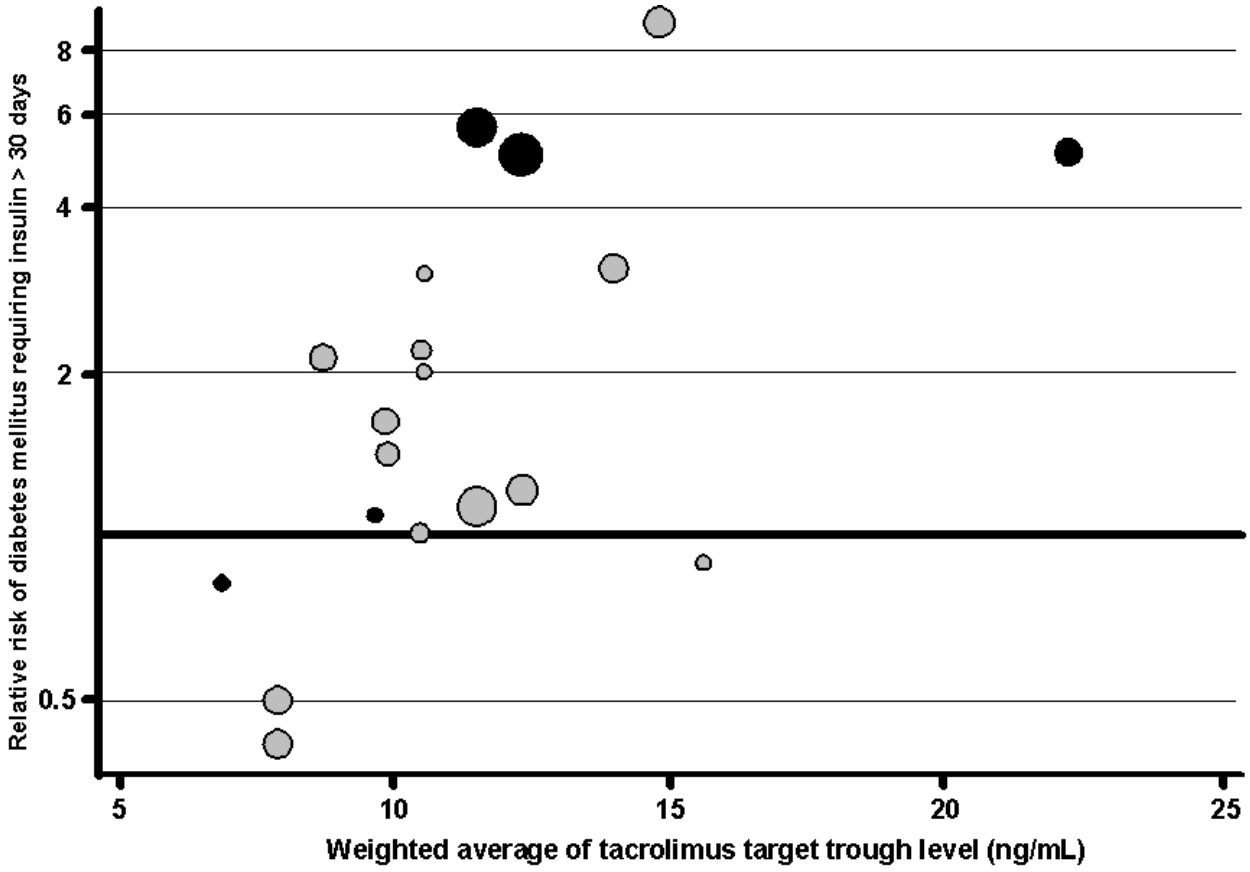
Figure 2. Figure 2. Risk ratio of graft loss (censored for death) versus the weighted average of the target tacrolimus trough levels over the first year after transplantation *.
*** Each circle represents a study, with the area proportional to the inverse of the variance of the estimated treatment effect (larger circles show studies given more weight in the meta-analysis). The colour of the circles represents the formulation of cyclosporin used in each study; dark circles are cyclosporin solution, light grey circles are cyclosporin microemulsion.**



The benefit of tacrolimus over cyclosporin in reducing the number of patients experiencing acute rejection did not vary after allowing for tacrolimus dose (P = 0·77), cyclosporin formulation (P = 0·99), cyclosporin dosage (P = 0·14), or different antiproliferative agents (P = 0·98) Table 3 - *Meta-regression and confounding*. For patients with new diabetes mellitus requiring >30 days of insulin therapy, in univariate analysis there was no difference demonstrated for antiproliferative agent (P = 0·29) or steroid dose (> 10 mg/d versus < 10 mg/d at three months post-transplantation; adjusted RR 1·36, 95% CI 0·32 to 5·71; P = 0·27). However, univariate analysis did demonstrate reduced risk with microemulsion cyclosporin (P = 0·006) and an increased risk with higher tacrolimus trough levels (P = 0·007). Multivariate meta-regression demonstrated that the increased risk of diabetes conferred by tacrolimus therapy did not vary after allowing for cyclosporin dose (P = 0·61), but although the effect of microemulsion cyclosporin remained significant (P = 0·003), tacrolimus trough level no longer demonstrated a statistically significant effect (P=0·10). Such a change in the significance of tacrolimus levels suggests an interaction and residual confounding between the targeted levels of tacrolimus and the choice of cyclosporin formulation and levels across studies, and this relationship is demonstrated in Figure 3 (risk ratiostudy *of diabetes mellitus requiring insulin treatment for > 30 days)*. When the analysis was repeated, restricted to studies using microemulsion cyclosporin, tacrolimus level remained significant (P = 0.003) after allowing for differences in antiproliferative agent (P = 0.73), further suggesting that risk of diabetes rises with tacrolimus exposure level. Unfortunately there was not consistent reporting of all clinical details across all studies (e.g. only 10 studies reporting new diabetes also reported steroid dosage), so this prevented the intended more complex analyses examining clinical differences allowing for methodological differences.

Figure 3. Figure 3. Risk ratio of diabetes mellitus requiring insulin treatment for >30 days, in previously non-diabetic patients, versus the weighted average of the target tacrolimus trough levels over the first year after transplantation *.

*** Each circle represents a study, with the area proportional to the inverse of the variance of the estimated treatment effect (larger circles show studies given more weight in the meta-analysis). The colour of the circles represents the formulation of cyclosporin used in each study; dark circles are cyclosporin solution, light grey circles are cyclosporin microemulsion.**



DISCUSSION

Summary of key findings

Compared with cyclosporin, treating recipients of kidney transplants with tacrolimus resulted in a substantial improvement in graft survival, with a 44% reduction in graft loss (censored for death) within the first six months after transplantation; an effect revealed only by meta-analysis, and not evident when considering each study in isolation. Treating with tacrolimus led to 31% fewer patients experiencing acute rejection, and 51% fewer experiencing severe rejection episodes that required therapy more intensive than steroids, within the first year post-transplantation.

Evidence from meta-regression suggested that the benefit in graft survival diminished when higher levels of tacrolimus were targeted, but was unaltered by differences in cyclosporin formulation, cyclosporin target trough level, or antiproliferative co-interventions across studies. However, none of these factors significantly altered the risk of acute rejection.

Tacrolimus-treated patients were between two and three times more likely than cyclosporin-treated recipients to develop new insulin-requiring diabetes mellitus post-transplantation, and also to experience neurological side-effects, whereas those taking cyclosporin experienced more cosmetic side-effects.

Strengths and limitations

This systematic review was undertaken with widely inclusive criteria, in order to allow exploration of differences in effect that might arise as a result of obvious clinical and design differences among the studies, and also to highlight and summarise the totality of RCT evidence available. This approach led to identification of a large number of studies (30) involving 4102 participants, including unpublished and non-English language data sources, which were included. Confining a meta-analysis to published data or English language alone has been previously demonstrated to over-estimate positive treatment effects (Egger 2001).

The quality of data reporting the adverse effects of therapy was less informative than that for the benefits, and adverse effects were inconsistently expressed and grouped. The majority of studies did not report disturbances of glucose metabolism, or elicit new cases of diabetes that could be controlled by diet or oral hypoglycaemic agents, but used high diagnostic thresholds, recording only those cases requiring sustained insulin therapy. In addition, often the prevalent rather than incident cases were reported, with no indication of the numbers of patients with diabetes prior to transplantation. Both these aspects introduced bias, and are likely to contribute to the underestimation of the true burden of disturbed glucose metabolism within the post-transplant population. The value of increasing available evidence of potential harms associated with interventions (compared with potential benefits alone) has been widely recognised recently (Cuervo 2003; Tunis 2003) and is not a problem peculiar to this review, but is common to many RCTs.

Progressive improvements in short-term outcomes post-transplantation have restricted clinician's ability to assess new therapy, as the event-rate of clinically important outcomes and the margin of expected differences has decreased. Therefore the numbers of participants required to adequately power studies has become so large that many new therapies can only be assessed in the context of large international multi-centre studies. Whilst acute rejection has a strong impact on early graft survival, recent cohort data suggests that decreasing acute rejection rates have not been matched by an increase in long term graft survival (Mathew 2001; Meier-Kriesche 2004). Reliance on long-term 'hard' outcomes measured over many years is often cost-prohibitive, hence the reliance on composite and surrogate endpoints as study outcomes. Extended discussion on the validity of study endpoints is beyond the scope of this paper, though currently much debated by the transplantation community (Kasiske 2000a; Kasiske 2000b). What this review does demonstrate is that clearly defined, standardised, consistently used and reported clinical endpoints would greatly enhance clinician and consumer interpretation of study evidence (Hariharan 2003; Lachenbruch 2004).

The use of meta-regression to explore sources of heterogeneity in the meta-analysis was justified as the Cochran-Q and I^2 tests have low power (Thompson 2002). We investigated clinical differences that we had specified *a priori* likely to lead to differences in effect. The relationship described by meta-regression is an observational association across studies, and does not have the benefit of randomisation to under-pin interpretation of the results. Hence an association identified with one study characteristic may in reality reflect a true association with other correlated characteristics, which maybe unknown. The finding that studies undertaken with cyclosporin microemulsion showed a significantly lower risk of post-transplantation diabetes mellitus over those treated with cyclosporin solution (although no difference in graft loss or acute rejection) may be one such example of misclassification. Hence our interpretation is guarded. The finding that higher target levels of tacrolimus altered the risk of graft loss towards that experienced by patients on cyclosporin, so decreasing the advantage of tacrolimus over cyclosporin, we feel is more biologically plausible. This is based on what is known of the complex interplay between calcineurin nephrotoxicity, CAN and infection (de Mattos 2000; Gourishankar 2002), and the evidence that higher doses of calcineurin inhibitors increase progression of histological markers of graft damage (Nankivell 2003; Nankivell 2004). Our meta-regression was not exhaustive, and it is possible that we may have failed to identify clinically important differences between subgroups that do exist (Berlin 2002).

Clinical implications

Table 4 - *Applicability in clinical practice - absolute risk per 100 treated recipients* shows the applicability of our results to kidney transplant recipients. Based on this analysis, treating a 100 low risk patients (such as adult recipients of well matched, first transplants) with tacrolimus instead of cyclosporin would avoid six experiencing acute rejection; this number rises to 17 if considering high risk populations (such as sensitised recipients of subsequent grafts, or children). Tacrolimus therapy would avoid one low risk, but three high risk patients losing their grafts. In contrast, treating with tacrolimus would cause an extra five recipients excess harm by rendering them insulin-dependent diabetics. Evidence from meta-regression suggests that when tacrolimus is used, targeting lower trough levels will minimize graft loss and temper the increased risk of diabetes mellitus without increasing the risk of acute rejection.

One other systematic meta-analysis of four RCTs comparing tacrolimus to cyclosporin solution was published in 1999 (Knoll 1999). A more recent review of RCT and observational data examined post-transplant diabetes mellitus in solid organ

transplant recipients, and included a seven-study meta-analysis of RCT data for kidney recipients, where we were able to identify 15 studies (Heisel 2004). Our results largely concur with this previous work, and with recent clinical guidelines published in the United Kingdom (NICE 2004), although with a larger number of studies to analyse, our estimates have greater precision, and we have extended the range of outcomes assessed.

AUTHORS' CONCLUSIONS

Implications for practice

Tacrolimus is superior to cyclosporin in preventing acute rejection after kidney transplantation, and tacrolimus treated patients have improved graft survival, although this is at the expense of increased post-transplant diabetes, neurological and gastrointestinal side effects. In applying this evidence to patients, the choice of calcineurin inhibitor for an individual patient is neither automatic nor straightforward, as risks of benefit and of drawbacks of each therapy must be balanced.

Implications for research

Our goal was to distil the body of evidence amassed over more than a decade of large multinational comparative randomised studies of the two calcineurin inhibitors, and particularly to generate estimates of each drugs negative effects, to highlight the deficits in knowledge and so set the research priorities for the coming decade. Despite the large number of comparative RCTs that have been performed, uncertainties remain, but we have been able to highlight the deficits in current knowledge. There was insufficient information in RCT reports to undertake a formal economic analysis, and there was a general failure to consider global quality of life (QOL) for transplant recipients, despite evidence that using validated disease-specific QOL instruments in transplant recipients may inform our understanding of patient preference and compliance (Reimer 2002). The next step must be to construct a decision analysis, using this comprehensive summary of best available evidence, attaching utilities to the positive and adverse outcomes associated with each drug. This would provide clinicians with an algorithm trading off graft survival against the impact of diabetes and other complications of immunosuppression, so tailoring the choice of calcineurin inhibitor to an individual patient's circumstances. This would represent a translation of results of the best evidence currently available to inform individual patient care.

ACKNOWLEDGEMENTS

- This systematic review was presented at the 21st annual scientific meeting of the Transplantation Society of Australia and New Zealand, Canberra 2003, and the World Congress of Nephrology, Berlin 2003
- AW would like to acknowledge the help and support of all members of the Cochrane Renal Group, and wishes to thank all report authors who responded to our enquiries about their work.
- We would like to thank Rebecca Woodroffe who identified and extracted data from included studies.
- This review has been co-published with the *BMJ* (Webster 2005).
- We would also like to thank Dr Scott Campbell, Prof Bert Kasiske, Dr Petra Macaskill and Dr Helen Pilmore for their editorial advice during the preparation of this review.

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CHARACTERISTICS OF STUDIES

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

Agha 2001

Methods	ITT: unclear Completeness of follow-up: unclear Single centre
Participants	N = 28 Cadaveric donors: 68% First transplant: % not specified
Interventions	**Tacrolimus dose** • Not specified **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Not specified **Cointerventions** Aza (dose not specified); ATG induction; P
Outcomes	Infection
Notes	Reported in abstract only Three month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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Webster 2003

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Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005;**331**(7520):810-20. [MEDLINE: 16157605]

* Indicates the major publication for the study

Baskin 2002

Methods	ITT: unclear Completeness of follow-up: unclear Single centre
Participants	N = 81 Cadaveric donors: % not stated First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: 0.1-0.3 mg/kg/d • Trough initial: 10-25 ng/mL • 3 month: 10-25 ng/mL **Cyclosporin formulation** • Unclear **Cyclosporin dose** • Initial: 5-7 mg/kg/d • Trough initial: 150-200 ng/mL • 3 month: 150-250 ng/mL **Cointerventions** Aza (1.5 mg/kg); MMF (2 g/d); P
Outcomes	Dyslipidaemia
Notes	Reported in abstract only Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Busque 2001

Methods	ITT: unclear Completeness of follow-up: unclear Six centres
Participants	N = 67 Cadaveric donors: 100% First transplant: 100%
Interventions	**Tacrolimus dose** • Initial: not stated • Trough initial: 8-16 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation**

Busque 2001 *(Continued)*

	• Microemulsion (Neoral) **Cyclosporin dose** • Initial: not stated mg/kg/d • Trough initial: 200-400 ng/mL • 3 month: 100-300 ng/mL **Cointerventions** Aza (1.5-2 mg/kg); MMF (2 g/d); P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. Infection 6. DM 7. Dyslipidaemia
Notes	Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Campos 2002

Methods	ITT: not undertaken Completeness of follow-up: 99% 15 centres
Participants	N = 166 Cadaveric donors: 49% First transplant: 95%
Interventions	**Tacrolimus dose** • Initial: 0.2 mg/kg/d • Trough initial: 5-15 ng/mL • 3 month: 10-15 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 10 mg/kg/d • Trough initial: 300-400 ng/mL • 3 month: 200-400 ng/mL **Cointerventions** Aza (1.5-2 mg/kg); P
Outcomes	1. Mortality

Campos 2002 *(Continued)*

2. Graft loss
3. AR
4. DM

Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Charpentier 2002

Methods	ITT: undertaken Completeness of follow-up: 88% 30 centres
Participants	N = 555 Cadaveric donors: % not stated First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: 0.3 mg/kg/d • Trough initial: 10-20 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 8 mg/kg/d • Trough initial: 150-300 ng/mL • 3 month: 100-200 ng/mL **Cointerventions** Aza (1-2 mg/kg); ATG; P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. CMV 6. DM 7. Dyslipidaemia 8. Adverse reactions
Notes	Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement

Charpentier 2002 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Egfjord 2002

Methods	ITT: unclear Completeness of follow-up: % unclear Single centre
Participants	N = 60 Cadaveric donors: % not stated First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: not stated • Trough initial: not stated • 3 month: not stated **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: not stated • Trough initial: not stated • 3 month: not stated **Cointerventions** MMF (not stated); ATG; P
Outcomes	1. Mortality 2. Graft loss 3. AR
Notes	Reported in abstract only Three year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

El Haggan 2002

Methods	ITT: not undertaken Completeness of follow-up: 100% Single centre
Participants	N = 44 Cadaveric donors: 100% First transplant: % not stated

El Haggan 2002 *(Continued)*

Interventions	**Tacrolimus dose** • Initial: not stated • Trough initial: not stated • 3 month: 5-10 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: not stated • Trough initial: not stated • 3 month: 150-200 ng/mL **Cointerventions** MMF(2 g/d); ATG; P
Outcomes	AR
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Heering 1998

Methods	ITT: undertaken Completeness of follow-up: 100% Single centre
Participants	N= 16 Cadaveric donors: % not stated First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: not stated • Trough initial: 10-20 ng/mL • 3 month: 5-10 ng/mL **Cyclosporin formulation** • Unclear **Cyclosporin dose** • Initial: 10 mg/kg/d • Trough initial: 100-300 ng/mL • 3 month: 100-150 ng/mL **Cointerventions** Aza (2 mg/kg/d); P

Heering 1998 *(Continued)*

Outcomes	Graft function
Notes	Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ichimaru 2001

Methods	ITT: unclear Completeness of follow-up: 100% Single centre
Participants	N = 32 Cadaveric donors: % not stated First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: not stated • Trough initial: 10-15 ng/mL • 3 month: 10-15 ng/mL **Cyclosporin formulation** • Solution (Sandimmun) **Cyclosporin dose** • Initial: 10mg/kg/d • Trough initial: 150-200 ng/mL • 3 month: 150-200 ng/mL Cointerventions MMF (not stated); Mizoribine; P
Outcomes	1. Graft function 2. Dyslipidaemia
Notes	Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Johnson 2000

Methods	ITT: undertaken Completeness of follow-up: 100%

Johnson 2000 *(Continued)*

	15 centres
Participants	N = 223 CadaverIc donors: 100% First transplant: 100%
Interventions	**Tacrolimus dose** • Initial: 0.15-0.2 mg/kg/d • Trough initial: 8-16 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 8-10 mg/kg/d • Trough initial: 200-400 ng/mL • 3 month: 100-300 ng/mL **Cointerventions** Aza (1.5-2 mg/kg/d); MMF (2 g/d); ATG or OKT3; P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. Infection 6. CMV 7. DM 8. Dyslipidaemia 9. Malignancy 10.Adverse reactions
Notes	Three year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Laskow 1995

Methods	ITT: not undertaken Completeness of follow-up: 92% Five centres
Participants	N = 560 Cadaveric donors: 96% First transplant: 93%
Interventions	**Tacrolimus dose**

Laskow 1995 *(Continued)*

- Initial: 0.2-0.4 mg/kg/d
- Trough initial: 5-40 ng/mL
- 3 month: 5-40 ng/mL

Cyclosporin formulation

- Solution (Sandimmun)

Cyclosporin dose

- Initial: 6-14 mg/kg/d
- Trough initial: not stated
- 3 month: not stated

Cointerventions
Aza (1-1.5 mg/kg/d); ALG; P

Outcomes	1. AR 2. DM 3. Adverse reactions
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Liu 2003

Methods	ITT: unclear Completeness of follow-up: % unclear Single centre
Participants	N = 27 Cadaveric donors: 100% First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial 0.1-0.2 mg/kg/d • Trough initial: 6-8 ng/mL • 3 month: 6-8 ng/mL **Cyclosporin formulation** • Unclear **Cyclosporin dose** • Initial: 5-7 mg/kg/d • Trough initial: 220-300 ng/mL • 3 month: 220-300 ng/mL **Cointerventions** MMF (1.5-2 g/d); ALG; P

Liu 2003 *(Continued)*

Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. Infection 6. DM
Notes	Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Margreiter 2002

Methods	ITT: not undertaken Completeness of follow-up: 77% 50 centres
Participants	N = 560 Cadaveric donors: 96% First transplant: 93%
Interventions	**Tacrolimus dose** • Initial: 0.3 mg/kg/d • Trough initial: 10-20 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 8-10 mg/kg/d • Trough initial: 100-400 ng/mL • 3 month: 100-200 ng/mL **Cointerventions** Aza (1-2 mg/kg/d); P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. CAN 6. CMV 7. DM 8. Dyslipidaemia 9. Malignancy 10.Adverse reactions

Margreiter 2002 *(Continued)*

Notes	Three year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Mayer 1997

Methods	ITT: undertaken Completeness of follow-up: 100% 15 centres
Participants	N = 448 Cadaveric donors: 100% First transplant: 90%
Interventions	**Tacrolimus dose** • Initial: 0.3 mg/kg/d • Trough initial: 10-20 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation** • Solution (Sandimmun) **Cyclosporin dose** • Initial: 8 mg/kg/d • Trough initial: 100-300 ng/mL • 3 month: 100-150 ng/mL Cointerventions Aza (1-2 mg/kg/d); P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. CAN 6. Infection 7. CMV 8. DM 9. Dyslipidaemia 10. Malignancy 11. Adverse reactions
Notes	Five year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement

Mayer 1997 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Miller 2002

Methods	ITT: unclear Completeness of follow-up: % unclear
Participants	N = 53 Cadaveric donors: 100% First transplant: 100%
Interventions	**Tacrolimus dose** • Initial: 0.2 mg/kg/d • Trough initial: 10 ng/mL • 3 month: 6-8 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 10 mg/kg/d • Trough initial: 200-250 ng/mL • 3 month: 175-225 ng/mL **Cointerventions** MMF (2 g/d); Sirolimus (8 mg/d); daclizumab; P
Outcomes	1. Graft loss 2. AR 3. Graft function
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Morris-Stiff 1998

Methods	ITT: undertaken Completeness of follow-up: 100% Single centre
Participants	N = 179 Cadaveric donors: 100% First transplant: 83%
Interventions	**Tacrolimus dose**

Morris-Stiff 1998 *(Continued)*

- Initial: 0.2 mg/kg/d
- Trough initial: 5-15 ng/mL
- 3 month: 5-15 ng/mL

Cyclosporin formulation

- Microemulsion (Neoral)

Cyclosporin dose

- Initial: 8 mg/kg/d
- Trough initial: 100-200 ng/mL
- 3 month: 100-200 ng/mL

Cointerventions
Aza (1.5 mg/kg/d); P

Outcomes	1. Mortality 2. Graft loss 3. AR 4. CMV 5. DM 6. Dyslipidaemia
Notes	Three year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nichelle 2002

Methods	ITT: not undertaken Completeness of follow-up: % unclear Single centre
Participants	N = 94 Cadaveric donors: % not stated First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: 0.2 mg/kg/d • Trough initial: 5-10 ng/mL • 3 month: 5-10 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 6 mg/kg/d • Trough initial: 100-150 ng/mL • 3 month: 100-150 ng/mL

Nichelle 2002 *(Continued)*

	Cointerventions Aza (1 mg/kg/d); P
Outcomes	Graft function
Notes	Three year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pirsch 1997

Methods	ITT: undertaken Completeness of follow-up: 100% 19 centres
Participants	N = 412 Cadaveric donors: 100% First transplant: 87%
Interventions	**Tacrolimus dose** • Initial: 0.2 mg/kg/d • Trough initial: 10-25 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation** • Solution (Sandimmun) **Cyclosporin dose** • Initial: 10 mg/kg/d • Trough initial: 150-400 ng/mL • 3 month: 100-300 ng/mL Cointerventions Aza (1.5 mg/kg/d); ATG or OKT3; P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. CANInfection 6. CMV 7. DM 8. Dyslipidaemia 9. Malignancy 10.Adverse reactions
Notes	Five year follow-up

Pirsch 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Radermacher 1998

Methods	ITT: undertaken Completeness of follow-up: 85% Single centre
Participants	N = 48 Cadaveric donors: % not stated First transplant: 75%
Interventions	**Tacrolimus dose** • Initial: 0.2-0.3 mg/kg/d • Trough initial: 10-20 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation** • Solution (Sandimmun) **Cyclosporin dose** • Initial: 5-8 mg/kg/d • Trough initial: 150 ng/mL • 3 month: 100-150 ng/mL Cointerventions Aza (1 mg/kg/d); P
Outcomes	1. AR 2. Graft function 3. Infection 4. CMV 5. DM
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Raofi 1999

Methods	ITT: undertaken Completeness of follow-up: % unclear

Raofi 1999 *(Continued)*

	Single centre
Participants	N = 35 100% recipients African-American Cadaveric donors: 100% First transplant: 100%
Interventions	**Tacrolimus dose** • Initial: not stated mg/kg/d • Trough initial: 10-15 ng/mL • 3 month: 10-15 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: not stated • Trough initial: 150-200 ng/mL • 3 month: 150-200 ng/mL **Cointerventions** Aza (2 mg/kg/d); OKT3; P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. CAN 6. CMV 7. DM 8. Dyslipidaemia
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Shapiro 1991

Methods	ITT: not undertaken Completeness of follow-up: % unclear Single centre
Participants	N = 57 Cadaveric donors: 100% First transplant: 100%
Interventions	**Tacrolimus dose** • Initial: 0.3 mg/kg/d

Shapiro 1991 *(Continued)*

- Trough initial: not stated
- 3 month: not stated

Cyclosporin formulation

- Solution (Sandimmun)

Cyclosporin dose

- Initial: 4 mg/kg/d
- Trough initial: not stated
- 3 month: not stated

Cointerventions
P

Outcomes	1. Mortality 2. Graft loss 3. Graft function 4. DM 5. Dyslipidaemia
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Toz 2001

Methods	ITT: unclear Completeness of follow-up: 100 % Single centre
Participants	N = 17 Cadaveric donors: 65% First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: 0.1-0.2 mg/kg/d • Trough initial: 8-11 ng/mL • 3 month: not stated **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 5-7 mg/kg/d • Trough initial: 250-320 ng/mL • 3 month: not stated **Cointerventions**

Toz 2001 *(Continued)*

	Aza (not stated); P
Outcomes	1. AR 2. Graft function 3. CAN 4. CMV 5. DM
Notes	Reported in abstract only Three month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Trompeter 2002

Methods	ITT: not undertaken Completeness of follow-up: 90% 18 centres
Participants	N = 204 100% recipients children Cadaveric donors: 16% First transplant: 88%
Interventions	**Tacrolimus dose** • Initial: 0.3 mg/kg/d • Trough initial: 10-20 ng/mL • 3 month: 5-10 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 300 m^2/d • Trough initial: 150-200 ng/mL • 3 month 100-200 ng/mL **Cointerventions** Aza (2 mg/kg/d); P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. Infection 6. DM 7. Dyslipidaemia 8. Malignancy

Trompeter 2002 *(Continued)*

	9. Adverse reactions
Notes	Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Tsinalis 2000

Methods	ITT: unclear Completeness of follow-up: % unclear Single centre
Participants	N = 53 Cadaveric donors: % not stated First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: not stated • Trough initial: not stated • 3 month: not stated **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: not stated • Trough initial: not stated • 3 month: not stated **Cointerventions** Aza (not stated); MMF (not stated); P
Outcomes	AR
Notes	Six month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

van Duijnhoven 2002

Methods	ITT: not undertaken Completeness of follow-up: % unclear Single centre

van Duijnhoven 2002 *(Continued)*

Participants	N = 23 Cadaveric donors: 100% First transplant: 78%
Interventions	**Tacrolimus dose** • Initial: 0.3 mg/kg/d • Trough initial: 10-15 ng/mL • 3 month: 7-10 ng/mL **Cyclosporin formulation** • Unclear **Cyclosporin dose** • Initial: 8 mg/kg/d • Trough initial: 100-200 ng/mL • 3 month: 100-150 ng/mL **Cointerventions** Aza (2 mg/kg/d); P
Outcomes	1. Mortality 2. AR 3. Graft function 4. DM
Notes	Six months follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Wang 2000

Methods	ITT: undertaken Completeness of follow-up: 100% Single centre
Participants	N = 57 Cadaveric donors: 100% First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: 0.15-0.3 mg/kg/d • Trough initial: 10-20 ng/mL • 3 month: 5-10 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose**

Wang 2000 *(Continued)*

	• Initial: 6-8 mg/kg/d • Trough initial: 250-400 ng/mL • 3 month: 150-300 ng/mL **Cointerventions** MMF (2 g/d); P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. Infection 6. DM 7. Malignancy
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Weimer 2002

Methods	ITT: unclear Completeness of follow-up: % unclear More than 1 centre
Participants	N = 84 Cadaveric donors: 75% First transplant: < 100%
Interventions	**Tacrolimus dose** • Initial: not stated • Trough initial: not stated • 3 month: not stated **Cyclosporin formulation** • Unclear **Cyclosporin dose** • Initial: not stated • Trough initial: not stated • 3 month: not stated **Cointerventions** Aza (not stated); MMF (not stated); P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function

Weimer 2002 *(Continued)*

	5. DM
Notes	Three month follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

White 2000

Methods	ITT: unclear Completeness of follow-up: 98% Single centre
Participants	N = 102 Cadaveric donors: 79% (40% non heart-beating donors) First transplant: 88%
Interventions	**Tacrolimus dose** • Initial: 0.1-0.2 mg/kg/d • Trough initial: 8-15 ng/mL • 3 month: 5-10 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 7-15 mg/kg/d • Trough initial: 200-300 ng/mL • 3 month: 100-200 ng/mL **Cointerventions** P
Outcomes	1. Mortality 2. AR 3. DM
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Yang 1999

Methods	ITT: undertaken

Yang 1999 *(Continued)*

	Completeness of follow-up: 100% Single centre
Participants	N = 60 Cadaveric donors: 62% First transplant: 100%
Interventions	**Tacrolimus dose** • Initial: 0.3 mg/kg/d • Trough initial: 10-20 ng/mL • 3 month: 5-15 ng/mL **Cyclosporin formulation** • Microemulsion (Neoral) **Cyclosporin dose** • Initial: 8-10 mg/kg/d • Trough initial: 100-400 ng/mL • 3 month: 100-200 ng/mL **Cointerventions** Aza (1-2 mg/kg/d); P
Outcomes	1. Mortality 2. Graft loss 3. AR 4. Graft function 5. Infection 6. DM 7. Malignancy 8. Adverse reactions
Notes	One year follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Yu 2000

Methods	ITT: undertaken Completeness of follow-up: 99% Single centre
Participants	N = 90 Cadaveric donors: 100% First transplant: % not stated
Interventions	**Tacrolimus dose** • Initial: 0.15-0.3 mg/kg/d

Yu 2000 *(Continued)*

- Trough initial: 10-20 ng/mL
- 3 month: 10-20 ng/mL

Cyclosporin formulation

- Microemulsion (Neoral)

Cyclosporin dose

- Initial: 8 mg/kg/d
- Trough initial: not stated
- 3 month: 200-400 ng/mL

Cointerventions
Aza (not stated); MMF (1 g/d); OKT3; P

Outcomes	1. Mortality 2. Graft loss 3. AR 4. Infection 5. DM 6. Adverse reactions
Notes	Six months follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

N = total number of study participants
Co-interventions: Prednisolone was common to all studies. Aza = azathioprine, MMF = mycophenolate mofetil, P = steroid, ATG = anti-thymocyteglobulin, ALG = Antilymphocyteglobulin, OKT3 = monomurab-CD3
Outcomes: AR = acute rejection, CAN = chronic allograft nephropathy, CMV = cytomegalovirus, DM = diabetes mellitus

DATA AND ANALYSES

Comparison 1. Tacrolimus versus cyclosporin for primary therapy

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Graft loss (censored for death)	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.68]
1.2 6 months	7	1552	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.36, 0.86]
1.3 1 year	14	2604	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.02]
1.4 2 years	4	1259	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.46, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 3 years	7	1513	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.96]
1.6 4 years	1	448	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.21]
1.7 5 years	2	827	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.65, 1.14]
2 Acute rejection (clinical or biopsy proven)	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 3 months	5	248	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.44, 2.08]
2.2 6 months	10	1778	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.60, 0.78]
2.3 1 year	14	2751	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.79]
2.4 2 years	3	1102	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.46, 0.72]
2.5 3 years	2	643	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.04]
3 Acute rejection (biopsy proven)	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.68, 2.21]
3.2 6 months	7	1605	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.48, 0.96]
3.3 1 year	9	2094	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.52, 0.72]
3.4 2 years	1	223	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.45, 1.34]
3.5 3 years	1	223	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.45, 1.25]
4 Acute rejection (steroid resistant)	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 3 months	4	204	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.13, 7.15]
4.2 6 months	7	1511	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.33, 0.60]
4.3 1 year	9	1770	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.37, 0.64]
4.4 2 years	1	223	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.36, 1.74]
4.5 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Total graft loss (with death)	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.32]
5.2 6 months	8	1702	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.42, 0.86]
5.3 1 year	14	2604	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.13]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.4 2 years	4	1262	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.08]
5.5 3 years	7	1513	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.59, 0.93]
5.6 4 years	1	448	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.71, 1.32]
5.7 5 years	2	827	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.77, 1.14]
6 Mortality	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 3 months	2	164	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.68]
6.2 6 months	8	1702	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.36, 1.31]
6.3 1 year	14	2604	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.66, 1.68]
6.4 2 years	4	1262	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.48, 1.27]
6.5 3 years	6	1290	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.59, 1.40]
6.6 4 years	1	448	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.75, 2.13]
6.7 5 years	2	827	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.75, 1.33]
7 Chronic allograft nephropathy (CAN)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 6 months	1	557	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.09, 2.57]
7.3 1 year	3	914	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.11, 0.68]
7.4 2 years	1	144	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.68, 1.08]
7.5 3 years	1	179	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.88, 1.60]
7.6 4 years	1	448	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.26, 0.98]
7.7 5 years	1	451	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.24, 0.75]
8 Total infection	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 6 months	4	380	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.87, 1.28]
8.3 1 year	6	1572	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.07]
8.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Total CMV infection	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 3 months	2	97	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.02, 12.46]
9.2 6 months	3	1335	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.01]
9.3 1 year	7	1155	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.72, 1.29]
9.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Invasive CMV infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 6 months	1	223	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.13, 4.45]
10.3 1 year	3	622	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.77, 2.75]
10.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Delayed graft function	9	1688	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.13]
11.1 Requirement for dialysis within 1st week post-transplantation	9	1688	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.13]
12 Hypercholesterolaemia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 6 months	2	1112	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.24, 0.71]
12.3 1 year	1	412	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.30, 0.96]
12.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Neurological side effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 tremor	6	2152	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.50, 3.17]
13.2 Insomnia	3	980	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.83, 1.28]
13.3 Headache	3	980	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.00, 1.52]
13.4 Paraesthesia	2	532	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.85, 3.16]
13.5 Anxiety	1	412	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.98, 3.04]
13.6 Dizziness	1	412	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.80, 1.88]
13.7 Neuropathy	1	120	Risk Ratio (M-H, Random, 95% CI)	3.43 [0.20, 60.19]
13.8 Seizure	1	60	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.25, 99.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Gastrointestinal side effects	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Constipation	3	980	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 0.99]
14.2 Abdominal pain	1	448	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.83, 1.65]
14.3 Diarrhoea	7	1343	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.03, 3.83]
14.4 Nausea	2	860	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.84, 1.30]
14.5 Dyspepsia	3	980	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.00, 1.70]
14.6 Vomiting	3	980	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.05, 1.89]
14.7 Gastritis	1	557	Risk Ratio (M-H, Random, 95% CI)	8.53 [1.09, 66.86]
14.8 Haemorrhage/bleed	1	557	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.09]
15 Total malignancy	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 6 months	2	753	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.27, 5.47]
15.3 1 year	7	1765	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.37, 1.73]
15.4 3 years	2	608	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.52, 1.60]
15.5 5 years	2	860	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.60]
16 de novo hypertension	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 6 months	2	753	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.52, 1.52]
16.3 1 year	3	1024	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.80, 1.36]
16.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Bacterial infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 6 months	1	196	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.73, 1.43]
17.3 1 year	3	920	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 1.01]
17.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18 Viral infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

