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Treatment for lupus nephritis (Review)

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[Intervention Review]

Treatment for lupus nephritis

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ABSTRACT

Background

Cyclophosphamide, in combination with corticosteroids has been used to induce remission in proliferative lupus nephritis, the most common kidney manifestation of the multisystem disease, systemic lupus erythematosus. Cyclophosphamide therapy has reduced mortality from over 70% in the 1950s and 1960s to less than 10% in recent years. Cyclophosphamide combined with corticosteroids preserves kidney function but is only partially effective and may cause ovarian failure, infection and bladder toxicity. Several new agents, including mycophenolate mofetil (MMF), suggest reduced toxicity with equivalent rates of remission. This is an update of a Cochrane review first published in 2004.

Objectives

To assess the benefits and harms of different immunosuppressive treatments in biopsy-proven proliferative lupus nephritis.

Search methods

For this update, we searched the Cochrane Renal Group's Specialised Register (up to 15 April 2012) through contact with the Trials' Search Coordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs comparing any treatments for biopsy-proven lupus nephritis in both adult and paediatric patients with class III, IV, V +III and V +IV lupus nephritis were included. All immunosuppressive treatments were considered.

Data collection and analysis

Data were abstracted and quality assessed independently by two authors, with differences resolved by discussion. Dichotomous outcomes were reported as risk ratio (RR) and measurements on continuous scales reported as mean differences (MD) with 95% confidence intervals (CI).

Main results

We identified 50 RCTs involving 2846 participants. Of these, 45 studies (2559 participants) investigated induction therapy, and six studies (514 participants), considered maintenance therapy.

Compared with intravenous (IV) cyclophosphamide, MMF was as effective in achieving stable kidney function (5 studies, 523 participants: RR 1.05, 95% CI 0.94 to 1.18) and complete remission of proteinuria (6 studies, 686 participants: RR 1.16, 95% CI 0.85 to 1.58). No differences in mortality (7 studies, 710 participants: RR 1.02, 95% CI 0.52 to 1.98) or major infection (6 studies, 683 participants: RR 1.11, 95% CI 0.74 to 1.68) were observed. A significant reduction in ovarian failure (2 studies, 498 participants: RR 0.15, 95% CI 0.03 to 0.80) and alopecia (2 studies, 522 participants: RR 0.22, 95% CI 0.06 to 0.86) was observed with MMF. In maintenance therapy, the risk of renal relapse (3 studies, 371 participants: RR 1.83, 95% CI 1.24 to 2.71) was significantly higher with azathioprine compared with MMF. Multiple other interventions were compared but outcome data were relatively sparse. Overall study quality was variable. The internal validity of the design, conduct and analysis of the included RCTs was difficult to assess in some studies because of the omission of important methodological details. No study adequately reported all domains of the risk of bias assessment so that elements of internal bias may be present.

Authors' conclusions

MMF is as effective as cyclophosphamide in inducing remission in lupus nephritis, but is safer with a lower risk of ovarian failure. MMF is more effective than azathioprine in maintenance therapy for preventing relapse with no increase in clinically important side effects. Adequately powered trials with long term follow-up are required to more accurately define the risks and eventual harms of specific treatment regimens.

PLAIN LANGUAGE SUMMARY

Treatment for people with lupus nephritis

Lupus nephritis is an inflammatory condition affecting the kidneys which is caused by systemic lupus erythematosus (SLE), an autoimmune disease that is more common among women. About half of all people with SLE develop lupus nephritis, and of these about 1/10 experience chronic kidney disease or kidney failure. Treatment aims to delay disease progression and achieve remission by stabilising and improving kidney function and minimising side effects. For about the past 30 years, standard treatment for lupus nephritis has focused on a combination of cyclophosphamide (an alkylating agent) and corticosteroids.

We found that the drug mycophenolate mofetil (MMF) was as effective as cyclophosphamide in combination with corticosteroids in achieving remission in people with lupus nephritis. MMF has fewer harmful effects including ovarian failure, decreased ability to fight infections (leucopenia) and hair loss (alopecia). MMF was superior to azathioprine (an immunosuppressive drug) in combination with corticosteroids at preventing renal relapse when used as maintenance therapy.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. MMF versus IV cyclophosphamide for induction therapy

Patient or population: Patients with induction therapy in lupus nephritis
Settings:
Intervention: Mycophenolate mofetil
Comparison: Intravenous cyclophosphamide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intravenous cyclophosphamide	Mycophenolate mofetil				
Mortality Follow-up: mean 24 weeks	**Low**		**RR 1.02** (0.52 to 1.98)	710 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	40 per 1000	**41 per 1000** (21 to 79)				
	High					
	120 per 1000	**122 per 1000** (62 to 238)				
Complete renal remission Follow-up: mean 24 weeks	**Low**		**RR 1.39** (0.99 to 1.95)	686 (6 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	150 per 1000	**209 per 1000** (149 to 293)				
	Moderate					
	169 per 1000	**235 per 1000** (167 to 330)				
	High					
	200 per 1000	**278 per 1000**				

		(198 to 390)			
Alopecia Follow-up: mean 24 weeks	**Study population**		**RR 0.22** (0.06 to 0.86)	522 (2 studies)	⊕⊕⊙⊙ **low**[1,3]
	282 per 1000	**62 per 1000** (17 to 243)			
	Low				
	107 per 1000	**24 per 1000** (6 to 92)			
	High				
	356 per 1000	**78 per 1000** (21 to 306)			
Major infection Follow-up: mean 24 weeks	**Low**		**RR 1.11** (0.74 to 1.68)	683 (6 studies)	⊕⊕⊕⊙ **moderate**[1,2]
	80 per 1000	**89 per 1000** (59 to 134)			
	Moderate				
	109 per 1000	**121 per 1000** (81 to 183)			
	High				
	220 per 1000	**244 per 1000** (163 to 370)			
Ovarian failure	**Low**		**RR 0.15** (0.03 to 0.8)	498 (2 studies)	⊕⊕⊕⊕ **high**[1,2,4]
	30 per 1000	**5 per 1000** (1 to 24)			
	High				
	44 per 1000	**7 per 1000** (1 to 35)			
Leucopenia Follow-up: mean 24 weeks	**Low**		**RR 0.48** (0.25 to 0.91)	613 (5 studies)	⊕⊕⊕⊕ **high**[1,3]

	50 per 1000	**24 per 1000** (12 to 46)			
	Moderate				
	199 per 1000	**96 per 1000** (50 to 181)			
	High				
	520 per 1000	**250 per 1000** (130 to 473)			
Diarrhoea Follow-up: mean 24 weeks	**Low**		**RR 2.53** (1.54 to 4.16)	569 (3 studies)	⊕⊕⊕⊕ **high**[1,3]
	27 per 1000	**68 per 1000** (42 to 112)			
	Moderate				
	87 per 1000	**220 per 1000** (134 to 362)			
	High				
	128 per 1000	**324 per 1000** (197 to 532)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: Confidence interval; **RR:** risk ratio

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

[1] Total number of events small
[2] Confidence interval of pooled estimate of effect includes no effect and significant difference in effect RR increase > 25%)
[3] Large magnitude of effect
[4] Very large magnitude of effect

Summary of findings 2. Azathioprine versus MMF for maintenance therapy

Patient or population: Patients with maintenance treatment in lupus nephritis
Settings:
Intervention: Azathioprine
Comparison: Mycophenolate mofetil

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Mycophenolate mofetil	Azathioprine				
Mortality Follow-up: 36 to 72 months	**Low**		**RR 0.58** (0.1 to 3.49)	371 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	38 per 1000	**22 per 1000** (4 to 133)				
	High					
	50 per 1000	**29 per 1000** (5 to 175)				
Renal relapse Follow-up: 36 to 72 months	**Low**		**RR 1.83** (1.24 to 2.71)	371 (3 studies)	⊕⊕⊕⊖ **moderate**[2]	
	150 per 1000	**275 per 1000** (186 to 407)				
	Moderate					
	155 per 1000	**284 per 1000** (192 to 420)				
	High					
	189 per 1000	**346 per 1000** (234 to 512)				

Major infection Follow-up: median 53 months	**Moderate**		**RR 0.87** (0.31 to 2.43)	105 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2]
	132 per 1000	**115 per 1000** (41 to 321)			
Malignancy Follow-up: 36 to 72 months	**Moderate**		**RR 4.04** (0.45 to 36.07)	370 (3 studies)	⊕⊕⊕⊕ **high**[1, 2, 3]
	0 per 1000	**0 per 1000** (0 to 0)			
Leucopenia Follow-up: 36 to 53 months	**Low**		**RR 6.21** (1.69 to 22.85)	331 (2 studies)	⊕⊕⊕⊕ **high**[2, 4]
	0 per 1000	**0 per 1000** (0 to 0)			
	High				
	38 per 1000	**236 per 1000** (64 to 868)			
GI disturbance Follow-up: median 53 months	**Moderate**		**RR 1.02** (0.41 to 2.51)	105 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2]
	151 per 1000	**154 per 1000** (62 to 379)			
Alopecia Follow-up: median 53 months	**Moderate**		**RR 0.51** (0.05 to 5.45)	105 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2]
	38 per 1000	**19 per 1000** (2 to 207)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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

[1] Estimate of effect includes negligible difference and considerable benefit
[2] Small number of events
[3] Large magnitude of effect

4 Very large magnitude of effect

BACKGROUND

Lupus nephritis occurs in about half of all people with systemic lupus erythematosus (SLE), leading to end-stage kidney disease (ESKD) in 5% to 10% of patients at 10 years (Houssiau 2010). Predominantly affecting young women, lupus nephritis is also more common in certain racial groups, particularly African-Americans who may also have a more aggressive and less treatment-responsive form of the disease.

Kidney involvement ranges from mild subclinical disease, which is associated with a low chance of progression and favourable outcome, to full blown nephritic and/or nephrotic syndrome with kidney impairment and greater risk of progression to ESKD. In Australia, approximately 1% of patients commencing dialysis had ESKD as a consequence of lupus nephritis (ANZDATA 2009).

Renal biopsy is required for the precise diagnosis and classification of lupus nephritis. Histological classification was introduced by the World Health Organization (WHO) in 1982 and revised in 2003 by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS). ISN/RPS 2003 class I and II lesions have a good prognosis and are generally not an indication for specific therapy. Proliferative disease (WHO class III, IV, V + III and V + IV) is more fulminant and requires aggressive treatment to induce remission and prevent significant kidney injury and premature death. WHO class IV lupus nephritis is the most aggressive form of the condition, and has the worst prognosis without intensive immunosuppressive treatment. Without intensive immunosuppressive treatment, five-year survival has been reported at 17% (Cameron 1999).

Cyclophosphamide-containing regimens were established as first-line therapy for inducing remission based on studies undertaken at the National Institutes of Health in the 1970s and 1980s. Therapy increased survival to 82% by the early 1990s, and is now greater than 90% (Houssiau 2010; Mok 2002). Response to treatment is often slow, and although remission is induced in a significant proportion of patients, the risk or relapse or flare remains considerable; variably has been reported at between 18% and 46% (Ponticelli 1998).

We conducted a systematic review of immunosuppressive treatment of proliferative lupus nephritis in 2004. Our 2004 review identified 25 RCTs that enrolled a total of 915 participants were included for analysis. Our conclusion was that cyclophosphamide combined with steroids was the preferred option to preserve kidney function in people with proliferative lupus nephritis (Flanc 2004b). In the past five years, numerous trials evaluating newer agents (MMF, tacrolimus and rituximab) have been published, all of which have been proposed as alternative, potentially less toxic, and more effective therapies.The aim of our updated review was to evaluate the relative effects of all available immunosuppressive therapies for the induction and maintenance treatment of lupus nephritis.

OBJECTIVES

Our objective was to assess the evidence and evaluate the benefits and harms of different immunosuppressive treatments in people with biopsy-proven lupus nephritis.

The following questions relating to management of proliferative lupus nephritis were addressed:

1. Are new immunosuppressive agents superior to or as effective as cyclophosphamide plus corticosteroids?
2. If so, which agents, doses, routes of administration and duration of therapy should be used?
3. Which toxicities occur with the different treatment regimens?

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-RCTs, whether published or available only in abstract form, that evaluated any of the treatment options in the focus of this review, singularly or in combination determining the benefits and harms of different treatment options for lupus nephritis.

Types of participants

We included all adult and paediatric patients with biopsy-proven proliferative lupus nephritis.

Types of interventions

We considered studies that investigated the following treatment options for either induction or maintenance therapies for lupus nephritis.

- Corticosteroids including prednisone and methylprednisolone
- Other immunosuppressive agents including azathioprine, cyclophosphamide, mycophenolate mofetil (MMF), tacrolimus and cyclosporin
- Plasma exchange or plasmapheresis
- Antibody agents (e.g. B cell depleting agents).

Non-specific treatment options (e.g. antihypertensive agents) were not included in the present analysis because these do not specifically aim to treat underlying lupus nephritis, but rather more generally, aim to prevent the progression of chronic kidney disease (CKD).

Types of outcome measures

The following dichotomous outcome measures were considered.

- All-cause mortality
- ESKD, requirement for renal replacement therapy
- Relapse of lupus nephritis
- Doubling of serum creatinine
- Deterioration of kidney function, defined as more than 20% worsening of serum creatinine
- Stable kidney function, defined as a less than 20% worsening of serum creatinine
- Remission in proteinuria: complete and partial. Complete remission in proteinuria was defined as urinary protein excretion ≤ 0.3 g/24 h (Chan 2000). Partial remission in proteinuria was defined as < 3.0 g/d protein if baseline ≥ 3.0 g/d or ≥ 50% reduction if < 3.0 g/d at baseline (Appel 2009)
- Renal remission: complete and partial. Complete renal remission was defined as return to normal serum creatinine, urinary protein excretion < 0.5 g/24 h, and inactive urinary sediment and partial renal remission as a fall to < 3.0 g/d protein

if baseline ≥ 3.0 g/d or ≥ 50% reduction if < 3.0 g/d at baseline and stabilisation of serum creatinine ± 25% (Appel 2009).

The following side effects (toxicity) of treatments were considered.

- Major infection (all cause infection excluding herpes zoster infection)
- Herpes zoster virus infection
- Ovarian failure (sustained amenorrhoea)
- Bone toxicity (avascular necrosis or fracture)
- Bladder toxicity (haemorrhagic cystitis)
- Development of any malignancy
- Alopecia
- Leucopenia defined as < 4 x 10^9 cells/L
- Gastrointestinal adverse effects including diarrhoea, vomiting and nausea.

The following continuous outcomes were analysed at the end of treatment.

- Serum creatinine (µmol/L)
- Creatinine clearance (mL/min)
- Daily proteinuria (24 hour urinary protein excretion) (g/24 h).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register (up to 15 April 2012) through contact with the Trials' Search Coordinator using search terms relevant to this review.

The Cochrane Renal Group's Specialised Register contains studies identified from:

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

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Renal Group.

See Appendix 1 for search terms used in strategies for this review.

Please refer to previous version of this review (Flanc 2004b) for a detailed description of the initial literature search methods.

Searching other resources

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

Data collection and analysis

Selection of studies

The search strategy described was performed to identify eligible studies. The titles and abstracts resulting from the searches were screened by two authors (LKH, PM) who independently assessed retrieved abstracts, and if necessary the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third author (ACW).

Where duplication reports of the same study were confirmed, the initial first complete publication was selected (the index publication) and was the primary data source, but any other additional prior or subsequent reports were also included. These additional prior or subsequent reports containing supplementary outcome data (such as longer-term follow up, or different outcomes) also contributed to the meta-analysis.

Data extraction and management

Data abstraction was performed independently by two authors (LKH, PM) using a standardised form. Unclear data were clarified by contacting the author of the study report and any relevant data obtained in this manner was included in the review (see Acknowledgements). Data were entered into RevMan 5.1 (LKH).

Assessment of risk of bias in included studies

The following items were independently assessed by two authors (LKH, PM) using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

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

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, ESKD, renal relapse, doubling of serum creatinine, stable kidney function, major infection, herpes zoster infection, ovarian failure, bone toxicity, bladder toxicity, alopecia, malignancy, gastrointestinal disorders, leucopenia, complete or partial renal remission, complete or partial remission of proteinuria) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (serum creatinine, creatinine clearance, urinary protein excretion) the mean difference (MD) with 95% CI was used at the end of treatment.

Dealing with missing data

Where a study reported outcome data after excluding some randomised participants from the denominator, if sufficient information was reported elsewhere, or was supplied by the study authors, we included missing participants in the analyses.

Assessment of heterogeneity

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 2011).

Assessment of reporting biases

Detection of potential for publication bias was planned for among the primary outcomes using funnel plots of the log odds ratio (OR) (Higgins 2011). However, the limited amount of study data published did not enable meaningful interpretation. We had also planned to conduct subgroup analysis and meta-regression to evaluate potential sources of heterogeneity but this was not possible because of the small number of studies of paired interventions.

Data synthesis

Data were abstracted from individual studies and then pooled for summary estimates using a random-effects model. The random-effects model was chosen because it provides a more conservative estimate of effect in the presence of known or unknown potential heterogeneity (Deeks 2001).

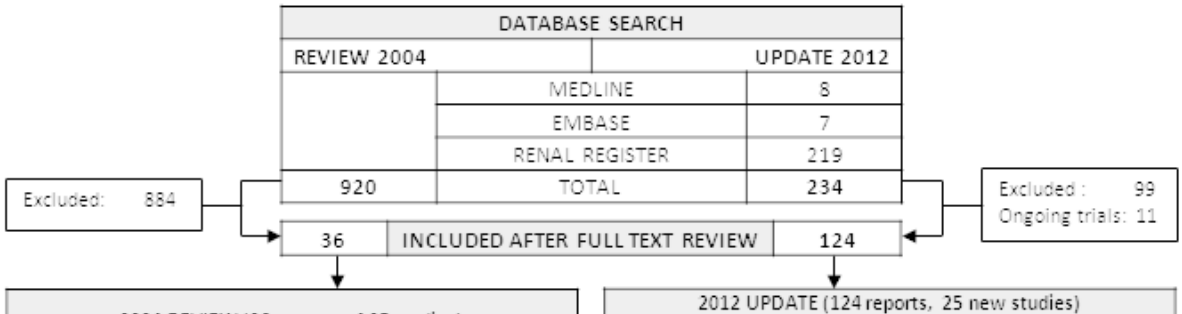
RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

The process of identifying reports of RCTs for inclusion in the original review and in the update are outlined (Figure 1). In this updated review, a total of 231 articles were initially identified, of which 99 were excluded. The major reasons for exclusion were:

Figure 1. Flow chart showing study selection and interventions used for the original and current review update. *Includes continuation of 227 'induction' patients to 'maintenance' phase of Appel 2009; †further data published on 22 new patients from Chan 2000.



2004 REVIEW (36 reports of 25 studies)

Intervention	Studies	Participants
Induction	23	861
MMF vs CPA	1	42
High vs low dose CPA	1	90
Long vs short course CPA	1	65
CPA ± steroid vs steroid	6	200
CYC or AZA + steroid vs steroid	1	111
AZA ± steroid vs steroid	3	94
CSA vs steroid	1	10
PEX + IS vs IS	5	173
IV vs oral steroid	1	22
PEX vs IS	2	40
Misoprostol + steroid vs steroid	1	14
Maintenance	2	54
CPA vs IVIG	1	14
CPAvs CSA	1	40
Total	25	915

2012 UPDATE (124 reports, 25 new studies)
(32 new reports of previously included studies)

Intervention	Studies	Participants
Induction	22	1676
MMF vs CPA	6	680
AZA vs CPA	1	59
TAC vs CPA	2	106
TAC vs MMF	1	109
CPA vs CSA vs AZA	1	22
CPA vs MMF vs TAC	2	100
RTX vs steroid	1	144
RTX vs CPA	1	19
IV vs oral CPA	1	32
CPA vs CSA	2	74
High vs low dose steroid	1	81
High vs low dose CPA	2	163
IV CPA + oral steroid vs IV steroid + AZA	1	87
Maintenance	4*	460*
MMF vs AZA or CPA*	3*	391*
AZA vs CSA	1	69
Total	25	1909

TOTAL: 50 studies, 160 reports, 2846 participants

Intervention	Studies	Participants
Induction	45	2559
MMF vs CPA**	7	744
MMF vs TAC	1	109
High vs low dose CPA	3	253
IV vs oral CYC	1	32
Long vs short CPA	1	65
IV vs oral steroid	1	22
IV CPA + oral steroid vs IV steroid + AZA	1	87
AZA, TAC or CSA vs CPA	5	239
CPA, AZA or CSA ± steroid vs steroid	11	415
RTX vs steroid	1	144
RTX vs CPA	1	19
PEX + IS vs IS	5	173
PEX vs IS	2	40
Misoprostol + steroid vs steroid	1	14
High vs low dose steroid	1	81
CPA vs CSA vs AZA	1	22
CPA vs MMF vs TAC	2	100
Maintenance	6*	514*
MMF vs AZA or CPA*	3*	391*
AZA vs CSA	1	69

Figure 1. (Continued)

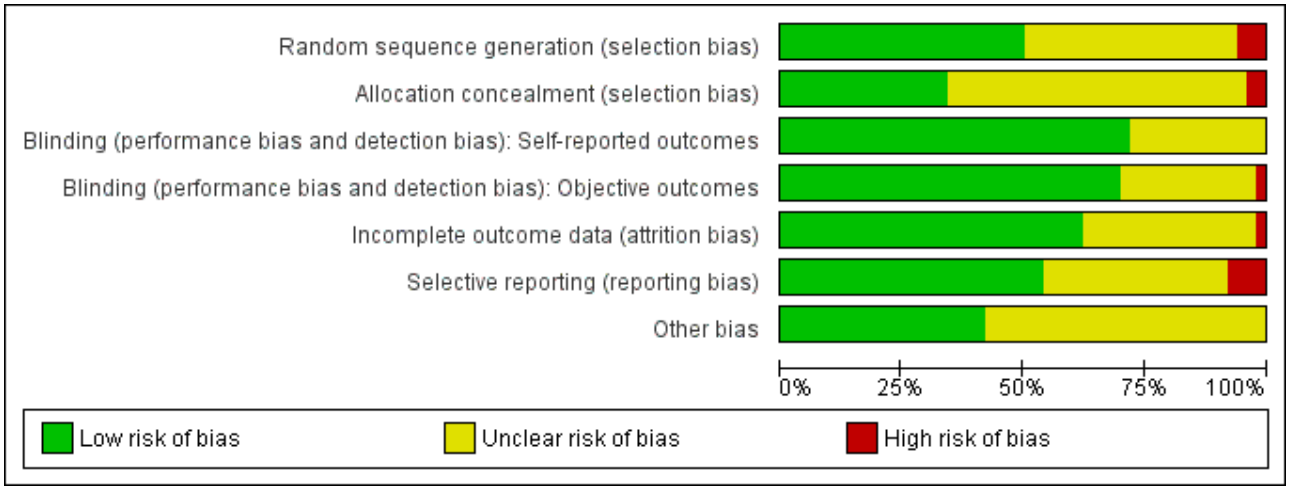
MMF vs AZA or CPA*	3*	391*
AZA vs CSA	1	69
CPA vs IVIG	1	14
CPA vs CSA	1	40

1. Selected studies were not randomised
2. Diagnosis of lupus nephritis was not biopsy-proven or was not proliferative lupus nephritis
3. That the randomised treatment comparison was not immunosuppression
4. That the study was conducted in animals or was a basic science study.

The review update contributed an additional 121 reports from 25 unique studies. Of these 121 reports, 32 were new, additional publications of studies already included in the original review, and 89 were reports of new studies.

After including the studies identified from the update search, a total of 157 reports of 50 studies were included in this review (Figure 1 and Figure 2) which included a total of 2846 randomised participants (Adam 2004; Appel 2009; Austin 1986; Balletta 1992; Bao 2008; Barron 1982; Belmont 1995; Boletis 1998; Boumpas 1992; Cade 1973; Chan 2000; Chen 2011; Clark 1981; Clark 1984; Contreras 2002; CYCLOFA-LUNE Study 2010; Derksen 1988; Donadio 1974; Donadio 1978; Doria 1994; Dyadyk 2001; El-Shafey 2010; Fries 1973; Fu 1998; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Hong 2007; Houssiau 2002; MAINTAIN Nephritis Study; Lewis 1992; Li 2009a; Li 2009b; Lui 1997; LUNAR Study; Mitwalli 2011; Mok 2009; Moroni 2004; Mulic-Bacic 2008; MyLupus Study 2010; Nakamura 2002; Ong 2005; Sabry 2009; Sesso 1994; Steinberg 1971; Sundel 2008; Wallace 1998; Yee 2004).

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



There were 45 studies of induction therapy (2559 participants), and 6 studies of maintenance therapy (514 participants; 227 had already participated in an induction phase study (Appel 2009)). Follow-up ranged from six to 12 months for induction therapy, and 12 to 72 months for maintenance therapy. The numbers of patients included in studies ranged from 10 to 370 with a median number of 45.5 patients.

Of all authors contacted for further clarification, nine responded (Drs Belmont, Doria, Donadio, Fries, Gourley, Houssiau, Solomons, Wofsy and Florez-Suarez). For the update, two authors provided supplementary data (Drs Solomons and Wofsy).

Induction therapy

Comparators for induction therapy included the following.

- MMF with or without tacrolimus plus corticosteroid versus cyclophosphamide plus corticosteroid (9 studies, 826 participants: Appel 2009; Bao 2008; Chan 2000; El-Shafey 2010; Ginzler 2005; Li 2009b; Mulic-Bacic 2008; Ong 2005; Sundel 2008)
- MMF plus corticosteroids versus tacrolimus plus corticosteroids (2 studies, 149 participants; Li 2009b; Mok 2009)
- Standard dose corticosteroid versus reduced dose corticosteroid with both arms receiving enteric-coated mycophenolate sodium (EC-MPS) (1 study, 81 participants; MyLupus Study 2010)
- Rituximab plus standard immunosuppressive therapy versus MMF or rituximab alone (2 studies, 163 participants; LUNAR Study; Li 2009a)
- High dose versus low dose intravenous cyclophosphamide (3 studies, 253 participants; Houssiau 2002; Mitwalli 2011; Sabry 2009)

- Long-term versus short-term intravenous (IV) cyclophosphamide (1 study, 40 participants; Boumpas 1992)
- Oral versus IV cyclophosphamide (1 study, 32 participants; Yee 2004)
- Cyclophosphamide plus corticosteroid versus azathioprine, tacrolimus or cyclosporin plus corticosteroid (8 studies, 388 participants; Adam 2004; Chen 2011; Dyadyk 2001; Grootscholten 2006; Hong 2007; Li 2009b; Lui 1997; CYCLOFALUNE Study 2010)
- Cyclophosphamide, azathioprine or cyclosporin with or without corticosteroid versus corticosteroid alone (12 studies, 482 participants; Austin 1986; Balletta 1992; Boumpas 1992; Cade 1973; Donadio 1974; Donadio 1978; Fries 1973; Ginzler 1976; Gourley 1996; Hahn 1975; Sesso 1994; Steinberg 1971)
- Plasma exchange plus cytotoxics and corticosteroid versus cytotoxics and corticosteroid alone (5 studies, 174 participants; Clark 1981; Clark 1984; Doria 1994; Lewis 1992; Wallace 1998)
- Plasma exchange versus cytotoxics alone (2 studies, 40 participants; Derksen 1988; Nakamura 2002)
- Misoprostol plus corticosteroid versus corticosteroid (1 study, 14 participants; Belmont 1995)
- IV versus oral corticosteroid (1 study, 22 participants; Barron 1982).

Maintenance therapy

Four studies (460 participants) compared azathioprine plus corticosteroid to another immunosuppressive agent (MMF, cyclophosphamide or cyclosporin (Appel 2009; Contreras 2002; MAINTAIN Nephritis Study; Moroni 2004); one study (40 participants) compared cyclophosphamide with cyclosporin (Fu 1998) and one study (14 participants) compared IV cyclophosphamide to IV immunoglobulin (IVIG) (Boletis 1998).

The maintenance phase of one study (Chan 2000) underwent a significant post-randomisation protocol adjustment originally randomised to induction with MMF. The MMF induction arm originally switched to maintenance azathioprine at one year, but the protocol changed mid-trial to continue MMF for two years. This was prompted by an unexpectedly high rate of renal relapse in the azathioprine maintenance group. Data for those participants on the original protocol were not reported separately from the adjusted protocol, so accordingly, only the induction phase data of this study could be included in our synthesis.

Risk of bias in included studies

Reporting of details of study methodology were incomplete for the majority of studies, and are summarised in Figure 2 and Figure 3.

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

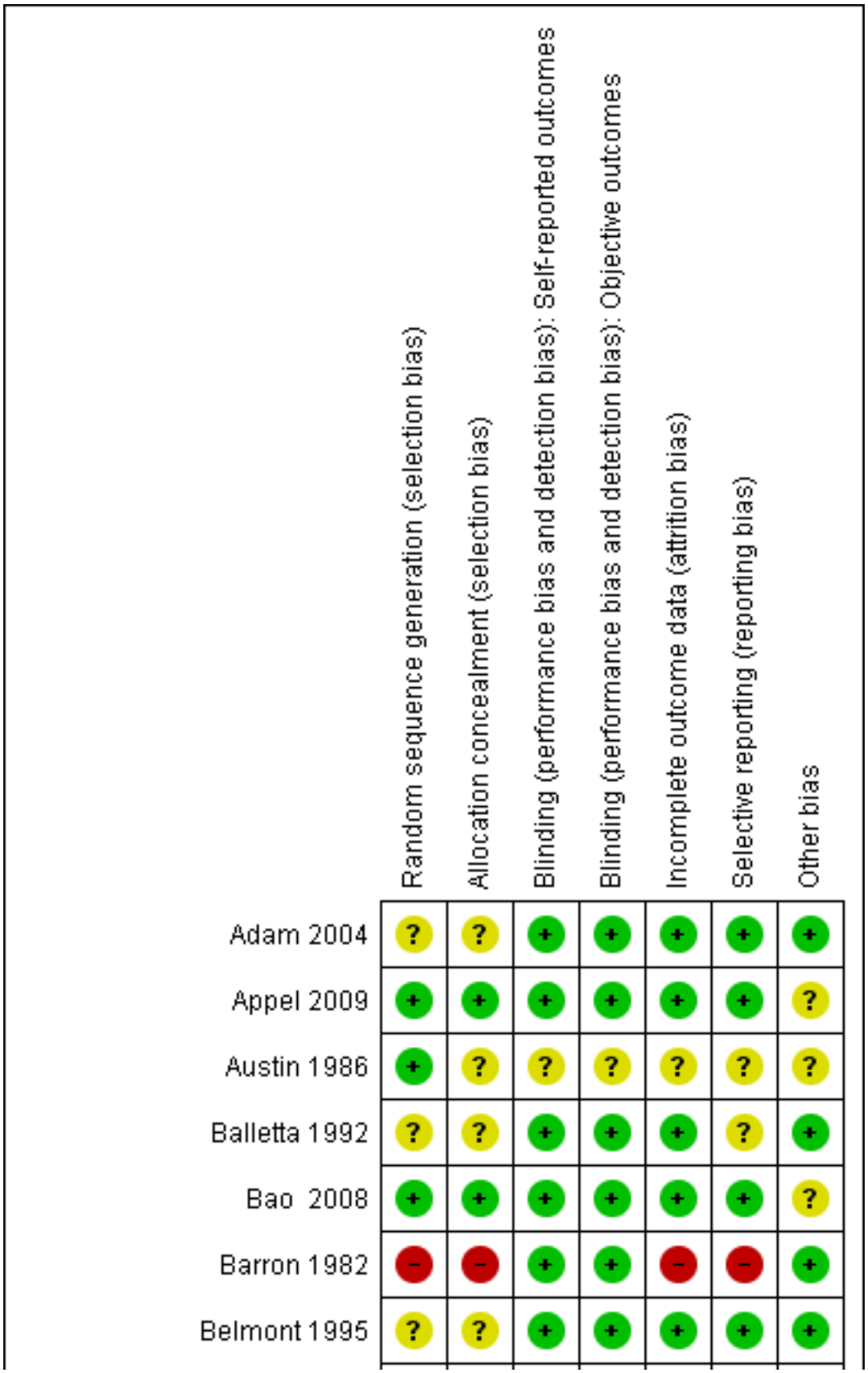


Figure 3. (Continued)

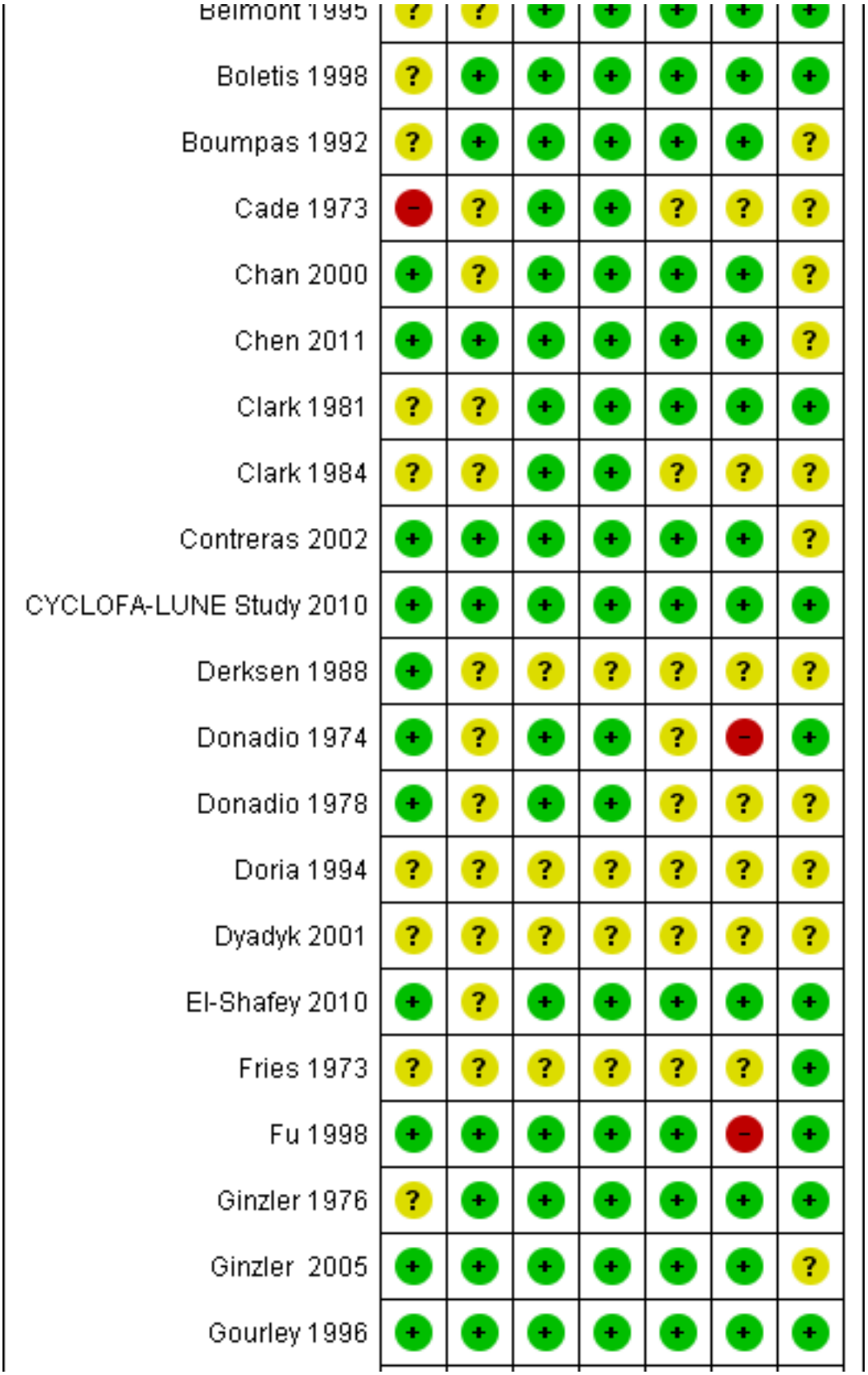


Figure 3. (Continued)

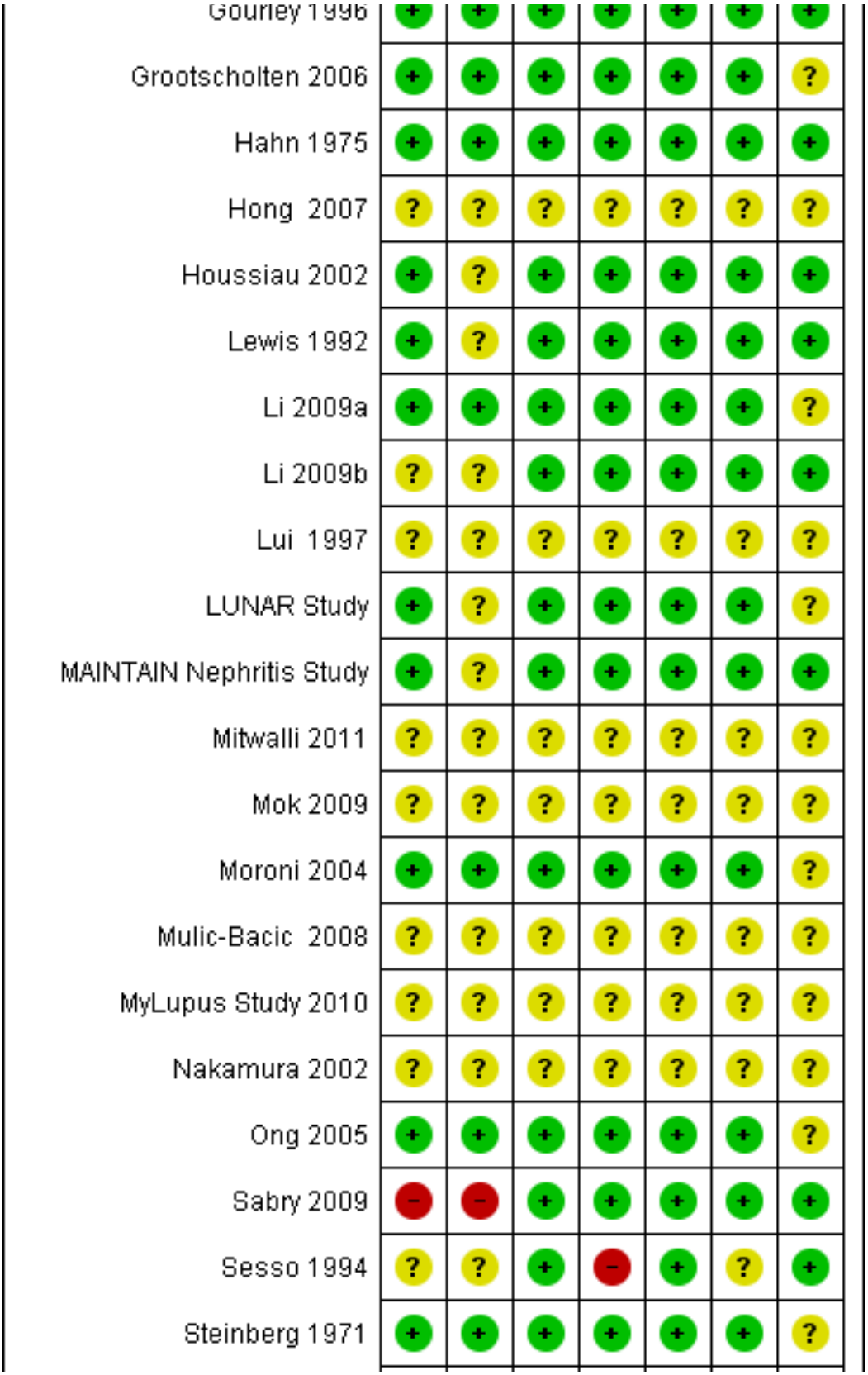
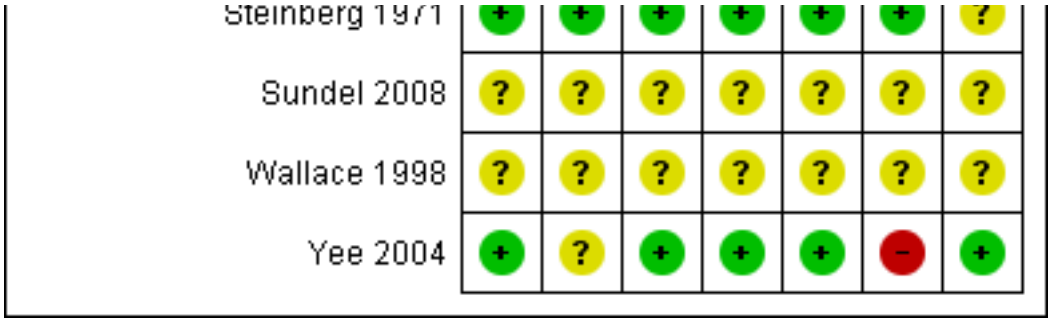


Figure 3. (Continued)



Allocation

Of the included studies, 25 reported adequate sequence generation (Appel 2009; Austin 1986; Bao 2008; Chan 2000; Chen 2011; Contreras 2002; Derksen 1988; Donadio 1974; Donadio 1978; El-Shafey 2010; Fu 1998; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Houssiau 2002; Lewis 1992; Li 2009a; LUNAR Study; MAINTAIN Nephritis Study; Moroni 2004; Ong 2005; Steinberg 1971; Yee 2004; CYCLOFA-LUNE Study 2010) and 17 studies reported adequate allocation concealment (Appel 2009; Bao 2008; Boletis 1998; Boumpas 1992; Chen 2011; Contreras 2002; Fu 1998; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Li 2009a; Moroni 2004;Ong 2005; Steinberg 1971; CYCLOFA-LUNE Study 2010). Sequence generation was inadequate in three studies where alternation was used to allocate patients to treatment groups (Barron 1982; Cade 1973; Sabry 2009). These studies were included in the review but deemed high risk for selection bias. Sequence generation was unclear in the remaining 22 studies.

Allocation concealment was clearly inadequate in two studies (Barron 1982; Sabry 2009), 17 studies were judged to be low risk (Appel 2009; Bao 2008; Boletis 1998; Boumpas 1992; Chen 2011; Contreras 2002; CYCLOFA-LUNE Study 2010; Fu 1998; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Li 2009a; Moroni 2004; Ong 2005; Steinberg 1971) and the remaining 31 studies did not report methodology in sufficient detail to enable assessment.

Blinding

Five studies reported blinding of objective and subjective outcomes adequately (Belmont 1995; Chan 2000; Ginzler 1976; LUNAR Study; Steinberg 1971), and four studies reported blinding of subjective outcomes adequately (Belmont 1995; Ginzler 1976; LUNAR Study; Steinberg 1971). One study was considered to have high risk of detection bias for objective outcomes (Sesso 1994). Participants, investigators and outcome assessors were not blinded in any of the remaining studies; however, the authors deemed that outcomes and outcome measurement was not likely to be influenced by blinding, and therefore, these studies were listed as low risk of performance and detection bias.

Incomplete outcome data

Incomplete outcome data was addressed adequately in 31 studies (Adam 2004; Appel 2009; Balletta 1992; Bao 2008; Belmont 1995; Boletis 1998; Boumpas 1992; Chan 2000; Chen 2011; Clark 1981; Contreras 2002; CYCLOFA-LUNE Study 2010; El-Shafey 2010; Fu 1998; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Houssiau 2002; Lewis 1992; Li 2009a; Li 2009b; LUNAR Study; MAINTAIN Nephritis Study; Moroni 2004; Ong 2005; Sabry 2009; Sesso 1994; Steinberg 1971; Yee 2004). One was inadequate (Barron 1982), and the remainder were unclear.

Selective reporting

We found that 27 studies were free of selective reporting (Adam 2004; Appel 2009; Bao 2008; Belmont 1995; Boletis 1998; Boumpas 1992; Chan 2000; Chen 2011; Clark 1981; Contreras 2002; CYCLOFA-LUNE Study 2010; El-Shafey 2010; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Houssiau 2002; Lewis 1992; Li 2009a; Li 2009b; LUNAR Study; MAINTAIN Nephritis Study; Moroni 2004; Ong 2005; Sabry 2009; Steinberg 1971). Four studies were considered to be at high risk of reporting bias (Barron 1982; Donadio 1974; Fu 1998; Yee 2004), and the remaining 19 studies were unclear.

Other potential sources of bias

Six studies declared their funding sources to be independent or academic funding bodies and were judged to be free of other potential bias (Clark 1981; Gourley 1996; Houssiau 2002; MAINTAIN Nephritis Study; Li 2009b; Yee 2004). A further 13 studies either declared sponsorship by a pharmaceutical industry company, or included an author who declared pharmaceutical company affiliation; these were judged as carrying high risk of a potential source of bias. The remaining 31 did not disclose study funding sources.

Intention-to-treat analysis

Of the 50 included studies, 34 were analysed by intention-to-treat (Adam 2004; Appel 2009; Balletta 1992; Bao 2008; Belmont 1995; Boletis 1998; Boumpas 1992; Clark 1981; Contreras 2002; CYCLOFA-LUNE Study 2010; Derksen 1988; Donadio 1978; Doria 1994; Dyadyk 2001; El-Shafey 2010; Fries 1973; Ginzler 2005; Grootscholten 2006; Hong 2007; Houssiau 2002; MAINTAIN Nephritis Study; Lewis 1992; Li 2009a; Li 2009b; Lui 1997; LUNAR Study; Mitwalli 2011; Moroni 2004; Mulic-Bacic 2008; MyLupus Study 2010; Nakamura 2002; Sabry 2009; Sesso 1994; Sundel 2008). A further 2 were unclear, and 14 did not use intention-to-treat analysis, so were judged as being at high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** MMF versus IV cyclophosphamide for induction therapy; **Summary of findings 2** Azathioprine versus MMF for maintenance therapy

Induction therapy

MMF plus corticosteroids versus cyclophosphamide plus corticosteroid

Overall, there was no difference for mortality or any renal outcome between MMF and intravenous (IV) or oral cyclophosphamide, but there was a significant reduction in adverse events in favour of MMF.

Compared with IV cyclophosphamide, there was no difference in mortality (Analysis 1.1.2 (7 studies, 710 participants): RR 1.02, 95% CI 0.52 to 1.98). MMF was as effective at inducing complete renal remission (Analysis 1.12.1 (6 studies, 686 participants): RR 1.39, 95% CI 0.99 to 1.95); partial renal remission (Analysis 1.12.3 (6 studies, 686 participants): RR 1.04, 95% CI 0.86 to 1.25); or stabilisation in kidney function (Analysis 1.3.1 (5 studies, 523 participants): RR 1.05, 95% CI 0.94 to 1.18) with MMF therapy. Incidences of ESKD, (Analysis 1.2.2), doubling of serum creatinine (Analysis 1.2.6) and renal relapse (Analysis 1.2.4) were similar.

Oral cyclophosphamide had similar effects to MMF on mortality (Analysis 1.1.1), incidence of ESKD (Analysis 1.2.1) and doubling of serum creatinine (Analysis 1.2.5). The risk of renal relapse was no different with MMF compared with oral cyclophosphamide, but this was only in one small study (Analysis 1.2.3 (1 study, 62 participants): RR 1.15, 95% CI 0.55 to 2.37).

