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Immunosuppressive treatment for proliferative lupus nephritis (Review)

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[Intervention Review]

Immunosuppressive treatment for proliferative lupus nephritis

David J Tunnicliffe[1,2], Suetonia C Palmer[3], Lorna Henderson[4], Philip Masson[5], Jonathan C Craig[1,6,7], Allison Tong[1,2], Davinder Singh-Grewal[8], Robert S Flanc[9], Matthew A Roberts[10], Angela C Webster[1,6,11], Giovanni FM Strippoli[1,6,12,13,14]

[1]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [2]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [3]Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand. [4]Renal Department, NHS Lothian, Edinburgh, UK. [5]Department of Renal Medicine, Royal Free London NHS Foundation Trust, London, UK. [6]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [7]College of Medicine and Public Health, Flinders University, Adelaide, Australia. [8]Department Paediatric Rheumatology, The Sydney Children's Hospitals Network, Westmead, Australia. [9]Department of Nephrology, Monash Medical Centre, Clayton, Australia. [10]Eastern Health Clinical School, Monash University, Box Hill, Australia. [11]Centre for Transplant and Renal Research, Westmead Millennium Institute, The University of Sydney at Westmead, Westmead, Australia. [12]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [13]Medical Scientific Office, Diaverum, Lund, Sweden. [14]Diaverum Academy, Bari, Italy

Contact address: David J Tunnicliffe, Sydney School of Public Health, The University of Sydney, c/- Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, 2145, Australia. david.tunnicliffe@health.nsw.gov.au.

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ABSTRACT

Background

Cyclophosphamide, in combination with corticosteroids, has been first-line treatment for inducing disease remission for proliferative lupus nephritis, reducing death at five years from over 50% in the 1950s and 1960s to less than 10% in recent years. Several treatment strategies designed to improve remission rates and minimise toxicity have become available. Treatments, including mycophenolate mofetil (MMF) and calcineurin inhibitors, alone and in combination, may have equivalent or improved rates of remission, lower toxicity (less alopecia and ovarian failure) and uncertain effects on death, end-stage kidney disease (ESKD) and infection. This is an update of a Cochrane review first published in 2004 and updated in 2012.

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) Which agents, dosages, routes of administration and duration of therapy should be used? 3) Which toxicities occur with the different treatment regimens?

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register up to 2 March 2018 with support from the Cochrane Information Specialist using search terms relevant to this review. Studies in the Specialised Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs comparing any immunosuppressive treatment for biopsy-proven class III, IV, V+III and V+VI lupus nephritis in adult or paediatric patients were included.

Data collection and analysis

Data were abstracted and the risks of bias were assessed independently by two authors. Dichotomous outcomes were calculated as risk ratio (RR) and measures on continuous scales calculated as mean differences (MD) with 95% confidence intervals (CI). The primary outcomes were death (all causes) and complete disease remission for induction therapy and disease relapse for maintenance therapy. Evidence certainty was determined using GRADE.

Main results

In this review update, 26 new studies were identified, to include 74 studies involving 5175 participants overall. Twenty-nine studies included children under the age of 18 years with lupus nephritis, however only two studies exclusively examined the treatment of lupus nephritis in patients less than 18 years of age.

Induction therapy

Sixty-seven studies (4791 participants; median 12 months duration (range 2.5 to 48 months)) reported induction therapy. The effects of all treatment strategies on death (all causes) and ESKD were uncertain (very low certainty evidence) as this outcome occurred very infrequently. Compared with intravenous (IV) cyclophosphamide, MMF may have increased complete disease remission (RR 1.17, 95% CI 0.97 to 1.42; low certainty evidence), although the range of effects includes the possibility of little or no difference.

Compared to IV cyclophosphamide, MMF is probably associated with decreased alopecia (RR 0.29, 95% CI 0.19 to 0.46; 170 less (129 less to 194 less) per 1000 people) (moderate certainty evidence), increased diarrhoea (RR 2.42, 95% CI 1.64 to 3.58; 142 more (64 more to 257 more) per 1000 people) (moderate certainty evidence) and may have made little or no difference to major infection (RR 1.02, 95% CI 0.67 to 1.54; 2 less (38 less to 62 more) per 1000 people) (low certainty evidence). It is uncertain if MMF decreased ovarian failure compared to IV cyclophosphamide because the certainty of the evidence was very low (RR 0.36, 95% CI 0.06 to 2.18; 26 less (39 less to 49 more) per 1000 people). Studies were not generally designed to measure ESKD.

MMF combined with tacrolimus may have increased complete disease remission (RR 2.38, 95% CI 1.07 to 5.30; 336 more (17 to 1048 more) per 1000 people (low certainty evidence) compared with IV cyclophosphamide, however the effects on alopecia, diarrhoea, ovarian failure, and major infection remain uncertain. Compared to standard of care, the effects of biologics on most outcomes were uncertain because of low to very low certainty of evidence.

Maintenance therapy

Nine studies (767 participants; median 30 months duration (range 6 to 63 months)) reported maintenance therapy. In maintenance therapy, disease relapse is probably increased with azathioprine compared with MMF (RR 1.75, 95% CI 1.20 to 2.55; 114 more (30 to 236 more) per 1000 people (moderate certainty evidence). Multiple other interventions were compared as maintenance therapy, but patient-outcome data were sparse leading to imprecise estimates.

Authors' conclusions

In this review update, studies assessing treatment for proliferative lupus nephritis were not designed to assess death (all causes) or ESKD. MMF may lead to increased complete disease remission compared with IV cyclophosphamide, with an acceptable adverse event profile, although evidence certainty was low and included the possibility of no difference. Calcineurin combined with lower dose MMF may improve induction of disease remission compared with IV cyclophosphamide, but the comparative safety profile of these therapies is uncertain. Azathioprine may increase disease relapse as maintenance therapy compared with MMF.

PLAIN LANGUAGE SUMMARY

Immunosuppressive treatment for people with proliferative lupus nephritis

What is the issue?

In lupus, the body’s immune system for fighting infection attacks different parts of the body, including the kidneys. About half of all people with lupus have kidney problems. An estimated one in every 10 people who have lupus kidney disease (lupus nephritis) can develop kidney failure. The goal of treatment is to protect kidney function and avoid side-effects.

While the life expectancy of patients who have lupus has dramatically improved, available treatments can cause serious side effects such as hair loss, serious infection, and infertility. It is important to know about which treatments help to treat lupus while causing the fewest side-effects.

What did we do?

We searched the Cochrane Kidney and Transplant Specialised Register up to 2 March 2018 and we combined all studies testing treatments aimed to control the body’s immune system for lupus nephritis.

What did we find?

In this review update, 74 studies involving 5175 patients with lupus nephritis could be studied. Treatments included intravenous (given through a vein) cyclophosphamide, oral (tablets by mouth) mycophenolate mofetil (MMF), azathioprine, and tacrolimus (used alone or together with MMF). We also found studies of treatments called "biologic" therapies, that have been designed to change very specific parts of the body's immune system that cause it to attack itself. We looked particularly at key outcomes such as whether treatment prevented patients from needing dialysis and controlled the lupus damage to the kidney tissue (called remission). We also looked at serious side-effects including death, infection, infertility, and hair loss.

After combining the available studies, compared with cyclophosphamide, MMF may be better at getting the lupus damage to the kidneys under control. However, the range where the actual effect may suggest that MMF may make little or no difference to disease remission compared to treatment with cyclophosphamide. MMF treatment given with tacrolimus may lead to more disease remission. MMF may result in less hair loss and worse diarrhoea, but we were not certain whether MMF reduces infertility or other serious side effects. MMF was better than azathioprine for preventing kidney disease in the longer term. None of the studies told us whether treatment had any effect on death or need for dialysis, and there was very low certainty of evidence for the use of biologics in patients with lupus nephritis.

Conclusions

Patients with lupus nephritis may have similar or slightly better outcomes when treated with MMF or MMF with tacrolimus compared to those patients who receive intravenous cyclophosphamide. We are still not certain which is the best treatment for lupus nephritis to protect against needing dialysis in the longer term.

Summary of findings for the main comparison. Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA) for induction therapy

Patient or population: patients with induction therapy in lupus nephritis
Settings: all settings
Intervention: MMF
Comparison: IV CPA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IV CPA	MMF				
Death Follow-up: mean 24 weeks	**40 per 1000**	**53 per 1000** (29 to 98)	**RR 1.12** (0.61 to 2.06)	826 (8)	⊕⊖⊖⊖ very low[1,2,3]	Downgraded as follows: [1] Indirectness: time frame insufficient [2] Total number of events small [3] Severe imprecision (2 grades): risk estimate includes null effect and estimate consistent with both appreciable benefit and harm
ESKD Follow-up: mean 32 weeks	**85 per 1000**	**61 per 1000** (23 to 157)	**RR 0.71** (0.27 to 1.84)	231 (3)	⊕⊖⊖⊖ very low[1,2,3]	Downgraded as follows: [1] Indirectness: time frame insufficient [2] Total number of events small [3] Severe imprecision (2 grades): risk estimate includes null effect and estimate consistent with both appreciable benefit and harm
Complete renal remission Follow-up: mean 24 weeks	**222 per 1000**	**260 per 1000** (216 to 316)	**RR 1.17** (0.97 to 1.42)	828 (8)	⊕⊕⊖⊖ low[1,2,3]	Downgraded as follows: [1] Study limitations [2] Total number of events small

						[3] Imprecision (2 grades): risk estimate includes null effect and estimate consistent with both appreciable benefit and harm
Partial renal remission Follow-up: mean 24 weeks	**415 per 1000**	**423 per 1000** (369 to 490)	**RR 1.02** (0.89 to 1.18)	868 (9)	⊕⊕⊖⊖ low[1,2]	Downgraded as follows: [1] Study limitations [2] Serious indirectness: differences in the outcome definition between studies.
Ovarian failure	**41 per 1000**	**15 per 1000** (2 to 90)	**RR 0.36** (0.06 to 2.18)	539 (3)	⊕⊖⊖⊖ very low[1,2,3]	Downgraded as follows: [1] Study limitations [2] Severe heterogeneity: point estimates varied widely [3] Total number of events small [4] Severe imprecision (2 grades): risk estimate includes null effect and estimate consistent with both appreciable benefit and harm
Major infection Follow-up: mean 24 weeks	**114 per 1000**	**116 per 1000** (76 to 175)	**RR 1.02** (0.67 to 1.54)	699 (6)	⊕⊕⊖⊖ low[1,2]	Downgraded as follows: [1] Study limitations [2] Total number of events small [3] Severe imprecision (2 grades): risk estimate includes null effect and estimate consistent with both appreciable benefit and harm
Alopecia Follow-up: mean 24 weeks	**239 per 1000**	**69 per 1000** (45 to 110)	**RR 0.29** (0.19 to 0.46)	622 (3)	⊕⊕⊕⊖ moderate[1,2,3]	Downgraded as follows: [1] Study limitations [2] Total number of events small Upgraded as follows: [3] Large magnitude of effect
Diarrhoea Follow-up: mean 24 weeks	**100 per 1000**	**241 per 1000** (163 to 357)	**RR 2.42** (1.64 to 3.58)	609 (4)	⊕⊕⊕⊖ moderate[1,2,3]	Downgraded as follows: [1] Study limitations [2] Total number of events small

Upgraded as follows

[3] Large magnitude of effect

*The basis for the **assumed risk** for partial renal remission was prognostic studies (Fernandes das Neves 2015; Moroni 2007; So 2011; Zakharova 2016); and the assumed risk for other outcomes was calculated using the median control group risk across studies in the meta-analysis. 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 certainty of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: 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 certainty: We are very uncertain about the effect estimate

Summary of findings 2. Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA) for induction therapy

MMF + TAC compared with IV CPA for lupus nephritis

Patient or population: Patients with proliferative lupus nephritis

Settings: all settings

Intervention: MMF + TAC

Comparison: IV CPA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IV CPA	MMF + TAC				
Complete renal remission follow-up: mean 24 weeks	**244 per 1000**	**580 per 1000** (261 to 1000)	**RR 2.38** (1.07 to 5.30)	402 (2)	⊕⊕⊖⊖ low[1,2,3,4]	Downgraded as follows: [1]Study limitation: concern regarding the incomplete reporting of IV CPA group [2]Heterogeneity: substantial heterogeneity indicated by I^2 statistic. Although Chi^2 test was satisfied, the small number of studies may make this unreliable.

						[3]Indirectness: Concern regarding the population, as all studies have largely included patients of Asian ethnicity. Upgraded as follows: [4]Large effect size
Partial renal remission follow-up: mean 24 weeks	**378 per 1000**	**378 per 1000** (295 to 484)	**RR 1.00** (0.78 to 1.28)	402 (2)	⊕⊕⊖⊖ low[1,2]	Downgraded as follows: [1]Study limitation: concern regarding the incomplete reporting of IV CPA group [2] Indirectness: differences in the outcome definition between studies and concern regarding the population, as all studies have largely included patients of Asian ethnicity.
Stable kidney function follow-up: mean 24 weeks	**284 per 1000**	**505 per 1000** (397 to 641)	**RR 1.78** (1.40 to 2.26)	402 (2)	⊕⊕⊖⊖ low[1,2,3,4]	Downgraded as follows: [1]Study limitation: concern regarding the incomplete reporting of IV CPA group [2] Indirectness (2 grades): differences in the outcome definition between studies and concern regarding the population, as all studies have largely included patients of Asian ethnicity. [3]Total number of events small Upgraded as follows: [4]Large effect size

*The basis for the **assumed risk** was calculated using the median control group risk across studies in the meta-analyses. 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 **certainty** of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: 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 certainty: We are very uncertain about the estimate.

Summary of findings 3. Azathioprine (AZA) versus mycophenolate mofetil (MMF) for maintenance therapy

Patient or population: patients with maintenance treatment in lupus nephritis
Settings: all settings
Intervention: AZA
Comparison: MMF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	MMF	AZA				
Death Follow-up: 36 to 72 months	**22 per 1000**	**25 per 1000** (7 to 84)	**RR 1.15** (0.34 to 3.87)	451 (4)	⊕⊝⊝⊝ Very low[1,2,3]	Downgraded as follows: [1]Total number of events small [2]Severe imprecision (2 grades): risk estimate includes null effect and estimate consistent with both appreciable benefit and harm [3]Indirectness: time frame insufficient
ESKD Follow-up: 36 to 72 months	**17 per 1000**	**30 per 1000** (9 to 96)	**RR 1.70** (0.52 to 5.54)	452 (4)	⊕⊝⊝⊝ Very low[1,2,3]	Downgraded as follows: [1]Total number of events small [2]Severe imprecision (2 grades): risk estimate includes null effect and estimate consistent with both appreciable benefit and harm [3]Indirectness: time frame insufficient
Renal relapse Follow-up: 36 to 72 months	**152 per 1000**	**266 per 1000** (183 to 388)	**RR 1.75** (1.20 to 2.55)	452 (4)	⊕⊕⊕⊝ moderate[1]	Downgraded as follows: [1] Total number of events small
Doubling of serum creatinine Follow-up: 36 to 72 months	**39 per 1000**	**86 per 1000** (40 to 182)	**RR 2.19** (1.03 to 4.66)	452 (4)	⊕⊕⊝⊝ low[1,2]	Downgraded as follows: [1] Study limitations: (studies generally at unclear or high risk of bias for many domains) [2]Total number of events small

Major infection Follow-up: median 53 months	**91 per 1000**	**98 per 1000** (55 to 178)	**RR 1.08** (0.69 to 1.96)	412 (3)	⊕⊕⊖⊖ low[1,2]	Downgraded as follows: [1] Total number of events small [2] Imprecision: wide risk estimate includes null effect
Leucopenia Follow-up: 36 to 53 months	**10 per 1000**	**54 per 1000** (16 to 179)	**RR 5.61** (1.68 to 18.72)	412 (3)	⊕⊕⊖⊖ low[1,2]	Downgraded as follows: [1]Study limitations: (studies generally at unclear or high risk of bias for many domains) [2] Imprecision: wide risk estimates
Alopecia Follow-up: median 53 months	**67 per 1000**	**64 per 1000** (31 to 131)	**RR 0.95** (0.46 to 1.95)	412 (3)	⊕⊕⊖⊖ low[1,2]	Downgraded as follows: [1]Study limitations: (studies generally at unclear or high risk of bias for many domains) [2] Total number of events small

*The basis for the **assumed risk** for other outcomes was calculated using the median control group risk across studies in the meta-analysis. 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 **certainty** of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: 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 certainty: We are very uncertain about the estimate

BACKGROUND

Description of the condition

Lupus nephritis occurs in about 20% to 75% of all people with systemic lupus erythematosus (SLE) (Cervera 2009), leading to end-stage kidney disease (ESKD) in 10% to 17% of patients at 10 years (Houssiau 2010; Tektonidou 2016). Predominantly affecting young women, lupus nephritis is also more common in certain ethnic minority groups, particularly among African-Americans and Hispanics who may also have a more aggressive form of the disease that is less responsive to treatment (Hanly 2016; Korbet 2007; Sexton 2014).