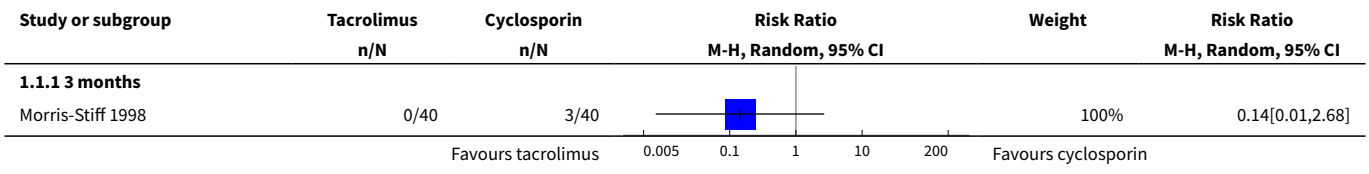
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 6 months	1	196	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.54, 1.50]
18.3 1 year	3	920	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.81, 1.28]
18.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19 Fungal infection	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.2 6 months	2	419	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.86, 3.33]
19.3 1 year	3	920	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.70, 2.37]
19.4 3 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20 Protozoal infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.1 3 months	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.2 6 months	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.3 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.4 3 years	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21 Other unclassifiable infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
21.1 3 months	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.2 6 months	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.3 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.4 3 years	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22 Serum creatinine µmol/L	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 1 month	2	67	Mean Difference (IV, Random, 95% CI)	-63.98 [-205.66, 77.69]
22.2 3 months	3	137	Mean Difference (IV, Random, 95% CI)	1.26 [-22.52, 25.04]
22.3 6 months	7	939	Mean Difference (IV, Random, 95% CI)	-15.88 [-30.30, -1.46]
22.4 1 year	8	569	Mean Difference (IV, Random, 95% CI)	-13.07 [-37.27, 11.12]
22.5 2 years	1	144	Mean Difference (IV, Random, 95% CI)	-7.95 [-23.83, 7.93]
22.6 3 years	2	506	Mean Difference (IV, Random, 95% CI)	2.50 [-6.93, 11.94]

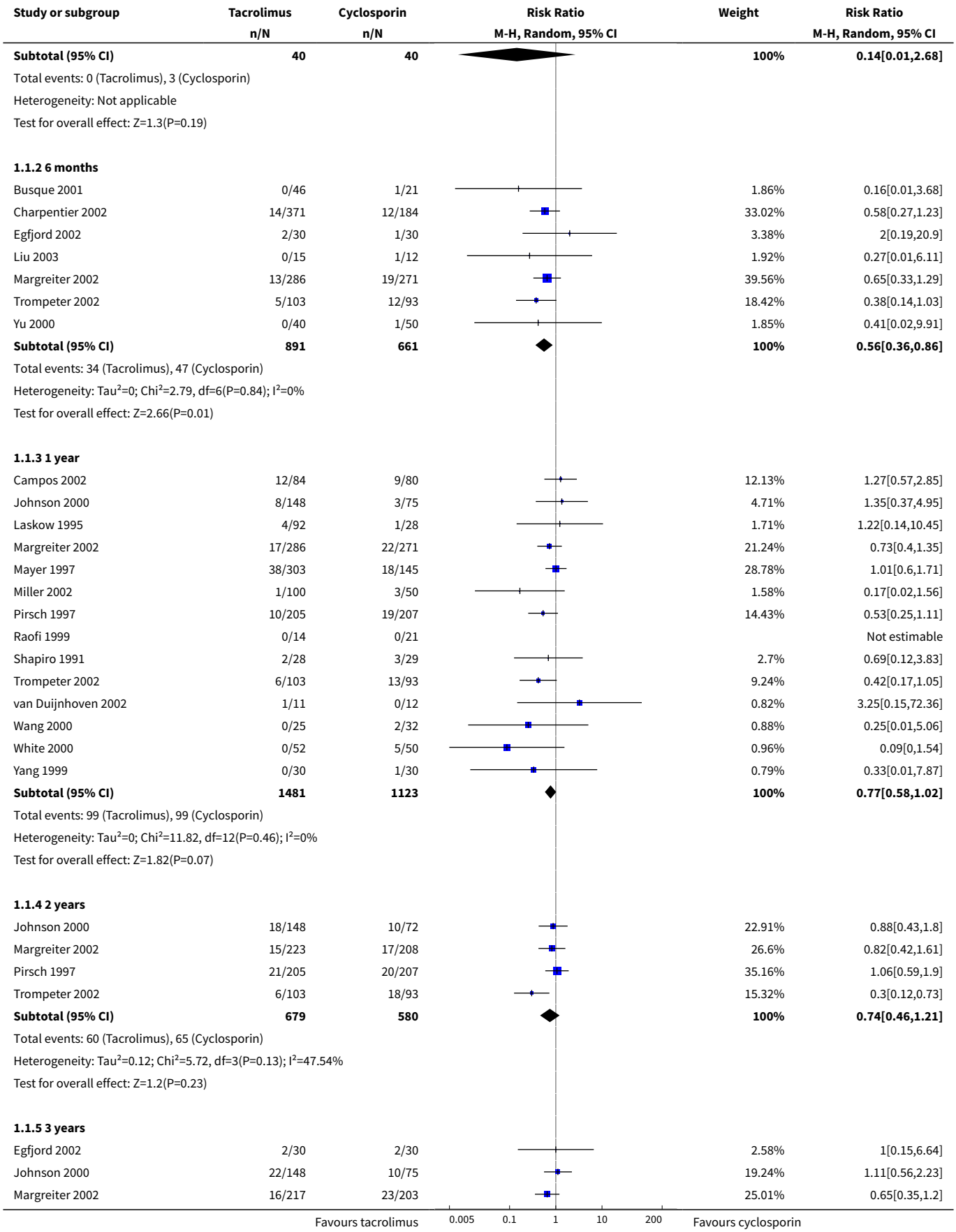
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.7 5 years	1	448	Mean Difference (IV, Random, 95% CI)	-13.0 [-27.38, 1.38]
23 Haematological side effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 Anaemia	1	448	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.68, 1.64]
23.2 Leucopaenia	2	1003	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.53, 1.31]
23.3 Thrombocytopeania	1	555	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.54, 1.84]
23.4 Erythrocytosis	1	17	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 6.47]
24 Cosmetic side effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 Acne	1	448	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.12, 0.64]
24.2 Hirsuitism	4	1613	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.01, 0.15]
24.3 Gingival hyperplasia	5	1673	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.06, 0.34]
24.4 Alopecia	2	969	Risk Ratio (M-H, Random, 95% CI)	10.55 [2.91, 38.23]
24.5 Pruritis	1	412	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.16, 3.75]
24.6 Other	1	17	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.16]
25 Lymphoma/PTLD	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 3 months	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25.2 6 months	1	196	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.04, 4.90]
25.3 1 year	5	1016	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.29, 2.08]
25.4 2 years	2	635	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.27, 2.95]
25.5 3 years	2	608	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.31, 1.93]
25.6 5 years	2	860	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.46, 3.22]
26 Biochemical side effects	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 Hypomagnesaemia	2	753	Risk Ratio (M-H, Random, 95% CI)	2.99 [1.78, 5.02]
26.2 Bilirubinaemia	1	557	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 0.83]
26.3 Cholestasis	2	647	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.05, 1.05]
26.4 Hyperkalaemia	2	568	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.97, 1.82]
27 Fever	2	751	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.10, 1.22]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
28 Surgical side effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 Lymphocoele	1	150	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.36, 2.04]
28.2 Dehiscence	1	150	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.07, 3.45]
28.3 Wound infection	1	150	Risk Ratio (M-H, Random, 95% CI)	4.54 [0.25, 82.78]
28.4 Fistulae	1	150	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.06, 36.53]
28.5 Other	1	150	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.00, 2.06]
29 GFR (mL/min)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 6 months	2	213	Mean Difference (IV, Random, 95% CI)	0.38 [-9.12, 9.89]
29.2 1 year	1	161	Mean Difference (IV, Random, 95% CI)	7.10 [0.50, 13.70]
29.3 2 years	1	137	Mean Difference (IV, Random, 95% CI)	13.20 [6.48, 19.92]
29.4 3 years	1	412	Mean Difference (IV, Random, 95% CI)	-0.30 [-6.16, 5.56]
29.5 5 years	1	376	Mean Difference (IV, Random, 95% CI)	7.00 [0.41, 13.59]
30 Total cholesterol (µmol/L)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
30.1 1 month	2	465	Mean Difference (IV, Random, 95% CI)	-0.87 [-1.08, -0.66]
30.2 3 months	2	530	Mean Difference (IV, Random, 95% CI)	-0.75 [-0.97, -0.54]
30.3 6 months	3	722	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.77, -0.39]
30.4 1 year	3	183	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.76, 0.17]
30.5 3 years	1	219	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.03, -0.39]
30.6 5 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
31 Total triglycerides (µmol/L)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
31.1 1 month	2	465	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.84, 0.16]
31.2 3 months	2	530	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.65, -0.00]
31.3 6 months	2	526	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.60, 0.05]
31.4 1 year	1	91	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.28, -0.26]
31.5 3 years	1	205	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.69, -0.09]
31.6 5 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32 Treament withdrawal/crossover	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.02, 1.64]
32.2 6 months	3	1311	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.47, 0.74]
32.3 1 year	6	1402	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.36, 1.45]
32.4 within first year	9	2713	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.47, 1.02]
33 Sustained diabetes mellitus requiring insulin	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 3 months	1	80	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.95]
33.2 6 months	6	915	Risk Ratio (M-H, Random, 95% CI)	2.61 [1.16, 5.85]
33.3 1 year	11	1956	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.04, 2.78]
33.4 2 years	1	145	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.34, 4.46]
33.5 3 years	2	447	Risk Ratio (M-H, Random, 95% CI)	3.26 [1.62, 6.57]
33.6 5 years	1	302	Risk Ratio (M-H, Random, 95% CI)	3.33 [1.38, 8.07]
34 Requirement for insulin >30 days in previously non-diabetic patients	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 3 months	2	97	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.10, 16.97]
34.2 6 months	7	1060	Risk Ratio (M-H, Random, 95% CI)	2.56 [1.37, 4.78]
34.3 1 year	12	2013	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.11, 3.09]
34.4 2 years	1	145	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.34, 4.46]
34.5 3 years	2	447	Risk Ratio (M-H, Random, 95% CI)	3.86 [2.01, 7.41]
34.6 5 years	1	302	Risk Ratio (M-H, Random, 95% CI)	4.86 [2.22, 10.61]

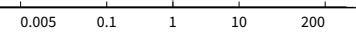
Analysis 1.1. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 1 Graft loss (censored for death).





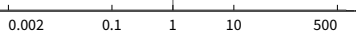
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**40**	**40**		**100%**	**0.14[0.01,2.68]**
Total events: 0 (Tacrolimus), 3 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					
1.1.2 6 months					
Busque 2001	0/46	1/21		1.86%	0.16[0.01,3.68]
Charpentier 2002	14/371	12/184		33.02%	0.58[0.27,1.23]
Egfjord 2002	2/30	1/30		3.38%	2[0.19,20.9]
Liu 2003	0/15	1/12		1.92%	0.27[0.01,6.11]
Margreiter 2002	13/286	19/271		39.56%	0.65[0.33,1.29]
Trompeter 2002	5/103	12/93		18.42%	0.38[0.14,1.03]
Yu 2000	0/40	1/50		1.85%	0.41[0.02,9.91]
Subtotal (95% CI)	**891**	**661**		**100%**	**0.56[0.36,0.86]**
Total events: 34 (Tacrolimus), 47 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=2.79, df=6(P=0.84); I^2=0%					
Test for overall effect: Z=2.66(P=0.01)					
1.1.3 1 year					
Campos 2002	12/84	9/80		12.13%	1.27[0.57,2.85]
Johnson 2000	8/148	3/75		4.71%	1.35[0.37,4.95]
Laskow 1995	4/92	1/28		1.71%	1.22[0.14,10.45]
Margreiter 2002	17/286	22/271		21.24%	0.73[0.4,1.35]
Mayer 1997	38/303	18/145		28.78%	1.01[0.6,1.71]
Miller 2002	1/100	3/50		1.58%	0.17[0.02,1.56]
Pirsch 1997	10/205	19/207		14.43%	0.53[0.25,1.11]
Raofi 1999	0/14	0/21			Not estimable
Shapiro 1991	2/28	3/29		2.7%	0.69[0.12,3.83]
Trompeter 2002	6/103	13/93		9.24%	0.42[0.17,1.05]
van Duijnhoven 2002	1/11	0/12		0.82%	3.25[0.15,72.36]
Wang 2000	0/25	2/32		0.88%	0.25[0.01,5.06]
White 2000	0/52	5/50		0.96%	0.09[0,1.54]
Yang 1999	0/30	1/30		0.79%	0.33[0.01,7.87]
Subtotal (95% CI)	**1481**	**1123**		**100%**	**0.77[0.58,1.02]**
Total events: 99 (Tacrolimus), 99 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=11.82, df=12(P=0.46); I^2=0%					
Test for overall effect: Z=1.82(P=0.07)					
1.1.4 2 years					
Johnson 2000	18/148	10/72		22.91%	0.88[0.43,1.8]
Margreiter 2002	15/223	17/208		26.6%	0.82[0.42,1.61]
Pirsch 1997	21/205	20/207		35.16%	1.06[0.59,1.9]
Trompeter 2002	6/103	18/93		15.32%	0.3[0.12,0.73]
Subtotal (95% CI)	**679**	**580**		**100%**	**0.74[0.46,1.21]**
Total events: 60 (Tacrolimus), 65 (Cyclosporin)					
Heterogeneity: Tau^2=0.12; Chi^2=5.72, df=3(P=0.13); I^2=47.54%					
Test for overall effect: Z=1.2(P=0.23)					
1.1.5 3 years					
Egfjord 2002	2/30	2/30		2.58%	1[0.15,6.64]
Johnson 2000	22/148	10/75		19.24%	1.11[0.56,2.23]
Margreiter 2002	16/217	23/203		25.01%	0.65[0.35,1.2]

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Morris-Stiff 1998	0/90	1/89		0.91%	0.33[0.01,7.99]
Pirsch 1997	21/205	34/207		35.83%	0.62[0.38,1.04]
Trompeter 2002	9/103	15/93		15.33%	0.54[0.25,1.18]
van Duijnhoven 2002	2/11	0/12		1.08%	5.42[0.29,101.77]
Subtotal (95% CI)	**804**	**709**		**100%**	**0.71[0.52,0.96]**
Total events: 72 (Tacrolimus), 85 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=4.61, df=6(P=0.59); I^2=0%					
Test for overall effect: Z=2.2(P=0.03)					
1.1.6 4 years					
Mayer 1997	40/303	25/145		100%	0.77[0.48,1.21]
Subtotal (95% CI)	**303**	**145**		**100%**	**0.77[0.48,1.21]**
Total events: 40 (Tacrolimus), 25 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.14(P=0.25)					
1.1.7 5 years					
Mayer 1997	46/303	22/148		34.88%	1.02[0.64,1.63]
Pirsch 1997	44/191	54/185		65.12%	0.79[0.56,1.11]
Subtotal (95% CI)	**494**	**333**		**100%**	**0.86[0.65,1.14]**
Total events: 90 (Tacrolimus), 76 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.76, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					

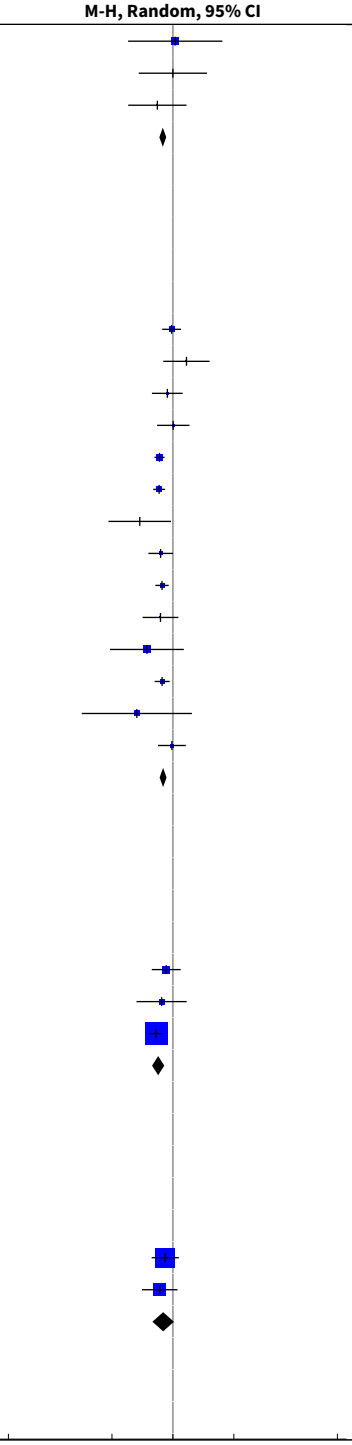


Analysis 1.2. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 2 Acute rejection (clinical or biopsy proven).

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 3 months					
El Haggan 2002	0/22	12/22		2.74%	0.04[0,0.64]
Morris-Stiff 1998	16/40	13/40		55.86%	1.23[0.68,2.21]
Toz 2001	2/9	2/8		7.11%	0.89[0.16,4.93]
van Duijnhoven 2002	2/11	2/12		6.58%	1.09[0.18,6.48]
Weimer 2002	7/28	10/56		27.71%	1.4[0.6,3.28]
Subtotal (95% CI)	**110**	**138**		**100%**	**0.95[0.44,2.08]**
Total events: 27 (Tacrolimus), 39 (Cyclosporin)					
Heterogeneity: Tau^2=0.35; Chi^2=7.99, df=4(P=0.09); I^2=49.93%					
Test for overall effect: Z=0.12(P=0.9)					
1.2.2 6 months					
Busque 2001	10/46	2/21		1.25%	2.28[0.55,9.52]
Charpentier 2002	95/371	64/184		25.18%	0.74[0.57,0.96]
Liu 2003	1/15	1/12		0.36%	0.8[0.06,11.5]
Margreiter 2002	93/286	139/271		34.5%	0.63[0.52,0.78]
Miller 2002	2/100	3/50		0.83%	0.33[0.06,1.93]
Trompeter 2002	38/103	55/93		20.58%	0.62[0.46,0.85]
Tsinalis 2000	15/26	19/27		12.86%	0.82[0.54,1.24]

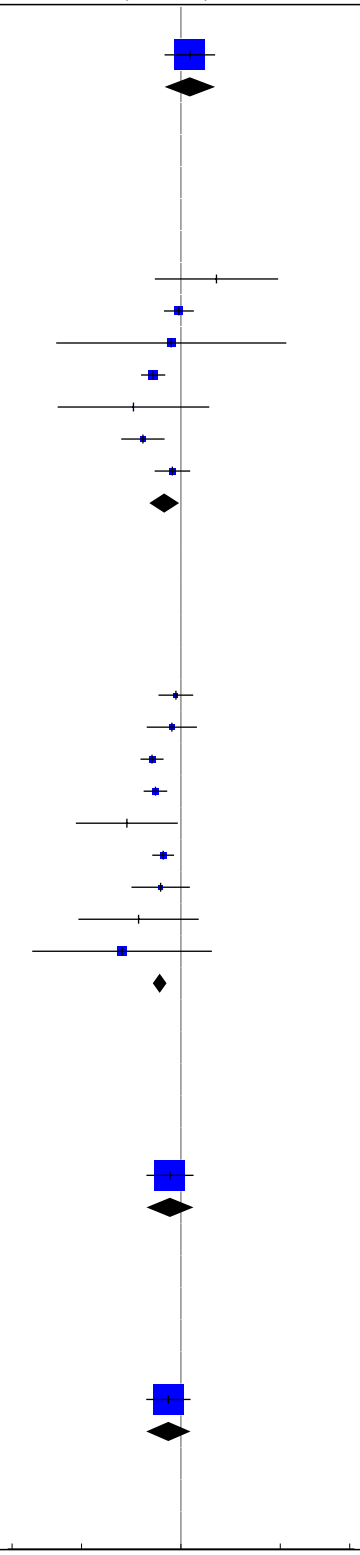


Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
van Duijnhoven 2002	2/11	2/12		0.81%	1.09[0.18,6.48]
Yang 1999	4/30	4/30		1.53%	1[0.28,3.63]
Yu 2000	4/40	9/50		2.08%	0.56[0.18,1.67]
Subtotal (95% CI)	**1028**	**750**		**100%**	**0.68[0.6,0.78]**
Total events: 264 (Tacrolimus), 298 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=6.07, df=9(P=0.73); I^2=0%					
Test for overall effect: Z=5.7(P<0.0001)					
1.2.3 1 year					
Campos 2002	35/84	35/80		9.12%	0.95[0.67,1.36]
Egfjord 2002	10/30	6/30		1.82%	1.67[0.69,4]
Johnson 2000	24/148	15/75		3.91%	0.81[0.45,1.45]
Laskow 1995	30/92	9/28		3.56%	1.01[0.55,1.87]
Margreiter 2002	98/286	154/271		20.65%	0.6[0.5,0.73]
Mayer 1997	98/303	79/145		17.63%	0.59[0.48,0.74]
Miller 2002	4/100	7/50		1.02%	0.29[0.09,0.93]
Morris-Stiff 1998	21/90	33/89		5.89%	0.63[0.4,1]
Pirsch 1997	63/205	96/207		14.91%	0.66[0.51,0.85]
Radermacher 1998	11/33	8/15		2.97%	0.63[0.32,1.23]
Raofi 1999	2/14	8/21		0.74%	0.38[0.09,1.51]
Trompeter 2002	42/103	57/93		12.75%	0.67[0.5,0.88]
Wang 2000	1/25	5/32		0.33%	0.26[0.03,2.05]
White 2000	18/52	18/50		4.7%	0.96[0.57,1.63]
Subtotal (95% CI)	**1565**	**1186**		**100%**	**0.69[0.6,0.79]**
Total events: 457 (Tacrolimus), 530 (Cyclosporin)					
Heterogeneity: Tau^2=0.01; Chi^2=17.85, df=13(P=0.16); I^2=27.17%					
Test for overall effect: Z=5.53(P<0.0001)					
1.2.4 2 years					
Johnson 2000	26/148	17/75		22.07%	0.78[0.45,1.34]
Margreiter 2002	7/223	10/208		7.84%	0.65[0.25,1.68]
Mayer 1997	74/303	67/145		70.09%	0.53[0.41,0.69]
Subtotal (95% CI)	**674**	**428**		**100%**	**0.57[0.46,0.72]**
Total events: 107 (Tacrolimus), 94 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.64, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=4.72(P<0.0001)					
1.2.5 3 years					
Johnson 2000	28/148	19/75		62.08%	0.75[0.45,1.25]
Margreiter 2002	13/217	20/203		37.92%	0.61[0.31,1.19]
Subtotal (95% CI)	**365**	**278**		**100%**	**0.69[0.46,1.04]**
Total events: 41 (Tacrolimus), 39 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.23, df=1(P=0.63); I^2=0%					
Test for overall effect: Z=1.77(P=0.08)					



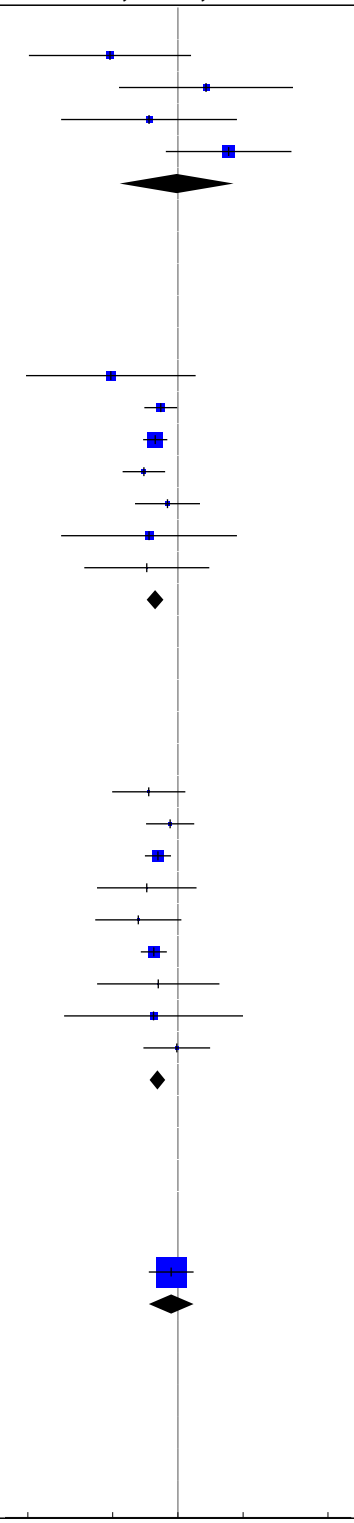
Analysis 1.3. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 3 Acute rejection (biopsy proven).

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 3 months					
Morris-Stiff 1998	16/40	13/40		100%	1.23[0.68,2.21]
Subtotal (95% CI)	**40**	**40**		**100%**	**1.23[0.68,2.21]**
Total events: 16 (Tacrolimus), 13 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
1.3.2 6 months					
Busque 2001	10/46	2/21		3.07%	2.28[0.55,9.52]
Charpentier 2002	75/371	39/184		25.51%	0.95[0.68,1.35]
Liu 2003	1/15	1/12		0.92%	0.8[0.06,11.5]
Margreiter 2002	56/286	101/271		30.03%	0.53[0.4,0.7]
Miller 2002	2/100	3/50		2.07%	0.33[0.06,1.93]
Trompeter 2002	17/103	37/93		16.95%	0.41[0.25,0.68]
Tsinalis 2000	15/26	19/27		21.45%	0.82[0.54,1.24]
Subtotal (95% CI)	**947**	**658**		**100%**	**0.68[0.48,0.96]**
Total events: 176 (Tacrolimus), 202 (Cyclosporin)					
Heterogeneity: Tau^2=0.1; Chi^2=14.83, df=6(P=0.02); I^2=59.53%					
Test for overall effect: Z=2.2(P=0.03)					
1.3.3 1 year					
Campos 2002	29/84	31/80		14.56%	0.89[0.6,1.33]
Johnson 2000	24/148	15/75		9.25%	0.81[0.45,1.45]
Margreiter 2002	60/286	111/271		20.77%	0.51[0.39,0.67]
Mayer 1997	73/303	63/145		20.44%	0.55[0.42,0.73]
Miller 2002	4/100	7/50		2.9%	0.29[0.09,0.93]
Pirsch 1997	63/205	96/207		21.5%	0.66[0.51,0.85]
Radermacher 1998	11/33	8/15		7.43%	0.63[0.32,1.23]
Raofi 1999	2/14	8/21		2.14%	0.38[0.09,1.51]
Wang 2000	1/25	5/32		1%	0.26[0.03,2.05]
Subtotal (95% CI)	**1198**	**896**		**100%**	**0.61[0.52,0.72]**
Total events: 267 (Tacrolimus), 344 (Cyclosporin)					
Heterogeneity: Tau^2=0.01; Chi^2=9.6, df=8(P=0.29); I^2=16.68%					
Test for overall effect: Z=6.06(P<0.0001)					
1.3.4 2 years					
Johnson 2000	26/148	17/75		100%	0.78[0.45,1.34]
Subtotal (95% CI)	**148**	**75**		**100%**	**0.78[0.45,1.34]**
Total events: 26 (Tacrolimus), 17 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.92(P=0.36)					
1.3.5 3 years					
Johnson 2000	28/148	19/75		100%	0.75[0.45,1.25]
Subtotal (95% CI)	**148**	**75**		**100%**	**0.75[0.45,1.25]**
Total events: 28 (Tacrolimus), 19 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.12(P=0.26)					



Analysis 1.4. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 4 Acute rejection (steroid resistant).

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 3 months					
Morris-Stiff 1998	0/40	5/40		22.8%	0.09[0.01,1.59]
Toz 2001	1/9	0/8		19.8%	2.7[0.13,58.24]
van Duijnhoven 2002	0/11	1/12		19.4%	0.36[0.02,8.04]
Weimer 2002	3/28	1/56		38%	6[0.65,55.09]
Subtotal (95% CI)	**88**	**116**		**100%**	**0.96[0.13,7.15]**
Total events: 4 (Tacrolimus), 7 (Cyclosporin)					
Heterogeneity: Tau^2=2.18; Chi^2=6.26, df=3(P=0.1); I^2=52.07%					
Test for overall effect: Z=0.04(P=0.97)					
1.4.2 6 months					
Busque 2001	0/46	2/21		0.98%	0.09[0,1.87]
Charpentier 2002	22/371	20/184		26.06%	0.55[0.31,0.97]
Margreiter 2002	27/286	57/271		48.02%	0.45[0.29,0.69]
Trompeter 2002	8/103	24/93		15.57%	0.3[0.14,0.64]
Tsinalis 2000	4/26	6/27		6.67%	0.69[0.22,2.18]
van Duijnhoven 2002	0/11	1/12		0.91%	0.36[0.02,8.04]
Yang 1999	1/30	3/30		1.8%	0.33[0.04,3.03]
Subtotal (95% CI)	**873**	**638**		**100%**	**0.45[0.33,0.6]**
Total events: 62 (Tacrolimus), 113 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=3.24, df=6(P=0.78); I^2=0%					
Test for overall effect: Z=5.34(P<0.0001)					
1.4.3 1 year					
Campos 2002	3/84	8/80		4.54%	0.36[0.1,1.3]
Johnson 2000	12/148	8/75		10.47%	0.76[0.32,1.78]
Mayer 1997	31/303	30/145		35.58%	0.49[0.31,0.78]
Miller 2002	2/100	3/50		2.45%	0.33[0.06,1.93]
Morris-Stiff 1998	2/90	8/89		3.27%	0.25[0.05,1.13]
Pirsch 1997	22/205	52/207		35.85%	0.43[0.27,0.68]
Raofi 1999	1/14	3/21		1.62%	0.5[0.06,4.33]
Wang 2000	0/25	1/32		0.76%	0.42[0.02,9.96]
White 2000	5/52	5/50		5.46%	0.96[0.3,3.12]
Subtotal (95% CI)	**1021**	**749**		**100%**	**0.49[0.37,0.64]**
Total events: 78 (Tacrolimus), 118 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=3.83, df=8(P=0.87); I^2=0%					
Test for overall effect: Z=5.15(P<0.0001)					
1.4.4 2 years					
Johnson 2000	14/148	9/75		100%	0.79[0.36,1.74]
Subtotal (95% CI)	**148**	**75**		**100%**	**0.79[0.36,1.74]**
Total events: 14 (Tacrolimus), 9 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
1.4.5 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**



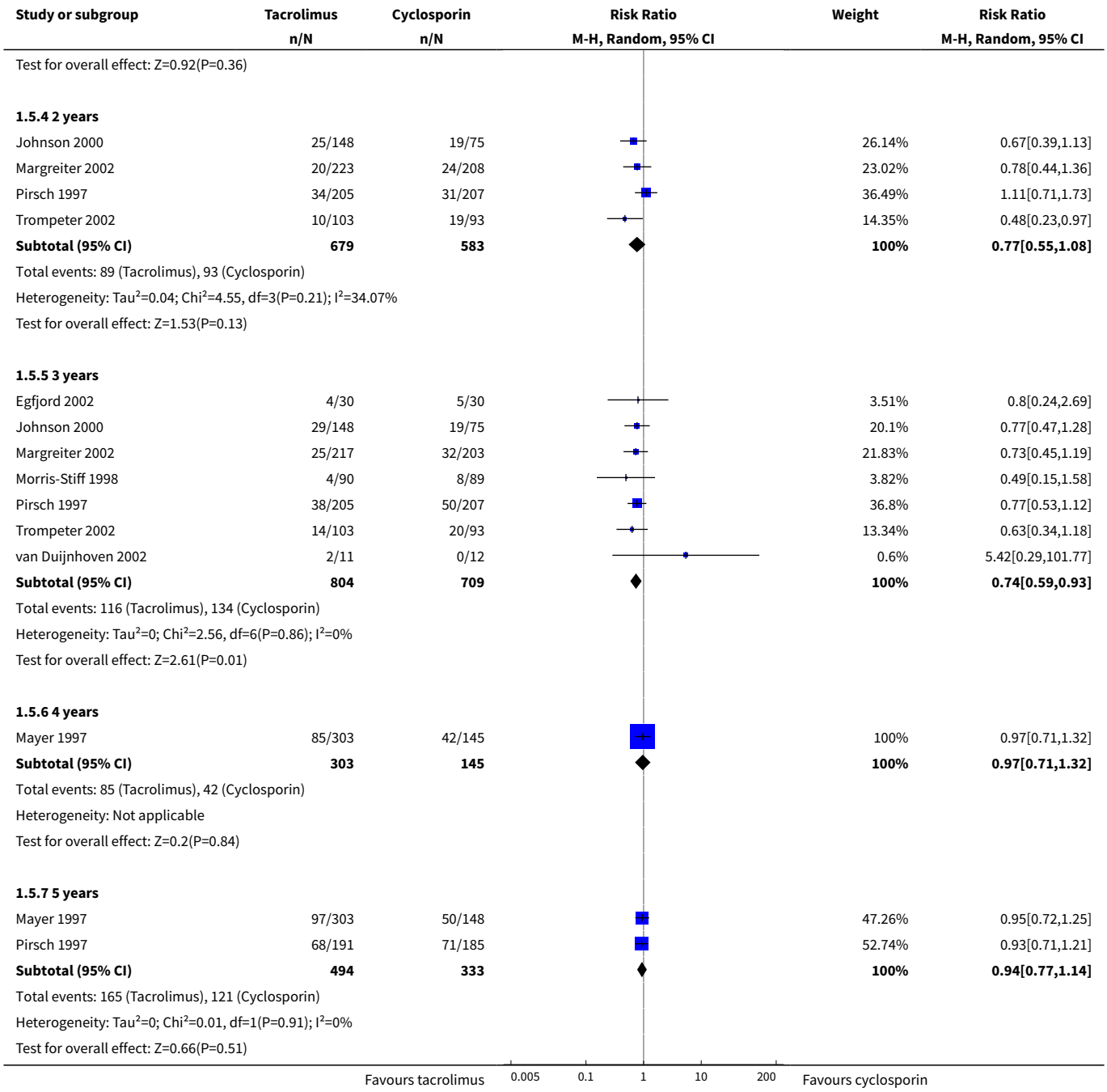
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours tacrolimus 0.005 0.1 1 10 200 Favours cyclosporin

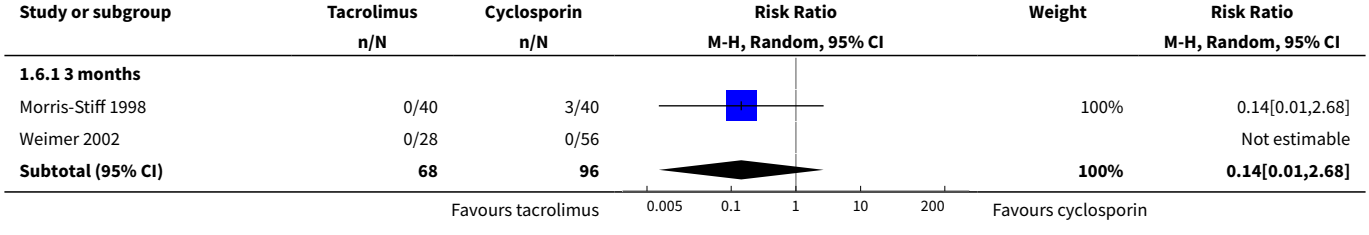
Analysis 1.5. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 5 Total graft loss (with death).