Comparing MMF with either oral (Analysis 1.12.5 (1 study, 62 participants) RR 0.98, 0.74 to 1.30)or IV (Analysis 1.12.6 (6 studies, 686 participants): RR 1.16, 95% CI 0.85 to 1.58) cyclophosphamide, there was no difference in complete remission in proteinuria; partial remission in proteinuria (Analysis 1.12.8; Analysis 1.12.9); or daily proteinuria (Analysis 1.13.1; Analysis 1.13.2). MMF-treated participants had an 85% to 90% reduction in risk of ovarian failure compared with either oral (Analysis 1.5.1 (1 study, 53 participants): RR 0.10, 95% CI 0.01 to 0.73) or IV cyclophosphamide (Analysis 1.5.2 (2 studies, 498 participants): RR 0.15, 95% CI 0.03 to 0.80). The incidence of alopecia was significantly reduced with MMF when compared with either oral cyclophosphamide (Analysis 1.8.2 (1 study, 62 participants): RR 0.05, 95% CI 0.00 to 0.81) or IV cyclophosphamide (Analysis 1.8.3 (2 studies, 522 participants): RR 0.22, 95% CI 0.06 to 0.86). Leucopenia was significantly reduced in MMF-treated patients compared with oral cyclophosphamide (Analysis 1.11.1 (1 study, 62 participants): RR 0.06, 95% CI 0.00 to 0.92) or IV cyclophosphamide (Analysis 1.11.2 (5 studies, 653 participants): RR 0.49, 95% CI 0.28 to 0.88). There was a significant reduction in major infective episodes in favour of MMF when compared with oral cyclophosphamide (Analysis 1.4.1 (1 study, 62 participants): RR 0.21, 95% CI 0.05 to 0.89) but no difference in major infection when compared with IV cyclophosphamide (Analysis 1.4.2 (6 studies, 683 participants): RR 1.11, 95% CI 0.74 to 1.68). No difference in herpes zoster virus infection was observed when MMF was compared with either oral cyclophosphamide (Analysis 1.4.4 (1 study, 62 participants): RR 0.38, 95% CI 0.08 to 1.79) or IV cyclophosphamide (Analysis 1.4.5 (4 studies, 613 participants): RR 1.35, 95% CI 0.71 to 2.58). Diarrhoea was significantly more common (Analysis 1.10.1 (3 studies, 569 participants): RR 2.53, 95% CI 1.54 to 4.16). There was no difference in the incidence of vomiting, nausea, or general gastrointestinal upset (Analysis 1.10.2; Analysis 1.10.3; Analysis 1.10.4). Malignancy was not a widely reported outcome, occurring with similar incidence rates in each treatment group in the single study in which it was reported (Analysis 1.9 (1 study, 364 participants): RR 0.65, 95% CI 0.11 to 3.86).

Significant heterogeneity was observed among studies examining mean daily proteinuria (Analysis 1.13.2). One study (Ong 2005) recruited patients with significantly greater proteinuria among cyclophosphamide-treated patients at baseline, an observation which persisted to follow-up. Exclusion of this study reveals a more consistent estimate of effect among studies (P = 0.28, I^2 = 22%).

MMF plus tacrolimus and corticosteroid versus IV cyclophosphamide plus corticosteroid

MMF in combination with tacrolimus resulted in a significant increase in number of patients with stable kidney function (Analysis 1.3.2 (1 study, 40 participants): RR 1.73, 95% CI 1.15 to 2.60); complete renal remission (Analysis 1.12.2 (1 study, 40 participants): RR 4.33, 95% CI 1.45 to 12.91); and complete remission in proteinuria (Analysis 1.12.7 (1 study, 40 participants): RR 4.33, 95% CI 1.45 to 12.91) when compared with IV cyclophosphamide. Daily proteinuria was also significantly lower for patients treated with MMF and tacrolimus (Analysis 1.13.3 (1 study, 40 participants): RR -5.89, 95% CI -7.01 to -4.77).

There was no difference between MMF in combination with tacrolimus compared to IV cyclophosphamide for partial renal remission (Analysis 1.12.4) or partial remission in proteinuria (Analysis 1.12.10).

MMF plus corticosteroid versus tacrolimus plus corticosteroid

There was no difference in any reported outcomes comparing MMF plus corticosteroid versus tacrolimus plus corticosteroid.

Specifically, the risk of mortality (Analysis 2.1: 2 studies, 130 participants); ESKD (Analysis 2.2.1: 1 study, 90 participants); deterioration in kidney function (Analysis 2.2.3: 1 study, 90 participants); renal relapse (Analysis 2.2.2: 1 study, 90 participants); stable kidney function (Analysis 2.3: 1 study, 40 participants); major infection (Analysis 2.4: 2 studies, 130 participants); leucopenia (Analysis 2.5: 1 study, 40 participants); complete renal remission (Analysis 2.6.1: 2 studies, 109 participants); either complete or partial renal remission (Analysis 2.6.2: 2 studies, 130 participants); complete remission in proteinuria (Analysis 2.6.3: 1 study, 40 participants); daily proteinuria (Analysis 2.7: 1 study, 40 participants); and creatinine clearance (Analysis 2.8: 1 study, 90 participants).

Differences in estimates of effect were seen among studies for the outcome of complete renal remission (Analysis 2.6.1). From reported details for study demographics and interventions, the potential source of heterogeneity was not clear.

Rituximab versus other immunosuppression (both arms included corticosteroids)

One study compared rituximab plus MMF versus MMF alone and another compared rituximab plus cyclophosphamide versus rituximab alone. There was no difference in any reported outcomes, specifically: the risk of mortality (Analysis 3.1: 1 study, 144 participants); stability in kidney function (Analysis 3.2: 1 study, 144 participants); major infection (Analysis 3.3.1: 1 study, 163 participants); leucopenia (1 study, 144 participants, Analysis 3.5); complete renal remission (Analysis 3.6.1: 2 studies, 163 participants); partial renal remission (Analysis 3.6.2: 2 studies,

163 participants); complete remission in proteinuria (Analysis 3.6.3: 1 study, 144 participants); daily proteinuria (Analysis 3.7: 1 study, 19 participants); creatinine clearance (Analysis 3.8; 1 study, 19 participants) and serum creatinine (Analysis 3.9: 1 study 19 participants).

Intravenous versus oral cyclophosphamide

There was no significant difference in all-cause mortality (Analysis 4.1); ESKD (Analysis 4.2.1); doubling of serum creatinine (Analysis 4.2.2); deteriorating kidney function (Analysis 4.2.3); stable kidney function (Analysis 4.3); major infection (Analysis 4.4.1); herpes zoster infection (Analysis 4.4.2); ovarian failure (Analysis 4.5); gastrointestinal upset (Analysis 4.8); bladder toxicity (Analysis 4.6); or malignancy (Analysis 4.7).

Standard versus reduced dose oral corticosteroid

There was no difference in mortality (Analysis 5.1), complete remission (Analysis 5.2.1) or partial remission (Analysis 5.2.2) among interventions.

Cyclophosphamide plus corticosteroid versus other immunosuppressive agent plus corticosteroids

Azathioprine

Risk of mortality at 10 years was significantly reduced with azathioprine when compared with cyclophosphamide (Analysis 6.1.2 (1 study, 59 participants): RR 1.93, 95% CI 1.22 to 3.06) but with a greater risk of risk of doubling serum creatinine (Analysis 6.2.3 (2 studies, 144 participants): RR 0.48, 95% CI 0.24 to 0.95) and renal relapse (Analysis 6.2.2 (1 study, 87 participants): RR 0.15, 95% CI 0.03 to 0.64).

There was no difference between any other reported outcomes, including mortality at five years (Analysis 6.1.1 (2 studies, 146 participants): RR 1.39, 95% CI 0.25 to 7.77); stable kidney function (Analysis 6.3); major infection (Analysis 6.4.1); herpes zoster virus (Analysis 6.4.2); ovarian failure (Analysis 6.5); bone toxicity (Analysis 6.6); bladder toxicity (Analysis 6.7); malignancy (Analysis 6.8); and complete or partial remission in proteinuria (Analysis 6.9).

A significant difference in estimate of effect was seen for five year mortality (Analysis 6.1.1). Outcome reporting bias may explain heterogeneity with only two small studies reporting this outcome and the potential for loss to follow-up.

Tacrolimus

Comparing cyclophosphamide versus tacrolimus, there was no significant difference in mortality (Analysis 7.1); stable kidney function (Analysis 7.2); major infection (Analysis 7.3); ovarian failure (Analysis 7.4); alopecia (Analysis 7.5); gastrointestinal upset (Analysis 7.6); leucopenia (Analysis 7.7); complete renal remission (Analysis 7.8.1); partial renal remission (Analysis 7.8.2); complete remission in proteinuria (Analysis 7.8.3); and daily proteinuria (Analysis 7.9).

Cyclosporin

Comparing cyclophosphamide versus cyclosporin, there was no significant difference in mortality (Analysis 8.1); major infection (Analysis 8.2.1); herpes zoster virus (Analysis 8.2.2); alopecia (Analysis 8.4); leucopenia (Analysis 8.5); or partial renal remission (Analysis 8.6.2). Complete renal remission was 44% less likely (Analysis 8.6.1 (2 studies, 74 participants): RR 0.66, 95% CI 0.45 to 0.97) and ovarian failure significantly more common with cyclophosphamide (Analysis 8.3 (2 studies, 74 participants): RR 9.00, 95% CI 1.03 to 78.91). Reduction in daily proteinuria observed at 9 months with cyclosporin (Analysis 8.7.1 (1 study, 40 participants): MD 0.89, 95% CI 0.24 to 1.55) was not sustained at 18 months (Analysis 8.7.2 (1 study, 40 participants): MD 0.46, 95% CI -0.17 to 1.09). Likewise, a benefit in serum creatinine seen at nine months with cyclosporin (Analysis 8.8.1 (1 study, 40 participants): MD -0.73, 95% CI -1.37 to -0.08) was not sustained at 18 months follow-up (Analysis 8.8.2 (1 study, 40 participants): MD -0.12, 95% CI -0.74 to 0.50).

Intravenous versus oral corticosteroid

There was no difference in renal relapse - the only outcome reported for this comparison - among groups (Analysis 9.1).

High versus low dose cyclophosphamide

Ovarian failure was more than twice as likely in those exposed to high dose cyclophosphamide (Analysis 10.5 (3 studies, 252 participants): RR 2.18, 95% CI 1.03 to 4.59).

There was no difference in any other reported outcomes including mortality (Analysis 10.1); ESKD (Analysis 10.2.1); doubling of serum creatinine (Analysis 10.2.5); relapse (Analysis 10.2.4); stable kidney function (Analysis 10.3); major infection (Analysis 10.4.1); herpes zoster infection (Analysis 10.4.2); bone toxicity (Analysis 10.6); malignancy (Analysis 10.7); leucopenia (Analysis 10.8); complete or partial remission of proteinuria (Analysis 10.9.1; Analysis 10.9.2); daily proteinuria (Analysis 10.10); or serum creatinine (Analysis 10.11).

One study (Sabry 2009) allocated six patients with severe kidney disease to the high dose treatment arm, which may account for the difference in effect seen between the studies included in data synthesis for daily proteinuria (Analysis 10.10.1).

Older comparisons and outcomes (long- versus short-duration cyclophosphamide, immunosuppressive agent plus corticosteroids versus corticosteroids alone, plasma exchange plus immunosuppression versus immunosuppression alone and plasma exchange (no immunosuppression) versus immunosuppression) were reported in the original Cochrane review (Flanc 2004a) and can also be found in the data and analyses section of this review.

Additional comparisons were also identified in the remaining studies; however, we were unable to extract outcome data for the treatment comparison arms, and thus, report the triallists' conclusions here.

Maintenance therapy

Azathioprine plus corticosteroid versus other immunosuppression plus corticosteroid

There was a lower risk of relapse for patients when maintained on MMF compared with azathioprine (Analysis 15.3.1 (3 studies, 371 participants): RR 1.83, 95% CI 1.24 to 2.71) but no significant difference in relapse when compared with cyclosporin (Analysis 15.3.2: 1 study, 69 participants) or cyclophosphamide (Analysis 15.3.3: 1 study, 39 participants). There was a significant difference in leucopenia when comparing azathioprine with MMF in favour of

MMF (Analysis 15.11.1 (2 studies, 331 participants): RR 6.21, 95% CI 1.69 to 22.85).

There was no difference between azathioprine and MMF or cyclosporin or cyclophosphamide in terms of mortality (Analysis 15.1: 4 studies, 440 participants) or ESKD (Analysis 15.2: 4 studies, 440 participants) and no difference between azathioprine and MMF or cyclophosphamide in doubling of serum creatinine (Analysis 15.4: 4 studies, 440 participants), bladder toxicity (Analysis 15.7: 1 study, 59 participants), or malignancy (Analysis 15.9.1: 3 studies, 370 participants). Comparing azathioprine to cyclosporin, there was no difference in major infection (Analysis 15.5.1: 1 study, 69 participants), gastrointestinal disturbance (Analysis 15.10: 1 study, 69 participants), leucopenia (Analysis 15.11: 1 study, 69 participants), and daily proteinuria (Analysis 15.12.1: 1 study, 69 participants).

Intravenous immunoglobulin versus intravenous cyclophosphamide

There was no reported difference in serum creatinine, creatinine clearance or proteinuria. There were no deaths, no incidences of doubling of serum creatinine, and no difference in toxicity (Boletis 1998).

Comparisons among all interventions including results from studies published in the original review are detailed in Table 1 and Table 2. Main outcomes, graded by quality of evidence, are presented in Summary of findings for the main comparison and Summary of findings 2.

DISCUSSION

The management of lupus nephritis has become complex and difficult to navigate and interpret because of the recent proliferation new interventions and studies, which have been compared in numerous combination regimens.

In the 1970s it was demonstrated that compared with corticosteroids alone, the combined use of cyclophosphamide and corticosteroids induced remission, reduced ESKD and mortality, resulting in use of this regimen as first-line therapy for over 30 years.

Our earlier systematic review (Flanc 2004a) of immunosuppressive treatment of proliferative lupus nephritis found that adding cyclophosphamide or azathioprine to steroids improved or preserved kidney function when compared to steroids alone, and that plasma exchange conferred no additional benefit. Data regarding newer agents such as MMF and tacrolimus were insufficient to permit any meaningful conclusions at time of publication.

Summary of main results

As shown by nine studies involving over 800 participants with proliferative lupus nephritis in our recent analysis for this updated review, MMF dosed at 2 g to 3 g daily is as effective as cyclophosphamide in preventing death, inducing complete remission in proteinuria, and achieving stable kidney function at six months, with reduced risk of ovarian failure, alopecia and leucopenia but with increased risk of diarrhoea. With comparable benefit and overall reduced adverse events, these data suggest that MMF may be the preferred first-line agent in proliferative lupus nephritis.

For maintenance therapy, MMF was more effective than azathioprine at preventing renal relapse with less leucopenia. Mortality, doubling of serum creatinine and other adverse effects including major infection were no different between the therapies.

Many other interventions, including rituximab (an agent increasingly used in clinical practice), tacrolimus and cyclosporin, have only been trialed in small studies with inconsistent outcome reporting, thereby precluding their inclusion in data synthesis. The clinical role for these therapies therefore remains unclear and warrants caution. Only one study compared standard versus reduced steroid dosing (MyLupus Study 2010). No other studies addressed dosing and duration of steroid therapy. In contrast to recent evidence supporting the beneficial effects of plasma exchange in the treatment of vasculitis, our original review found plasma exchange conferred no benefit.

Strengths and limitations

In contrast to previous meta-analyses (Mak 2009; Moore 2006), we re-organised interventions according to treatments for induction of disease remission or maintenance therapy, which better reflects clinical practice. Broad inclusion criteria also helped explore the totality of evidence available, rather than limiting meta-analysis by specific immunosuppression regimens as have previously published systematic reviews (Kamanamool 2010; Lee 2010; Mak 2009; Moore 2006; Radhakrishnan 2010; Touma 2011; Walsh 2007; Zhu 2007). Unpublished data from conference abstracts were included in the meta-analysis to minimise publication bias. In the update, 52 new reports came from hand-searching conference proceedings in addition to those already searched by the Cochrane Renal Group. To our knowledge, this is the most comprehensive evidence summary on this topic.

Nevertheless, there are some potential limitations in our study. Considerable clinical heterogeneity in interventions, definitions of remission, and outcome reporting among studies hampered interpretation and presentation of important outcomes in this review. For example, comparing MMF with cyclophosphamide, there was variability among studies in therapeutic dosing, route of administration and co-interventions. While some studies had moderate periods of follow-up over one to two years, others were much shorter and inadequately powered to detect events in the clinically important outcomes. The average time to remission with cyclophosphamide is about 10 months (Ioannidis 2000); however, the follow-up in 10 induction therapy studies was six months. Furthermore, the risk of adverse events such as ovarian failure increases after six months, so the power of existing studies, even when combined, to detect significant differences among interventions is limited. Lack of long-term follow-up data in some studies is particularly relevant to the outcome of ESKD, where a difference between groups may not become apparent for several years. Incomplete reporting of outcomes also increases uncertainty. For example, although 10 studies with 953 participants compared MMF with cyclophosphamide, only four reported on ovarian failure and two on doubling of serum creatinine.

Overall completeness and applicability of evidence

The disease spectrum and the proportion of patients within each class of lupus nephritis differed among studies. Furthermore, patient demographics differed among studies where environmental, socioeconomic, as well as clinical and genetic

factors have been thought to play an important role explaining ethnic differences in the outcome of lupus nephritis. Comparing MMF with cyclophosphamide, three studies included primarily Asian patients (Bao 2008; Chan 2000; Ong 2005) and two of the largest studies comparing MMF with cyclophosphamide included higher proportions of African-American and Hispanic patients (Appel 2009; Ginzler 2005). Non-Caucasian populations have higher risk of relapse, death and CKD compared with Caucasian populations (Contreras 2006; Korbet 2007) and often fail to respond to cyclophosphamide (Adler 2006; Contreras 2006; Dooley 1997). Ginzler 2005 included the largest percentage of black patients, where 56% of patients were of African-American origin. This was the only study that showed a clear benefit in favour of MMF over IV cyclophosphamide for induction of remission and reduction in daily proteinuria (Ginzler 2005). The Aspreva Lupus Management Study (ALMS) data which included 12% African-American and 35% Hispanic patients, suggested interactions between group interventions and race that were not explained by differences in disease characteristics (Appel 2009). ALMS was the only study to provide stratified results according to ethnicity and class of lupus in the update, and no studies provided stratified results according to severity of renal impairment reducing the power to examine potential differences between these groups. Despite lack of result stratification, variation among studies could be considered a strength. Of 10 studies comparing MMF with cyclophosphamide, seven included either Asian and/or African American patients, and all studies included patients with the more severe histological classification of class IV lupus nephritis. Despite clinical differences in population and histological classification, uniformity of effect demonstrated in the meta analysis suggest that results were valid across race and class of lupus nephritis.

Quality of the evidence

Overall study quality was variable (Figure 3). The internal validity of the design, conduct and analysis of the included RCTs was difficult to assess in some studies because of the omission of important methodological details. No study adequately reported all domains of the risk of bias assessment so that elements of internal bias may be present in the meta-analysis (Begg 1996; Moher 1999).

AUTHORS' CONCLUSIONS

Implications for practice

In this review we found similar effects for induction of remission of proliferative lupus nephritis comparing MMF with cyclophosphamide. A significant reduction in toxic effects (ovarian failure, alopecia and leucopenia) was observed with MMF, though with a significant increase in diarrhoea which may limit its widespread tolerability. Particularly for women of child-bearing age, the equivalent remission rates combined with a more favourable side-effect profile would support MMF as being superior to cyclophosphamide as induction therapy for lupus nephritis. Recently published American College of Rheumatology Guidelines concur with our findings, recommending MMF (2 to 3 g daily) or IV cyclophosphamide with corticosteroids for induction therapy in patients with ISN class III/IV lupus nephritis (Hahn 2012).

Although there are few study data on maintenance therapy, meta-analyses from two recent large RCTs (Appel 2009; MAINTAIN Nephritis Study) showed that MMF is superior to azathioprine in preventing renal relapse with no difference between the therapies in doubling of serum creatinine, mortality, major infection, gastrointestinal disturbance and leucopenia. There were very limited data for newer agents such as rituximab (two studies investigating different treatment comparisons, with a total of 159 patients), so no conclusions about the relative benefit and harms of this agent could be made. Until further research becomes available, the lack of data on other agents and heterogeneity of dosing schedules make it difficult to offer recommendations about other agents and to be more specific about optimal dosing schedules.

Implications for research

There are two main implications for future research: firstly to make better use of existing data, and secondly to strategically plan any new studies. Given the overall inconsistency of outcomes that were reported, and timing of outcome measurement, access to study outcome data sets of existing studies may permit a more informative analysis. Although there have been several multicentre studies since the original review was published in 2004, diversity in interventions has continued to hamper informative synthesis and cross-comparison. Lupus nephritis is uncommon, requiring multicentre collaboration for any study to have an adequate sample size. The importance of follow-up prolonged beyond six months is vital to clarify risks and eventual harms of specific treatment regimens. There is also a paucity of data for patient subgroups who may carry greater disease burden, such as African-Americans and Asians, and patients presenting with advanced renal impairment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adam 2004

Methods	• Country: Egypt • Setting: Single centre • Study design: RCT
Participants	• 22 participants; all female; class III (1), class IV (10), class Vc (5), class Va or b (4), class V (1), unclassified (1) • Group I: randomised/analysed (7/7); mean follow-up (13.86 ± 6.52) • Group II: randomised/analysed (7/7); mean follow-up (13.43 ± 3.6) • Group III: randomised/analysed (8/8); mean follow-up (9.50 ± 2.56)
Interventions	1. CPA: 0.75 mg/m^2 2. CSA: 1 to 2 mg/kg/d 3. AZA: 1 to 2 mg/kg/d All groups received MP 500 to 1000 mg/kg/d for 3 to 5 days then oral prednisolone 0.5 mg/kg/d for 4 weeks then tapered dose
Outcomes	1. Major infection 2. Ovarian failure 3. Proteinuria 4. CrCl
Notes	Three participants from group I and one participant from group III shifted to group II due to side effects or no response Follow-up 6 months Induction therapy
Risk of bias	

Adam 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stated but no information on method used available
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used available
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but outcome not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Appel 2009

Methods	• Country: Multinational • Setting: NIH trials, multicentre • Study design: Prospective, RCT, open-label, parallel-group
Participants	Induction therapy • Group 1: randomised/analysed (185/185); 1 lost to follow-up; median age 32.4 years • Group 2: randomised/analysed (185/185); 2 lost to follow-up; median age 31.3 years • M/F: 57/313 Maintenance therapy • Group 1: randomised/analysed (116/116) • Group 2: randomised/analysed (111/111) • Class: III (22); IV (147); III/V (7); IV/V (16); V (35) • M/F: 32/195 Inclusion criteria • Age 12 to 75 years, diagnosis of SLE (ACR criteria), biopsy proven lupus nephritis (active or chronic) within 6 months before randomisation, ISN/RPS 2003 class III, IV-S, IV-G, V, III+V, IV+V, class III or V must have proteinuria > 2 g/d Exclusion criteria • Treatment with MMF or i.v. CPA within the previous year, continuous dialysis for > 2 weeks before randomisation or anticipated duration > 8 weeks, pancreatitis, gastrointestinal haemorrhage within 6 months or active peptic ulcer within 3 months, severe viral infection, severe cardiovascular disease,

Appel 2009 *(Continued)*

	bone marrow insufficiency with cytopenias not attributable to SLE, or current infection requiring intravenous antibiotics
Interventions	Induction therapy 1. Oral MMF: titrated from 0.5 g twice daily in week 1 to 1.0 g twice daily in week 2, target dose 1.5 g twice daily in week 3 2. i.v. CPA: monthly pulses 0.5 to 1.0 g/m^2 Both groups received oral prednisolone with defined taper, maximum starting dose 60 mg/d Maintenance therapy 1. Oral MMF: 2 g/d plus placebo 2. Oral AZA: 2 mg/kg/d plus placebo Both groups received oral prednisolone with defined taper, maximum starting dose 10 mg/d
Outcomes	Induction 1. All-cause mortality 2. Stable kidney function (stabilisation ± 25% or improvement in SCr) 3. Complete renal remission (return to normal creatinine, proteinuria ≤ 0.5 g/d and inactive urine sediment) 4. Partial renal remission (prespecified decrease in urine protein/creatinine ratio (fall in < 3.0 g/d protein if baseline ≥ 3 or ≥ 50% reduction if < 3 at baseline and stabilisation of SCr ± 25%) 5. Major infection 6. Systemic disease activity and damage 7. Adverse events (reported by > 10% participants) Maintenance 1. Mortality 2. ESKD 3. Doubling SCr 4. Renal flare (proteinuric or nephritic) 5. Complete renal remission 6. Combined renal and extra-renal remission
Notes	For induction arm, median follow-up was 24 weeks. For maintenance arm, median follow-up was 36 months Induction and maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned (1:1, stratified by race and biopsy class, non-blocked)
Allocation concealment (selection bias)	Low risk	Central, computerised, interactive voice response system. Method would not allow investigator/participant to know or influence intervention group
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding, but the outcome is not likely to be influenced by lack of blinding; blinded clinical endpoints committee

Appel 2009 *(Continued)*

Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Sponsored by Aspreva Pharmaceuticals Corporation

Austin 1986

Methods	• Country: USA • Setting: NIH trials, multicentre • Study design: RCT, open
Participants	• M/F: 15/92 • Median age at entry: 27 years • Biopsy-proven lupus nephritis (60/107) • Group 1: randomised/analysed (30/28) • Group 2: randomised/analysed (20/19) • Group 3: randomised (18) • Group 4: randomised/analysed (23/22) • Group 5: randomised (20) Exclusion criteria • CrCl < 20 mL/min, major infection within 2 weeks, pregnancy, leucocyte count < 2000/mm^3, cytotoxic therapy within 8 weeks, sensitivity to study drugs
Interventions	1. Prednisolone alone: 1 mg/kg/body weight for 4 to 8 weeks, then tapering 2. AZA with prednisolone: up to 4 mg/kg/d 3. Oral CPA with low dose prednisolone: up to 4 mg/kg/d 4. CPA and AZA with low dose prednisolone: up to 1 mg/kg/d of each 5. i.v. pulse CPA every three months with low dose prednisolone: i.v. every 3 months 0.5 to 1.0 g/m^2 body surface area
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Toxicity 5. Stable kidney function 6. Herpes zoster virus infection 7. Major infection 8. Cancer 9. Premature ovarian failure 10. Haemorrhagic cystitis
Notes	4/111 participants excluded - did not complete 3 months of treatment NIH trial

Austin 1986 *(Continued)*

	Median follow-up: 7 years Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...drawing marked card sequence from a table of random numbers..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Balletta 1992

Methods	• Country: Italy • Setting: NS • Study design: RCT
Participants	• Group 1: randomised (5); age (23.4 ± 3.7 years); M/F (1/4) • Group 2: randomised (5); age (25.6 ± 6.2 years); M/F (0/5) Exclusion criteria: NS
Interventions	1. Prednisolone alone: pulse form 2 to 3 mg/kg/d 3 consecutive days, then 1 mg/kg/d for 2 months and tapered 2. Prednisolone plus CSA: CSA 15 mg/kg twice daily
Outcomes	1. SCr 2. CrCl 3. Proteinuria
Notes	Follow-up: > 12 months 6/10 participants had biopsy Induction therapy

Balletta 1992 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stated but no information on method used available
Allocation concealment (selection bias)	Unclear risk	Randomisation stated but no information on method used available
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	The study appears to be free of other sources of bias

Bao 2008

Methods	• Country: China • Setting: Single centre • Study design: RCT, open-label
Participants	• 40 class V + IV • Group 1: randomised/analysed (20/20); age (27.2 ± 7.1 years); M/F (4/16) • Group 2: randomised/analysed (20/20); age (30.6 ± 4.6 years); M/F (2/18) Inclusion criteria • Age 12 to 60 years, diagnosis of SLE (ACR 1997), SLE DAI ≥ 12', Biopsy-proven lupus nephritis class IV + V (ISN/RDS 2003) within 3 weeks before enrolment, overt proteinuria (≥ 1.5 g/d) ± active urine sediment Exclusion criteria • Creatinine > 3.0 mg/dL (265.2 µmol/L) or CrCl < 30 mL/min, deranged liver function tests, abnormal glucose, known hypersensitivity or contraindication to any of the regimens, use of CTX, MMF or TAC within the past 12 weeks, pregnancy or lactation, cerebral lupus, leflunomide and methotrexate forbidden
Interventions	1. MMF: 1.0 g/d twice daily (0.75 g/d twice daily if ≤ 50 kg); TAC 4 mg/d twice daily (3 mg/d twice daily if ≤ 50 kg) 2. i.v. CPA: 0.75g/m^2 of body surface area first month then adjusted to 0.5 to 1.0 g/m^2 monthly based on white cell count (≤ 2.5) Both groups received MP 0.5 g/d for 3 days then oral prednisolone

Bao 2008 *(Continued)*

Outcomes	1. All-cause mortality 2. Doubling of SCr 3. Deterioration of kidney function 4. Stable kidney function (normal value SCr or no more than 15% above baseline) 5. Complete remission: proteinuria (< 0.4 g/24 h), normal urine sediment, serum albumin ≥ 3.5 g/dL, normal SCr or not > 15% from baseline 6. Partial remission: resumption of normal or at least 50% improvement in proteinuria and haematuria, serum albumin ≥ 3.5 g/dL, normal SCr or not > 15% from baseline 7. Major infection 8. Herpes zoster virus infection 9. Irregular menstruation 10.Gastrointestinal syndrome 11.Alopecia
Notes	6 month follow-up prolonged to 9 months if complete remission not achieved within 6 months Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list drawn up by statistician with a block of every 4 participants and list given to pharmacy department. Enrolled participants allocated the next available number on entry to the study
Allocation concealment (selection bias)	Low risk	Researchers enrolled participants and allocated the next available number upon entry into the study
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Supported by Roche and Astellas Ireland. Co. Ltd. Partially supported but no role in design, study or analysis

Barron 1982

Methods	• Country: USA • Setting: Children's hospital • Study design: Quasi-RCT
Participants	• All children had biopsies

Barron 1982 *(Continued)*

	• Group 1: randomised (15); age (NS); M/F (2/13) • Group 2: randomised (7); age (NS); M/F (1/6) Exclusion criteria • Drug-induced SLE
Interventions	1. High dose oral corticosteroid: oral prednisone 2 mg/kg/d for 3 to 6 months then tapered 2. Pulse MP then oral prednisolone: 30 mg/kg body weight i.v., total of 6 treatments every other day
Outcomes	1. CrCl 2. C3, ANA 3. Exacerbations 4. Infection 5. Aseptic necrosis
Notes	Follow-up: 59 months Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were entered in alternating fashion into one of two treatment groups
Allocation concealment (selection bias)	High risk	Knowledge of prior allocation due to lack of random sequence generation and blinding
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Only those with > 6 months follow-up included in analysis
Selective reporting (reporting bias)	High risk	Not all of the pre-specified primary outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Belmont 1995

Methods	• Country: USA • Setting: Hospital clinic and private practices • Study design: RCT
Participants	• People with proliferative lupus nephritis: 7/14 • M/F: 3/11

Belmont 1995 *(Continued)*

- Age: 35 ± 2 years
- Group 1: randomised (7); age (NS); M/F (NS)
- Group 2: randomised (7); age (NS); M/F (NS)
- Exclusion criteria: NS

Interventions	1. Misoprostol plus prednisolone: 20 µg orally 4 times daily plus 1 mg/kg orally 4 times daily of prednisone 2. Placebo plus prednisolone: identical capsule plus prednisone
Outcomes	1. SCr 2. CrCl 3. ESKD 4. Complete remission of proteinuria 5. C3, C4 6. Anti-dsDNA
Notes	Follow-up: 2, 4, 6 and 12 weeks and 18 months Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of randomisation
Allocation concealment (selection bias)	Unclear risk	No details of randomisation or concealment
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	Blinding of participants and personnel
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Boletis 1998

Methods	• Country: Greece • Setting: NS • Study design: RCT
Participants	• Participants with class III or IV lupus nephritis: 14 • Median age: 31 ± 10.8 years

Boletis 1998 *(Continued)*

	• Group 1: randomised (9); age (NS); M/F (3/6) • Group 2: randomised (5); age (NS); M/F (2/3) Exclusion criteria • Previous CPA for more than 6 months, pregnancy, aged < 18 or > 75 years, history of malignant disorders
Interventions	1. i.v. CPA: CPA every 2 months for 6 months and then every 3 months for 1 year 2. IVIG: 400 mg/kg monthly for 18 months
Outcomes	1. SCr 2. CrCl 3. Proteinuria
Notes	Follow-up: 18 months Maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on randomisation
Allocation concealment (selection bias)	Low risk	Randomisation was done with sealed envelopes
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Boumpas 1992

Methods	• Country: USA • Setting: NS • Study design: RCT
Participants	• 65 participants • All class IV lupus nephritis • CrCl: 25 to 80 mL/min

Boumpas 1992 *(Continued)*

- Group 1: randomised (25); age (31 ± 2 SE); M/F (1/24)
- Group 2: randomised (20); age (30 ± 2 SE); M/F (3/17)
- Group 3: randomised (20); age (28 ± 2 SE); M/F (1/19)

Exclusion criteria

- Pregnancy, received cytotoxic drugs for mor than 10 weeks, active infections, insulin-dependent diabetes, previous malignancy

Interventions	1. i.v. MP: 3 doses 1 g/m^2, then monthly single doses for 6 months 2. i.v. CPA: monthly for 6 months + prednisolone 3. i.v. CPA: monthly for 6 months then 3 monthly for 18 months + prednisolone
Outcomes	1. ESKD 2. Doubling SCr 3. Major infection 4. Herpes zoster virus 5. Malignancy 6. Haemorrhagic cystitis 7. Premature ovarian failure 8. Osteonecrosis 9. Relapse 10.Stable kidney function
Notes	Maximal follow-up: 10 years 2 withdrawals Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were assigned randomly to one of three treatment groups". No further details on randomisation
Allocation concealment (selection bias)	Low risk	Allocation drawn from a set of masked cards
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Cade 1973

Methods	• Country: USA • Setting: Teaching hospital • Study design: Quasi-RCT
Participants	• All lupus nephritis • Group 1: randomised (15); age (26.1, range 12 to 51 years); M/F (3/12) • Group 2: randomised (13); age (30.5, range 11 to 62 years); M/F (1/12) • Group 3: randomised (13); age (22.4 range 12 to 51 years); M/F (3/10) • Group 4: randomised (13); age (24.8 range 14 to 51 years); M/F (6/7)
Interventions	1. Prednisone alone 2. AZA alone 3. Prednisone with AZA 4. AZA with heparin
Outcomes	1. All-cause mortality 2. ESKD 3. CrCl
Notes	Follow-up: 36 months Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Rotational, by division secretary
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Chan 2000

Methods	• Country: Hong Kong • Setting: Multicentre • Study design: RCT
Participants	• Class IV-S, class IV-G • Group 1: randomised/analysed (33/32); age (38.1 ± 10.2 years); M/F (6/26) • Group 2: randomised/analysed (31/30); age (41.8 ± 8.9 years); M/F (4/26) Exclusion criteria • SCr > 4.2 mg/dL, life-threatening complications, history of poor compliance, pregnancy, women unwilling to use contraception, CPA in the last 6 months, oral prednisolone 0.4 mg/kg/d for more than 2 weeks
Interventions	1. Oral MMF: 1 g twice daily for 6 months then 500 mg twice daily for 6 months followed by AZA 1 to 1.5 mg/kg/d for at least 1 year then tapered. From Jan 2002, protocol changed to reducing dose of MMF to 750 mg twice daily at 6 months then 500 mg twice daily at 12 months and continued for further 12 months before tapering 2. Oral CPA: 2.5 mg/kg/d for 6 months followed by AZA 1.5 to 2 mg/kg/d for 6 months then 1 to 1.5 mg/kg/d for at least 1 year before tapering Both groups received prednisolone 0.8 mg/kg/d and tapered to 10 mg/d at 6 months then maintenance dose of 5 to 7.5 mg/kg at 12 to 15 months. MMF dosing subsequently changed from 2002: MMF 1 g twice daily reduced to 750 mg twice daily after 6 months then 500 mg twice daily for at least 1 year before tapering
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Doubling kidney function 5. Relapse 6. Major infection 7. Herpes zoster virus infection 8. Ovarian failure 9. Bone toxicity 10.Alopecia 11.Gastrointestinal upset 12.Lymphopenia 13.Complete remission of proteinuria (< 0.3 g/24 h) 14.Partial remission of proteinuria (> 50% reduction in proteinuria, proteinuria between 0.3 and 3 g/24 h) 15.SCr 16.CrCl 17.Daily proteinuria
Notes	Follow-up: 3585 patient-months (median follow-up 63 months); 2 withdrawals (1 in each group); 62/64 followed-up Induction and maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned by drawing envelopes to one of two treatment groups in an open-label manner

Chan 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	The assessment and categorisation of clinical outcomes was based on review of anonymised data by a single investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Roche pharmaceuticals supplied MMF

Chen 2011

Methods	• Country: China • Setting: Multicentre • Study design: RCT
Participants	• Classes III, IV-S, IV-G (A, A/C), V, V + III, V + IV • Group 1: randomised/analysed (42/39); age (32.0 ± 10.8 years); M/F (5/37) • Group 2: randomised/analysed (39/34); age (31.9 ± 10.1 years); M/F (7/32) Exclusion criteria • SCr > 4 mg/dL, cerebral lupus, severe infection, pregnancy, women unwilling to use contraception, MMF, CPA, CSA, methotrexate or other immunosuppression within the 1 month before randomisation
Interventions	1. Group 1: TAC 0.05 mg/kg divided in 2 doses with target trough of 5 to 10 ng/mL 2. Group 2: i.v. CPA 750 mg/m^2 of body surface area every 4 weeks for a total of 6 pulses (25% decrease in dose if older than 60 years or creatinine > 3.4 mg/dL) Both arms received oral prednisolone 1 mg/kg/d (maximum 60 mg) tapered by 10 mg/d every 2 weeks to 40 mg, followed by decrease of 5 mg/d every 2 weeks until a dose of 10 mg/d achieved
Outcomes	1. Mortality 2. Herpes zoster virus infection 3. Ovarian failure 4. Alopecia 5. Gastrointestinal upset 6. Lymphopenia 7. Complete renal remission (daily proteinuria < 0.3 g/24 h, normal urinary sediment, serum albumin ≥ 3.5 g/dL and stable kidney function) 8. Partial renal remission (protein excretion of 0.3 to 2.9 g/24 h and a decrease of at least 50% of baseline level), serum albumin level of at least 3.0 g/dL and stable kidney function 9. SCr 10. Daily proteinuria

Chen 2011 *(Continued)*

Notes	6 month follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted at a central office using a computer-based random allocation sequence table; randomisation not stratified by centre or baseline characteristic
Allocation concealment (selection bias)	Low risk	Allocation concealment performed by enclosing assignments in sequentially numbered, opaque, closed envelopes
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and prespecified outcomes were reported
Other bias	Unclear risk	Astellas Phamaceutics supplied TAC butt had no role in the design or conduct of the study or analysis or interpretation of results

Clark 1981

Methods	• Country: Canada • Setting: Outpatient • Study design: RCT
Participants	• All diffuse proliferative lupus nephritis patients • Group 1: randomised (6); age (NS); M/F (NS) • Group 2: randomised (6); age (NS); M/F (NS) • Exclusion criteria: NS
Interventions	1. Corticosteroids ± AZA 2. Corticosteroids ± AZA with plasmapheresis
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. SCr 5. CrCl 6. Proteinuria

Clark 1981 *(Continued)*

Notes	Follow-up: 12 months Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	Supported from a grant from Physicians' Services Incorporated Foundation. The study appears to be free of other sources of bias

Clark 1984

Methods	• Country: Canada and West Indies • Setting: Multicentre • Study design: RCT
Participants	• All diffuse proliferative lupus nephritis patients • Group 1: randomised (19); age (25 ± 2 years); M/F (1/19) • Group 2: randomised (20); age (26 ± 2 years); M/F (5/15) Exclusion criteria • CrCl < 30 mL/min or SCr > 3 mg/dL
Interventions	1. Steroid ± cytotoxics 2. Conventional therapy with plasmapheresis
Outcomes	1. Mortality 2. Doubling SCr 3. SCr
Notes	Follow-up: 19 months

Clark 1984 *(Continued)*

	Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement; split equal randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Contreras 2002

Methods	• Country: USA • Setting: Single centre • Study design: Open-labelled RCT
Participants	• 59 participants; classes III (12), IV (46) or Vb (1) • Group 1: randomised/analysed (19/19); age (33 ± 10 years); M/F (1/19) • Group 2: randomised/analysed (20/20); age (33 ± 12 years); M/F (2/18) • Group 3: randomised/analysed (20/20); age (32 ± 11 years); M/F (1/19)
Interventions	1. i.v. CPA: 0.5 to 1.0 g/m^2 every 3 months 2. AZA: 1 to 3 mg/kg/d 3. MMF: 500 to 3000 mg/d All participants had received induction therapy of 7 monthly boluses of i.v. CPA 0.5 to 1.0 g/m^2 and corticosteroids and maintenance therapy included prednisolone (up to 0.5 mg/kg/d) for 1 to 3 years
Outcomes	1. ESKD 2. Death 3. Doubling SCr 4. Stable kidney function 5. Relapse 6. Major infection 7. Herpes zoster virus infection

Contreras 2002 *(Continued)*

	8. Ovarian failure
Notes	Follow-up: 72 months Maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After induction, participants were randomly assigned, in order of enrolment by means of sealed envelopes (stratified in two groups: blacks and other participants)
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Roche pharmaceutical providing research nurse support and MMF 1999 to 2003

CYCLOFA-LUNE Study 2010

Methods	• Country: European countries • Setting: Multicentre • Study design: RCT, open label
Participants	• 40 participants • Group 1: analysed (21); age (30 ± 9 years); M/F 6/15 • Group 2: analysed (19); age (28 ± 5 years); M/F 5/14 Inclusion criteria • ACR criteria for SLE, biopsy-proven lupus nephritis Exclusion criteria • Previous CPA or CSA ever before, treatment with immunosuppressive drugs or corticosteroids within the last 3 months, persistent elevation of SCr > 140 µmol/L, pregnancy or lactation, bone marrow insufficiency not attributable to SLE, severe co-existing conditions such as infection, liver disease, active peptic ulcer

CYCLOFA-LUNE Study 2010 *(Continued)*

Interventions	1. Intermittent i.v. CYC: 10 mg/kg x 8 over 9 months followed by 4 or 5 oral pulses (10 mg/d in 6 to 8 week intervals) 2. Daily oral CSA: 4 to 5 mg/kg/d for 9 months followed by tapering dose of 3.75 to 1.25 mg/kg/d for further 9 months Both arms received MP 0.8 mg/kg/d tapering to 0.2 mg/kg/d over 8 weeks. Additional 1 to 3 doses of MP (15 mg/kg) were administered if felt insufficient control of kidney or extra-kidney disease, or a 30% to 50% increase in oral steroids with a change in timing of CPA or increase in dose of CSA was also allowed
Outcomes	1. Mortality 2. Renal relapse 3. Major infection 4. Herpes zoster virus 5. Ovarian failure 6. Bladder toxicity 7. Alopecia 8. Lymphopenia 9. Complete renal remission 10.Partial renal remission 11.SCr 12.Proteinuria
Notes	Induction and maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation 1:1, non-blocked
Allocation concealment (selection bias)	Low risk	Central computerised system
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	Research grants from the IGA Ministry of Health, Czech Republic. The study appears to be free of other sources of bias

Derksen 1988

Methods	• Country: The Netherlands • Setting: Multicentre university hospitals • Study design: RCT
Participants	• All class III or IV • Group 1: randomised (11); age (28, range 15 to 55 years); M/F (3/8) • Group 2: randomised (9); age (36, range 18 to 60 years); M/F (2/7)
Interventions	1. Prednisone ± cytotoxics 2. Plasma exchange alone, short course
Outcomes	1. Mortality 2. ESKD 3. CrCl
Notes	Follow-up: 26 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing lots from card sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Donadio 1974

Methods	• Country: USA • Setting: NS • Study design: RCT
Participants	• All proliferative lupus nephritis • Females (14); age range (17 to 56 years) • Males (2); age range (17 to 68 years) • Group 1: randomised (9); age (NS); M/F (NS)

Donadio 1974 *(Continued)*

	• Group 2: randomised (7; age (NS); M/F (NS)
Interventions	1. Prednisone alone 2. Prednisone with AZA
Outcomes	1. Mortality 2. Relapse 3. Toxicity 4. CrCl 5. Proteinuria
Notes	Induction Follow-up: 3 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Biopsy activity scored and categorised. Participants allocated within each category to treatment group A or B according to random selection. Table of random numbers used. Each incoming set of 4 participants assigned to 2 As and 2 Bs in random order
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	One or more reported primary outcomes were not pre-specified
Other bias	Low risk	The study appears to be free of other sources of bias

Donadio 1978

Methods	• Country: USA • Setting: Mayo Clinic • Study design: Open RCT
Participants	• All diffuse proliferative lupus nephritis on biopsy • Group 1: randomised (26); age (32.3, range 17 to 50 years); M/F (4/22) • Group 2: randomised (24); age (30.2, range 16 to 60 years); M/F (5/19) Exclusion criteria

Donadio 1978 *(Continued)*

	• Previous CPA or immunosuppressive drugs in the last 6 months
Interventions	1. Prednisone: 60 mg/d tapered after 1 to 3 months 2. CPA: 2 mg/kg/d for 6 months + maintenance dose of prednisone to control other systemic manifestations
Outcomes	1. ESKD 2. Death 3. Toxicity 4. Treatment failure 5. Relapse 6. Current status on kidney function 7. Proteinuria
Notes	Follow-up: 4 years Induction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables used
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Doria 1994

Methods	• Country: Italy • Setting: Single centre • Study design: RCT
Participants	• All proliferative lupus nephritis • M/F (2/16) • Group 1: randomised (6); age (25, range 15 to 46 years); M/F (NS) • Group 2: randomised (5); age (30, range 20 to 55 years); M/F (NS)

Doria 1994 *(Continued)*

	• Group 3: randomised (7); age (23, range 15 to 32 years); M/F (NS) Exclusion criteria • Pregnancy, aged < 15 and > 80 years, infections, insulin-dependent diabetes, history of malignancy, immunosuppressive therapy within 6 month period prior to renal biopsy
Interventions	1. Prednisone with AZA 2. Standard therapy with plasma exchange 3. Standard therapy with i.v. MP
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. 24 h urinary protein 5. Partial remission 6. Complete remission
Notes	Induction Follow-up: every 4 weeks for 24 months and then every 8 weeks thereafter

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation: NS
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Dyadyk 2001

Methods	• Country: Ukraine • Setting: NS • Study design: RCT

Dyadyk 2001 *(Continued)*

Participants	• 59 patients with diffuse proliferative lupus nephritis class IV (WHO class) • M/F: 9/50 • Mean age: 36 years • Group 1: randomised/analysed (21/21); M/F (4/17) • Group 2: randomised/analysed (38/38); M/F (5/33)
Interventions	1. AZA: 1.5 to 2.0 mg/kg/d; mean total duration of therapy (18.9 months) 2. CPA: 1.5 to 3.5 mg/kg/d; mean total duration of therapy (21.7 months)
Outcomes	1. All-cause mortality 2. Complete remission 3. Partial remission
Notes	5 and 10 year survival follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

El-Shafey 2010

Methods	• Country: Egypt • Study design: RCT, open-label
Participants	• 47 randomised • Group 1: 24 (4 withdrawn) 24 analysed; 20 completed 24 week induction phase; M/F (1/23) • Group 2: 23 (4 withdrawn) 23 analysed; 19 completed 24 week induction phase; M/F (1/22) • All participants had biopsy proven class III or IV lupus nephritis • Aged > 15 years

El-Shafey 2010 *(Continued)*

	Exclusion criteria • eGFR < 30 mL/min, SCr > 200 µmol/L, white blood cell count < 3.5 x 10^9/L, major infection, history of cancer, alcohol or substance abuse, active peptic ulcer disease, pregnant or lactating women, allergy to MMF or CPA and use of study drugs in preceding 6 months
Interventions	1. MMF: 1 g twice daily for 6 months 2. i.v. CPA: 0.5 to 1.0 g/m^2 for 6 months, median monthly dose 0.75 g/m^2 Both groups received prednisolone 60 mg/d for 4 to 6 weeks, then 40 mg/d for 2 weeks followed by tapering dose to 5 to 10 mg/d
Outcomes	1. All-cause mortality 2. ESKD 3. Remission (combined complete and partial remission) at 6 months 4. Complete renal remission (normal SCr, proteinuria < 0.5 g/d and urine red blood cell count < 5 per HPF, without red cell cast) 5. Partial renal remission (improvement of 50% in all abnormal renal measurements without deterioration (within 20%) of any measurement) 6. Major infection 7. Herpes zoster virus 8. Diarrhoea 9. Lymphopenia 10.SCr 11.eGFR 12.Proteinuria
Notes	Induction therapy 24 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised in a 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Fries 1973

Methods	• Country: USA • Setting: Single centre • Study design: RCT
Participants	• 22 participants, only 10 had lupus nephritis • Group 1: randomised (12, 5 lupus nephritis); age (NS); M/F (NS) • Group 2: randomised (10, 5 lupus nephritis); age (NS); M/F (NS)
Interventions	1. Prednisone 2. CPA alone
Outcomes	1. Relapse 2. Failure or response of treatment
Notes	Induction Follow-up: 40 months Significant cross-over