Kidney involvement ranges from mild subclinical disease, which is associated with favourable outcomes and a low chance of progression to ESKD, to severe nephritic and/or nephrotic syndrome with kidney impairment and greater risk of progression to ESKD. In the United States of America, and Australia and New Zealand, approximately 1% of patients commencing dialysis had ESKD as a consequence of lupus nephritis (ANZDATA 2016; Costenbader 2011). Patients with SLE and active lupus nephritis have reduced health-related quality of life (Daleboudt 2011; McElhone 2006; Vu 1999). Fatigue is a frequent symptom and often identified as the most disrupting aspect of the disease in patients with lupus nephritis (Daleboudt 2011; Tench 2000), as it can limit their capacity to participate in the workforce, family, and social activities (Sutanto 2013).

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). The ISN/RPS 2003 Class I and II lesions have a good prognosis and are generally not an indication for specific therapy, although some guidelines recommend therapy for people with WHO Class II lupus nephritis and proteinuria (> 2 g/d) (Tunnicliffe 2015). Proliferative disease (WHO Class III, IV, V +III and V+IV; ISN/RPS 2003 Class III (A) and (A/C), Class IV-G and IV-S, and Class III or IV in combination with Class V) is usually symptomatic, more fulminant, and requires treatment to induce remission and prevent significant kidney injury and premature death. Active proliferative (WHO Class IV) lupus nephritis is the most aggressive form of the condition, and has the worst prognosis without intensive immunosuppressive treatment.

Description of the intervention

Immunosuppressive therapy in the management of proliferative lupus nephritis aims to induce and maintain disease remission, in order to maximise patient and renal survival while minimising complications or treatment related adverse effects. The induction phase of therapy usually lasts six to 12 months. Common immunosuppressive agents in induction therapy include corticosteroid and an anti-proliferative agent such as cyclophosphamide, mycophenolate mofetil (MMF), or azathioprine. Less commonly used treatments that are added to corticosteroids include tacrolimus, cyclosporin, plasma exchange or plasmapheresis, or a biologic therapy such as rituximab. Intravenous (IV) cyclophosphamide in combination with corticosteroids became standard of care therapy for inducing remission based on a landmark National Institutes of Health (NIH) trial that showed cyclophosphamide was superior over corticosteroids alone in preventing renal flares and kidney failure (Decker 1975). A meta-analysis (Bansal 1997) and our earlier systematic review (Flanc 2004a) identified that the addition of an immunosuppressant to corticosteroids was superior to corticosteroids alone in managing proliferative lupus nephritis. Subsequently, low-dose cyclophosphamide (Euro-lupus regimen) has been reported to have equivalent efficacy to the NIH protocol (Houssiau 2002). The dose of corticosteroid is tapered as the disease activity is controlled and the anti-proliferative therapy is replaced with a less toxic alternative once remission is induced. Maintenance therapy aims to maintain remission and potential treatments include: azathioprine, MMF, tacrolimus and cyclosporin.

How the intervention might work

Active lupus nephritis is characterised by an inflammatory response to immune complexes in the kidneys. Mediators of inflammation, including complement, leukocytes, and cytokines injure the kidney and amplify inflammation. The release of kidney antigens in response to this inflammatory kidney injury may result in the production of kidney-specific autoantibodies. This organ-specific autoimmunity may perpetuate inflammation and result in kidney injury (Rovin 2014). The mechanisms of action of therapies used in the management of lupus nephritis are diverse, and aim to attenuate inflammation. Corticosteroids and IV cyclophosphamide and other conventional treatments have a broad spectrum immunosuppressive effect, while biologic therapies, which have been of increasing focus of trials in the last decade, target B-cells, T-cells, cytokines or growth factors to suppress the immune response (Murphy 2013).

First-line therapy has transformed lupus nephritis from an acute illness with five-year survival rates at less than 50% in the 1950s to a chronic illness with five-year survival rates 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 of relapse has been reported between 18% and 46% (Ponticelli 1998), and treatment can cause considerable toxicity, and increase the risk of infertility (Henderson 2012).

Why it is important to do this review

We conducted a systematic review of immunosuppressive treatment of proliferative lupus nephritis in 2004 (Flanc 2004a), and updated this systematic review in 2012 (Henderson 2012). The 2012 review identified 50 randomised controlled trials (RCTs) that enrolled a total of 2846 participants. The conclusion was that compared with IV cyclophosphamide, MMF was as effective in inducing disease remission, but with a lower risk of ovarian failure. MMF was more effective than azathioprine in maintaining disease remission. A recent network meta-analysis identified that compared to IV cyclophosphamide either MMF or tacrolimus or their combination was more effective in inducing remission. Compared with IV cyclophosphamide, the combination of MMF and tacrolimus reduced ovarian failure, but either treatment alone conferred a similar risk of ovarian failure. The use of these newer therapies on outcomes such as: death, ESKD and doubling of serum creatinine (SCr) were inconclusive (Palmer 2017).

In the past five years, numerous studies have evaluated a number of regimens including MMF, tacrolimus or their combination and various biologic agents. Given the uncertainty that surrounds the safety and efficacy of these 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 using IV cyclophosphamide as the main comparator in induction therapy and azathioprine as the main comparator in maintenance therapy.

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. Which agents, dosages, 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 RCTs and quasi-RCTs, whether published or available only in abstract form, which 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 adults and children 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, MMF, tacrolimus and cyclosporin
- Plasma exchange or plasmapheresis
- Biologic therapy (for example, abatacept, atacicept, laquinimod, ocrelizumab, rituximab and sirukumab).

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

Primary outcomes

- Death (all causes)
- ESKD, requirement for renal replacement therapy
- Complete renal remission: defined as return to normal SCr, urinary protein excretion < 0.5 g/24 h, and inactive urinary sediment) following induction therapy
- Relapse of lupus nephritis: maintenance therapy

Secondary outcomes

The following dichotomous outcome measures were considered:

- Partial renal remission: defined 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 SCr ± 25% (ALMS 2007)
- Remission in proteinuria: complete and partial.
  - Complete remission in proteinuria: defined as urinary protein excretion ≤ 0.3 g/24 h (Chan 2000)
  - Partial remission in proteinuria: defined as < 3.0 g/d protein if baseline ≥ 3.0 g/d or ≥ 50% reduction if < 3.0 g/d at baseline (ALMS 2007)
- Relapse of lupus nephritis - induction therapy
- Doubling of SCr
- Deterioration of kidney function: defined as more than 20% worsening of SCr
- Stable kidney function: defined as a less than 20% worsening of SCr.

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

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

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

- Daily proteinuria (24 hour urinary protein excretion) (g/24 h)
- Creatinine clearance (CrCl) (mL/min)
- SCr (µmol/L)
- Health-related quality of life
- Fatigue
- Disease activity (e.g. British Isles Lupus Assessment Group (BILAG), SLE Disease Activity Index (SLEDAI)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 2 March 2018 through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)

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

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

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

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines
2. Handsearching of proceedings of major rheumatology conferences
3. 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 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.

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 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).

Assessment of risk of bias in included studies

The following items were independently assessed by two authors 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 (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Disagreements regarding the risk of bias adjudications were resolved by consultation with a third review author.

Measures of treatment effect

Dichotomous data

For dichotomous outcomes (death (all causes), complete or partial renal remission, complete or partial remission in proteinuria, ESKD, renal relapse, doubling of SCr, stable kidney function, ovarian failure, menstrual irregularities, major infection, herpes zoster virus infection, malignancy, leucopenia, bone toxicity, bladder toxicity, alopecia and GI disorders) results were expressed as risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

Where continuous scales of measurement were used to assess the effects of treatment (urinary protein excretion, CrCl, SCr, health-related quality of life, fatigue, disease activity) the mean difference (MD) with 95% CI was used.

Unit of analysis issues

Studies with multiple treatment groups

In studies comparing the efficacy of more than two interventions we considered the following:

1. If different interventions were of different classes (for example, MMF or tacrolimus versus IV cyclophosphamide), we included each treatment group in separate meta-analyses, ensuring we did not include outcome data for the control group participants more than once in a single meta-analysis.
2. If interventions were of the same therapy (for example, high dose or low dose abatacept, laquinimod), we summarised into a single group that was compared with the control group for dichotomous outcomes (we summed the sample sizes and the number of people with events across the treatment groups). For continuous data, we entered the means and standard deviations of a single intervention group (usually the highest dosage) for comparison with the control group. Where appropriate, we considered sensitivity analyses, testing the impact of including the alternative intervention group in analyses.

Dealing with missing data

Where a study reported outcome data after excluding some randomised participants from the denominator, further information required from the original author was requested by electronic mail and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population were

carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) was critically appraised (Higgins 2011).

Assessment of heterogeneity

We first assessed for statistical heterogeneity visually by inspecting forest plots of standardised mean effect sizes and of risk ratios. Furthermore, we applied a Chi^2 test to assess heterogeneity. 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) and we used conventions of interpretation that were defined by Higgins 2003.

Assessment of reporting biases

Detection of potential for publication bias was planned for among the primary outcomes. We made every attempt to minimise publication bias by including unpublished studies (for example, by searching online trial registries). In order to assess publication bias we used funnel plots of the log odds ratio (OR) (effect versus standard error of the effect size) when sufficient number of studies were available (Higgins 2011). For the analysis and the interpretation of the funnel plots, other reasons for asymmetry besides publication bias were considered (for example, differences in methodological quality and true heterogeneity in intervention effects). 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).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be treated with caution. We considered subgroup analyses on the ethnicity of participants, class of lupus nephritis, age of the patient (adults versus children) and the type of induction therapy patients were treated with before randomisation in maintenance therapy studies in order to explore whether clinical differences between the studies may have systematically influenced the differences that were observed in the treatment outcomes. However, insufficient data were available to conduct subgroup analyses for the primary outcomes.

Sensitivity analysis

The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry versus other), and country the study was conducted in.

However insufficient data were available to determine these factors influence of the on effect size.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Death (all causes)
- ESKD, requirement for renal replacement therapy
- Complete renal remission
- Partial renal remission
- Renal relapse
- Doubling of SCr
- Stable kidney function
- Ovarian failure
- Major infection
- Leucopenia
- Alopecia
- Diarrhoea

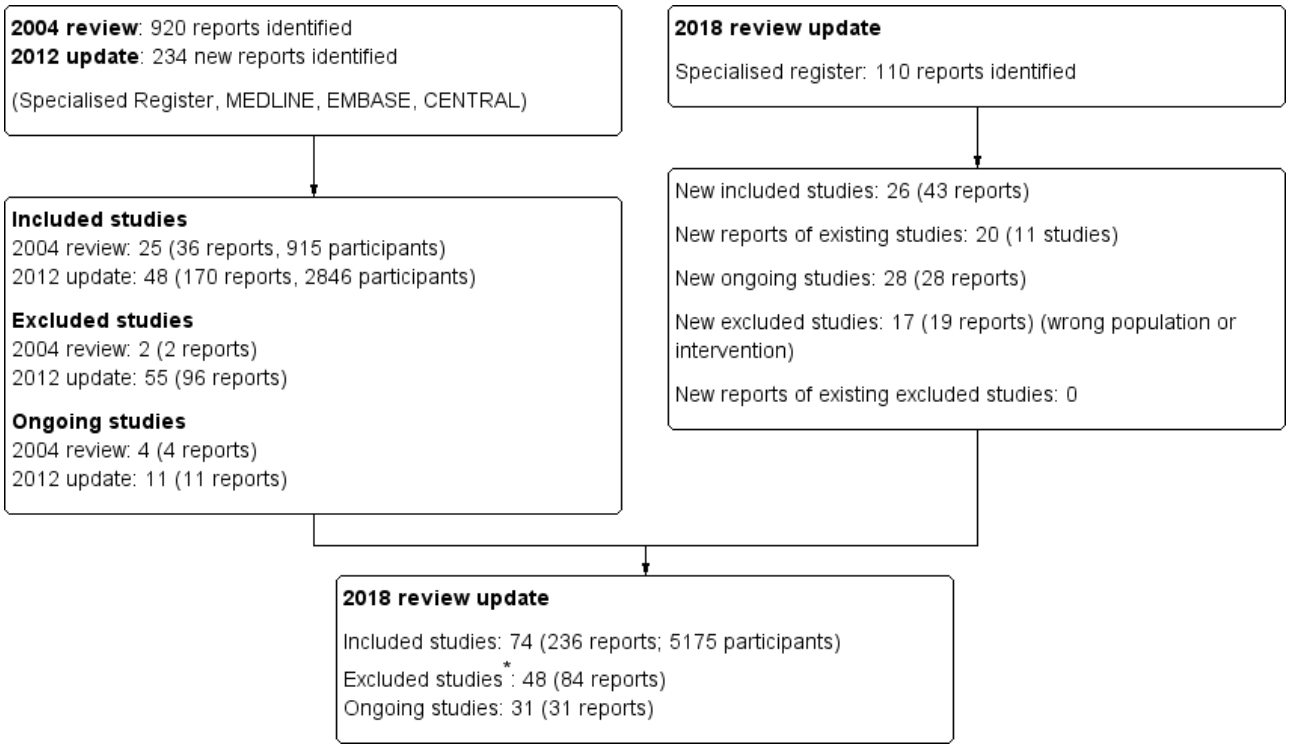
RESULTS

Description of studies

Results of the search

For this update, a search was conducted on 2 March 2018 (Figure 1). This new search identified 110 reports. After full-text review 71 new studies were identified. Twenty-six (43 reports) new studies were included and 17 (19 reports) were excluded. We identified 26 ongoing studies which will be assessed in a future update of this review. We also identified 20 new reports of 11 existing included studies. One study identified as a primary study in the 2012 review update was reallocated as a secondary report of ALMS 2007 (Sundel 2008). Four previously excluded studies have been included as they met our inclusion criteria (Abedi 2007; Florez-Suarez 2004; Loo 2010; Zhang 1995a).

Figure 1. Study flow diagram. *Non-RCTs have been deleted from this update



Included studies

See Characteristics of included studies

After including the studies identified from the 2018 update search, a total of 236 reports of 74 studies were included in this review (Figure 1) which included a total of 5175 randomised participants (Abedi 2007; ACCESS 2014; ALMS 2007; APRIL-LN 2012; AURA-LV 2016; Balletta 1992; Bao 2008; Barron 1982; Belmont 1995; BELONG 2013; Boedigheimer 2017; Boletis 1999; Boumpas 1992; Cade 1973; Chan 2000; Chen 2011; Clark 1981; Clark 1984; Contreras 2004; CYCLOFA-LUNE 2010; Decker 1975; Deng 2016; Derksen 1988; Donadio 1972; Donadio 1976; Doria 1994; Dyadyk 2001; El-Sehemy 2006; El-Shafey 2010; Florez-Suarez 2004; Fries 1973; Fu 1997; Furie 2014; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Hong 2007; Houssiau 2002; Jayne 2013; Kaballo 2016; Kamanamool 2017; Lewis 1992; Li 2009c; Li 2012; Liou 2007; Liu 2015; Loo 2010; Lui 1997; LUNAR 2012; MAINTAIN Nephritis 2010; Mehra 2018; Mendonca 2017; Mitwalli 2011; Mok 2016; Moroni 2006; Mulic-Bacic 2008; MyLupus 2011; Nakamura 2002e; Ong 2005; Pal 2017; Rathi 2016; Rovin 2016; Sabry 2009; Sedhain 2016; Sesso 1994a; SIMPL 2014; Steinberg 1971; Sun 2015; Wallace 1998; Yap 2017; Yee 2004; Zhang 1995a).