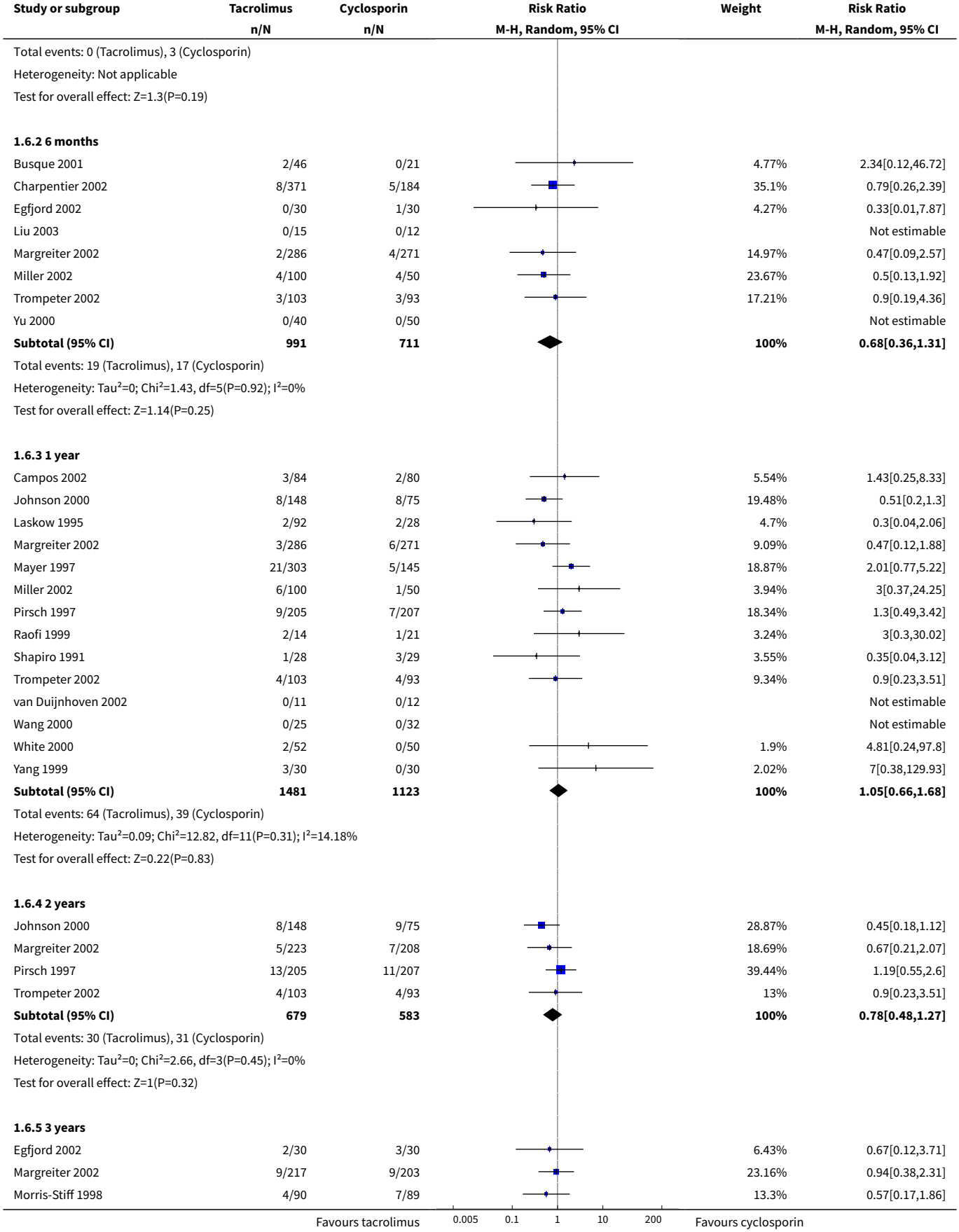
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 3 months					
Morris-Stiff 1998	0/40	6/40		100%	0.08[0,1.32]
Subtotal (95% CI)	**40**	**40**		**100%**	**0.08[0,1.32]**
Total events: 0 (Tacrolimus), 6 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.77(P=0.08)					
1.5.2 6 months					
Busque 2001	2/46	1/21		2.3%	0.91[0.09,9.52]
Charpentier 2002	22/371	17/184		34.16%	0.64[0.35,1.18]
Egfjord 2002	2/30	2/30		3.52%	1[0.15,6.64]
Liu 2003	0/15	1/12		1.3%	0.27[0.01,6.11]
Margreiter 2002	15/286	22/271		31.3%	0.65[0.34,1.22]
Miller 2002	4/100	4/50		6.99%	0.5[0.13,1.92]
Trompeter 2002	8/103	15/93		19.18%	0.48[0.21,1.08]
Yu 2000	0/40	1/50		1.25%	0.41[0.02,9.91]
Subtotal (95% CI)	**991**	**711**		**100%**	**0.6[0.42,0.86]**
Total events: 53 (Tacrolimus), 63 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.16, df=7(P=0.99); I^2=0%					
Test for overall effect: Z=2.8(P=0.01)					
1.5.3 1 year					
Campos 2002	15/84	11/80		10.43%	1.3[0.64,2.66]
Johnson 2000	19/148	8/75		8.81%	1.2[0.55,2.62]
Laskow 1995	6/92	3/28		3.06%	0.61[0.16,2.28]
Margreiter 2002	18/286	24/271		15.42%	0.71[0.39,1.28]
Mayer 1997	53/303	20/145		23.66%	1.27[0.79,2.04]
Miller 2002	7/100	4/50		3.83%	0.88[0.27,2.85]
Pirsch 1997	18/205	25/207		16.17%	0.73[0.41,1.29]
Raofi 1999	2/14	1/21		1.01%	3[0.3,30.02]
Shapiro 1991	3/28	6/29		3.23%	0.52[0.14,1.87]
Trompeter 2002	10/103	17/93		10.03%	0.53[0.26,1.1]
van Duijnhoven 2002	1/11	0/12		0.55%	3.25[0.15,72.36]
Wang 2000	0/25	2/32		0.6%	0.25[0.01,5.06]
White 2000	2/52	5/50		2.1%	0.38[0.08,1.89]
Yang 1999	3/30	1/30		1.1%	3[0.33,27.23]
Subtotal (95% CI)	**1481**	**1123**		**100%**	**0.9[0.71,1.13]**
Total events: 157 (Tacrolimus), 127 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=12.39, df=13(P=0.5); I^2=0%					

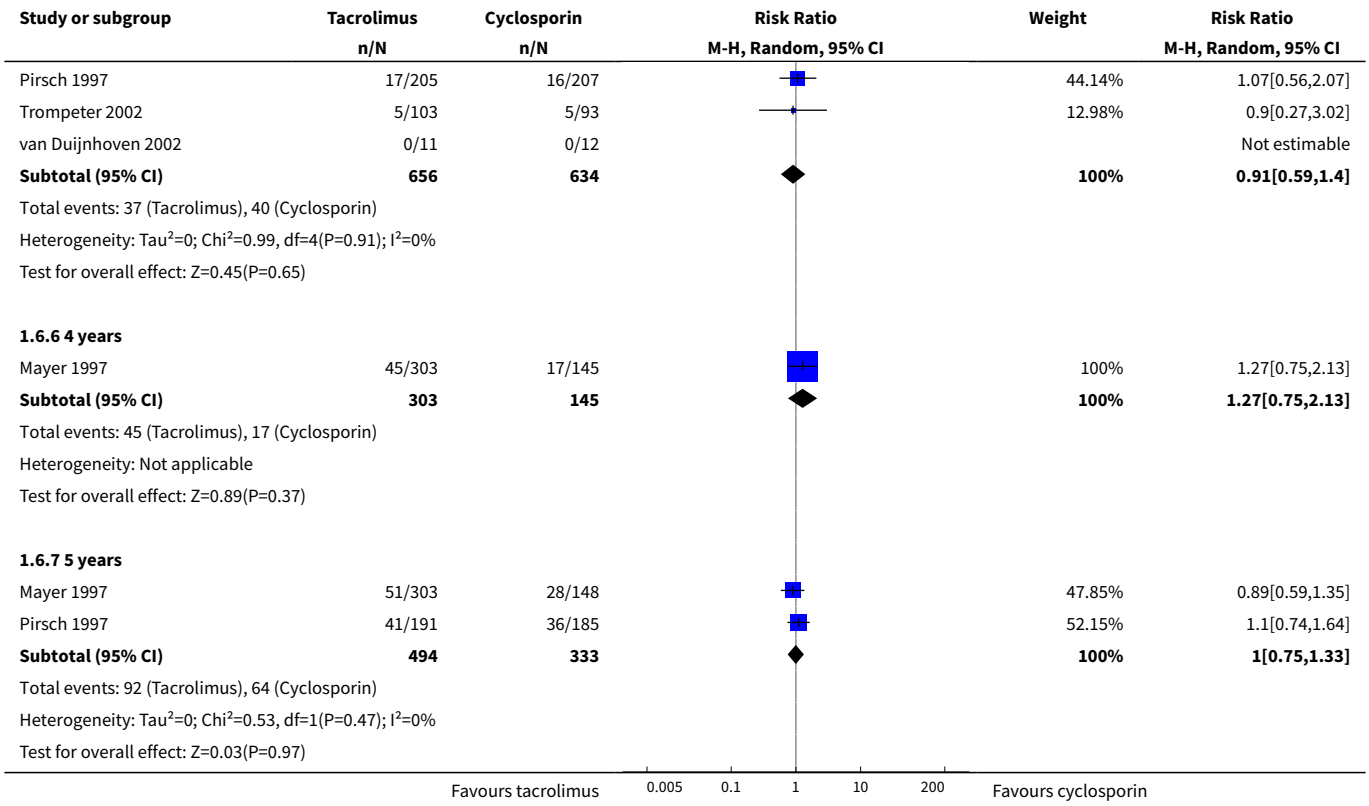
Favours tacrolimus 0.005 0.1 1 10 200 Favours cyclosporin



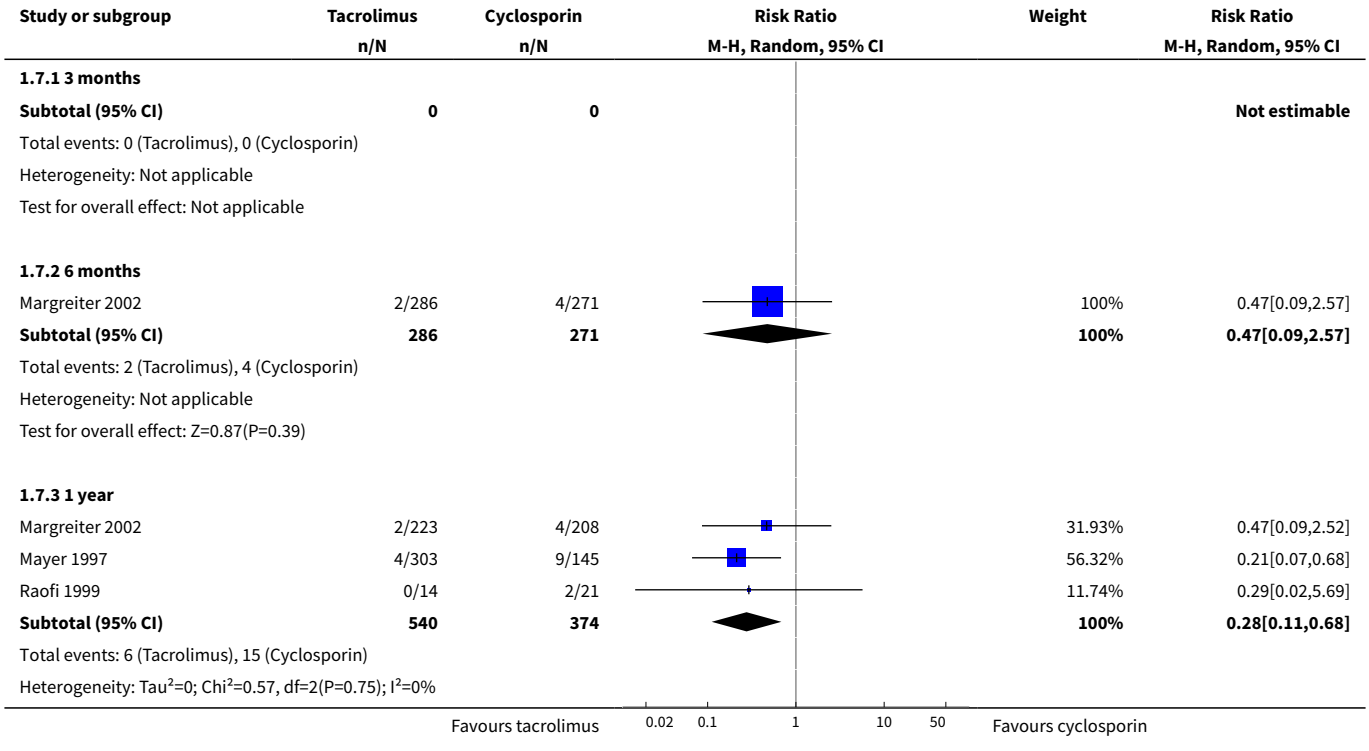
Analysis 1.6. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 6 Mortality.

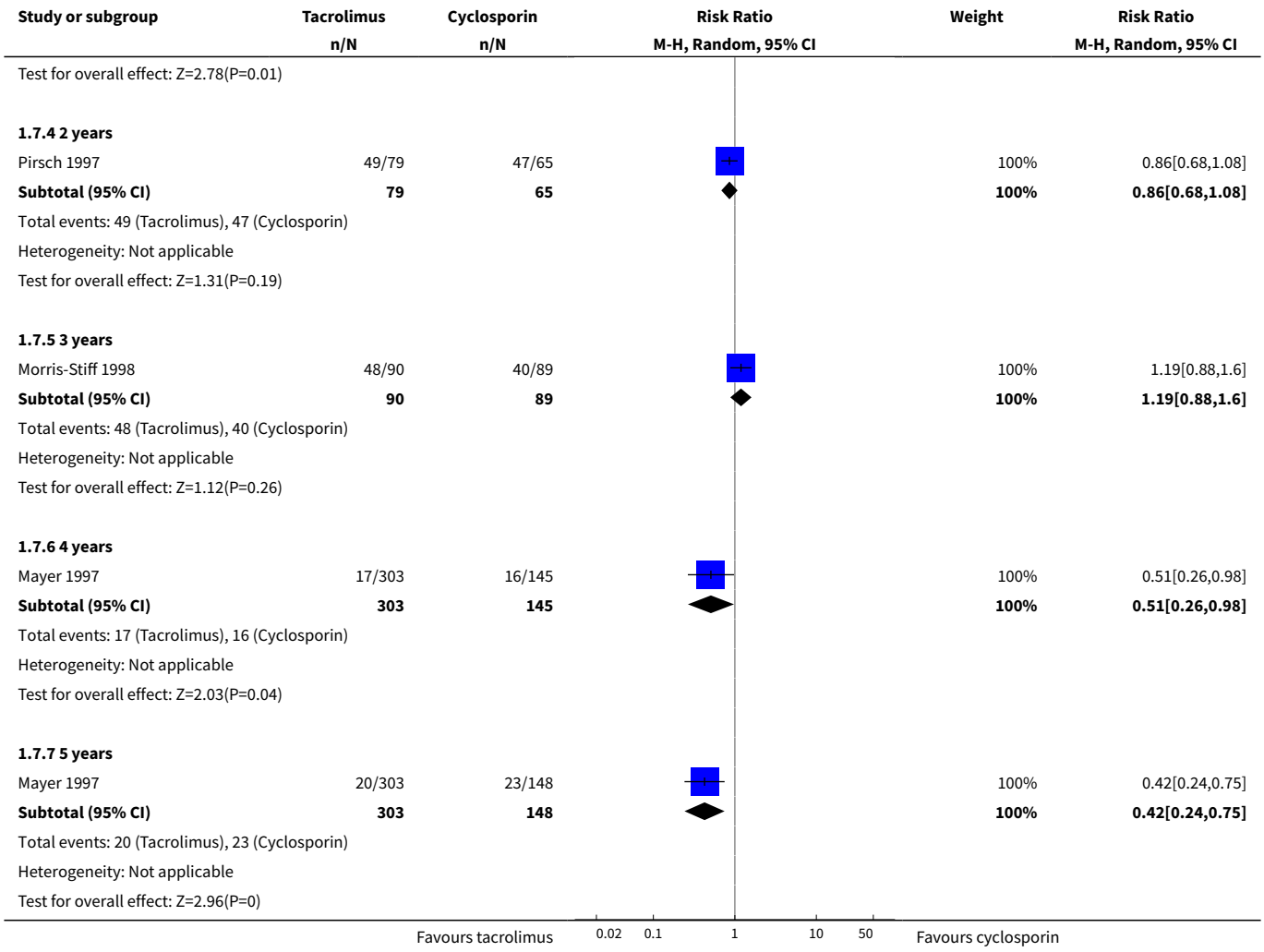




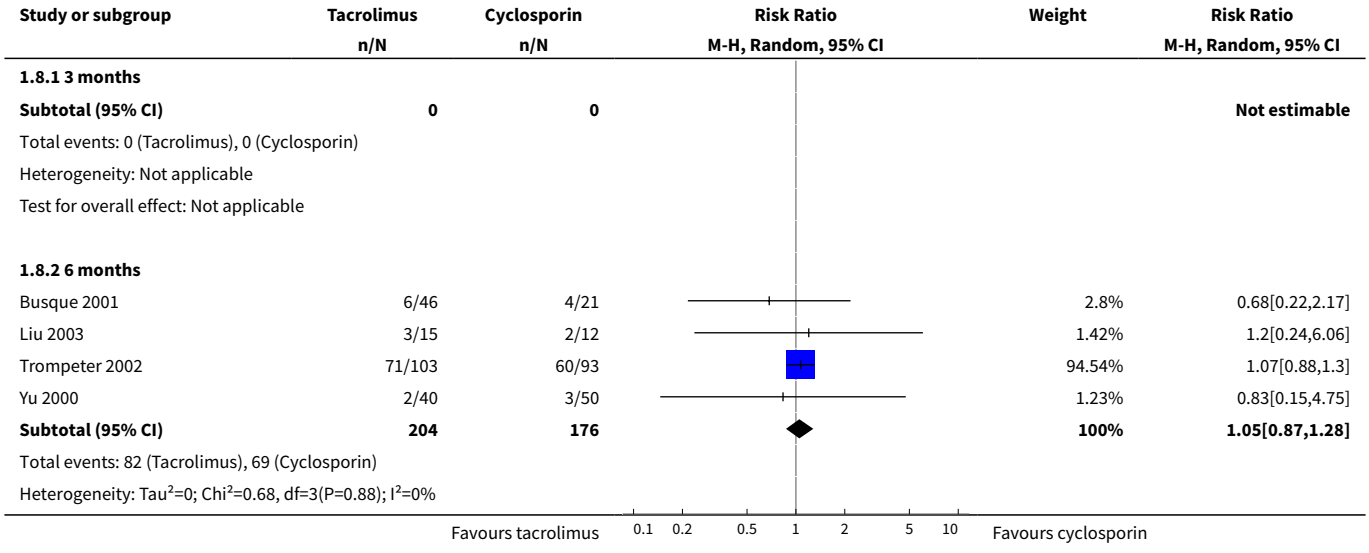


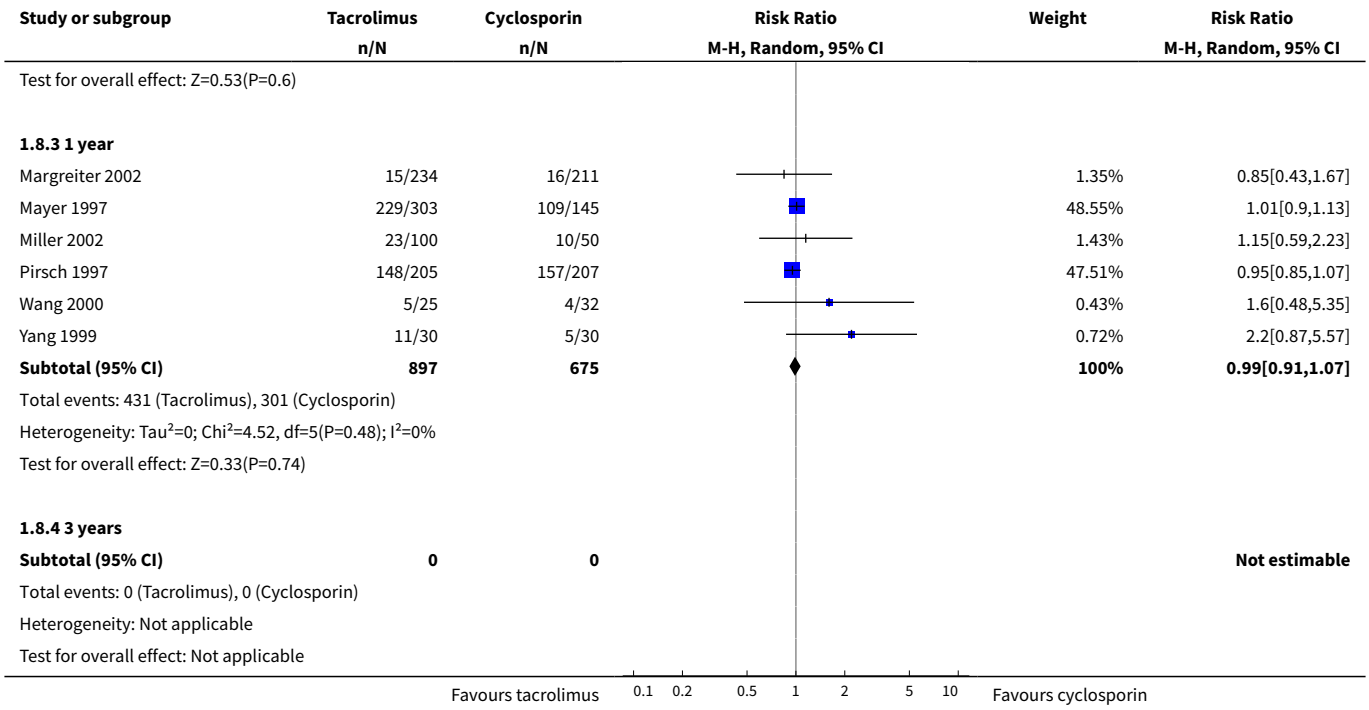
Analysis 1.7. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 7 Chronic allograft nephropathy (CAN).



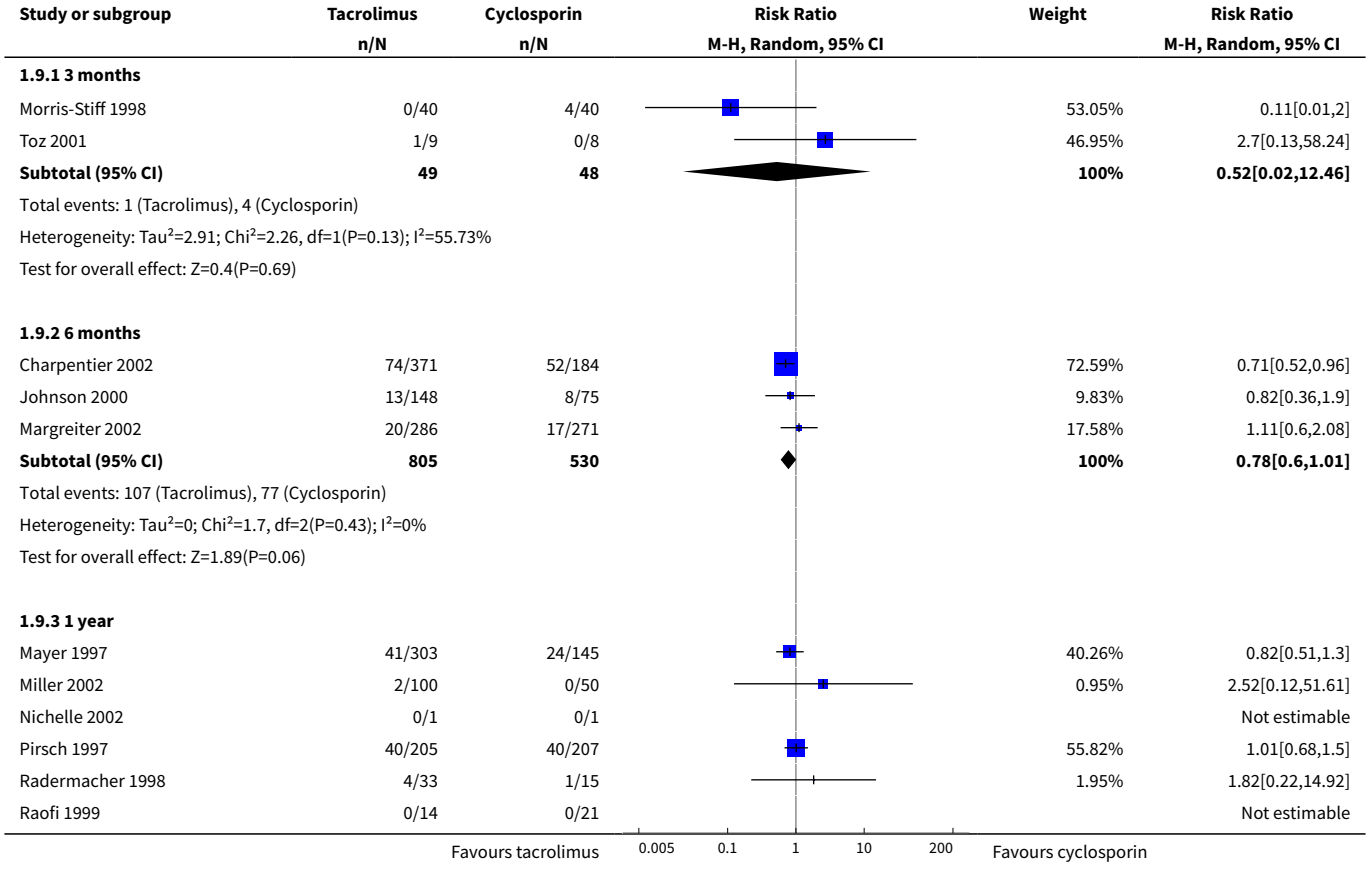


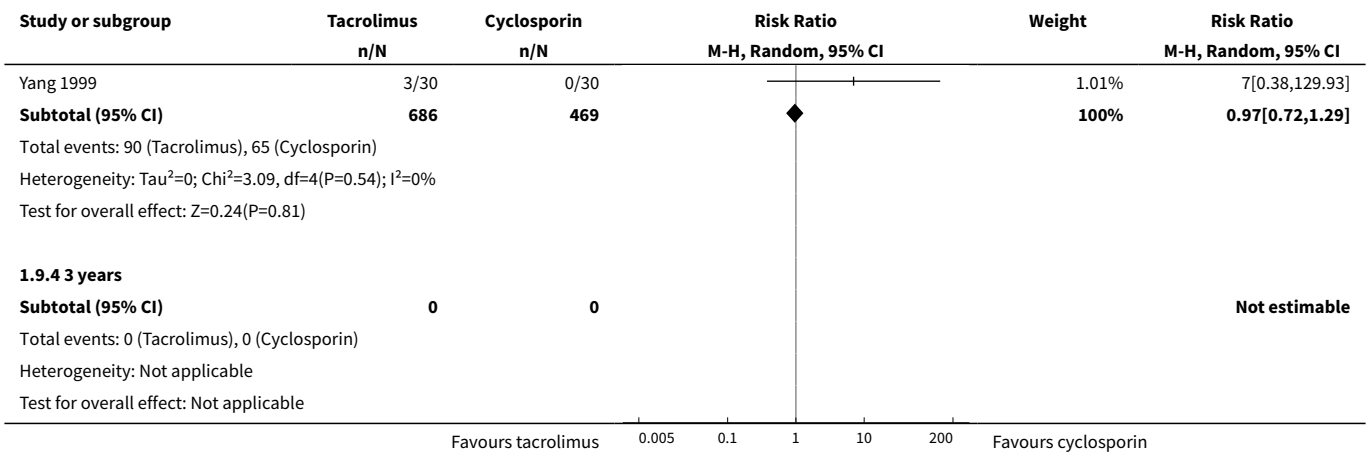
Analysis 1.8. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 8 Total infection.



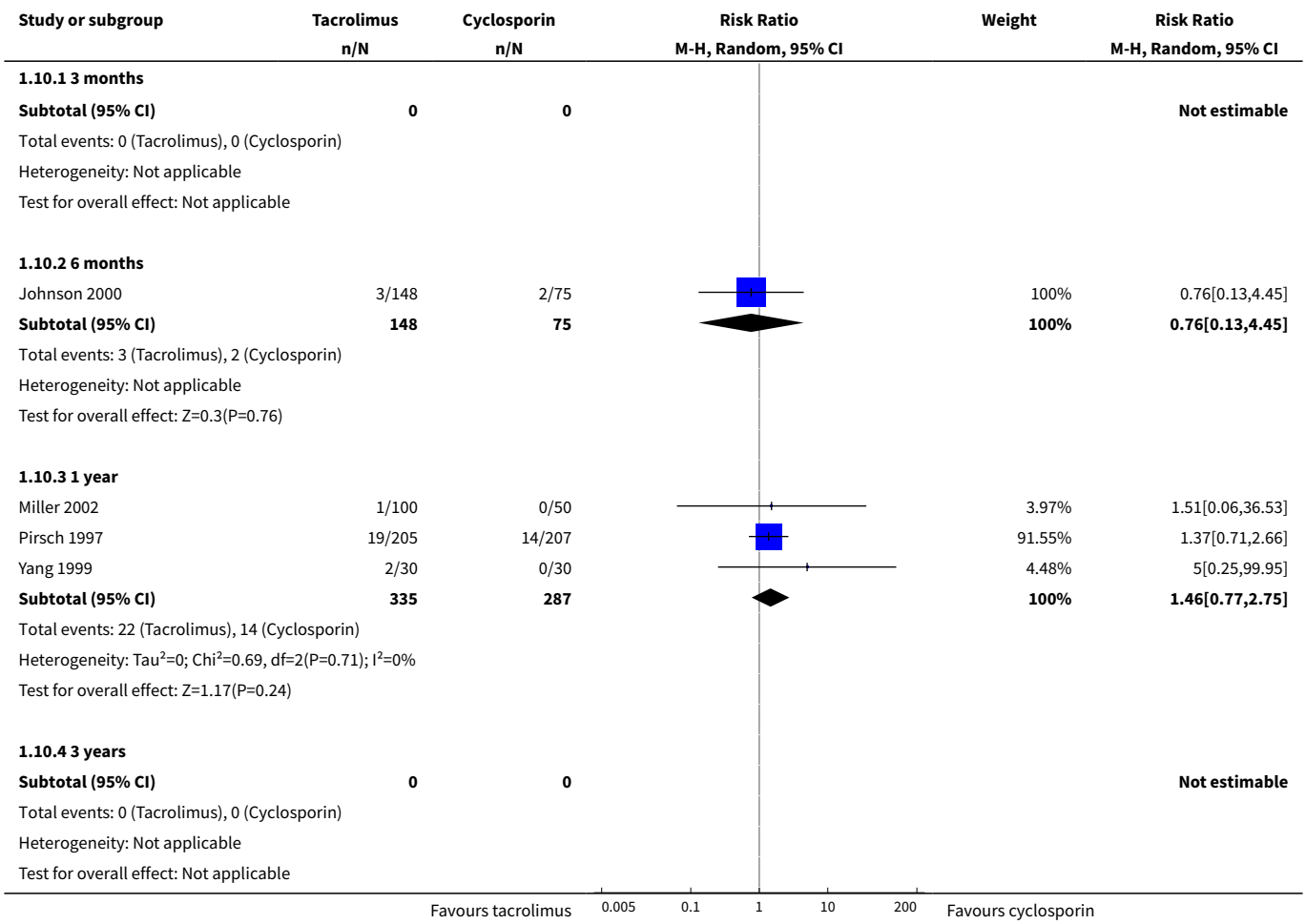


Analysis 1.9. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 9 Total CMV infection.



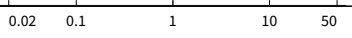


Analysis 1.10. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 10 Invasive CMV infection.