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	No clear prespecified primary outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Fu 1998

Methods	• Country: Taiwan • Setting: Single centre • Study design: RCT

Fu 1998 *(Continued)*

	• Randomisation: Completely sealed envelopes with number sequence determined by random number table • Blinding: No • Intention-to-treat: No
Participants	• 40 paediatric patients aged 9 to 14 years, persistent proteinuria > 2 g/d • 24/40 class IV lupus nephritis • Group 1: randomised (20); age (10.2 ± 3.4 years); M/F (NS) • Group 2: randomised (20); age (10.4 ± 3.1 years); M/F (NS)
Interventions	1. Oral CPA: 2 mg/kg/d + prednisolone 2 mg/kg/d 2. CSA: 5 mg/kg/d q.12 h Participants received oral prednisolone 2 mg/kg/d for 4 weeks ± pulsed MP (if unresponsive). Dose of prednisolone tapered to 0.5 to 1 mg/kg as maintenance therapy for > 1 year before randomisation
Outcomes	1. Proteinuria 2. SCr 3. CrCl 4. Height velocity 5. Height SDS
Notes	Follow-up: 1 year Maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned (1:1, stratified by race and biopsy class, non-blocked) by a central computerised, interactive voice response system
Allocation concealment (selection bias)	Low risk	Used sealed, completely opaque, envelopes numbered in sequence according to a table of random numbers
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all of the study's prespecified primary outcomes were reported
Other bias	Low risk	Funding source not declared. The study appears to be free of other sources of bias

Ginzler 2005

Methods	• Country: USA • Setting: Multicentre • Study design: RCT, open-label, non-inferiority
Participants	• 113/140 diffuse proliferative lupus nephritis (27/140 pure membranous) • Group 1: randomised/analysed (71/71); age (32.5 ± 10 years); M/F (10/61) • Group 2: randomised/analysed (69/69); age (31.0 ± 9.0 years); M/F (4/65) • Group 1: Black/white/Hispanic/Asian/other (43/12/10/6/0) • Group 2: Black/white/Hispanic/Asian/other (36/12/18/2/1) Inclusion criteria • Diagnosis of SLE (ACR), biopsy proven lupus nephritis class III, IV or V, clinical activity defined by one of; incident decrease in kidney function, proteinuria (> 0.5 g/24 h), microscopic haematuria (> 5 RBC/HPF). Participants with class III or V required to have SCr > 1.0 mg/dL or proteinuria > 2 g/24 h Exclusion criteria • CrCl < 30 mL/min, SCr > 3.0 mg/dL, severe co-existing conditions precluding immunosuppression or requiring i.v. antibiotics, prior treatment with MMF, treatment with i.v. CPA in last 12 months, treatment within last 30 days, pregnancy or lactation
Interventions	1. MMF: 0.5 g twice daily to increase to max 1 g three times daily; prednisone 1 mg/kg/d 2. i.v. CPA: 0.5 g/m^2 BSA increased to 1.0 g/m^2; prednisone 1 mg/kg/d
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Relapse 5. Stable kidney function 6. Major infection 7. Herpes zoster 8. Ovarian failure 9. Gastrointestinal upset 10. Diarrhoea 11. Lymphopenia 12. Complete remission in proteinuria 13. Partial remission in proteinuria 14. Complete renal remission 15. Partial renal remission 16. SCr 17. Daily proteinuria
Notes	Complete remission defined at 24 weeks as return to within 10% of normal values of SCr levels, proteinuria and urine sediment. Partial remission defined at 24 weeks as improvement of 50% in all abnormal renal measurements, without worsening (within 10%) of any measurement 1 MMF crossed-over to CPA and 2 i.v. CPA crossed over to MMF Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement

Ginzler 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Treatment assigned at central site with the use of sealed envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and prespecified outcomes were reported
Other bias	Unclear risk	Supplemental grant from Roche laboratories

Ginzler 1976

Methods	• Country: USA • Setting: Single centre • Study design: Cross-over RCT
Participants	• 14 diffuse proliferative lupus nephritis • Group 1: randomised (8) • Group 2: randomised (6) Exclusion criteria • SCr > 3 mg/dL, previous exposure to cytotoxic drugs
Interventions	1. AZA + CPA 2. Prednisone + AZA
Outcomes	1. Mortality 2. ESKD 3. Toxicity 4. Proteinuria 5. CrCl 6. Ovarian failure 7. Infection
Notes	Induction Follow-up: 4 months until cross-over commenced
Risk of bias	

Ginzler 1976 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Double-blind with a cross-over to other treatment under certain conditions (predetermined therapeutic failures)
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	Blinding of participants and personnel
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Unclear if blinding of outcome assessors but measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and prespecified outcomes were reported
Other bias	Low risk	Supported by a grant from Lupus Erythematosus Foundation. The study appears to be free of other sources of bias

Gourley 1996

Methods	• Country: USA • Setting: Single centre • Study design: RCT
Participants	• 82 participants • 79/82 class III/IV on biopsy; 3/82 no biopsy • Group 1: randomised (27); mean age (30 years); M/F (5/22) • Group 2: randomised (27); mean age (30 years); M/F (6/21) • Group 3: randomised (28); mean age (31 years); M/F (3/25) Exclusion criteria • Cytotoxic drug treatment > 2 weeks and with 6 weeks of start date, 10 weeks of CPA therapy, pulse therapy of corticosteroids within 6 weeks of start of study, oral corticosteroids > 0.5 mg/kg/d, active or chronic infection, pregnancy, insulin-dependent diabetes, allergy to trial medication
Interventions	1. i.v. MP: 3 doses then monthly for 12 months if remission 2. i.v. CPA: monthly for 6 months then 3 monthly for at least 2 years 3. i.v. MP + i.v. CPA
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Renal remission 5. Relapse 6. One or more infections

Gourley 1996 *(Continued)*

	7. Herpes zoster virus infection 8. Amenorrhoea 9. Avascular necrosis
Notes	Follow-up: > 5 years, 2 participants lost to follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Masked cards from table of random numbers
Allocation concealment (selection bias)	Low risk	Using masked card
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; participants at endpoints censored but considered in final analysis
Selective reporting (reporting bias)	Low risk	Study protocol available and prespecified outcomes were reported
Other bias	Low risk	Grant support in part by a fellowship from the Arthritis Foundation. No other funding source identified. The study appears to be free of other sources of bias

Grootscholten 2006

Methods	• Country: Netherlands • Setting: Multicentre • Study design: RCT
Participants	• 87 participants • Group 1: randomised/analysed (50/50); mean age (30, 24 to 47 years); M/F (6/44) • Group 2: randomised/analysed (37/37); mean age (33, 26 to 39 years); M/F (9/28) Inclusion criteria • Biopsy-proven lupus nephritis (PALGA), ≥ 4 ACR criteria for SLE, 18 to 60 years, CrCl > 25 mL/min, if already known to have proliferative lupus nephritis, renal biopsy < 1 year before, WHO class IV or Vd must have signs of active nephritis or deterioration of kidney function, class III or Vc lupus nephritis had to meet both criteria Exclusion criteria • Decline in kidney function (> 30% increase in SCr) in month before inclusion, active infection, malignancy < 5 years before randomisation, pregnancy or no contraceptives during first 2.5 years of treat-

Grootscholten 2006 *(Continued)*

	ment, hepatitis or cirrhosis of liver, active peptic ulcer, leucocytopenia (< 3 x 10^9/L) or thrombocytopenia (< 100 x 10^9/L with suppressed bone marrow, allergy to AZA or CPA
Interventions	1. i.v. CPA: 750 mg/m^2, 13 pulses in 2 years, oral prednisolone cumulative corticosteroid dose (11 g) 2. AZA: 2 mg/kg/d in 2 years, i.v. MP (3 x 3 pulses of 1000 mg) and oral prednisolone Both groups switched to long term AZA plus prednisolone after 2 years
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Deterioration of kidney function 5. major infection 6. Ovarian failure 7. Daily proteinuria 8. Renal relapse
Notes	Median follow-up 5.7 years (interquartile range 4.1 to 7.2 years) Unintentional skewed distribution (resulting from stratification per centre and small contribution of some centres). 8/87 class III or Vc class IV or Vd 79/97 13/87 given previous cytotoxics i.v. CYC:7/50 (14%) AZA: 6/37 (16%) If 1ʸ failure (DSC) switched to other arm of study 1 lost to follow-up in each group Induction and maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed at a central office with a computer program, using the minimisation determinants: centre, SCr (< 150 or > 150 µmol/L), WHO class III or IV, previous treatment with immunosuppressive medication for lupus nephritis
Allocation concealment (selection bias)	Low risk	Randomisation performed at a central office
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Funding from Dutch Kidney Foundation and Dutch League against Rheumatism. One author disclosed speaking fees from Novartis. The study appears to be free of other sources of bias

Hahn 1975

Methods	• Country: USA • Setting: Single centre • Study design: RCT
Participants	• 9/24 diffuse proliferative lupus nephritis • Group 1: randomised (13); age (31.7 ± 13.9 years); M/F (2/11) • Group 2: randomised (11); age (33.5 ± 13.2 years); M/F (2/9) Exclusion criteria • Prior treatment with cytotoxic drugs, 20 mg prednisone/d during the preceding 6 weeks
Interventions	1. Prednisone 2. AZA + prednisone
Outcomes	1. Mortality 2. Toxicity 3. Infection 4. Proteinuria 5. CrCl 6. SCr
Notes	Follow-up: 2 year follow-up, 2/24 lost to follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Slips of paper bearing letters A or B sealed in envelopes then placed in a drawer. On randomising patient, envelopes drawn randomly from drawer
Allocation concealment (selection bias)	Low risk	Sealed envelopes used in randomisation
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Hong 2007

Methods	• Country: China • Setting: NS • Study design: RCT
Participants	• 25 diffuse proliferative lupus nephritis; M/F (2/23) mean age (30.7± 5.1 years); all > 2 g/d proteinuria and SCr < 3 mg/dL • Group 1: randomised/analysed (13/13) • Group 2: randomised/analysed (12/12) Inclusion criteria • Diffuse proliferative lupus nephritis on renal biopsy • Exclusion criteria: NS
Interventions	1. Oral FK506 (TAC): 0.1 mg/kg/d, prednisolone (0.8 mg/kg/d) 2. i.v. CPA: 0.5 to 0.75g/m^2 monthly, prednisolone (0.8 mg/kg/d)
Outcomes	1. Stable kidney function 2. No response 3. Infection 4. Complete remission 5. Partial remission 6. Proteinuria
Notes	6 month follow-up period complete remission: Proteinuria < 0.4 g/d, urinary RBC < 10 x 10^4/mL, serum albumin > 35 g/L, SCr in normal range No response: Proteinuria still > 2 g/d or the reduction less than the baseline value, albumin < 30 g/L or increase in SCr to more than 50% of baseline value. Partial remission: between complete remission and no response Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Hong 2007 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

Houssiau 2002

Methods	• Country: European • Setting: Multicentre • Study design: RCT
Participants	• 69/90 class IV or Vc/Vd • Group 1: randomised (46); age (30 ± 11 years); M/F (3/43) • Group 2: randomised (44); age (33 ± 12 years); M/F (3/41) Exclusion criteria • CPA or AZA in previous year, > 15 mg/d prednisolone during preceding month, renal thrombotic microangiopathy, pre-existing CKD, pregnancy, previous malignancy - except skin or cervical intraepithelial neoplasias, diabetes, severe toxicity or immunosuppressive drugs, anticipated poor compliance
Interventions	1. High dose intravenous CPA 2. Low dose intravenous CPA
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Relapse 5. Toxicity 6. Proteinuria 7. Infection
Notes	Follow-up: Median 41 month follow-up; 1 patient lost to follow-up. 73 month follow-up; 5 participants lost to follow-up, 10 year follow-up Induction and maintenance therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by minimisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data

Houssiau 2002 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	Supported by the European League Against Rheumatism. The study appears to be free of other sources of bias

Lewis 1992

Methods	• Country: USA • Setting: Multicentre • Study design: RCT
Participants	• 86 participants; 35 participants with class IV disease • Group 1: randomised (40); age (31 ± 11 years); M/F (7/33) • Group 2: randomised (46); age (33 ± 14 years); M/F (7/39) Exclusion criteria • Pregnancy, SCr > 6 mg/dL, previous plasmapheresis, history of primary myocardial disease, cancer within last 5 years, prednisone-associated psychosis, peptic ulcer, active liver disease
Interventions	1. Oral CPA with corticosteroids plus plasma exchange 3 x weekly for 4 weeks 2. Oral CPA with corticosteroids
Outcomes	1. Mortality 2. ESKD 3. Toxicity 4. SCr 5. Proteinuria
Notes	Follow-up: 1 patient lost to Mean follow-up 2.5 years with termination of study Induction therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified according to clinic by central coordination centre
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding

Lewis 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	Funding from the National Institutes of Health. The study appears to be free of other sources of bias

Li 2009a

Methods	• Country: Hong Kong • Setting: Single centre • Study design: RCT
Participants	• 19 participants • 3 participants with class IV disease • Group 1: randomised/analysed (9/9); age (40.3 ± 13.9 years) • Group 2: randomised/analysed (10/10); age (39.6 ± 8.6 years) Inclusion criteria • Biopsy proven lupus nephritis class III or IV, clinical activity index ≥ 6/24, proteinuria ≥ 1.5 g/24 h, albumin ≤ 35 g/L Exclusion criteria • Severe infection in last 3/12, HIV, hepatitis B or C, active tuberculosis, pregnancy, on oral/i.v. CPA, AZA or MMF within 8/52 or prednisolone ≥ 0.5 mg/kg/d for > 4/52, history of cancer, diabetes mellitus or kidney failure leading to dialysis
Interventions	1. RTX: 1000 mg, 250 mg MP day 1, oral prednisolone 30 mg/d 2 to 5, then 0.5 mg/kg for 4/52 then dose reduction 5 mg every 2/52 2. RTX: 1000 mg, 250 mg MP day 1, followed by i.v. CPA 750 mg, oral prednisolone 30 mg/d 2 to 5, then 0.5 mg/kg for 4/52 then dose reduction 5 mg every 2/52 Treatment repeated once on day 15 All participants on ACEI before the study and continued on same dose
Outcomes	1. Major infection 2. Herpes zoster virus infection 3. Complete response 4. CrCl 5. Proteinuria
Notes	48 week treatment period and follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to a randomisation table kept by a third party

Li 2009a *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomisation table kept by a third party
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	"...Roche provided study drug but had no role in study design, data collection, data analysis, data interpretation or writing of the report..." The study appears to be free of other sources of bias.

Li 2009b

Methods	• Country: China • Setting: NS • Study design: RCT
Participants	• 60 participants with classes III, IV and V disease; 35 participants with class IV disease • Group 1: randomised/analysed (20/20) • Group 2: randomised/analysed (20/20) • Group 3: randomised/analysed (20/20)
Interventions	1. MMF: 1.5 to 2.0 g/d, corticosteroids 2. TAC: 0.08 to 0.1 mg/kg/d, target 12 hour trough 6 to 8 ng/mL, corticosteroids 3. i.v. CPA: 0.5 to 0.75 g/1.73 m^2, corticosteroids Corticosteroids 0.8 to 1 mg/kg/d (max dose 60 mg/d). Reduced by 10 mg every 2 weeks until at 40 mg/d, then reduced by 5 mg/d every 2 weeks to maintenance dose of 10 mg/d
Outcomes	1. Mortality 2. Stable kidney function 3. Major infection 4. Leucopenia 5. Complete renal remission 6. Partial renal remission 7. Complete remission in proteinuria 8. Proteinuria
Notes	Complete remission defined as urine protein excretion < 0.3 g/24 h, normal urine sediment, serum albumin > 35 g/L, stabilisation of SCr (15% or less above baseline). Partial remission defined as urinary protein excretion between 0.3 and 2.9 g/24 h, having decreased by at least 50% from baseline, serum albumin at least 30 g/L and stabilisation of SCr (30% or less above baseline)

Li 2009b *(Continued)*

	Induction therapy. follow-up 24 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	"Disclosure of financial relationship: nothing to disclose" The study appears to be free of other sources of bias

Lui 1997

Methods	• Country: Hong Kong • Setting: NS • Study design: RCT
Participants	• 34 participants • 17/17 participants with class IV disease • Group 1: randomised/analysed (17/17) • Group 2: randomised/analysed (17/17)
Interventions	1. CSA: 5 mg/kg/d, reduced to 2.5 mg/kg/d, AZA (1 mg/kg/d), prednisolone (0.5 mg/kg/d) 2. CPA: 1 mg/kg/d, AZA (1 mg/kg/d), prednisolone (0.5 mg/kg/d)
Outcomes	1. Failure to respond 2. Partial response 3. Complete response 4. Proteinuria 5. CrCl 6. Infection 7. Herpres zoster virus 8. Amenorrhoea
Notes	12 month follow-up

Lui 1997 *(Continued)*

	Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

LUNAR Study

Methods	• Setting: NIH trials, multicentre • Study design: Phase III, RCT
Participants	• 144 participants with class III or IV lupus nephritis (ISN/RPS 2003) • Group 1: randomised/analysed (72/72) • Group 2: randomised/analysed (72/72) Inclusion criteria • Diagnosis of SLE (ACR criteria), diagnosis of ISN/RPS 2003 class III or IV lupus nephritis with either active or active chronic disease, proteinuria (urine polymerase chain reaction > 1.0), 16 to 75 years Exclusion criteria • Active infection, recurrent or chronic infection, CPA or calcineurin inhibitor treatment within 90 days prior to screening, MMF > 2 g daily > 90 d prior to screening, use of prednisolone >20 mg/d > 14 days prior to screening, previous treatment with CAMPATH-1H, B-cell targeted therapy, pregnancy or lactation, history of cancer
Interventions	1. RTX: 1000 mg i.v. (days 1, 15, 168, 182); MMF (3 g/d) 2. Placebo, MMF (3 g/d) Protocol-defined tapering schedule corticosteroids after MP in both groups
Outcomes	1. All-cause mortality 2. Stable creatinine

LUNAR Study *(Continued)*

	3. Major infection 4. Complete response in proteinuria 5. Partial response in proteinuria 6. Serious adverse events
Notes	follow-up 52 weeks Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised 1:1. No further details
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Some authors declared grants/research support from Genentech and Aspreva

MAINTAIN Nephritis Study

Methods	• Country: European • Setting: Multicentre • Study design: RCT
Participants	• 105 class III, IV, Vc or Vd and proteinuria ≥ 0.5 g • Group 1: randomised (52) • Group 2: randomised (53) Inclusion criteria • SLE ≥ 14 years, proteinuria ≥ 0.5 g/d, biopsy proven lupus nephritis Exclusion criteria • Recent treatment with high dose corticosteroids or immunosuppressive drugs
Interventions	1. AZA: 2 mg/kg/d 2. MMF: 2 g/d

MAINTAIN Nephritis Study *(Continued)*

	All participants received induction therapy of 3 x 750 mg i.v. MP followed by oral glucocorticoids 0.5 mg/kg/d and 6 fortnightly pulses i.v. CPA 500 mg. Maintenance treatment started in both groups at week 12
Outcomes	1. Time to renal flare 2. Doubling SCr 3. Number of withdrawals due to toxicity 4. Number of treatment failures 5. kidney function over time 6. 24 hour proteinuria over time
Notes	Median follow-up 53 months Maintanance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by minimisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	No competing interests declared. The study appears to be free of other sources of bias

Mitwalli 2011

Methods	• Country: Saudi Arabia • Setting: Single centre • Study design: RCT
Participants	• class IV • Group 1: randomised/analysed (73/73); age (36.4 ± 12.7 years); M/F (12/61) • Group 2: randomised/analysed (44/44); age (30.34 ± 10.4 years); M/F (5/3)
Interventions	1. i.v. CPA: 10 mg/kg monthly for 6 months then 2 monthly for 12 months 2. i.v. CPA: 5 mg/kg monthly for 6 months then 2 monthly for 36 months

Mitwalli 2011 *(Continued)*

	Both groups received oral prednisolone 1 mg/kg/d for 4 weeks followed by taper to 0.2 mg/kg/d alternate days for 24 months Maintenance therapy in both arms included: hydroxychloroquine 200 mg/d and AZA 1 mg/kg/d for 24 months
Outcomes	1. Mortality 2. Doubling SCr 3. Stable kidney function 4. Major infection 5. Ovarian failure 6. Malignancy 7. Lymphopenia 8. Complete remission of proteinuria (<0.3 g/24 h) 9. Partial remission of proteinuria (> 50% reduction in proteinuria) 10.SCr 11.Daily proteinuria
Notes	Mean follow-up 6.77 ± 3.3 years Induction and maintenance

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Mok 2009

Methods	• Country: Hong Kong, China • Setting: NS • Study design: RCT

Mok 2009 *(Continued)*

Participants	• 109 participants • M/F 11/98; mean age (35.9 ± 13 years) • 76/109 (76%) CrCl < 90 mL/min • 43/109 (39%) ≥ 3.5 g/d • Class III, class IVG/IVS, class V or V + IV/III • Group 1: randomised/analysed (56/46) • Group 2: randomised/analysed (53/44)
Interventions	1. TAC: 0.06 to 0.1 mg/kg/d for 6 months 2. MMF: 2 to 3 g/d for 6 months Both groups received prednisolone 0.6 mg/kg/d for 6 weeks then tapered. At end of intervention, if complete clinical response or good partial response, changed to AZA (2 mg/kg/d) for maintenance. Poor responders re-induced with oral CPA 2 mg/kg/d
Outcomes	1. Mortality 2. ESKD 3. Doubling kidney function 4. Stable kidney function 5. Relapse 6. Major infection 7. Herpes zoster virus 8. Diarrhoea 9. Nausea 10. Complete renal remission 11. Partial renal remission 12. Proteinuria 13. CrCl
Notes	Median follow-up 30 months Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Mok 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	No disclosures stated. Insufficient information to permit judgement.

Moroni 2004

Methods	• Country: Italy • Setting: Multicentre • Study design: RCT
Participants	• 69 participants • Class IV, Vb or c • Group 1: randomised/analysed (36/36); M/F (3/33); age (31.7 ± 9.1 years) • Group 2: randomised/analysed (33/33); M/F (4/29); age (31.2 ± 11.7 years)
Interventions	1. CSA: 4 mg/kg/d and reduced to maintenance dose (2.5 to 3.0 mg/kg/d) if proteinuria < 1 g/d 2. AZA: 2 mg/kg/d optional reduction at 1 month to 1.5 mg/kg/d if proteinuria < 1 g/d and creatinine stable Both groups received induction therapy of 3 x i.v. MP 0.5 g if ≤ 50 kg and 1 g if > 50 kg. followed by prednisolone 1 mg/kg/d for 10 to 15 days then tapered
Outcomes	1. Mortality 2. ESKD 3. Major infection 4. Lymphopenia 5. Gastrointestinal disorders 6. Complete remission proteinuria 7. Proteinuria at 2 and 4 years 8. CrCl at 2 and 4 years 9. 24 hour proteinuria
Notes	Duration of therapy 24 months. At least 1 year follow-up, invited to continue to 4 years. Maintenance therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to a coin based design
Allocation concealment (selection bias)	Low risk	Stratified by centre and performed centrally. Phone calls to randomisation centre-computer program assigned participants
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding

Moroni 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Educational grant from Novartis Pharma AG. Data management and analysis: Novartis Farma

Mulic-Bacic 2008

Methods	• Country: Bosnia Herzegovina • Setting: NS • Study design: RCT
Participants	• 45 participants • Class III, IV or V • Group 1: randomised/analysed (20/20) • Group 2: randomised/analysed (25/25)
Interventions	1. MMF: 2 g/d for 6 months then 1 g/d for 18 months 2. i.v. CPA: 0.5 g/m^2 monthly Both groups received prednisolone 0.75 to 1 mg/kg/d with determined tapering
Outcomes	1. Mortality 2. Stable kidney function 3. Complete remission proteinuria 4. Partial remission proteinuria 5. Complete remission 6. Partial remission
Notes	24 week study Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement

Mulic-Bacic 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Funding source not disclosed. Insufficient information to permit judgement

MyLupus Study 2010

Methods	• Country: Multinational • Setting: Multicentre • Study design: RCT, open label
Participants	• 81 participants • class III or IV on biopsy • Group 1: randomised (42) • Group 2: randomised (39)
Interventions	1. Enteric coated mycophenolate sodium (EC-MPS; Myfortic©) plus prednisolone (1 mg/kg/d) 2. EC-MPS plus prednisolone (0.5 mg/kg/d) Both groups received MP 0.5 g i.v./d for 3 days. EC-MPS started at 1440 mg/d for first 2 weeks then 2160 mg in remaining 22 weeks. Prednisolone tapered in both groups according to guidelines
Outcomes	• Mortality • Infection • Complete remission • Partial remission • Urine protein/creatinine ratio • Creatinine Complete remission defined as urine protein/creatinine ratio < 0.5, urine sediment normalised, SCr within 10% of normal value after 24 weeks. Partial remission defined as urine protein/creatinine ratio reduced by at least 50% from baseline and SCr stable (within 10% baseline) or improved
Notes	Follow-up 6 months Induction therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement

MyLupus Study 2010 *(Continued)*

Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Disclosure of consulting fees from Novartis Pharma, Amgen, BMS and Roche

Nakamura 2002

Methods	• Country: Japan • Setting: NS • Study design: RCT
Participants	• 20/20 class IV • Group 1: randomised (10(; age (30.5 years); M/F (2/8) • Group 2: randomised (10); age (29.5 years); M/F (2/8)
Interventions	1. Plasma exchange 2. i.v. CPA
Outcomes	1. Proteinuria 2. Urinary podocyte number
Notes	Induction Follow-up: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Nakamura 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Ong 2005

Methods	• Country: Malaysia • Setting: Multicentre • Study design: Prospective, randomised, open-labelled
Participants	• 54 participants • Class III or IV • Group 1: randomised/analysed (28/25); age (30.5 ± 8.7 years); M/F (3/23) • Group 2: randomised/analysed (26/19); age (31.3 ± 9.9 years); M/F (4/15) Inclusion criteria • WHO classified III or IV lupus nephritis, age >16 years Exclusion criteria • Creatinine > 200 µmol/L, white blood cell count < 3.5, major infection, history of cancer, alcohol or substance misuse, pregnancy, active peptic ulcer disease, allergy to MMF or CPA, use of study drugs in preceding 6/12
Interventions	1. i.v. CPA: 0.75 to 1 g/m^2 monthly for 6 months 2. MMF: 1 g twice daily for 6 months Both groups received prednisolone 60mg/d for 4-6 weeks then tapering dose to 5 to 10 mg/d
Outcomes	1. Mortality 2. ESKD 3. Stable kidney function 4. Major infection 5. Herpes zoster virus infection 6. Leucopenia 7. Oligomenorrhea 8. Gastrointestinal side effects 9. Complete renal remission (stabilisation or improvement in kidney function, red blood cell count < 10, proteinuria < 3 g) 10. Combined partial remission (stabilisation or improvement in kidney function, red blood cell count < 10, proteinuria < 3 g if was > 3 g or at least 50% reduction or to < 1.0 g if subnephrotic) 11. Proteinuria
Notes	Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code generated separately for each centre using random permutated block method with randomly varying block size (1:1)

Ong 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Performed centrally
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	MMF supplied by Roche Malaysia

Sabry 2009

Methods	• Country: Egypt • Setting: Single centre • Study design: Quasi-RCT
Participants	• 46 participants • Group 1: randomised/analysed (26/ 26); age (26.4 years); M/F (4/22) • Group 2: randomised/analysed (20/20); age (25.7 years); M/F (2/18) Inclusion criteria • ACR criteria for SLE ≥ 18; biopsy proven proliferative lupus nephritis (WHO class IV), urine protein > 0.5 g/d Exclusion criteria • CSA or AZA in previous year or > 15 mg/d prednisolone in previous month, renal thrombotic microangiopathy, pre-existing CKD, pregnancy, previous malignancy, diabetes mellitus, documented toxicity, anticipated poor compliance
Interventions	1. Low dose CPA: 6 x monthly pulses + 2 x quarterly pulses fixed dose of 500 mg/d 2. High dose CPA: 6 x monthly pulses + 2 x quarterly pulses. Initial dose (0.5 g/1.73 m^2 body surface area) then dose increased by 250 mg according to white cell count on day 14 with final increment to maximum dose of 1 g/1.73m^2 Prednisolone (0.5 mg/kg) and AZA (2 mg/kg/d) given in both treatment arms. Prednisolone given at high dose for 4 weeks then given alternate days after being tapered by 5 mg each week to minimal dose to control extrarenal SLE manifestations or 0.25 mg/kg/d. AZA started 2 weeks after last infusion and continued until the end of the study Six participants with most severe form of lupus nephritis allocated to high dose arm
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr

Sabry 2009 *(Continued)*

	4. Relapse 5. Major infection 6. Ovarian failure 7. Anaemia 8. Leucopenia 9. Gastrointestinal side effects 10. Proteinuria 11. SCr
Notes	1 year follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	All participants meeting inclusion criteria randomised. Manual randomisation to allocate every other patient to either group and then assigned to one of 2 regimens. Six participants with most severe form of lupus nephritis allocated to high dose arm
Allocation concealment (selection bias)	High risk	Use of alternation to allocate
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	Funding not disclosed. The study appears to be free of other sources of bias.

Sesso 1994

Methods	• Country: Brazil • Setting: Single centre • Study design: RCT
Participants	• 23/29 diffuse proliferative lupus nephritis • Group 1: randomised (14); age (30.0 ± 2.7 years); M/F (2/12) • Group 2: randomised (15); age (24.3 ± 1.5 years); M/F (2/13) Exclusion criteria

Sesso 1994 *(Continued)*

	• CrCl < 20 mL/min, SCr > 6 mg/dL, major infection within 2 weeks of study entry, pregnancy, low leucocyte count, pulse MP or CPA within 1 year
Interventions	1. i.v. CPA: 0.5 to 1.0 g/m^2 body surface area, monthly pulse for 4 months, bimonthly for 4 months then quarterly for 6 months 2. i.v. MP: 10 to 20 mg/kg; max 1.0 g x 3 daily, then monthly for 4 months, bimonthly for 4 months then quarterly for 6 months Both groups received low dose oral prednisolone (0.5 mg/kg/d initially then tapered) to control extra-renal manifestations
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Bone toxicity 5. Bladder toxicity 6. Malignancy 7. Proteinuria
Notes	Follow-up: 15 months, 2 participants lost to follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding-no self reported outcomes in this study
Blinding (performance bias and detection bias) Objective outcomes	High risk	No blinding but some outcomes such as remission of kidney disease not clearly defined (defined in paper as a "... trend of improvement of SCr and of urine sediment or proteinuria....") allowing potential detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Study protocol available and pre-specified outcomes were reported
Other bias	Low risk	Work supported by Instituto Paulista de Estudos e Pesquisas em Nefrologia e Hipertensao. The study appears to be free of other sources of bias

Steinberg 1971

Methods	• Country: USA • Setting: Single centre

Steinberg 1971 *(Continued)*

	• Study design: RCT
Participants	• 15 participants • 8/15 diffuse proliferative lupus nephritis • Mean age: (24, range 11 to 36 years) • Group 1: randomised (7); age (23 years); M/F (0/7) • Group 2: randomised (6); age (23 years); M/F (0/6) Exclusion criteria • Major infection within the preceding 2 weeks, pregnancy, granulocyte count < 1500/mm^3, immunosuppressive therapy within 3 months, severe liver disease
Interventions	1. Oral CPA with corticosteroids 2. Corticosteroids alone
Outcomes	1. Mortality 2. Toxicity 3. Proteinuria 4. CrCl
Notes	Follow-up: 10 weeks, 2 participants lost to follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used consecutively numbered envelopes, each containing a randomly assigned prescription for placebo or CPA.
Allocation concealment (selection bias)	Low risk	As each patient entered the trial, the next sequential envelope was opened in the pharmacy
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	Investigators and participants blinded, unlikely blinding was broken
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Assessors blinded, unlikely blinding was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	Unclear risk	Drug and placebo were supplied through the kindness of Dr Martin E. Vancif, Mead Johnson Laboratories, Evansville, Ind. The study appears to be free of other sources of bias

Sundel 2008

Methods	• Country: International • Setting: Multicentre • Study design: RCT
Participants	• 24 participants all < 18 years • Mean age (15, range 12 to 17 years) • M/F (5/19) • Mean disease duration: 1 year (range 1 to 3 years) Inclusion criteria • Diagnosis of SLE (ACR criteria), biopsy-proven class III, IV or V disease within 6 months before randomisation
Interventions	1. MMF: target dose of 3g/d by third week 2. i.v. CPA: 0.5 to 1 g/m^2 monthly Both groups received prednisolone 60 mg/d with defined taper
Outcomes	1. Mortality 2. Stable kidney function 3. Major infection 4. Response: defined as decrease in urine polymerase chain reaction over 24 hours to < 3, and stabilisation (± 25%) or improvement in SCr
Notes	24 week follow-up period. Two participants withdrew from each group Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Clinical trial supported by Aspreva

Wallace 1998

Methods	• Country: International • Setting: Multicentre • Study design: RCT
Participants	• 19 participants • 12/19 class IV • Group 1: randomised (9); age (33.0 ± 10.0 years); M/F (1/8) • Group 2: randomised (9); age (32.0 ± 14.0 years); M/F (0/9) Exclusion criteria • SCr > 3 mg/dL, renal biopsy chronicity index ≥ 6, pregnancy, < 16 years, immunosuppression in last 3 months
Interventions	1. Plasma exchange: x 3 daily preceding CPA plus i.v. CPA (750 mg/m^2 x 6) over 8 months 2. i.v. CPA: 750 mg/m^2 x 6 over 8 months with corticosteroids Both groups received prednisolone 1 mg/kg/d for 6 weeks then tapering dose
Outcomes	1. Mortality 2. ESKD 3. SCr 4. Proteinuria
Notes	Follow-up: greater than 24 months, 1 patient lost to follow-up Induction therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Yee 2004

Methods	• Country: European • Setting: Multicentre • Study design: RCT, open label
Participants	• 32 participants • Group 1: randomised/analysed (16/13); age (42.4 ± 11.8 years); M/F (2/11) • Group 2: randomised/analysed (16/16); age (32.2 ± 11.7 years); M/F (2/14) Inclusion criteria • ACR criteria for SLE, biopsy proven lupus nephritis, aged 16 to 65 years Exclusion criteria • Previous CPA or AZA in preceding 3 weeks, pure membranous or mesangial proliferative glomerular nephritis on biopsy, previous treatment with CPA for > 3 months, allergy to study drugs, previous malignancy, primary immunodeficiency (except complement components), or non-lupus-related kidney disease
Interventions	1. Intermittent i.v. CPA: 10 mg/kg three weekly, max 1 g for 4 doses, then orally (same dose split over 2/7) four weekly for 9 months and six weekly for 12 months. i.v. MP 6.6 mg/kg before each pulse of CPA then orally at same dose split over 2 days before each oral dose plus oral prednisolone 0.3 mg/kg/d reducing to 0.1 mg/kg/d to maintenance dose of 0.05 to 0.1 mg/kg/d 2. Daily oral CPA: 2 mg/kg/d for 3 months then 1.5 mg/kg/d plus oral prednisolone 0.85 mg/kg/d (max dose 60 mg) reducing to 0.11 mg/kg/d by week 53
Outcomes	1. Mortality 2. ESKD 3. Doubling SCr 4. Major infection 5. Ovarian failure 6. Malignanacy 7. Bladder toxicity 8. Alopecia 9. Nausea/vomiting
Notes	Intended follow-up for 5 to 10 years. Study terminated after 4 years due to poor recruitment and high withdrawal rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were stratified according to the presence of kidney failure and underwent block randomisation to either therapy
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) Self-reported outcomes	Low risk	No blinding but the outcome is not likely to be influenced by lack of blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding

Yee 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes reported: alopecia
Other bias	Low risk	Support from Swedish Medical Council and Lupus UK

ACR - American College of Rheumatology; AZA - azathioprine; CKD - chronic kidney disease; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporin A; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; IVIG - intravenous immunoglobulin; i.v. - intravenous; MMF - mycophenolate mofetil; MP - methyl prednisolone; NS - not stated; RCT - randomised controlled trial; RTX - rituximab; SCr - serum creatinine; SLE - systemic lupus erythematosus; TAC - tacrolimus; WHO, World Health Organization

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

Study	Reason for exclusion
Abedi 2007	Insufficient data
Amosova 1997	Not biopsy-proven lupus nephritis; and not RCT
Andrade-Ortega 2010	Not biopsy proven lupus nephritis
Antunes 2001	Not comparing immunosuppression
ASPEN Study 2009	Not biopsy-proven lupus nephritis
Austin 1996	Not biopsy-proven lupus nephritis but membranous
Balow 1981	Not biopsy proven lupus nephritis
Balow 1984	No relevant outcomes
Ble 2011	Not immunosuppressive intervention
Bosque 2001	Not RCT or comparing immunosuppression
Cao 2006	Not RCT
Chanchairujira 2009	No relevant outcomes
Clark 1992	Not biopsy-proven lupus nephritis
Clark 1998	Not biopsy-proven lupus nephritis
Cui 2003	Not RCT
Danieli 2002	Not RCT
Davis 1999	Not biopsy-proven lupus nephritis or comparing immunosuppression
Daza 2005	Not comparing immunosuppression
Felson 1984	Not RCT

Study	Reason for exclusion
Flores-Suarez 2006	Not an RCT. Case series only
Florez-Suarez 2004	Unclear total number in each treatment allocation arm. Information sought but not supplied
Frutos 1997	Insufficient information
Futrakul 1978	Not RCT
Gonzales-Diaz 2011	Not RCT
Harisdangkul 1989	Not RCT
Hebert 1987	Not biopsy-proven lupus nephritis
Honma 1994	Not RCT
Hu 2002	Not RCT
Jigui 1995	Not RCT
Jigui 2000	Not RCT
Kuo 2001	Not comparing immunosuppression
Li 2005	Unclear if randomised
Li 2006	No mention if RCT
LJP 394-90-05	Not biopsy proven lupus nephritis
LJP 394-90-09	Not biopsy-proven lupus nephritis
Loo 2010	Included class II lupus nephritis
Lu 2002	Not biopsy-proven lupus nephritis
Miyasaka 2009	Included class II and class V lupus nephritis
Monova 2000	Not RCT
Nakayamada 2007	Not RCT. Not lupus nephritis
NCT00001212	Membranous lupus nephritis
Pierucci 1988	Not comparing immunosuppression
Qi 2006	Not RCT
Schaumann 1992	Unclear if biopsy-proven lupus nephritis
Spertini 1999	Not RCT
Steinberg 1992	Not RCT
Su 2007	Not biopsy-proven lupus nephritis

Study	Reason for exclusion
Wallace 1992	Not RCT
Wallace 2006	Not biopsy-proven lupus nephritis
Wang 2007	Non-invasive necrotising vasculopathy-severe variant not usually responsive to standard therapy
Witte 1993	Unclear if biopsy-proven lupus nephritis
Wu 1998	Not RCT
Ye 1997	Not RCT
Ye 2001	Not biopsy-proven lupus nephritis
Yin 1994	Non randomised trial
Yoshida 1996	Not comparing immunosuppression
Zhang 1995	Insufficient information
Zheng 2005	Unclear if biopsy-proven lupus nephritis

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

ACCESS Study

Trial name or title	Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis (ACCESS)
Methods	Randomised, controlled, double-blind
Participants	Adults, active proliferative lupus nephritis, positive ANA
Interventions	Abatacept (CTLA4Ig) + cyclophosphamide versus cyclophosphamide
Outcomes	Complete response, partial response, maintained complete response, time to complete or partial response, adverse events
Starting date	November 2008
Contact information	David Wofsy, Betty Diamond
Notes	NCT00774852

BELONG Study

Trial name or title	A study to evaluate Ocrlizumab in patients with nephritis due to systemic lupus nephritis (BELONG)
Methods	Randomised, double-blind.
Participants	Adults, class III & IV lupus nephritis.

BELONG Study *(Continued)*

Interventions	Ocrelizumab + IV cyclophosphamide + steroids + MMF versus IV cyclophosphamide + steroids + MMF
Outcomes	Complete and partial renal response
Starting date	February 2008
Contact information	Jorn Drappa
Notes	NCT00626197

CONTROL study

Trial name or title	The Efficacy of Enteric-coated Mycophenolate (EC-MPS) (Myfortic) in The Treatment of Relapse or Resistant Proliferative Lupus Nephritis (CONTROL)
Methods	Randomised, open label
Participants	Adults, biopsy proven proliferative lupus nephritis, relapse or resistant to IV Cyclophosphamide or cumulative lifetime dose > 6 g
Interventions	Myfortic 1440 mg bd versus IV cyclophosphamide
Outcomes	Efficacy - not defined
Starting date	January 2010
Contact information	Yingyos Avihingsanon, Chulalongkorn University
Notes	

NCT00425438

Trial name or title	A study of Cellcept (mycophenolate mofetil) in patients with lupus nephritis
Methods	Randomised, open label.
Participants	Adults, systemic lupus nephritis, class unspecified.
Interventions	MMF (1 g bd) + steroid induction followed by MMF 750 mg bd maintenance versus IV cyclophosphamide + steroid induction followed by AZA maintenance
Outcomes	Complete remission rate
Starting date	January 2007
Contact information	Hoffman-La Roche
Notes	

NCT00876616

Trial name or title	Assess the Efficacy and Safety of Multi-target Therapy in Lupus Nephritis
Methods	Open, prospective
Participants	Adults, classes III-V lupus nephritis, renal biopsy-proven, proteinuria ≥1.5 g/24 hs, or active urinary sediment.
Interventions	Tacrolimus + IV cyclophosphamide versus MMF + IV cyclophosphamide
Outcomes	Efficacy - undefined
Starting date	April 2009
Contact information	Zhi-Hong Liu, Nanjing University School of Medicine
Notes	

NCT00881309

Trial name or title	To compare the Efficacy and Safety of Tripterygium (TW) versus AZA in the Maintenance Therapy for Lupus Nephritis
Methods	Randomised, open label
Participants	Adults, class III-V Lupus Nephritis (biopsy-proven)
Interventions	Induction with MMF, cyclophosphamide, tacrolimus or multi-target therapy followed by randomisation to either AZA maintenance therapy or tripterygium 90 mg od
Outcomes	Complete remission
Starting date	March 2009
Contact information	Weixin Hu, Nanjing University School of Medicine
Notes	

NCT01172002

Trial name or title	Leflunomide versus AZA for Maintenance Therapy of Lupus Nephritis
Methods	Randomised, prospective, open label
Participants	Adults, biopsy-proven proliferative lupus nephritis
Interventions	Leflunomide versus AZA
Outcomes	Lupus nephritis flare
Starting date	March 2010
Contact information	Bao Chun De, Renji Hospital

NCT01172002 *(Continued)*

Notes	

NCT01273389

Trial name or title	A Study of the Safety and Efficacy of an Interleukin-6 Inhibitor in Patients with Lupus Nephritis
Methods	Randomised, double-blind
Participants	Adults, biopsy-proven proliferative lupus nephritis
Interventions	CNTO 136 (IL-6 antibody) + conventional treatment versus placebo + conventional treatment
Outcomes	Proteinuria, estimated glomerular filtration rate, physician and patient assessment of disease activity
Starting date	December 2010
Contact information	Director, Clinical Research, Janssen Research & Development
Notes	

NCT01299922

Trial name or title	Clinical Trial in Lupus Nephritis (NCT01299922)
Methods	Randomised, open label
Participants	Adults, biopsy-proven proliferative lupus nephritis
Interventions	CsA + MMF/MPS + steroid versus MMF/MPS + steroid
Outcomes	Complete remission in proteinuria, partial remission in proteinuria.
Starting date	February 2011
Contact information	Manuel Praga Terente, Hospital Universitario Doce de Octubre, Madrid, Spain
Notes	

NCT01342016

Trial name or title	A Study to Compare the Efficacy and Safety of Tacrolimus Capsules With Leflunomide Tablets in Lupus Nephritis Paients
Methods	Randomised, double-blind
Participants	Adults, biopsy-proven lupus nephritis
Interventions	Tacrolimus + leflunomide placebo versus tacrolimus placebo + leflunomide

NCT01342016 *(Continued)*

Outcomes	Complete and partial remission, urinary protein excretion, albumin, serum creatinine, estimated glomerular filtration rate
Starting date	April 2011
Contact information	Astellas Pharma Inc
Notes	

Second Dutch Lupus Trial

Trial name or title	Comparison of short course cyclophosphamide followed by mycophenolate mofetil versus long course cyclophosphamide in the treatment of proliferative lupus nephritis
Methods	Mulitcentre, randomised controlled
Participants	Adult, proliferative lupus nephritis, biopsy proven, active urinary sediment, proteinuria
Interventions	6 months IV cyclophosphamide induction followed by either 3 monthly IV cyclophosphamide or MMF for 18 months, then 2 years AZA in both arms
Outcomes	Renal relapse
Starting date	January 2003
Contact information	Marc Bijl, University Medical Centre Groningen
Notes	

AZA - azathioprine

DATA AND ANALYSES

Comparison 1. Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	9	812	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.49, 1.80]
1.1 MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.76]
1.2 MMF versus IV CPA	7	710	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.52, 1.98]
1.3 MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

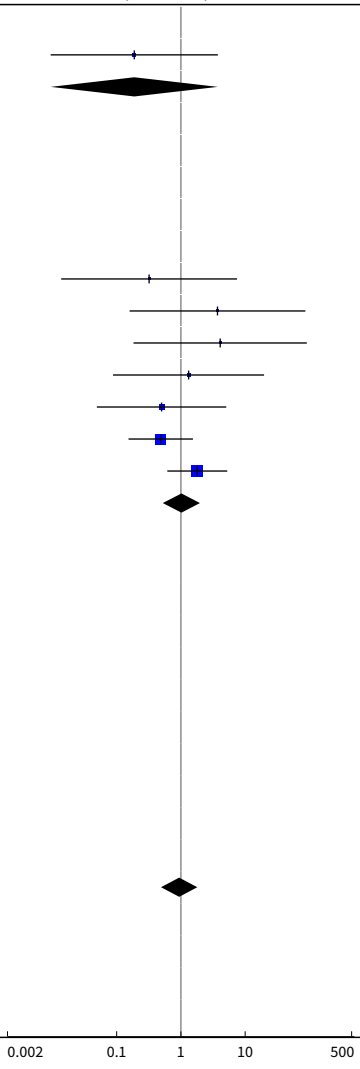
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Adverse renal outcomes	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 ESKD: MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.76]
2.2 ESKD: MMF versus IV CPA	3	231	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.27, 1.84]
2.3 Renal relapse: MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.55, 2.37]
2.4 Renal relapse: MMF versus IV CPA	1	140	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.39, 2.44]
2.5 Doubling of serum creatinine: MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.11, 3.48]
2.6 Doubling of serum creatinine: MMF + tacrolimus verus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.72]
3 Stable kidney function	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 MMF versus IV CPA	5	523	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.94, 1.18]
3.2 MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.15, 2.60]
4 Infection	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Major: MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.05, 0.89]
4.2 Major: MMF versus IV CPA	6	683	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.74, 1.68]
4.3 Major: MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.14, 1.73]
4.4 Herpes zoster virus: MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.79]
4.5 Herpes zoster virus: MMF versus IV CPA	4	613	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.71, 2.58]
4.6 Herpes zoster virus: MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.90]
5 Ovarian failure	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 MMF versus oral CPA	1	53	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.73]
5.2 MMF versus IV CPA	2	498	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.80]
5.3 MMF + tacrolimus versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Bone toxicity	1	62	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Bladder toxicity	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Alopecia	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.29, 3.45]
8.2 MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.81]
8.3 MMF versus IV CPA	2	522	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.06, 0.86]
9 Malignancy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 GI disorders	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Diarrhoea	3	569	Risk Ratio (M-H, Random, 95% CI)	2.53 [1.54, 4.16]
10.2 Vomiting	2	522	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.24]
10.3 Nausea	1	158	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.33]
10.4 GI upset	5	671	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.66, 1.13]
11 Leucopenia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 0.92]
11.2 MMF versus IV CPA	5	653	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.10, 2.43]
12 Remission	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Complete renal remission: MMF versus IV CPA	6	686	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.99, 1.95]
12.2 Complete renal remission: MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	4.33 [1.45, 12.91]
12.3 Partial renal remission: MMF versus IV CPA	6	686	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.86, 1.25]
12.4 Partial renal remission: MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.47, 2.14]
12.5 Complete remission in proteinuria: MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.30]
12.6 Complete remission in proteinuria: MMF versus IV CPA	6	686	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.85, 1.58]
12.7 Complete remission in proteinuria: MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	4.33 [1.45, 12.91]
12.8 Partial remission in proteinuria: MMF versus oral CPA	1	62	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.44, 2.59]
12.9 Partial remission in proteinuria: MMF versus IV CPA	4	602	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.89, 1.25]
12.10 Partial remission in proteinuria: MMF + TAC versus IV CPA	1	40	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.32, 1.77]
13 Daily proteinuria	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 MMF versus oral CPA	1	42	Mean Difference (IV, Random, 95% CI)	0.3 [-0.19, 0.79]
13.2 MMF versus IV CPA	4	271	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.64, 0.42]
13.3 MMF + TAC versus IV CPA	1	40	Mean Difference (IV, Random, 95% CI)	-5.89 [-7.01, -4.77]
14 Serum creatinine	4	619	Mean Difference (IV, Random, 95% CI)	0.06 [-0.02, 0.14]

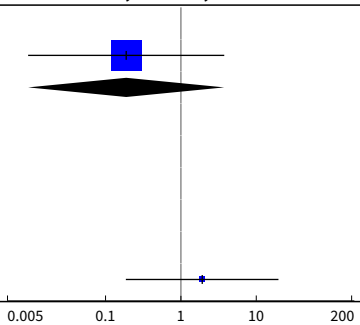
Analysis 1.1. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 1 Mortality.