Twenty-nine studies enrolled adults and children (< 18 years) (ACCESS 2014; ALMS 2007; Bao 2008; BELONG 2013; Boumpas 1992; Cade 1973; Chen 2011; Derksen 1988; Donadio 1972; Donadio 1976; Doria 1994; El-Shafey 2010; Houssiau 2002; Kaballo 2016; Lewis 1992; Li 2012; Loo 2010; LUNAR 2012; MAINTAIN Nephritis 2010; Mehra 2018; Mendonca 2017; Moroni 2006; Ong 2005; Rathi 2016; Sesso 1994a; Steinberg 1971; Sun 2015; Wallace 1998; Yee 2004), 29 only enrolled adults (APRIL-LN 2012; AURA-LV 2016; Balletta 1992; Belmont 1995; Boedigheimer 2017; Boletis 1999; Chan 2000; Clark 1984; Contreras 2004; CYCLOFA-LUNE 2010; Dyadyk 2001; El-Sehemy 2006; Furie 2014; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Hong 2007; Kamanamool 2017; Li 2009c; Lui 1997; Mitwalli 2011; Mok 2016; MyLupus 2011; Nakamura 2002e; Rovin 2016; Sabry 2009; SIMPL 2014), 2 only enrolled children (Barron 1982; Fu 1997), and 14 studies did not specify the age of the participants.

There were 67 studies of induction therapy (4791 participants), and nine studies of maintenance therapy (767 participants; 297 had already completed an induction phase study (ALMS 2007; Chen 2011)). Follow-up ranged from median 12 months duration (range 2.5 to 48 months) for induction therapy, and median 30 months duration (range 6 to 63 months) for maintenance therapy. The numbers of patients included in the studies ranged from 6 to 378 with a median number of 45 patients.

Of all authors contacted for further clarification for the 2012 review update, nine responded (Drs Belmont, Doria, Donadio, Fries, Gourley, Houssiau, Solomons, Wofsy and Florez-Suarez). For the 2018 update, one author provided supplementary data (Dr Rathi).

Induction therapy

Comparators for induction therapy included the following.

1. MMF plus corticosteroid versus IV cyclophosphamide plus corticosteroid (10 studies, 878 participants: Abedi 2007; ALMS 2007; El-Shafey 2010; Florez-Suarez 2004; Ginzler 2005; Li 2012; Mulic-Bacic 2008; Ong 2005; Rathi 2016; Sedhain 2016)
2. MMF plus corticosteroid versus oral cyclophosphamide plus corticosteroids (1 study, 62 participants: Chan 2000)
3. MMF plus tacrolimus plus corticosteroid versus IV cyclophosphamide plus corticosteroid (2 studies, 402 participants: Bao 2008; Liu 2015)

4. MMF plus IV cyclophosphamide and corticosteroids versus cyclophosphamide plus corticosteroids (1 study, 82 participants: Sun 2015)
5. MMF plus corticosteroids versus tacrolimus plus corticosteroids (2 studies, 190 participants: Li 2012; Mok 2016)
6. Calcineurin inhibitors (tacrolimus or cyclosporin) plus corticosteroids versus IV cyclophosphamide plus corticosteroids (4 studies, 178 participants: Chen 2011; CYCLOFA-LUNE 2010; Hong 2007; Li 2012) or oral cyclophosphamide plus corticosteroids (1 study, 34 participants: Lui 1997)
7. Cyclophosphamide plus corticosteroid versus azathioprine plus corticosteroid (4 studies, 219 participants: El-Sehemy 2006; Decker 1975; Dyadyk 2001; Grootscholten 2006) or lefluomide plus corticosteroid (1 study, 30 participants: Deng 2016)
8. Rituximab plus MMF versus placebo plus MMF (both arms included corticosteroids) (1 study, 144 participants: LUNAR 2012)
9. Rituximab plus cyclophosphamide versus rituximab alone (both arms included corticosteroids) (1 study, 19 participants: Li 2009c)
10. Abatacept versus placebo (2 studies; 432 participants: ACCESS 2014, Furie 2014)
11. Low dose or high dose laquinimod versus placebo (1 study, 46 participants: Jayne 2013)
12. Low dose or high dose ocrelizumab versus placebo (1 study; 378 participants: BELONG 2013)
13. Sirukumab with or without corticosteroids plus MMF or azathioprine versus placebo with or without corticosteroids plus MMF or azathioprine (1 study, 25 participants: Rovin 2016)
14. IV versus oral cyclophosphamide (2 studies, 74 participants: Decker 1975; Yee 2004)
15. Low versus high dose IV cyclophosphamide (3 studies, 253 participants: Houssiau 2002; Mitwalli 2011; Sabry 2009)
16. Standard dose corticosteroid versus reduced dose corticosteroid with both arms receiving enteric-coated mycophenolate sodium (EC-MPS) (1 study, 81 participants: MyLupus 2011)
17. IV versus oral corticosteroid (1 study, 22 participants: Barron 1982).
18. IV cyclophosphamide with or without corticosteroid versus corticosteroid alone (5 studies, 261 participants: Decker 1975; Boumpas 1992; Gourley 1996; Sesso 1994a; Steinberg 1971)
19. Cyclophosphamide versus azathioprine with or without corticosteroids versus corticosteroid alone (4 studies, 94 participants: Decker 1975; Cade 1973; Donadio 1972; Hahn 1975)
20. Azathioprine plus corticosteroids versus corticosteroids alone (3 studies, 78 participants: Cade 1973; Decker 1975; Hahn 1975)
21. Cyclosporin plus corticosteroids versus corticosteroids alone (1 study, 10 participants: Balletta 1992)
22. Misoprostol plus corticosteroids versus corticosteroids alone (1 study, 14 participants: Belmont 1995)
23. Plasma exchange plus immunosuppression plus corticosteroids versus immunosuppression plus corticosteroids (5 studies, 174 participants; Clark 1981; Clark 1984; Doria 1994; Lewis 1992; Wallace 1998)
24. Plasma exchange versus immunosuppression alone (2 studies, 40 participants; Derksen 1988; Nakamura 2002e)
25. Long versus short duration IV cyclophosphamide (1 study, 40 participants: Boumpas 1992)

Other comparisons

- Plasma exchange versus immunoadsorption (1 study, 28 participants; Loo 2010)
- MMF versus cyclophosphamide (unclear if oral or IV) (1 study, 14 participants: Yap 2017)
- Tacrolimus + azathioprine versus IV cyclophosphamide (1 study, 58 participants: Pal 2017)
- Atacicept plus MMF and corticosteroid versus placebo plus MMF and corticosteroid (1 study, 6 participants: APRIL-LN 2012)
- Low dose or high dose voclosporin versus placebo (1 study; 256 participants: AURA-LV 2016)
- AMG811 (anti-IFN-γ antibody) versus placebo (1 study; 28 participants: Boedigheimer 2017)
- Cyclophosphamide till remission versus cyclophosphamide for 1 year (1 study, 36 participants: Zhang 1995a).

Maintenance therapy

Six studies (541 participants) compared azathioprine plus corticosteroid to another immunosuppressive agent (MMF, cyclophosphamide, cyclosporin or tacrolimus) (ALMS 2007; Chen 2011; Contreras 2004; Kaballo 2016; MAINTAIN Nephritis 2010; Moroni 2006); two studies had already completed an induction phase (ALMS 2007; Chen 2011). One study (40 participants) compared cyclophosphamide with cyclosporin (Fu 1997), one study (14 participants) compared IV cyclophosphamide to IV immunoglobulin (IVIG) (Boletis 1999) and one study compared prednisone withdrawal versus prednisone continuation (SIMPL 2014).

The maintenance phase of one study (Chan 2000) underwent a significant post-randomisation protocol adjustment. 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.

Excluded studies

See Characteristics of excluded studies.

Forty-eight studies were excluded (Andrade-Ortega 2010; Antunes 2001; ASPEN 2008; ATLAS 2016; Austin 2009; Balow 1981; Balow 1984; Ble 2011; Chanchairujira 2009; Clark 1993; Clark 2001a; CONTROL 2016; Davis 1999; Daza 2005; Deng 2017a; Feng 2014; Frutos 1997; Hebert 1987; Khajehdehi 2012; Kuo 2001; Li 2005; Li 2014a; LJP 394-90-05 2003; LJP 394-90-09 2005; Lu 2002; Miyasaka 2009; NCT00001212; NCT00404157; NCT00429377; NCT00436438; NCT00539799; NCT00659217; NCT01299922; NCT01342016; NCT01930890; NCT02176486; Pierucci 1989; Schaumann 1992; Su 2007; Sztejnbok 1971; Wallace 2006; Wang 2007; Witte 1993; Yap 2012; Ye 2001; Yoshida 1996; Zhang 2015c; Zheng 2005a).

The major reasons for exclusion were:

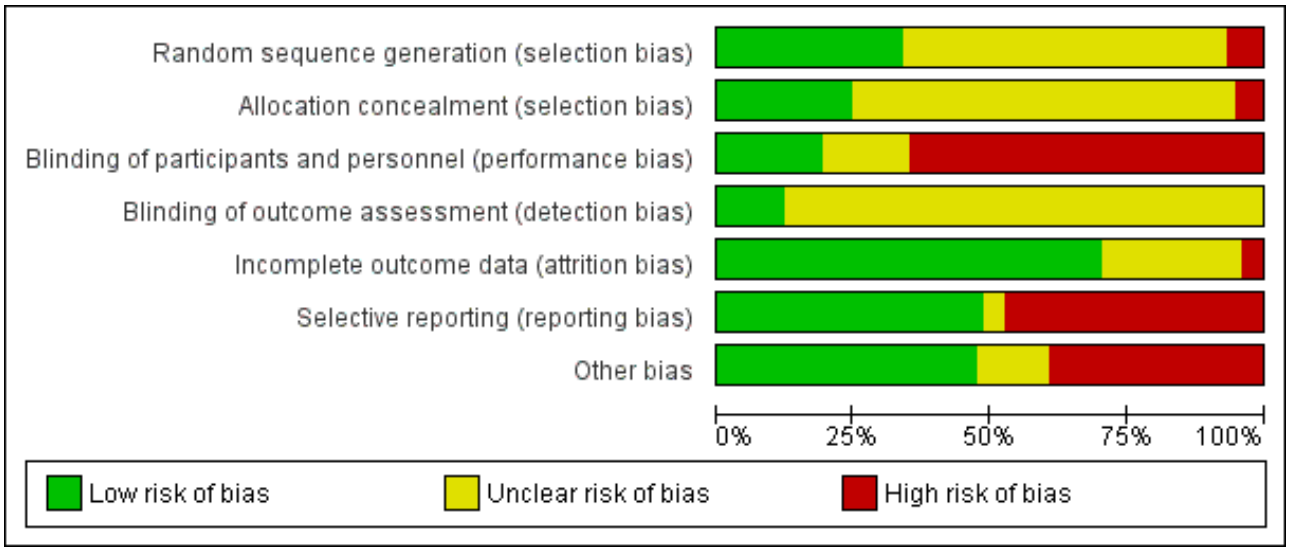
1. Diagnosis of lupus nephritis was not biopsy-proven or was not proliferative lupus nephritis
2. That the randomised treatment comparison was not immunosuppression.

For this update non-RCTs have been deleted.

Risk of bias in included studies

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

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



Allocation

Random sequence generation

Of the included studies, 25 reported adequate sequence generation (Bao 2008; Chan 2000; Chen 2011; Decker 1975; Derksen 1988; Donadio 1972; Donadio 1976; Fu 1997; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Houssiau 2002; Kaballo 2016; Kamanamool 2017; Lewis 1992; Li 2009c; Liu 2015; Mehra 2018; Mok 2016; Moroni 2006; Ong 2005; SIMPL 2014; Steinberg 1971; Yee 2004). Sequence generation was inadequate in five studies where alternation was used to allocate patients to treatment groups (Barron 1982; Cade 1973; Contreras 2004; Loo 2010; Sabry 2009). These studies were included in the review but deemed high risk for selection bias. Sequence generation was unclear in the remaining 44 studies.

Allocation concealment

Allocation concealment was adequate in 17 studies (ALMS 2007; Boletis 1999; Boumpas 1992; Chen 2011; Contreras 2004; CYCLOFA-LUNE 2010; Fu 1997; Ginzler 2005; Hahn 1975; Kamanamool 2017; Lewis 1992; Li 2009c; Liu 2015; Moroni 2006; Ong 2005; SIMPL 2014; Steinberg 1971), inadequate in four studies (Barron 1982; Cade 1973; MyLupus 2011; Sabry 2009), and unclear in the remaining 53 studies.

Blinding

Performance bias

Low risk of bias was assigned to 14 studies (ACCESS 2014; APRIL-LN 2012; AURA-LV 2016; Belmont 1995; BELONG 2013; Boedigheimer 2017; Furie 2014; Ginzler 1976; Jayne 2013; LUNAR 2012; Mitwalli 2011; Rovin 2016; SIMPL 2014; Steinberg 1971).

High risk was assigned to 47 studies, with 46 studies being open-label (Abedi 2007; ALMS 2007; Bao 2008; Barron 1982; Boumpas 1992; Cade 1973; Chen 2011; Clark 1981; Clark 1984; Contreras 2004; CYCLOFA-LUNE 2010; Donadio 1972; Donadio 1976; Doria 1994; Dyadyk 2001; El-Shafey 2010; Florez-Suarez 2004; Fries 1973; Fu 1997; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Hong 2007; Kamanamool 2017; Lewis 1992; Li 2009c; Li 2012; Liou 2007; Liu 2015; Lui 1997; MAINTAIN Nephritis 2010; Mehra 2018; Mendonca 2017; Mok 2016; Moroni 2006; Mulic-Bacic 2008; MyLupus 2011; Nakamura 2002e; Ong 2005; Pal 2017; Rathi 2016; Sedhain 2016; Sun 2015; Wallace 1998; Yee 2004; Zhang 1995a), and one study was unlikely to have treatment allocation blinded (Loo 2010). The remaining 13 studies were unclear, as they did not report blinding.

Detection bias

Nine studies reported blinding of subjective outcomes adequately (ALMS 2007; AURA-LV 2016; Bao 2008; Chan 2000; Gourley 1996; Liu 2015; Mitwalli 2011; Moroni 2006; SIMPL 2014), the remaining studies were classified as unclear, as blinding of the outcome assessor was not reported.

Incomplete outcome data

Incomplete outcome data was addressed adequately in 54 studies (ACCESS 2014; ALMS 2007; APRIL-LN 2012; AURA-LV 2016; Balletta 1992; Bao 2008; Belmont 1995; Boedigheimer 2017; Boletis 1999; Boumpas 1992; Cade 1973; Chan 2000; Chen 2011; Clark 1981; Clark 1984; Contreras 2004; CYCLOFA-LUNE 2010; Decker 1975; Doria 1994; El-Sehemy 2006; Fu 1997; Furie 2014; Ginzler 1976; Ginzler 2005; Gourley 1996; Grootscholten 2006; Hahn 1975; Houssiau 2002; Jayne 2013; Kaballo 2016; Kamanamool 2017; Lewis 1992; Li 2009c; Li 2012; LUNAR 2012; MAINTAIN Nephritis 2010; Mehra

2018; Mendonca 2017; Mitwalli 2011; Mok 2016; Moroni 2006; Mulic-Bacic 2008; MyLupus 2011; Ong 2005; Rovin 2016; Sabry 2009; Sesso 1994a; SIMPL 2014; Steinberg 1971; Sun 2015; Wallace 1998; Yee 2004). Three studies were inadequate (Barron 1982; BELONG 2013; Liu 2015), and the remainder were unclear.