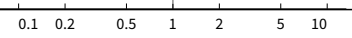
Analysis 1.11. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 11 Delayed graft function.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Requirement for dialysis within 1st week post-transplantation					
Busque 2001	10/46	4/21		7.01%	1.14[0.4,3.22]
Johnson 2000	38/148	17/75		14.51%	1.13[0.69,1.87]
Margreiter 2002	58/286	73/271		18.25%	0.75[0.56,1.02]
Mayer 1997	116/303	119/145		20.41%	0.47[0.4,0.55]
Morris-Stiff 1998	5/40	7/40		6.82%	0.71[0.25,2.06]
Raofi 1999	1/14	1/21		1.45%	1.5[0.1,22.05]
Trompeter 2002	15/103	15/93		11.73%	0.9[0.47,1.74]
White 2000	8/11	9/11		15.33%	0.89[0.56,1.4]
Yang 1999	4/30	3/30		4.48%	1.33[0.33,5.45]
Subtotal (95% CI)	**981**	**707**		**100%**	**0.81[0.58,1.13]**
Total events: 255 (Tacrolimus), 248 (Cyclosporin)					
Heterogeneity: Tau^2=0.14; Chi^2=27.3, df=8(P=0); I^2=70.7%					
Test for overall effect: Z=1.25(P=0.21)					
Total (95% CI)	**981**	**707**		**100%**	**0.81[0.58,1.13]**
Total events: 255 (Tacrolimus), 248 (Cyclosporin)					
Heterogeneity: Tau^2=0.14; Chi^2=27.3, df=8(P=0); I^2=70.7%					
Test for overall effect: Z=1.25(P=0.21)					



Analysis 1.12. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 12 Hypercholesterolaemia.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.12.2 6 months					
Charpentier 2002	8/371	12/184		37.05%	0.33[0.14,0.79]
Margreiter 2002	12/286	24/271		62.95%	0.47[0.24,0.93]
Subtotal (95% CI)	**657**	**455**		**100%**	**0.41[0.24,0.71]**
Total events: 20 (Tacrolimus), 36 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=3.23(P=0)					
1.12.3 1 year					
Pirsch 1997	16/205	30/207		100%	0.54[0.3,0.96]
Subtotal (95% CI)	**205**	**207**		**100%**	**0.54[0.3,0.96]**
Total events: 16 (Tacrolimus), 30 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.11(P=0.03)					
1.12.4 3 years					



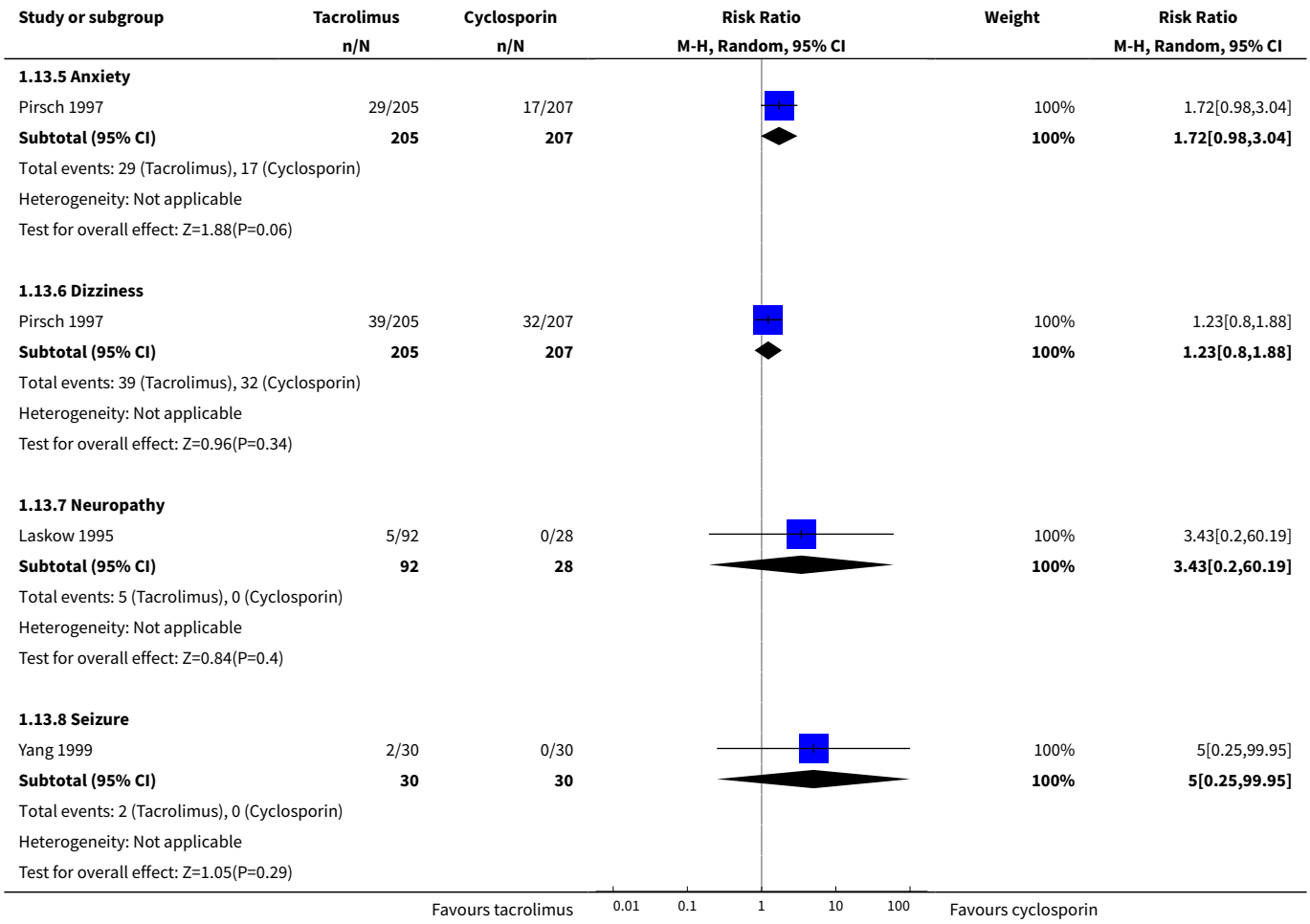
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours tacrolimus 0.1 0.2 0.5 1 2 5 10 Favours cyclosporin

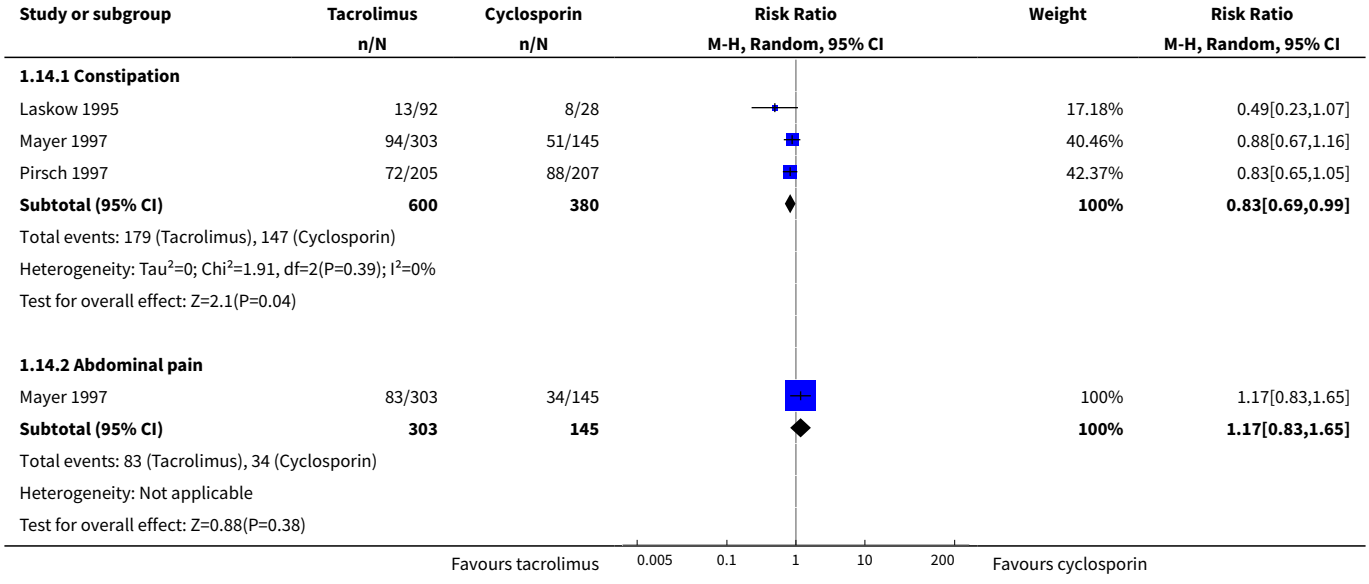
Analysis 1.13. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 13 Neurological side effects.

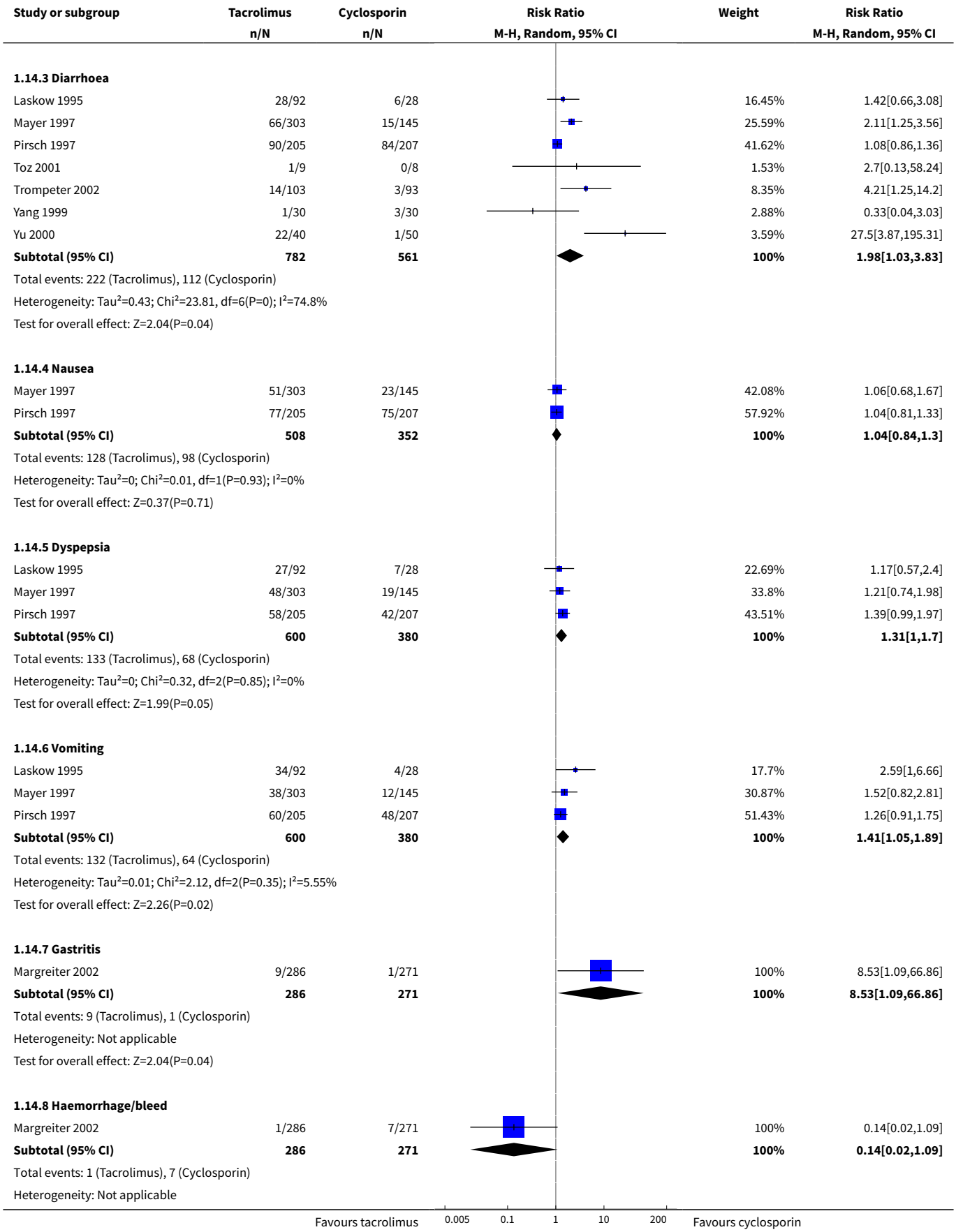
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 tremor					
Charpentier 2002	29/371	5/184		10.15%	2.88[1.13,7.31]
Laskow 1995	15/92	4/28		8.82%	1.14[0.41,3.16]
Margreiter 2002	35/286	11/271		16.72%	3.01[1.56,5.81]
Mayer 1997	105/303	17/145		24.12%	2.96[1.84,4.74]
Pirsch 1997	111/205	70/207		37.97%	1.6[1.27,2.01]
Yang 1999	3/30	1/30		2.22%	3[0.33,27.23]
Subtotal (95% CI)	**1287**	**865**		**100%**	**2.18[1.5,3.17]**
Total events: 298 (Tacrolimus), 108 (Cyclosporin)					
Heterogeneity: Tau^2=0.09; Chi^2=10.12, df=5(P=0.07); I^2=50.57%					
Test for overall effect: Z=4.09(P<0.0001)					
1.13.2 Insomnia					
Laskow 1995	15/92	2/28		7.14%	2.28[0.56,9.38]
Mayer 1997	72/303	38/145		44.32%	0.91[0.65,1.27]
Pirsch 1997	66/205	61/207		48.54%	1.09[0.82,1.46]
Subtotal (95% CI)	**600**	**380**		**100%**	**1.03[0.83,1.28]**
Total events: 153 (Tacrolimus), 101 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=0.26(P=0.79)					
1.13.3 Headache					
Laskow 1995	8/92	1/28		3.98%	2.43[0.32,18.64]
Mayer 1997	62/303	20/145		37.91%	1.48[0.93,2.36]
Pirsch 1997	90/205	78/207		58.11%	1.17[0.92,1.47]
Subtotal (95% CI)	**600**	**380**		**100%**	**1.23[1,1.52]**
Total events: 160 (Tacrolimus), 99 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.33, df=2(P=0.52); I^2=0%					
Test for overall effect: Z=1.97(P=0.05)					
1.13.4 Paraesthesia					
Laskow 1995	10/92	0/28		4.79%	6.55[0.4,108.36]
Pirsch 1997	48/205	32/207		95.21%	1.51[1.01,2.27]
Subtotal (95% CI)	**297**	**235**		**100%**	**1.64[0.85,3.16]**
Total events: 58 (Tacrolimus), 32 (Cyclosporin)					
Heterogeneity: Tau^2=0.08; Chi^2=1.07, df=1(P=0.3); I^2=6.85%					
Test for overall effect: Z=1.47(P=0.14)					

Favours tacrolimus 0.01 0.1 1 10 100 Favours cyclosporin



Analysis 1.14. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 14 Gastrointestinal side effects.





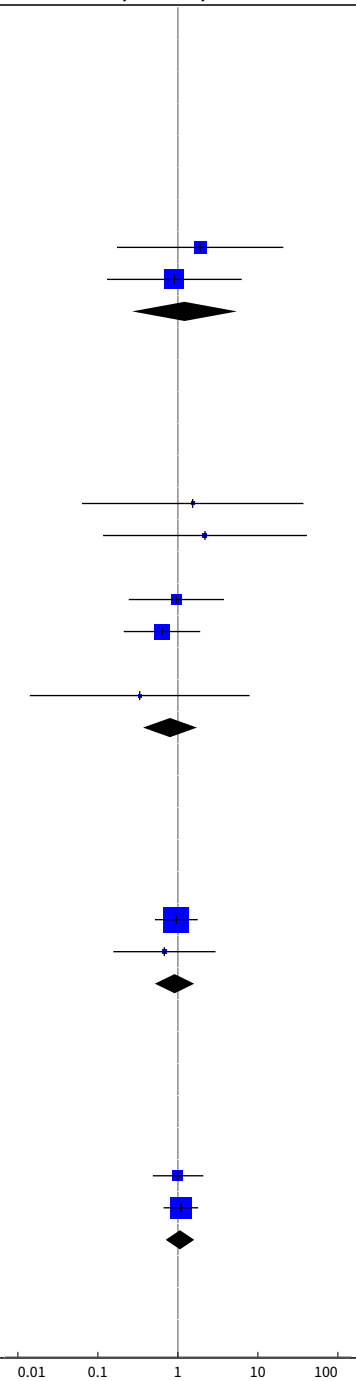
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.88(P=0.06)					

Favours tacrolimus

Favours cyclosporin

Analysis 1.15. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 15 Total malignancy.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.15.2 6 months					
Margreiter 2002	2/286	1/271		39.62%	1.9[0.17,20.78]
Trompeter 2002	2/103	2/93		60.38%	0.9[0.13,6.28]
Subtotal (95% CI)	**389**	**364**		**100%**	**1.21[0.27,5.47]**
Total events: 4 (Tacrolimus), 3 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.22, df=1(P=0.64); I^2=0%					
Test for overall effect: Z=0.25(P=0.8)					
1.15.3 1 year					
Johnson 2000	1/148	0/75		5.88%	1.53[0.06,37.12]
Laskow 1995	3/92	0/28		6.95%	2.18[0.12,41.03]
Margreiter 2002	0/234	0/211			Not estimable
Mayer 1997	6/303	3/145		31.79%	0.96[0.24,3.77]
Pirsch 1997	5/205	8/207		49.39%	0.63[0.21,1.9]
Wang 2000	0/25	0/32			Not estimable
Yang 1999	0/30	1/30		5.98%	0.33[0.01,7.87]
Subtotal (95% CI)	**1037**	**728**		**100%**	**0.8[0.37,1.73]**
Total events: 15 (Tacrolimus), 12 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.15, df=4(P=0.89); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					
1.15.4 3 years					
Pirsch 1997	18/205	19/207		85.11%	0.96[0.52,1.77]
Trompeter 2002	3/103	4/93		14.89%	0.68[0.16,2.95]
Subtotal (95% CI)	**308**	**300**		**100%**	**0.91[0.52,1.6]**
Total events: 21 (Tacrolimus), 23 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					
1.15.5 5 years					
Mayer 1997	21/303	10/145		31.93%	1[0.49,2.08]
Pirsch 1997	28/205	26/207		68.07%	1.09[0.66,1.79]
Subtotal (95% CI)	**508**	**352**		**100%**	**1.06[0.7,1.6]**
Total events: 49 (Tacrolimus), 36 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=0.28(P=0.78)					



Favours tacrolimus

Favours cyclosporin

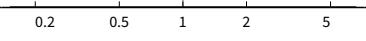
Analysis 1.16. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 16 de novo hypertension.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.16.2 6 months					
Margreiter 2002	45/286	63/271		40.6%	0.68[0.48,0.96]
Trompeter 2002	71/103	57/93		59.4%	1.12[0.91,1.38]
Subtotal (95% CI)	**389**	**364**		**100%**	**0.89[0.52,1.52]**
Total events: 116 (Tacrolimus), 120 (Cyclosporin)					
Heterogeneity: Tau^2=0.13; Chi^2=7.27, df=1(P=0.01); I^2=86.25%					
Test for overall effect: Z=0.43(P=0.66)					
1.16.3 1 year					
Campos 2002	20/84	9/80		11.61%	2.12[1.03,4.37]
Mayer 1997	111/303	56/145		40.56%	0.95[0.74,1.22]
Pirsch 1997	102/205	108/207		47.83%	0.95[0.79,1.15]
Subtotal (95% CI)	**592**	**432**		**100%**	**1.04[0.8,1.36]**
Total events: 233 (Tacrolimus), 173 (Cyclosporin)					
Heterogeneity: Tau^2=0.03; Chi^2=4.57, df=2(P=0.1); I^2=56.23%					
Test for overall effect: Z=0.29(P=0.77)					
1.16.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 1.17. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 17 Bacterial infection.

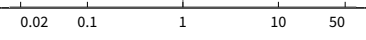
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.17.2 6 months					
Trompeter 2002	43/103	38/93		100%	1.02[0.73,1.43]
Subtotal (95% CI)	**103**	**93**		**100%**	**1.02[0.73,1.43]**
Total events: 43 (Tacrolimus), 38 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.13(P=0.9)					

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.3 1 year					
Mayer 1997	132/303	77/145		90.03%	0.82[0.67,1]
Pirsch 1997	15/205	16/207		7.81%	0.95[0.48,1.86]
Yang 1999	4/30	4/30		2.15%	1[0.28,3.63]
Subtotal (95% CI)	**538**	**382**		**100%**	**0.83[0.69,1.01]**
Total events: 151 (Tacrolimus), 97 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=2(P=0.88); I^2=0%					
Test for overall effect: Z=1.89(P=0.06)					
1.17.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

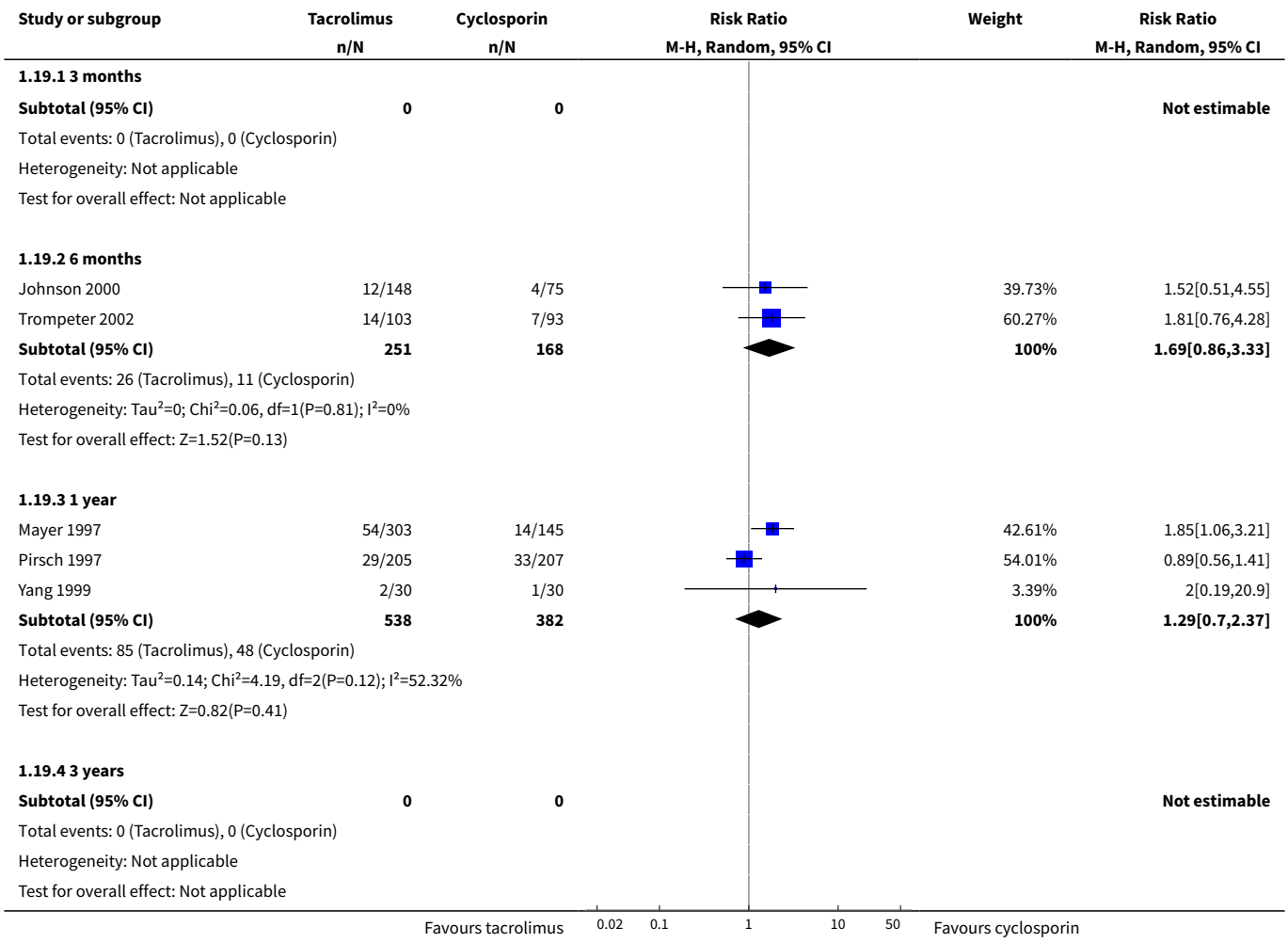


Analysis 1.18. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 18 Viral infection.

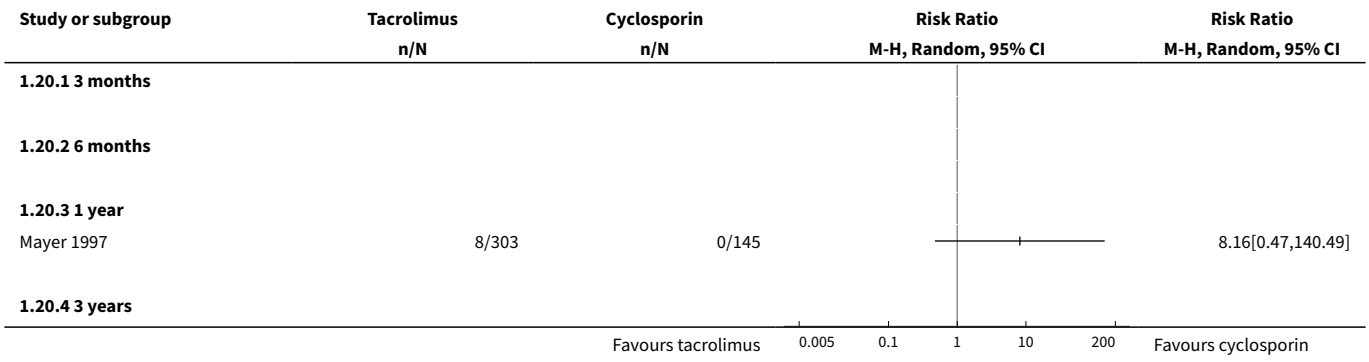
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 3 months					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.18.2 6 months					
Trompeter 2002	23/103	23/93		100%	0.9[0.54,1.5]
Subtotal (95% CI)	**103**	**93**		**100%**	**0.9[0.54,1.5]**
Total events: 23 (Tacrolimus), 23 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
1.18.3 1 year					
Mayer 1997	81/303	39/145		48.4%	0.99[0.72,1.38]
Pirsch 1997	55/205	55/207		50.46%	1.01[0.73,1.39]
Yang 1999	4/30	1/30		1.14%	4[0.47,33.73]
Subtotal (95% CI)	**538**	**382**		**100%**	**1.02[0.81,1.28]**
Total events: 140 (Tacrolimus), 95 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.62, df=2(P=0.45); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					
1.18.4 3 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Tacrolimus), 0 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 1.19. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 19 Fungal infection.

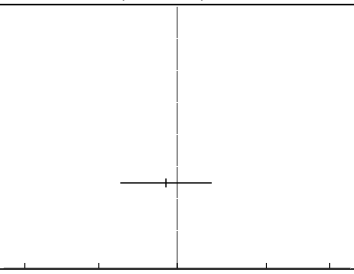


Analysis 1.20. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 20 Protozoal infection.



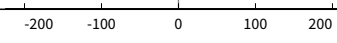
Analysis 1.21. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 21 Other unclassifiable infection.

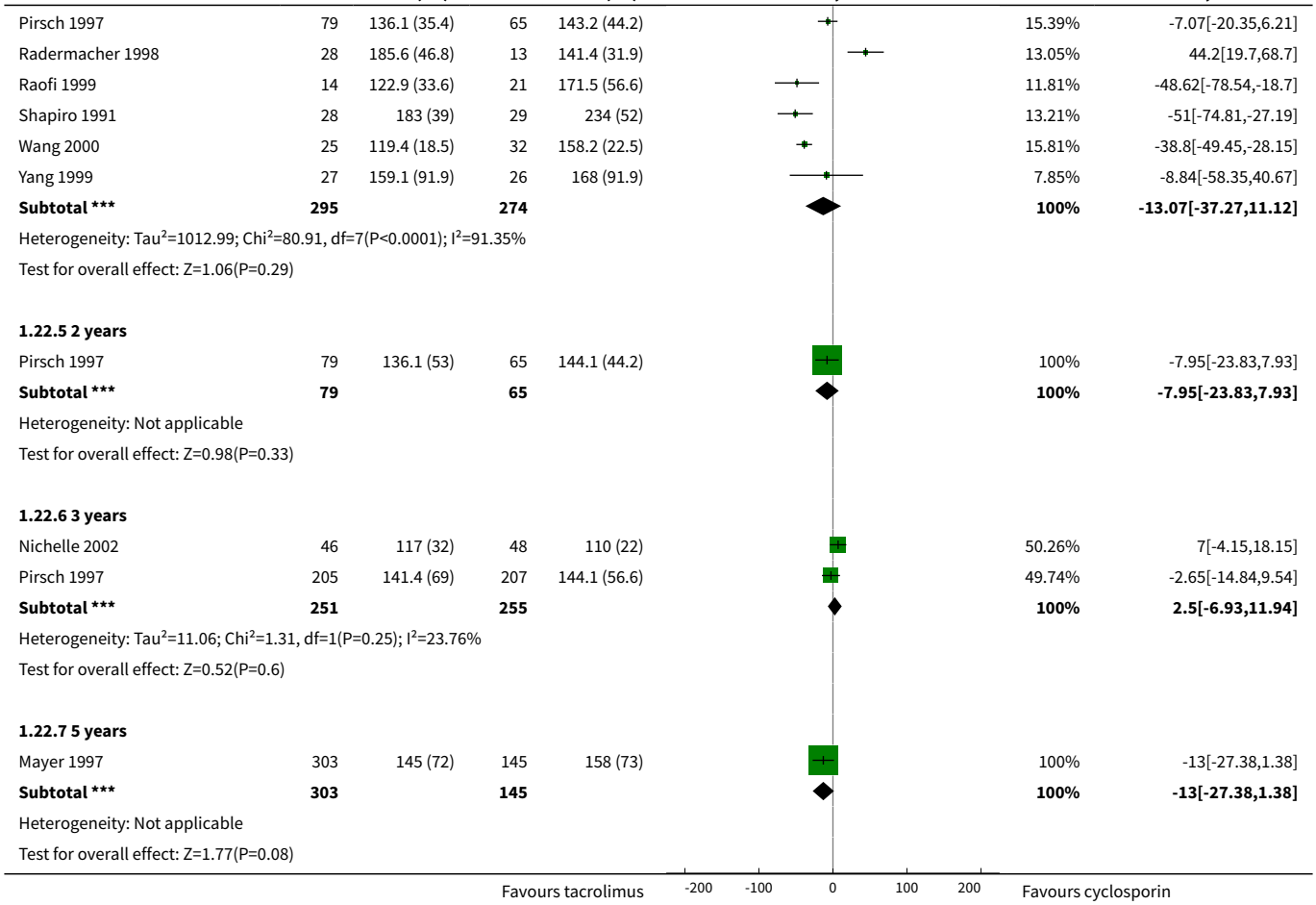
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.21.1 3 months				
1.21.2 6 months				
1.21.3 1 year				
Mayer 1997	139/303	70/145		0.95[0.77,1.17]
1.21.4 3 years				



Analysis 1.22. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 22 Serum creatinine µmol/L.

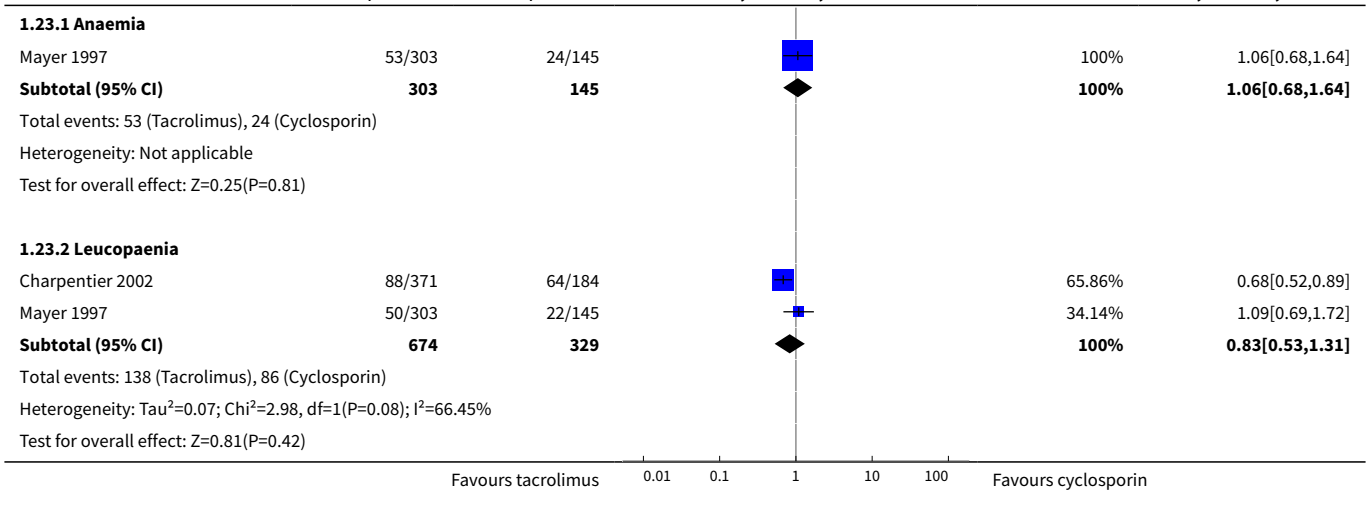
Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Cyclosporin N	Cyclosporin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.22.1 1 month							
Ichimaru 2001	17	141.4 (53)	15	132.6 (53)		45.38%	8.84[-27.99,45.67]
Raofi 1999	14	14.6 (38.9)	21	150.3 (43.2)		54.62%	-135.73[-163.24,-108.22]
Subtotal ***	**31**		**36**			**100%**	**-63.98[-205.66,77.69]**
Heterogeneity: Tau^2=10175.21; Chi^2=38, df=1(P<0.0001); I^2=97.37%							
Test for overall effect: Z=0.89(P=0.38)							
1.22.2 3 months							
Liu 2003	15	110.8 (4.6)	11	117.5 (10.9)		36.61%	-6.7[-13.55,0.15]
Nichelle 2002	46	147 (43)	48	121 (32)		33.75%	26[10.63,41.37]
Toz 2001	9	106.1 (26.5)	8	123.8 (23.9)		29.63%	-17.68[-41.63,6.27]
Subtotal ***	**70**		**67**			**100%**	**1.26[-22.52,25.04]**
Heterogeneity: Tau^2=374.04; Chi^2=16.19, df=2(P=0); I^2=87.64%							
Test for overall effect: Z=0.1(P=0.92)							
1.22.3 6 months							
Heering 1998	8	141.4 (100)	8	132.6 (100)		4.06%	8.84[-89.17,106.85]
Margreiter 2002	284	139 (50.2)	267	147 (86.5)		20.54%	-8[-19.91,3.91]
Miller 2002	48	122.9 (123.8)	47	137.9 (123.8)		10.26%	-15.02[-64.8,34.76]
Pirsch 1997	79	142.3 (44.2)	65	144.1 (35.4)		20.3%	-1.77[-14.77,11.23]
Radermacher 1998	28	291.7 (46.8)	13	362.4 (63.8)		12.97%	-70.72[-109.46,-31.98]
Raofi 1999	12	129.1 (32.2)	20	162.7 (61.9)		14.7%	-33.59[-66.25,-0.93]
Yang 1999	30	132.6 (48.4)	30	141.4 (48.4)		17.16%	-8.84[-33.34,15.66]
Subtotal ***	**489**		**450**			**100%**	**-15.88[-30.3,-1.46]**
Heterogeneity: Tau^2=165.66; Chi^2=13.28, df=6(P=0.04); I^2=54.81%							
Test for overall effect: Z=2.16(P=0.03)							
1.22.4 1 year							
Miller 2002	48	130.8 (114.9)	45	149.4 (132.6)		7.67%	-18.57[-69.15,32.01]
Nichelle 2002	46	139 (35)	43	118 (34)		15.21%	21[6.66,35.34]