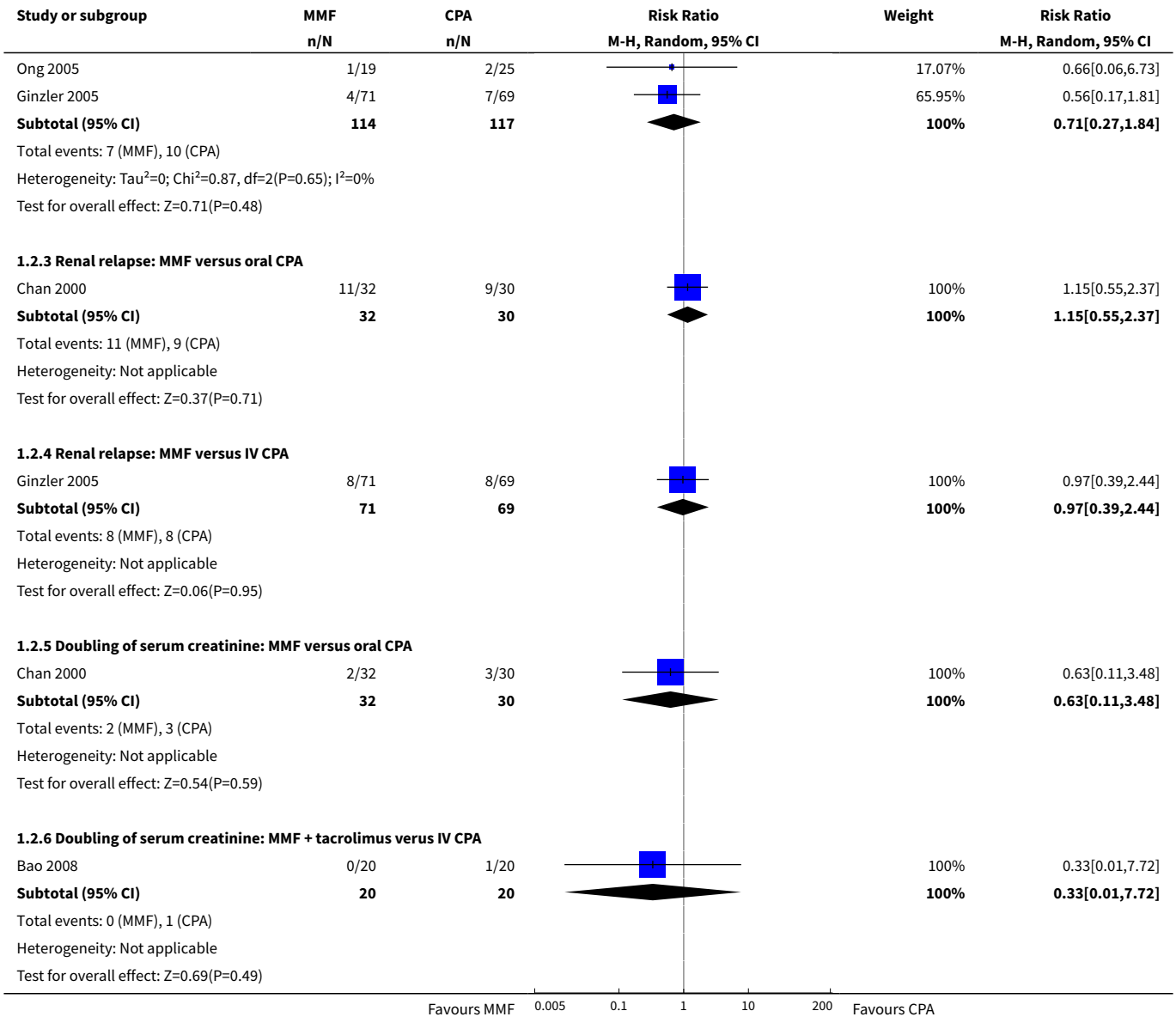
Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 MMF versus oral CPA					
Chan 2000	0/32	2/30		4.72%	0.19[0.01,3.76]
Subtotal (95% CI)	**32**	**30**		**4.72%**	**0.19[0.01,3.76]**
Total events: 0 (MMF), 2 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.09(P=0.27)					
1.1.2 MMF versus IV CPA					
El-Shafey 2010	0/24	1/23		4.27%	0.32[0.01,7.48]
Mulic_x002d_Bacic 2008	1/20	0/25		4.28%	3.71[0.16,86.55]
Sundel 2008	1/10	0/14		4.4%	4.09[0.18,91.23]
Ong 2005	1/19	1/25		5.79%	1.32[0.09,19.71]
Li 2009b	1/20	2/20		7.89%	0.5[0.05,5.08]
Ginzler 2005	4/71	8/69		31.88%	0.49[0.15,1.54]
Appel 2009	9/185	5/185		36.77%	1.8[0.61,5.27]
Subtotal (95% CI)	**349**	**361**		**95.28%**	**1.02[0.52,1.98]**
Total events: 17 (MMF), 17 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=5, df=6(P=0.54); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					
1.1.3 MMF + TAC versus IV CPA					
Bao 2008	0/20	0/20			Not estimable
Subtotal (95% CI)	**20**	**20**			**Not estimable**
Total events: 0 (MMF), 0 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**401**	**411**		**100%**	**0.94[0.49,1.8]**
Total events: 17 (MMF), 19 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=6.16, df=7(P=0.52); I^2=0%					
Test for overall effect: Z=0.19(P=0.85)					
Test for subgroup differences: Chi^2=1.16, df=1 (P=0.28), I^2=14.06%					



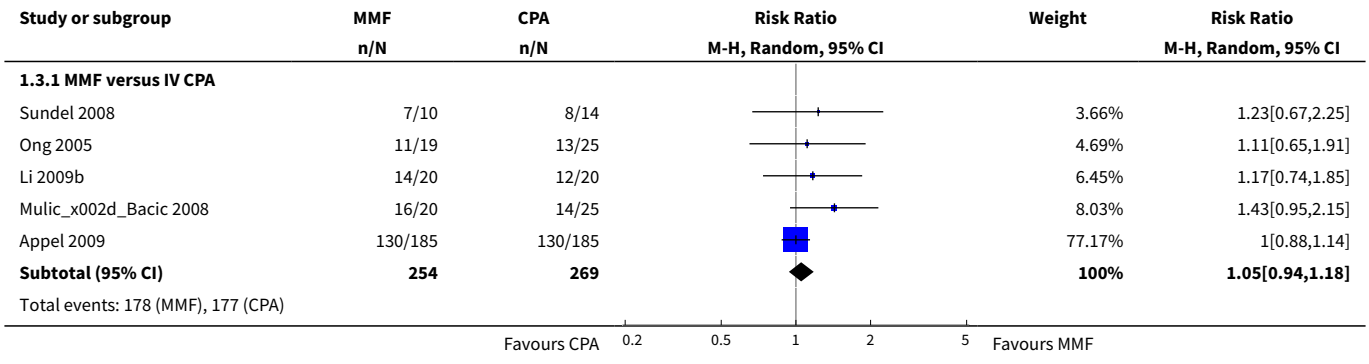
Analysis 1.2. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 2 Adverse renal outcomes.

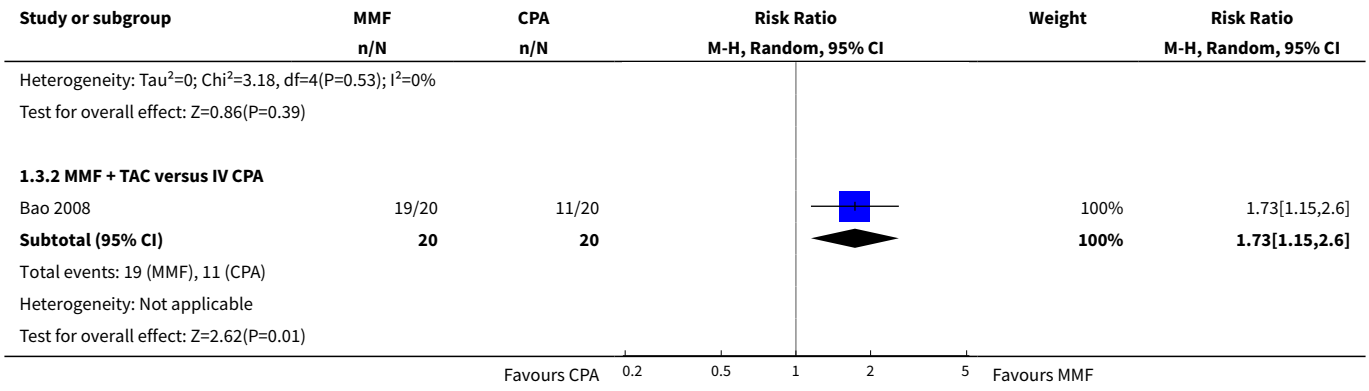
Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 ESKD: MMF versus oral CPA					
Chan 2000	0/32	2/30		100%	0.19[0.01,3.76]
Subtotal (95% CI)	**32**	**30**		**100%**	**0.19[0.01,3.76]**
Total events: 0 (MMF), 2 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.09(P=0.27)					
1.2.2 ESKD: MMF versus IV CPA					
El-Shafey 2010	2/24	1/23		16.98%	1.92[0.19,19.73]



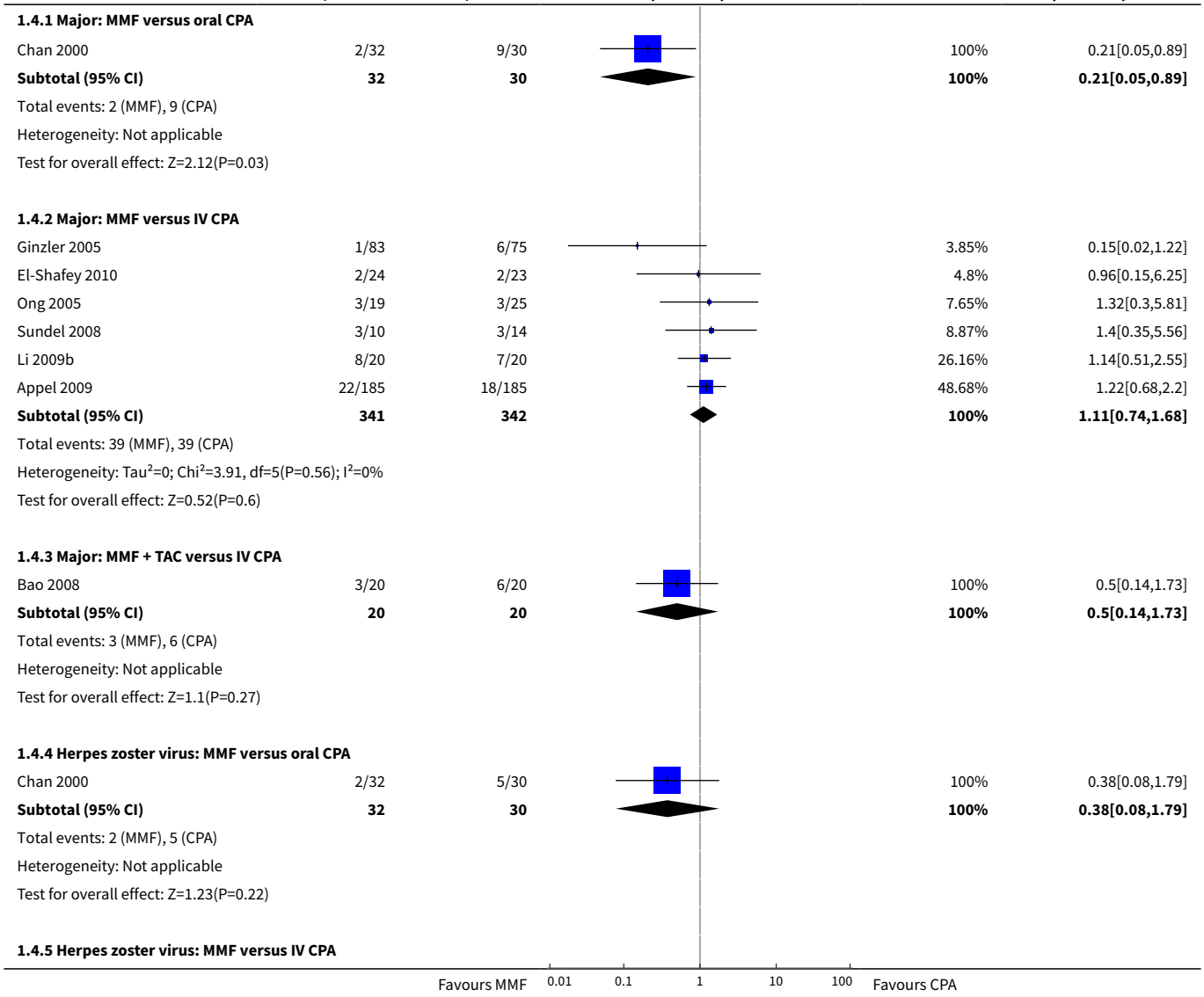


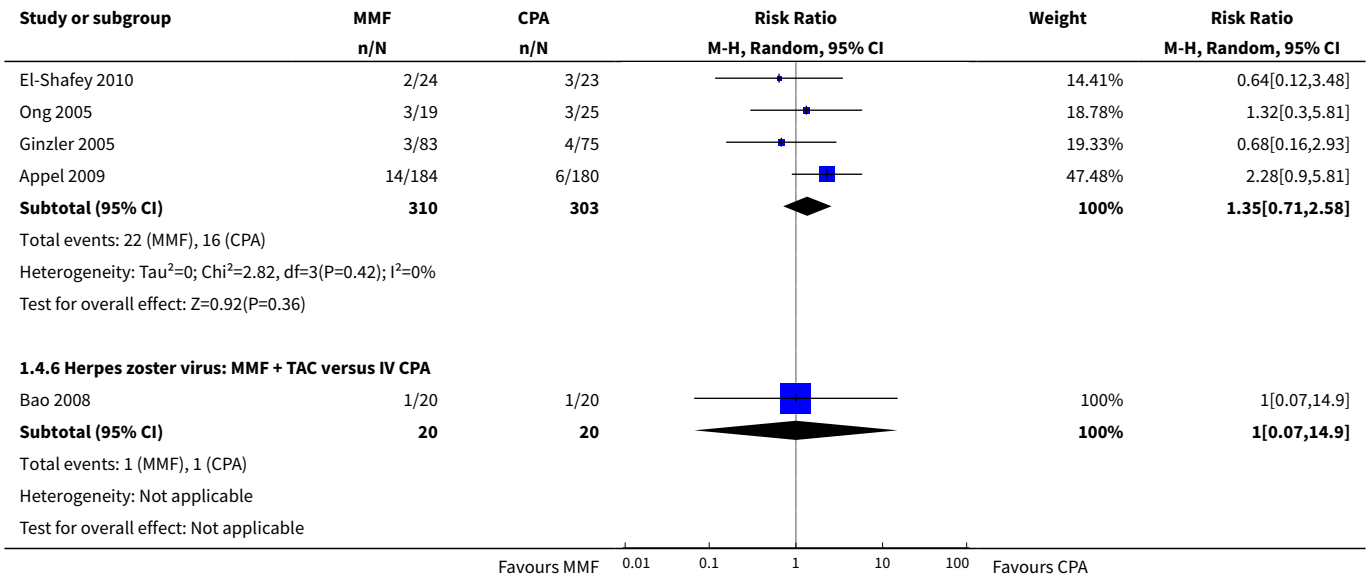
Analysis 1.3. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 3 Stable kidney function.



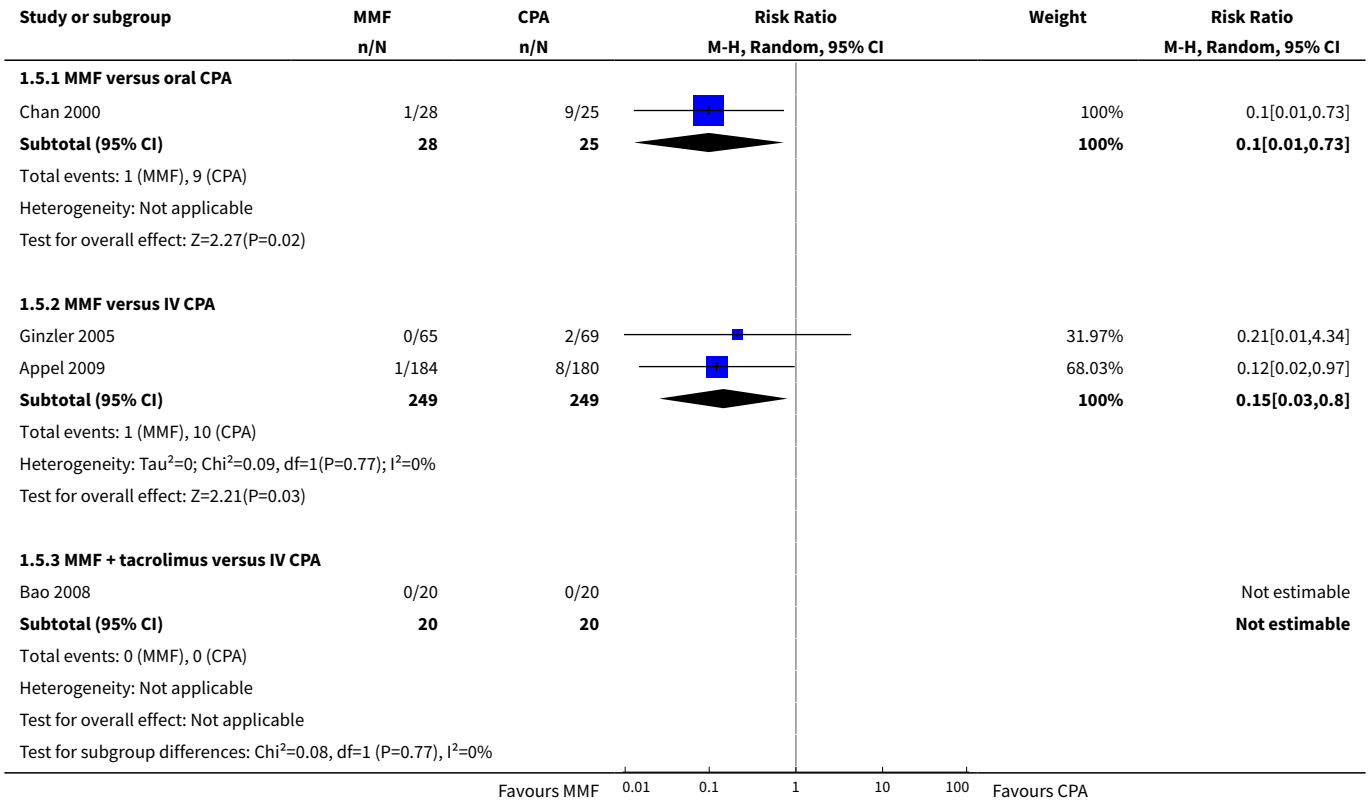


Analysis 1.4. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 4 Infection.





Analysis 1.5. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 5 Ovarian failure.



Analysis 1.6. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 6 Bone toxicity.

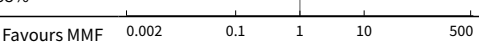
Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chan 2000	0/32	0/30			Not estimable
Total (95% CI)	**32**	**30**			**Not estimable**
Total events: 0 (MMF), 0 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 1.7. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 7 Bladder toxicity.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Appel 2009	0/184	1/180		0%	0.33[0.01,7.95]

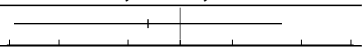
Analysis 1.8. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 8 Alopecia.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 MMF + TAC versus IV CPA					
Bao 2008	4/20	4/20		100%	1[0.29,3.45]
Subtotal (95% CI)	**20**	**20**		**100%**	**1[0.29,3.45]**
Total events: 4 (MMF), 4 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.8.2 MMF versus oral CPA					
Chan 2000	0/32	9/30		100%	0.05[0,0.81]
Subtotal (95% CI)	**32**	**30**		**100%**	**0.05[0,0.81]**
Total events: 0 (MMF), 9 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.1(P=0.04)					
1.8.3 MMF versus IV CPA					
Ginzler 2005	0/83	8/75		18.22%	0.05[0,0.91]
Appel 2009	20/184	64/180		81.78%	0.31[0.19,0.48]
Subtotal (95% CI)	**267**	**255**		**100%**	**0.22[0.06,0.86]**
Total events: 20 (MMF), 72 (CPA)					
Heterogeneity: Tau^2=0.53; Chi^2=1.49, df=1(P=0.22); I^2=33.03%					
Test for overall effect: Z=2.18(P=0.03)					
Test for subgroup differences: Chi^2=4.96, df=1 (P=0.08), I^2=59.68%					



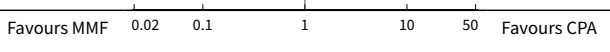
Analysis 1.9. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 9 Malignancy.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Appel 2009	2/184	3/180		0.65[0.11,3.86]



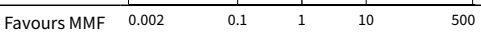
Analysis 1.10. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 10 GI disorders.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Diarrhoea					
El-Shafey 2010	5/24	2/23		10%	2.4[0.52,11.14]
Ginzler 2005	15/83	2/75		11.29%	6.78[1.6,28.66]
Appel 2009	52/184	23/180		78.71%	2.21[1.42,3.45]
Subtotal (95% CI)	**291**	**278**		**100%**	**2.53[1.54,4.16]**
Total events: 72 (MMF), 27 (CPA)					
Heterogeneity: Tau^2=0.03; Chi^2=2.19, df=2(P=0.34); I^2=8.52%					
Test for overall effect: Z=3.65(P=0)					
1.10.2 Vomiting					
Ginzler 2005	23/83	25/75		48.99%	0.83[0.52,1.33]
Appel 2009	25/184	68/180		51.01%	0.36[0.24,0.54]
Subtotal (95% CI)	**267**	**255**		**100%**	**0.54[0.24,1.24]**
Total events: 48 (MMF), 93 (CPA)					
Heterogeneity: Tau^2=0.31; Chi^2=7, df=1(P=0.01); I^2=85.71%					
Test for overall effect: Z=1.45(P=0.15)					
1.10.3 Nausea					
Ginzler 2005	23/83	25/75		100%	0.83[0.52,1.33]
Subtotal (95% CI)	**83**	**75**		**100%**	**0.83[0.52,1.33]**
Total events: 23 (MMF), 25 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					
1.10.4 GI upset					
Chan 2000	3/32	1/30		1.44%	2.81[0.31,25.58]
Bao 2008	2/20	7/20		3.31%	0.29[0.07,1.21]
El-Shafey 2010	4/24	5/23		4.86%	0.77[0.23,2.5]
Ginzler 2005	7/83	10/75		7.92%	0.63[0.25,1.58]
Appel 2009	113/184	120/180		82.47%	0.92[0.79,1.07]
Subtotal (95% CI)	**343**	**328**		**100%**	**0.87[0.66,1.13]**
Total events: 129 (MMF), 143 (CPA)					
Heterogeneity: Tau^2=0.02; Chi^2=4.31, df=4(P=0.37); I^2=7.22%					
Test for overall effect: Z=1.05(P=0.29)					



Analysis 1.11. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 11 Leucopenia.

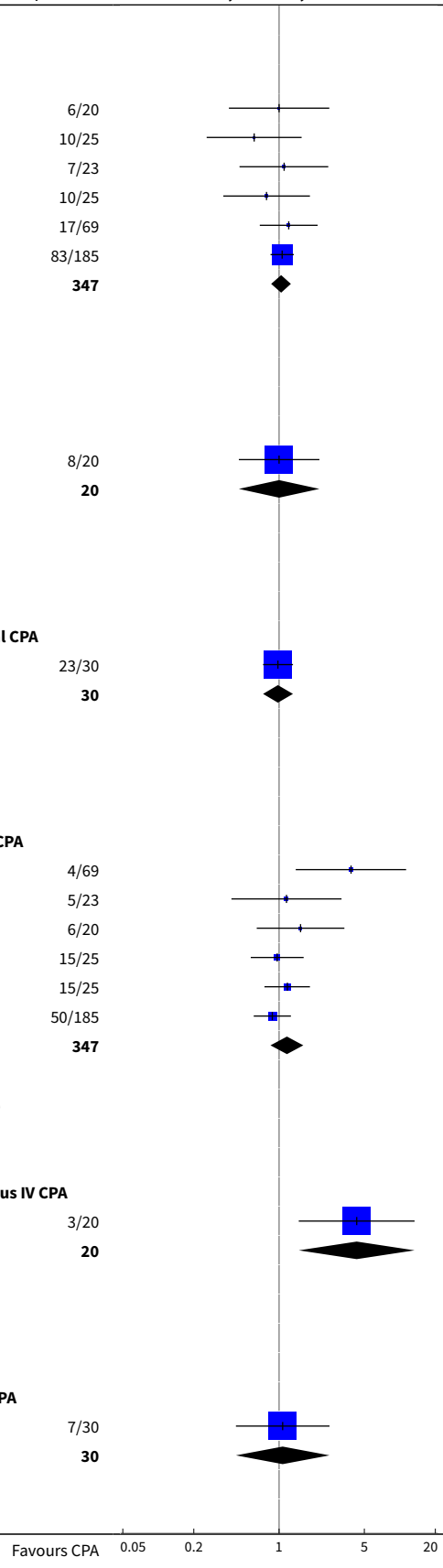
Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 MMF versus oral CPA					
Chan 2000	0/32	8/30		100%	0.06[0,0.92]
Subtotal (95% CI)	**32**	**30**		**100%**	**0.06[0,0.92]**
Total events: 0 (MMF), 8 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.02(P=0.04)					
1.11.2 MMF versus IV CPA					
Li 2009b	1/20	1/20		4.23%	1[0.07,14.9]
El-Shafey 2010	4/24	3/23		13.13%	1.28[0.32,5.1]
Ginzler 2005	5/83	14/75		21.13%	0.32[0.12,0.85]
Ong 2005	7/19	13/25		29.63%	0.71[0.35,1.43]
Appel 2009	11/184	38/180		31.88%	0.28[0.15,0.54]
Subtotal (95% CI)	**330**	**323**		**100%**	**0.49[0.28,0.88]**
Total events: 28 (MMF), 69 (CPA)					
Heterogeneity: Tau^2=0.17; Chi^2=6.81, df=4(P=0.15); I^2=41.28%					
Test for overall effect: Z=2.4(P=0.02)					
1.11.3 MMF + TAC versus IV CPA					
Bao 2008	2/20	4/20		100%	0.5[0.1,2.43]
Subtotal (95% CI)	**20**	**20**		**100%**	**0.5[0.1,2.43]**
Total events: 2 (MMF), 4 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					

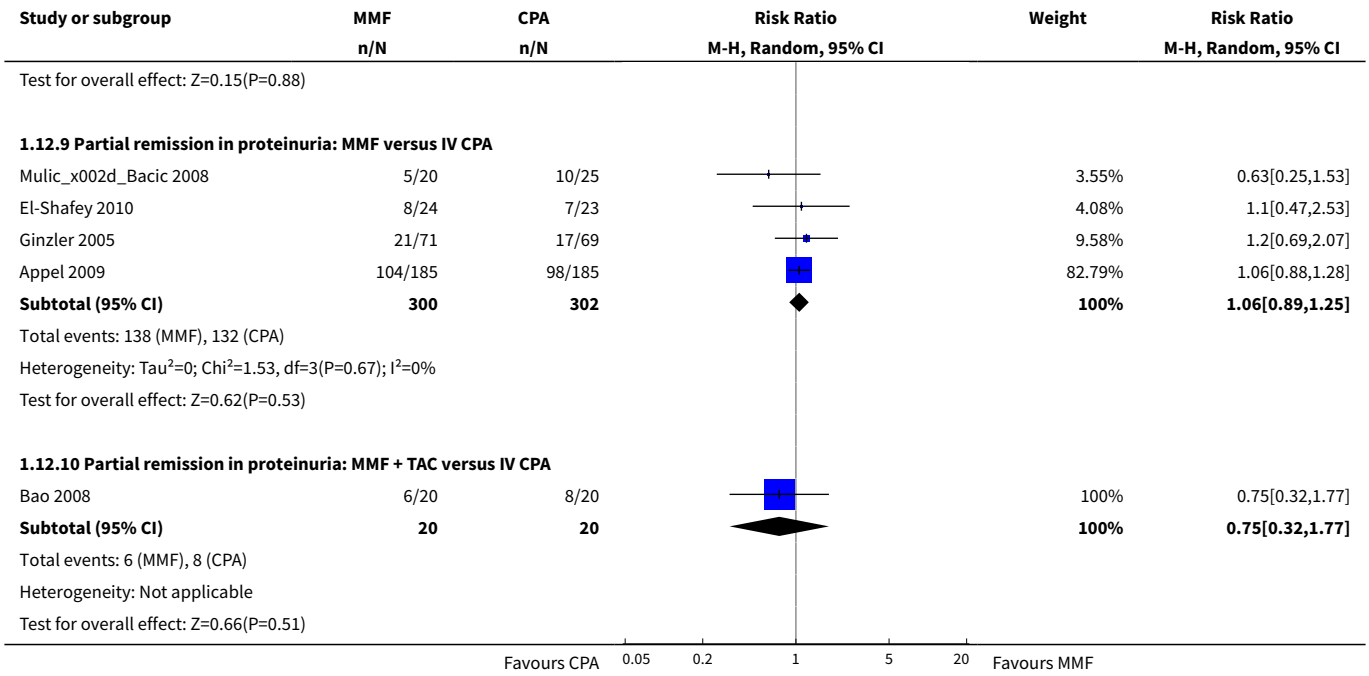


Analysis 1.12. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 12 Remission.

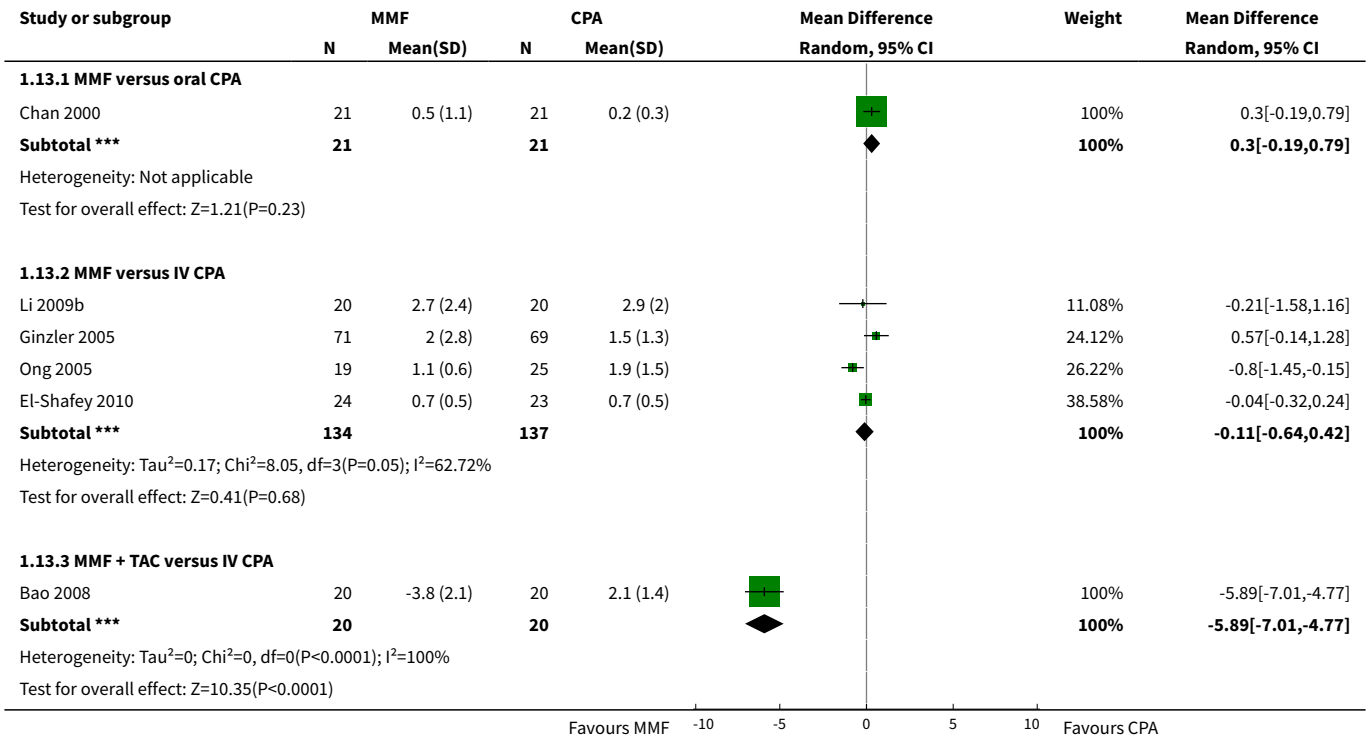
Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Complete renal remission: MMF versus IV CPA					
Ong 2005	5/19	3/25		6.42%	2.19[0.6,8.06]
Ginzler 2005	16/71	4/69		9.64%	3.89[1.37,11.05]
El-Shafey 2010	6/24	5/23		9.71%	1.15[0.41,3.25]
Li 2009b	9/20	6/20		14.59%	1.5[0.66,3.43]
Appel 2009	16/185	15/185		20.47%	1.07[0.54,2.09]
Mulic_x002d_Bacic 2008	14/20	15/25		39.18%	1.17[0.76,1.79]
Subtotal (95% CI)	**339**	**347**		**100%**	**1.39[0.99,1.95]**
Total events: 66 (MMF), 48 (CPA)					
Heterogeneity: Tau^2=0.03; Chi^2=5.91, df=5(P=0.32); I^2=15.33%					
Test for overall effect: Z=1.89(P=0.06)					
1.12.2 Complete renal remission: MMF + TAC versus IV CPA					
Bao 2008	13/20	3/20		100%	4.33[1.45,12.91]
Subtotal (95% CI)	**20**	**20**		**100%**	**4.33[1.45,12.91]**
Total events: 13 (MMF), 3 (CPA)					
Heterogeneity: Not applicable					

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.63(P=0.01)					
1.12.3 Partial renal remission: MMF versus IV CPA					
Li 2009b	6/20	6/20		3.81%	1[0.39,2.58]
Mulic_x002d_Bacic 2008	5/20	10/25		4.23%	0.63[0.25,1.53]
El-Shafey 2010	8/24	7/23		4.87%	1.1[0.47,2.53]
Ong 2005	6/19	10/25		5.11%	0.79[0.35,1.79]
Ginzler 2005	21/71	17/69		11.42%	1.2[0.69,2.07]
Appel 2009	88/185	83/185		70.56%	1.06[0.85,1.32]
Subtotal (95% CI)	**339**	**347**		**100%**	**1.04[0.86,1.25]**
Total events: 134 (MMF), 133 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=1.99, df=5(P=0.85); I^2=0%					
Test for overall effect: Z=0.37(P=0.71)					
1.12.4 Partial renal remission: MMF + TAC versus IV CPA					
Bao 2008	8/20	8/20		100%	1[0.47,2.14]
Subtotal (95% CI)	**20**	**20**		**100%**	**1[0.47,2.14]**
Total events: 8 (MMF), 8 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.12.5 Complete remission in proteinuria: MMF versus oral CPA					
Chan 2000	24/32	23/30		100%	0.98[0.74,1.3]
Subtotal (95% CI)	**32**	**30**		**100%**	**0.98[0.74,1.3]**
Total events: 24 (MMF), 23 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					
1.12.6 Complete remission in proteinuria: MMF versus IV CPA					
Ginzler 2005	16/71	4/69		7.36%	3.89[1.37,11.05]
El-Shafey 2010	6/24	5/23		7.41%	1.15[0.41,3.25]
Li 2009b	9/20	6/20		10.74%	1.5[0.66,3.43]
Ong 2005	11/19	15/25		20.97%	0.96[0.59,1.59]
Mulic_x002d_Bacic 2008	14/20	15/25		24.45%	1.17[0.76,1.79]
Appel 2009	44/185	50/185		29.08%	0.88[0.62,1.25]
Subtotal (95% CI)	**339**	**347**		**100%**	**1.16[0.85,1.58]**
Total events: 100 (MMF), 95 (CPA)					
Heterogeneity: Tau^2=0.05; Chi^2=8.15, df=5(P=0.15); I^2=38.66%					
Test for overall effect: Z=0.93(P=0.35)					
1.12.7 Complete remission in proteinuria: MMF + TAC versus IV CPA					
Bao 2008	13/20	3/20		100%	4.33[1.45,12.91]
Subtotal (95% CI)	**20**	**20**		**100%**	**4.33[1.45,12.91]**
Total events: 13 (MMF), 3 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.63(P=0.01)					
1.12.8 Partial remission in proteinuria: MMF versus oral CPA					
Chan 2000	8/32	7/30		100%	1.07[0.44,2.59]
Subtotal (95% CI)	**32**	**30**		**100%**	**1.07[0.44,2.59]**
Total events: 8 (MMF), 7 (CPA)					
Heterogeneity: Not applicable					





Analysis 1.13. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 13 Daily proteinuria.



Analysis 1.14. Comparison 1 Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA), Outcome 14 Serum creatinine.

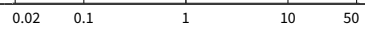
Study or subgroup	MMF N	MMF Mean(SD)	CPA N	CPA Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ong 2005	19	109.5 (168.4)	25	94.4 (61.5)		0%	15.1[-64.37,94.57]
El-Shafey 2010	24	81.7 (29.7)	23	93 (24.6)		0%	-11.27[-26.83,4.29]
Appel 2009	185	130 (70.3)	185	125 (67.6)		0%	5[-9.05,19.05]
Ginzler 2005	83	0.9 (0.3)	75	0.9 (0.3)		99.99%	0.06[-0.02,0.14]
Total ***	**311**		**308**			**100%**	**0.06[-0.02,0.14]**
Heterogeneity: Tau^2=0; Chi^2=2.65, df=3(P=0.45); I^2=0%							
Test for overall effect: Z=1.41(P=0.16)							

Comparison 2. Mycophenolate mofetil (MMF) versus tacrolimus (TAC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	130	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.34, 10.44]
2 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 End-stage kidney disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Renal relapse	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Deterioration in kidney function	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Stable kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Major infection	2	130	Risk Ratio (M-H, Random, 95% CI)	2.11 [0.92, 4.80]
5 Leucopenia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Complete renal remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Complete renal remission	2	109	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.58, 4.41]
6.2 Complete or partial renal remission	2	130	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.13]
6.3 Complete remission in proteinuria	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.50, 1.98]
7 Daily proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Creatinine clearance	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

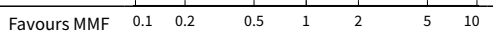
Analysis 2.1. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 1 Mortality.

Study or subgroup	MMF n/N	TAC n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2009b	1/20	1/20		40.42%	1[0.07,14.9]
Mok 2009	3/46	1/44		59.58%	2.87[0.31,26.56]
Total (95% CI)	**66**	**64**		**100%**	**1.87[0.34,10.44]**
Total events: 4 (MMF), 2 (TAC)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					



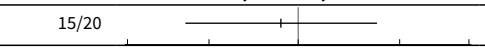
Analysis 2.2. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 2 Adverse renal outcomes.

Study or subgroup	MMF n/N	TAC n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.2.1 End-stage kidney disease				
Mok 2009	2/46	2/44		0.96[0.14,6.5]
2.2.2 Renal relapse				
Mok 2009	10/46	14/44		0.68[0.34,1.37]
2.2.3 Deterioration in kidney function				
Mok 2009	5/46	12/44		0.4[0.15,1.04]



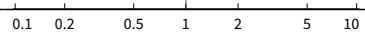
Analysis 2.3. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 3 Stable kidney function.

Study or subgroup	MMF n/N	TAC n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2009b	14/20	15/20		0.93[0.64,1.37]



Analysis 2.4. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 4 Major infection.

Study or subgroup	MMF n/N	TAC n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2009b	8/20	3/20		49.3%	2.67[0.82,8.62]
Mok 2009	7/46	4/44		50.7%	1.67[0.53,5.32]
Total (95% CI)	**66**	**64**		**100%**	**2.11[0.92,4.8]**
Total events: 15 (MMF), 7 (TAC)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=1.77(P=0.08)					

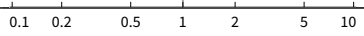


Analysis 2.5. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 5 Leucopenia.

Study or subgroup	MMF n/N	TAC n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2009b	1/20	1/20		0%	1[0.07,14.9]

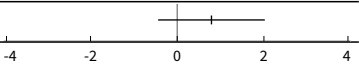
Analysis 2.6. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 6 Complete renal remission.

Study or subgroup	MMF n/N	TAC n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Complete renal remission					
Mok 2009	15/36	5/33		46.03%	2.75[1.12,6.73]
Li 2009b	9/20	9/20		53.97%	1[0.5,1.98]
Subtotal (95% CI)	**56**	**53**		**100%**	**1.59[0.58,4.41]**
Total events: 24 (MMF), 14 (TAC)					
Heterogeneity: Tau^2=0.38; Chi^2=3.29, df=1(P=0.07); I^2=69.58%					
Test for overall effect: Z=0.9(P=0.37)					
2.6.2 Complete or partial renal remission					
Li 2009b	15/20	15/20		19.68%	1[0.7,1.43]
Mok 2009	38/46	38/44		80.32%	0.96[0.8,1.14]
Subtotal (95% CI)	**66**	**64**		**100%**	**0.96[0.82,1.13]**
Total events: 53 (MMF), 53 (TAC)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					
2.6.3 Complete remission in proteinuria					
Li 2009b	9/20	9/20		100%	1[0.5,1.98]
Subtotal (95% CI)	**20**	**20**		**100%**	**1[0.5,1.98]**
Total events: 9 (MMF), 9 (TAC)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



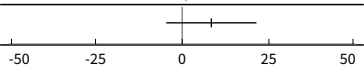
Analysis 2.7. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 7 Daily proteinuria.

Study or subgroup	MMF N	MMF Mean(SD)	TAC N	TAC Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Li 2009b	20	2.7 (2.4)	20	1.9 (1.5)		0.79[-0.44,2.02]



Analysis 2.8. Comparison 2 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 8 Creatinine clearance.

Study or subgroup	MMF		TAC		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Mok 2009	46	88.4 (32)	44	80 (31)		8.4[-4.62,21.42]



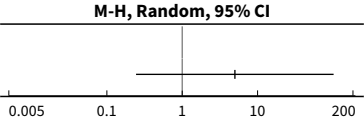
Comparison 3. Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 RTX + MMF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Stable kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 RTX + MMF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Major Infection	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 RTX + MMF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 RTX + CPA versus RTX	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Herpes zoster	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 RTX + CPA versus RTX	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Leucopenia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 RTX + MMF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Remission	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Complete renal response: RTX + MMF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Complete renal response: RTX + CPA versus RTX	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.3 Partial renal response: RTX + MMF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 Partial renal response: RTX + CPA versus RTX	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.5 Complete remission in proteinuria: RTX + MMF versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Daily proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Creatinine clearance	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

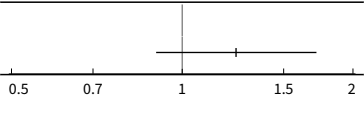
Analysis 3.1. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 1 Mortality.

Study or subgroup	RTX + MMF n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 RTX + MMF versus MMF				
LUNAR Study	2/72	0/72		5[0.24,102.35]



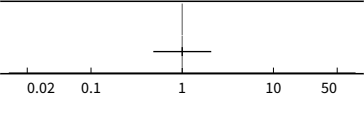
Analysis 3.2. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 2 Stable kidney function.

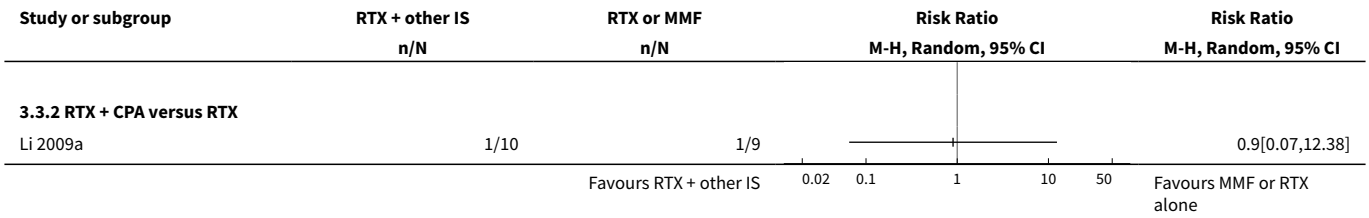
Study or subgroup	RTX + MMF n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.2.1 RTX + MMF versus MMF				
LUNAR Study	41/72	33/72		1.24[0.9,1.71]



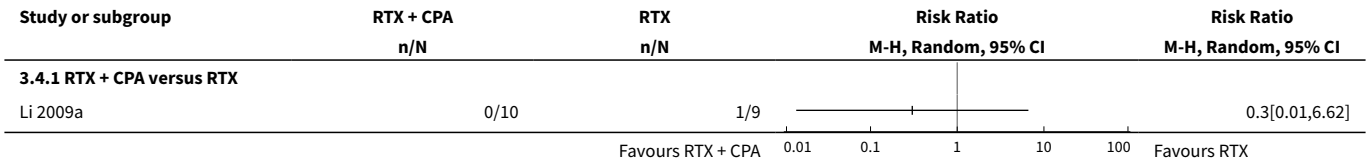
Analysis 3.3. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 3 Major Infection.