Selective reporting

We found that 36 studies were free of selective reporting bias (ACCESS 2014; ALMS 2007; Bao 2008; Belmont 1995; BELONG 2013; Boletis 1999; Boumpas 1992; Cade 1973; Chan 2000; Chen 2011; Clark 1981; Contreras 2004; CYCLOFA-LUNE 2010; Decker 1975; Donadio 1976; Doria 1994; El-Shafey 2010; Furie 2014; Ginzler 1976; Gourley 1996; Grootscholten 2006; Houssiau 2002; Kaballo 2016; Kamanamool 2017; Lewis 1992; Li 2012; LUNAR 2012; MAINTAIN Nephritis 2010; Mitwalli 2011; Mok 2016; Moroni 2006; Ong 2005; Rathi 2016; Sesso 1994a; Steinberg 1971; Sun 2015). Thirty-five studies were considered to be at high risk of reporting bias (Abedi 2007; APRIL-LN 2012; AURA-LV 2016; Balletta 1992; Barron 1982; Boedigheimer 2017; Clark 1984; Deng 2016; Derksen 1988; Donadio 1972; Dyadyk 2001; El-Sehemy 2006; Florez-Suarez 2004; Fries 1973; Fu 1997; Ginzler 2005; Hahn 1975; Hong 2007; Jayne 2013; Li 2009c; Liou 2007; Liu 2015; Loo 2010; Mehra 2018; Mendonca 2017; Mulic-Bacic 2008; MyLupus 2011; Nakamura 2002e; Pal 2017; Rovin 2016; SIMPL 2014; Wallace 1998; Yap 2017; Yee 2004; Zhang 1995a), and the remaining three studies (Lui 1997; Sabry 2009; Sedhain 2016) were unclear.

Other potential sources of bias

Eighteen studies declared their funding sources to be independent or academic funding bodies and were judged to be free of other potential bias (Boumpas 1992; Clark 1981; Clark 1984; CYCLOFA-LUNE 2010; Donadio 1972; Donadio 1976; Gourley 1996; Grootscholten 2006; Houssiau 2002; Kamanamool 2017; Li 2012; Liou 2007; Liu 2015; MAINTAIN Nephritis 2010; Mendonca 2017; Mok 2016; Sun 2015; Yap 2017). Eight studies that declared independent funding sources were deemed high risk because of either early termination (Ginzler 2005; Lewis 1992; Yee 2004), heavy cross-over between treatment arms (Fries 1973; Ginzler 1976; Ginzler 2005; Steinberg 1971), pooling of studies (Decker 1975) or differences between treatment arms at baseline (Sesso 1994a). A further 20 studies declared sponsorship by a pharmaceutical industry company. Ten of the pharmaceutical sponsored studies included an author who declared pharmaceutical company affiliation; these were judged as carrying high risk of a potential source of bias (ACCESS 2014; ALMS 2007; APRIL-LN 2012; AURA-LV 2016; BELONG 2013; Contreras 2004; Furie 2014; LUNAR 2012; Moroni 2006; MyLupus 2011; Rovin 2016). Thirty-three studies did not disclose study funding sources. Eleven studies exhibited potential biases, which included inadequate reporting of results (Deng 2016; Sedhain 2016), pooling of interventions into study arms (Derksen 1988), low statistical power (Boedigheimer 2017; SIMPL 2014), and differences between treatment arms at baseline (El-Sehemy 2006; Mehra 2018; Mitwalli 2011; Loo 2010; Rathi 2016; Sabry 2009).

Effects of interventions

See: **Summary of findings for the main comparison** Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA) for induction therapy; **Summary of findings 2** Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA) for induction therapy; **Summary of findings 3** Azathioprine (AZA) versus mycophenolate mofetil (MMF) for maintenance therapy

Induction therapy

Main comparisons and outcomes for induction therapy, graded by certainty of the evidence, are presented in Summary of findings for the main comparison and Summary of findings 2.

1 & 2. MMF plus corticosteroids versus cyclophosphamide plus corticosteroid

1. Intravenous cyclophosphamide

Primary outcomes

Compared to IV cyclophosphamide, treatment with MMF may have led to increased complete disease remission (Analysis 1.2.2 (8 studies, 828 participants): RR 1.17, 95% CI 0.97 to 1.42; I^2 = 0%) (low certainty evidence), although the range of effects includes the possibility of little or no difference. It is uncertain if MMF compared to IV cyclophosphamide reduced death and ESKD because the certainty of the evidence is very low (Analysis 1.1; Analysis 1.3.1).

Secondary outcomes

The studies reported that MMF may be as effective as IV cyclophosphamide in the stabilisation of kidney function (Analysis 1.4 (6 studies, 641 participants): RR 1.05, 95% CI 0.94 to 1.17; I^2 = 0%) (low certainty evidence), and may be as effective in inducing partial renal remission (Analysis 1.2.2 (9 studies, 868 participants): RR 1.02, 95% CI 0.89 to 1.18; I^2 = 0%). It is uncertain if MMF compared to IV cyclophosphamide increased complete remission in proteinuria (Analysis 1.2.1) and partial renal remission in proteinuria (Analysis 1.2.4) because the certainty of the evidence was very low. In terms of adverse kidney outcomes, it is uncertain if MMF compared to IV cyclophosphamide reduced renal relapse (Analysis 1.3.2) and doubling of SCr (Analysis 1.3.3) because the certainty of the evidence was very low, as few studies reported these outcomes.

Compared to IV cyclophosphamide, treatment with MMF may have made little to no difference to SCr at the end of the study (Analysis 1.14 (6 studies, 759 participants): MD 2.14 µmol/L, 95% CI -3.09 to 7.37; I^2 = 0%) (low certainty evidence), although we cannot be certain of its effect on daily proteinuria (Analysis 1.13) because the certainty of evidence was very low. A considerable level of heterogeneity was observed among studies examining daily proteinuria (I^2 = 63%). 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 reduced the level of heterogeneity slightly (I^2 = 26%).

MMF probably reduced alopecia (Analysis 1.11 (3 studies, 622 participants): RR 0.29, 95% CI 0.19 to 0.46; I^2 = 0%), but probably increased diarrhoea (Analysis 1.12.1 (4 studies, 609 participants): RR 2.42, 95% CI 1.64 to 3.58) (moderate certainty evidence). Compared to IV cyclophosphamide, MMF may have made little or no difference to major infection (Analysis 1.7.1 (6 studies, 699 participants): RR 1.02, 95% CI 0.67 to 1.54; I^2 = 0%) (low certainty evidence). We were unable to determine if MMF reduced ovarian failure (Analysis 1.5), herpes zoster virus infection (Analysis 1.7.2), malignancy (Analysis 1.8), leucopenia (Analysis 1.9), vomiting (Analysis 1.12.2), nausea (Analysis 1.12.3), or GI upset (Analysis 1.12.4) compared to IV cyclophosphamide because the certainty of evidence was very low, as few studies reported these outcomes and events. In this review update, the introduction of a new study increased heterogeneity and imprecision of the effect estimates,

to include both appreciable benefit and harm for the outcomes ovarian failure (RR 0.36, 95% CI 0.06 to 2.18; I^2 = 39%) and leucopenia (RR 0.59, 95% CI 0.33 to 1.08; I^2 = 59%). As a result, the certainty of the evidence for these outcomes was downgraded to very low. For the ovarian failure outcome, the inclusion Rathi 2016 which compared a low dose IV cyclophosphamide ("Euro-lupus") to MMF, introduced three events and the benefit of MMF demonstrated in the 2012 Cochrane review update was no longer apparent.

2. Oral cyclophosphamide

Only one study examined the use of MMF plus corticosteroids versus oral cyclophosphamide and corticosteroids in induction therapy of proliferative lupus nephritis (Chan 2000).

Primary outcome

We were unable to determine if MMF compared to oral cyclophosphamide reduced death because the certainty of the evidence was very low (Analysis 2.1). However, MMF may have made little or no difference to ESKD (Analysis 2.3.1 (62 participants): RR 0.19, 95% CI 0.01 to 3.76)

Secondary outcomes

Chan 2000 reported MMF compared to oral cyclophosphamide may make little or no difference in the inducing complete remission in proteinuria (Analysis 2.2.1 (62 participants): RR 0.98, 95% CI 0.74 to 1.30) and partial remission in proteinuria (Analysis 2.2.2 (62 participants): RR 1.07, 95% CI 0.44 to 2.59) (low certainty evidence). Similarly, MMF may have made little or no difference to renal relapse (Analysis 2.3.2 (62 participants): RR 1.15, 95% CI 0.55 to 2.37), doubling of SCr (Analysis 2.3.3 (62 participants): RR 0.63, 95% CI 0.11 to 3.48), and daily proteinuria (Analysis 2.10 (42 participants): MD 0.30 g/24 h, 95% CI -0.19 to 0.79) (low certainty evidence).

Chan 2000 reported the use of MMF may have reduced ovarian failure (Analysis 2.4 (53 participants): RR 0.10, 95% CI 0.01 to 0.73), major infection (Analysis 2.5.1 (62 participants): RR 0.21, 95% CI 0.05 to 0.89), leucopenia (Analysis 2.6 (62 participants): RR 0.06, 95% CI 0.00 to 0.92), and alopecia (Analysis 2.8 (62 participants): RR 0.05, 95% CI 0.00 to 0.81) compared to oral cyclophosphamide (low certainty evidence). MMF compared to oral cyclophosphamide may have made little or no difference to: herpes zoster virus infection (Analysis 2.5.2 (62 participants): RR 0.38, 95% CI 0.08 to 1.79) and GI upset (Analysis 2.9 (62 participants): RR 2.81, 95% CI 0.31 to 25.58) (low certainty evidence). We were unable to determine if MMF compared to oral cyclophosphamide reduced bone toxicity (Analysis 2.7) because the certainty of the evidence was very low.

3. MMF plus tacrolimus and corticosteroid versus IV cyclophosphamide plus corticosteroid

Primary outcomes

MMF in combination with tacrolimus may improve the induction of complete renal remission (Analysis 3.2.1 (2 studies, 402 participants): RR 2.38, 95% CI 1.07 to 5.30; I^2 = 57%) (low certainty evidence), while it is uncertain whether combination therapy reduces death (Analysis 3.1) because the certainty of the evidence was very low.

Secondary outcomes

MMF in combination with tacrolimus may have increased induction of complete remission in proteinuria (Analysis 3.2.3 (2 studies, 402 participants): RR 2.38, 95% CI 1.07 to 5.30; I^2 = 57%), and achievement of stable kidney function stable kidney function (Analysis 3.4 (2 studies, 402 participants): RR 1.78, 95% CI 1.40 to 2.26; I^2 = 0%) (low certainty evidence). Combination therapy may have made little or no difference in inducing partial renal remission (Analysis 3.2.2 (2 studies, 402 participants): RR 1.00, 95% CI 0.78 to 1.28; I^2 = 0%) and partial remission in proteinuria (Analysis 3.2.4 (2 studies, 402 participants): RR 0.98, 95% CI 0.76 to 1.26; I^2 = 0%) when compared with IV cyclophosphamide (low certainty evidence). It is uncertain if combination therapy compared to IV cyclophosphamide reduced daily proteinuria (Analysis 3.12 (1 study, 40 participants): MD -1.69 g/24 h, 95% CI -2.8 to -0.57) because the certainty of the evidence was very low.

MMF plus tacrolimus compared to IV cyclophosphamide may have made little or no difference to menstrual irregularities (Analysis 3.6 (1 study, 323 participants): RR 0.28, 95% CI 0.06 to 1.35) (low certainty of evidence). It is uncertain the effects that MMF plus tacrolimus may have had on the following outcomes: doubling of SCr (Analysis 3.3.1), ovarian failure (Analysis 3.5), major infection (Analysis 3.7.1), herpes zoster virus infection (Analysis 3.7.2), leucopenia (Analysis 3.8), bone toxicity (Analysis 3.9), alopecia (Analysis 3.10), diarrhoea (Analysis 3.11.1) and GI upset (Analysis 3.11.2), because the certainty of the evidence was very low, due to risk of bias concerns, indirectness of the population and imprecision of the point estimates because of a small sample size and few event numbers.

4. MMF plus IV cyclophosphamide versus IV cyclophosphamide alone

One study compared MMF plus Iv cyclophosphamide versus IV cyclophosphamide alone (Sun 2015).

Primary outcomes

Compared to IV cyclophosphamide alone, It is uncertain if MMF in combination with cyclophosphamide improves the induction of complete renal remission (Analysis 4.2.1) and reduces death (Analysis 4.1) because the certainty of the evidence was very low.

Secondary outcomes

MMF in combination with IV cyclophosphamide may reduce major infection compared to treatment with IV cyclophosphamide alone (Analysis 4.4.1 (82 participants): RR 0.37, 95% CI 0.14 to 0.93) and may make little or no difference to daily proteinuria (Analysis 4.6 (77 participants): MD -0.54 g/24 h, 95% CI -1.12 to 0.04).

Compared to IV cyclophosphamide alone, It is uncertain if the combination of MMF and IV cyclophosphamide reduces menstrual irregularities (Analysis 4.3) or leucopenia (Analysis 4.5).

5. MMF plus corticosteroid versus tacrolimus plus corticosteroid

Primary outcomes

MMF compared to tacrolimus may have made little or no difference in inducing complete renal remission (Analysis 5.2.1 (3 studies, 273 participants): RR 1.02, 95% CI 0.83 to 1.26; I^2 = 0%) (low certainty evidence). It is uncertain if MMF compared to tacrolimus reduced

death (Analysis 5.1) or ESKD (Analysis 5.3.1) because the certainty of the evidence was very low.

Secondary outcomes

For secondary efficacy outcomes, MMF compared to tacrolimus may have made little or no difference in achieving partial renal remission (Analysis 5.2.2 (2 studies, 190 participants): RR 0.83, 95% CI 0.51 to 1.36; I^2 = 0%), complete remission in proteinuria (Analysis 5.2.3 (1 study, 40 participants): RR 1.00, 95% CI 0.50 to 1.98), partial remission in proteinuria (Analysis 5.2.4 (2 studies, 190 participants): RR 0.90, 95% CI 0.79 to 1.03; I^2 = 0%), deterioration in kidney function (Analysis 5.3.5 (1 study, 150 participants): RR 0.54, 95% CI 0.27 to 1.09), and stable kidney function (Analysis 5.4 (1 study, 40 participants): RR 1.00, 95% CI 0.50 to 1.98) (low certainty evidence). The use of MMF may have reduced renal relapse (Analysis 5.3.2 (1 study, 150 participants): RR 0.67, 95% CI 0.48 to 0.98) compared to tacrolimus (low certainty evidence). It is uncertain whether MMF improves daily proteinuria (Analysis 5.9), SCr (Analysis 5.11), and CrCl (Analysis 5.12), because the certainty of the evidence was very low. MMF compared to tacrolimus may have made little or no difference to renal disease activity (SLEDAI) (Analysis 5.10.1 (2 studies, 233 participants): MD -0.21, 95% CI -2.05 to 1.63; I^2 = 71%) and extrarenal disease activity (SLEDAI) (Analysis 5.10.2 (2 studies, 233 participants): MD -0.26, 95% CI -0.74, 0.22; I^2 = 0%) (low evidence certainty).

For outcomes, menstrual irregularities (Analysis 5.5: 1 study, 40 participants), major infection (Analysis 5.6.1: 2 studies, 190 participants), herpes zoster virus infection (Analysis 5.6.2: 1 study, 150 participants), leucopenia (Analysis 5.7: 1 study, 40 participants), and alopecia (Analysis 5.8: 1 study, 150 participants), we were unable to be certain of the effect of the MMF compared to tacrolimus because the certainty of the evidence was very low.

6. Calcineurin inhibitors plus corticosteroids versus cyclophosphamide plus corticosteroid

Primary outcomes

Compared to IV cyclophosphamide, calcineurin inhibitors (tacrolimus and cyclosporin) may have made little or no difference to the induction of complete renal remission (Analysis 6.2.1 (4 studies, 178 participants): RR 1.35, 95% CI 0.94 to 1.93; I^2 = 0%) (low certainty evidence). It is uncertain if calcineurin inhibitors decreased death (Analysis 6.1) or ESKD (Analysis 6.3.1) compared to IV cyclophosphamide because the certainty of the evidence was very low.