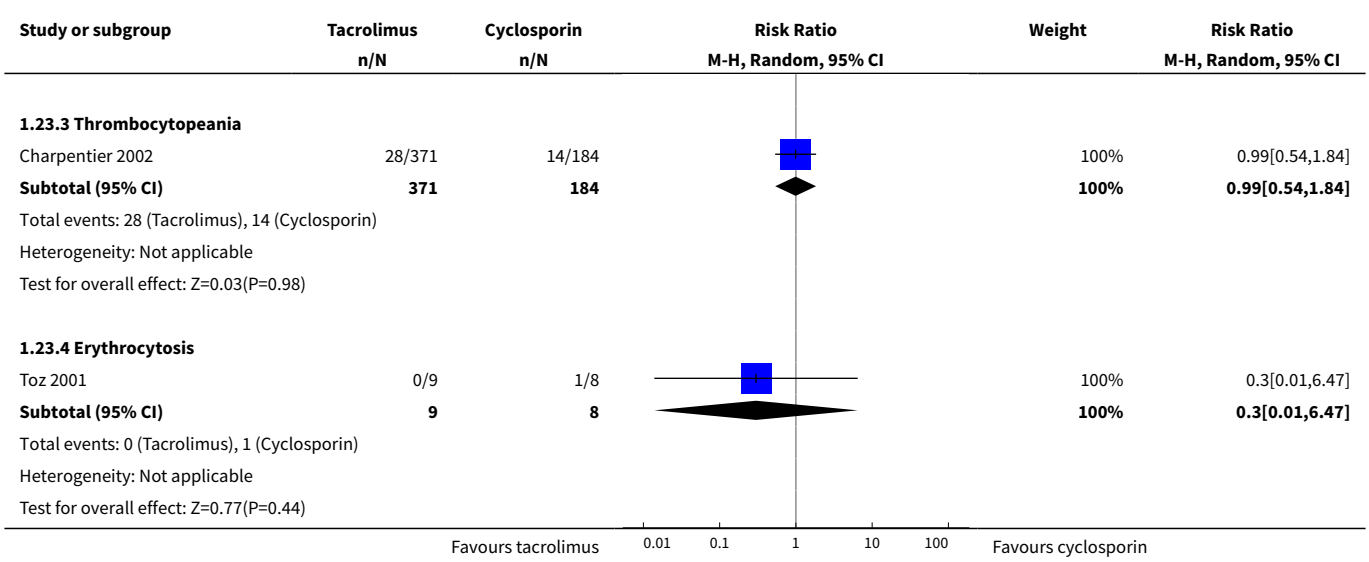


Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Cyclosporin N	Cyclosporin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Pirsch 1997	79	136.1 (35.4)	65	143.2 (44.2)		15.39%	-7.07[-20.35,6.21]
Radermacher 1998	28	185.6 (46.8)	13	141.4 (31.9)		13.05%	44.2[19.7,68.7]
Raofi 1999	14	122.9 (33.6)	21	171.5 (56.6)		11.81%	-48.62[-78.54,-18.7]
Shapiro 1991	28	183 (39)	29	234 (52)		13.21%	-51[-74.81,-27.19]
Wang 2000	25	119.4 (18.5)	32	158.2 (22.5)		15.81%	-38.8[-49.45,-28.15]
Yang 1999	27	159.1 (91.9)	26	168 (91.9)		7.85%	-8.84[-58.35,40.67]
Subtotal * **	**295**		**274**			**100%**	**-13.07[-37.27,11.12]**
Heterogeneity: Tau²=1012.99; Chi²=80.91, df=7(P<0.0001); I²=91.35%							
Test for overall effect: Z=1.06(P=0.29)							
1.22.5 2 years							
Pirsch 1997	79	136.1 (53)	65	144.1 (44.2)		100%	-7.95[-23.83,7.93]
Subtotal * **	**79**		**65**			**100%**	**-7.95[-23.83,7.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.98(P=0.33)							
1.22.6 3 years							
Nichelle 2002	46	117 (32)	48	110 (22)		50.26%	7[-4.15,18.15]
Pirsch 1997	205	141.4 (69)	207	144.1 (56.6)		49.74%	-2.65[-14.84,9.54]
Subtotal * **	**251**		**255**			**100%**	**2.5[-6.93,11.94]**
Heterogeneity: Tau²=11.06; Chi²=1.31, df=1(P=0.25); I²=23.76%							
Test for overall effect: Z=0.52(P=0.6)							
1.22.7 5 years							
Mayer 1997	303	145 (72)	145	158 (73)		100%	-13[-27.38,1.38]
Subtotal * **	**303**		**145**			**100%**	**-13[-27.38,1.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.77(P=0.08)							

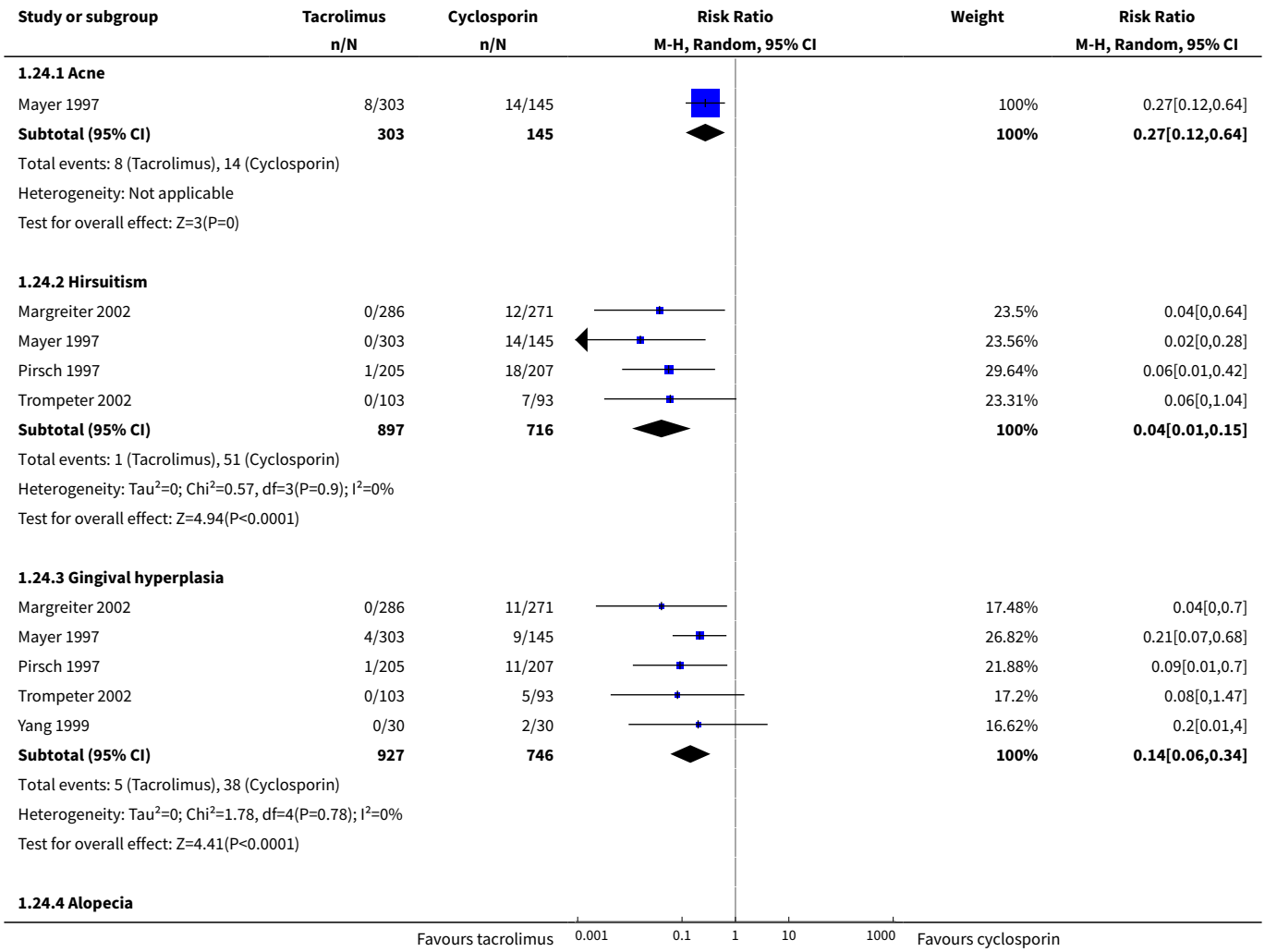
Analysis 1.23. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 23 Haematological side effects.

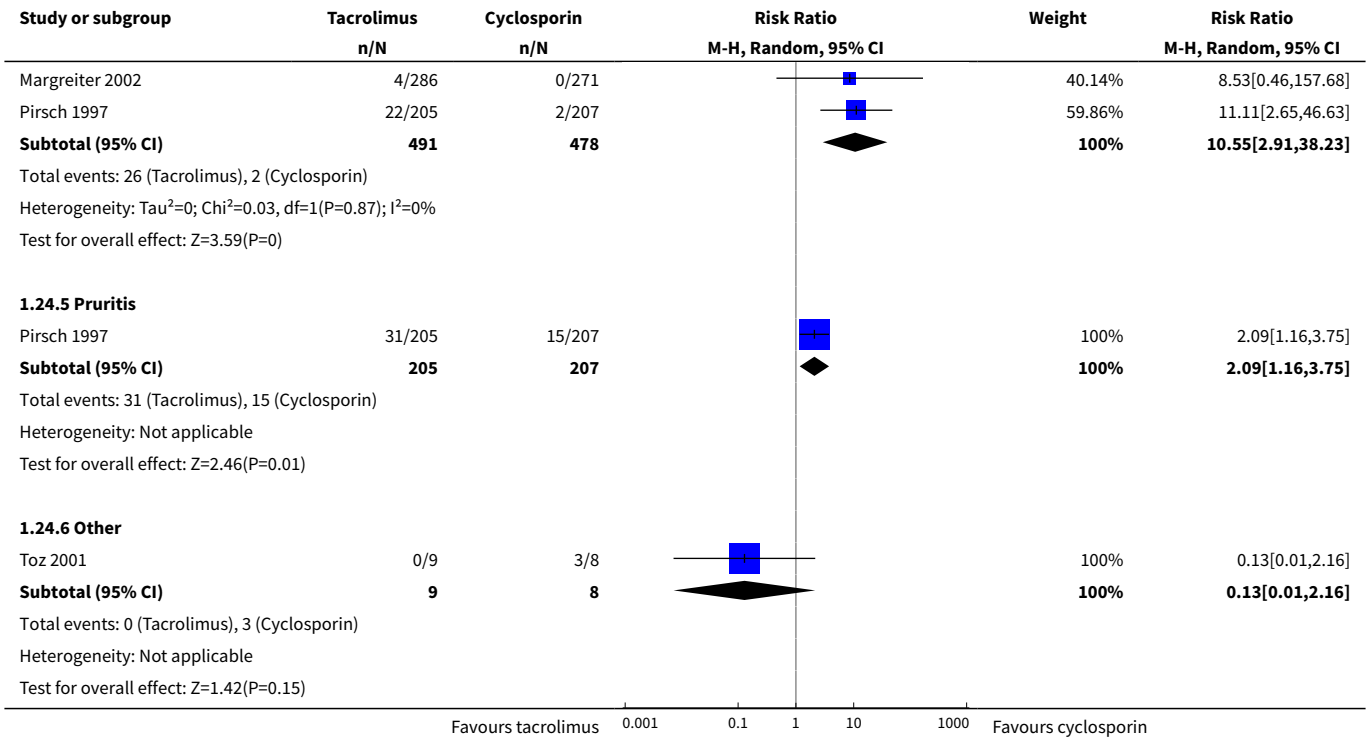


Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 Anaemia					
Mayer 1997	53/303	24/145		100%	1.06[0.68,1.64]
Subtotal (95% CI)	**303**	**145**		**100%**	**1.06[0.68,1.64]**
Total events: 53 (Tacrolimus), 24 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.81)					
1.23.2 Leucopaenia					
Charpentier 2002	88/371	64/184		65.86%	0.68[0.52,0.89]
Mayer 1997	50/303	22/145		34.14%	1.09[0.69,1.72]
Subtotal (95% CI)	**674**	**329**		**100%**	**0.83[0.53,1.31]**
Total events: 138 (Tacrolimus), 86 (Cyclosporin)					
Heterogeneity: Tau²=0.07; Chi²=2.98, df=1(P=0.08); I²=66.45%					
Test for overall effect: Z=0.81(P=0.42)					

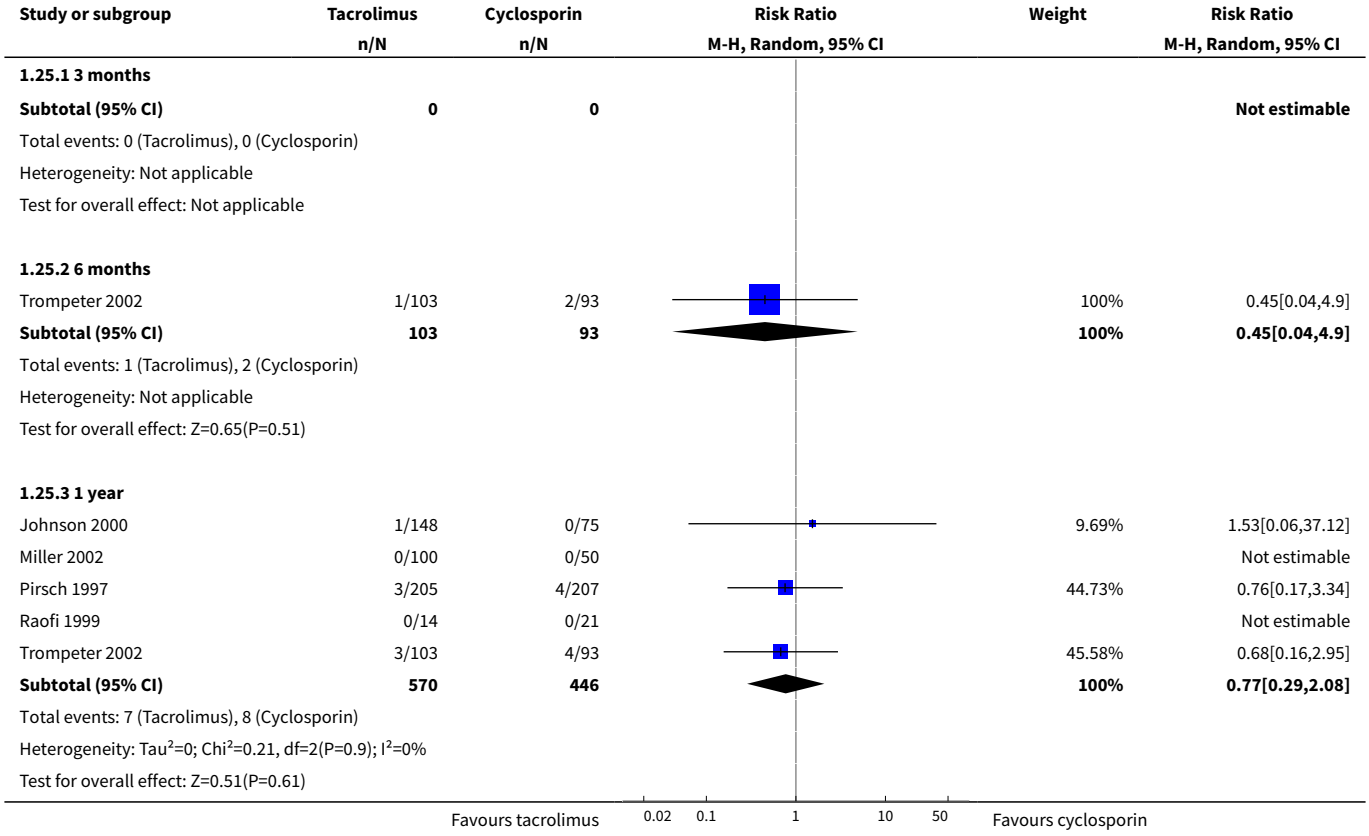


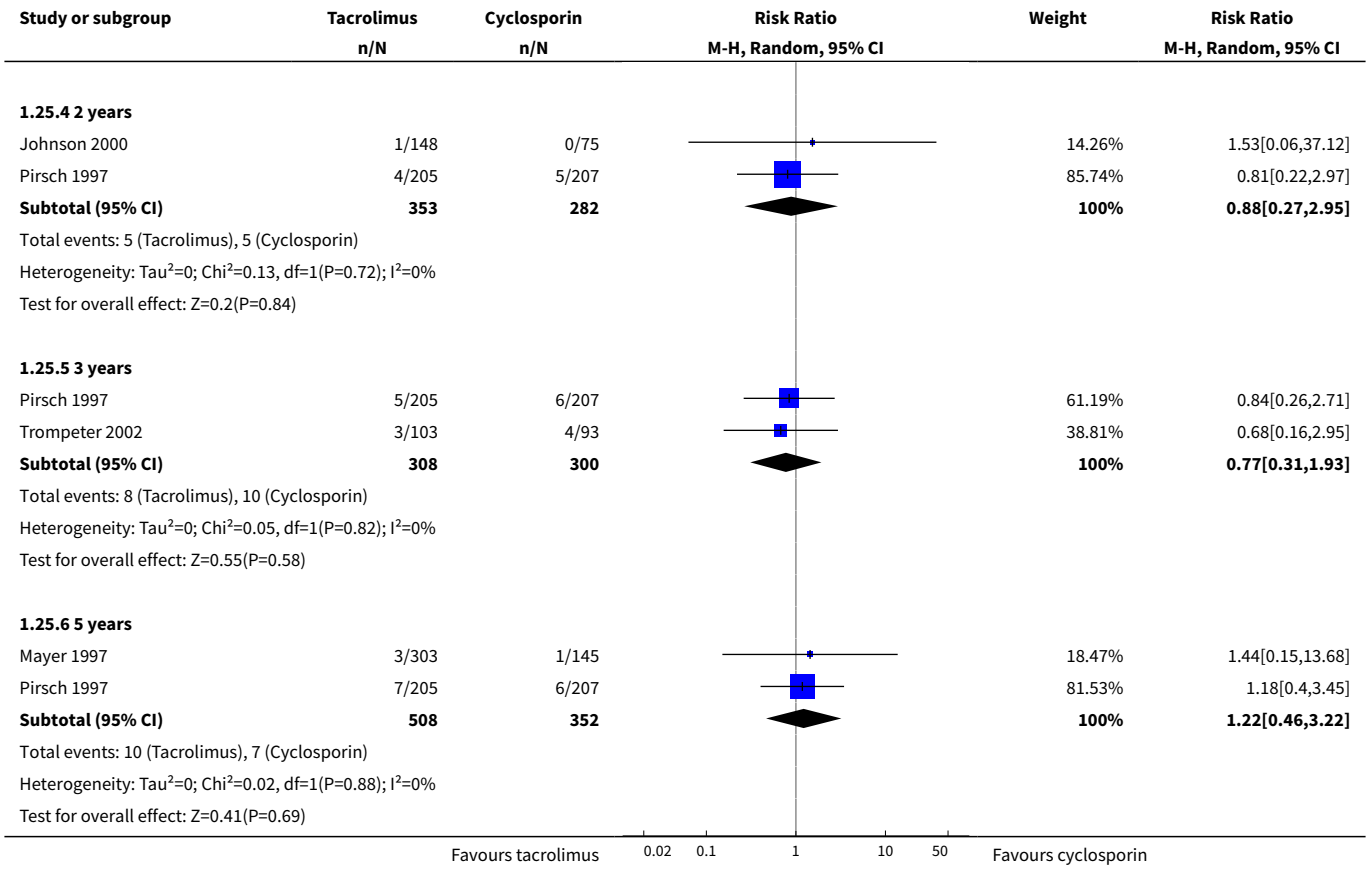
Analysis 1.24. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 24 Cosmetic side effects.



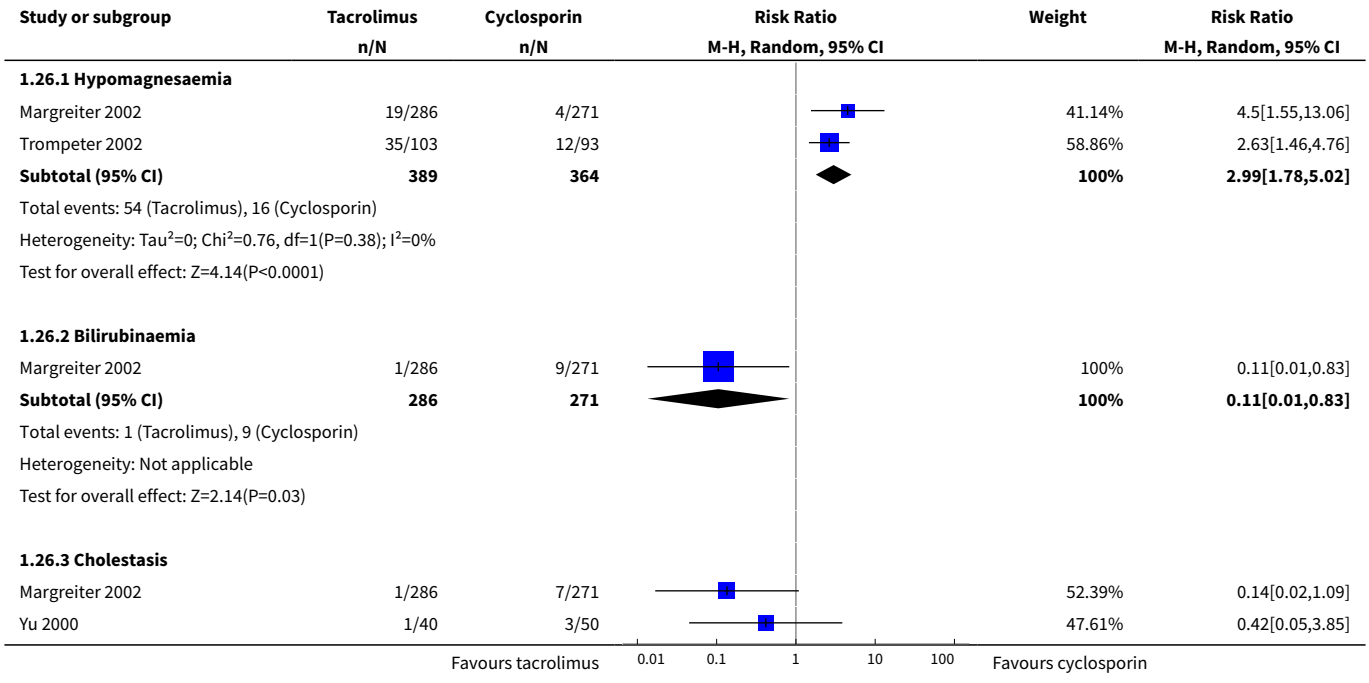


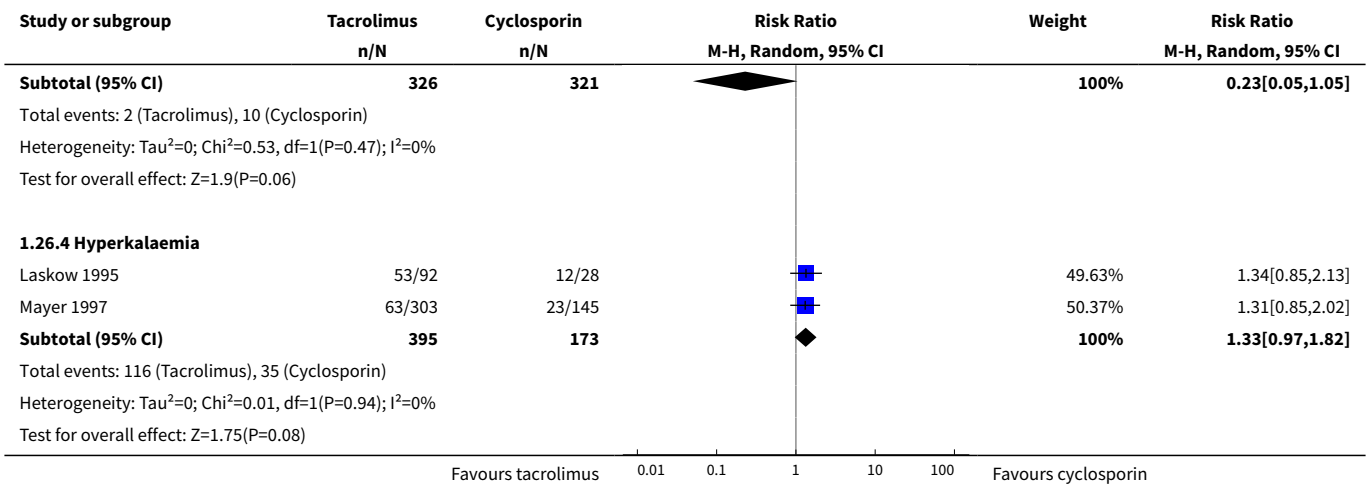
Analysis 1.25. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 25 Lymphoma/PTLD.



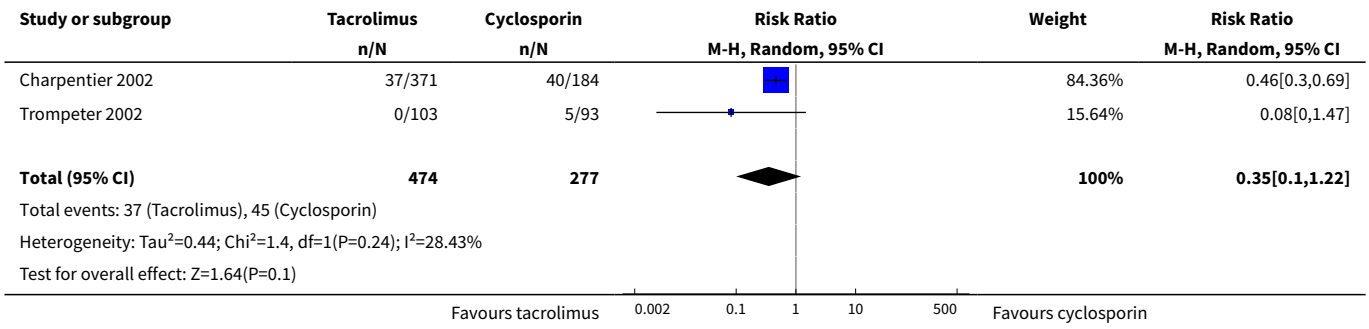


Analysis 1.26. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 26 Biochemical side effects.

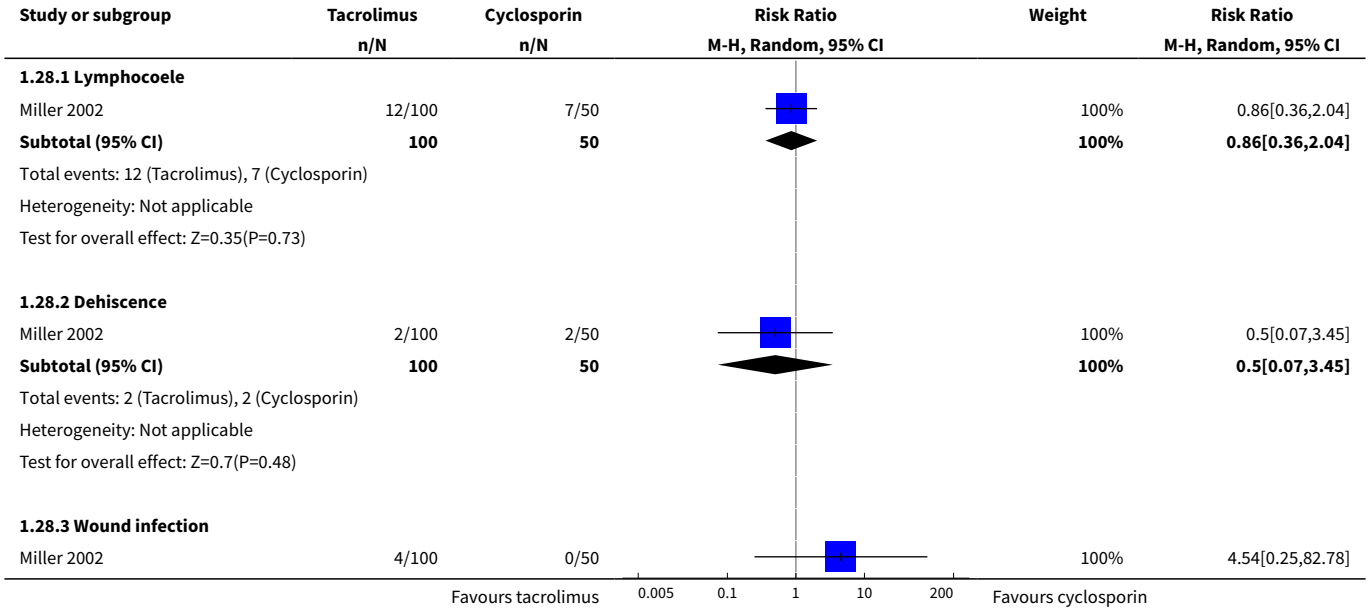


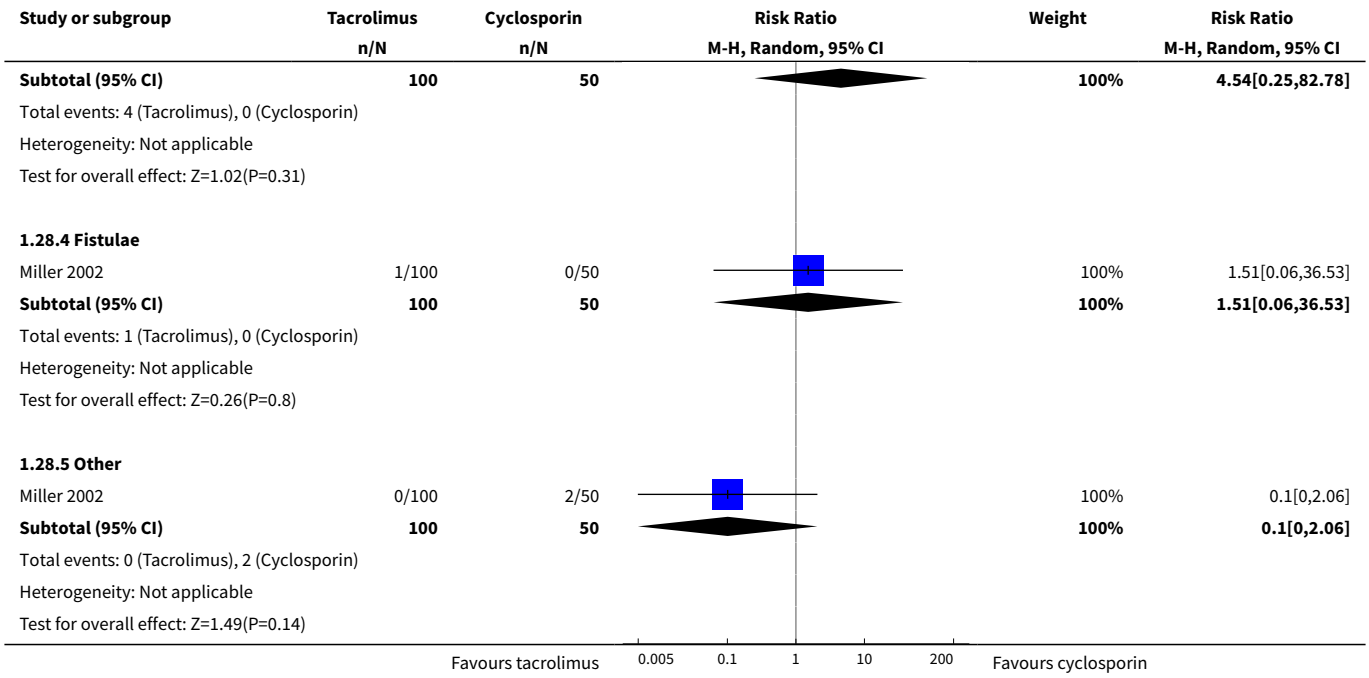


Analysis 1.27. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 27 Fever.

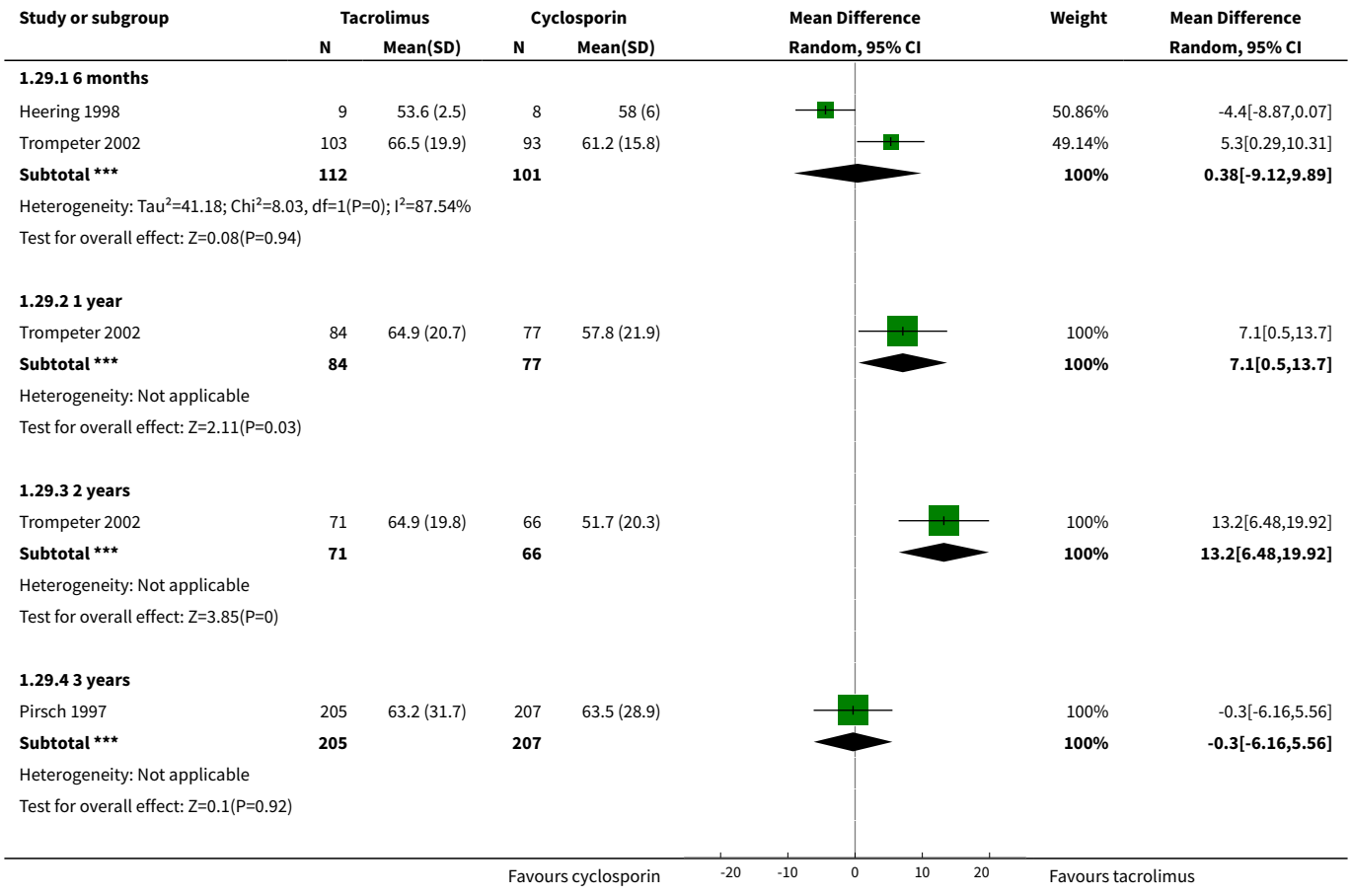


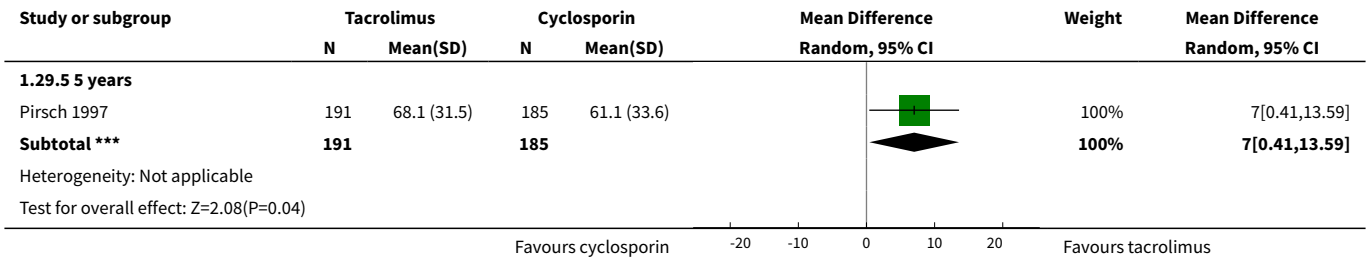
Analysis 1.28. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 28 Surgical side effects.