Study or subgroup	RTX + other IS n/N	RTX or MMF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.3.1 RTX + MMF versus MMF				
LUNAR Study	12/72	12/72		1[0.48,2.08]

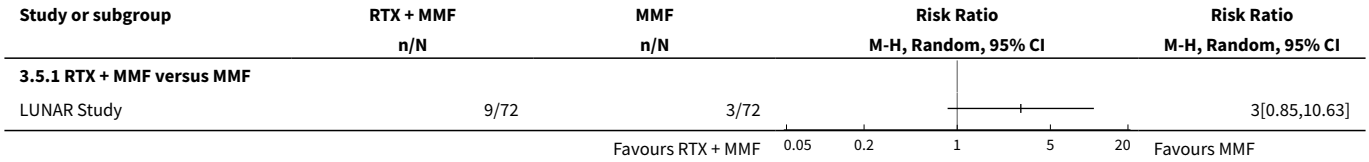




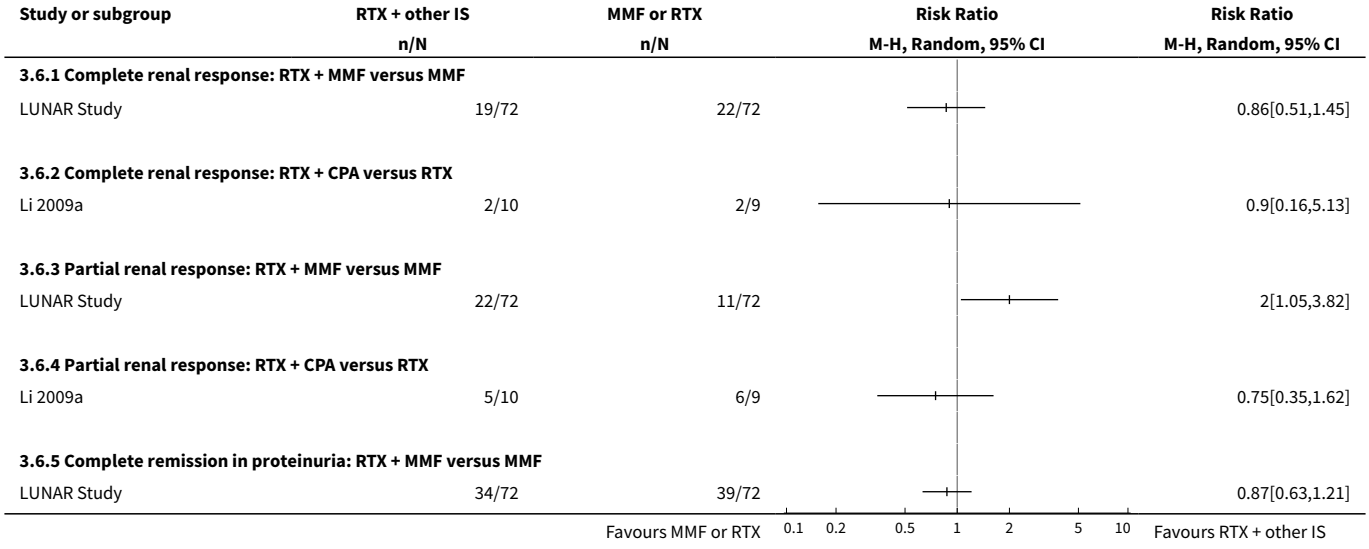
Analysis 3.4. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 4 Herpes zoster.



Analysis 3.5. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 5 Leucopenia.

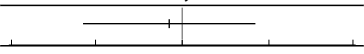


Analysis 3.6. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 6 Remission.



Analysis 3.7. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 7 Daily proteinuria.

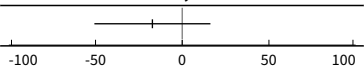
Study or subgroup	RTX + other IS		MMF or RTX		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Li 2009a	10	3.8 (2.1)	9	4.1 (2.3)		-0.3[-2.29,1.69]



Favours RTX + other IS — Favours RTX or MMF

Analysis 3.8. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 8 Creatinine clearance.

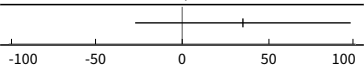
Study or subgroup	RTX + other IS		MMF or RTX		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Li 2009a	10	64.2 (27.8)	9	81.4 (43.9)		-17.2[-50.66,16.26]



Favours MMF or RTX — Favours RTX + other IS

Analysis 3.9. Comparison 3 Rituximab (RTX) + other immunosuppressive agent (IS) versus mycophenolate mofetil (MMF) or RTX alone, Outcome 9 Serum creatinine.

Study or subgroup	RTX + other IS		MMF or RTX		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Li 2009a	10	134.8 (84.7)	9	99.8 (50.9)		35[-27.14,97.14]



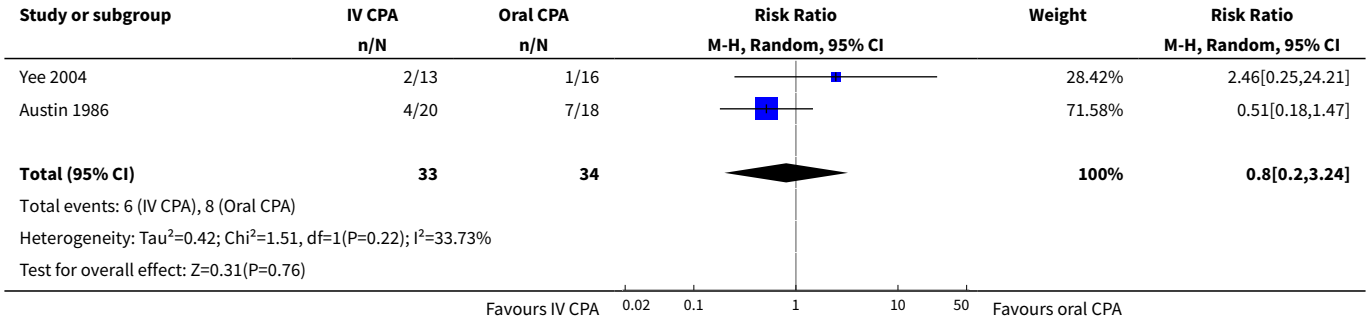
Favours RTX + other IS — Favours MMF or RTX

Comparison 4. IV versus oral cyclophosphamide (CPA)

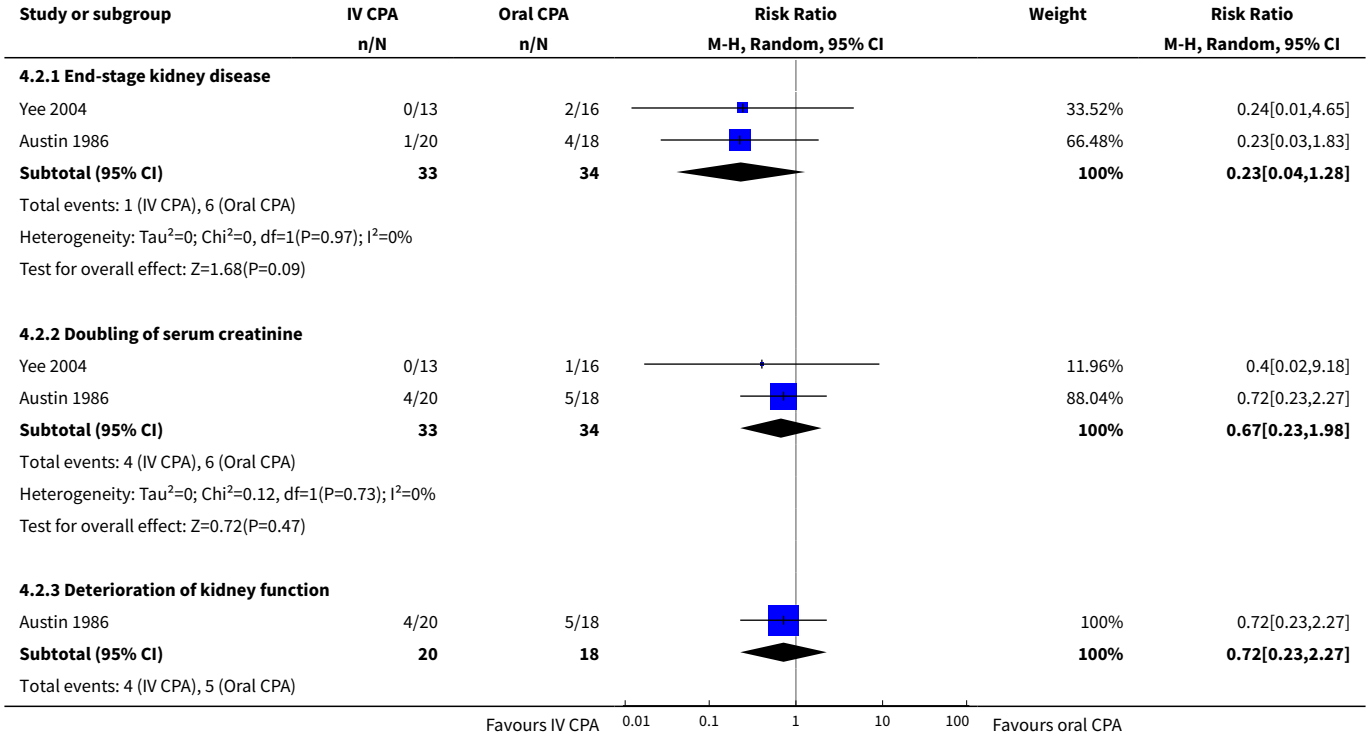
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mortality	2	67	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.20, 3.24]
2 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 End-stage kidney disease	2	67	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.28]
2.2 Doubling of serum creatinine	2	67	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.23, 1.98]
2.3 Deterioration of kidney function	1	38	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.23, 2.27]
3 Stable kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Major infection	2	67	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.47, 2.90]
4.2 Herpes zoster virus	1	38	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.28, 2.04]

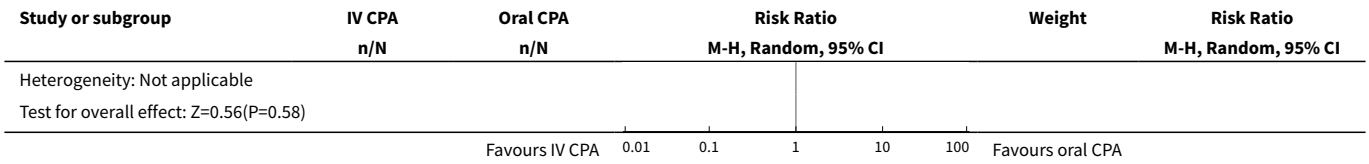
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Ovarian failure	2	56	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.37, 1.30]
6 Bladder toxicity	2	67	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.83]
7 Malignancy	2	67	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.41, 4.96]
8 GI upset	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 1 Mortality.

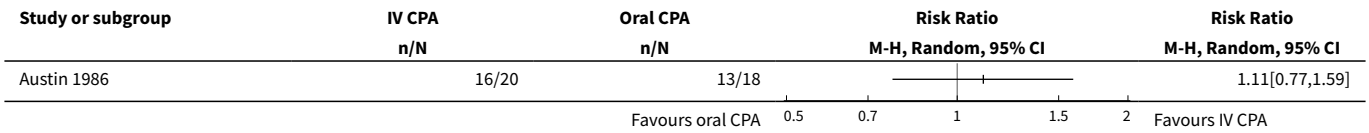


Analysis 4.2. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 2 Adverse renal outcomes.

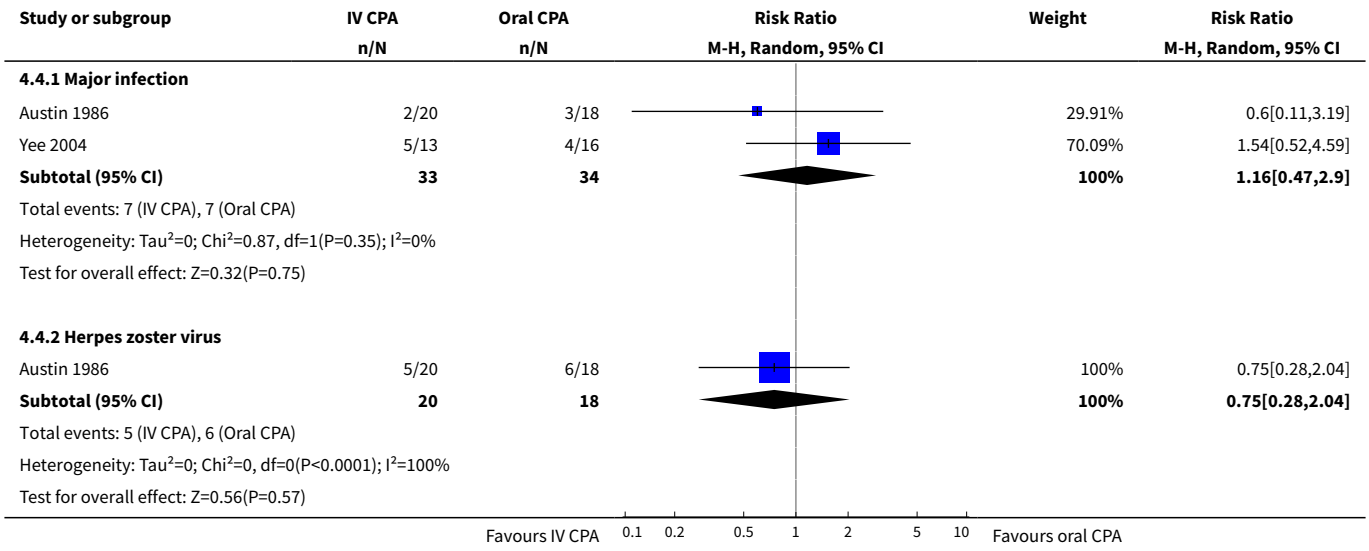




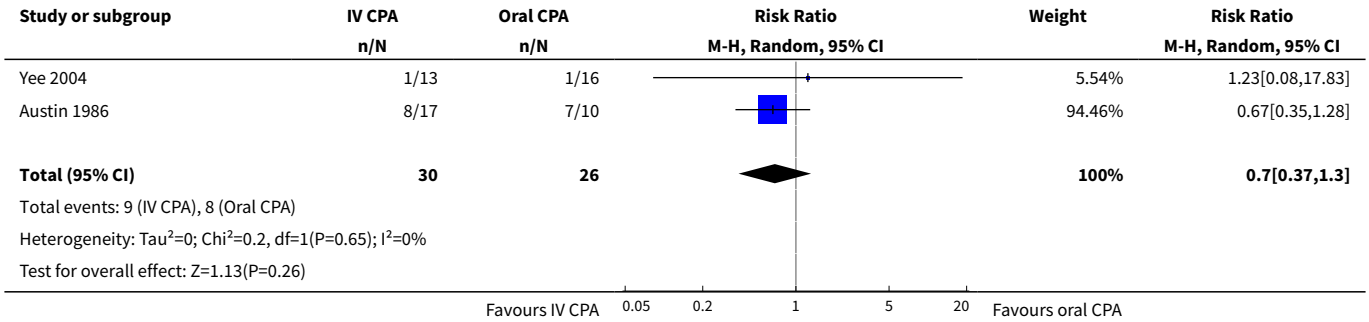
Analysis 4.3. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 3 Stable kidney function.



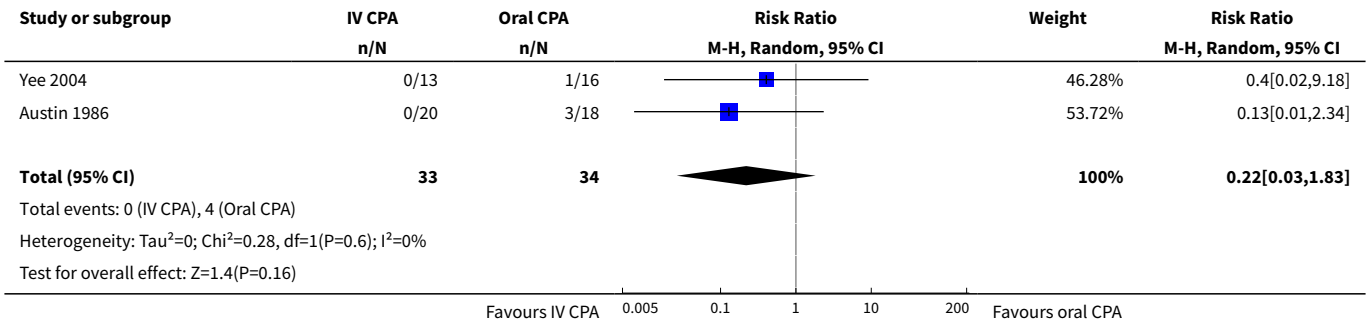
Analysis 4.4. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 4 Infection.



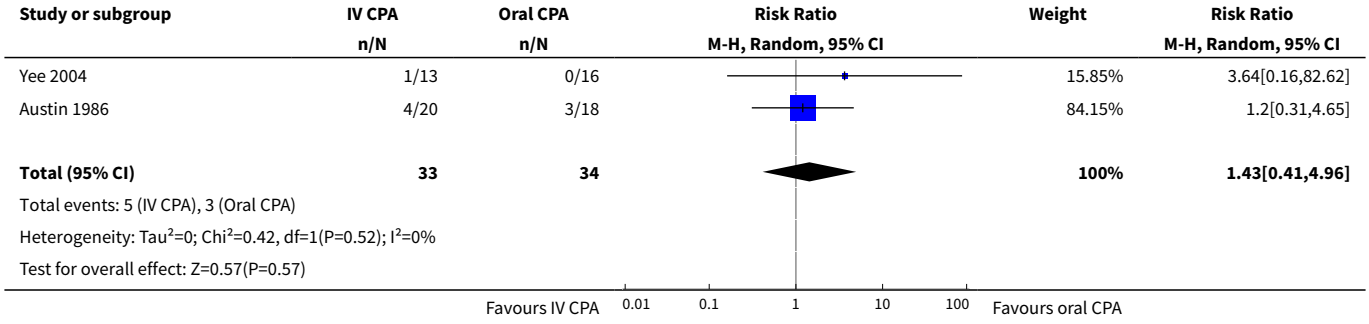
Analysis 4.5. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 5 Ovarian failure.



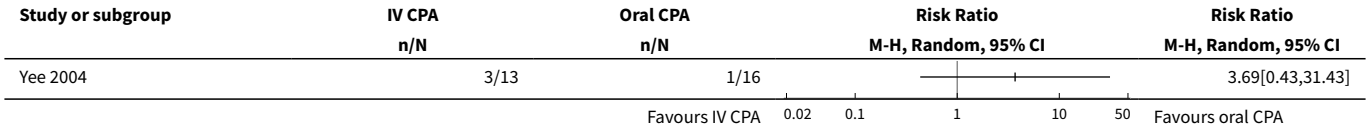
Analysis 4.6. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 6 Bladder toxicity.



Analysis 4.7. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 7 Malignancy.



Analysis 4.8. Comparison 4 IV versus oral cyclophosphamide (CPA), Outcome 8 GI upset.

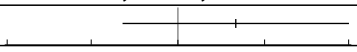


Comparison 5. Standard versus reduced dose oral corticosteroid

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Complete renal remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Partial renal remission	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Standard versus reduced dose oral corticosteroid, Outcome 1 Mortality.

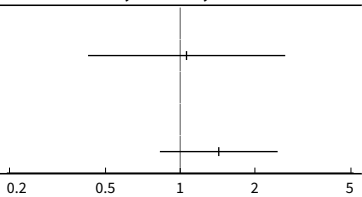
Study or subgroup	Standard dose n/N	Reduced dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MyLupus Study 2010	2/42	0/39		0%	4.65[0.23,93.95]



Favours standard dose — Favours reduced dose

Analysis 5.2. Comparison 5 Standard versus reduced dose oral corticosteroid, Outcome 2 Remission.

Study or subgroup	Standard dose n/N	Reduced dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.2.1 Complete renal remission				
MyLupus Study 2010	8/42	7/39		1.06[0.42,2.65]
5.2.2 Partial renal remission				
MyLupus Study 2010	20/42	13/39		1.43[0.83,2.47]



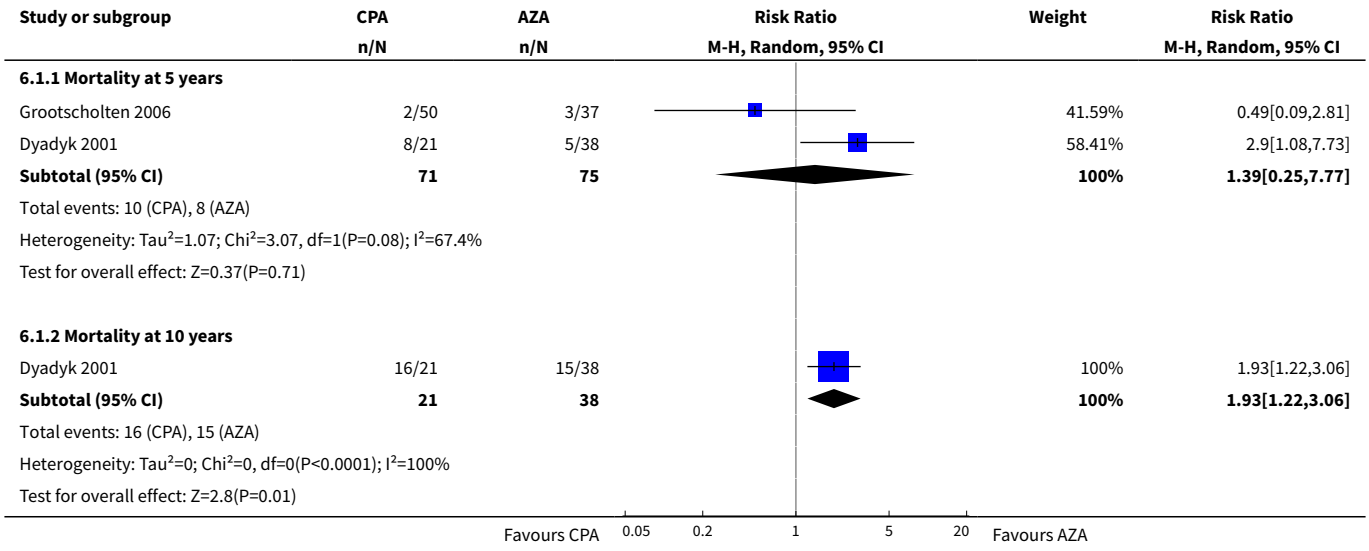
Favours reduced dose — Favours standard dose

Comparison 6. Cyclophosphamide (CPA) versus azathioprine (AZA)

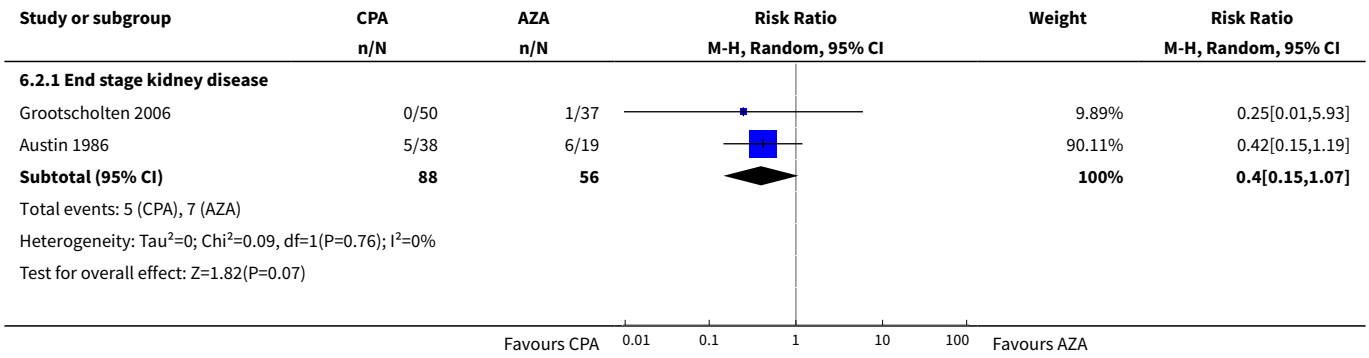
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mortality at 5 years	2	146	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.25, 7.77]
1.2 Mortality at 10 years	1	59	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.22, 3.06]
2 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 End stage kidney disease	2	144	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.15, 1.07]
2.2 Renal relapse	1	87	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.64]
2.3 Doubling of serum creatinine	2	144	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.95]
2.4 Deterioration of kidney function	1	30	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.18, 2.42]
3 Stable kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Major infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Herpes zoster virus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Ovarian failure	2	126	Risk Ratio (M-H, Random, 95% CI)	2.11 [0.59, 7.53]

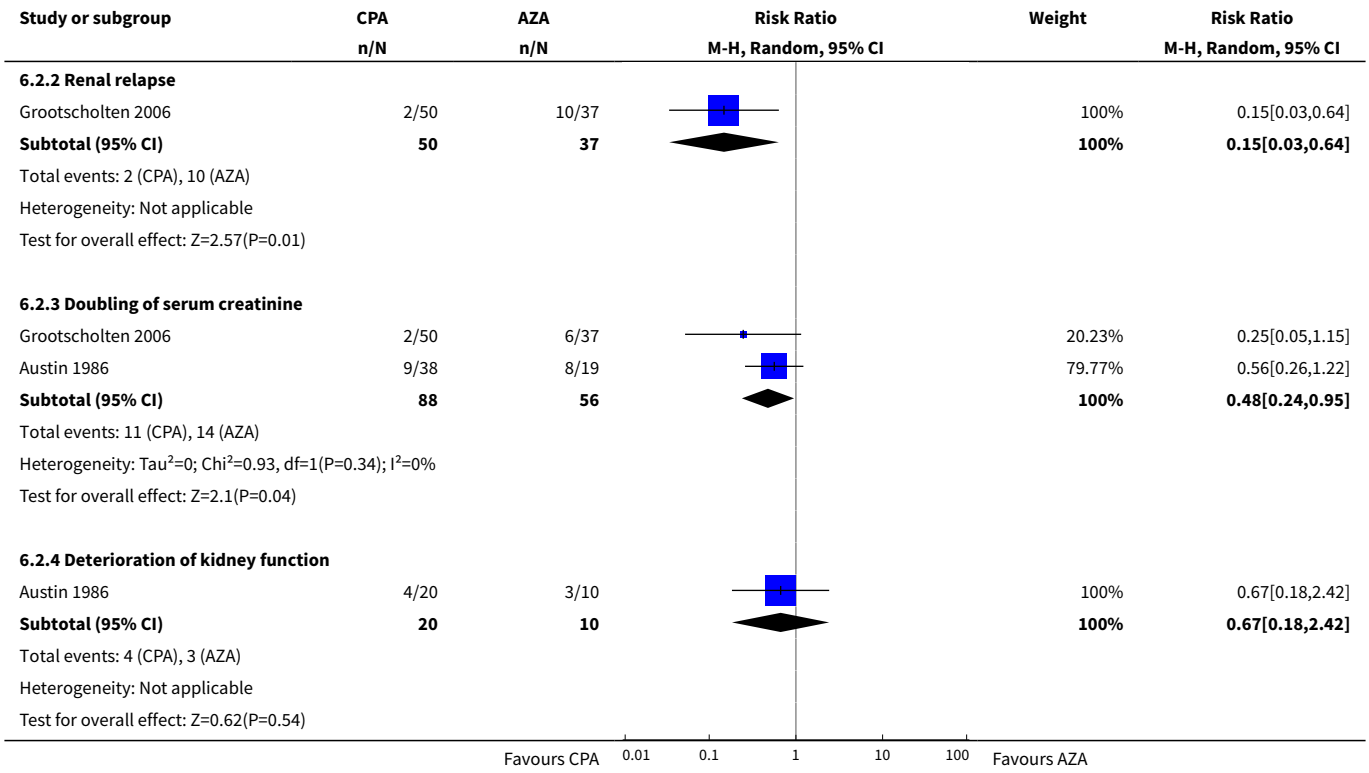
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Bone toxicity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Bladder toxicity	2	144	Risk Ratio (M-H, Random, 95% CI)	3.59 [0.19, 66.14]
8 Malignancy	2	144	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.63]
9 Remission in proteinuria	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Complete	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Partial	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 1 Mortality.

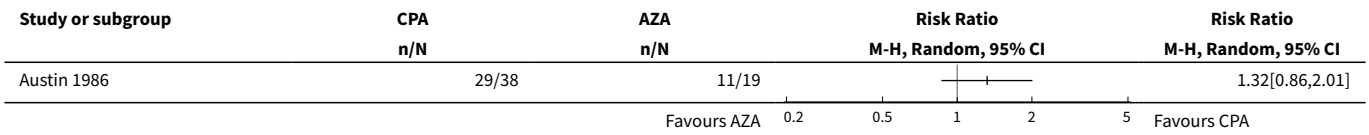


Analysis 6.2. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 2 Adverse renal outcomes.

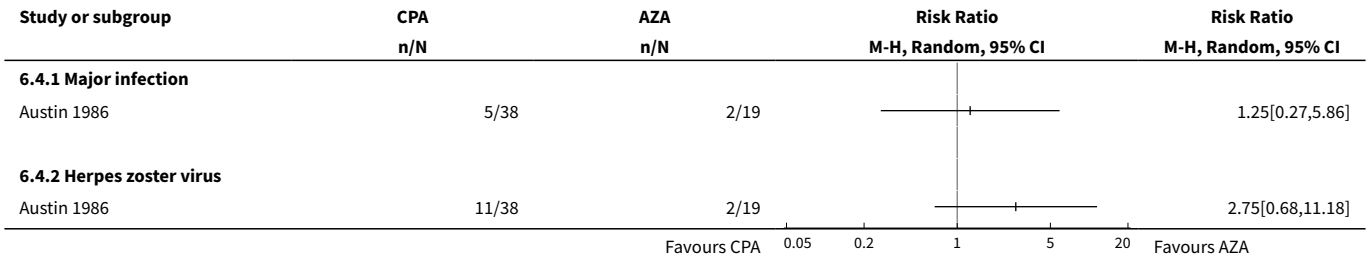




Analysis 6.3. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 3 Stable kidney function.



Analysis 6.4. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 4 Infection.

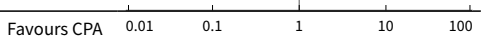


Analysis 6.5. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 5 Ovarian failure.

Study or subgroup	CPA n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Grootscholten 2006	2/44	2/37		33.06%	0.84[0.12,5.68]
Austin 1986	15/27	3/18		66.94%	3.33[1.12,9.88]
Total (95% CI)	**71**	**55**		**100%**	**2.11[0.59,7.53]**
Total events: 17 (CPA), 5 (AZA)					
Heterogeneity: Tau²=0.32; Chi²=1.51, df=1(P=0.22); I²=33.7%					
Test for overall effect: Z=1.16(P=0.25)					

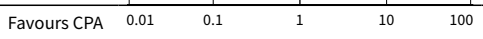
Analysis 6.6. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 6 Bone toxicity.

Study or subgroup	CPA n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Grootscholten 2006	0/50	0/37		Not estimable



Analysis 6.7. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 7 Bladder toxicity.

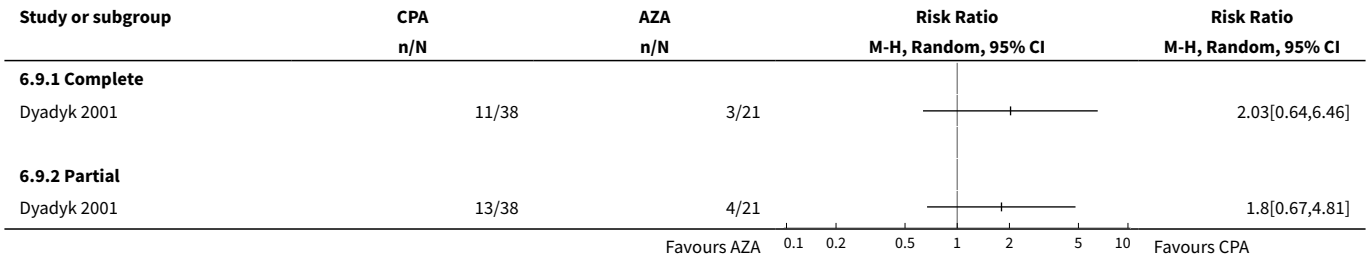
Study or subgroup	CPA n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Grootscholten 2006	0/50	0/37			Not estimable
Austin 1986	3/38	0/19		100%	3.59[0.19,66.14]
Total (95% CI)	**88**	**56**		**100%**	**3.59[0.19,66.14]**
Total events: 3 (CPA), 0 (AZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					



Analysis 6.8. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 8 Malignancy.

Study or subgroup	CPA n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Grootscholten 2006	0/50	1/37		22.35%	0.25[0.01,5.93]
Austin 1986	3/38	2/19		77.65%	0.75[0.14,4.12]
Total (95% CI)	**88**	**56**		**100%**	**0.59[0.13,2.63]**
Total events: 3 (CPA), 3 (AZA)					
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.54); I²=0%					
Test for overall effect: Z=0.7(P=0.48)					

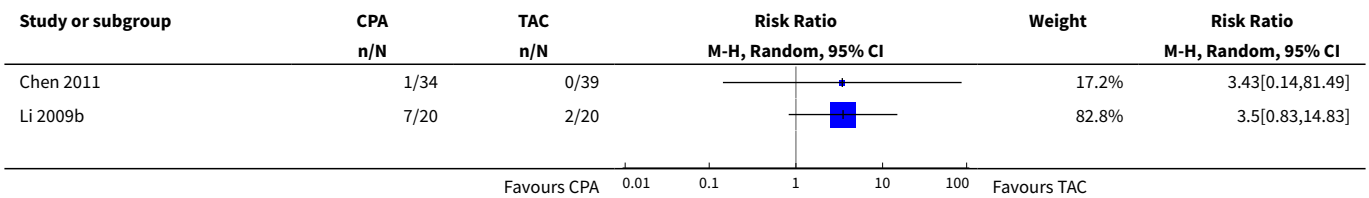
Analysis 6.9. Comparison 6 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 9 Remission in proteinuria.

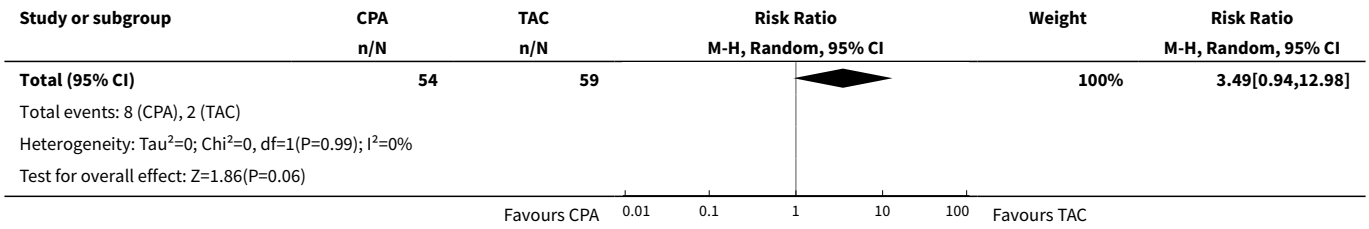


Comparison 7. Cyclophosphamide (CPA) versus tacrolimus (TAC)

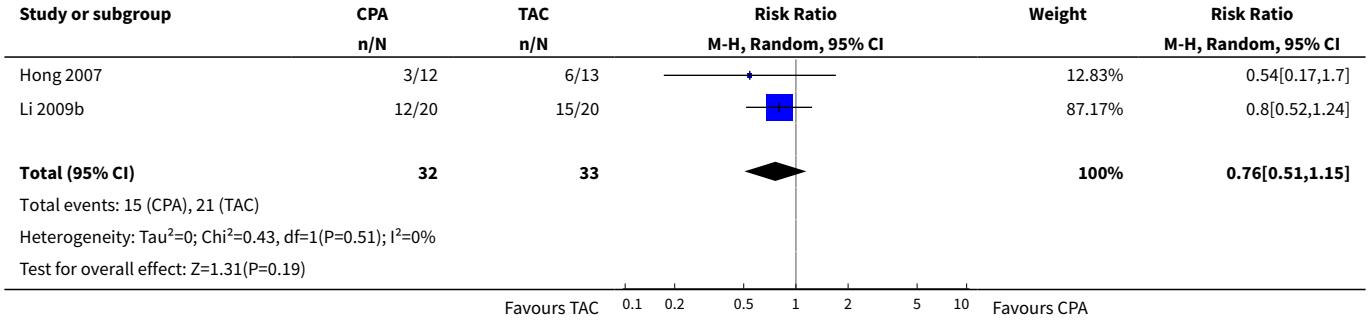
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	113	Risk Ratio (M-H, Random, 95% CI)	3.49 [0.94, 12.98]
2 Stable kidney function	2	65	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.51, 1.15]
3 Major infection	2	65	Risk Ratio (M-H, Random, 95% CI)	2.30 [0.79, 6.74]
4 Ovarian failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Alopecia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 GI symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Leucopenia	2	113	Risk Ratio (M-H, Random, 95% CI)	3.40 [0.26, 44.54]
8 Remission	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Complete renal remission	3	138	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.06]
8.2 Partial renal remission	3	138	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.72, 1.68]
8.3 Complete remission in proteinuria	2	65	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.21]
9 Daily proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 1 Mortality.

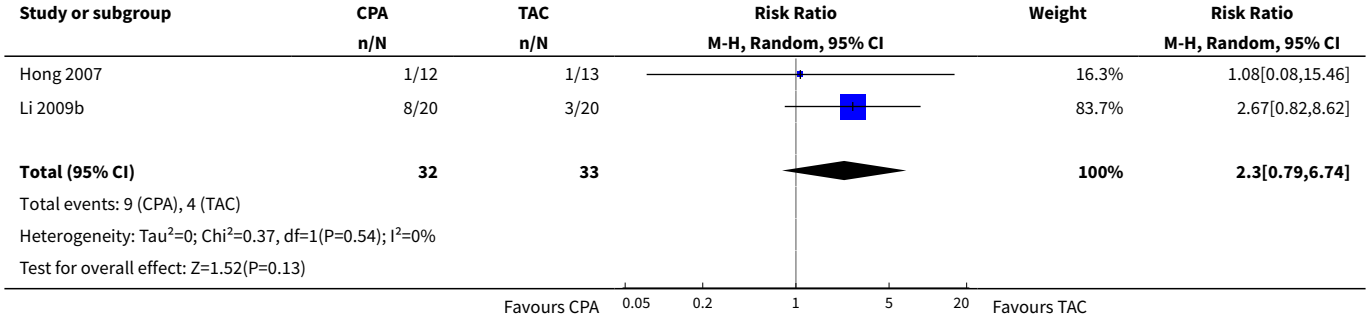




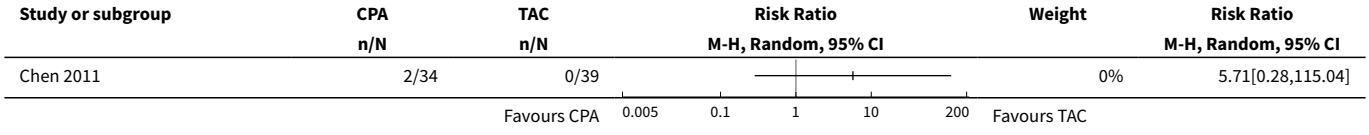
Analysis 7.2. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 2 Stable kidney function.



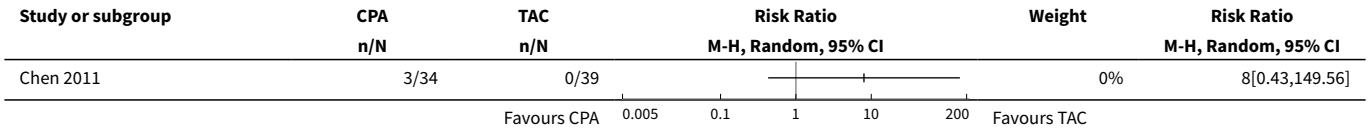
Analysis 7.3. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 3 Major infection.



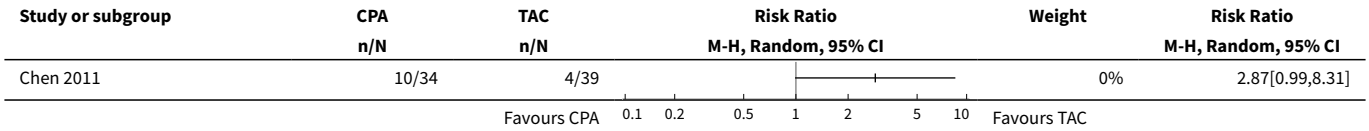
Analysis 7.4. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 4 Ovarian failure.



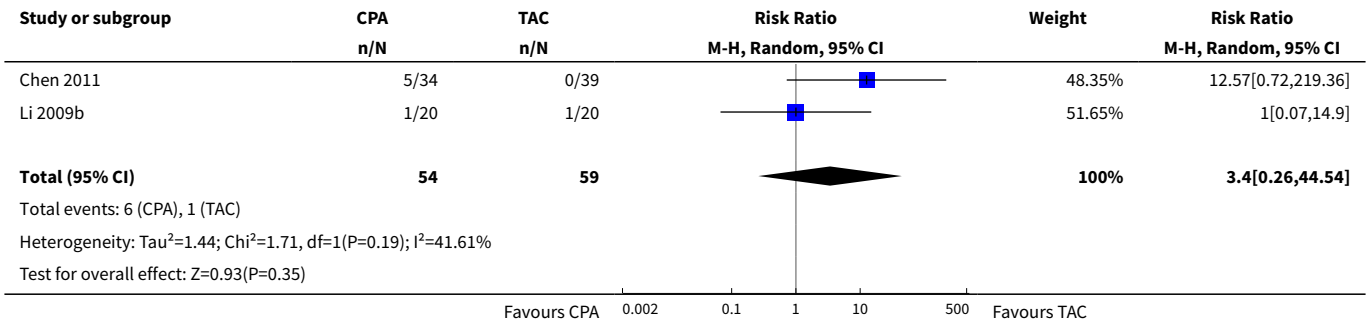
Analysis 7.5. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 5 Alopecia.



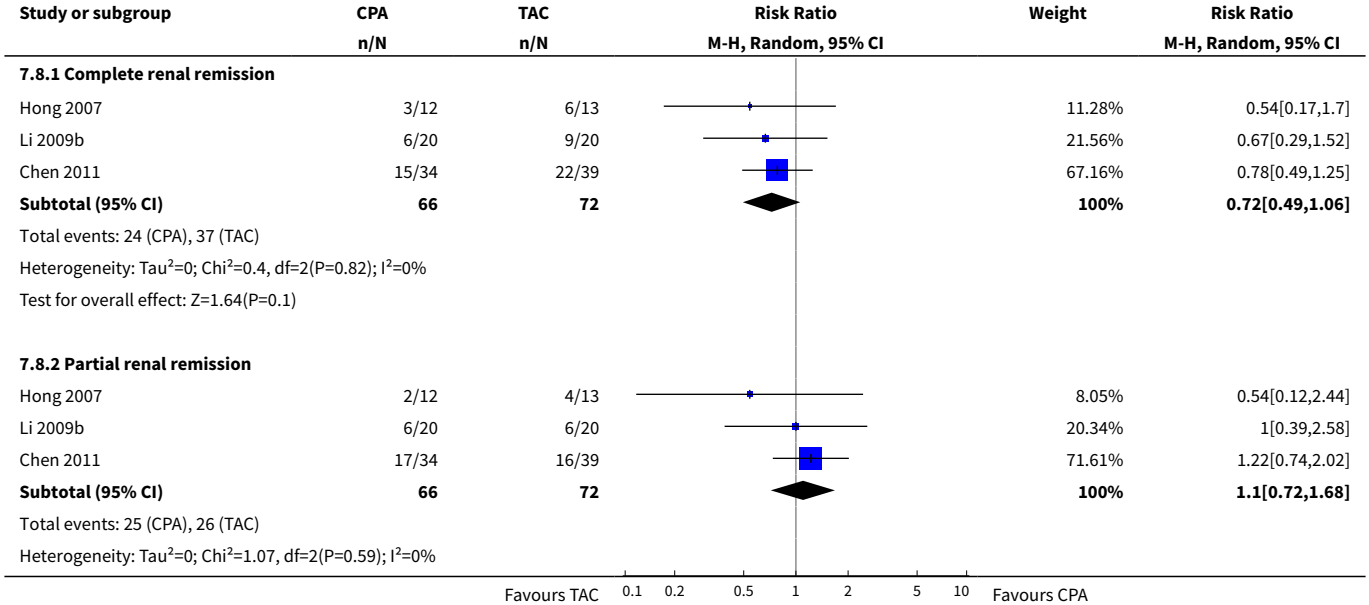
Analysis 7.6. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 6 GI symptoms.

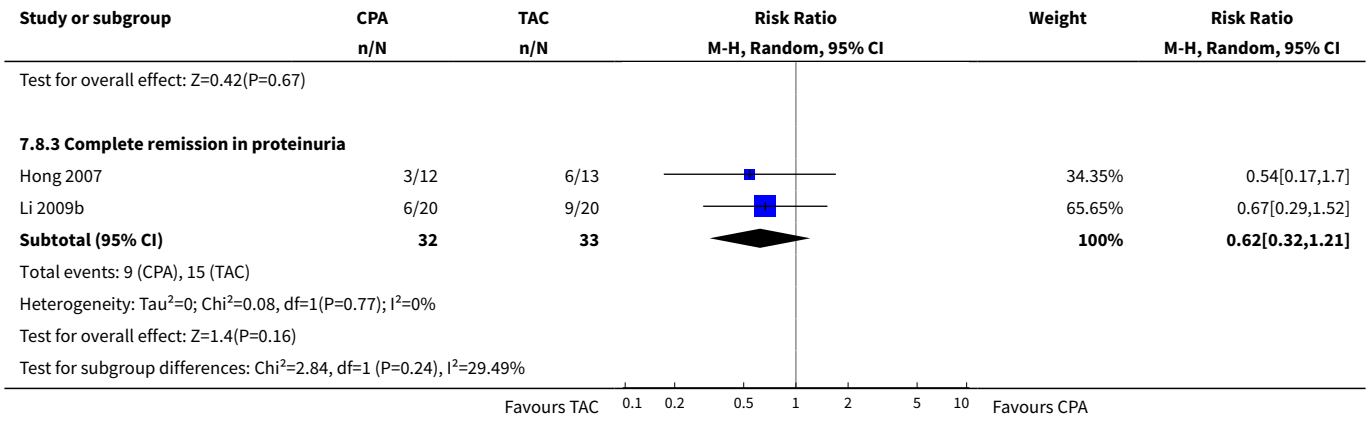


Analysis 7.7. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 7 Leucopenia.

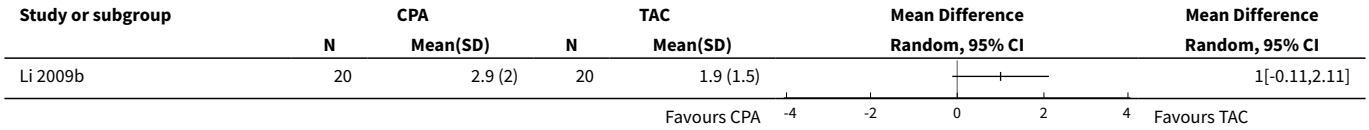


Analysis 7.8. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 8 Remission.





Analysis 7.9. Comparison 7 Cyclophosphamide (CPA) versus tacrolimus (TAC), Outcome 9 Daily proteinuria.

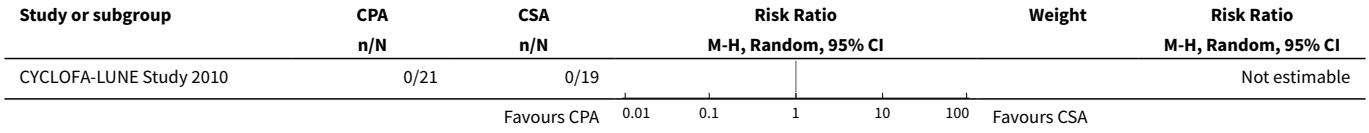


Comparison 8. Cyclophosphamide (CPA) versus cyclosporin A (CSA)

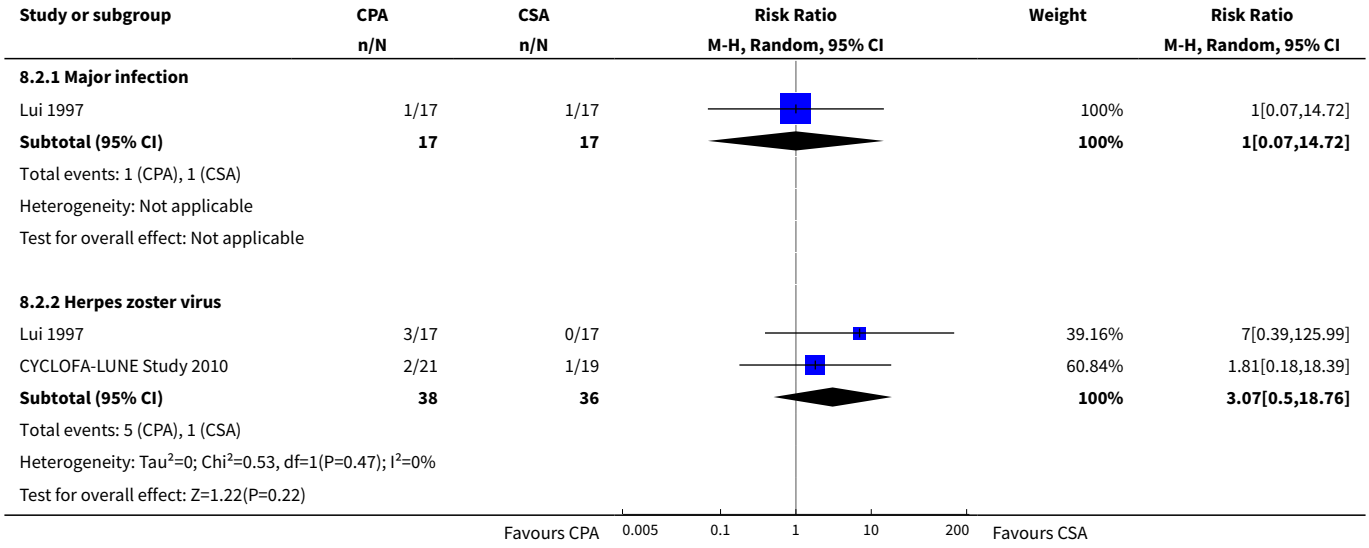
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Major infection	1	34	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.72]
2.2 Herpes zoster virus	2	74	Risk Ratio (M-H, Random, 95% CI)	3.07 [0.50, 18.76]
3 Ovarian failure	2	74	Risk Ratio (M-H, Random, 95% CI)	9.00 [1.03, 78.91]
4 Alopecia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Leucopenia	2	74	Risk Ratio (M-H, Random, 95% CI)	4.29 [0.42, 43.95]
6 Remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Complete renal remission	2	74	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.97]
6.2 Partial renal remission	1	34	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.20, 20.04]
7 Daily proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 9 months	1		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
7.2 18 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 9 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 18 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

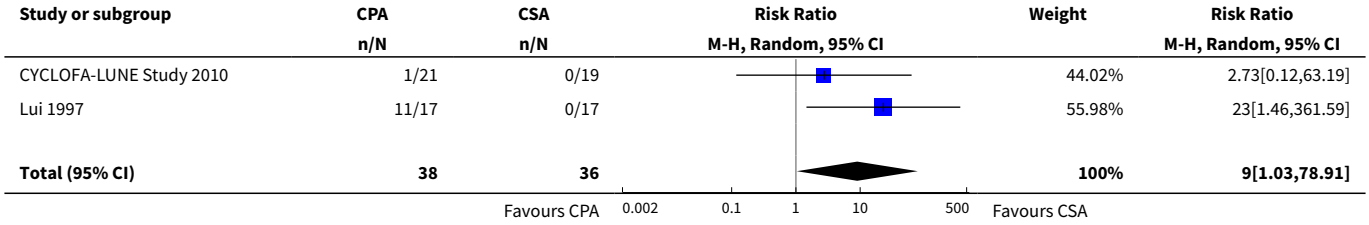
Analysis 8.1. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 1 Mortality.