Secondary outcomes

Compared to IV cyclophosphamide, calcineurin inhibitors may have improved the induction of complete remission in proteinuria (Analysis 6.2.3 (3 studies, 105 participants): RR 1.71, 95% CI 1.08 to 2.70; I^2 = 0%) and may have made little or no difference to the induction of partial renal remission (Analysis 6.2.2 (4 studies, 178 participants): RR 0.88, 95% CI 0.61 to 1.26) (low certainty evidence). The effect of calcineurin inhibitors compared to IV cyclophosphamide on doubling of SCr (Analysis 6.3.2), stable kidney function (Analysis 6.4), ovarian failure (Analysis 6.5), menstrual irregularities (Analysis 6.6), major infection (Analysis 6.7.1), herpes zoster virus infection (Analysis 6.7.2), leucopenia (Analysis 6.9), alopecia (Analysis 6.10), and GI symptoms (Analysis 6.11) is unclear because the certainty of the evidence was very low. It is unclear the effect that calcineurin inhibitors have on continuous outcomes daily proteinuria (Analysis 6.12), CrCl (Analysis 6.13), and SCr (Analysis 6.14) at 9, 12 and 18 months compared to IV cyclophosphamide because the certainty of the evidence was very low.

An extended follow-up study of 38 participants from CYCLOFALUNE 2010 examined long-term safety and efficacy outcomes, but it was uncertain if cyclosporin reduced doubling of SCr (Analysis 6.3.3), premature ovarian failure (Analysis 6.5.3), and malignancy (Analysis 6.8), or improved daily proteinuria (Analysis 6.12) and SCr (Analysis 6.14) because the certainty of the evidence was very low.

7. Cyclophosphamide plus corticosteroid versus azathioprine plus corticosteroids

Primary outcome

The risk of death at five years (Analysis 7.1.1: 2 studies, 146 participants) and at 10 years (Analysis 7.1.2: 1 study, 59 participants) is uncertain because the certainty of the evidence was very low. Additionally, it is uncertain if azathioprine compared to cyclophosphamide reduced ESKD (Analysis 7.3.1: 2 studies, 144 participants).

Secondary outcomes

For efficacy outcomes it is uncertain if azathioprine compared to cyclophosphamide improved the rates of complete remission in proteinuria (Analysis 7.2.1: 1 study, 59 participants), partial remission in proteinuria (Analysis 7.2.2: 1 study, 59 participants), and stable kidney function (Analysis 7.4: 1 study, 57 participants) because the certainty of the evidence was very low. Similarly, for adverse renal outcomes it is not certain if azathioprine compared to cyclophosphamide reduced renal relapse (Analysis 7.3.3: 1 study, 87 participants) and deterioration of kidney function (Analysis 7.3.6: 1 study, 30 participants) because the certainty of evidence was very low; although, it may have reduced doubling of SCr (Analysis 7.3.5 (2 studies, 144 participants): RR 0.48, 95% CI 0.24 to 0.95; I^2 = 0%) (low certainty evidence).

For safety outcomes, azathioprine may have made little or no difference to ovarian failure (Analysis 7.5 (2 studies, 126 participants): RR 2.11, 95% CI 0.59 to 7.53; I^2 = 34%) (low certainty evidence). However, it is uncertain if it reduced menstrual irregularities (Analysis 7.6: 1 study, 15 participants), major infection (Analysis 7.7.1: 1 study 57 participants), herpes zoster virus infection (Analysis 7.7.2: 1 study, 57 participants), malignancy (Analysis 7.8: 2 studies, 144 participants), bone toxicity (Analysis 7.9: 1 study, 87 participants), and bladder toxicity (Analysis 7.10: 2 studies, 144 participants) because the certainty of the evidence was very low.

8. Rituximab + MMF versus placebo + MMF (both arms included corticosteroids)

Primary outcomes

It is uncertain if rituximab plus MMF versus placebo plus MMF improved the induction of complete renal remission (Analysis 8.2.1) or reduced death (Analysis 8.1.1), because the certainty of the evidence was very low.

Secondary outcomes

Rituximab plus MMF compared to placebo plus MMF may have made little or no difference in the stabilisation of kidney function (Analysis 8.3 (1 study, 144 participants): RR 1.24, 95% CI 0.90 to 1.7) (low certainty evidence). It is uncertain if it improved the induction of complete remission in proteinuria (Analysis 8.2.3), partial renal remission (Analysis 8.2.2), or reduced major infection (Analysis 8.4.1), herpes zoster virus infection (Analysis 8.4.2), and leucopenia (Analysis 8.5) because the certainty of the evidence was very low.

9. Rituximab plus cyclophosphamide versus rituximab alone

One study compared rituximab plus cyclophosphamide versus rituximab alone (Li 2009c).

Primary outcomes

It is uncertain if rituximab plus cyclophosphamide compared to rituximab alone improved the induction of complete renal remission (Analysis 9.1.1) because the certainty of the evidence was very low.

Secondary outcomes

Similarly, it is uncertain if rituximab plus cyclophosphamide improved the induction of partial renal remission (Analysis 9.1.2), reduced major infection (Analysis 9.2.1) and herpes zoster virus infection (Analysis 9.2.2), or improved daily proteinuria (Analysis 9.3), CrCl (Analysis 9.4), and SCr (Analysis 9.5) compared to rituximab alone because the certainty of the evidence was very low.

10, 11, 12, & 13. Other biologics versus placebo (both arms included standard of care therapy (MMF or CPA))

Primary outcomes

It is uncertain if biologics: abatacept, atacicpet, laquinimod, ocrelizumab and sirukumab improved the induction of complete renal remission (Analysis 10.2.(1,2,3); Analysis 11.2.(1,2,3); Analysis 12.2.(1,2,3)), reduced death (Analysis 10.1.(1,2,3); Analysis 11.1.(1.2.3); Analysis 12.1.(1,2,3); Analysis 13.1), and reduced ESKD (Analysis 10.3.(1,2,3)) compared to standard of care therapy because the certainty of the evidence was very low.

Secondary outcomes

It was uncertain if the abatacept or ocrelizumab improved the induction of partial renal remission (Analysis 10.2.(4.5.6); Analysis 12.2.(4,5,6)) because the certainty of the evidence was very low. Likewise, it was uncertain if the biologics compared to placebo plus standard of care therapy reduced renal relapse (Analysis 10.3.4); major infection (Analysis 10.4.(1,2,3); Analysis 12.3.(1,2,3); Analysis 13.2), herpes zoster virus infection (Analysis 10.5), malignancy (Analysis 13.3), and diarrhoea (Analysis 13.4) because the certainty of the evidence was very low.

It is uncertain if abatacept with standard of care therapy compared to placebo with standard of care therapy improved the physical and mental component of the health-related quality of life (SF-36) (Analysis 10.6) and disease activity (BILAG) (Analysis 10.7) because the certainty of the evidence was very low.

14. Intravenous versus oral cyclophosphamide

Primary outcomes

We were unable to determine if IV cyclophosphamide compared to oral cyclophosphamide reduced death (Analysis 14.1) because the certainty of the evidence was very low. IV cyclophosphamide compared to oral cyclophosphamide may have made little or no difference to ESKD (Analysis 14.2.1 (2 studies, 67 participants): RR 0.23, 95% CI 0.04 to 1.28; I^2 = 0%) (low certainty evidence).

Secondary outcomes

For adverse renal outcomes, IV cyclophosphamide may have made little or no difference to doubling of SCr (Analysis 14.2.2 (2 studies, 67 participants): RR 0.67, 95% CI 0.23 to 1.98; I^2 = 0%) (low certainty evidence). It is uncertain if IV compared to oral cyclophosphamide reduced the deterioration of kidney function (Analysis 14.2.3) and improved the achievement of stable kidney function (Analysis 14.3) because the certainty of the evidence was very low. For safety outcomes, IV compared to oral cyclophosphamide may have made little or no difference to ovarian failure (Analysis 14.4 (2 studies, 56 participants): RR 0.70, 95% CI 0.37 to 1.30; I^2 = 0%) and major infection (Analysis 14.5.1 (2 studies, 67 participants): RR 1.16, 95% CI 0.47 to 2.90; I^2 = 0%) (low certainty evidence), and it is uncertain if IV cyclophosphamide reduced herpes zoster virus infection (Analysis 14.5.2), malignancy (Analysis 14.6), bladder toxicity (Analysis 14.7), and GI upset (Analysis 14.8.1) because the certainty of the evidence was very low.

15. High versus low dose cyclophosphamide

Primary outcomes

Compared to high dose cyclophosphamide, the use of low dose cyclophosphamide may have been as effective in inducing complete renal remission (Analysis 15.2.1 (3 studies, 267 participants): RR 1.09, 95% CI 0.63 to 1.86; I^2 = 67%) and may have made little or no difference to ESKD (Analysis 15.3.1 (2 studies, 135 participants): RR 0.49, 95% CI 0.05 to 5.20) (low certainty evidence). However, it is uncertain if compared to high dose cyclophosphamide, low dose cyclophosphamide reduced ESKD at 5 years (Analysis 15.3.2) and 10 years (Analysis 15.3.3), and reduced death at 6 months (Analysis 15.1.1), 12 months (Analysis 15.1.2), 5 years (Analysis 15.1.3), and 10 years (Analysis 15.1.4) because the certainty of the evidence was very low.

Secondary outcomes

Low dose cyclophosphamide may have made little or no difference to efficacy outcomes of partial renal remission (Analysis 15.2.2 (3 studies, 267 participants): RR 0.88, 95% CI 0.69 to 1.14; I^2 = 0%) and stabilisation of kidney function at 3 years (Analysis 15.4.1 (1 study, 89 participants): RR 0.72, 95% CI 0.50 to 1.03), and at 5 years (Analysis 15.4.2 (1 study, 85 participants): RR 0.96, 95% 0.77 to 1.20) compared to high dose cyclophosphamide (low certainty evidence). It is uncertain if low dose cyclophosphamide improved daily proteinuria (Analysis 15.12: 3 studies, 242 participants), CrCl (Analysis 15.13: 1 study, 177 participants), and SCr (Analysis 15.14 (3 studies, 247 participants) compared to high dose cyclophosphamide because the certainty of the evidence was very low.

Compared to high dose cyclophosphamide, low dose cyclophosphamide may have made little or no difference to renal

relapse (Analysis 15.3.4 (3 studies, 211 participants): RR 2.75, 95% CI 0.47 to 15.98; I^2 = 66%) (low certainty evidence). The risk of ovarian failure may be two times higher in patients on high dose cyclophosphamide compared to those on low dose cyclophosphamide (Analysis 15.5 (4 studies, 299 participants): RR 1.73, 95% CI 0.70 to 4.31; I^2 = 19%) (low certainty evidence). Compared to high dose cyclophosphamide, low dose cyclophosphamide may make little or no difference to major infection (Analysis 15.6.1 (4 studies, 327 participants): RR 1.44, 95% CI 0.83 to 2.49; I^2 = 25%), herpes zoster virus infection (Analysis 15.6.2 (3 studies, 281 participants): RR 1.58, 95% CI 0.41 to 6.05), malignancy (Analysis 15.7 (2 studies, 206 participants): RR 1.44, 95% CI 0.09 to 23.31; I^2 = 41%), and leucopenia (Analysis 15.8 (3 studies, 281 participants): RR 0.82, 95% CI 0.13 to 5.15; I^2 = 51%) (low certainty evidence). It is uncertain if low dose cyclophosphamide use reduced bone toxicity (Analysis 15.9: 2 studies, 164 participants) compared to high dose cyclophosphamide because the certainty of the evidence was very low.

16. Standard versus reduced dose oral corticosteroid

One study compared standard versus reduced dose oral corticosteroid (MyLupus 2011).

Primary outcomes

It was uncertain if reduced dose oral corticosteroid compared to standard dose oral corticosteroid improved the induction of complete renal remission (Analysis 16.2.1: 81 participants) and reduced death (Analysis 16.1: 81 participants) because the certainty of the evidence was very low.

Secondary outcomes

It is uncertain of the effect of reduced dose oral corticosteroid compared to standard dose oral corticosteroid improved the induction of partial renal remission (Analysis 16.2.2: 81 participants), CrCl (Analysis 16.6: 74 participants), and SCr (Analysis 16.7: 81 participants), or reduced renal relapse (Analysis 16.3: 50 participants) because the certainty of the evidence was very low. For safety outcomes, compared to standard dose corticosteroids it was uncertain if reduced dose oral corticosteroids reduced major infection (Analysis 16.4.1: 81 participants), herpes zoster virus infection (Analysis 16.4.2: 81 participants), diarrhoea (Analysis 16.5.1: 81 participants), vomiting (Analysis 16.5.2: 81 participants), and nausea (Analysis 16.5.3: 81 participants) because the certainty of the evidence was very low

17. Intravenous versus oral corticosteroids

One study compared IV versus oral corticosteroids (Barron 1982).

It was uncertain if the use of pulsed methylprednisolone compared to oral corticosteroids alone reduced death (Analysis 17.1) or renal relapse (Analysis 17.2) because the certainty of the evidence was very low. The certainty of the evidence was downgraded because of the potential risk of bias, small sample size and small event numbers.

Other comparisons (18 to 25)

Older comparisons - immunosuppressive agent plus corticosteroids versus corticosteroids alone (18 to 22), plasma exchange plus immunosuppression versus immunosuppression alone (23), plasma exchange (no immunosuppression) versus immunosuppression (24) and long versus short-duration cyclophosphamide (25) - have been reported in the original Cochrane review (Flanc 2004a) and can also be found in the Data and analyses section of this review.

Maintenance therapy

Main outcomes for maintenance therapy, graded by certainty of the evidence, are presented in Summary of findings 3.

26. Azathioprine plus corticosteroid versus mycophenolate mofetil plus corticosteroid

Primary outcomes

Compared to MMF, azathioprine probably increased renal relapse (Analysis 26.2 (4 studies, 452 participants): RR 1.75, 95% CI 1.20 to 2.55; I^2 = 0%) (moderate certainty evidence). However, it is uncertain if azathioprine compared to MMF reduced death Analysis 26.1) or ESKD because the certainty of the evidence was very low (Analysis 26.3).

Secondary outcomes

It is uncertain if azathioprine compared to MMF improved daily proteinuria (Analysis 26.12) because the certainty of the evidence was very low; while it may have increased doubling of SCr (Analysis 26.4 (4 studies, 452 participants): RR 2.19, 95% CI 1.03, 4.66; I^2 = 0%) (low certainty evidence).

For safety outcomes, the use of azathioprine compared to MMF may have increased leucopenia (Analysis 26.8 (3 studies, 412 participants): RR 5.61, 95% CI 1.68 to 18.72; I^2 = 0%) and may have made little or no difference to major infection (Analysis 26.6 (3 studies, 412 participants): RR 1.08, 95% CI 0.60 to 1.96; I^2 = 0%), alopecia (Analysis 26.10 (3 studies, 412 participants): RR 0.95, 95% CI 0.46 to 1.95; I^2 = 0%), nausea (Analysis 26.11.2 (2 studies, 307 participants): RR 1.08, 95% CI 0.65 to 1.80; I^2 = 0%), and diarrhoea (Analysis 26.11.3 (2 studies, 307 participants): RR 0.74, 95% CI 0.31 to 1.73; I^2 = 33%) (low certainty evidence). It is unclear if azathioprine compared to MMF reduced ovarian failure (Analysis 26.5), herpes zoster virus infection (Analysis 26.6.2), malignancy (Analysis 26.7), bone toxicity (Analysis 26.9), and vomiting (Analysis 26.11.4) because the certainty of the evidence was very low.

27, 28 & 29. Azathioprine plus corticosteroid versus cyclophosphamide, cyclosporin or tacrolimus plus corticosteroid

Primary outcomes

It is uncertain if azathioprine compared to cyclosporin, cyclophosphamide and tacrolimus made little or no difference to death (Analysis 27.1; Analysis 28.1; Analysis 29.1), ESKD (Analysis 27.2.1; Analysis 28.2.1), and renal relapse (Analysis 27.2.2; Analysis 28.2.2; Analysis 29.1.1) because the certainty of the evidence was very low.