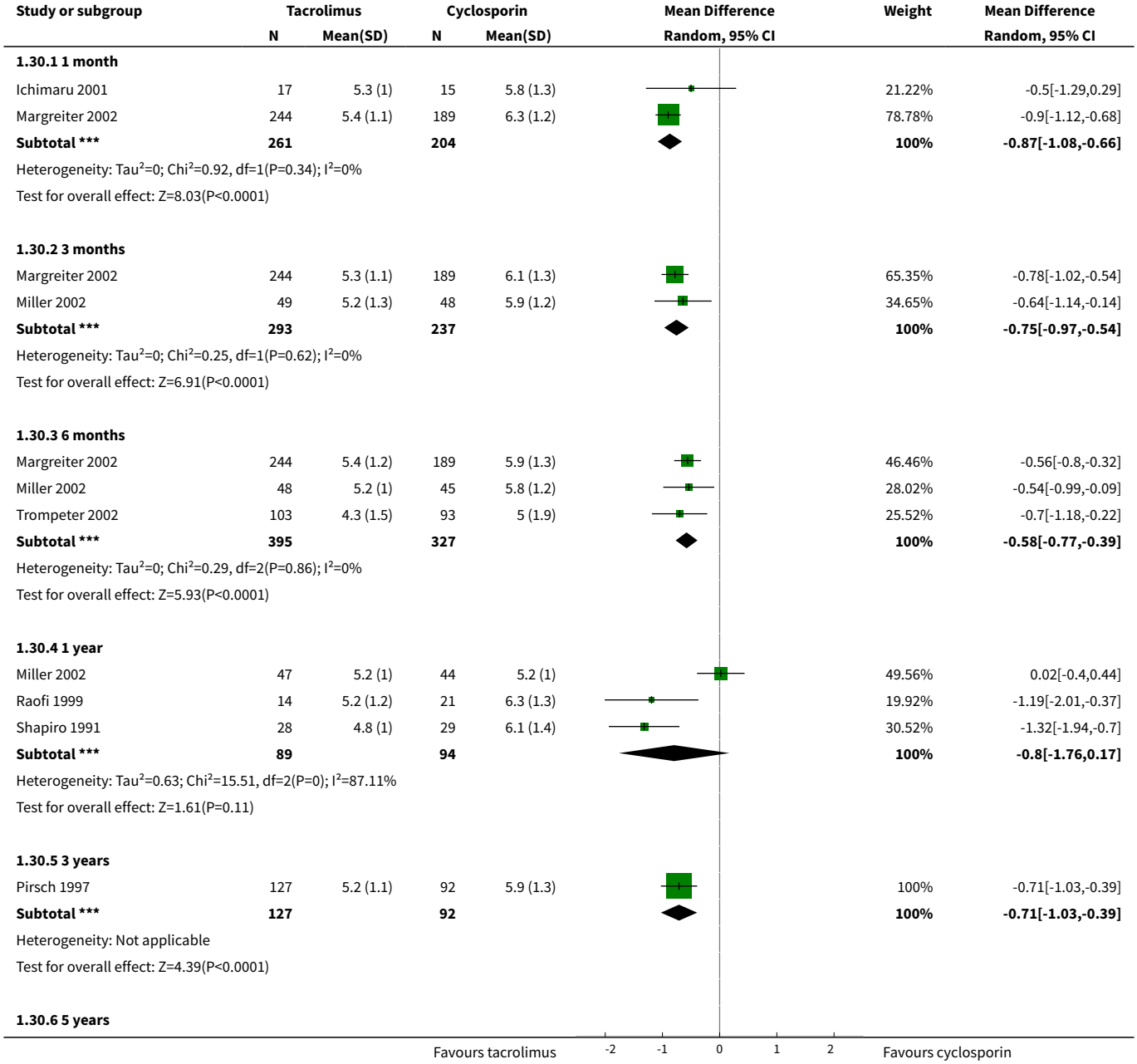


Analysis 1.29. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 29 GFR (mL/min).





Analysis 1.30. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 30 Total cholesterol (µmol/L).



Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Cyclosporin N	Cyclosporin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

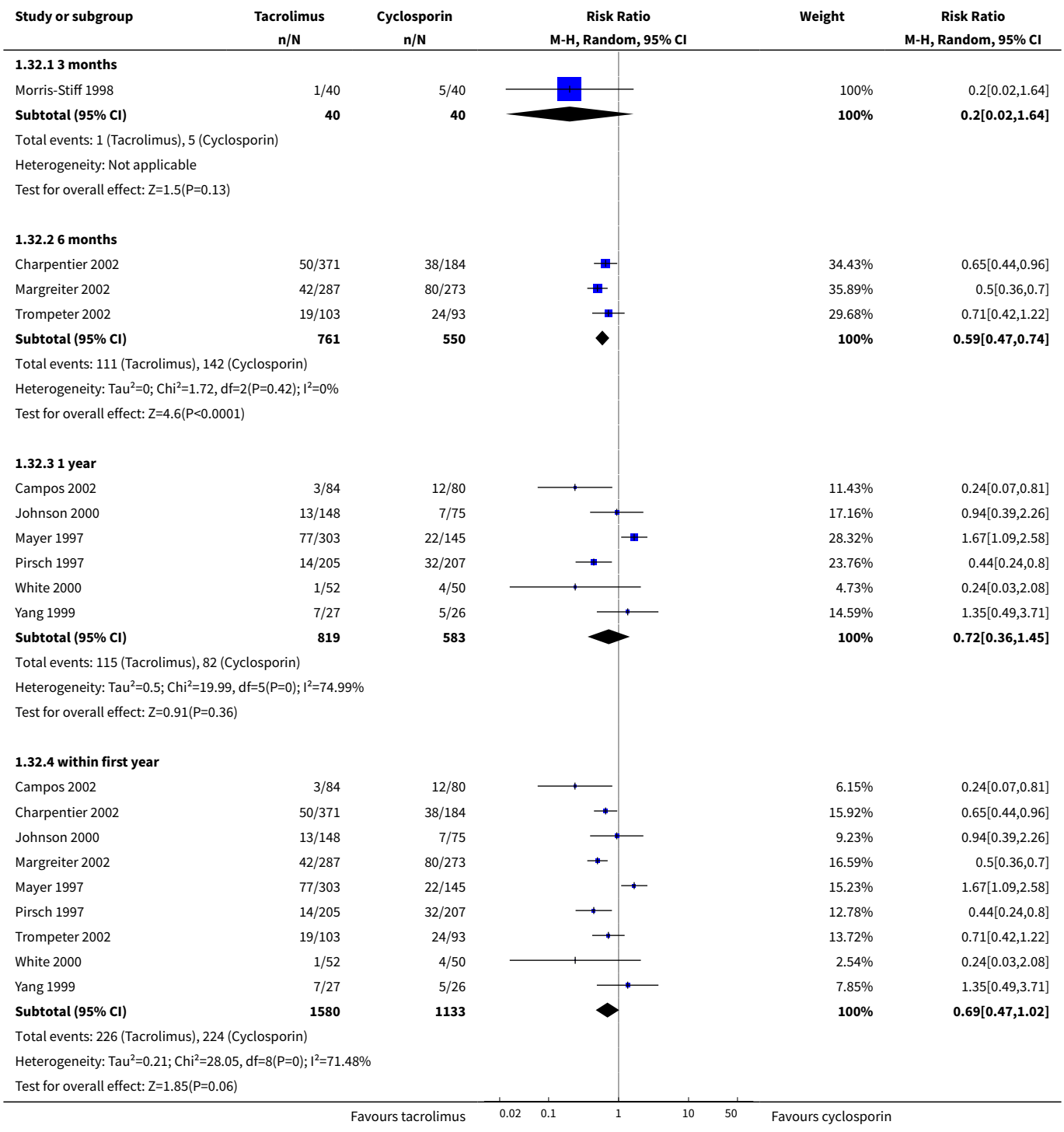
Favours tacrolimus -2 -1 0 1 2 Favours cyclosporin

Analysis 1.31. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 31 Total triglycerides (µmol/L).

Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Cyclosporin N	Cyclosporin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.31.1 1 month							
Ichimaru 2001	17	1.6 (0.7)	15	2.3 (1.3)		12.42%	-0.74[-1.47,-0.01]
Margreiter 2002	244	1.8 (0.9)	189	2 (1.1)		87.58%	-0.18[-0.37,0.01]
Subtotal ***	**261**		**204**			**100%**	**-0.34[-0.84,0.16]**
Heterogeneity: Tau^2=0.08; Chi^2=2.11, df=1(P=0.15); I^2=52.59%							
Test for overall effect: Z=1.35(P=0.18)							
1.31.2 3 months							
Margreiter 2002	244	1.8 (0.9)	189	1.9 (0.9)		37.69%	-0.15[-0.32,0.02]
Miller 2002	49	2.2 (0)	48	2.7 (0)		62.31%	-0.48[-0.49,-0.47]
Subtotal ***	**293**		**237**			**100%**	**-0.33[-0.65,-0]**
Heterogeneity: Tau^2=0.05; Chi^2=13.76, df=1(P=0); I^2=92.73%							
Test for overall effect: Z=1.99(P=0.05)							
1.31.3 6 months							
Margreiter 2002	244	1.7 (0.9)	189	1.8 (0.8)		38.98%	-0.1[-0.26,0.06]
Miller 2002	48	1.9 (0)	45	2.3 (0)		61.02%	-0.43[-0.44,-0.42]
Subtotal ***	**292**		**234**			**100%**	**-0.28[-0.6,0.05]**
Heterogeneity: Tau^2=0.05; Chi^2=15.89, df=1(P<0.0001); I^2=93.71%							
Test for overall effect: Z=1.67(P=0.09)							
1.31.4 1 year							
Miller 2002	47	1.8 (0)	44	2.1 (0)		100%	-0.27[-0.28,-0.26]
Subtotal ***	**47**		**44**			**100%**	**-0.27[-0.28,-0.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=64.36(P<0.0001)							
1.31.5 3 years							
Pirsch 1997	119	1.8 (0.9)	86	2.2 (1.2)		100%	-0.39[-0.69,-0.09]
Subtotal ***	**119**		**86**			**100%**	**-0.39[-0.69,-0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.56(P=0.01)							
1.31.6 5 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favours tacrolimus -2 -1 0 1 2 Favours cyclosporin

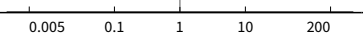
Analysis 1.32. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 32 Treament withdrawal/crossover.



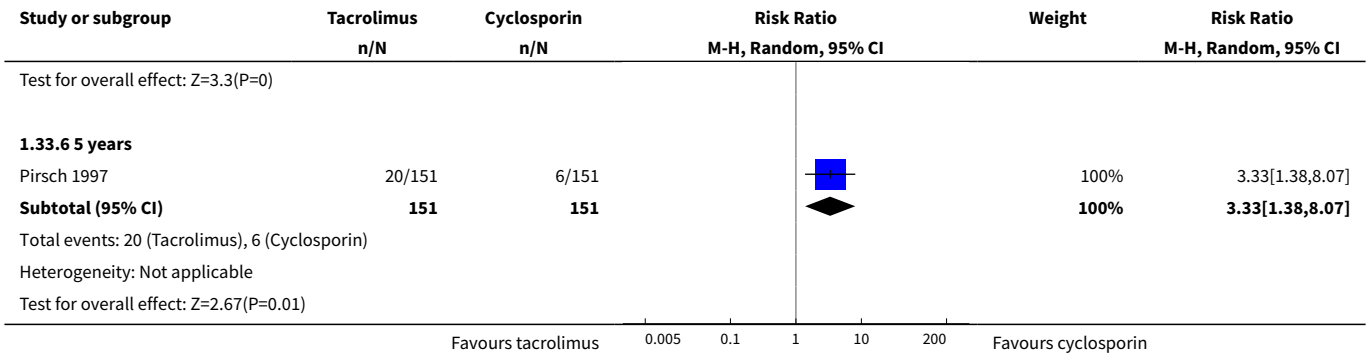
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.32.1 3 months					
Morris-Stiff 1998	1/40	5/40		100%	0.2[0.02,1.64]
Subtotal (95% CI)	**40**	**40**		**100%**	**0.2[0.02,1.64]**
Total events: 1 (Tacrolimus), 5 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.5(P=0.13)					
1.32.2 6 months					
Charpentier 2002	50/371	38/184		34.43%	0.65[0.44,0.96]
Margreiter 2002	42/287	80/273		35.89%	0.5[0.36,0.7]
Trompeter 2002	19/103	24/93		29.68%	0.71[0.42,1.22]
Subtotal (95% CI)	**761**	**550**		**100%**	**0.59[0.47,0.74]**
Total events: 111 (Tacrolimus), 142 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.72, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=4.6(P<0.0001)					
1.32.3 1 year					
Campos 2002	3/84	12/80		11.43%	0.24[0.07,0.81]
Johnson 2000	13/148	7/75		17.16%	0.94[0.39,2.26]
Mayer 1997	77/303	22/145		28.32%	1.67[1.09,2.58]
Pirsch 1997	14/205	32/207		23.76%	0.44[0.24,0.8]
White 2000	1/52	4/50		4.73%	0.24[0.03,2.08]
Yang 1999	7/27	5/26		14.59%	1.35[0.49,3.71]
Subtotal (95% CI)	**819**	**583**		**100%**	**0.72[0.36,1.45]**
Total events: 115 (Tacrolimus), 82 (Cyclosporin)					
Heterogeneity: Tau^2=0.5; Chi^2=19.99, df=5(P=0); I^2=74.99%					
Test for overall effect: Z=0.91(P=0.36)					
1.32.4 within first year					
Campos 2002	3/84	12/80		6.15%	0.24[0.07,0.81]
Charpentier 2002	50/371	38/184		15.92%	0.65[0.44,0.96]
Johnson 2000	13/148	7/75		9.23%	0.94[0.39,2.26]
Margreiter 2002	42/287	80/273		16.59%	0.5[0.36,0.7]
Mayer 1997	77/303	22/145		15.23%	1.67[1.09,2.58]
Pirsch 1997	14/205	32/207		12.78%	0.44[0.24,0.8]
Trompeter 2002	19/103	24/93		13.72%	0.71[0.42,1.22]
White 2000	1/52	4/50		2.54%	0.24[0.03,2.08]
Yang 1999	7/27	5/26		7.85%	1.35[0.49,3.71]
Subtotal (95% CI)	**1580**	**1133**		**100%**	**0.69[0.47,1.02]**
Total events: 226 (Tacrolimus), 224 (Cyclosporin)					
Heterogeneity: Tau^2=0.21; Chi^2=28.05, df=8(P=0); I^2=71.48%					
Test for overall effect: Z=1.85(P=0.06)					

Analysis 1.33. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 33 Sustained diabetes mellitus requiring insulin.

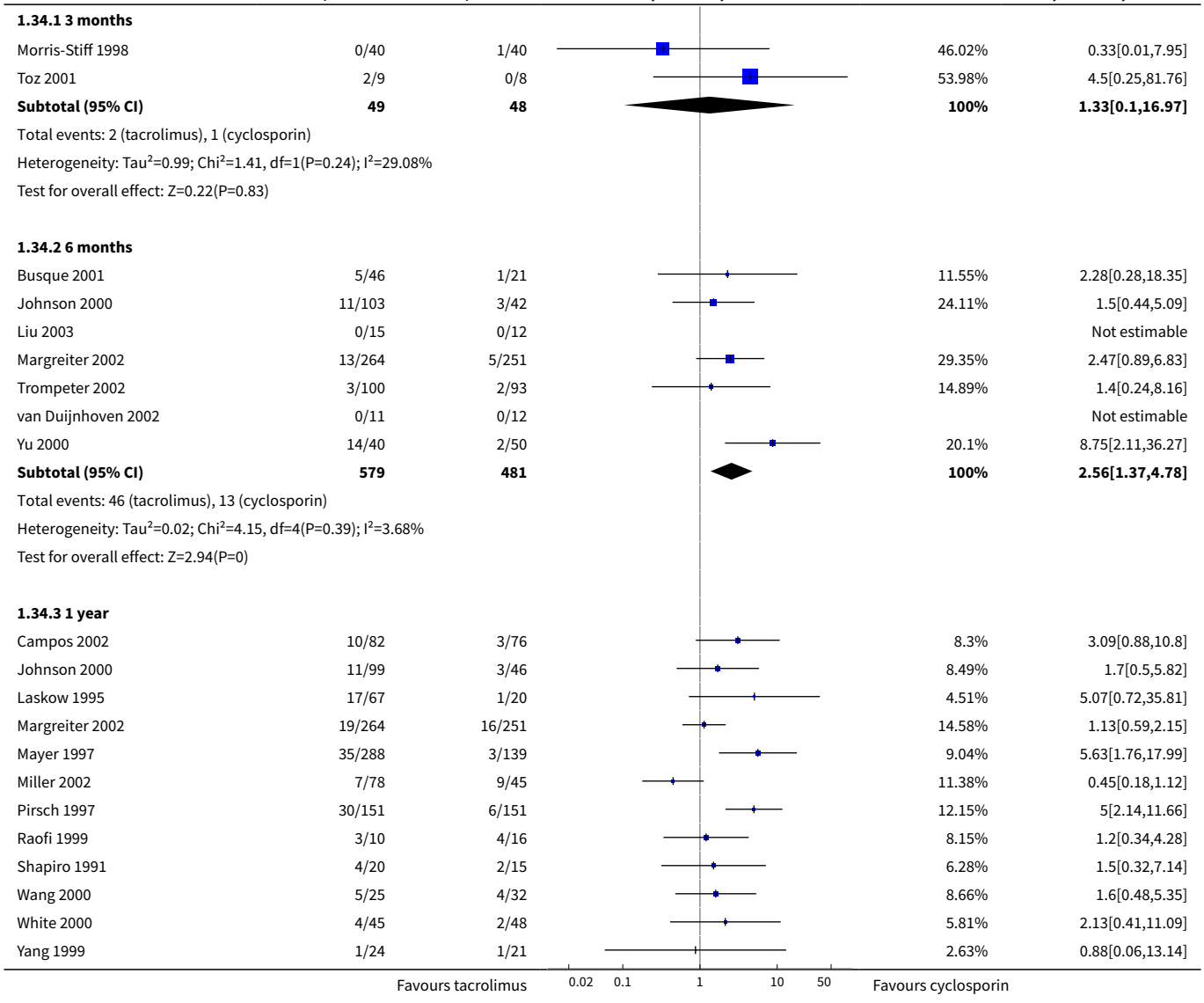
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.33.1 3 months					
Morris-Stiff 1998	0/40	1/40		100%	0.33[0.01,7.95]
Subtotal (95% CI)	**40**	**40**		**100%**	**0.33[0.01,7.95]**
Total events: 0 (Tacrolimus), 1 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
1.33.2 6 months					
Busque 2001	3/46	0/21		9.17%	3.28[0.18,60.73]
Liu 2003	0/15	0/12			Not estimable
Margreiter 2002	13/264	5/251		57.87%	2.47[0.89,6.83]
Trompeter 2002	3/100	2/93		23.34%	1.4[0.24,8.16]
van Duijnhoven 2002	0/11	0/12			Not estimable
Yu 2000	6/40	0/50		9.63%	16.17[0.94,278.69]
Subtotal (95% CI)	**476**	**439**		**100%**	**2.61[1.16,5.85]**
Total events: 25 (Tacrolimus), 7 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=2.21, df=3(P=0.53); I^2=0%					
Test for overall effect: Z=2.32(P=0.02)					
1.33.3 1 year					
Campos 2002	5/82	2/76		6.47%	2.32[0.46,11.59]
Johnson 2000	8/99	3/46		9.53%	1.24[0.34,4.46]
Laskow 1995	12/67	1/20		4.48%	3.58[0.5,25.89]
Margreiter 2002	14/264	7/251		16.41%	1.9[0.78,4.63]
Mayer 1997	17/288	3/139		10.42%	2.73[0.82,9.18]
Miller 2002	7/78	9/45		15.77%	0.45[0.18,1.12]
Pirsch 1997	23/151	5/151		15.22%	4.6[1.8,11.78]
Raofi 1999	3/10	4/16		9.63%	1.2[0.34,4.28]
Shapiro 1991	2/20	1/15		3.37%	1.5[0.15,15.04]
White 2000	4/45	2/48		6.21%	2.13[0.41,11.09]
Yang 1999	1/24	1/21		2.49%	0.88[0.06,13.14]
Subtotal (95% CI)	**1128**	**828**		**100%**	**1.7[1.04,2.78]**
Total events: 96 (Tacrolimus), 38 (Cyclosporin)					
Heterogeneity: Tau^2=0.21; Chi^2=14.85, df=10(P=0.14); I^2=32.66%					
Test for overall effect: Z=2.12(P=0.03)					
1.33.4 2 years					
Johnson 2000	8/99	3/46		100%	1.24[0.34,4.46]
Subtotal (95% CI)	**99**	**46**		**100%**	**1.24[0.34,4.46]**
Total events: 8 (Tacrolimus), 3 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.33(P=0.74)					
1.33.5 3 years					
Johnson 2000	17/99	3/46		39.31%	2.63[0.81,8.54]
Pirsch 1997	22/151	6/151		60.69%	3.67[1.53,8.79]
Subtotal (95% CI)	**250**	**197**		**100%**	**3.26[1.62,6.57]**
Total events: 39 (Tacrolimus), 9 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.66); I^2=0%					

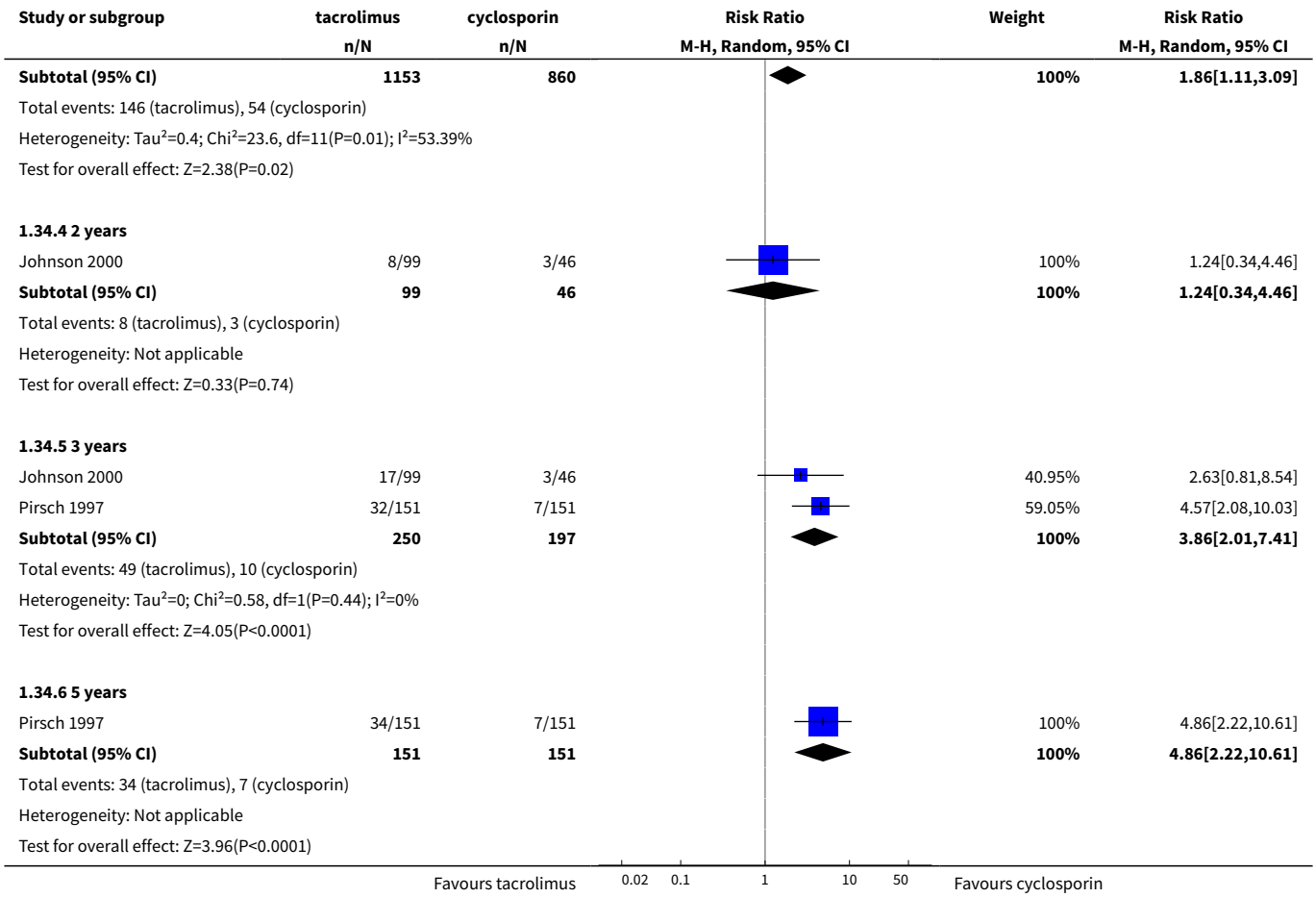


Favours tacrolimus — Favours cyclosporin



Analysis 1.34. Comparison 1 Tacrolimus versus cyclosporin for primary therapy, Outcome 34 Requirement for insulin >30 days in previously non-diabetic patients.





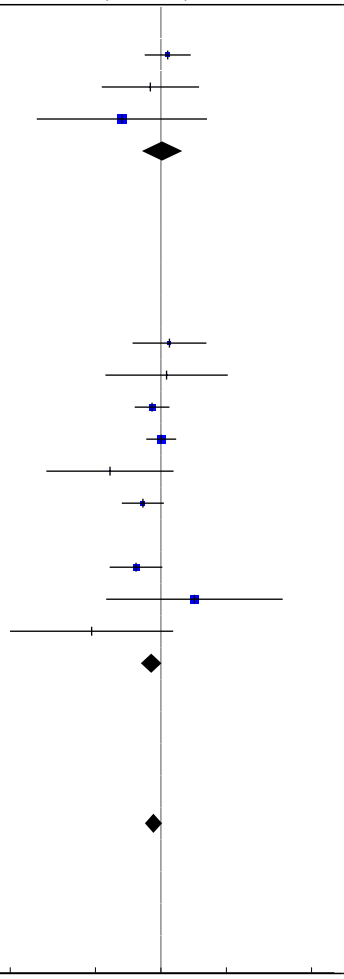
Comparison 2. Stratified analysis, by publication type

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Graft loss (death censored) 1 year	13	2544	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.57, 1.04]
1.1 Transplantation proceedings +/- abstract	3	278	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.51, 2.12]
1.2 Peer reviewed journal	10	2266	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.49, 1.02]
2 Acute rejection (all) 1 year	14	2751	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.80]
2.1 Transplantation proceedings +/- abstract	3	281	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.57, 1.82]
2.2 Peer reviewed journal	11	2470	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.57, 0.72]
3 New requirement for insulin >30 days	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Transplantation proceedings +/- abstract	3	250	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.94, 4.29]
3.2 Peer reviewed journal	9	1763	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.95, 3.57]

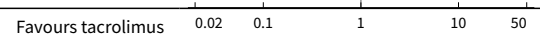
Analysis 2.1. Comparison 2 Stratified analysis, by publication type, Outcome 1 Graft loss (death censored) 1 year.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Transplantation proceedings +/- abstract					
Campos 2002	12/84	9/80		12.61%	1.27[0.57,2.85]
Shapiro 1991	2/28	3/29		2.98%	0.69[0.12,3.83]
Wang 2000	0/25	2/32		0.99%	0.25[0.01,5.06]
Subtotal (95% CI)	**137**	**141**		**16.58%**	**1.04[0.51,2.12]**
Total events: 14 (Tacrolimus), 14 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.33, df=2(P=0.52); I^2=0%					
Test for overall effect: Z=0.12(P=0.9)					
2.1.2 Peer reviewed journal					
Johnson 2000	8/148	3/75		5.13%	1.35[0.37,4.95]
Laskow 1995	4/92	1/28		1.9%	1.22[0.14,10.45]
Margreiter 2002	17/286	22/271		20.91%	0.73[0.4,1.35]
Mayer 1997	38/303	18/145		27.14%	1.01[0.6,1.71]
Miller 2002	1/100	3/50		1.76%	0.17[0.02,1.56]
Pirsch 1997	10/205	19/207		14.79%	0.53[0.25,1.11]
Raofi 1999	0/14	0/21			Not estimable
Trompeter 2002	6/103	13/93		9.78%	0.42[0.17,1.05]
van Duijnhoven 2002	1/11	0/12		0.92%	3.25[0.15,72.36]
White 2000	0/52	5/50		1.07%	0.09[0,1.54]
Subtotal (95% CI)	**1314**	**952**		**83.42%**	**0.71[0.49,1.02]**
Total events: 85 (Tacrolimus), 84 (Cyclosporin)					
Heterogeneity: Tau^2=0.04; Chi^2=9.4, df=8(P=0.31); I^2=14.91%					
Test for overall effect: Z=1.84(P=0.07)					
Total (95% CI)	**1451**	**1093**		**100%**	**0.77[0.57,1.04]**
Total events: 99 (Tacrolimus), 98 (Cyclosporin)					
Heterogeneity: Tau^2=0.01; Chi^2=11.54, df=11(P=0.4); I^2=4.7%					
Test for overall effect: Z=1.73(P=0.08)					
Test for subgroup differences: Not applicable					



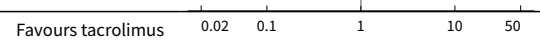
Analysis 2.2. Comparison 2 Stratified analysis, by publication type, Outcome 2 Acute rejection (all) 1 year.

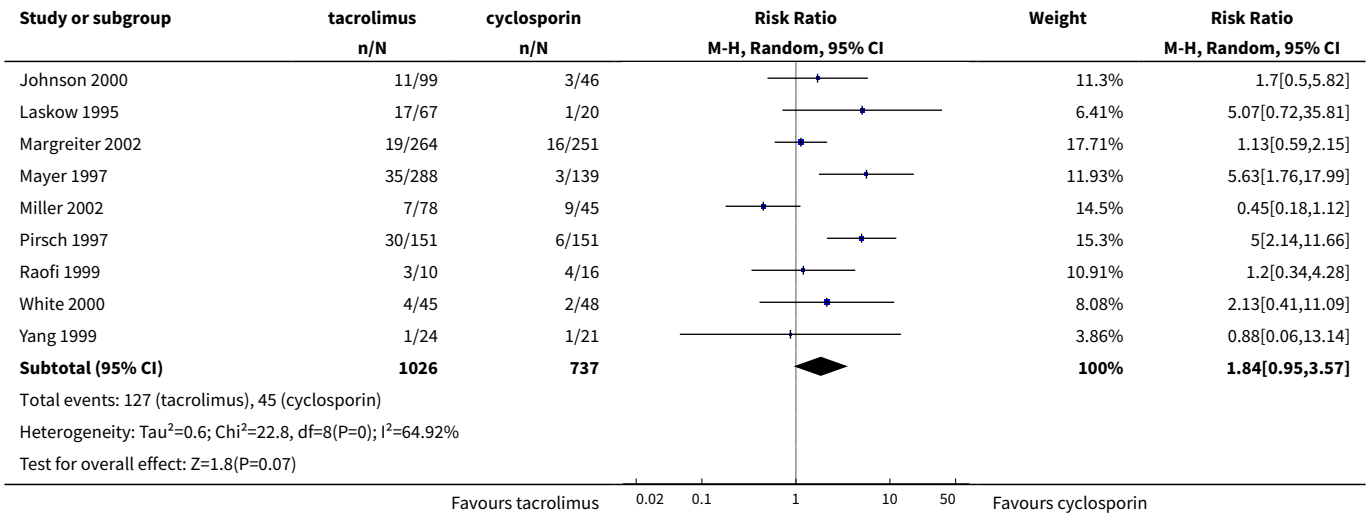
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Transplantation proceedings +/- abstract					
Campos 2002	35/84	35/80		9.81%	0.95[0.67,1.36]
Egfjord 2002	10/30	6/30		2.43%	1.67[0.69,4]
Wang 2000	1/25	5/32		0.47%	0.26[0.03,2.05]
Subtotal (95% CI)	**139**	**142**		**12.71%**	**1.02[0.57,1.82]**
Total events: 46 (Tacrolimus), 46 (Cyclosporin)					
Heterogeneity: Tau^2=0.1; Chi^2=3.03, df=2(P=0.22); I^2=34.05%					
Test for overall effect: Z=0.07(P=0.95)					
2.2.2 Peer reviewed journal					
Johnson 2000	24/148	15/75		4.88%	0.81[0.45,1.45]
Laskow 1995	30/92	9/28		4.49%	1.01[0.55,1.87]
Margreiter 2002	98/286	154/271		16.98%	0.6[0.5,0.73]
Mayer 1997	98/303	79/145		15.45%	0.59[0.48,0.74]
Miller 2002	4/100	10/50		1.58%	0.2[0.07,0.61]
Morris-Stiff 1998	21/90	33/89		6.93%	0.63[0.4,1]
Pirsch 1997	63/205	96/207		13.89%	0.66[0.51,0.85]
Radermacher 1998	11/33	8/15		3.82%	0.63[0.32,1.23]
Raofi 1999	2/14	8/21		1.02%	0.38[0.09,1.51]
Trompeter 2002	42/103	57/93		12.5%	0.67[0.5,0.88]
White 2000	18/52	18/50		5.73%	0.96[0.57,1.63]
Subtotal (95% CI)	**1426**	**1044**		**87.29%**	**0.64[0.57,0.72]**
Total events: 411 (Tacrolimus), 487 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=10.87, df=10(P=0.37); I^2=8.05%					
Test for overall effect: Z=7.67(P<0.0001)					
Total (95% CI)	**1565**	**1186**		**100%**	**0.69[0.6,0.8]**
Total events: 457 (Tacrolimus), 533 (Cyclosporin)					
Heterogeneity: Tau^2=0.02; Chi^2=20.4, df=13(P=0.09); I^2=36.28%					
Test for overall effect: Z=5.05(P<0.0001)					
Test for subgroup differences: Not applicable					



Analysis 2.3. Comparison 2 Stratified analysis, by publication type, Outcome 3 New requirement for insulin >30 days.

Study or subgroup	tacrolimus n/N	cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Transplantation proceedings +/- abstract					
Campos 2002	10/82	3/76		35.48%	3.09[0.88,10.8]
Shapiro 1991	4/20	2/15		27.71%	1.5[0.32,7.14]
Wang 2000	5/25	4/32		36.82%	1.6[0.48,5.35]
Subtotal (95% CI)	**127**	**123**		**100%**	**2.01[0.94,4.29]**
Total events: 19 (tacrolimus), 9 (cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.74, df=2(P=0.69); I^2=0%					
Test for overall effect: Z=1.8(P=0.07)					
2.3.2 Peer reviewed journal					



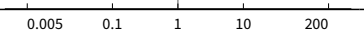


Comparison 3. Stratified analysis, by ITT quality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss (death censored) 1 year	14	2604	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.02]
1.1 Not ITT	6	1117	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.52, 1.18]
1.2 unclear ITT	1	102	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.00, 1.54]
1.3 Confirmed ITT	7	1385	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.50, 1.18]
2 Acute rejection (all) 1 year	14	2751	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.80]
2.1 Not ITT	4	1037	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.58, 0.93]
2.2 Unclear ITT	2	162	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.69, 1.84]
2.3 Confirmed ITT	8	1552	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.53, 0.71]
3 New requirement for insulin >30 days	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ITT not undertaken, or unclear	5	888	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.97, 2.59]
3.2 Confirmed ITT	7	1125	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.78, 4.01]

Analysis 3.1. Comparison 3 Stratified analysis, by ITT quality, Outcome 1 Graft loss (death censored) 1 year.