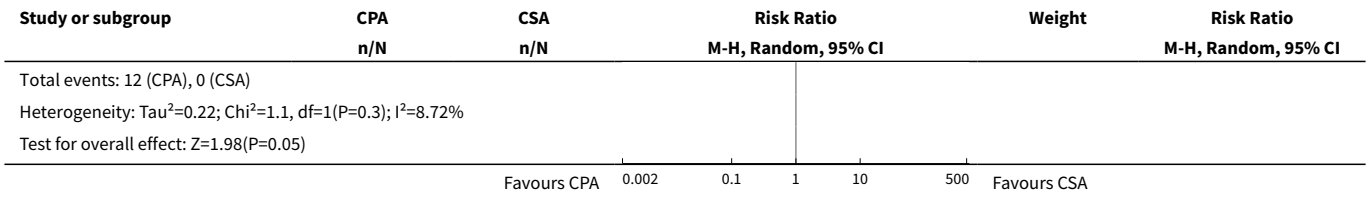


Analysis 8.2. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 2 Infection.

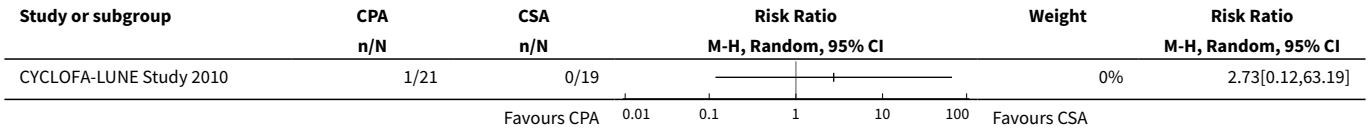


Analysis 8.3. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 3 Ovarian failure.

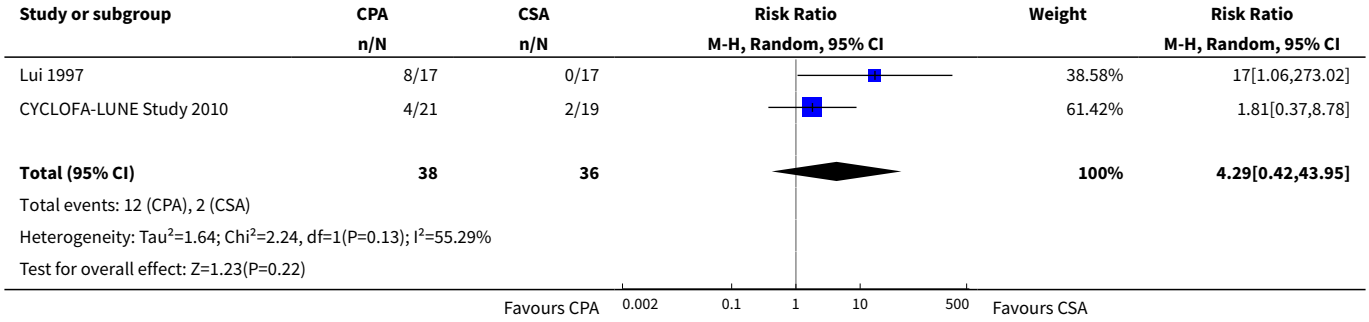




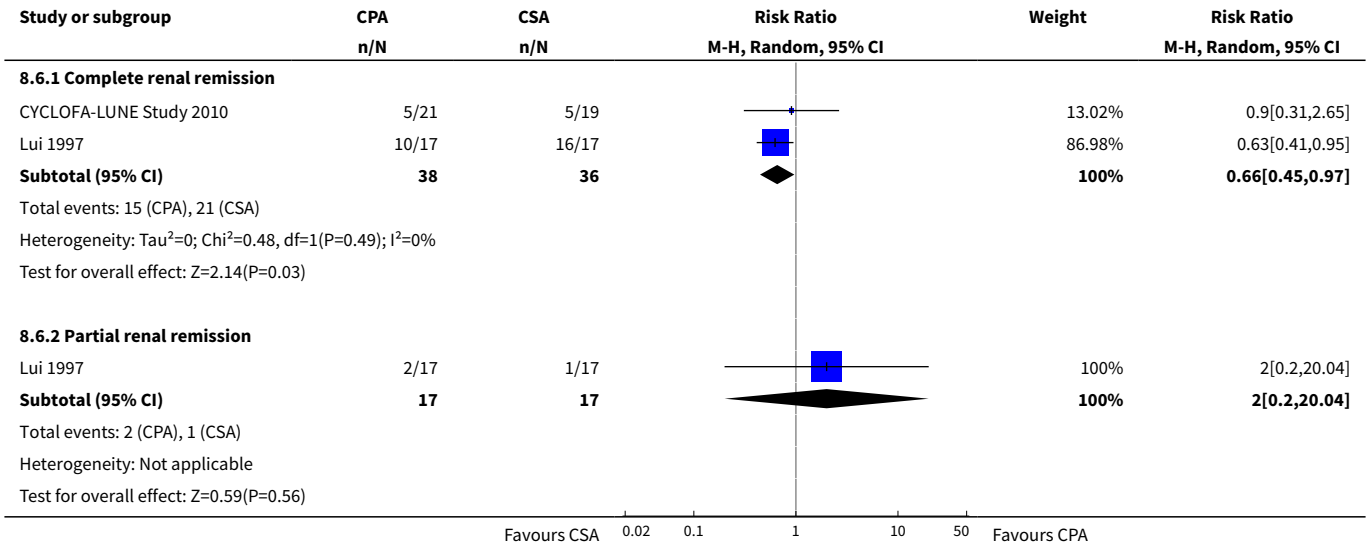
Analysis 8.4. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 4 Alopecia.



Analysis 8.5. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 5 Leucopenia.

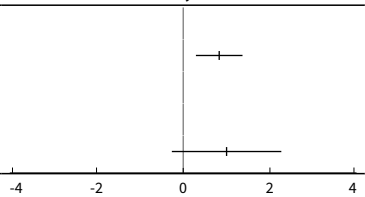


Analysis 8.6. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 6 Remission.



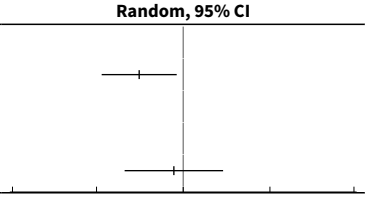
Analysis 8.7. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 7 Daily proteinuria.

Study or subgroup	CPA N	CPA Mean(SD)	CSA N	CSA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
8.7.1 9 months						
CYCLOFA-LUNE Study 2010	21	1 (1.2)	19	0.2 (0.2)		0.83[0.29,1.37]
8.7.2 18 months						
CYCLOFA-LUNE Study 2010	21	1.4 (2.8)	19	0.4 (0.9)		1[-0.26,2.26]



Analysis 8.8. Comparison 8 Cyclophosphamide (CPA) versus cyclosporin A (CSA), Outcome 8 Serum creatinine.

Study or subgroup	CPA N	CPA Mean(SD)	CSA N	CSA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
8.8.1 9 months						
CYCLOFA-LUNE Study 2010	21	75.5 (13.9)	19	88.2 (20.1)		-12.7[-23.52,-1.88]
8.8.2 18 months						
CYCLOFA-LUNE Study 2010	21	84 (21.6)	19	86.7 (24)		-2.7[-16.9,11.5]

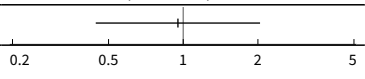


Comparison 9. IV versus oral corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Renal relapse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 IV versus oral corticosteroids, Outcome 1 Renal relapse.

Study or subgroup	IV n/N	Oral n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Barron 1982	4/7	9/15		0.95[0.44,2.04]



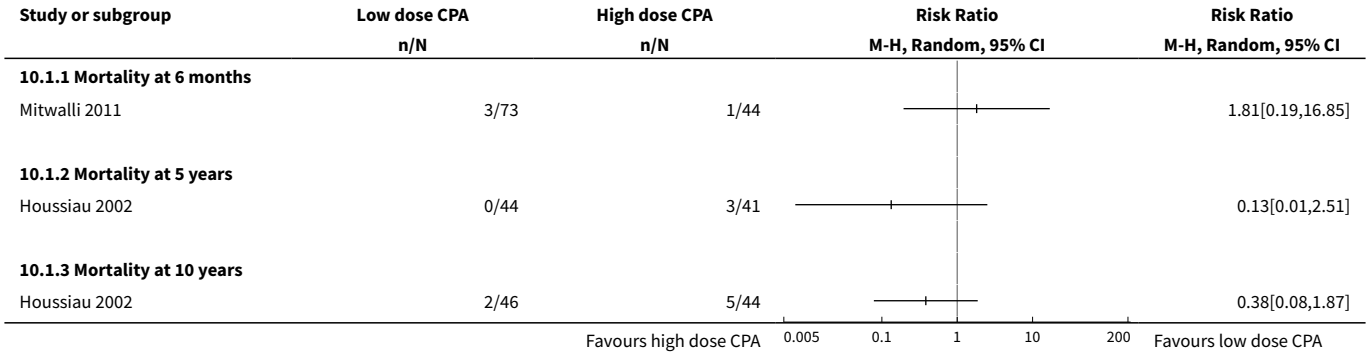
Comparison 10. High versus low dose cyclophosphamide (CPA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

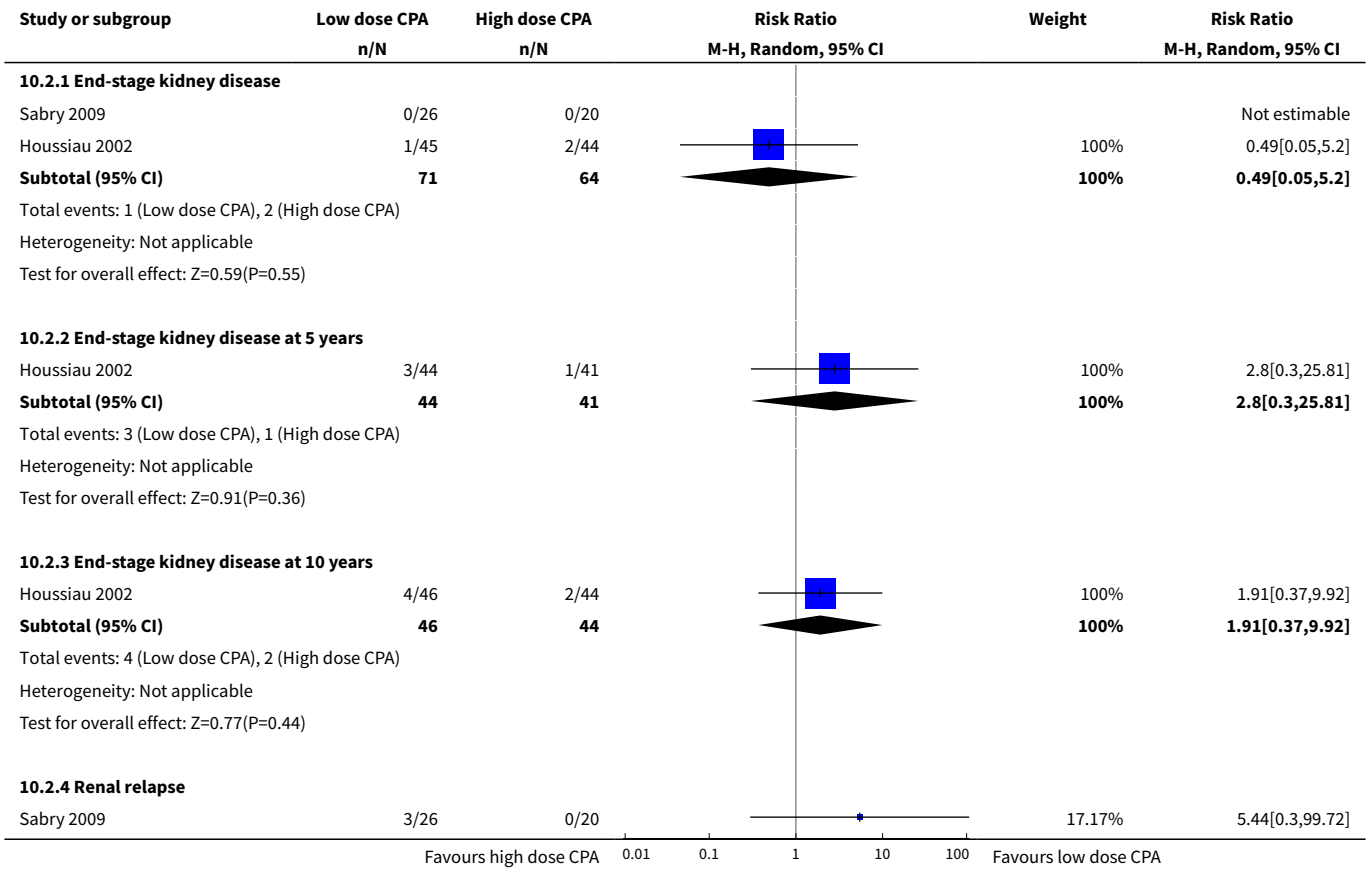
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Mortality at 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Mortality at 5 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Mortality at 10 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 End-stage kidney disease	2	135	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.05, 5.20]
2.2 End-stage kidney disease at 5 years	1	85	Risk Ratio (M-H, Random, 95% CI)	2.80 [0.30, 25.81]
2.3 End-stage kidney disease at 10 years	1	90	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.37, 9.92]
2.4 Renal relapse	2	136	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.35, 4.85]
2.5 Doubling of serum creatinine	2	135	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.02]
2.6 Doubling of serum creatinine at 6 years	1	85	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 1.04]
2.7 Doubling of serum creatinine at 10 years	1	90	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.26, 2.42]
3 Stable kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 At 3 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 At 5 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Infection	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Major infection	3	252	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.73, 3.25]
4.2 Herpes zoster virus	1	89	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.50, 11.94]
5 Ovarian failure	3	252	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.03, 4.59]
6 Bone toxicity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Malignancy	2	206	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.09, 23.31]
8 Leucopenia	2	206	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.34, 5.95]
9 Remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Complete renal remission	2	192	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.94, 2.20]
9.2 Partial renal remission	2	192	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.15]
10 Daily proteinuria	2	121	Mean Difference (IV, Random, 95% CI)	0.13 [-1.06, 1.32]

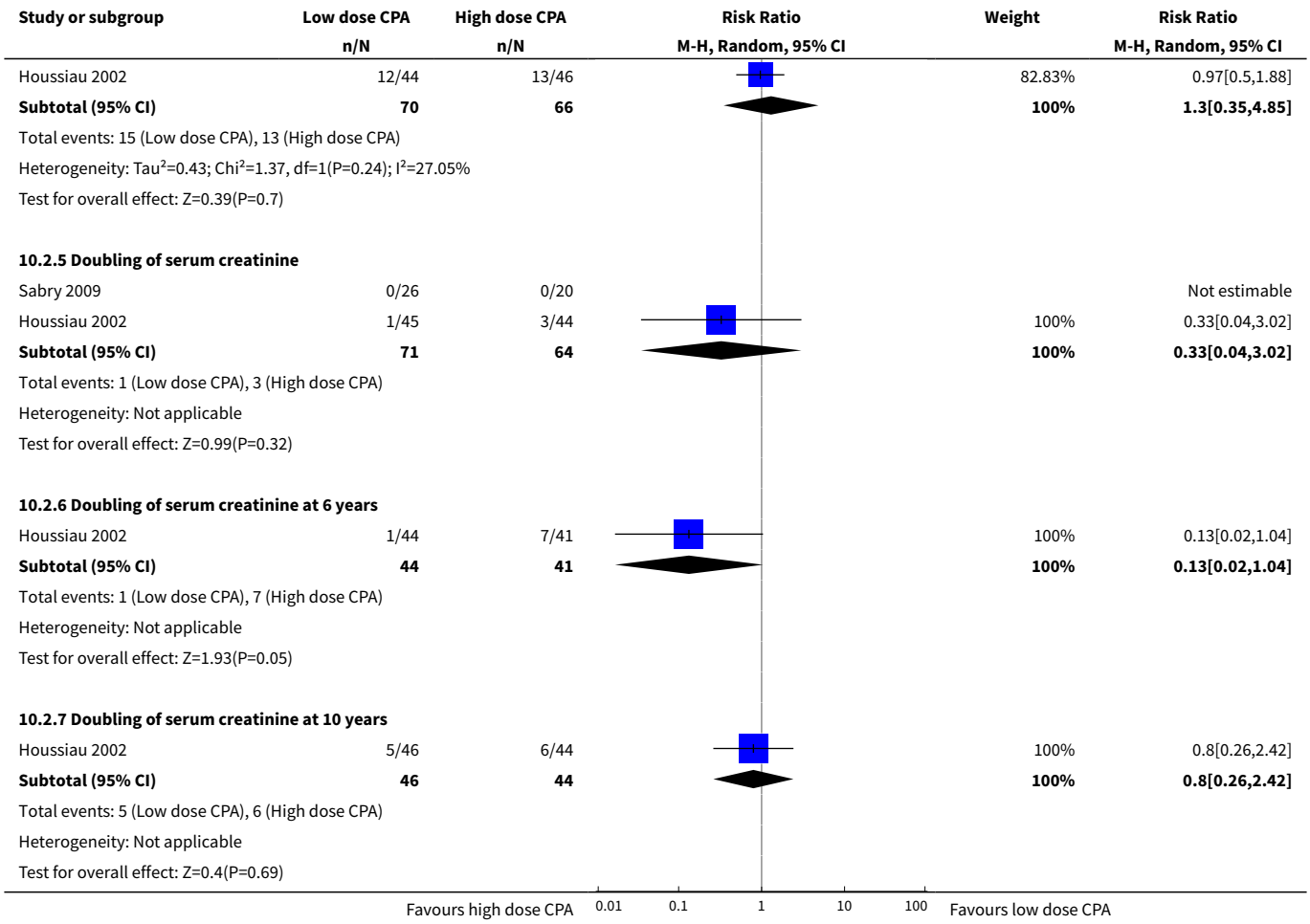
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11 Serum creatinine	2	130	Mean Difference (IV, Random, 95% CI)	0.0 [-0.50, 0.50]

Analysis 10.1. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 1 Mortality.

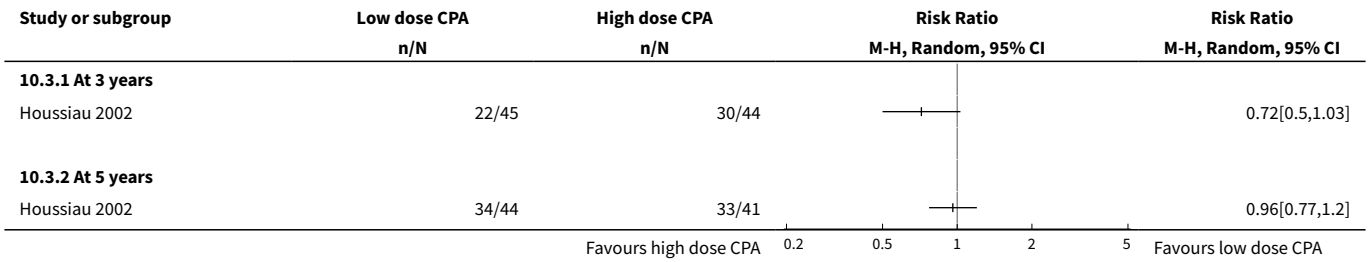


Analysis 10.2. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 2 Adverse renal outcomes.

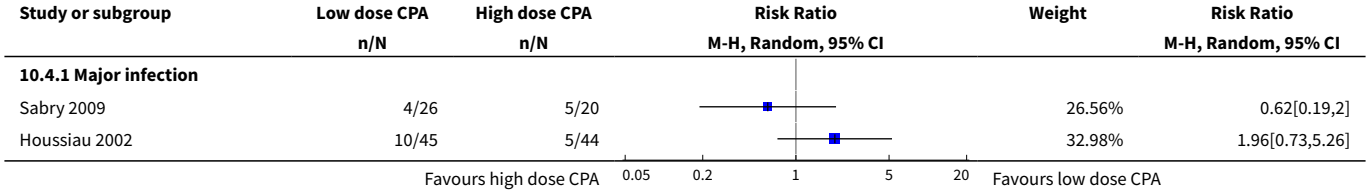


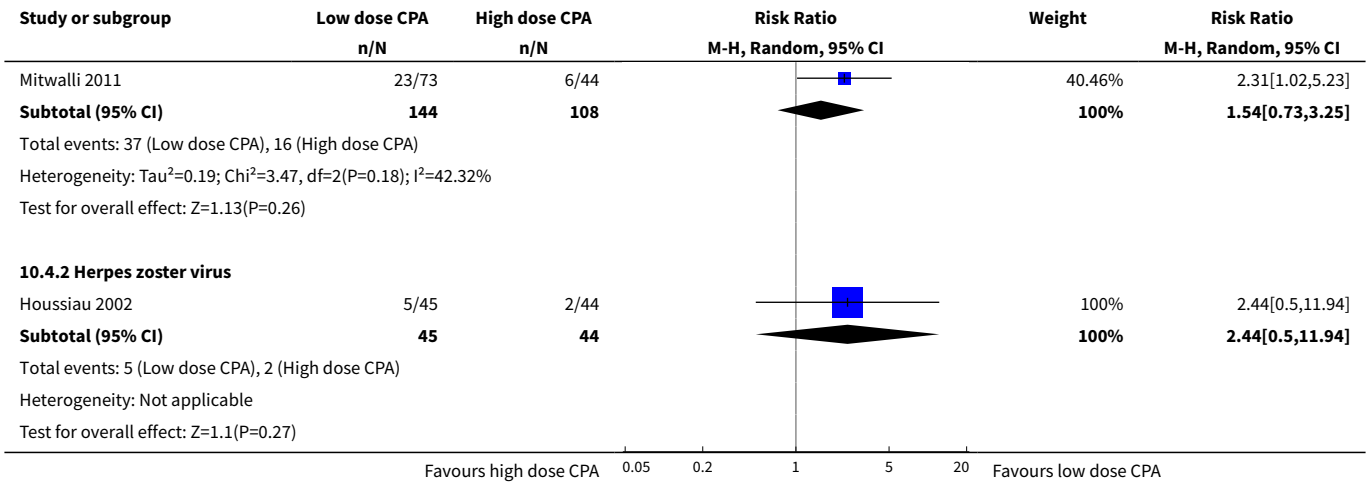


Analysis 10.3. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 3 Stable kidney function.

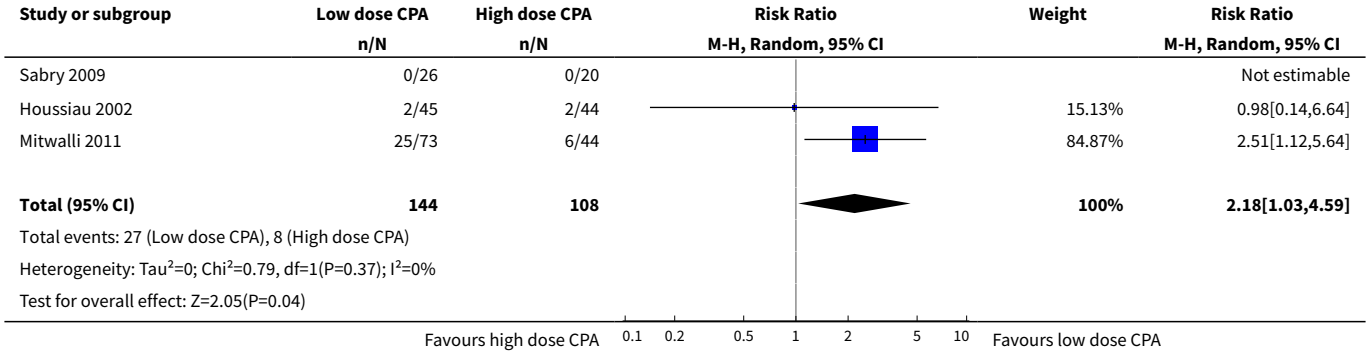


Analysis 10.4. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 4 Infection.

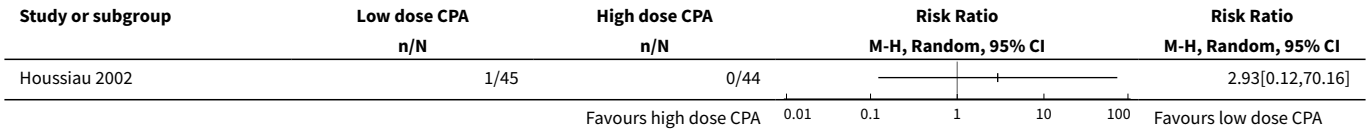




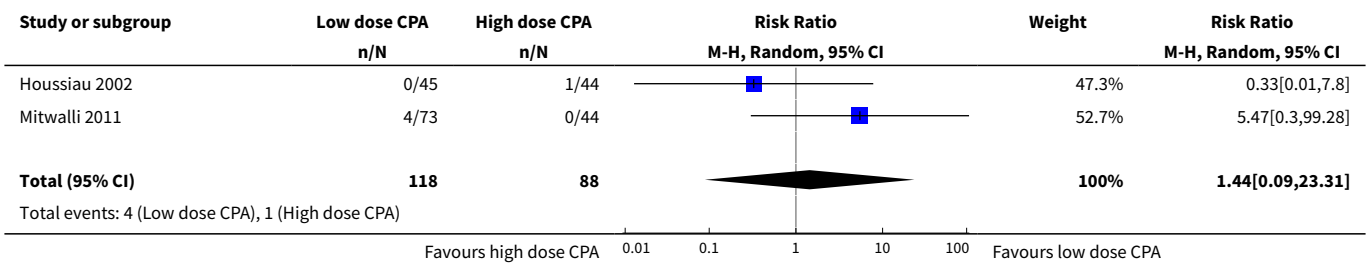
Analysis 10.5. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 5 Ovarian failure.

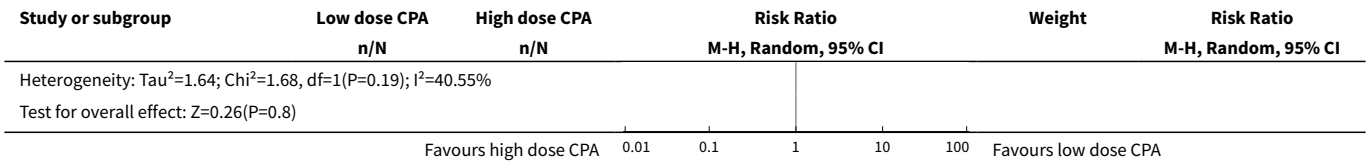


Analysis 10.6. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 6 Bone toxicity.

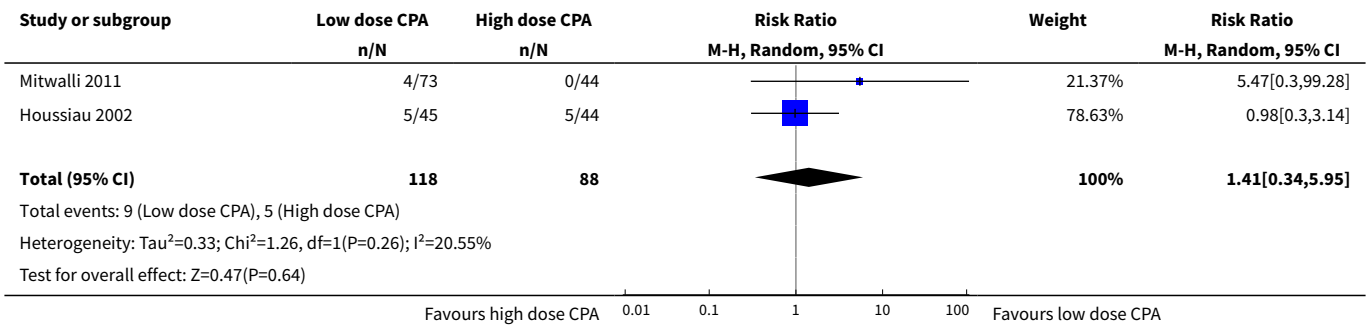


Analysis 10.7. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 7 Malignancy.

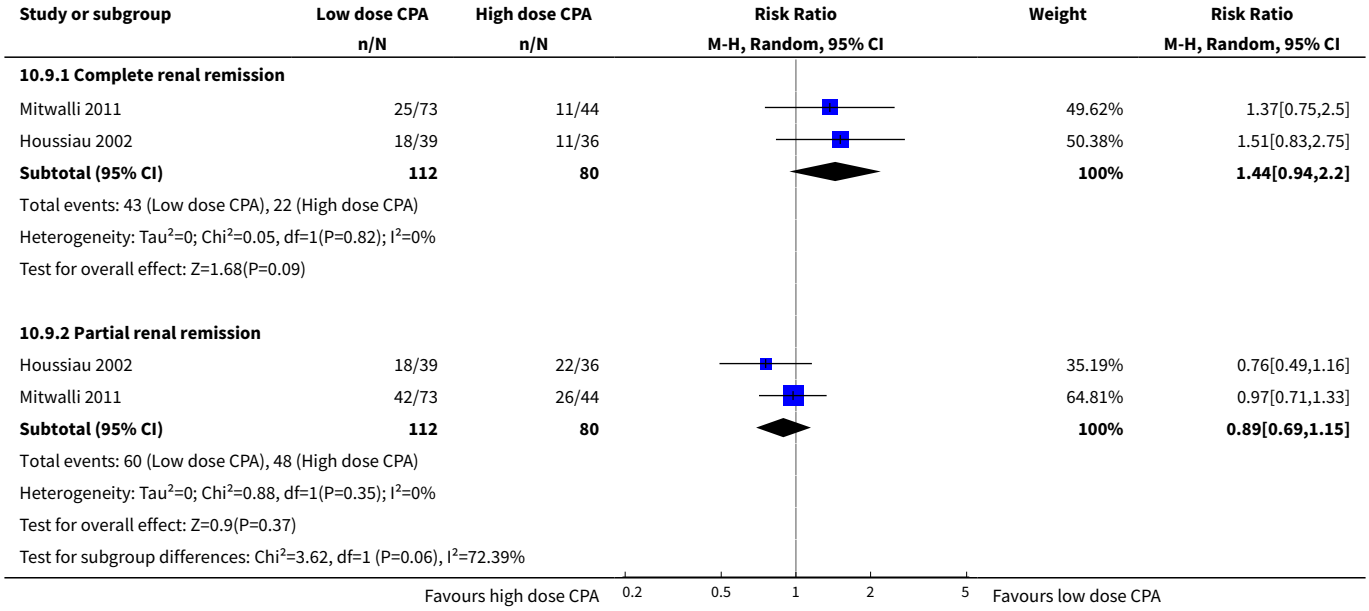




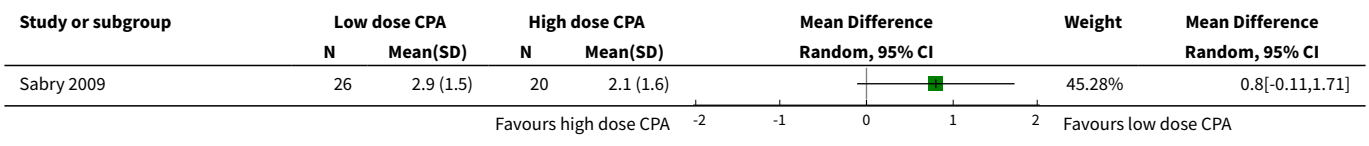
Analysis 10.8. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 8 Leucopenia.

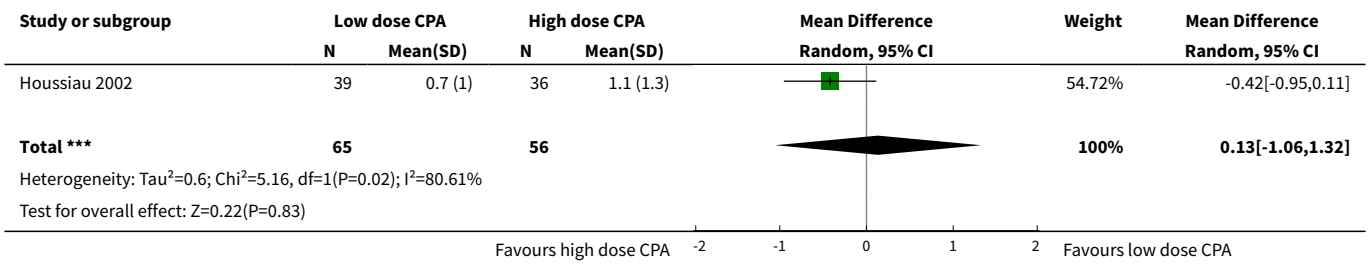


Analysis 10.9. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 9 Remission.

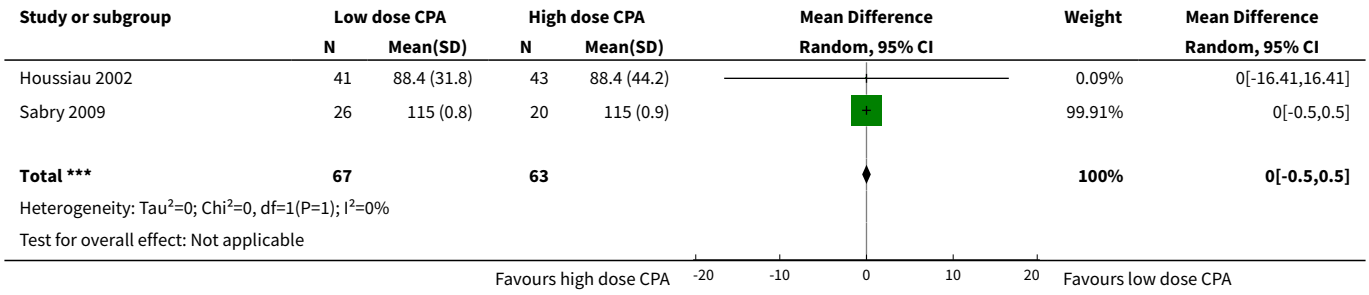


Analysis 10.10. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 10 Daily proteinuria.





Analysis 10.11. Comparison 10 High versus low dose cyclophosphamide (CPA), Outcome 11 Serum creatinine.

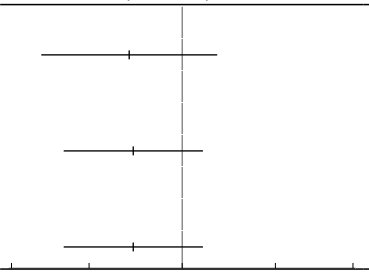


Comparison 11. Long versus short duration cyclophosphamide (CPA)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 End-stage kidney disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Doubling of serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Deterioration of kidney function	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Stable kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Major infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Herpes zoster virus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Ovarian failure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Bone toxicity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Malignancy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

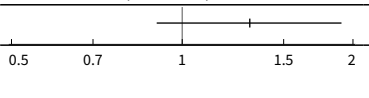
Analysis 11.1. Comparison 11 Long versus short duration cyclophosphamide (CPA), Outcome 1 Adverse renal outcomes.

Study or subgroup	Long duration CPA n/N	Short duration CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.1.1 End-stage kidney disease				
Boumpas 1992	2/20	5/20		0.4[0.09,1.83]
11.1.2 Doubling of serum creatinine				
Boumpas 1992	3/20	7/20		0.43[0.13,1.43]
11.1.3 Deterioration of kidney function				
Boumpas 1992	3/20	7/20		0.43[0.13,1.43]



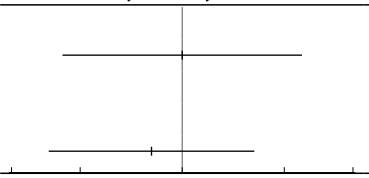
Analysis 11.2. Comparison 11 Long versus short duration cyclophosphamide (CPA), Outcome 2 Stable kidney function.

Study or subgroup	Long duration CPA n/N	Short duration CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Boumpas 1992	17/20	13/20		1.31[0.9,1.89]



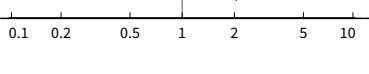
Analysis 11.3. Comparison 11 Long versus short duration cyclophosphamide (CPA), Outcome 3 Infection.

Study or subgroup	Long duration CPA n/N	Short duration CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.3.1 Major infection				
Boumpas 1992	1/20	1/20		1[0.07,14.9]
11.3.2 Herpes zoster virus				
Boumpas 1992	1/20	2/20		0.5[0.05,5.08]



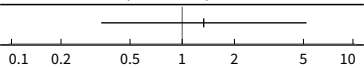
Analysis 11.4. Comparison 11 Long versus short duration cyclophosphamide (CPA), Outcome 4 Ovarian failure.

Study or subgroup	Long duration CPA n/N	Short duration CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Boumpas 1992	5/13	3/16		2.05[0.6,7.02]



Analysis 11.5. Comparison 11 Long versus short duration cyclophosphamide (CPA), Outcome 5 Bone toxicity.

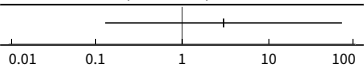
Study or subgroup	Long duration CPA n/N	Short duration CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Boumpas 1992	4/20	3/20		1.33[0.34,5.21]



Favours long duration CPA | Favours short duration CPA

Analysis 11.6. Comparison 11 Long versus short duration cyclophosphamide (CPA), Outcome 6 Malignancy.

Study or subgroup	Long duration CPA n/N	Short duration CPA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Boumpas 1992	1/20	0/20		3[0.13,69.52]



Favours long duration CPA | Favours short duration CPA

Comparison 12. Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone

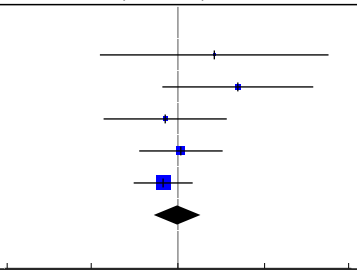
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Cyclophosphamide	5	226	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.53, 1.82]
1.2 Cyclophosphamide + azathioprine	1	29	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.17, 1.68]
1.3 Azathioprine	3	78	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 0.99]
2 End-stage kidney disease	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Cyclophosphamide	5	278	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.39, 1.03]
2.2 Cyclophosphamide + azathioprine	1	29	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.04, 1.02]
2.3 Azathioprine	2	54	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.17, 2.55]
3 Relapse	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Cyclophosphamide	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Azathioprine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Doubling of serum creatinine	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Cyclophosphamide	4	228	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.88]
4.2 Cyclophosphamide + azathioprine	1	29	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.69]
4.3 Azathioprine	1	26	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.36, 2.68]
5 Deterioration of kidney function	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

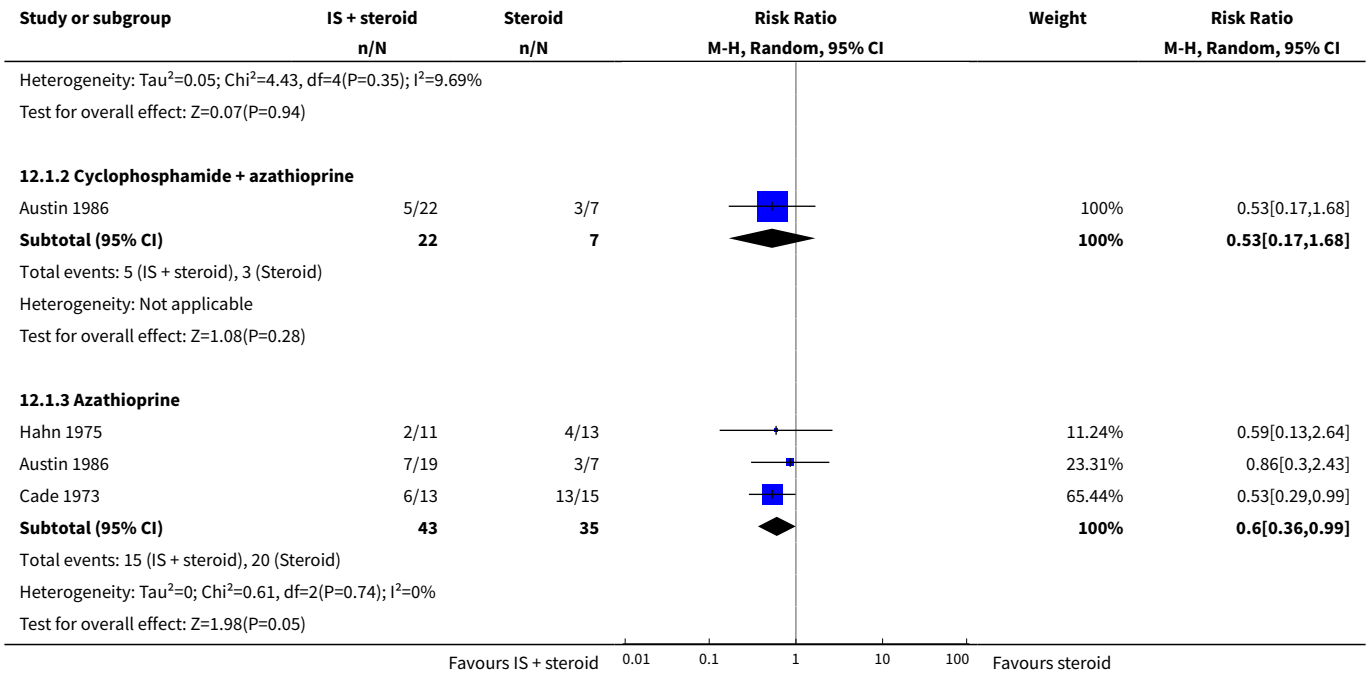
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Cyclophosphamide	5	179	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.52, 1.18]
6 Stable kidney function	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Cyclophosphamide	5	278	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.00, 1.45]
6.2 Cyclophosphamide + azathioprine	1	29	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.83, 3.06]
6.3 Azathioprine	1	26	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.48, 2.14]
7 Major infection	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Cyclophosphamide	6	291	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.50, 1.51]
7.2 Cyclophosphamide + azathioprine	1	29	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.10, 2.30]
7.3 Azathioprine	4	94	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.56, 2.01]
8 Herpes zoster infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Cyclophosphamide	3	199	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.63, 4.99]
8.2 Cyclophosphamide + azathioprine	1	29	Risk Ratio (M-H, Random, 95% CI)	5.22 [0.33, 81.40]
8.3 Azathioprine	2	42	Risk Ratio (M-H, Random, 95% CI)	3.56 [0.46, 27.79]
9 Ovarian failure	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Cyclophosphamide	3	147	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.10, 4.34]
9.2 Cyclophosphamide + azathioprine	1	27	Risk Ratio (M-H, Random, 95% CI)	7.32 [0.49, 108.96]
9.3 Azathioprine	1	24	Risk Ratio (M-H, Random, 95% CI)	2.58 [0.15, 43.86]
10 Bone toxicity	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Cyclophosphamide	3	197	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.40, 1.75]
10.2 Azathioprine	1	24	Risk Ratio (M-H, Random, 95% CI)	3.55 [0.43, 29.42]
11 Bladder toxicity	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Cyclophosphamide	2	65	Risk Ratio (M-H, Random, 95% CI)	2.66 [0.33, 21.68]
11.2 Cyclophosphamide + azathioprine	1	29	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.14, 42.17]
12 Malignancy	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Cyclophosphamide	2	117	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.07, 9.90]
12.2 Azathioprine	1	26	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.11, 37.22]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
13 Complete remission of proteinuria	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Cyclophosphamide	1	13	Risk Ratio (M-H, Random, 95% CI)	2.63 [0.13, 54.64]
13.2 Azathioprine	2	37	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.54, 1.69]
14 Daily proteinuria	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Cyclophosphamide	3	92	Mean Difference (IV, Random, 95% CI)	0.15 [-0.23, 0.54]
14.2 Cyclosporin A	1	10	Mean Difference (IV, Random, 95% CI)	-1.8 [-2.59, -1.01]
15 Serum creatinine	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
15.1 Cyclophosphamide	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Cyclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16 Creatinine clearance	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Cyclophosphamide	2	63	Mean Difference (IV, Random, 95% CI)	12.23 [-0.13, 24.58]
16.2 Azathioprine	1	24	Mean Difference (IV, Random, 95% CI)	5.0 [-3.14, 13.14]
16.3 Cyclosporin A	1	10	Mean Difference (IV, Random, 95% CI)	-42.5 [-85.02, 0.02]

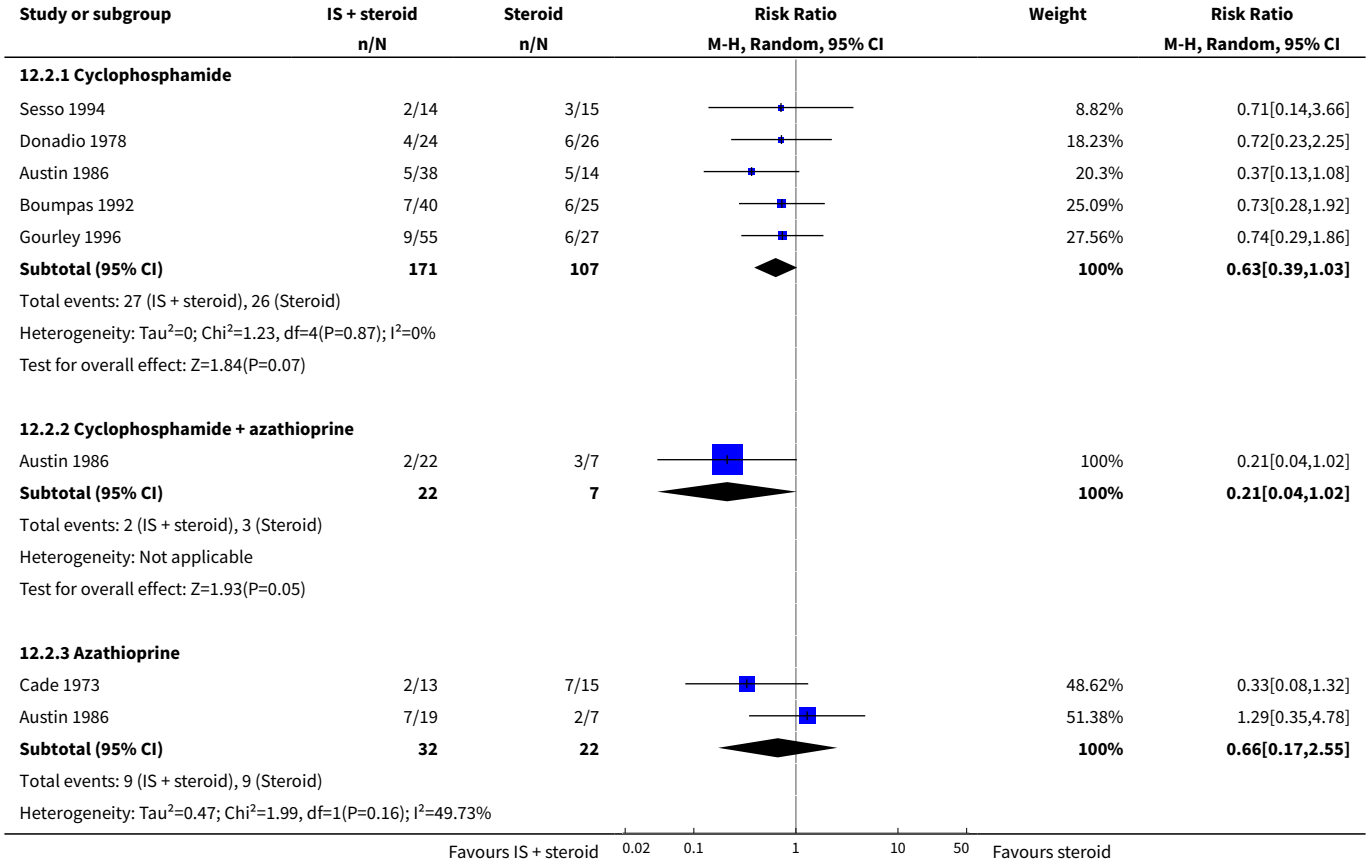
Analysis 12.1. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 1 All-cause mortality.