Secondary outcomes

It is uncertain if azathioprine compared to cyclosporin, cyclophosphamide and tacrolimus made little or no difference to daily proteinuria (Analysis 27.6), CrCl (Analysis 28.4), disease activity (SLEDAI) (Analysis 27.7), doubling of SCr (Analysis 28.2.3), major infection (Analysis 27.3.1; Analysis 29.2.1), leucopenia (Analysis 27.4), bladder toxicity (Analysis 28.3), and GI disturbance

(Analysis 27.5.1; Analysis 29.3.1) because the certainty of the evidence was very low.

30. Prednisone withdrawal versus prednisone continuation

Primary outcomes

It is uncertain if prednisone withdrawal compared to prednisone continuation made little or no difference to renal and non-renal relapse (Analysis 30.1) because the certainty of the evidence was very low.

Secondary outcomes

It is uncertain if prednisone withdrawal compared to prednisone continuation made little or no difference to major infection (Analysis 30.2) because the certainty of the evidence was very low.

31. Intravenous immunoglobulin versus intravenous cyclophosphamide

Secondary outcomes

It is uncertain if IV immunoglobulin compared to IV cyclophosphamide improved SCr, CrCl or proteinuria (Analysis 31.1; Analysis 31.2; Analysis 31.3) because the certainty of the evidence was very low.

Three studies reported health-related quality of life, one study reported fatigue and 21 studies reported disease activity. Given the heterogeneity of reporting of these outcomes, the results have been presented in tables (Table 1; Table 2; Table 3).

DISCUSSION

The management of lupus nephritis has become complex and difficult to navigate because of the recent proliferation of 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 death, resulting in the 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. In the subsequent update of the review (Henderson 2012), we found that MMF compared to cyclophosphamide had similar effects on death and inducing complete renal remission at six months, with a better safety profile as indicated by a reduced risk of ovarian failure, alopecia and leucopenia but with an increased risk of diarrhoea. Additionally, for maintenance therapy, MMF was more effective than azathioprine at preventing renal relapse with less leucopenia and no difference in other safety outcomes. Data regarding newer agents such as tacrolimus, cyclosporin and rituximab were insufficient to permit any meaningful conclusions at the time of publication. Numerous recent studies have examined the combination of MMF and tacrolimus and the use of biologics in induction therapy.

Summary of main results

As shown by eight studies involving over 800 participants with proliferative lupus nephritis in the analysis of this updated review, MMF dosed at 2 g to 3 g daily may have increased the induction of complete disease remission and stable kidney function at six months compared to cyclophosphamide, although the certainty of the evidence was low, because of study limitations and imprecision concerns, with the risk estimate including the possibility of no effect. Treatment with MMF compared to cyclophosphamide reduced the risk of alopecia but increased the risk of diarrhoea. These data justify the current use of MMF as the first-line agent in proliferative lupus nephritis. MMF provided no benefit for other adverse events compared with cyclophosphamide, although its effect on ovarian failure is unclear. As the inclusion of one new study (Rathi 2016) has introduced greater imprecision in the ovarian failure treatment estimate, a total of three events has altered the summary estimate to suggest no benefit. This finding cannot be definitively stated as the treatment estimate is susceptible to change with addition of a few events; as a result, the certainty of the evidence has been downgraded to very low.

Compared to IV cyclophosphamide, the use of calcineurin inhibitors (tacrolimus and cyclosporin) may be as effective in inducing complete renal remission, while the combination of MMF and tacrolimus may improve the induction of complete renal remission, and achieving stable kidney function at six months. The generalisability of these findings may be limited as the two studies of combination therapy have largely included patients of Asian ethnicity, and have had serious concerns regarding selection bias and reporting bias. The safety of these therapies is unclear as the certainty of evidence is generally low to very low due to substantial imprecision in treatment effects and a small sample size and event numbers, limiting the applicability of the findings.

For maintenance therapy, MMF is probably more effective than azathioprine at preventing renal relapse with less leucopenia but there may be no difference in other outcomes (major infection, alopecia, and GI adverse events). The effectiveness and safety of many other interventions, including biologics (for example, rituximab and abatacept) and cyclosporin, is unclear because of very low certainty of the evidence, as they have only been trialled in a small number of studies with low numbers of events and inconsistent outcome reporting. The clinical role of these therapies therefore remains unclear and warrants caution.

Overall completeness and applicability of evidence

Our review was based on a highly sensitive electronic search of the Cochrane Kidney and Transplant's Specialised Register, which includes journal alerts and handsearching of all relevant conference proceedings, the reporting of existing studies evaluating induction and maintenance therapy of lupus nephritis means there are considerable gaps in the evidence. 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 the majority of induction therapy studies was six months. Furthermore, the risk of adverse events such as ovarian failure and the development of ESKD increases after six months, so there is considerable uncertainty in treatment effects across interventions, which results in an inability of patients and

clinicians to evaluate the benefits and harms of therapy. Health-related quality of life and fatigue are included in a core set of outcomes for SLE developed by OMERACT (Strand 2000). Yet, very few lupus nephritis studies have reported these patient-reported outcomes. No standardised set of outcomes have been developed specifically for lupus nephritis studies. The development of a core set of outcomes by all stakeholders, including patients, with defined measures and definitions of renal remission (Liang 2006; van Vollenhoven 2017) would ease comparisons across studies and assist with building evidence for the induction and maintenance therapy of lupus nephritis. There were limited studies examining biologics, with sparse outcome data and confidence intervals were frequently very wide, indicating substantial uncertainty. Studies may not reflect usual clinical practice due to selection bias, with rituximab increasingly being used and showing benefit in patients who have not achieved remission with standard therapies (Weidenbusch 2013).

The disease spectrum and the proportion of patients within each class of lupus nephritis differed among studies. Furthermore, patient demographics varied among studies where environmental, socioeconomic, as well as clinical and genetic factors have been thought to play an important role explaining differences in the outcome of lupus nephritis by ethnicity. Comparing MMF with cyclophosphamide in induction therapy, six studies included primarily Asian patients (Bao 2008; Chan 2000; Li 2012; Liu 2015; Ong 2005; Rathi 2016; Sedhain 2016) and two of the largest studies comparing MMF with cyclophosphamide included higher proportions of African-American and Hispanic patients (ALMS 2007; Ginzler 2005). Non-Caucasian populations have a higher risk of relapse, death and CKD compared with Caucasian populations (Adler 2006; Contreras 2006) and often fail to respond to cyclophosphamide (Adler 2006; Contreras 2006; Dooley 1997). Ginzler 2005 included the largest percentage (56%) of patients 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. 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 (ALMS 2007). ALMS 2007 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 kidney impairment reducing the power to examine potential differences between these groups. Despite the lack of stratification of results, variation among studies could be considered a strength as despite clinical differences in population and histological classification, uniformity of effect demonstrated in the meta-analysis suggest that the results were valid across race and class of lupus nephritis.

Quality of the evidence

We graded our confidence in the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADE 2011), which considers study limitations, imprecision, indirectness, inconsistency and publication bias. Overall, most studies had high or unclear risks of bias for most domains of study reporting assessed (Figure 2). 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).

Estimated effects on efficacy and safety outcomes were frequently imprecise with confidence intervals that exhibited both considerable benefit and harm. The generalisability (directness) of the evidence was limited by the number of available studies on many treatment comparisons. Additionally, considerable clinical heterogeneity in interventions, definitions of remission and renal relapse 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, definition of outcomes and co-interventions. The small number of studies for some treatment comparisons limited the power of statistical testing and important inconsistencies between studies could not excluded. Publication bias (the effects of small studies on treatment effects) could not be assessed, new reports from hand-searching conference proceedings in addition to those already searched by Cochrane Kidney and Transplant were included in the meta-analysis to minimise publication bias. Overall, based on important limitations, we have generally moderate to very low confidence in the certainty of the evidence for the benefits and harms of induction and maintenance therapy in people with proliferative lupus nephritis.

Potential biases in the review process

Although this systematic review is reported using Cochrane methods and includes a comprehensive evidence summary for this topic, the review has limitations that might be considered. Firstly, the analysis was limited by the reporting of outcomes in the primary studies. For example, the definitions of renal remission were variable across studies. While for the analysis of these outcomes, there was evidence of low heterogeneity, indicating the meta-analysis was appropriate, the small number of studies for treatment comparisons in this review may limit the statistical power to detect heterogeneity, and as a result it may still be present. Second, incomplete reporting of outcomes also limits the power of this review to detect differences among interventions. For example, although eight studies with 828 participants compared MMF with IV cyclophosphamide in induction therapy, only three reported on ovarian failure and one on doubling of SCr. Finally, different treatment effects for patients of different ethnic backgrounds has been hypothesised and observed (Isenberg 2010), although it could not be explored in this systematic review because of insufficient data for ethnicity in the original study reports to perform meta-regression analyses.

Agreements and disagreements with other studies or reviews

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 (Cao 2015; Deng 2012; Feng 2013; Hannah 2016; Kamanamool 2010; Lee 2010; Lee 2011; Liu 2012; Mak 2009; Maneiro 2014; Moore 2006; Radhakrishnan 2010; Touma 2011; Walsh 2007; Zhang 2016; Zhou 2011; Zhu 2007). A review

of systematic reviews of meta-analyses of RCTs and observational studies (Chen 2017) also showed that induction therapy with MMF compared to IV cyclophosphamide had a higher response rate and decreased alopecia. However, in contrast, the review found that MMF decreased ovarian failure and leucopenia, and calcineurin inhibitors (tacrolimus) increased complete remission and decreased ovarian failure and GI adverse events. These differences may be because the other overview included systematic reviews of observational studies and did not assess the certainty of the available evidence, and we included more recent RCTs in our review. For example, our review included Rathi 2016, which introduced further uncertainty regarding the outcomes of ovarian failure and leucopenia for MMF versus cyclophosphamide induction therapy.

Similar findings between this review and recent network meta-analysis strengthen the conclusion that there is inconclusive evidence for therapy based on treatment effects on important safety outcomes and that MMF is the most effective therapy in maintaining disease remission (Palmer 2017; Tian 2015). While, some network meta-analyses found similar findings in that there may be no difference between MMF, calcineurin inhibitors or their combination in inducing renal remission compared to cyclophosphamide (Tian 2014; Singh 2016), other network meta-analyses have found that these therapies may be more effective than cyclophosphamide in inducing renal remission (Lee 2015; Palmer 2017). As there are vast options available for treatment, of which some have not been directly compared, a network meta-analysis may allow for greater certainty about all treatment options through the use of indirect evidence. Although, given the small number of studies, an imbalance of evidence in the network, particularly tacrolimus alone or its combination with MMF may affect the power and reliability for the overall analysis, and also the network meta-analysis may be underpowered to check for statistical heterogeneity, leading to incoherence between direct and indirect results. Considering the apparent lack of evidence and possible incoherency, the results from the network meta-analysis should be interpreted with a degree of caution (Mills 2013).

AUTHORS' CONCLUSIONS

Implications for practice

In this review, we found that MMF may lead to increased complete disease remission compared to IV cyclophosphamide, although the certainty of the evidence was low and included the possibility of no effect, however there was some evidence of better tolerability. The equivalent remission rates combined with a more favourable side-effect profile compared to cyclophosphamide support the current practice of MMF along with corticosteroids as first-line induction therapy for proliferative lupus nephritis. Numerous published guidelines concur with our findings, recommending MMF or IV cyclophosphamide with corticosteroids for induction therapy in patients with ISN class III/IV lupus nephritis (Tunnicliffe 2015). The combination of MMF and tacrolimus may be more effective in inducing renal remission and achieving stable kidney function but this needs to be interpreted with a degree of caution, as it has largely been informed by one large study with participants of mainly Chinese ethnicity.

Although there are few study data on maintenance therapy, meta-analyses from two recent large RCTs (ALMS 2007; MAINTAIN Nephritis 2010) showed that MMF is superior to azathioprine in preventing renal relapse with no difference between the therapies in death, doubling of SCr, major infection, leucopenia and GI disturbance. The data for newer biologic agents, including rituximab was very limited, so no conclusions about the relative benefit and harms of these agents 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 four main implications for future research. In no particular order, firstly for the design of future studies, given the short duration of studies and imprecision for treatment estimates for death and ESKD, registry-based RCTs may clarify the risks and eventual harms of specific treatment regimens, as outcomes, are captured automatically during routine follow-up with registry databases. Efficient data linkage between hospital records, national and state-wide mortality databases and cancer registries may also help clarify the efficacy and safety of specific therapies. Secondly, standardisation of the reporting of safety and efficacy outcomes in studies evaluating therapies for lupus nephritis might facilitate better comparison and improve our understanding of the benefits and harms of treatment. Thirdly, future studies should further examine the long-term safety and efficacy of MMF as maintenance therapy to provide guidance around tapering or when to stop treatment; further studies should also examine the safety and efficacy of MMF plus tacrolimus as induction therapy in the management of lupus nephritis across all ethnic groups. Further studies are needed in patient populations that carry greater disease burden, such as children, African-Americans, Hispanics and Asians, different histopathological classes of lupus nephritis 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]*

Abedi 2007

Methods	• Study design: parallel RCT • Study timeframe: not reported • Duration of follow-up: 18 months
Participants	• Country: Iran • Setting: not reported • Inclusion criteria: SLE patients with newly diagnosed lupus nephritis, WHO class III or IV (biopsy proven) • Number (randomised): 30 (numbers per group not reported) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy: duration of treatment was 18 months
	• Treatment group 1
	  * MMF: 2 g/d
	• Treatment group 2
	  * IV CPA: 0.75 to 1 g/month for 6 months then every 3 months for 1 year
	• Both groups
	  * Corticosteroids

Outcomes	• Complete remission • Partial remission • Proteinuria

Abedi 2007 *(Continued)*

	• Serum albumin • Hb, ESR, serum complement, urinary activity • Serious infection • Leucopenia • Amenorrhoea • Diarrhoea
Notes	• Abstract-only publication • Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Data unable to be meta-analysed
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

ACCESS 2014

Methods	• Study design: double-blind, parallel RCT • Study timeframe: November 2008 to June 2012 • Duration of follow-up: 24 and 52 weeks
Participants	• Countries: USA and Mexico • Setting: multicentre (19 sites) • Inclusion criteria: ≥16 years; diagnosis of SLE (ACR criteria) positive ANA and/or positive anti-double-stranded DNA (anti-dsDNA) antibody test result at study entry; active lupus nephritis defined by kidney biopsy findings within the last 12 months of proliferative nephritis (ISN/RPS criteria (class III or class IV with or without features of class V)) and UPCR of > 1 • Number (randomised/analysed): treatment group (66/66); control group (68/68) • Mean age ± SD (years): treatment group (32 ± 10.1); control group (32.7 ± 12) • Sex (M/F): treatment group (8/58); control group (12/56) • Exclusion criteria: not reported

ACCESS 2014 *(Continued)*

Interventions	Induction therapy: duration of treatment was 6 months
	• Treatment group
	  * Abatacept: monthly infusions at doses that were adjusted for body weight according to the abatacept dose that is recommended for rheumatoid arthritis (for < 60 kg, 500 mg; for 60-100 kg; 750 mg for > 100 kg, 1 g)
	• Control group
	  * Placebo
	• Both groups
	  * Six IV pulses of 500 mg of CPA at two-week intervals followed by oral AZA at 2 mg/kg/d based on the ELNT regimen
	  * Oral glucocorticoid treatment was begun at 60 mg/d for 2 weeks in all subjects, followed by a prescribed taper to 10 mg/d over the next 10 weeks

Outcomes	• Death (all causes) • Complete response: UPCR of 0.5 based on a 24 h urine collection, SCr level of 1.2 mg/dL or 125% of baseline, and adherence to the prednisone taper to 10 mg/d by week 12 • Partial response: UPCR required only 50% improvement from baseline (rather than a decline to < 0.5 based in complete response) on a 24 h urine collection, SCr level of 1.2 mg/dL or 125% of baseline, and adherence to the prednisone taper to 10 mg/d by week 12 • Relapse: renal flare was defined as the recurrence of proteinuria of > 1 g/24 h; for all others, a renal flare was defined as either of the following: SCr level at least 25% higher than baseline or above the upper limit of normal, plus proteinuria at least 75% of baseline; or doubling of the UPCR compared with the lowest previous value • Major infection
Notes	• The ACCESS study did not use an initial IV pulse MP, but rather left that decision to the site investigator's discretion, unlike Euro-lupus nephritis treatment regimen • Funding source: NIH National Institute of Allergy and Infectious Diseases contract N01-AI-15416, protocol number ITN034AI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