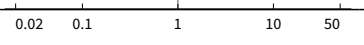
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Not ITT					
Campos 2002	12/84	9/80		12.13%	1.27[0.57,2.85]
Laskow 1995	4/92	1/28		1.71%	1.22[0.14,10.45]
Margreiter 2002	17/286	22/271		21.24%	0.73[0.4,1.35]
Shapiro 1991	2/28	3/29		2.7%	0.69[0.12,3.83]
Trompeter 2002	6/103	13/93		9.24%	0.42[0.17,1.05]
van Duijnhoven 2002	1/11	0/12		0.82%	3.25[0.15,72.36]
Subtotal (95% CI)	**604**	**513**		**47.86%**	**0.79[0.52,1.18]**
Total events: 42 (Tacrolimus), 48 (Cyclosporin)					
Heterogeneity: Tau²=0; Chi²=4.2, df=5(P=0.52); I²=0%					
Test for overall effect: Z=1.16(P=0.25)					
3.1.2 unclear ITT					
White 2000	0/52	5/50		0.96%	0.09[0,1.54]
Subtotal (95% CI)	**52**	**50**		**0.96%**	**0.09[0,1.54]**
Total events: 0 (Tacrolimus), 5 (Cyclosporin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					
3.1.3 Confirmed ITT					
Johnson 2000	8/148	3/75		4.71%	1.35[0.37,4.95]
Mayer 1997	38/303	18/145		28.78%	1.01[0.6,1.71]
Miller 2002	1/100	3/50		1.58%	0.17[0.02,1.56]
Pirsch 1997	10/205	19/207		14.43%	0.53[0.25,1.11]
Raofi 1999	0/14	0/21			Not estimable
Wang 2000	0/25	2/32		0.88%	0.25[0.01,5.06]
Yang 1999	0/30	1/30		0.79%	0.33[0.01,7.87]
Subtotal (95% CI)	**825**	**560**		**51.18%**	**0.77[0.5,1.18]**
Total events: 57 (Tacrolimus), 46 (Cyclosporin)					
Heterogeneity: Tau²=0.02; Chi²=5.32, df=5(P=0.38); I²=6.1%					
Test for overall effect: Z=1.2(P=0.23)					
Total (95% CI)	**1481**	**1123**		**100%**	**0.77[0.58,1.02]**
Total events: 99 (Tacrolimus), 99 (Cyclosporin)					
Heterogeneity: Tau²=0; Chi²=11.82, df=12(P=0.46); I²=0%					
Test for overall effect: Z=1.82(P=0.07)					
Test for subgroup differences: Not applicable					



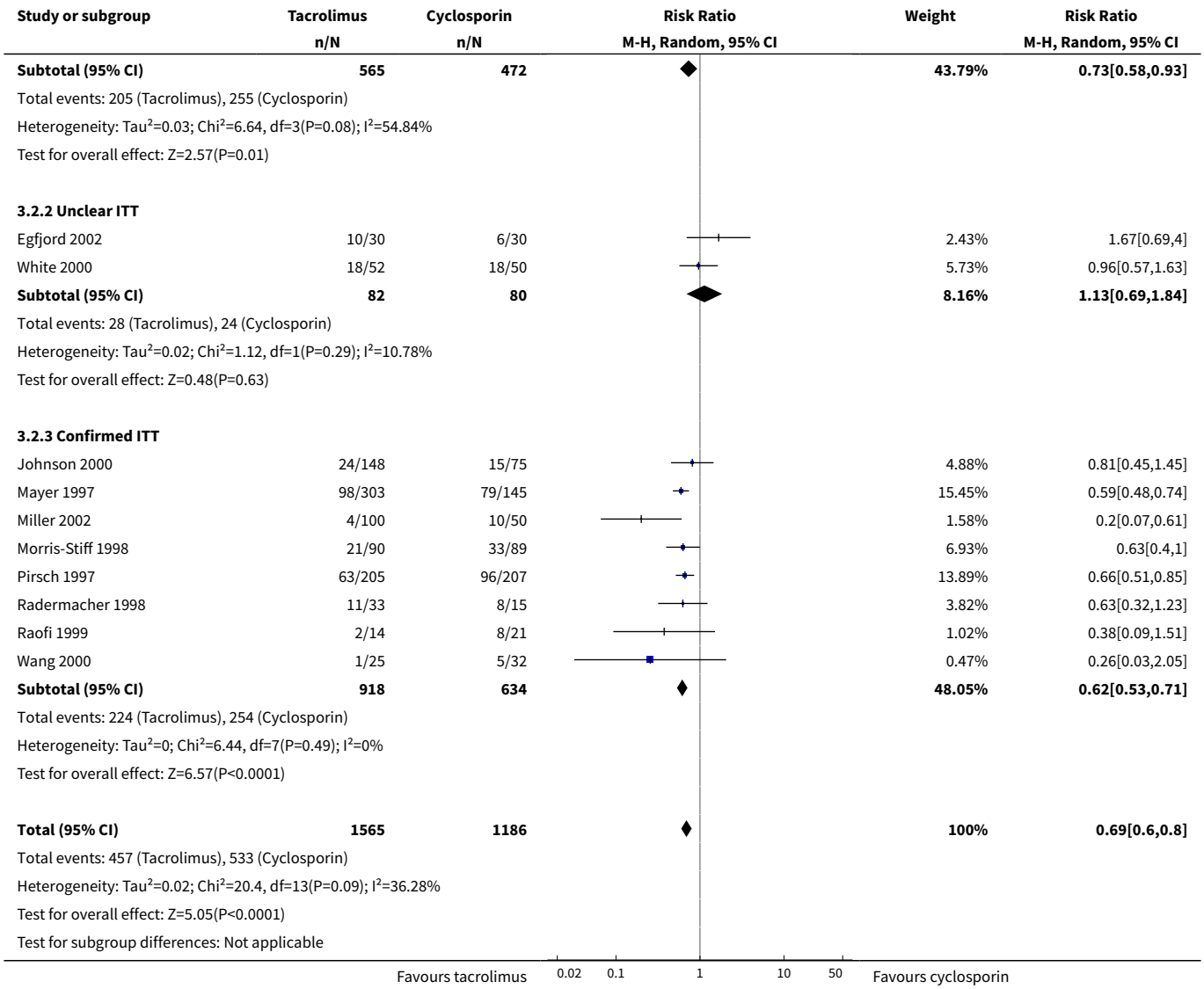
Favours tacrolimus — Favours cyclosporin

Analysis 3.2. Comparison 3 Stratified analysis, by ITT quality, Outcome 2 Acute rejection (all) 1 year.

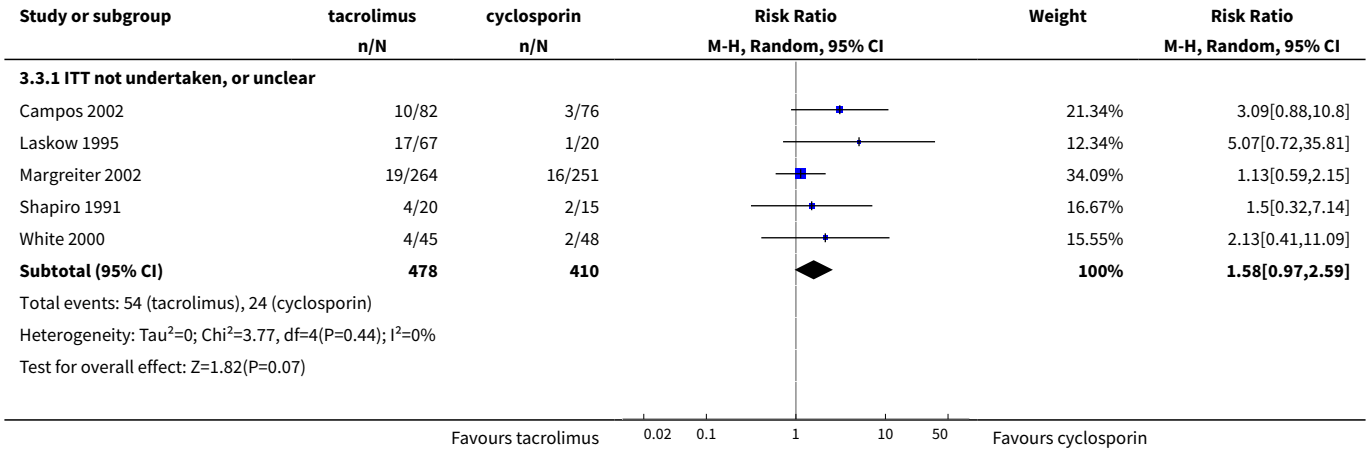
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Not ITT					
Campos 2002	35/84	35/80		9.81%	0.95[0.67,1.36]
Laskow 1995	30/92	9/28		4.49%	1.01[0.55,1.87]
Margreiter 2002	98/286	154/271		16.98%	0.6[0.5,0.73]
Trompeter 2002	42/103	57/93		12.5%	0.67[0.5,0.88]

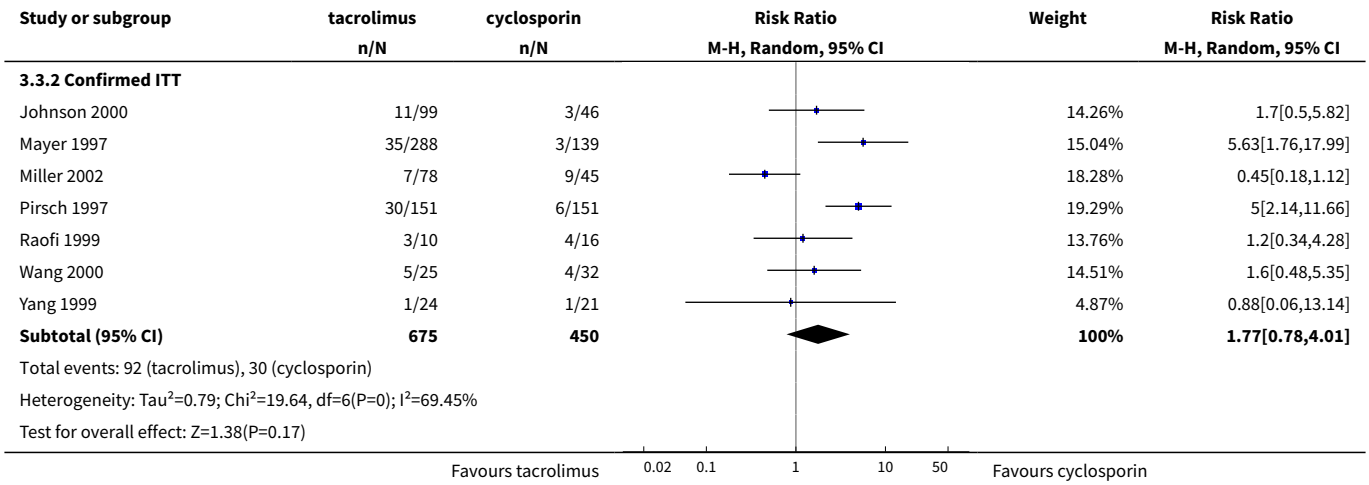


Favours tacrolimus — Favours cyclosporin



Analysis 3.3. Comparison 3 Stratified analysis, by ITT quality, Outcome 3 New requirement for insulin >30 days.

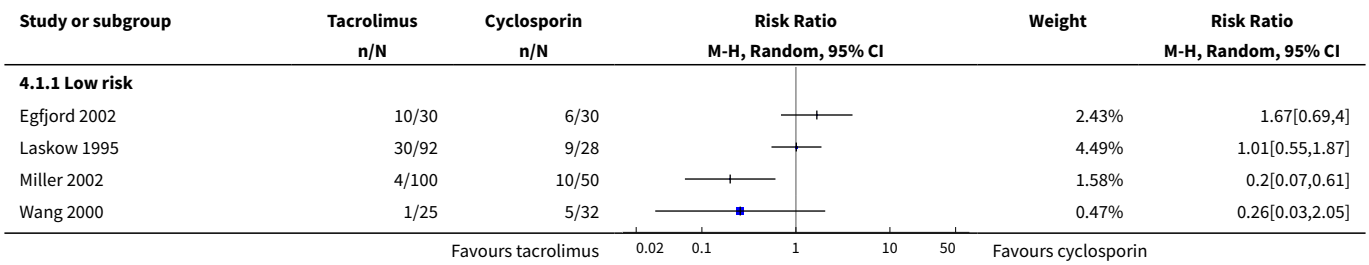




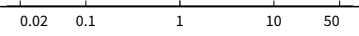
Comparison 4. Stratified analysis, by immunological risk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection (all) 1 year	14	2751	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.80]
1.1 Low risk	4	387	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.25, 1.69]
1.2 Mixed and high risk	10	2364	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.60, 0.73]
2 Graft loss (death censored) 1 year	14	2604	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.02]
2.1 Low risk	5	444	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.17, 1.33]
2.2 Mixed and high risk	9	2160	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.55, 1.12]
3 New requirement for insulin >30 days	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Low risk	5	347	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.49, 2.77]
3.2 Mixed or high risk	7	1666	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.31, 4.19]

Analysis 4.1. Comparison 4 Stratified analysis, by immunological risk, Outcome 1 Acute rejection (all) 1 year.

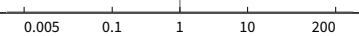


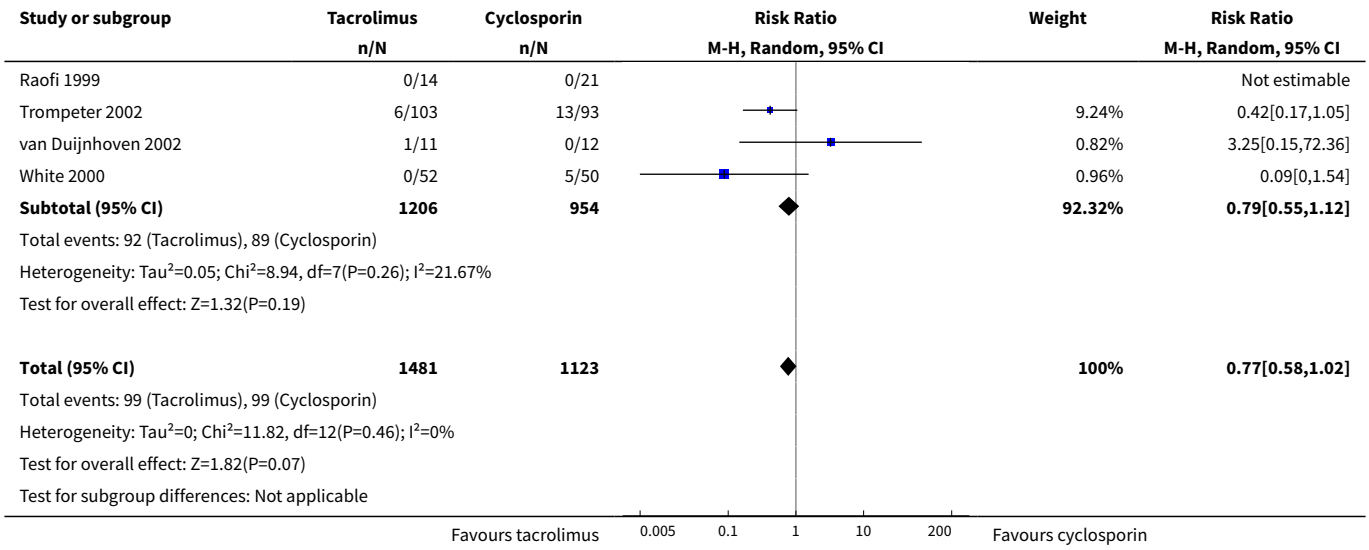
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**247**	**140**		**8.97%**	**0.65[0.25,1.69]**
Total events: 45 (Tacrolimus), 30 (Cyclosporin)					
Heterogeneity: Tau^2=0.64; Chi^2=10.66, df=3(P=0.01); I^2=71.85%					
Test for overall effect: Z=0.89(P=0.37)					
4.1.2 Mixed and high risk					
Campos 2002	35/84	35/80		9.81%	0.95[0.67,1.36]
Johnson 2000	24/148	15/75		4.88%	0.81[0.45,1.45]
Margreiter 2002	98/286	154/271		16.98%	0.6[0.5,0.73]
Mayer 1997	98/303	79/145		15.45%	0.59[0.48,0.74]
Morris-Stiff 1998	21/90	33/89		6.93%	0.63[0.4,1]
Pirsch 1997	63/205	96/207		13.89%	0.66[0.51,0.85]
Radermacher 1998	11/33	8/15		3.82%	0.63[0.32,1.23]
Raofi 1999	2/14	8/21		1.02%	0.38[0.09,1.51]
Trompeter 2002	42/103	57/93		12.5%	0.67[0.5,0.88]
White 2000	18/52	18/50		5.73%	0.96[0.57,1.63]
Subtotal (95% CI)	**1318**	**1046**		**91.03%**	**0.66[0.6,0.73]**
Total events: 412 (Tacrolimus), 503 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=9.01, df=9(P=0.44); I^2=0.06%					
Test for overall effect: Z=8.1(P<0.0001)					
Total (95% CI)	**1565**	**1186**		**100%**	**0.69[0.6,0.8]**
Total events: 457 (Tacrolimus), 533 (Cyclosporin)					
Heterogeneity: Tau^2=0.02; Chi^2=20.4, df=13(P=0.09); I^2=36.28%					
Test for overall effect: Z=5.05(P<0.0001)					
Test for subgroup differences: Not applicable					



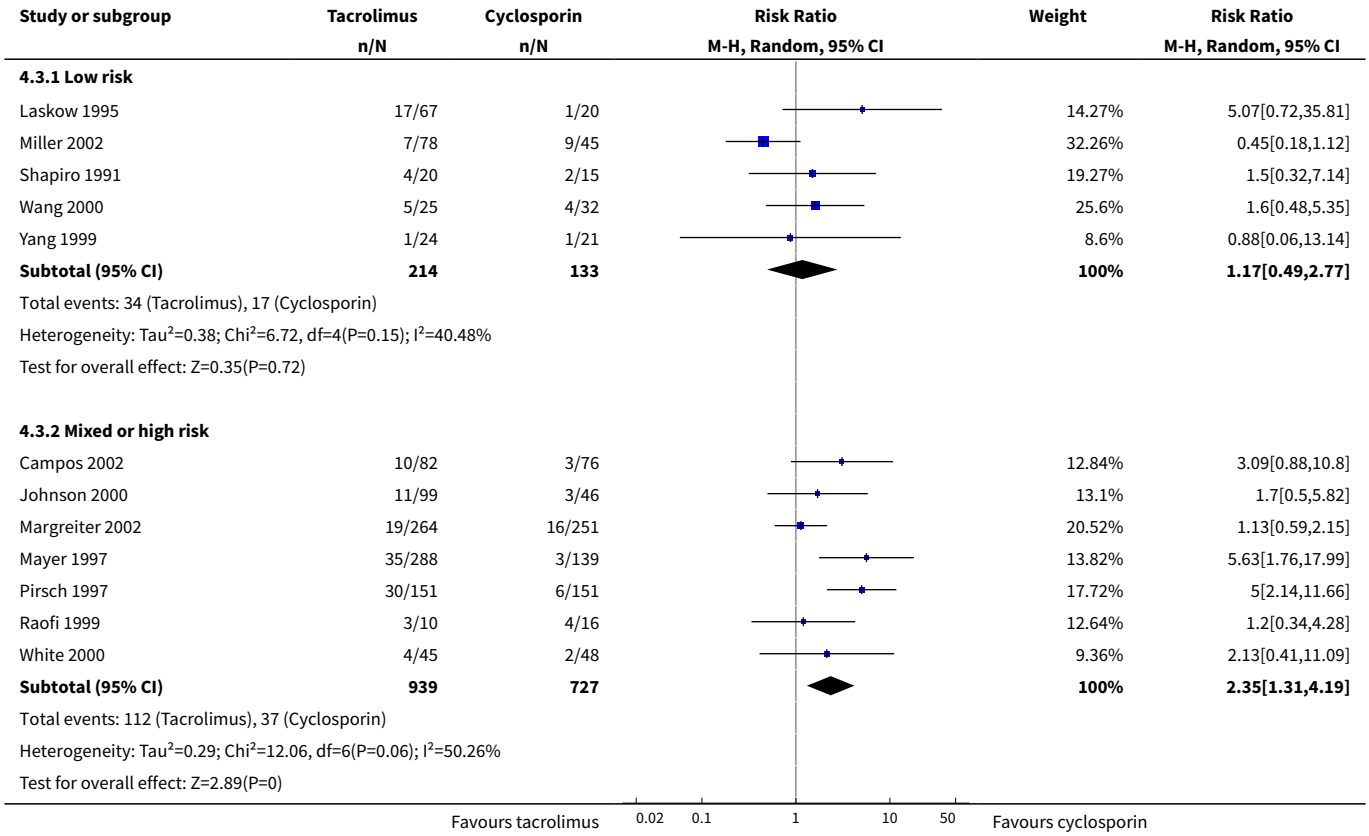
Analysis 4.2. Comparison 4 Stratified analysis, by immunological risk, Outcome 2 Graft loss (death censored) 1 year.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Low risk					
Laskow 1995	4/92	1/28		1.71%	1.22[0.14,10.45]
Miller 2002	1/100	3/50		1.58%	0.17[0.02,1.56]
Shapiro 1991	2/28	3/29		2.7%	0.69[0.12,3.83]
Wang 2000	0/25	2/32		0.88%	0.25[0.01,5.06]
Yang 1999	0/30	1/30		0.79%	0.33[0.01,7.87]
Subtotal (95% CI)	**275**	**169**		**7.68%**	**0.48[0.17,1.33]**
Total events: 7 (Tacrolimus), 10 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=1.98, df=4(P=0.74); I^2=0%					
Test for overall effect: Z=1.4(P=0.16)					
4.2.2 Mixed and high risk					
Campos 2002	12/84	9/80		12.13%	1.27[0.57,2.85]
Johnson 2000	8/148	3/75		4.71%	1.35[0.37,4.95]
Margreiter 2002	17/286	22/271		21.24%	0.73[0.4,1.35]
Mayer 1997	38/303	18/145		28.78%	1.01[0.6,1.71]
Pirsch 1997	10/205	19/207		14.43%	0.53[0.25,1.11]





Analysis 4.3. Comparison 4 Stratified analysis, by immunological risk, Outcome 3 New requirement for insulin >30 days.

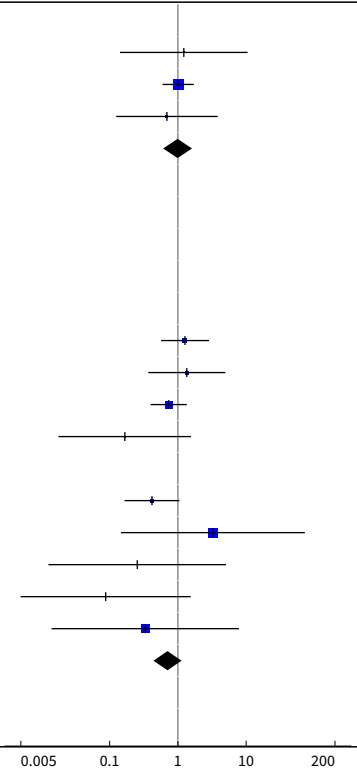


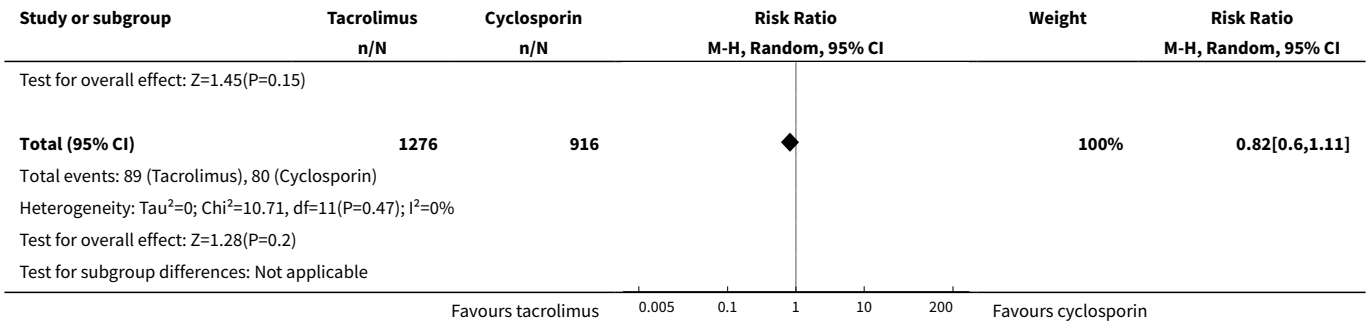
Comparison 5. Stratified analysis, by cyclosporin formulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss (death censored) 1 year	13	2192	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.11]
1.1 Solution	3	625	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.61, 1.61]
1.2 Microemulsion	10	1567	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.44, 1.13]
2 Acute rejection (all) 1 year	14	2751	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.80]
2.1 Solution	4	1028	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.55, 0.75]
2.2 Microemulsion	10	1723	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.57, 0.89]
3 New requirement for insulin >30 days	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Solution	4	851	Risk Ratio (M-H, Random, 95% CI)	4.33 [2.38, 7.87]
3.2 Microemulsion	8	1162	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.79, 1.82]

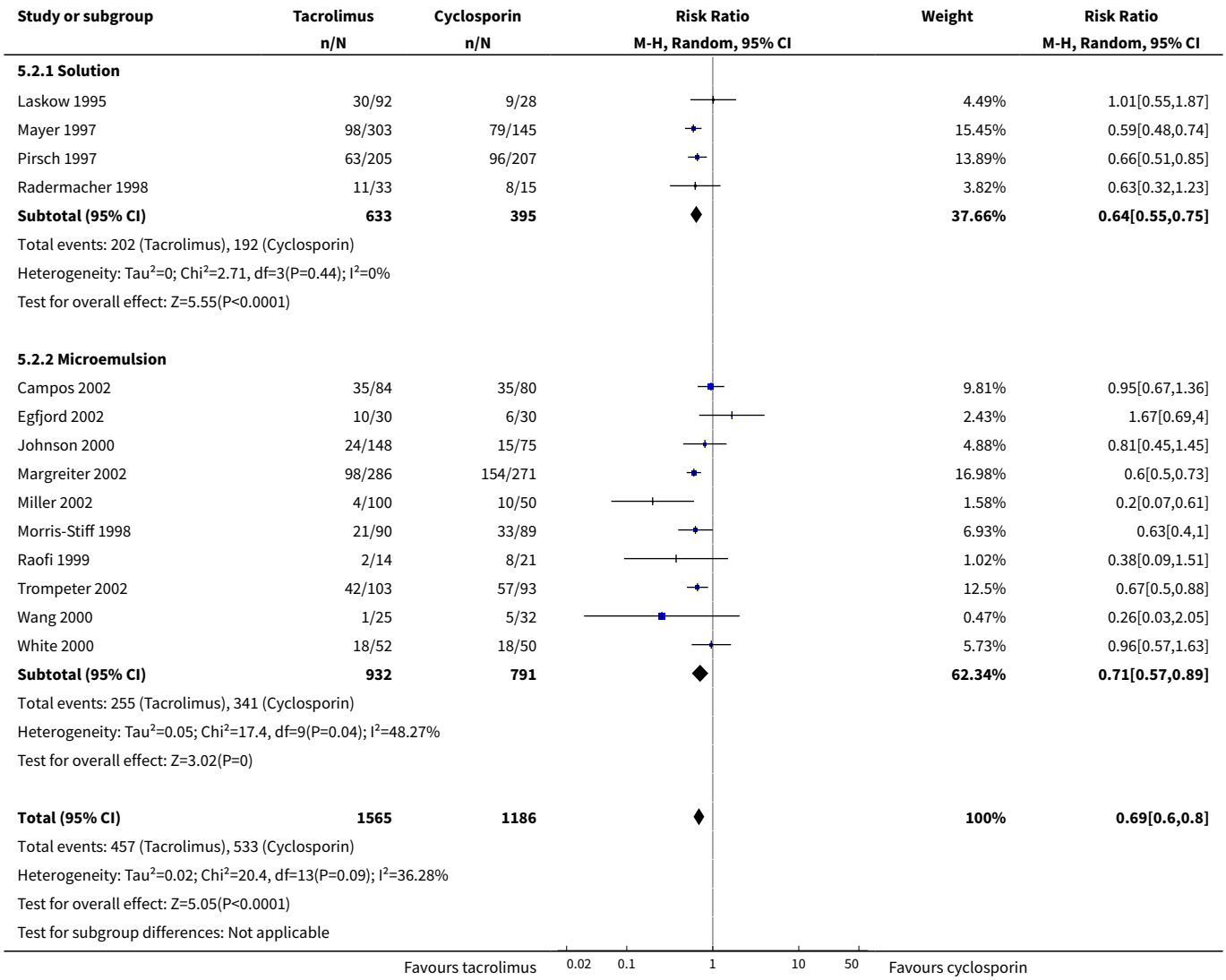
Analysis 5.1. Comparison 5 Stratified analysis, by cyclosporin formulation, Outcome 1 Graft loss (death censored) 1 year.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Solution					
Laskow 1995	4/92	1/28		2%	1.22[0.14,10.45]
Mayer 1997	38/303	18/145		33.63%	1.01[0.6,1.71]
Shapiro 1991	2/28	3/29		3.16%	0.69[0.12,3.83]
Subtotal (95% CI)	**423**	**202**		**38.79%**	**0.99[0.61,1.61]**
Total events: 44 (Tacrolimus), 22 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=2(P=0.9); I^2=0%					
Test for overall effect: Z=0.04(P=0.96)					
5.1.2 Microemulsion					
Campos 2002	12/84	9/80		14.18%	1.27[0.57,2.85]
Johnson 2000	8/148	3/75		5.5%	1.35[0.37,4.95]
Margreiter 2002	17/286	22/271		24.83%	0.73[0.4,1.35]
Miller 2002	1/100	3/50		1.85%	0.17[0.02,1.56]
Raofi 1999	0/14	0/21			Not estimable
Trompeter 2002	6/103	13/93		10.8%	0.42[0.17,1.05]
van Duijnhoven 2002	1/11	0/12		0.96%	3.25[0.15,72.36]
Wang 2000	0/25	2/32		1.03%	0.25[0.01,5.06]
White 2000	0/52	5/50		1.12%	0.09[0,1.54]
Yang 1999	0/30	1/30		0.93%	0.33[0.01,7.87]
Subtotal (95% CI)	**853**	**714**		**61.21%**	**0.7[0.44,1.13]**
Total events: 45 (Tacrolimus), 58 (Cyclosporin)					
Heterogeneity: Tau^2=0.08; Chi^2=9.56, df=8(P=0.3); I^2=16.33%					

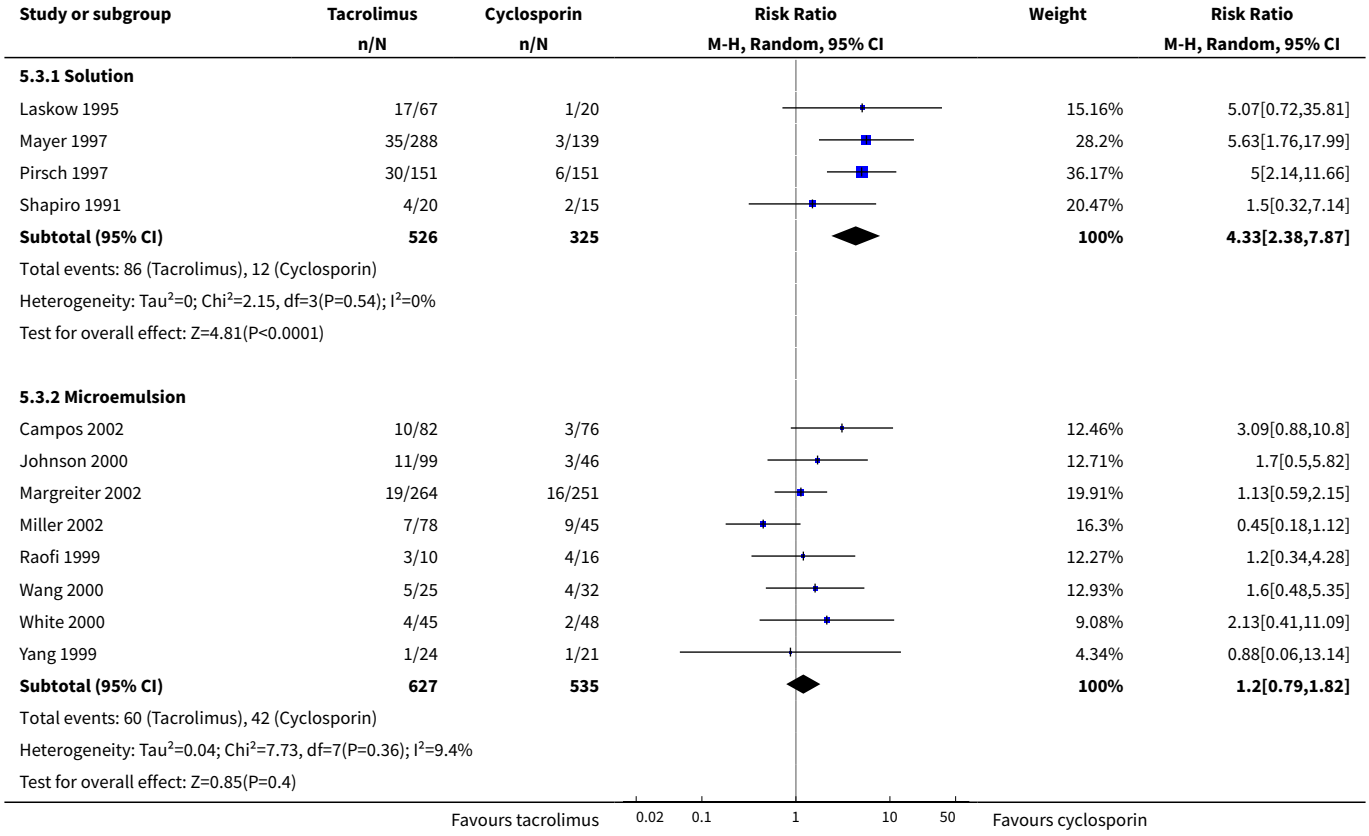




Analysis 5.2. Comparison 5 Stratified analysis, by cyclosporin formulation, Outcome 2 Acute rejection (all) 1 year.



Analysis 5.3. Comparison 5 Stratified analysis, by cyclosporin formulation, Outcome 3 New requirement for insulin >30 days.