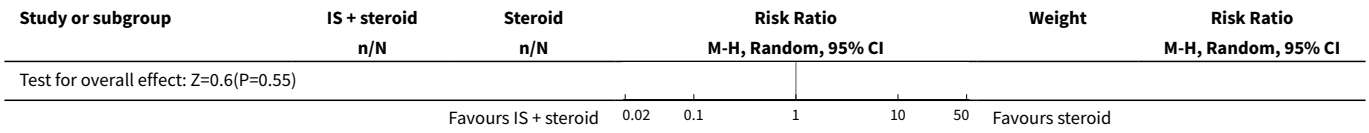
Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.1.1 Cyclophosphamide					
Steinberg 1971	1/7	0/6		4.08%	2.63[0.13,54.64]
Gourley 1996	10/55	1/27		9.1%	4.91[0.66,36.4]
Sesso 1994	2/14	3/15		13.35%	0.71[0.14,3.66]
Donadio 1978	5/24	5/26		26.74%	1.08[0.36,3.28]
Austin 1986	11/38	6/14		46.74%	0.68[0.31,1.48]
Subtotal (95% CI)	**138**	**88**		**100%**	**0.98[0.53,1.82]**
Total events: 29 (IS + steroid), 15 (Steroid)					



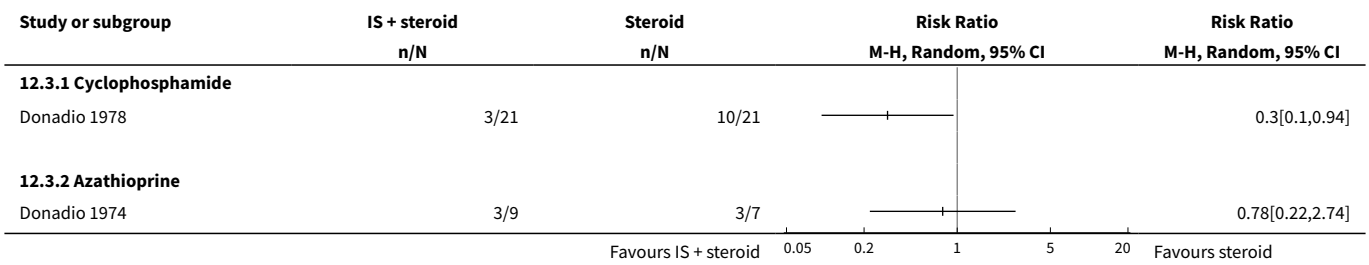


Analysis 12.2. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 2 End-stage kidney disease.

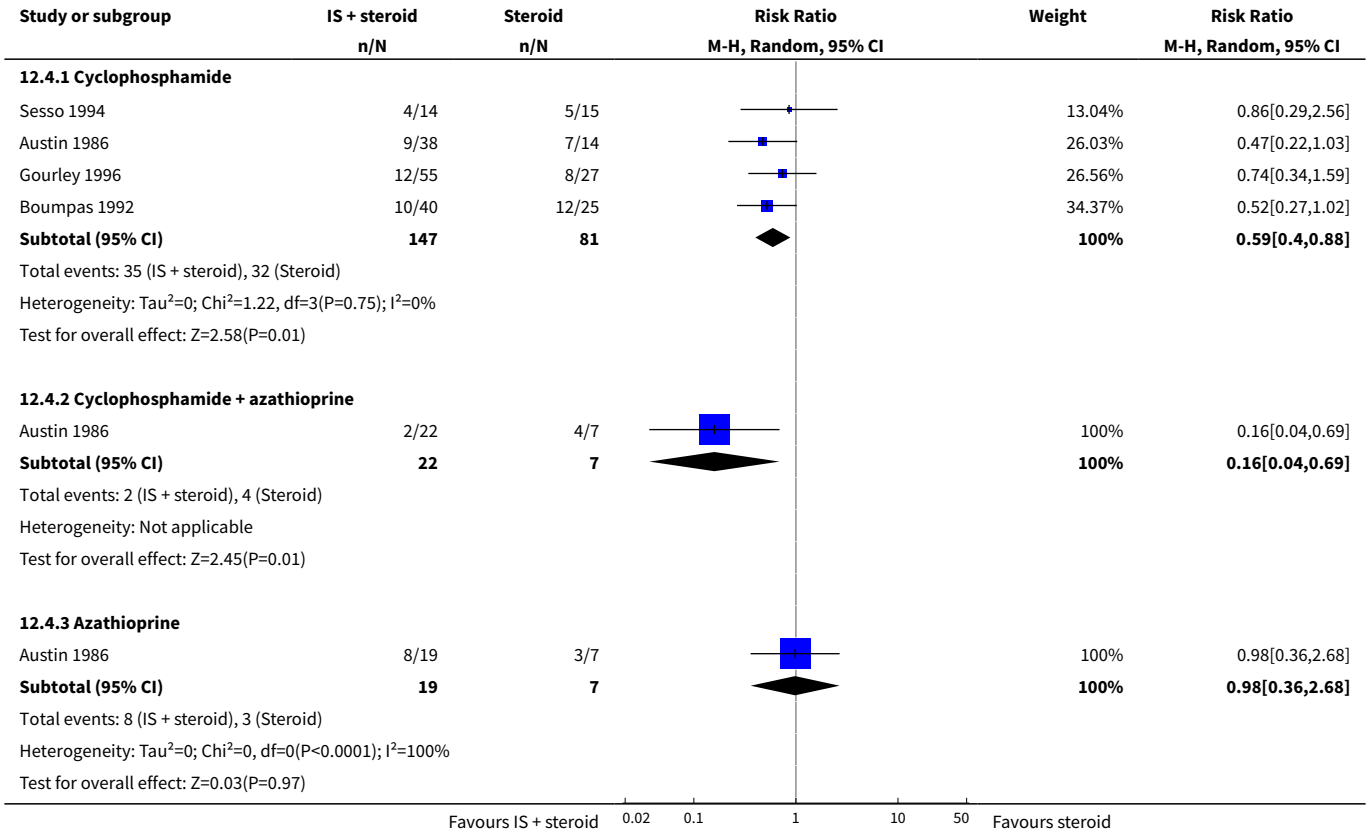




Analysis 12.3. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 3 Relapse.



Analysis 12.4. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 4 Doubling of serum creatinine.

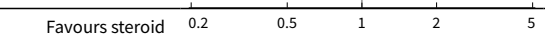


Analysis 12.5. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 5 Deterioration of kidney function.

Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.5.1 Cyclophosphamide					
Gourley 1996	8/27	3/13		12.6%	1.28[0.41,4.06]
Sesso 1994	4/14	5/15		13.91%	0.86[0.29,2.56]
Austin 1986	4/20	4/7		14.13%	0.35[0.12,1.04]
Boumpas 1992	7/20	6/13		23.76%	0.76[0.33,1.75]
Donadio 1978	9/24	11/26		35.6%	0.89[0.45,1.76]
Subtotal (95% CI)	**105**	**74**		**100%**	**0.78[0.52,1.18]**
Total events: 32 (IS + steroid), 29 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=3, df=4(P=0.56); I^2=0%					
Test for overall effect: Z=1.19(P=0.24)					

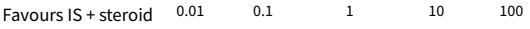
Analysis 12.6. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 6 Stable kidney function.

Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.6.1 Cyclophosphamide					
Austin 1986	29/38	6/14		8.4%	1.78[0.95,3.34]
Sesso 1994	10/14	10/15		14.03%	1.07[0.66,1.74]
Donadio 1978	15/24	15/26		16.33%	1.08[0.69,1.7]
Boumpas 1992	30/40	13/25		19.2%	1.44[0.95,2.19]
Gourley 1996	43/55	19/27		42.04%	1.11[0.84,1.47]
Subtotal (95% CI)	**171**	**107**		**100%**	**1.2[1,1.45]**
Total events: 127 (IS + steroid), 63 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=3.11, df=4(P=0.54); I^2=0%					
Test for overall effect: Z=1.99(P=0.05)					
12.6.2 Cyclophosphamide + azathioprine					
Austin 1986	20/22	4/7		100%	1.59[0.83,3.06]
Subtotal (95% CI)	**22**	**7**		**100%**	**1.59[0.83,3.06]**
Total events: 20 (IS + steroid), 4 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.39(P=0.16)					
12.6.3 Azathioprine					
Austin 1986	11/19	4/7		100%	1.01[0.48,2.14]
Subtotal (95% CI)	**19**	**7**		**100%**	**1.01[0.48,2.14]**
Total events: 11 (IS + steroid), 4 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.97)					



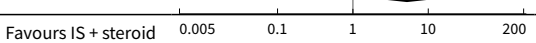
Analysis 12.7. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 7 Major infection.

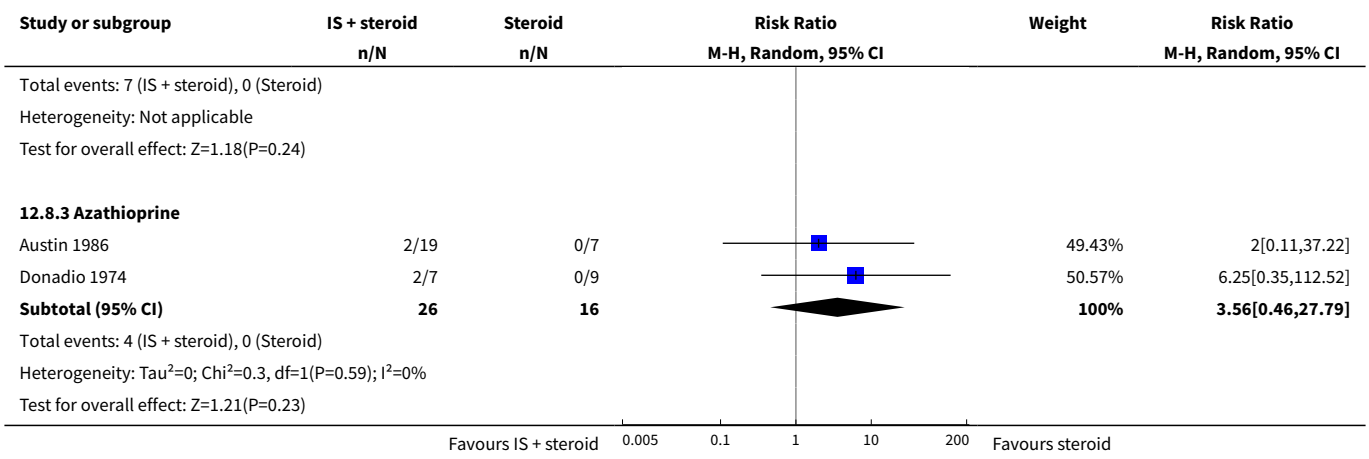
Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.7.1 Cyclophosphamide					
Steinberg 1971	0/7	1/6		3.32%	0.29[0.01,6.07]
Boumpas 1992	2/40	0/25		3.4%	3.17[0.16,63.45]
Sesso 1994	2/14	1/15		5.84%	2.14[0.22,21.1]
Donadio 1978	2/24	4/26		11.87%	0.54[0.11,2.69]
Austin 1986	5/38	4/14		22.58%	0.46[0.14,1.47]
Gourley 1996	16/55	7/27		52.98%	1.12[0.53,2.4]
Subtotal (95% CI)	**178**	**113**		**100%**	**0.87[0.5,1.51]**
Total events: 27 (IS + steroid), 17 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=3.73, df=5(P=0.59); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					
12.7.2 Cyclophosphamide + azathioprine					
Austin 1986	3/22	2/7		100%	0.48[0.1,2.3]
Subtotal (95% CI)	**22**	**7**		**100%**	**0.48[0.1,2.3]**
Total events: 3 (IS + steroid), 2 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.92(P=0.36)					
12.7.3 Azathioprine					
Donadio 1974	1/7	0/9		4.36%	3.75[0.18,80.19]
Austin 1986	2/19	1/7		8.15%	0.74[0.08,6.91]
Cade 1973	2/13	2/15		12.42%	1.15[0.19,7.08]
Hahn 1975	6/11	7/13		75.07%	1.01[0.48,2.12]
Subtotal (95% CI)	**50**	**44**		**100%**	**1.06[0.56,2.01]**
Total events: 11 (IS + steroid), 10 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=0.8, df=3(P=0.85); I^2=0%					
Test for overall effect: Z=0.18(P=0.85)					



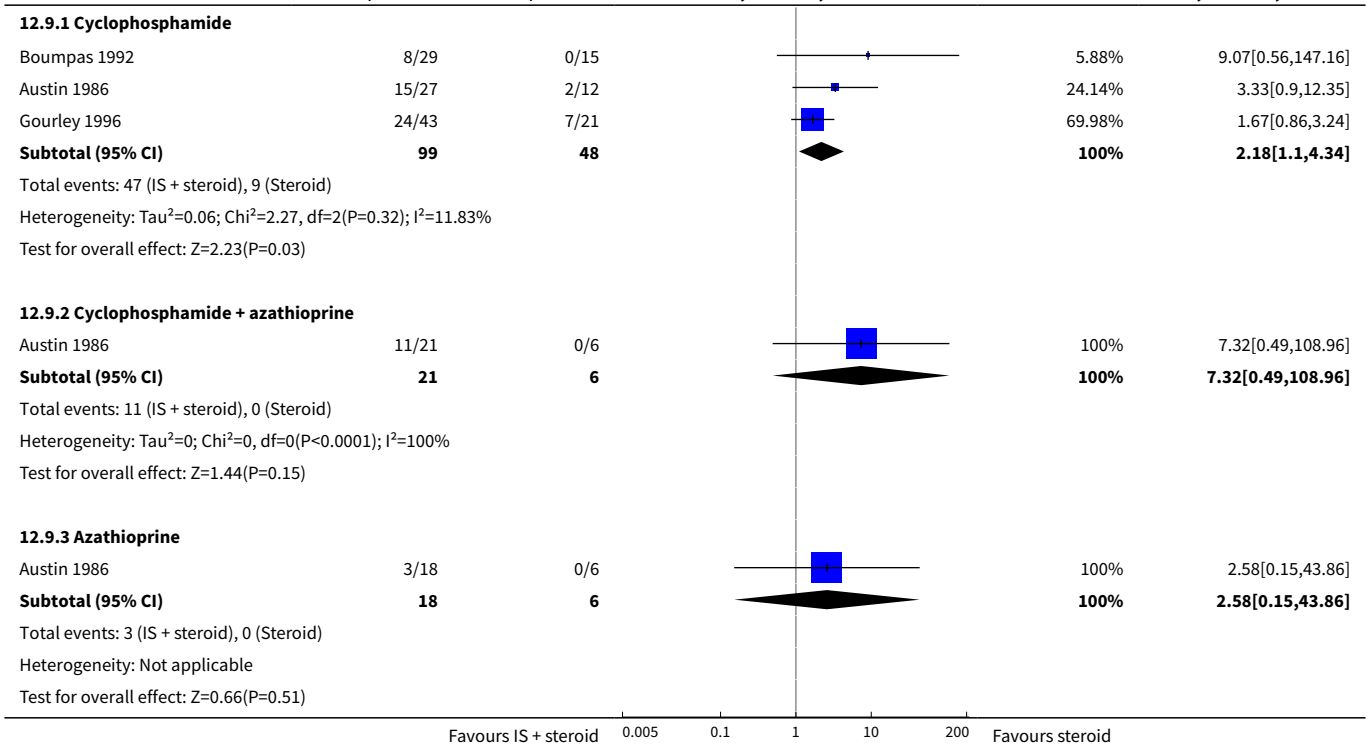
Analysis 12.8. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 8 Herpes zoster infection.

Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.8.1 Cyclophosphamide					
Boumpas 1992	3/40	3/25		30.76%	0.63[0.14,2.86]
Gourley 1996	16/55	2/27		34.32%	3.93[0.97,15.86]
Austin 1986	11/38	2/14		34.92%	2.03[0.51,8.03]
Subtotal (95% CI)	**133**	**66**		**100%**	**1.77[0.63,4.99]**
Total events: 30 (IS + steroid), 7 (Steroid)					
Heterogeneity: Tau^2=0.31; Chi^2=3.16, df=2(P=0.21); I^2=36.66%					
Test for overall effect: Z=1.08(P=0.28)					
12.8.2 Cyclophosphamide + azathioprine					
Austin 1986	7/22	0/7		100%	5.22[0.33,81.4]
Subtotal (95% CI)	**22**	**7**		**100%**	**5.22[0.33,81.4]**



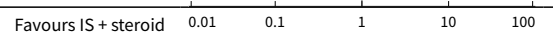


Analysis 12.9. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 9 Ovarian failure.



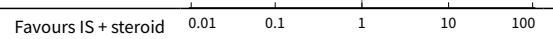
Analysis 12.10. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 10 Bone toxicity.

Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.10.1 Cyclophosphamide					
Donadio 1978	0/24	1/26		5.48%	0.36[0.02,8.43]
Boumpas 1992	7/40	3/25		34.51%	1.46[0.41,5.12]
Gourley 1996	8/55	6/27		60.01%	0.65[0.25,1.7]
Subtotal (95% CI)	**119**	**78**		**100%**	**0.84[0.4,1.75]**
Total events: 15 (IS + steroid), 10 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=1.28, df=2(P=0.53); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
12.10.2 Azathioprine					
Hahn 1975	3/11	1/13		100%	3.55[0.43,29.42]
Subtotal (95% CI)	**11**	**13**		**100%**	**3.55[0.43,29.42]**
Total events: 3 (IS + steroid), 1 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.17(P=0.24)					



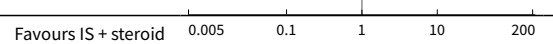
Analysis 12.11. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 11 Bladder toxicity.

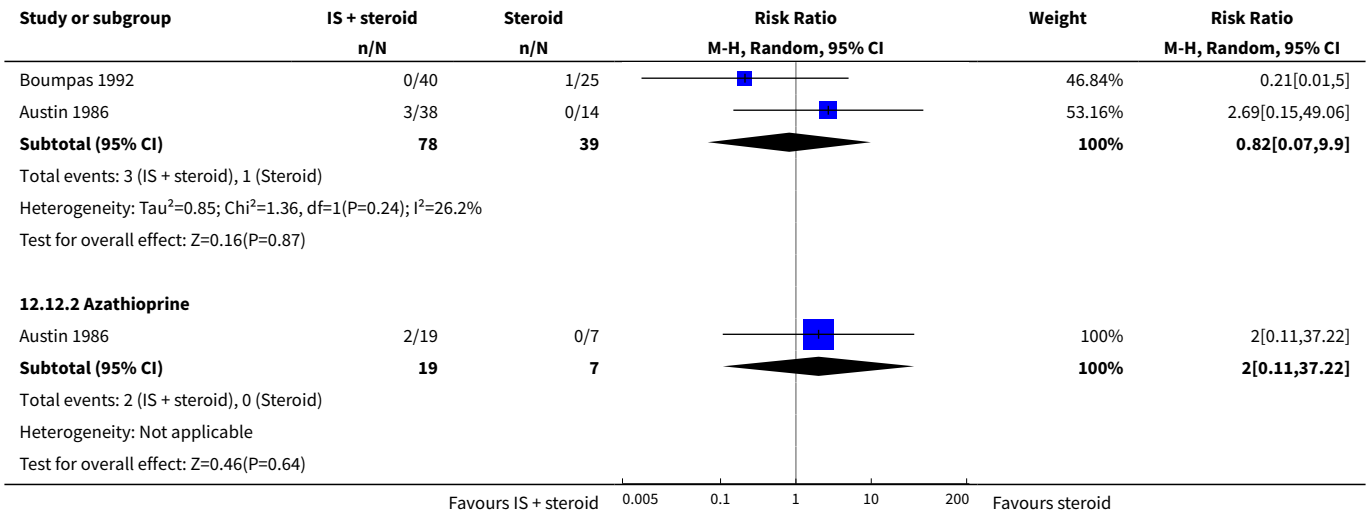
Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.11.1 Cyclophosphamide					
Steinberg 1971	1/7	0/6		47.76%	2.63[0.13,54.64]
Austin 1986	3/38	0/14		52.24%	2.69[0.15,49.06]
Subtotal (95% CI)	**45**	**20**		**100%**	**2.66[0.33,21.68]**
Total events: 4 (IS + steroid), 0 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					
12.11.2 Cyclophosphamide + azathioprine					
Austin 1986	3/22	0/7		100%	2.43[0.14,42.17]
Subtotal (95% CI)	**22**	**7**		**100%**	**2.43[0.14,42.17]**
Total events: 3 (IS + steroid), 0 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					



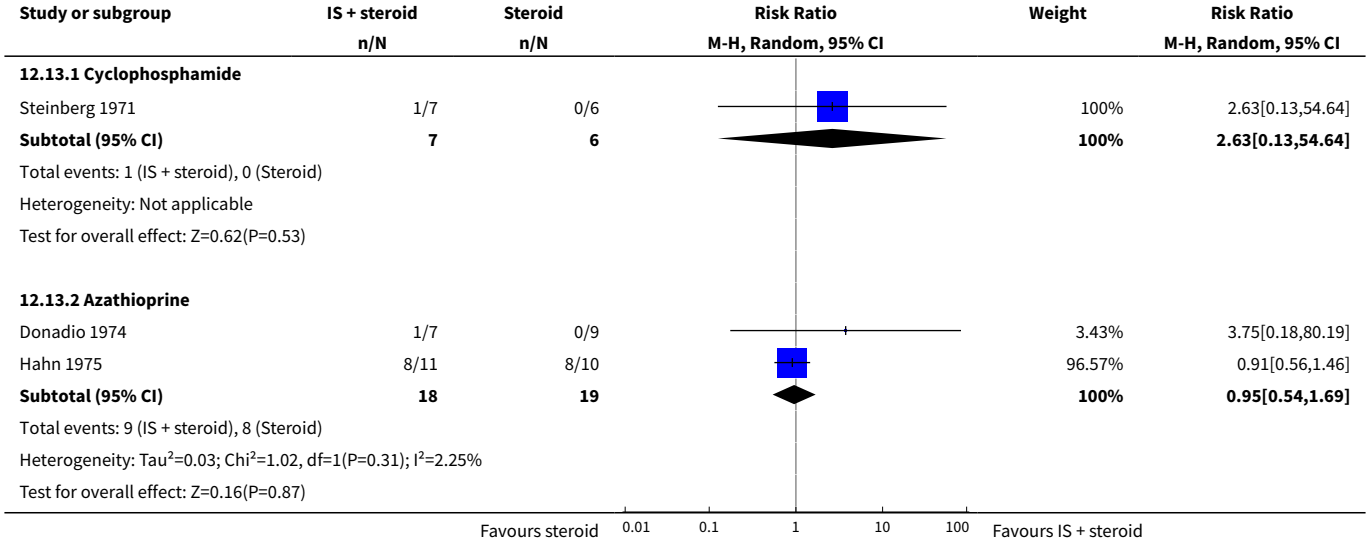
Analysis 12.12. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 12 Malignancy.

Study or subgroup	IS + steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.12.1 Cyclophosphamide					

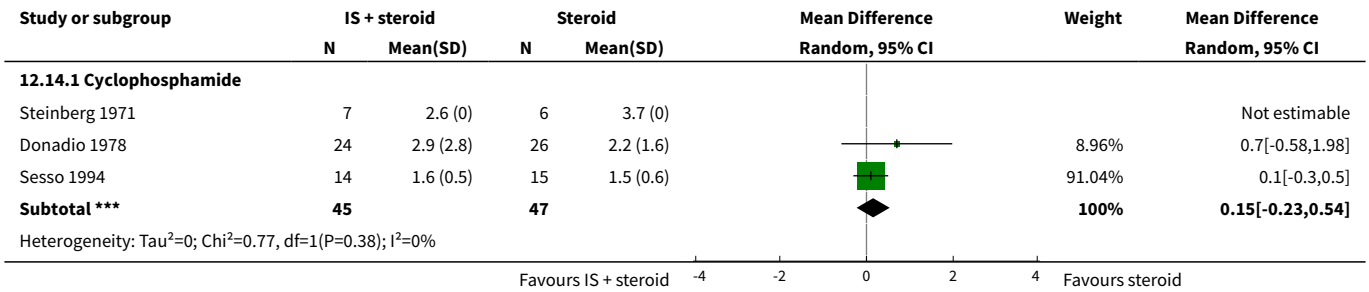


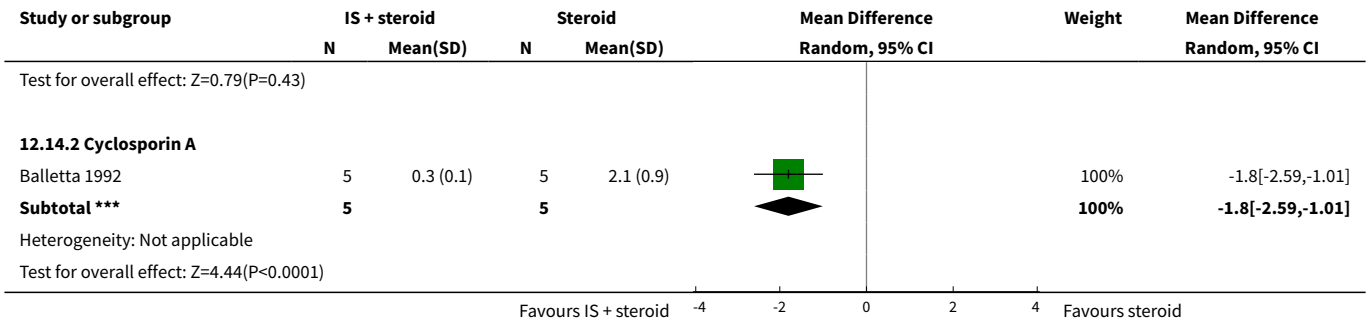


Analysis 12.13. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 13 Complete remission of proteinuria.

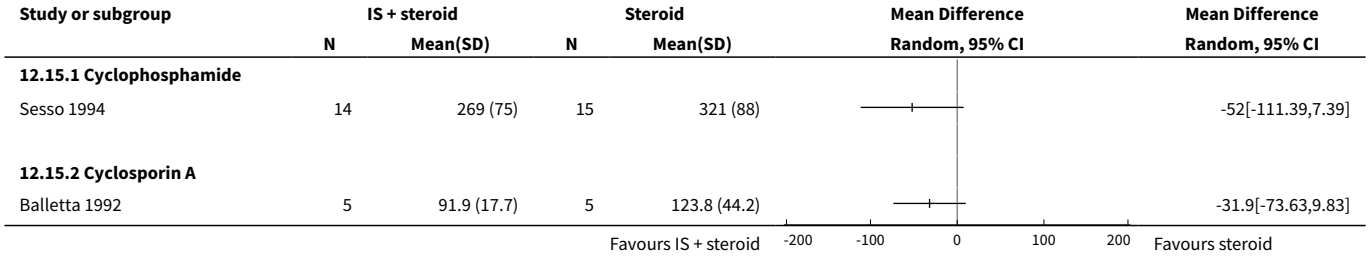


Analysis 12.14. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 14 Daily proteinuria.

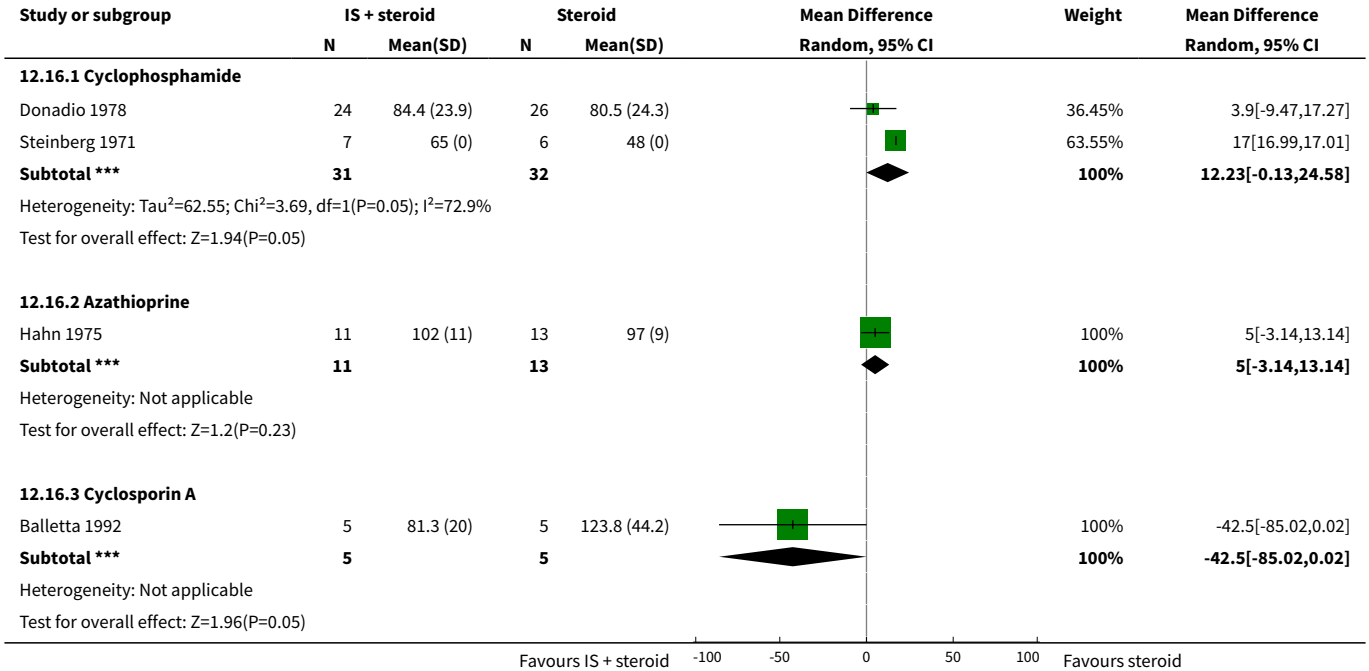




Analysis 12.15. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 15 Serum creatinine.



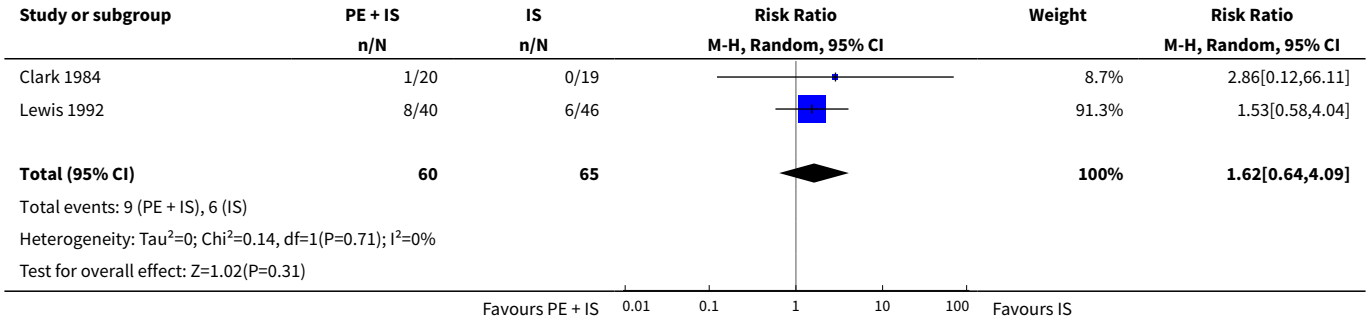
Analysis 12.16. Comparison 12 Immunosuppressive agent (IS) + corticosteroids versus corticosteroids alone, Outcome 16 Creatinine clearance.



Comparison 13. Plasma exchange (PE) + immunosuppression (IS) versus IS alone

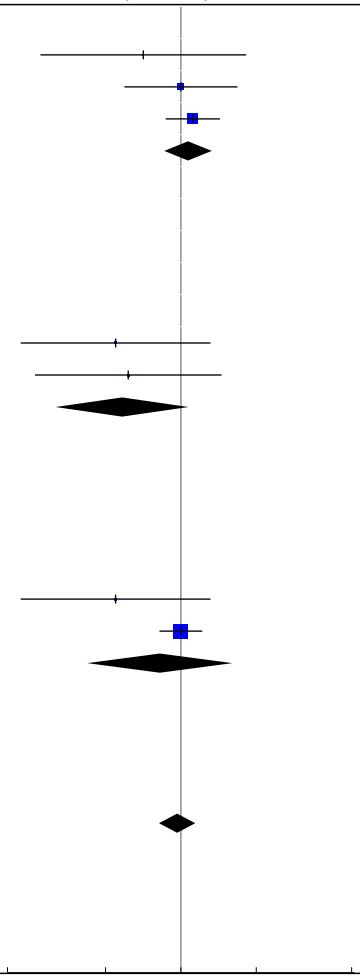
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	125	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.64, 4.09]
2 Adverse renal outcomes	4	251	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.51, 1.55]
2.1 End-stage kidney disease	3	143	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.60, 2.57]
2.2 Doubling of serum creatinine	2	51	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.26]
2.3 Deterioration of kidney function	2	57	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.06, 4.83]
3 Stable kidney function	3	75	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.94, 1.30]
4 Infection	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Major infection	2	125	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.37]
4.2 Herpes zoster virus	2	104	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.10, 29.42]
5 Daily proteinuria	2	30	Mean Difference (IV, Random, 95% CI)	-0.56 [-5.23, 4.11]
6 Serum creatinine	3	69	Mean Difference (IV, Random, 95% CI)	-17.90 [-23.41, -12.39]
7 Creatinine clearance	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 1 Mortality.



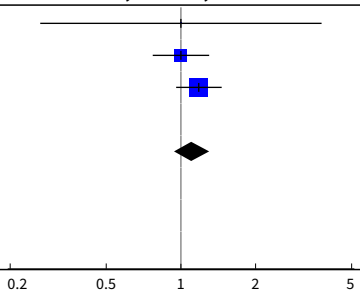
Analysis 13.2. Comparison 13 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 2 Adverse renal outcomes.

Study or subgroup	PE + IS n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.2.1 End-stage kidney disease					
Clark 1984	0/20	1/19		3.01%	0.32[0.01,7.35]
Wallace 1998	2/9	2/9		9.4%	1[0.18,5.63]
Lewis 1992	10/40	8/46		32.36%	1.44[0.63,3.29]
Subtotal (95% CI)	**69**	**74**		**44.77%**	**1.24[0.6,2.57]**
Total events: 12 (PE + IS), 11 (IS)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=2(P=0.63); I^2=0%					
Test for overall effect: Z=0.59(P=0.56)					
13.2.2 Doubling of serum creatinine					
Clark 1984	0/20	3/19		3.52%	0.14[0.01,2.47]
Clark 1981	0/6	2/6		3.64%	0.2[0.01,3.46]
Subtotal (95% CI)	**26**	**25**		**7.16%**	**0.17[0.02,1.26]**
Total events: 0 (PE + IS), 5 (IS)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					
13.2.3 Deterioration of kidney function					
Clark 1984	0/20	3/19		3.52%	0.14[0.01,2.47]
Wallace 1998	6/9	6/9		44.54%	1[0.52,1.92]
Subtotal (95% CI)	**29**	**28**		**48.06%**	**0.53[0.06,4.83]**
Total events: 6 (PE + IS), 9 (IS)					
Heterogeneity: Tau^2=1.78; Chi^2=2.55, df=1(P=0.11); I^2=60.75%					
Test for overall effect: Z=0.57(P=0.57)					
Total (95% CI)	**124**	**127**		**100%**	**0.89[0.51,1.55]**
Total events: 18 (PE + IS), 25 (IS)					
Heterogeneity: Tau^2=0.07; Chi^2=6.75, df=6(P=0.34); I^2=11.13%					
Test for overall effect: Z=0.41(P=0.68)					
Test for subgroup differences: Chi^2=3.64, df=1 (P=0.16), I^2=45.07%					



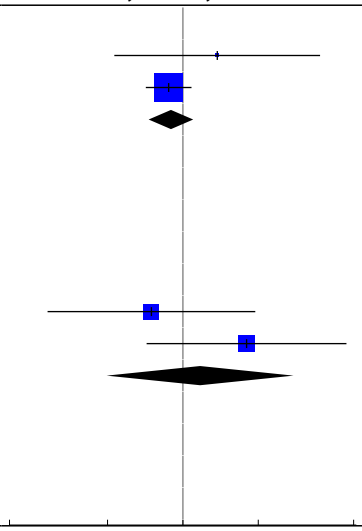
Analysis 13.3. Comparison 13 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 3 Stable kidney function.

Study or subgroup	PE + IS n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Wallace 1998	3/9	3/9		1.57%	1[0.27,3.69]
Doria 1994	5/5	13/13		39.18%	1[0.77,1.3]
Clark 1984	20/20	16/19		59.25%	1.18[0.96,1.46]
Total (95% CI)	**34**	**41**		**100%**	**1.1[0.94,1.3]**
Total events: 28 (PE + IS), 32 (IS)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=2(P=0.61); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					



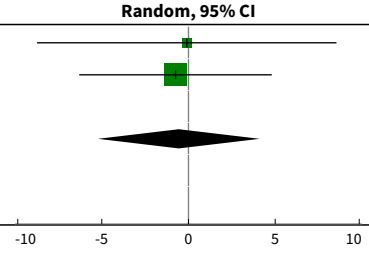
Analysis 13.4. Comparison 13 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 4 Infection.

Study or subgroup	PE + IS n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.4.1 Major infection					
Clark 1984	1/20	0/19		4.71%	2.86[0.12,66.11]
Lewis 1992	9/40	16/46		95.29%	0.65[0.32,1.3]
Subtotal (95% CI)	**60**	**65**		**100%**	**0.69[0.35,1.37]**
Total events: 10 (PE + IS), 16 (IS)					
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=1.05(P=0.29)					
13.4.2 Herpes zoster virus					
Lewis 1992	0/40	1/46		48.87%	0.38[0.02,9.13]
Doria 1994	1/5	0/13		51.13%	7[0.33,148.46]
Subtotal (95% CI)	**45**	**59**		**100%**	**1.69[0.1,29.42]**
Total events: 1 (PE + IS), 1 (IS)					
Heterogeneity: Tau^2=1.73; Chi^2=1.68, df=1(P=0.19); I^2=40.61%					
Test for overall effect: Z=0.36(P=0.72)					
Test for subgroup differences: Chi^2=0.35, df=1 (P=0.55), I^2=0%					



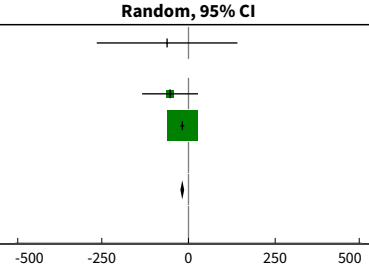
Analysis 13.5. Comparison 13 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 5 Daily proteinuria.

Study or subgroup	PE + IS N	PE + IS Mean(SD)	IS N	IS Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Clark 1981	6	7.2 (6.1)	6	7.3 (8.9)		29.24%	-0.1[-8.73,8.53]
Wallace 1998	9	4.4 (6.5)	9	5.2 (5.5)		70.76%	-0.75[-6.3,4.8]
Total ***	**15**		**15**			**100%**	**-0.56[-5.23,4.11]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%							
Test for overall effect: Z=0.24(P=0.81)							



Analysis 13.6. Comparison 13 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 6 Serum creatinine.

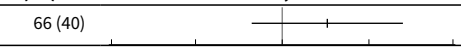
Study or subgroup	PE + IS N	PE + IS Mean(SD)	IS N	IS Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Wallace 1998	9	178.8 (157.5)	9	240.5 (267.5)		0.07%	-61.7[-264.51,141.11]
Clark 1981	6	97.2 (26.5)	6	150.3 (97.2)		0.47%	-53.1[-133.71,27.51]
Clark 1984	20	97.2 (8.8)	19	114.9 (8.8)		99.46%	-17.7[-23.23,-12.17]
Total ***	**35**		**34**			**100%**	**-17.9[-23.41,-12.39]**
Heterogeneity: Tau^2=0; Chi^2=0.92, df=2(P=0.63); I^2=0%							



Study or subgroup	PE + IS N	PE + IS Mean(SD)	IS N	IS Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=6.37(P<0.0001)							

Analysis 13.7. Comparison 13 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 7 Creatinine clearance.

Study or subgroup	PE + IS N	PE + IS Mean(SD)	IS N	IS Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Clark 1981	6	92 (37)	6	66 (40)		26[-17.6,69.6]

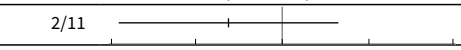


Comparison 14. Plasma exchange (PE) versus immunosuppression (IS)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 End-stage kidney disease	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Major infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

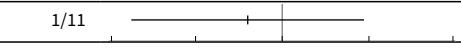
Analysis 14.1. Comparison 14 Plasma exchange (PE) versus immunosuppression (IS), Outcome 1 End-stage kidney disease.

Study or subgroup	PE n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Derksen 1988	0/9	2/11		0.24[0.01,4.44]



Analysis 14.2. Comparison 14 Plasma exchange (PE) versus immunosuppression (IS), Outcome 2 Major infection.

Study or subgroup	PE n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Derksen 1988	0/9	1/11		0.4[0.02,8.78]

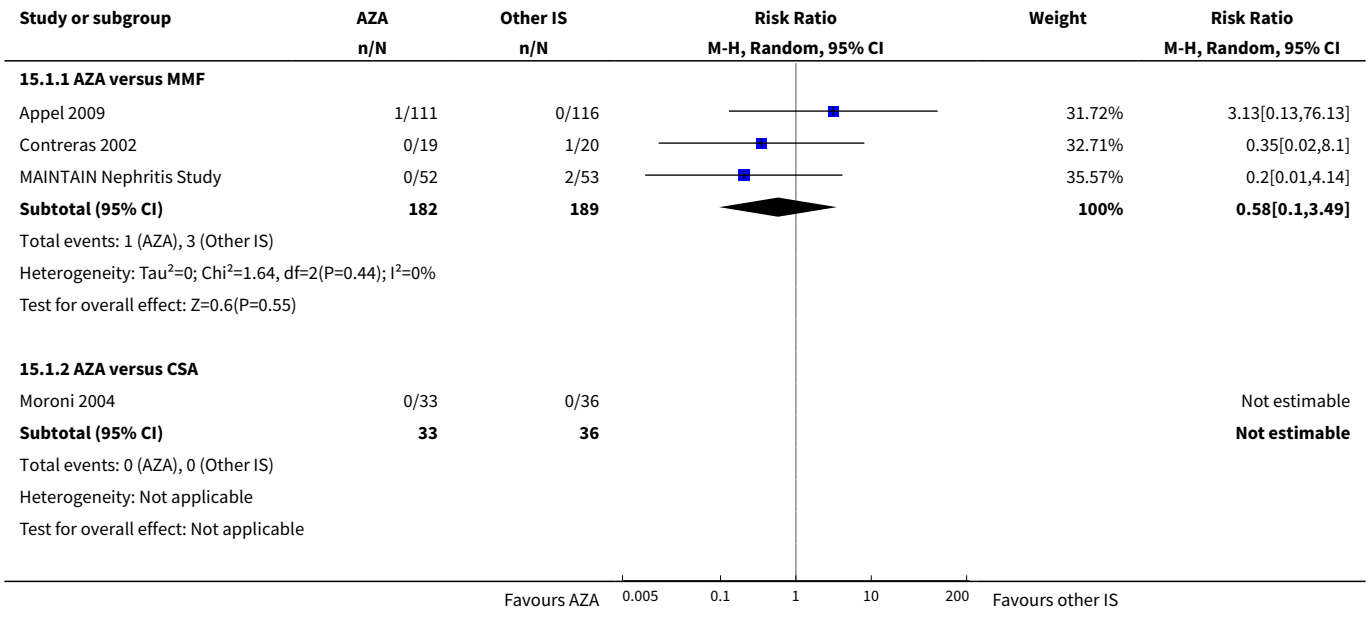


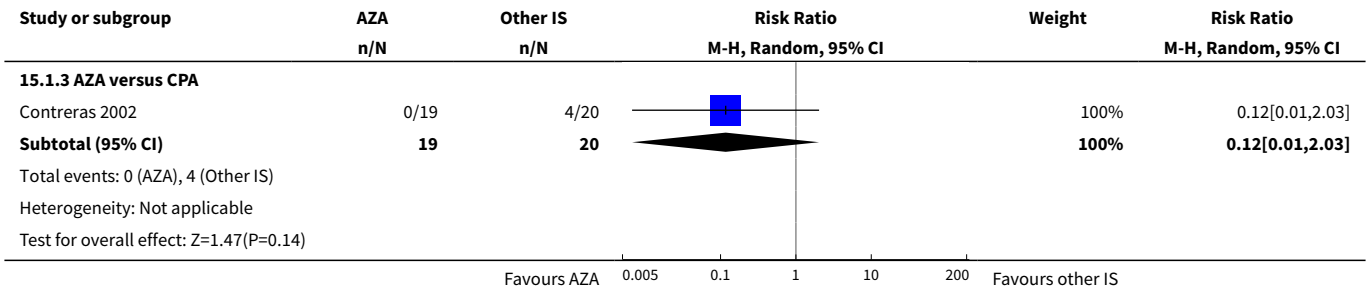
Comparison 15. Maintenance therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 AZA versus MMF	3	371	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.10, 3.49]
1.2 AZA versus CSA	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 AZA versus CPA	1	39	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.03]
2 End-stage kidney disease	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 AZA versus MMF	3	371	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.37, 9.31]
2.2 AZA versus CSA	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 AZA versus CPA	1	39	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.09]
3 Renal relapse	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 AZA versus MMF	3	371	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.24, 2.71]
3.2 AZA versus CSA	1	69	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.51, 3.06]
3.3 AZA versus CPA	1	39	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.34, 1.85]
4 Doubling serum creatinine	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 AZA versus MMF	3	371	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.89, 4.94]
4.2 AZA versus CPA	1	39	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.34, 1.85]
5 Infection	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Major: AZA versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Major: AZA versus CSA	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Herpes zoster virus: AZA versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Bone toxicity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 AZA versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Bladder toxicity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 AZA versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 AZA versus CPA	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Alopecia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 AZA versus MMF	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

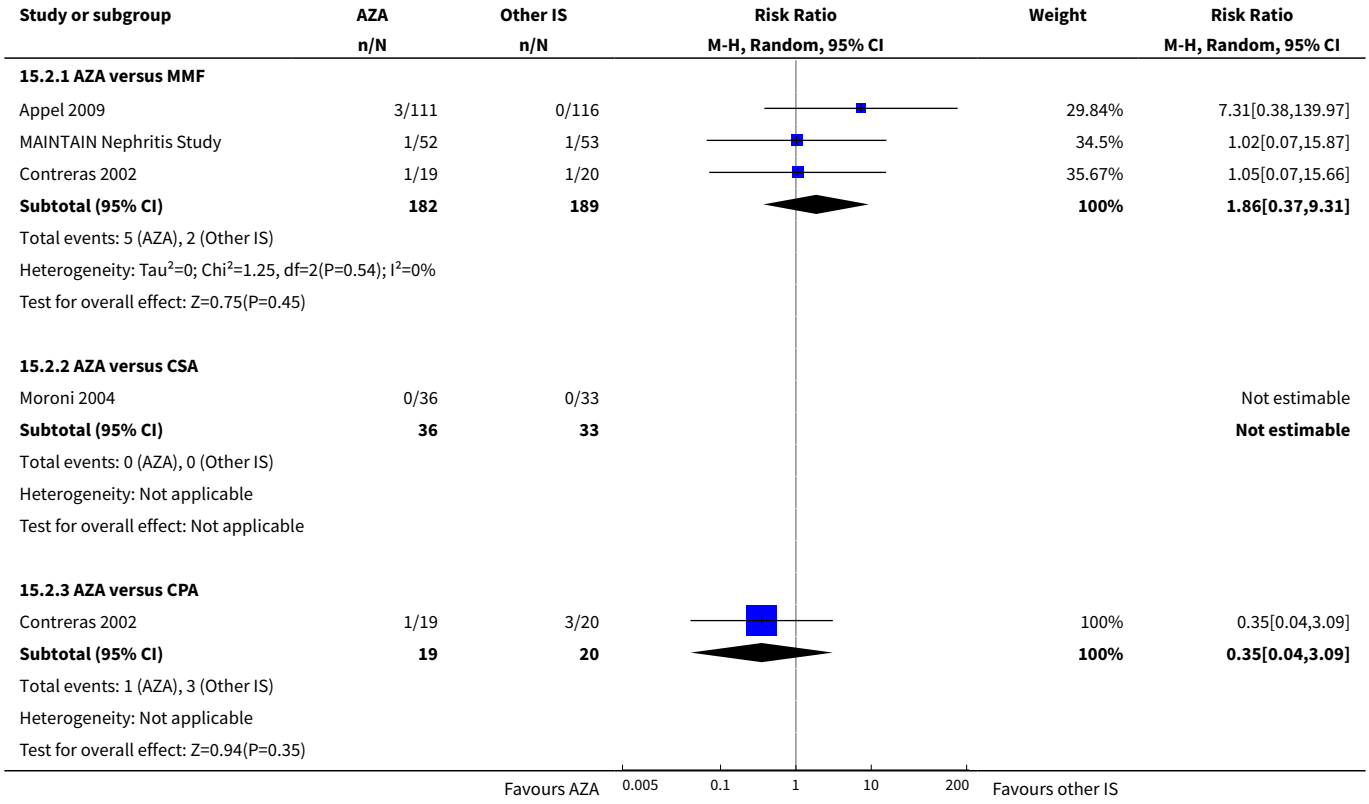
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9 Malignancy	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 AZA versus MMF	3	370	Risk Ratio (M-H, Random, 95% CI)	4.04 [0.45, 36.07]
9.2 AZA versus CPA	1	39	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 GI disturbance	2	174	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.18, 1.96]
10.1 AZA versus MMF	1	105	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.41, 2.51]
10.2 AZA versus CSA	1	69	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.09, 0.97]
11 Leucopenia	3	400	Risk Ratio (M-H, Random, 95% CI)	3.78 [1.66, 8.60]
11.1 AZA versus MMF	2	331	Risk Ratio (M-H, Random, 95% CI)	6.21 [1.69, 22.85]
11.2 AZA versus CSA	1	69	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.95, 7.86]
12 Daily proteinuria	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.1 CSA versus AZA	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 CSA versus CPA	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Creatinine clearance	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.1 CSA versus CPA	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 15.1. Comparison 15 Maintenance therapy, Outcome 1 Mortality.