ACCESS 2014 *(Continued)*

Other bias	High risk	Some authors involved in data acquisition and analysis are employees of pharmaceutical companies

ALMS 2007

Methods	• Study design: open-label, parallel RCT • Study timeframe (enrolment): 27 July 2005 to 6 October 2006 • Duration of follow-up (median): 6 months (induction therapy) and 36 months (maintenance therapy)

Participants	• Country: international (countries not reported)
	• Setting: multinational (˜ 100 sites)
	• Inclusion criteria: aged 12 to 75 years with 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; class III (22); IV (147); III/V (7); IV/V (16); V (35)
	• Number (randomised/analysed)
	  * Induction therapy: treatment group 1 (185/185); treatment group 2 (185/185)
	  * Maintenance therapy: treatment group 1 (116/116); treatment group 2 (111/111)
	• Mean age ± SD (years)
	  * Induction therapy: treatment group 1 (32.4 ± 11.2); treatment group 2 (31.3 ± 10.3)
	  * Maintenance therapy: treatment group 1 (31.8 ± 10.6); treatment group 2 (31 ± 10.8)
	• Sex (M/F)
	  * Induction therapy: treatment group 1 (28/157); treatment group 2 (29/156)
	  * Maintenance therapy: treatment group 1 (15/101); treatment group 2 (17/94)
	• Exclusion criteria: treatment with MMF or IV CPA within the previous year; continuous dialysis for > 2 weeks before randomisation or anticipated duration > 8 weeks; pancreatitis, GI haemorrhage within 6 months or active peptic ulcer within 3 months; severe viral infection; severe cardiovascular disease; bone marrow insufficiency with cytopenias not attributable to SLE; current infection requiring IV antibiotics

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 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
	• Treatment group 2
	  * IV CPA: monthly pulses 0.5 to 1.0 g/m^2
	• Both groups
	  * Oral prednisolone with defined taper, maximum starting dose 60 mg/d
	Maintenance therapy: duration of therapy was 36 months
	• Treatment group 1
	  * Oral MMF: 2 g/d
	  * AZA placebo
	• Treatment group 2
	  * Oral AZA: 2 mg/kg/d
	  * MMF placebo
	• Both groups
	  * Oral prednisolone with defined taper, maximum starting dose 10 mg/d

Outcomes	Induction therapy • Death (all causes) • Stable kidney function: stabilisation ± 25% or improvement in SCr

ALMS 2007 *(Continued)*

	• Complete renal remission: return to normal creatinine, proteinuria ≤ 0.5 g/d and inactive urine sediment • Partial renal remission: prespecified decrease in UPCR (fall in < 3.0 g/d protein if baseline ≥ 3 or ≥ 50% reduction if < 3 at baseline and stabilisation of SCr ± 25%) • Major infection • Systemic disease activity and damage • Adverse events (reported by > 10% participants) Maintenance therapy • Death • ESKD • doubling of SCr • Renal flare: proteinuric or nephritic • Complete renal remission • Combined renal and extra-renal remission
Notes	• Funding source: Aspreva Pharmaceuticals Corporation as part of the Roche-Aspreva collaboration agreement

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomly assigned (1:1, stratified by race and biopsy class, non-blocked) but sequence of generation is not reported
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 of participants and personnel (performance bias) All outcomes	High risk	Induction therapy - Open-label study; maintenance therapy - double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome assessed by blinded Clinical EndPoints Committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; Induction therapy (group 1: 1 lost to follow-up; group 2: 2 lost to follow-up)
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	High risk	Sponsored by Aspreva Pharmaceuticals Corporation included in the data analysis & authorship

APRIL-LN 2012

Methods	• Study design: double-blind, double dummy RCT • Study timeframe: not reported • Duration of follow-up: 12 months planned

APRIL-LN 2012 *(Continued)*

Participants	• Country: USA • Setting: multicentre (4 sites) • Inclusion criteria: diagnosis of SLE (ACR criteria); positive ANA test (Hep-2 ANA ≥ 1:80) and/or anti-dsDNA ≥ 30 IU/mL); biopsy proven (within the 12 months preceding study entry) class III or IV lupus nephritis (ISN/RPS 2003 classification criteria); active lupus nephritis, defined by proteinuria (UPCR > 1.0 mg/mg) and haematuria (> 10 RBC/HPF with or without RBC casts) • Number (randomised): treatment group (4); control group (2) • Age range 18 to 54 years • Sex (M/F): 2/4 • Exclusion criteria: causes of haematuria of non-glomerular origin; kidney disease unrelated to SLE; calculated eGFR ≤ 30 mL/min/1.73 m^2 at screening

Interventions	Induction therapy: duration of therapy was 12 months
	• Treatment group
	  * SC atacicept: 150 mg twice weekly for 4 weeks then 150 mg weekly for a planned 48 weeks
	• Control group
	  * SC placebo
	• Both groups
	  * On study Day 14, patients commenced MMF (500 mg, twice daily, orally) and prednisone or equivalent (the lesser of 0.8 mg/kg/d or 60 mg/d, orally). MMF dose was increased to 1,000 mg twice daily at Day 7, thereafter up to a maximum of 1.5 g twice daily by Day 1

Outcomes	• Major infection • Treatment failure
Notes	• Follow-up was planned for 12 months • Early termination of the project • Funding source: Merck Serono S.A.; ZymoGenetics Inc; EMD Serono Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy placebo study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Study protocol available and not all prespecified outcomes were reported

APRIL-LN 2012 *(Continued)*

Other bias	High risk	Sponsor involved in authorship. The study was terminated early; there were differences in characteristics (for example eGFR) between groups at baseline

AURA-LV 2016

Methods	• Study design: double-blind, parallel RCT • Study timeframe: not reported • Duration of follow-up: 24 and 48 weeks
Participants	• Country: > 20 countries (not reported) • Setting: multinational (number of sites not reported) • Inclusion criteria: patients aged 18 to 75 years; diagnosis of SLE (ACR criteria); biopsy proven classes III, IV-S or IV-G, (A) or (A/C); or Class V, alone or in combination with Class III or IV (ISN/RPS 2003) (within 6 months prior to screening (Visit 1); laboratory evidence of active nephritis at screening, defined as Class III, IV-S or IV-G (confirmed proteinuria ≥ 1,500 mg/24 h, UPCR of ≥ 1.5 mg/mg; Class V (alone or in combination with Class III or IV: proteinuria ≥ 2,000 mg/24 h, a UPCR of ≥ 2 mg/mg) • Number (randomised): 265 patients (numbers not reported for groups) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: eGFR of ≤ 45 mL/min/1.73 m^2; currently requiring or expected to require HD or PD during the study period; previous kidney transplant or planned transplant within study period; in the opinion of the investigator, subject does not require long-term immunosuppressive treatment (in addition to corticosteroids); current or medical history of: pancreatitis or GI haemorrhage within 6 months prior to screening; active unhealed peptic ulcer within 3 months prior to screening; congenital or acquired immunodeficiency; clinically significant drug or alcohol abuse 2 years prior to screening; malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision; cervical dysplasia that is cervical intraepithelial neoplasia 1, but have been treated with conization or loop electrosurgical excision procedure, and have had a normal repeat PAP are allowed; lymphoproliferative disease or previous total lymphoid irradiation; severe viral infection (e.g. CMV, HBV, HCV) within 3 months of screening; or known HIV infection; active TB, or known history of TB; other known clinically significant active medical conditions, such as severe cardiovascular disease including congestive heart failure, history of cardiac dysrhythmia or congenital long QT syndrome; liver dysfunction at screening and confirmed before randomisation; chronic obstructive pulmonary disease or asthma requiring oral steroids; bone marrow insufficiency unrelated to active SLE (according to Investigator judgment) with WCC < 2500/mm^3; absolute neutrophil count < 1.3 x 10^3/μL; thrombocytopenia (platelet count < 50,000/mm^3); active bleeding disorders; current infection requiring IV antibiotics; any overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes; overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes are not excluded; pregnant, breast feeding or, if of childbearing potential, not using adequate contraceptive precautions

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * Low-dose oral voclosporin: 23.7 mg twice/d
	• Treatment group 2
	  * High-dose oral voclosporin: 39.5 mg twice/d
	• Control group
	  * Oral placebo
	• Both groups
	  * Oral MMF and corticosteroids

Outcomes	• Death • Complete remission

AURA-LV 2016 *(Continued)*

	• Major infection
Notes	• Abstract-only publications • Funding source: Aurinia Pharmaceuticals Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded according to protocol
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
Other bias	High risk	Pharma funded; some authors involved are employees of Aurinia

Balletta 1992

Methods	• Study design: parallel RCT • Study timeframe: not reported • Duration of follow-up: > 12 months
Participants	• Country: Italy • Setting: not reported • Inclusion criteria: lupus nephritis shown on biopsy (diffuse proliferative, mesangioproliferative, membranoproliferative, focal proliferative, diffuse proliferative) • Number (randomised): treatment group (5); control group (5) • Mean age ± SD (years): treatment group (25.6 ± 6.2); control group (23.4 ± 3.7) • Sex (M/F): treatment group (0/5); control group (1/4) • Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group
	  * Oral CSA: 1.5 mg/kg twice/d
	  * Prednisolone: as per control

Balletta 1992 *(Continued)*

	• Control group * Prednisolone: pulse, 2 to 3 mg/kg/d for 3 consecutive days, then oral dose 1 mg/kg/d for 2 months and tapered
Outcomes	• SCr • CrCl • Proteinuria
Notes	• 6/10 participants had biopsy • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Bao 2008

Methods	• Study design: open-label RCT • Study timeframe: September 2005 to December 2006 • Duration of follow-up: 6 months prolonged to 9 months if complete remission not achieved within 6 months
Participants	• Country: China • Setting: single centre • Inclusion criteria: aged 12 to 60 years; diagnosis of SLE (ACR 1997 criteria); SLEDAI ≥ 12', biopsy-proven lupus nephritis class IV + V (ISN/RPS 2003) within 3 weeks before enrolment; overt proteinuria (≥ 1.5 g/d) ± active urine sediment • Number (randomised/analysed): treatment group 1 (20/20); treatment group 2 (20/20) • Mean age ± SD (years): treatment group 1 (27.2 ± 7.1); treatment group 2 (30.6 ± 4.6) • Sex (M/F): treatment group 1 (4/16); treatment group 2 (2/18)

Bao 2008 *(Continued)*

	• Exclusion criteria: creatinine > 3.0 mg/dL (265.2 µmol/L) or CrCl < 30 mL/min/1.73 m^2 on repeated testing; deranged liver function tests; abnormal glucose; known hypersensitivity or contraindication to any of the regimens; use of CPA, MMF or TAC within the past 12 weeks; pregnancy or lactation; cerebral lupus; leflunomide and methotrexate forbidden

Interventions	Induction therapy
	• Treatment group 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)
	• Treatment group 2
	  * IV 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 WCC (≤ 2.5)
	• Both groups
	  * IV MP: 0.5 g/d for 3 days then oral prednisolone (0.6 to 0.8 mg/kg/d for 4 wk) followed by a taper (reduced by 5 mg/d every week to 20 mg/d then 2.5 mg every week until maintenance dosage of 10 mg/d)

Outcomes	• Death (all causes) • Doubling of SCr • Deterioration of kidney function • Stable kidney function (normal value SCr or no more than 15% above baseline) • Complete remission: proteinuria (< 0.4 g/24 h), normal urine sediment, serum albumin ≥ 3.5 g/dL, normal SCr or not > 15% from baseline • 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 • Major infection • Herpes zoster virus infection • Irregular menstruation • GI syndrome • Alopecia • Leucopenia • Proteinuria
Notes	• Funding source: Roche China and Astellas Ireland Co. Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list was drawn up by a statistician with a block of every four participants. They enrolled participants were allocated the next available number upon entry into the study
Allocation concealment (selection bias)	Unclear risk	A computer-generated randomisation list was given to the pharmacy department. Each patient collected medication directly from the pharmacy department. Unclear whether participants and or investigators might have an opportunity to influence assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Bao 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adjudication of primary and key secondary outcome judged at coordinating centre by personnel who had no knowledge of the treatment assignment and ratings were confirmed by repeat testing after a 1 month interval
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Supported by Roche China and Astellas Ireland. Co. Ltd. Partially supported but no role in design, study or analysis

Barron 1982

Methods	• Study design: quasi-RCT • Study timeframe: 1965 to 1980 • Duration of follow-up: mean follow-up 59 months (range: 7 to 137 months)
Participants	• Country: USA • Setting: single centre • Inclusion criteria: children with SLE (ACR criteria) and severe biopsy-proven lupus nephritis, defined by a nephrotic urine sediment and impaired kidney function with a CrCl between 25 and 80 mL/min. If CrCl > 80 mL/min, the candidate had to have very active renal histology with crescents or necrosis in more than 25% of glomeruli; renal biopsies were obtained during the 6 weeks before study entry and were evaluated by light and electron microscopy • Number (randomised): treatment group 1 (15); treatment group 2 (7) • Mean age (at onset) ± SD (years):treatment group 1 (11.9 ± 2.9); treatment group 2 (11.4 ± 3.6) • Sex (M/F): treatment group 1 (2/13); treatment group 2 (1/6) • Exclusion criteria: drug-induced SLE

Interventions	Induction therapy
	• Treatment group 1
	  * High dose oral corticosteroid: prednisone 2 mg/kg/d for 3 to 6 months then tapered
	• Treatment group 2
	  * Pulse MP then oral prednisone: 30 mg/kg body weight (maximum 1 g) IV, total of 6 treatments every other day; following completion of MP, oral prednisone 2mg/kg/d by then tapered

Outcomes	• Death (all causes) • CrCl • C3, ANA • Exacerbations • Infection • Aseptic necrosis
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Barron 1982 *(Continued)*

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 of participants and personnel (performance bias) All outcomes	High risk	No blinding due to lack of allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Other patients were randomised, but only those with > 6 months follow-up included in analysis. It is unclear how many other patients were randomised.
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	• Study design: parallel RCT (pilot study) • Study timeframe: not reported • Duration of follow-up: 18 months
Participants	• Country: USA • Setting: multicentre (number of sites not reported) • Inclusion criteria: aged 18 to 70 years; SLE (ACR criteria); active kidney disease (in the absence of infection, at least one of the following: (1) RBC casts, (2) WBC casts plus either haematuria (> 10/HPF) or pyuria (> 10/HPF), (3) proteinuria at ≥ 3 g, (4) proteinuria ≥ 1.5 g plus (a) haematuria or (b) pyuria or (c) a 25% decrease in C3 and/or C4 • Number (randomised): treatment group (7); control group (7) • Mean age ± SD: 35 ± 2 years • Sex (M/F): 3/11 • Proliferative lupus nephritis: 7/14 • Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group
	  * Oral misoprostol: 20 µg orally 4 times daily
	• Control group
	  * Oral placebo: identical capsule
	• Both groups
	  * Oral prednisone: 1 mg/kg, 4 times/d

Outcomes	• SCr • doubling of SCr • CrCl

Belmont 1995 *(Continued)*

	• ESKD • Complete remission of proteinuria • C3, C4 • Anti-dsDNA
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomly assigned but methods of sequence generation are not described
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