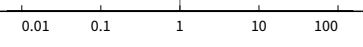
Comparison 6. Stratified analysis, by antiproliferative cointervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft loss (death censored) 1 year	11	1827	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.61, 1.14]
1.1 Azathioprine	8	1600	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.19]
1.2 MMF	3	227	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.10, 1.71]
2 Acute rejection (all) 1 year	12	2386	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.60, 0.76]
2.1 Azathioprine	9	2159	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.59, 0.73]
2.2 MMF	3	227	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.39, 2.08]
3 New requirement for insulin >30 days	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Azathioprine	7	1550	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.34, 4.72]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.2 MMF	4	287	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.65, 3.16]

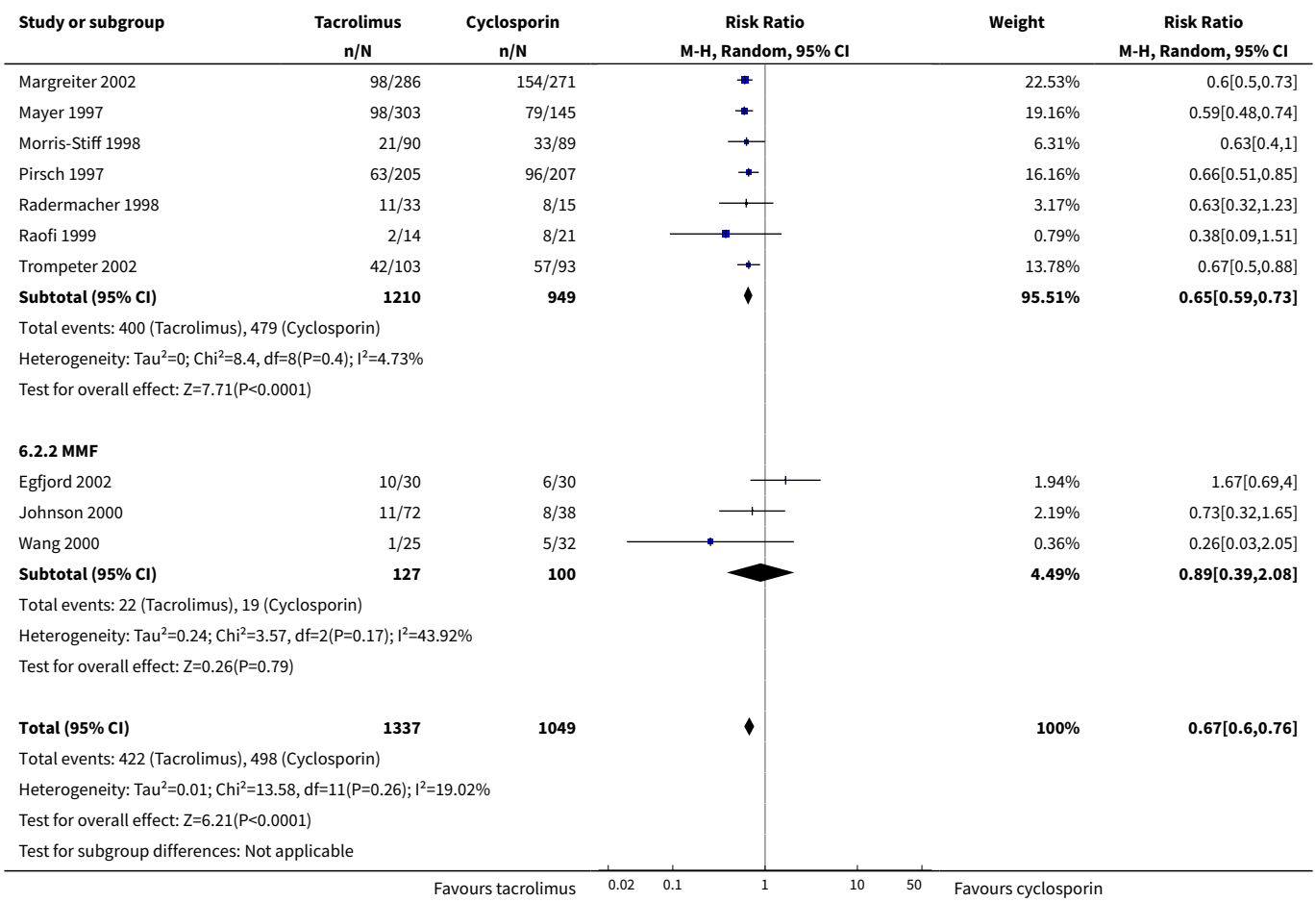
Analysis 6.1. Comparison 6 Stratified analysis, by antiproliferative cointervention, Outcome 1 Graft loss (death censored) 1 year.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Azathioprine					
Campos 2002	12/84	9/80		15.08%	1.27[0.57,2.85]
Laskow 1995	4/92	1/28		2.13%	1.22[0.14,10.45]
Margreiter 2002	17/286	22/271		26.4%	0.73[0.4,1.35]
Mayer 1997	38/303	18/145		35.77%	1.01[0.6,1.71]
Raofi 1999	0/14	0/21			Not estimable
Shapiro 1991	2/28	3/29		3.36%	0.69[0.12,3.83]
Trompeter 2002	6/103	13/93		11.49%	0.42[0.17,1.05]
van Duijnhoven 2002	1/11	0/12		1.02%	3.25[0.15,72.36]
Subtotal (95% CI)	**921**	**679**		**95.24%**	**0.86[0.63,1.19]**
Total events: 80 (Tacrolimus), 66 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=4.75, df=6(P=0.58); I^2=0%					
Test for overall effect: Z=0.89(P=0.37)					
6.1.2 MMF					
Johnson 2000	2/72	2/38		2.67%	0.53[0.08,3.6]
Wang 2000	0/25	2/32		1.1%	0.25[0.01,5.06]
Yang 1999	0/30	1/30		0.99%	0.33[0.01,7.87]
Subtotal (95% CI)	**127**	**100**		**4.76%**	**0.41[0.1,1.71]**
Total events: 2 (Tacrolimus), 5 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=2(P=0.91); I^2=0%					
Test for overall effect: Z=1.23(P=0.22)					
Total (95% CI)	**1048**	**779**		**100%**	**0.83[0.61,1.14]**
Total events: 82 (Tacrolimus), 71 (Cyclosporin)					
Heterogeneity: Tau^2=0; Chi^2=5.95, df=9(P=0.75); I^2=0%					
Test for overall effect: Z=1.14(P=0.25)					
Test for subgroup differences: Not applicable					



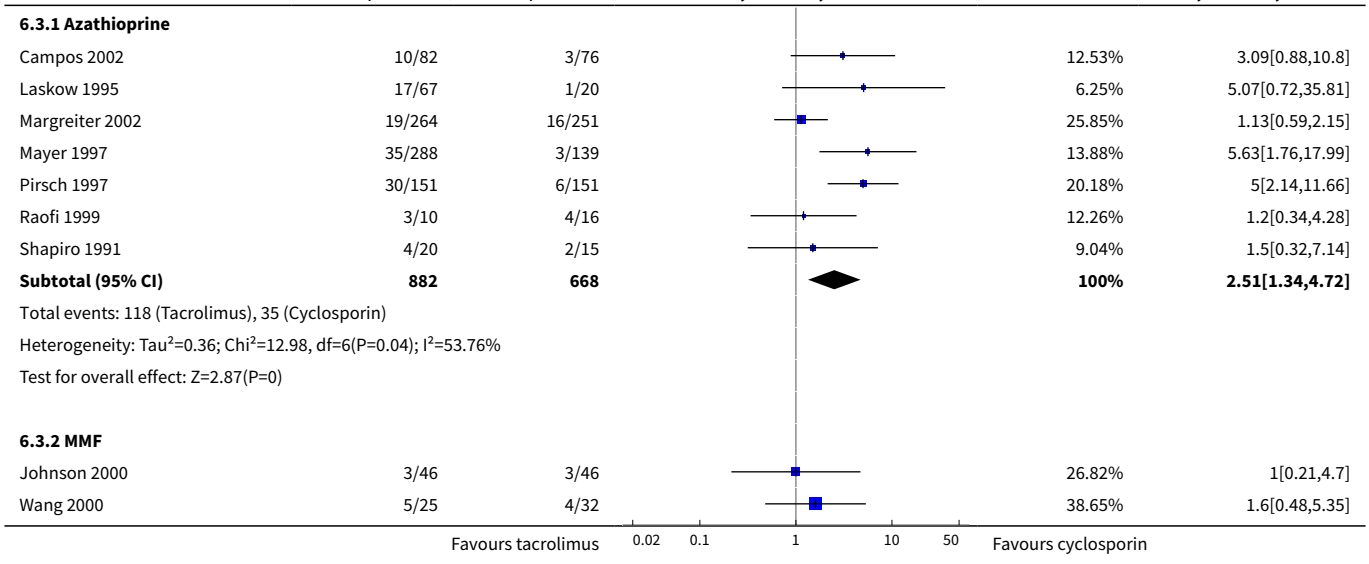
Analysis 6.2. Comparison 6 Stratified analysis, by antiproliferative cointervention, Outcome 2 Acute rejection (all) 1 year.

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Azathioprine					
Campos 2002	35/84	35/80		9.82%	0.95[0.67,1.36]
Laskow 1995	30/92	9/28		3.8%	1.01[0.55,1.87]

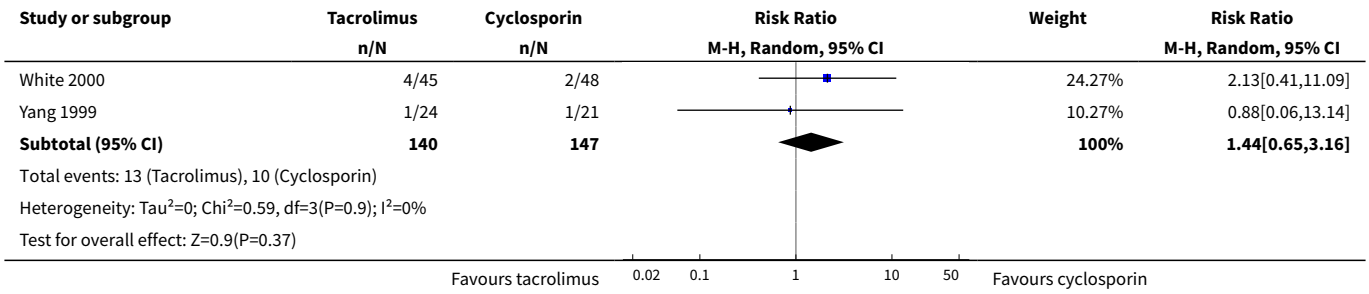


Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Margreiter 2002	98/286	154/271		22.53%	0.6[0.5,0.73]
Mayer 1997	98/303	79/145		19.16%	0.59[0.48,0.74]
Morris-Stiff 1998	21/90	33/89		6.31%	0.63[0.4,1]
Pirsch 1997	63/205	96/207		16.16%	0.66[0.51,0.85]
Radermacher 1998	11/33	8/15		3.17%	0.63[0.32,1.23]
Raofi 1999	2/14	8/21		0.79%	0.38[0.09,1.51]
Trompeter 2002	42/103	57/93		13.78%	0.67[0.5,0.88]
Subtotal (95% CI)	**1210**	**949**		**95.51%**	**0.65[0.59,0.73]**
Total events: 400 (Tacrolimus), 479 (Cyclosporin)					
Heterogeneity: Tau²=0; Chi²=8.4, df=8(P=0.4); I²=4.73%					
Test for overall effect: Z=7.71(P<0.0001)					
6.2.2 MMF					
Egfjord 2002	10/30	6/30		1.94%	1.67[0.69,4]
Johnson 2000	11/72	8/38		2.19%	0.73[0.32,1.65]
Wang 2000	1/25	5/32		0.36%	0.26[0.03,2.05]
Subtotal (95% CI)	**127**	**100**		**4.49%**	**0.89[0.39,2.08]**
Total events: 22 (Tacrolimus), 19 (Cyclosporin)					
Heterogeneity: Tau²=0.24; Chi²=3.57, df=2(P=0.17); I²=43.92%					
Test for overall effect: Z=0.26(P=0.79)					
Total (95% CI)	**1337**	**1049**		**100%**	**0.67[0.6,0.76]**
Total events: 422 (Tacrolimus), 498 (Cyclosporin)					
Heterogeneity: Tau²=0.01; Chi²=13.58, df=11(P=0.26); I²=19.02%					
Test for overall effect: Z=6.21(P<0.0001)					
Test for subgroup differences: Not applicable					

Analysis 6.3. Comparison 6 Stratified analysis, by antiproliferative cointervention, Outcome 3 New requirement for insulin >30 days.



Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Azathioprine					
Campos 2002	10/82	3/76		12.53%	3.09[0.88,10.8]
Laskow 1995	17/67	1/20		6.25%	5.07[0.72,35.81]
Margreiter 2002	19/264	16/251		25.85%	1.13[0.59,2.15]
Mayer 1997	35/288	3/139		13.88%	5.63[1.76,17.99]
Pirsch 1997	30/151	6/151		20.18%	5[2.14,11.66]
Raofi 1999	3/10	4/16		12.26%	1.2[0.34,4.28]
Shapiro 1991	4/20	2/15		9.04%	1.5[0.32,7.14]
Subtotal (95% CI)	**882**	**668**		**100%**	**2.51[1.34,4.72]**
Total events: 118 (Tacrolimus), 35 (Cyclosporin)					
Heterogeneity: Tau²=0.36; Chi²=12.98, df=6(P=0.04); I²=53.76%					
Test for overall effect: Z=2.87(P=0)					
6.3.2 MMF					
Johnson 2000	3/46	3/46		26.82%	1[0.21,4.7]
Wang 2000	5/25	4/32		38.65%	1.6[0.48,5.35]



Comparison 7. Heterogeneity investigation

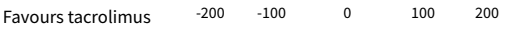
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection (biopsy proven)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 6 months - Charpentier 2002 excluded	6	1050	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.42, 0.87]
1.2 6 months -Margreiter 2002 excluded	6	1048	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.49, 1.12]
1.3 6 months	7	1605	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.48, 0.96]
2 Serum creatinine	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Number participants measured not stated, therefore inferred	4	771	Mean Difference (IV, Random, 95% CI)	-5.47 [-13.71, 2.76]
2.2 Number of participants measured stated	3	168	Mean Difference (IV, Random, 95% CI)	-41.63 [-71.89, -11.36]
3 Graft loss (death censored)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All trials reporting within 1st year, so contributing to meta-regression	19	3403	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.95]
4 New requirement for insulin >30 days	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 1 year	12	2013	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.11, 3.09]
4.2 1 year - Miller 2002 excluded	11	1890	Risk Ratio (M-H, Random, 95% CI)	2.19 [1.42, 3.38]

Analysis 7.1. Comparison 7 Heterogeneity investigation, Outcome 1 Acute rejection (biopsy proven).

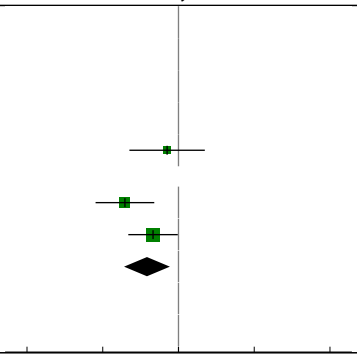
Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 6 months - Charpentier 2002 excluded					
Busque 2001	10/46	2/21		5.69%	2.28[0.55,9.52]
Liu 2003	1/15	1/12		1.79%	0.8[0.06,11.5]
Margreiter 2002	56/286	101/271		35.55%	0.53[0.4,0.7]
Miller 2002	2/100	3/50		3.93%	0.33[0.06,1.93]
Trompeter 2002	17/103	37/93		24.33%	0.41[0.25,0.68]
Tsinalis 2000	15/26	19/27		28.7%	0.82[0.54,1.24]
Subtotal (95% CI)	**576**	**474**		**100%**	**0.61[0.42,0.87]**
Total events: 101 (Tacrolimus), 163 (Cyclosporin)					
Heterogeneity: Tau²=0.07; Chi²=9.04, df=5(P=0.11); I²=44.68%					
Test for overall effect: Z=2.75(P=0.01)					
7.1.2 6 months -Margreiter 2002 excluded					
Busque 2001	10/46	2/21		5.89%	2.28[0.55,9.52]
Charpentier 2002	75/371	39/184		33.29%	0.95[0.68,1.35]
Liu 2003	1/15	1/12		1.86%	0.8[0.06,11.5]
Miller 2002	2/100	3/50		4.07%	0.33[0.06,1.93]
Trompeter 2002	17/103	37/93		25.19%	0.41[0.25,0.68]
Tsinalis 2000	15/26	19/27		29.71%	0.82[0.54,1.24]
Subtotal (95% CI)	**661**	**387**		**100%**	**0.74[0.49,1.12]**
Total events: 120 (Tacrolimus), 101 (Cyclosporin)					
Heterogeneity: Tau²=0.11; Chi²=10.53, df=5(P=0.06); I²=52.51%					
Test for overall effect: Z=1.4(P=0.16)					
7.1.3 6 months					
Busque 2001	10/46	2/21		4.31%	2.28[0.55,9.52]
Charpentier 2002	75/371	39/184		24.33%	0.95[0.68,1.35]
Liu 2003	1/15	1/12		1.36%	0.8[0.06,11.5]
Margreiter 2002	56/286	101/271		26.9%	0.53[0.4,0.7]
Miller 2002	2/100	3/50		2.97%	0.33[0.06,1.93]
Trompeter 2002	17/103	37/93		18.41%	0.41[0.25,0.68]
Tsinalis 2000	15/26	19/27		21.71%	0.82[0.54,1.24]
Subtotal (95% CI)	**947**	**658**		**100%**	**0.68[0.48,0.96]**
Total events: 176 (Tacrolimus), 202 (Cyclosporin)					
Heterogeneity: Tau²=0.1; Chi²=14.83, df=6(P=0.02); I²=59.53%					
Test for overall effect: Z=2.2(P=0.03)					

Analysis 7.2. Comparison 7 Heterogeneity investigation, Outcome 2 Serum creatinine.

Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Cyclosporin N	Cyclosporin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
7.2.1 Number participants measured not stated, therefore inferred							
Heering 1998	8	141.4 (100)	8	132.6 (100)		2.84%	8.84[-89.17,106.85]
Margreiter 2002	284	139 (50.2)	267	147 (86.5)		37.43%	-8[-19.91,3.91]
Pirsch 1997	79	142.3 (44.2)	65	144.1 (35.4)		36.17%	-1.77[-14.77,11.23]
Yang 1999	30	132.6 (48.4)	30	141.4 (48.4)		23.55%	-8.84[-33.34,15.66]
Subtotal * **	**401**		**370**			**100%**	**-5.47[-13.71,2.76]**

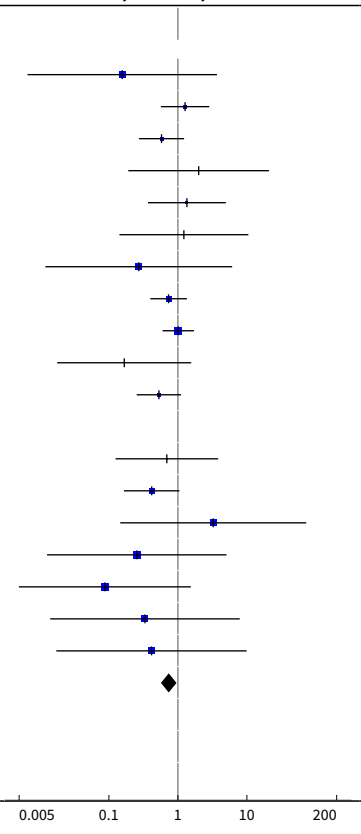


Study or subgroup	Tacrolimus N	Tacrolimus Mean(SD)	Cyclosporin N	Cyclosporin Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.64, df=3(P=0.89); I²=0%							
Test for overall effect: Z=1.3(P=0.19)							
7.2.2 Number of participants measured stated							
Miller 2002	48	122.9 (123.8)	47	137.9 (123.8)		23.34%	-15.02[-64.8,34.76]
Radermacher 1998	28	291.7 (46.8)	13	362.4 (63.8)		34%	-70.72[-109.46,-31.98]
Raofi 1999	12	129.1 (32.2)	20	162.7 (61.9)		42.67%	-33.59[-66.25,-0.93]
Subtotal ***	**88**		**80**			**100%**	**-41.63[-71.89,-11.36]**
Heterogeneity: Tau²=306.89; Chi²=3.49, df=2(P=0.17); I²=42.76%							
Test for overall effect: Z=2.7(P=0.01)							

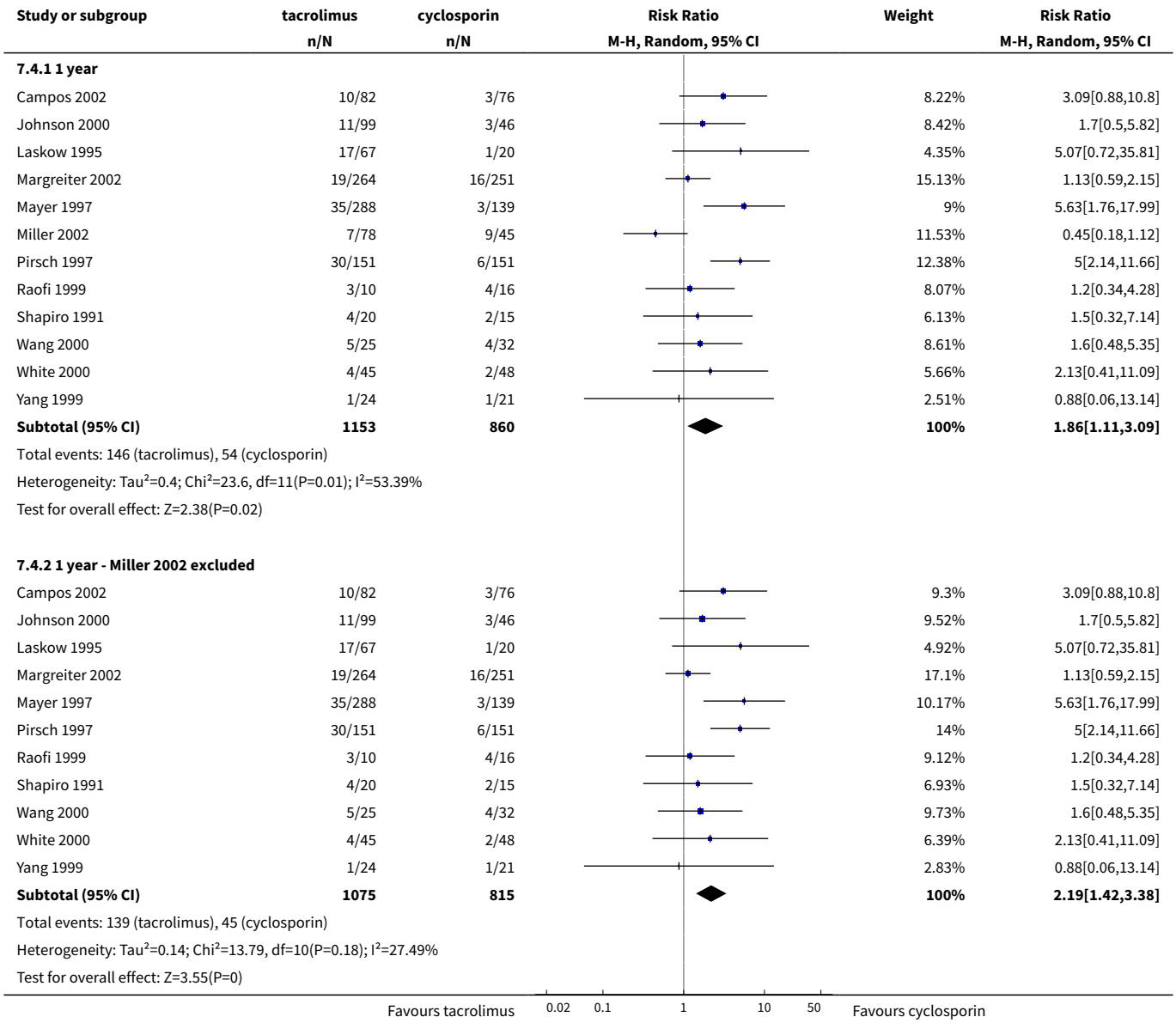


Analysis 7.3. Comparison 7 Heterogeneity investigation, Outcome 3 Graft loss (death censored).

Study or subgroup	Tacrolimus n/N	Cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.3.1 All trials reporting within 1st year, so contributing to meta-regression					
Busque 2001	0/46	1/21		0.67%	0.16[0.01,3.68]
Campos 2002	12/84	9/80		10.29%	1.27[0.57,2.85]
Charpentier 2002	14/371	12/184		11.93%	0.58[0.27,1.23]
Egfjord 2002	2/30	1/30		1.22%	2[0.19,20.9]
Johnson 2000	8/148	3/75		3.99%	1.35[0.37,4.95]
Laskow 1995	4/92	1/28		1.45%	1.22[0.14,10.45]
Liu 2003	0/15	1/12		0.69%	0.27[0.01,6.11]
Margreiter 2002	17/286	22/271		18.02%	0.73[0.4,1.35]
Mayer 1997	38/303	18/145		24.41%	1.01[0.6,1.71]
Miller 2002	1/100	3/50		1.34%	0.17[0.02,1.56]
Pirsch 1997	10/205	19/207		12.24%	0.53[0.25,1.11]
Raofi 1999	0/14	0/21			Not estimable
Shapiro 1991	2/28	3/29		2.29%	0.69[0.12,3.83]
Trompeter 2002	6/103	13/93		7.84%	0.42[0.17,1.05]
van Duijnhoven 2002	1/11	0/12		0.7%	3.25[0.15,72.36]
Wang 2000	0/25	2/32		0.75%	0.25[0.01,5.06]
White 2000	0/52	5/50		0.82%	0.09[0,1.54]
Yang 1999	0/30	1/30		0.67%	0.33[0.01,7.87]
Yu 2000	0/40	1/50		0.67%	0.41[0.02,9.91]
Subtotal (95% CI)	**1983**	**1420**		**100%**	**0.74[0.57,0.95]**
Total events: 115 (Tacrolimus), 115 (Cyclosporin)					
Heterogeneity: Tau²=0; Chi²=14.44, df=17(P=0.64); I²=0%					
Test for overall effect: Z=2.32(P=0.02)					



Analysis 7.4. Comparison 7 Heterogeneity investigation, Outcome 4 New requirement for insulin >30 days.



Study or subgroup	tacrolimus n/N	cyclosporin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.4.1 1 year					
Campos 2002	10/82	3/76		8.22%	3.09[0.88,10.8]
Johnson 2000	11/99	3/46		8.42%	1.7[0.5,5.82]
Laskow 1995	17/67	1/20		4.35%	5.07[0.72,35.81]
Margreiter 2002	19/264	16/251		15.13%	1.13[0.59,2.15]
Mayer 1997	35/288	3/139		9%	5.63[1.76,17.99]
Miller 2002	7/78	9/45		11.53%	0.45[0.18,1.12]
Pirsch 1997	30/151	6/151		12.38%	5[2.14,11.66]
Raofi 1999	3/10	4/16		8.07%	1.2[0.34,4.28]
Shapiro 1991	4/20	2/15		6.13%	1.5[0.32,7.14]
Wang 2000	5/25	4/32		8.61%	1.6[0.48,5.35]
White 2000	4/45	2/48		5.66%	2.13[0.41,11.09]
Yang 1999	1/24	1/21		2.51%	0.88[0.06,13.14]
Subtotal (95% CI)	**1153**	**860**		**100%**	**1.86[1.11,3.09]**
Total events: 146 (tacrolimus), 54 (cyclosporin)					
Heterogeneity: Tau^2=0.4; Chi^2=23.6, df=11(P=0.01); I^2=53.39%					
Test for overall effect: Z=2.38(P=0.02)					
7.4.2 1 year - Miller 2002 excluded					
Campos 2002	10/82	3/76		9.3%	3.09[0.88,10.8]
Johnson 2000	11/99	3/46		9.52%	1.7[0.5,5.82]
Laskow 1995	17/67	1/20		4.92%	5.07[0.72,35.81]
Margreiter 2002	19/264	16/251		17.1%	1.13[0.59,2.15]
Mayer 1997	35/288	3/139		10.17%	5.63[1.76,17.99]
Pirsch 1997	30/151	6/151		14%	5[2.14,11.66]
Raofi 1999	3/10	4/16		9.12%	1.2[0.34,4.28]
Shapiro 1991	4/20	2/15		6.93%	1.5[0.32,7.14]
Wang 2000	5/25	4/32		9.73%	1.6[0.48,5.35]
White 2000	4/45	2/48		6.39%	2.13[0.41,11.09]
Yang 1999	1/24	1/21		2.83%	0.88[0.06,13.14]
Subtotal (95% CI)	**1075**	**815**		**100%**	**2.19[1.42,3.38]**
Total events: 139 (tacrolimus), 45 (cyclosporin)					
Heterogeneity: Tau^2=0.14; Chi^2=13.79, df=10(P=0.18); I^2=27.49%					
Test for overall effect: Z=3.55(P=0)					

ADDITIONAL TABLES

Table 1. Electronic search strategies

Database	Search terms
Cochrane Renal Group's Specialised Register	1. Kidney Transplant* 2. *Kidney-Transplant* 3. Kidney Allograft* 4. Graft Rejection*
CENTRAL	1. kidney transplant$ 2. kidney transplantation/

Table 1. Electronic search strategies *(Continued)*

	3. #1 or #2
MEDLINE and pre-MEDLINE	1. exp kidney transplantation/ 2. exp tacrolimus/ 3. tacrolimus.tw. 4. prograf.tw. 5. FK 506.tw. 6. FK506.tw. 7. Tsukubaenolide.tw. 8. fr-900506.tw. 9 . fujimycin.tw. 10. protopic.tw. 11. or/2-10 12. 1 and 11
EMBASE	1. exp Tsukubaenolide/ 2. prograf?.tw. 3. protopic.tw. 4. tacrolimus.tw. 5. fujimycin.tw. 6. fk506.tw. 7. fk 506.tw. 8. fr-900506.tw. 9. Tsukubaenolide.tw. 10. or/1-9 11. exp Kidney Transplantation/ 12. 10 and 11

Table 2. Subgroup analyses

Potential bias	Graft loss*	P (for interaction)	Acute rejection	P (for interaction)	New diabetes	P (for interaction)
STATISTICAL METHOD - Random effect - Fixed effects	14; 10.77 (0.58 to 1.02)# 14; 0.74 (0.56 to 0.97)	-	14; 0.69 (0.60 to 0.80) 14; 0.67 (0.60 to 0.73)	-	12; 1.86 (1.11 to 3.09) 12; 2.03 (1.49 to 2.76)	-
PUBLICATION TYPE - Abstract or non-peer reviewed journal - Peer reviewed journal	4; 0.75 (0.31 to 1.79) 10; 0.75 (0.55 to 1.02)	0.36	3; 1.02 (0.57 to 1.82) 11; 0.64 (0.57 to 0.72)	0.01	3; 2.10 (0.94 to 4.29) 9; 1.84 (0.95 to 3.57)	0.89
TRIAL QUALITY	8; 0.70 (0.44 to 1.12) 6; 0.83 (0.55 to 1.23)	0.86	7; 0.77 (0.59 to 1.01) 7; 0.63 (0.54 to 0.73)	0.10	5; 2.09 (1.11 to 3.96) 7; 1.49 (0.74 to 3.01)	0.87

Table 2. Subgroup analyses *(Continued)*

- ITT analysis unclear or not undertaken - ITT analysis performed						
TRIAL POPULATION - low immunological risk - Mixed and high immunological risk	5; 0.48 (0.17 to 1.33) 9; 0.79 (0.55 to 1.12)	0.35	4; 0.65 (0.25 to 1.69) 10; 0.66 (0.60 to 0.73)	0.33	5; 1.02 (0.46 to 2.27) 7; 2.24 (1.43 to 3.49)	0.16
* censored for death	# Number of studies; RR (95% CI)					

Table 3. Meta-regression and confounding

Potential confounder	Graft loss*		Acute rejection		New diabetes#	
	UNADJUSTED RR (95% CI); P value	ADJUSTED ++ RR (95% CI); P value	UNADJUSTED RR (95% CI); P value	ADJUSTED RR (95% CI); P value	UNADJUSTED RR (95% CI); P value	UNADJUSTED RR (95% CI); P value
Cyclosporin microemulsion versus solution	0.83 (0.49 to 1.40); 0.48	1.01 (0.52 to 1.95); 0.97	1.10 (0.88 to 1.36); 0.40	0.99 (0.78 to 1.28); 0.99	0.35 (0.17 to 0.74); 0.006	0.30 (0.13 to 0.66); 0.003
Cyclosporin trough (per 25 ng/mL)+	1.02 (0.89 to 1.47); 0.76	0.92 (0.77 to 1.11); 0.38	1.06 (1.01 to 1.11); 0.02	1.07 (0.98 to 1.17); 0.14	1.03 (0.79 to 1.33); 0.83	1.05 (0.86 to 1.29); 0.61
Cyclosporin trough (per 1 ng/mL)+	1.20 (1.02 to 1.41); 0.04	1.33 (1.02 to 1.74); 0.04	1.04 (0.99 to 1.08); 0.10	0.98 (0.83 to 1.14); 0.77	1.20 (1.05 to 1.38); 0.007	1.18 (0·97 to 1·45); 0.10
Mycophenolate versus azathioprine	0.73 (0.23 to 2.29); 0.59	NA[a]	1.47 (0.88 to 2.48); 0.14	0.99 (0.52 to 1.91); 0.98	NA	NA

Table 3. Meta-regression and confounding *(Continued)*

+ see results section	* censored for death	++ See results section [a] Not available. See text	# new insulin-treated see results section

(*) Censored for death.
(#) New insulin-treated diabetes mellitus.
(+) Cyclosporin and tacrolimus levels are calculated by taking the weighted average of the 'intention-to-treat' target trough range values over the first year post transplantation, in ng/mL, using the stated initial target trough range and the target from three months post-transplantation.
(++) Adjusted ratio for each outcome is for multivariate model containing all explanatory variables that have an adjusted ratio quoted.
([a]) Not available. Insufficient data reported across studies, so limiting the number of possible confounders that could be controlled for in the multivariate model. Multivariate model limited to those factors felt, a priori, to be of most clinical interest and have most potential to confound the analysis.

Table 4. Applicability in clinical practice - absolute risk per 100 treated recipients

Immunological risk	Acute rejection*			Graft loss			Diabetes mellitus		
	Cyclosporin	Tacrolimus	Avoided cases+	Cyclosporin	Tacrolimus	Avoided cases	Cyclosporin	Tacrolimus	Avoided cases
LOW	20	14	6	6	5	1	6	11	5
MEDIUM	40	28	12	9	7	2	6	11	5
HIGH	55	38	17	11	8	3	6	11	5
+ see results section	* see results section								

(+) Calculated as absolute risk reduction/increase.
(*) Cyclosporin rates for acute rejection were calculated using summary rate in cyclosporin (control) arms of studies. Studies were grouped by immunological risk of participating population, based on known associations; age, race, PRA level, prior transplantation. These estimates were corroborated with current cohort data (ANZDATA). Rates of graft loss and diabetes were derived from the summary rates of these outcomes in the cyclosporine (control) arms of studies reported at one year. Tacrolimus rate calculated on basis of overall RR 0.69 for acute rejection, RR 0.77 for death-censored graft loss, and RR 1.86 for new onset diabetes mellitus requiring insulin for >30 days, all at one year post-transplantation.

WHAT'S NEW

Date	Event	Description
26 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Angela Webster conceived, designed and developed the protocol and search strategy for the review, contacted authors and pharmaceutical companies, identified and extracted data from included studies, analysed and interpreted the results and wrote the manuscript. She takes responsibility for the integrity of the data and the accuracy of the data analysis, and is guarantor for this manuscript.
- Rod Taylor identified and extracted data from included studies, and participated in interpretation of results and revision of the manuscript.
- Jeremy Chapman contributed to the protocol development, and participated in interpretation of results and revision of the manuscript.
- Jonathan Craig contributed to the conception, design and development of the protocol, the analysis and interpretation of the results and to the drafting and revision of the manuscript.

DECLARATIONS OF INTEREST

- **Cochrane Renal Group (AW, JCC)**: The Cochrane renal group receives financial support from several sources including government and industry. These funds go into a general fund managed by the Children's Hospital at Westmead. These funds are used to support key activities including hand-searching, the development of a studies registry, training and support for reviewers conducting reviews, and consumer participation in the group. Those contributing funds have no rights of authorship or publication. The authors of the review retain the right to interpretation of the results and the right to publish. Funding sources are/have been ; Amgen Australia (past), Amgen Inc (past), Aventis Pharma (past), Janssen-Cilag (past), Novartis Pharmaceuticals (past), Servier (past), Wyeth Australia (past), Australian Department of Health and Ageing, Australian Kidney Foundation, Australian and New Zealand Society of Nephrology, National Health and Medical Research Council of Australia.
- **AW** receives indirect support for infrastructure costs associated with unrelated research with ANZDATA, the dialysis and transplant registry of Australia and New Zealand, in the form of an unrestricted educational grant from Novartis Pharmaceuticals Australia.
- **JRC** has advisory board and clinical study involvement with Novartis, Roche, Janssen-Cilag, Fujisawa and Wyeth, and has also been an invited speaker at national and international meetings sponsored by these companies.
- **RT** declares no conflicts of interest
- **RW** declares no conflicts of interest

INDEX TERMS

Medical Subject Headings (MeSH)

*Kidney Transplantation; Cyclosporine [*therapeutic use]; Graft Rejection [*prevention & control]; Immunosuppressive Agents [*therapeutic use]; Kidney Failure, Chronic [surgery]; Randomized Controlled Trials as Topic; Tacrolimus [*therapeutic use]

MeSH check words

Humans