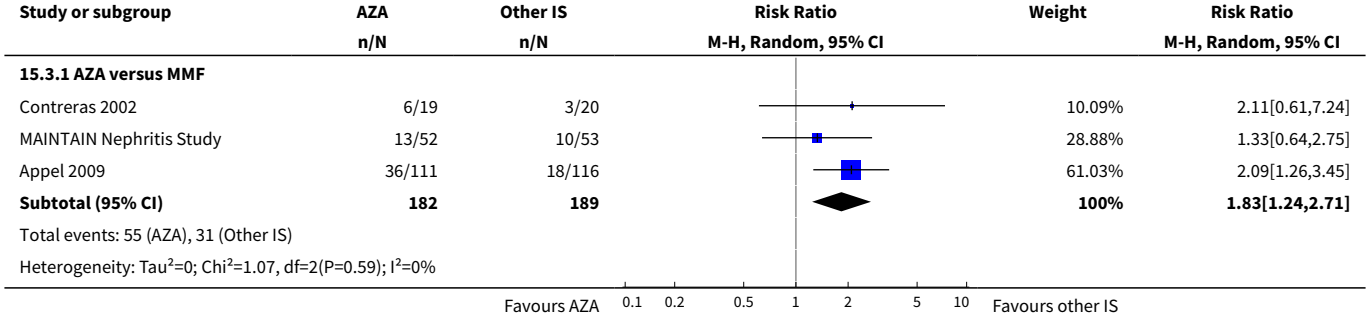


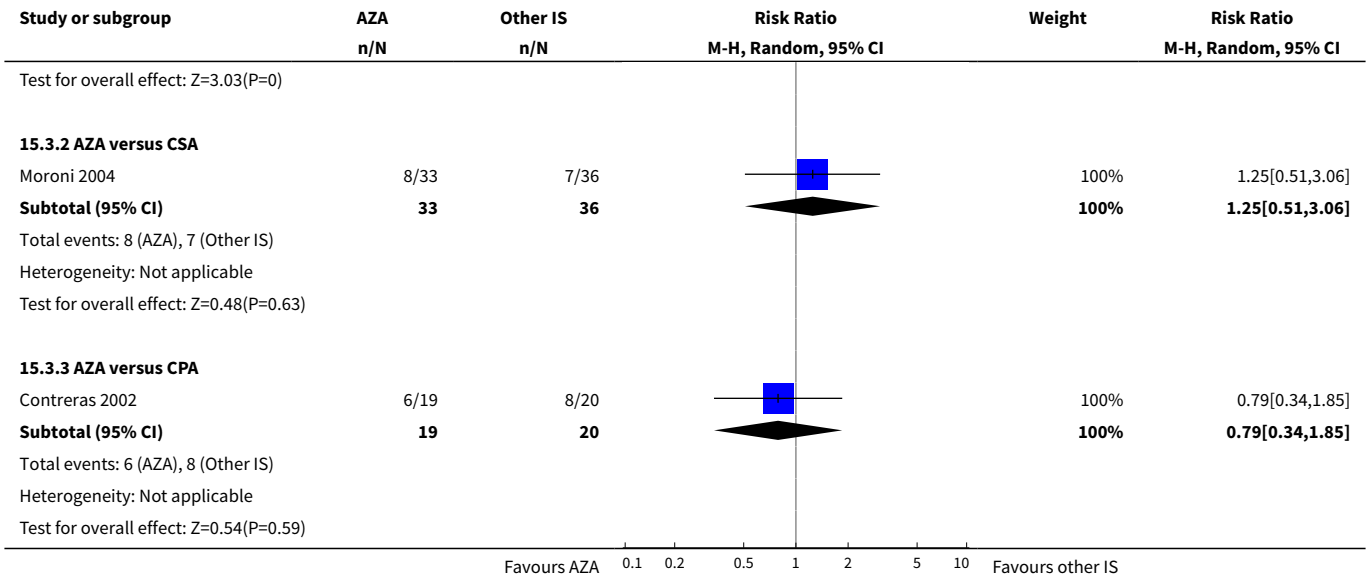


Analysis 15.2. Comparison 15 Maintenance therapy, Outcome 2 End-stage kidney disease.

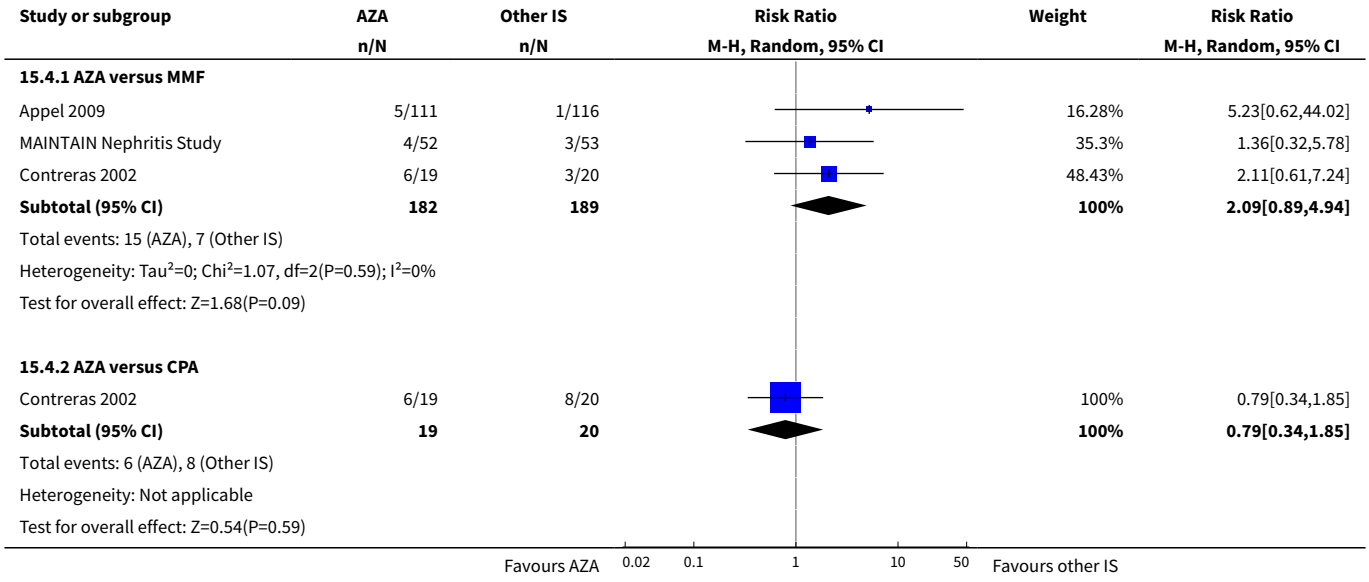


Analysis 15.3. Comparison 15 Maintenance therapy, Outcome 3 Renal relapse.

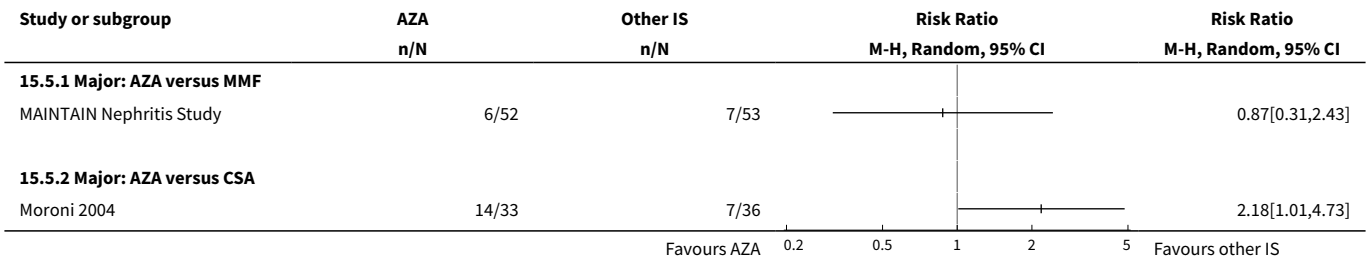


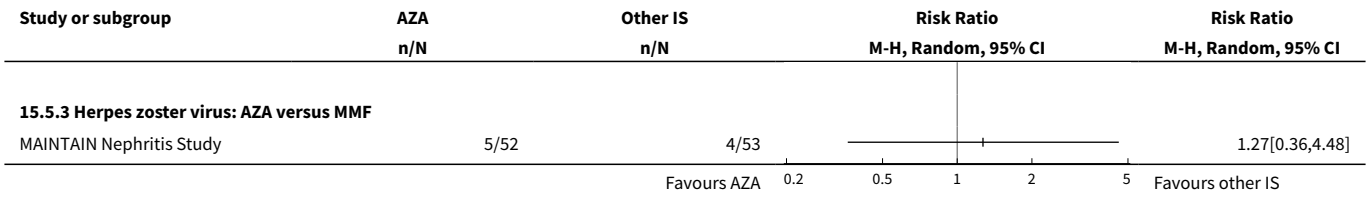


Analysis 15.4. Comparison 15 Maintenance therapy, Outcome 4 Doubling serum creatinine.

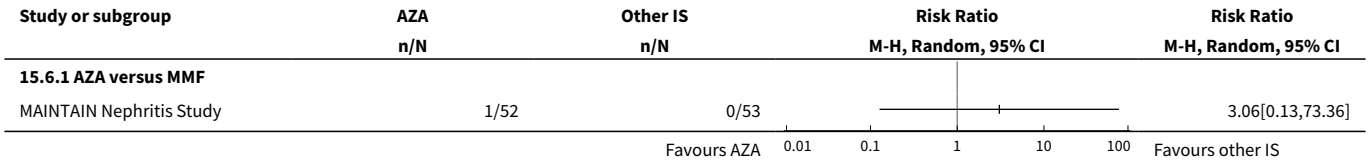


Analysis 15.5. Comparison 15 Maintenance therapy, Outcome 5 Infection.

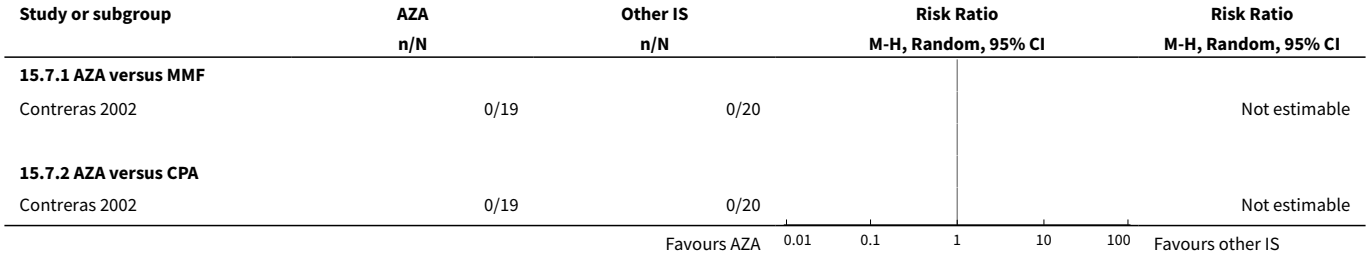




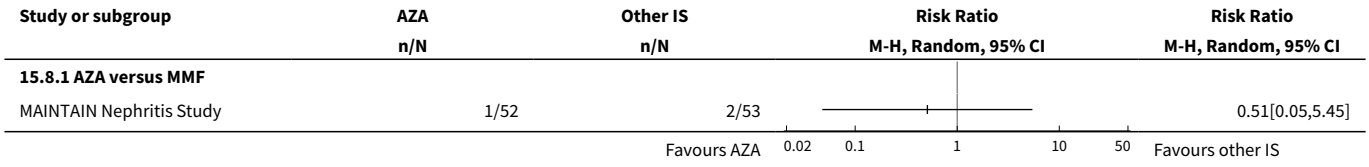
Analysis 15.6. Comparison 15 Maintenance therapy, Outcome 6 Bone toxicity.



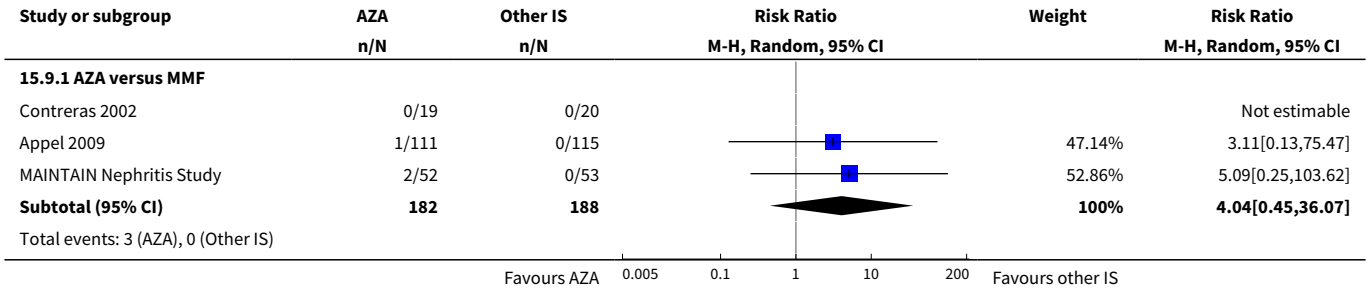
Analysis 15.7. Comparison 15 Maintenance therapy, Outcome 7 Bladder toxicity.

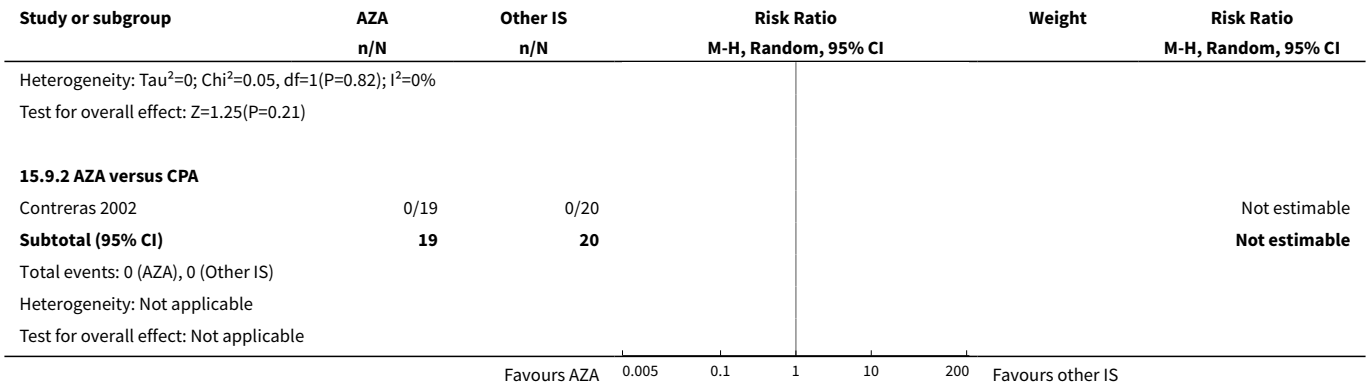


Analysis 15.8. Comparison 15 Maintenance therapy, Outcome 8 Alopecia.

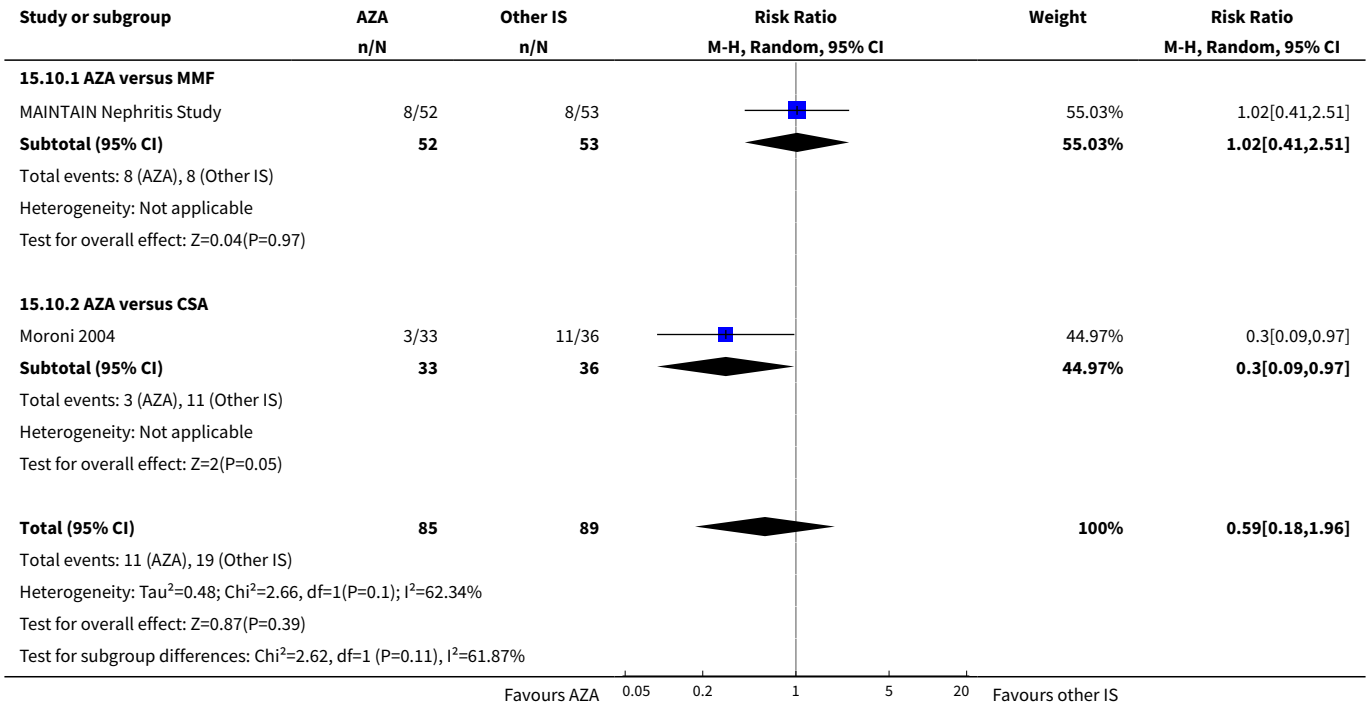


Analysis 15.9. Comparison 15 Maintenance therapy, Outcome 9 Malignancy.

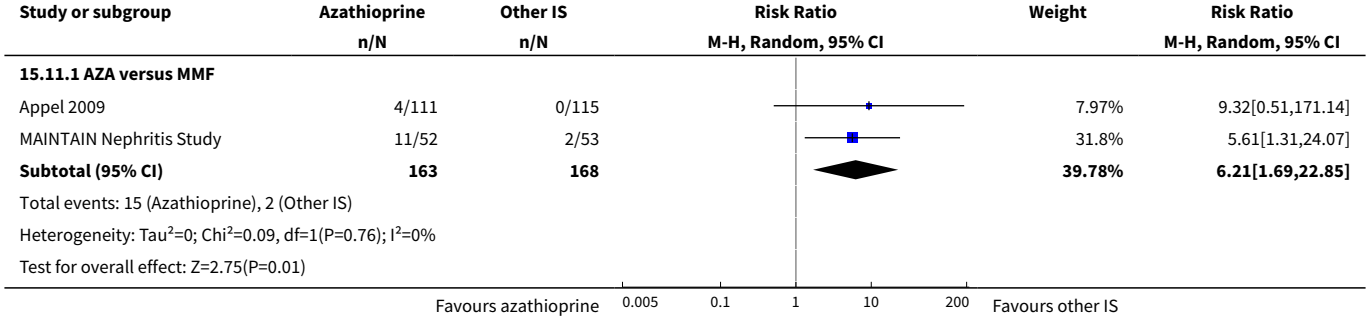


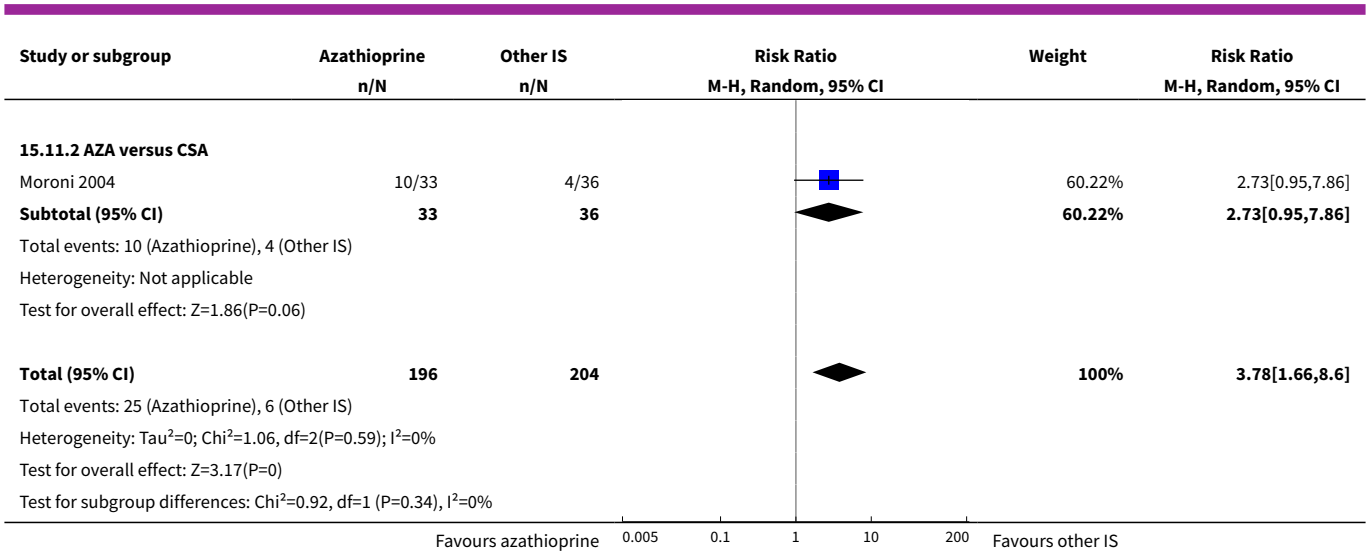


Analysis 15.10. Comparison 15 Maintenance therapy, Outcome 10 GI disturbance.

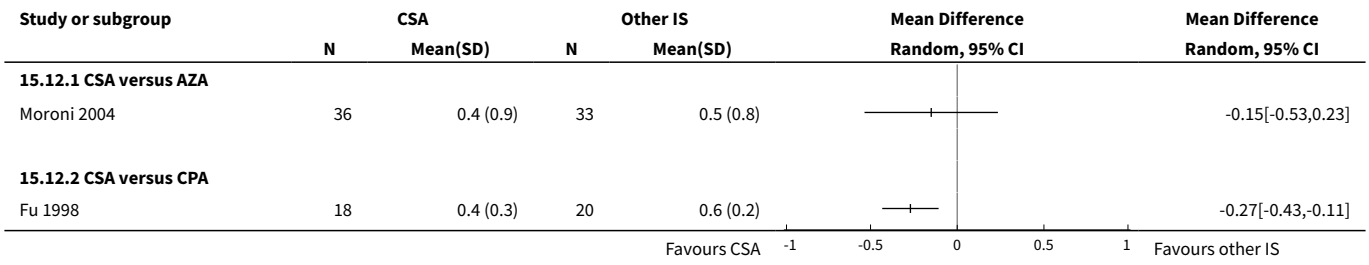


Analysis 15.11. Comparison 15 Maintenance therapy, Outcome 11 Leucopenia.

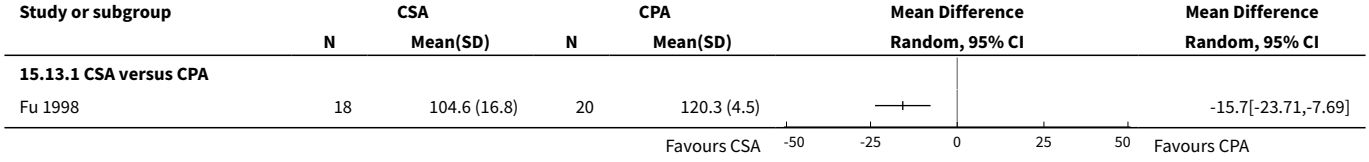




Analysis 15.12. Comparison 15 Maintenance therapy, Outcome 12 Daily proteinuria.



Analysis 15.13. Comparison 15 Maintenance therapy, Outcome 13 Creatinine clearance.



ADDITIONAL TABLES

Table 1. Induction therapy

Comparison	(n)	(N)	Outcome	Point estimate	[95% CI]	I^2
MMF versus other immunosuppression						
*MMF versus oral CPA	1	62	Mortality	0.19	[0.01, 3.76]	n/a
	1	62	ESKD	0.19	[0.01, 3.76]	n/a

Table 1. Induction therapy *(Continued)*

	1	62	Renal relapse	1.15	[0.55, 2.37]	n/a
	1	62	Doubling SCr	0.63	[0.11, 3.48]	n/a
	1	62	Infection	0.21	[0.05, 0.89]	n/a
	1	62	Herpes zoster virus	0.38	[0.08, 1.79]	n/a
	1	53	Ovarian failure	0.10	[0.01, 0.73]	n/a
	1	62	Bone toxicity	n/e	[0.00, 0.81]	n/a
	1	62	Alopecia	0.05	[0.00, 0.92]	n/a
	1	62	Leucopenia	0.06	[0.74, 1.30]	n/a
	1	62	CRP	0.98	[0.44, 2.59]	n/a
	1	62	PRP	1.07	[-0.19, 0.79]	n/a
	1	42	Proteinuria	0.30 (MD, g/d)		
*MMF versus IV CPA	7	710	Mortality	1.02	[0.52, 1.98]	0%
	3	231	ESKD	0.71	[0.27, 1.84]	0%
	1	140	Renal relapse	0.97	[0.39, 2.44]	n/a
	5	523	SKF	1.05	[0.94, 1.18]	0%
	6	683	Infection	1.11	[0.74, 1.68]	0%
	4	613	Herpes zoster virus	1.35	[0.71, 2.58]	0%
	2	498	Ovarian failure	0.15	[0.03, 0.80]	0%
	2	522	Alopecia	0.22	[0.06, 0.82]	33%
	1	364	Malignancy	0.65	[0.11, 3.86]	n/a
	3	569	Diarrhoea	2.53	[1.54, 4.16]	9%
	2	522	Vomiting	0.54	[0.24, 1.24]	86%
	1	158	Nausea	0.83	[0.52, 1.33]	n/a
	5	671	GI upset	0.87	[0.66, 1.13]	7%
	5	653	Leucopenia	0.49	[0.28, 0.88]	41%
	6	686	CRR	1.39	[0.99, 1.95]	15%
	6	686	PRR	1.04	[0.86, 1.25]	0%
	6	686	CRP	1.16	[0.85, 1.58]	39%
	4	602	PRP	1.06	[0.89, 1.25]	0%
	4	271	Proteinuria	-0.11 (MD, g/d)	[-0.64, 0.42]	63%
*MMF + TAC versus IV CPA	1	40	Mortality	n/e	[0.01, 7.72]	n/a
	1	40	Doubling SCr	0.33	[1.15, 2.60]	n/a
	1	40	SKF	1.73	[0.14, 1.73]	n/a
	1	40	Infection	0.50	[0.07, 14.90]	n/a

Table 1. Induction therapy *(Continued)*

	1	40	Herpes zoster virus	1.00	[0.29, 3.45]	n/a
	1	40	Ovarian failure	n/e	[0.07, 1.21]	n/a
	1	40	Alopecia	1.00	[0.10, 2.43]	n/a
	1	40	GI upset	0.29	[1.45, 12.91]	n/a
	1	40	Leucopenia	0.50	[0.47, 2.14]	n/a
	1	40	CRR	4.33	[1.45, 12.91]	n/a
	1	40	PRR	1.00	[0.32, 1.77]	n/a
	1	40	CRP	4.33	[-7.01, -4.77]	n/a
	1	40	PRP	0.75		
	1	40	Proteinuria	-5.89		
*MMF versus TAC	2	130	Mortality	1.87	[0.34, 10.44]	0%
	1	90	ESKD	0.96	[0.14, 6.5]	n/a
	1	90	Renal relapse	0.68	[0.34, 1.37]	n/a
	1	90	DKF	0.40	[0.15, 1.04]	n/a
	1	40	SKF	0.93	[0.64, 1.37]	n/a
	2	130	Infection	2.11	[0.92, 4.80]	0%
	1	40	Leucopenia	1.00	[0.07, 14.90]	n/a
	2	109	CRR	1.59	[0.58, 4.41]	70%
	2	130	CRR or PRR	0.96	[0.82, 1.13]	0%
	1	40	CRP	1.00	[0.50, 1.98]	n/a
	1	40	Proteinuria	0.79	[-0.44, 2.02]	n/a
	1	90	CrCl	8.40	[-4.62, 21.42]	n/a
Standard dose corticosteroids + mycophenolate sodium versus reduced dose corticosteroids + mycophenolate sodium	1	81	Mortality	4.65	[0.23, 93.95]	n/a
	1	81	CRR	1.06	[0.42, 2.65]	n/a
	1	81	PRR	1.43	[0.83, 2.47]	n/a
IV versus oral corticosteroids	1	22	Renal relapse	0.95	[0.44, 2.04]	n/a

Table 1. Induction therapy *(Continued)*

RTX + other immunosuppression versus MMF or RTX alone						
*RTX + MMF versus MMF	1	144	Mortality	5.00	[0.24, 102.3]	n/a
	1	144	Infection	1.00	[0.48, 2.08]	n/a
	1	144	Leucopenia	3.00	[0.85, 10.63]	n/a
	1	144	CRR	0.86	[0.51, 1.45]	n/a
	1	144	PRR	2.00	[1.05, 3.82]	n/a
	1	144	CRP	0.87	[0.63, 1.21]	n/a
*RTX + cyclophosphamide versus RTX	1	19	Infection	0.90	[0.07, 12.38]	n/a
	1	19	Daily proteinuria	-0.30 (MD, g/d)	[-2.29, 1.69]	n/a
	1	19	CrCl	17.20 (MD, mL/min)	[-50.6, 16.26]	n/a
	1	19	SCr	35.00 (MD, µmol/L)	[-27.1, 97.14]	n/a
CPA versus other immunosuppression						
*CPA versus azathioprine	2	146	5 year mortality	1.39	[0.25, 7.77]	67%
	1	59	10 year mortality	1.93	[1.22, 3.06]	n/a
	2	144	ESKD	0.40	[0.15, 1.07]	0%
	1	87	Renal relapse	0.15	[0.03, 0.64]	n/a
	2	144	Doubling SCr	0.48	[0.24, 0.95]	0%
	1	30	DKF	0.67	[0.18, 2.42]	n/a
	1	57	SKF	1.32	[0.86, 2.01]	n/a
	1	57	Infection	1.25	[0.27, 5.86]	n/a
	1	57	Herpes zoster virus	2.75	[0.68, 11.18]	n/a
	2	126	Ovarian failure	2.11	[0.59, 7.53]	34%
	1	87	Bone toxicity	n/e	[0.19, 66.14]	n/a
	2	144	Bladder toxicity	3.59	[0.13, 2.63]	n/a
	2	144	Malignancy	0.59	[0.64, 6.46]	n/a
	1	59	CRP	2.03	[0.67, 4.81]	n/a
	1	59	PRP	1.80		
*CPA versus TAC	2	113	Mortality	3.49	[0.94, 12.98]	0%
	2	65	SKF	0.76	[0.51, 1.15]	0%
	2	65	Infection	2.30	[0.79, 6.74]	0%
	1	73	Ovarian failure	5.71	[0.28, 115.04]	n/a
	1	73	Alopecia	8.00	[0.43, 149.56]	n/a

Table 1. Induction therapy *(Continued)*

	1	73	GI upset	2.87	[0.99, 8.31]	n/a
	2	113	Leucopenia	3.40	[0.26, 44.54]	42%
	3	138	CRR	0.72	[0.49, 1.06]	0%
	3	138	PRR	1.10	[0.72, 1.68]	0%
	2	65	CR in proteinuria	0.62	[0.32, 1.21]	0%
	1	40	Daily proteinuria	1.00 (MD, g/d)	[-0.11-2.11]	n/a
*CPA versus CSA	1	40	Mortality	n/e	[0.07, 14.72]	n/a
	1	34	Infection	1.00	[0.50, 18.76]	0%
	2	74	Herpes zoster virus	3.07	[0.03, 78.91]	9%
	2	74	Ovarian failure	9.0	[0.12, 63.19]	n/a
	1	40	Alopecia	2.73	[0.42, 43.95]	55%
	2	74	Leucopenia	4.29	[0.45, 0.97]	0%
	2	74	CRR	0.66	[0.20, 20.04]	n/a
	1	34	PRR	2.00	[-23.52, -1.88]	n/a
	1	40	SCr at 9 months	-12.7	[-16.9, 11.5]	n/a
	1	40	SCr at 18 months	-2.7	[0.29, 1.37]	n/a
	1	40	Daily proteinuria 9 months	0.83 (MD, g/d)	[-0.26, 2.26]	n/a
	1	40	Daily proteinuria 18 months	1.0 (MD, g/d)		
*IV versus oral CPA	2	67	Mortality	0.80	[0.20, 3.24]	34%
	2	67	ESKD	0.23	[0.04, 1.28]	0%
	2	67	Doubling SCr	0.67	[0.23, 1.98]	0%
	1	38	DKF	0.72	[0.23, 2.27]	n/a
	1	38	SKF	1.11	[0.77, 1.59]	n/a
	2	67	Infection	1.16	[0.47, 2.90]	0%
	1	38	Herpes zoster virus	0.75	[0.28, 2.04]	n/a
	2	56	Ovarian failure	0.70	[0.37, 1.30]	0%
	2	67	Bladder toxicity	0.22	[0.03, 1.83]	0%
	2	67	Malignancy	1.43	[0.41, 4.96]	0%
	1	29	GI upset	3.69	[0.43, 31.43]	n/a
*High versus low dose CPA	1	117	6 month mortality	1.81	[0.19, 16.85]	n/a
	1	85	5 year mortality	0.13	[0.01, 2.51]	n/a
	1	90	10 year mortality	0.38	[0.08, 1.87]	n/a
	1	85	ESKD at 5 years	2.80	[0.30, 25.81]	n/a
	1	90	ESKD at 10 years	1.91	[0.37, 9.92]	n/a

Table 1. Induction therapy *(Continued)*

	2	136	Renal relapse	1.30	[0.35, 4.85]	27%
	1	85	Doubling SCr at 6 years	0.13	[0.02, 1.04]	n/a
	1	90	Doubling SCr at 10 years	0.80	[0.26, 2.42]	n/a
	1	89	SKF at 3 years	0.72	[0.50, 1.03]	n/a
	1	85	SKF at 5 years	0.96	[0.77, 1.20]	n/a
	3	252	Infection	1.54	[0.73, 3.25]	42%
	1	89	Herpes zoster virus	2.44	[0.50, 11.94]	n/a
	3	252	Ovarian failure	2.18	[1.03, 4.59]	0%
	1	89	Bone toxicity	2.93	[0.12, 70.16]	n/a
	2	206	Malignancy	1.44	[0.09, 23.31]	41%
	2	206	Leucopenia	1.41	[0.34, 5.95]	0%
	2	192	CRR	1.44	[0.94, 2.20]	n/a
	2	192	PRR	0.89	[0.69, 1.15]	n/a
	2	121	Daily proteinuria	0.13 (MD, g/d)	[-1.06, 1.32]	81%
	2	130	SCr	0.00 (MD, µmol/L)	[-0.50, 0.50]	0%
*Long versus short duration CPA	1	40	ESKD	0.40	[0.09, 1.83]	n/a
	1	40	Doubling SCr	0.43	[0.13, 1.43]	n/a
	1	40	DKF	0.43	[0.13, 1.43]	n/a
	1	40	SKF	1.31	[0.90, 1.89]	n/a
	1	40	Infection	1.00	[0.07, 14.90]	n/a
	1	40	Herpes zoster virus	0.50	[0.05, 5.08]	n/a
	1	29	Ovarian failure	2.05	[0.60, 7.02]	n/a
	1	40	Bone toxicity	1.33	[0.34, 5.21]	n/a
	1	40	Malignancy	3.00	[0.13, 69.52]	n/a
Immunosuppressive agent plus corticosteroids versus corticosteroids alone						
CPA + corticosteroids versus corticosteroids alone	5	226	Mortality	0.98	[0.53, 1.82]	10%
	5	278	ESKD	0.63	[0.39, 1.03]	0%
	1	42	Renal relapse	0.30	[0.10, 0.94]	n/a
	4	228	Doubling SCr	0.59	[0.40, 0.88]	0%
	5	179	DKF	0.78	[0.52, 1.18]	0%
	5	278	SKF	1.20	[1.00, 1.45]	0%
	6	291	Infection	0.87	[0.50, 1.51]	0%
	3	199	Herpes zoster virus	1.77	[0.63, 4.99]	37%

Table 1. Induction therapy *(Continued)*

	3	147	Ovarian failure	2.18	[1.10, 4.34]	12%
	3	197	Bone toxicity	0.84	[0.40, 1.75]	0%
	2	65	Bladder toxicity	2.66	[0.33, 21.68]	0%
	2	117	Malignancy	0.82	[0.07, 9.90]	26%
	1	13	CRP	2.63	[0.13, 54.64]	n/a
	3	92	Proteinuria	0.15 (MD, g/d)	[-0.23, 0.54]	0%
	1	29	SCr	-52.00 (MD, µmol/L)	[-111.39, 7.39]	n/a
	2	63	CrCl	12.23 (MD, mL/min)	[-0.13, 24.58]	n/a
CPA + AZA versus corticosteroids alone	1	29	Mortality	0.53	[0.17, 1.68]	n/a
	1	29	ESKD	0.21	[0.04, 1.02]	n/a
	1	29	Doubling SCr	0.16	[0.04, 0.69]	n/a
	1	29	SKF	1.59	[0.83, 3.06]	n/a
	1	29	Infection	0.48	[0.10, 2.30]	n/a
	1	29	Herpes zoster virus	5.22	[0.33, 81.40]	n/a
	1	27	Ovarian failure	7.32	[0.49, 108.96]	n/a
	1	29	Bladder toxicity	2.43	[0.14, 42.17]	n/a
AZA + corticosteroids versus corticosteroids alone	3	78	Mortality	0.60	[0.36, 0.99]	0%
	2	54	ESKD	0.66	[0.17, 2.55]	50%
	1	16	Renal relapse	0.78	[0.22, 2.74]	n/a
	1	26	Doubling SCr	0.98	[0.36, 2.68]	n/a
	1	26	SKF	1.01	[0.48, 2.14]	n/a
	4	94	Infection	1.06	[0.56, 2.01]	0%
	2	42	Herpes zoster virus	3.56	[0.46, 27.79]	0%
	1	24	Ovarian failure	2.58	[0.15, 43.86]	n/a
	1	24	Bone toxicity	3.55	[0.43, 29.42]	n/a
	1	26	Malignancy	2.00	[0.11, 37.22]	n/a
	2	37	CRP	0.95	[0.54, 1.69]	2%
	1	24	CrCl	5.00 (MD, mL/min)	[-3.14, 13.14]	n/a
CSA + corticosteroids versus corticosteroids alone	1	10	Daily proteinuria	-1.80 (MD, g/24 h)	[-2.59, -1.01]	n/a
	1	10	SCr		[-73.63, 9.83]	n/a
	1	10	CrCl	-31.90 (MD, µmol/L)	[-85.02, 0.02]	n/a

Table 1. Induction therapy *(Continued)*

				-42.50 (MD, mL/min)		
PEX + immunosuppression versus immunosuppression alone	2	125	Mortality	1.62	[0.64, 4.09]	0%
	3	143	ESKD	1.24	[0.60, 2.57]	0%
	2	51	Doubling SCr	0.17	[0.02, 1.26]	0%
	2	57	DKF	0.53	[0.06, 4.83]	0%
	3	75	SKF	1.10	[0.94, 1.30]	0%
	2	125	Infection	0.69	[0.35, 1.37]	0%
	2	104	Herpes zoster virus	1.69	[0.10, 29.42]	41%
	2	30	Daily proteinuria	-0.56 (MD, g/d)	[-5.23, 4.11]	0%
	3	69	SCr	-17.90 (MD, µmol/L)	[-23.41, -12.39]	0%
	1	12	CrCl	26.00 (MD, mL/min)	[-17.60, 69.60]	n/a
PEX (no immunosuppression) versus immunosuppression	1	20	ESKD	0.24	[0.01, 4.44]	n/a
	1	20	Infection	0.40	[0.02, 8.78]	n/a

AZA - azathioprine; CI - confidence interval; CR - complete remission; CPA - cyclophosphamide; CRP - complete remission in proteinuria; CRR - complete renal remission; CSA - cyclosporin A; CrCl - creatinine clearance; DKF - doubling of kidney function; ESKD - end-stage kidney disease; GI - gastrointestinal; MD - mean difference; MMF - mycophenolate mofetil; N - number of studies; n - number of participants; n/a - not applicable; n/e - not estimable; PEX - plasma exchange; PR - partial remission; PRP - partial remission in proteinuria (daily); PRR - partial renal remission; RTX - rituximab; SCr - serum creatinine; SKF - stable kidney function; TAC - tacrolimus
* Denotes both arms included corticosteroids

Table 2. Maintenance therapy

Comparison	(n)	(N)	Outcome	Point estimate	[95% CI]	I^2
AZA versus MMF	3	371	Mortality	0.58	[0.10, 3.49]	0%
	3	371	ESKD	1.86	[0.37, 9.31]	0%
	3	371	Renal relapse	1.83	[1.24, 2.71]	0%
	3	371	Doubling SCr	2.09	[0.89, 4.94]	0%
	1	105	Infection	0.87	[0.31, 2.43]	n/a
	1	105	Herpes zoster virus	1.27	[0.36, 4.48]	n/a
	1	105	Bone toxicity	3.06	[0.13, 73.36]	n/a
	1	39	Bladder toxicity	n/e	[0.05, 5.45]	n/a
	1	105	Alopecia	0.51	[0.45, 36.07]	0%

Table 2. Maintenance therapy *(Continued)*

	3	370	Malignancy	4.04	[0.41, 2.51]	n/a
	1	105	GI disturbance	1.02	[1.69, 22.85]	0%
	2	331	Leucopenia	6.21		
AZA versus CSA	1	69	Mortality	n/e	[0.51, 3.06]	n/a
	1	69	ESKD	n/e	[1.01, 4.73]	n/a
	1	69	Renal relapse	1.25	[0.09, 0.97]	n/a
	1	69	Infection	2.18	[0.95, 7.86]	n/a
	1	69	GI disturbance	0.30		
	1	69	Leucopenia	2.73		
AZA versus CPA	1	39	Mortality	0.12	[0.01, 2.03]	n/a
	1	39	ESKD	0.35	[0.04, 3.09]	n/a
	1	39	Renal relapse	0.79	[0.34, 1.85]	n/a
	1	39	Doubling SCr	0.79	[0.34, 1.85]	n/a
	1	39	Bladder toxicity	n/e		
	1	39	Malignancy	n/e		

AZA - azathioprine; CI - confidence interval; CPA - cyclophosphamide; CSA - cyclosporin; ESKD - end-stage kidney disease; GI - gastrointestinal; MMF - mycophenolate mofetil; n - number of studies; N - number of participants; n/a - not applicable; n/e - not estimable; SCr - serum creatinine
*Denotes both arms included corticosteroids

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
MEDLINE	1. Lupus Nephritis/ 2. lupus nephritis.tw 3. or/1-2
CENTRAL	1. MeSH descriptor Lupus Nephritis, this term only 2. (lupus):ti,ab,kw in Clinical Trials 3. (#1 OR #2)
EMBASE	1. exp Lupus Erythematosus Nephritis/ 2. lupus nephritis.tw. 3. or/1-2

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

(Continued)

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

WHAT'S NEW

Date	Event	Description
7 November 2012	New search has been performed	Review updated; 25 new studies added
7 November 2012	New citation required and conclusions have changed	New studies, interventions and authors

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 1, 2004

Date	Event	Description
15 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

The work of this review update has been in the main conducted by Lorna Henderson and Philip Masson.

Each author individually contributed the following:

- Lorna Henderson: Conduct data analysis, author
- Philip Masson: Conduct data analysis, author
- Angela Webster: Data analysis, reading drafts and co-author
- Jonathan Craig: Reading drafts and co-author
- Robert Flanc: Original design and author
- Matthew Roberts: Original design and author
- Giovanni FM Strippoli: Original design and author

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Cochrane Renal Group, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced quality assessment checklist.

INDEX TERMS

Medical Subject Headings (MeSH)

Azathioprine [adverse effects] [therapeutic use]; Calcineurin [therapeutic use]; Cyclophosphamide [adverse effects] [*therapeutic use]; Glucocorticoids [adverse effects] [therapeutic use]; Immunosuppressive Agents [adverse effects] [*therapeutic use]; Induction Chemotherapy [methods]; Lupus Nephritis [*drug therapy]; Maintenance Chemotherapy [methods]; Mycophenolic Acid [*analogs & derivatives] [therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Tacrolimus [adverse effects] [therapeutic use]

MeSH check words

Adult; Child; Female; Humans; Male