BELONG 2013

Methods	• Study design: double-blind, parallel RCT • Study timeframe: terminated 19 October 2009 • Duration of follow-up: 48 weeks treatment period extended to 96 week open-label
Participants	• Country: 23 countries • Setting: multinational (123 sites) • Inclusion criteria: aged ≥ 16 years; SLE (ACR criteria) including a history of anti-dsDNA positivity and active lupus nephritis (defined as UPCR ≥ 1 with biopsy-proven (within 6 months prior to randomisation)); Class III or IV with coexisting class V permitted or class III or IV GN provided that ≤ 50% of glomeruli showed sclerosis or fibrosis (WHO criteria or ISN/RPS criteria) • Number (randomised/analysed): treatment group 1 (127/73); treatment group 2 (126/75); control group (125/75) • Mean age, range (years): treatment group 1 (30.6, 16 to 60); treatment group 2 (31.9, 16 to 69); control group (31.3, 17 to 66) • Sex (M/F): treatment group 1 (18/109); treatment group 2 (12/114); control group (19/106) • Exclusion criteria: lupus class III (C), IV-S(C) and IV-G(C); retinitis; poorly controlled seizure disorder; acute confusional state; myelitis; stroke or stroke syndrome; cerebellar ataxia or dementia; severe renal impairment; estimated glomerular filtration rate <25 mL/min/1.73 m^2; ESKD requiring dialysis

BELONG 2013 *(Continued)*

	or transplant; thrombocytopenia; or experiencing or at high risk of developing clinically significant bleeding or organ dysfunction

Interventions	Induction therapy: duration of treatment 48 weeks
	• Treatment group 1
	  * IV ocrelizumab: 1000 mg infusion on days 1 and 15 followed by a single infusion at week 16 and every 16 weeks
	• Treatment group 2
	  * IV ocrelizumab: 400 mg infusion on days 1 and 15 followed by a single infusion at week 16 and every 16 weeks
	• Control group
	  * Placebo
	• All groups
	  * Groups were treated with background induction therapy at the discretion of the investigator MMF (target dose 3 g/d) or CPA (ELNT regimen: 0.5 g IV every 2 weeks). Patients receiving MMF continued to receive MMF, while patients receiving the ELNT CPA regimen were subsequently treated with azathioprine (AZA; 2 mg/kg up to 200 mg/d, dose selected by the investigator). IV MP (up to 3 g/d) was also permitted by day 15, given in divided pulses, and oral steroids (0.5–0.75 mg/kg (60 mg/d)) were allowed with taper to 10 mg over 10 weeks. Before each infusion, patients were administered IV MP (100 mg), acetaminophen/paracetamol (1 g), and an antihistamine (50 mg IV diphenhydramine HCl or equivalent)

Outcomes	• Complete renal response (normal SCr (25% increase from baseline) and improvement in UPCR to < 0.5) • Partial renal response (SCr 25% above baseline, and 50% improvement in UPCR, and if baseline ratio > 3.0, then UPCR < 3.0) • Death • Major infection • Adverse events • Proteinuria • CrCl
Notes	• Funding source: Genentech and Hoffman-La Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Study was terminated before completion. Only 36.8% of patients completed the 48-week treatment period and were included in the analysis

BELONG 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	High risk	Genentech and Hoffman-La Roche funded the study and were involved in study design; Conflict of interest of authors relating to the pharmaceutical companies that funded the study; High drop-out rates (around 52%) with the early termination of the study; The 1000 mg ocrelizumab-treated group had slightly higher proportion of Caucasian patients and a lower proportion of Asian patients than the other two groups

Boedigheimer 2017

Methods	• Study design: double-blind, phase 1b, parallel RCT • Study timeframe: 3 March 2009 to 3 June 2014 • Duration of follow-up: 6 months
Participants	• Country: USA, Mexico, France, Malaysia, Hong Kong • Setting: multinational (11 sites) • Inclusion criteria: aged 18 to 70 years; SLE (ACR criteria) with the presence of ANA at least 6 months before randomisation; any concurrent SLE medications (e.g. MMF, AZA, leflunomide, methotrexate, antimalarials) were at a stable dose for ≥ 30 days before randomisation; concurrent prednisone was 20 mg/d (or equivalent) and for subjects without lupus nephritis could be increased or decreased once by 5 mg/d within 30 days before randomisation; subjects met current recommendations for immunisations; subjects with lupus nephritis were required to have biopsy-proven active disease within 18 months of randomisation according to WHO or ISN/RPS classification class III or IV; UPCR > 1 or 24 h urine protein > 1 g following ≥ 12 weeks of standard-of-care induction treatment with prednisone plus CPA or MMF, then maintained on prednisone at 20 mg/d (or equivalent) and MMF or AZA • Number (randomised/analysed): treatment group (21/21); control group (0/21) • Mean age ± SD (years): treatment group (30.0 ± 8.1); control group (36.9 ± 11.7) • Sex (M/F): treatment group (7/7); control group (3/4) • Ethnicity: treatment group (Caucasian 6, African American 0, Hispanic 12, Asian 3, Other 0); control group (Caucasian 2, African American 0, Hispanic 2, Asian 3, Other 0) • Exclusion criteria: any disorder that would interfere with study evaluations including unstable or severe disease; presence or history of vasculitis or active central nervous system lupus requiring therapy within 3 years; uncontrolled hypertension; low CrCl (< 50 mL/min); low Hb levels, thrombocytopenia, neutropenia or low total WCC; poorly controlled diabetes; evidence of viral, bacterial or fungal infection within 30 days of randomisation or evidence of parasitic infestation; history of repeated infections or predisposition to infections; receipt of CPA, CSA, TAC, sirolimus, IVIG or plasmapheresis within 3 months of randomisation; or receipt of an investigational drug or device within 30 days or 5 half-lives of randomisation

Interventions	Induction therapy
	• Treatment group
	  * SC AMG 811: 20, 60 or 120 mg administered
	• Control group
	  * SC placebo
	• Both groups
	  * Concomitant therapy could include prednisone, MMF, AZA, methotrexate and antimalarials

Outcomes	• Death • Major infection • Adverse events • Proteinuria

Boedigheimer 2017 *(Continued)*

	• Disease activity
Notes	• Study included both patients with SLE with and without lupus nephritis, we have extracted data for patients with lupus nephritis only • Funding source: Amgen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected clinical outcomes reported
Other bias	High risk	Phase 1b study, study underpowered; study sponsor involved in data acquisition, data analysis and reporting of the study

Boletis 1999

Methods	• Study design: parallel RCT (pilot study) • Study timeframe: not reported • Duration of follow-up: 18 months
Participants	• Country: Greece • Setting: not reported • Inclusion criteria: lupus nephritis warranting CPA therapy; already received 6 months of CPA (1 g/m^2 once a month for 6 months and 0.5 mg/kg daily prednisone) with satisfactory response (absence of major side-effects requiring interruption of therapy); inactive or substantially improved urine sediment, and proteinuria of less than 1 g/d (for patients with baseline proteinuria < 3 g/d) or < 3 g/d (for patients with baseline proteinuria > 3 g/d) • Number (randomised/analysed): treatment group 1 (9); treatment group 2 (5) • Mean age ± SD (years): treatment group 1 (30.4 ± 10.9); treatment group 2 (32.4 ± 11.7) • Sex (M/F): treatment group 1 (3/6); treatment group 2 (2/3) • Exclusion criteria: previous CPA for more than 6 months, pregnancy, aged < 18 or > 75 years, history of malignant disorders
Interventions	Maintenance therapy: duration of treatment was 18 months

Boletis 1999 *(Continued)*

	• Treatment group 1
	  * IV CPA: every 2 months for 6 months and then every 3 months for 12 months
	• Treatment group 2
	  * IVIG: 400 mg/kg monthly for 18 months
	
	Both groups
	
	• Clinicians were allowed to increase the dose of prednisone if relapse or deterioration of kidney disease

Outcomes	• SCr • CrCl • Proteinuria
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Randomisation was done with sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Whether participants and investigators were blinded was not described and treatment options were quite different suggesting that personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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	• Study design: open-label, parallel RCT • Study timeframe: 1981 to 1986 • Duration of follow-up: 10 years
Participants	• Country: USA • Setting: not reported • Inclusion criteria: age range 10 to 48 years; SLE (ACR 1982 criteria) and severe lupus nephritis defined by a nephritic urine sediment and impaired kidney function with a CrCl between 25 to 80 mL/min; if the CrCl was > 80 mL/min, the candidate had to have very active renal histology with crescents or necrosis in more than 25% of glomeruli; renal biopsies were obtained during the 6 weeks before study entry and were evaluated by light and electron microscopy

Boumpas 1992 *(Continued)*

- Number (randomised): treatment group 1 (20); treatment group 2 (20); control group (25)
- Mean age ± SE (years): treatment group 1 (30 ± 2); treatment group 2 (30 ± 2); control group (31 ± 2)
- Sex (M/F): treatment group 1 (3/17); treatment group 2 (1/19); control group (1/24)
- Exclusion criteria: pregnancy; received cytotoxic drugs for more than 10 weeks; active infections; insulin-dependent DM, previous malignancy

Interventions	Induction therapy
	• Treatment group 1
	  * IV CPA: single doses 0.5 to 1 g/m^2 monthly for 6 months
	• Treatment group 2
	  * IV CPA: single doses 0.5 to 1 g/m^2 monthly for 6 months then 3 monthly for 18 months
	• Control group
	  * IV MP: 3 doses 1 g/m^2, then monthly single doses for 6 months
	Other/additional treatment
	• Patients were treated with prednisone 0.5 mg/kg/d and continuing for 4 weeks then tapered at a rate of 5 mg every other day but the minimum dose to prevent extra-renal disease

Outcomes	• ESKD • Doubling of SCr • Major infection • Herpes zoster virus • Malignancy • Haemorrhagic cystitis • Premature ovarian failure • Osteonecrosis • Relapse • Stable kidney function
Notes	• 2 withdrawals • Funding source: NIH trial

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data

Boumpas 1992 *(Continued)*

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

Cade 1973

Methods	• Study design: quasi-RCT • Study timeframe: not reported • Duration of follow-up: 36 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: Diagnosis of SLE; biopsy and functional findings of active proliferative GN due to SLE; renal biopsy classification as proliferative GN closely approximates those used by Baldwin 1970 • Number (randomised): treatment group 1 (15); treatment group 2 (13); treatment group 3 (13); treatment group 4 (13) • Mean age, range (years): treatment group 1 (26.1, 12 to 51); treatment group 2 (30.5, 11 to 62); treatment group 3 (22.4, 12 to 51); treatment group 4 (24.8, 14 to 51) • Sex (M/F): treatment group 1 (1/12); treatment group 2 (1/12); treatment group 3 (3/10); treatment group 4 (6/7) • Exclusion criteria: lupus glomerulitis; focal proliferative disease or predominantly membranous lupus nephritis

Interventions	Induction therapy
	• Treatment group 1
	  * Oral prednisone: 60 to 100 mg/d for 6 months then slowly tapered to the lowest dose that controlled the patients symptoms
	• Treatment group 2
	  * Oral AZA: started at 1.0 to 1.5 mg/kg/d, increased to 1.5 to 2.0 mg/kg/d after 6 to 8 weeks if the patient had not improved by clinical or laboratory criteria
	• Treatment group 3
	  * Oral prednisone: 60 to 100 mg/d for 6 months then slowly tapered to the lowest dose that controlled the patients symptoms
	  * Oral AZA: started at 1.0 to 1.5 mg/kg/d, increased to 1.5 to 2.0 mg/kg/d after 6 to 8 weeks if the patient had not improved by clinical or laboratory criteria
	• Treatment group 4
	  * Oral AZA: started at 1.0 to 1.5 mg/kg/d, increased to 1.5 to 2.0 mg/kg/d after 6 to 8 weeks if the patient had not improved by clinical or laboratory criteria
	  * SC heparin: doses ranging from 20,000 units every 8 hours to 5000 units every 6 hours

Outcomes	• Death (all causes) • ESKD • CrCl
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Cade 1973 *(Continued)*

Random sequence generation (selection bias)	High risk	Chronological appearance
Allocation concealment (selection bias)	High risk	Assigned in alternate fashion by division secretary
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Chan 2000

Methods	• Study design: parallel RCT • Study timeframe: November 1996 and October 1998 • Duration of follow-up: median follow-up was 63 months
Participants	• Country: Hong Kong • Setting: multicentre • Inclusion criteria: diagnosis of SLE (ACR criteria); biopsy-proven diffuse proliferative lupus nephritis (class IV) (WHO classification), urinary protein excretion of ≥ 1 g/d, a serum albumin ≤ 3.5 g/dL, SCr < 3.4 mg/dL (300 µmol/L) • Number (randomised/analysed): treatment group 1 (33/32); treatment group 2 (31/30) • Mean age ± SD (years): treatment group 1 (38.1 ± 10.2); treatment group 2 (41.8 ± 8.9) • Sex (M/F): treatment group 1 (6/26); treatment group 2 (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	Induction and maintenance therapy
	• Treatment group 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
	• Treatment group 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
	Other information

Chan 2000 *(Continued)*

	• 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	• Death • ESKD • Doubling of SCr • Doubling kidney function • Relapse • Major infection • Herpes zoster virus infection • Ovarian failure • Bone toxicity • Alopecia • GI upset • Lymphopenia • Complete remission of proteinuria: < 0.3 g/24 h • Partial remission of proteinuria: > 50% reduction in proteinuria, proteinuria between 0.3 and 3 g/24 h • SCr • CrCl • Daily proteinuria
Notes	• Follow-up: 3585 patient-months (median follow-up 63 months); 2 withdrawals (1 in each group); 62/64 followed-up • Funding source: Roche pharmaceuticals supplied MMF

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
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...Clinical status was reviewed and categorised at the coordinating centre by personnel who had no knowledge of the treatment assignment...."
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

Chen 2011

Methods	• Study design: open-label, parallel RCT • Study timeframe: June 2006 to March 2008 • Duration of follow-up: 6 month follow-up; extended median follow-up was 6 months

Participants	• Country: China
	• Setting: multicentre (9 sites)
	• Inclusion criteria: aged 14 to 65 years; diagnosis of SLE (ACR criteria); biopsy-proven (within 6 months) lupus nephritis class III, IV-S, IV-G, (A) or (A/C), or class V alone or in combination with class III or IV (ISN/RPS 2003 criteria); laboratory tests documented the presence of active nephritis, defined as proteinuria (protein excretion > 1 g/24 h) or increased SCr (> 1.3 mg/dL) with active urinary sediment (any of > 5 RBC/HPF, > 5 WBC/HPF, or RBC casts in the absence of infection or other causes) in patients with class IV-S or IV-G and significant proteinuria (protein excretion > 2 g/24 h) or increased SCr (> 1.3 mg/dL) in patients with class III or V
	• Number (randomised/analysed)
	  * Induction therapy: treatment group 1 (42/39); treatment group 2 (39/34)
	  * Maintenance therapy: treatment group 1 (34/34); treatment group 2 (36/36)
	• Mean age ± SD (years)
	  * Induction therapy: treatment group 1 (32.0 ± 10.8); treatment group 2 (31.9 ± 10.1)
	  * Maintenance therapy: treatment group 1 (30.7 ± 10.2); treatment group 2 (33.1 ± 10.9)
	• Sex (M/F)
	  * Induction therapy: treatment group 1 (5/37); treatment group 2 (7/32)
	  * Maintenance therapy: treatment group 1 (5/29); treatment group 2 (4/32)
	• 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	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * Oral TAC: 0.05 mg/kg divided in 2 doses with target trough of 5 to 10 ng/mL
	• Treatment group 2
	  * IV 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 groups
	  * 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
	Long-term maintenance therapy: duration of therapy was 6 months
	• Treatment group 1
	  * Oral TAC: trough blood concentrations were maintained at 4–6 ng/mL.
	• Treatment group 2
	  * AZA: 2 mg/kg/d
	• Both groups
	  * Oral prednisone: 10 mg/d

Outcomes	• Death • Major infection • Herpes zoster virus infection • Ovarian failure • Alopecia • GI upset • Lymphopenia

Chen 2011 *(Continued)*

	• Complete renal remission: daily proteinuria < 0.3 g/24 h, normal urinary sediment, serum albumin ≥ 3.5 g/dL and stable kidney function • 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 • Treatment failure: failure to meet complete or partial remission • SCr • Daily proteinuria
Notes	• Funding source: Scientific and Technologic Committee of Guangdong province, the Department of Health, Guangzhou city, the Ministry of Education, Peoples' Republic of China and the 5010 Clinical Program of Sun Yat-sen University. Astellas Pharmaceutics supplied TAC

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	The primary outcome (complete remission) and secondary outcomes partial remission and treatment failure were reported on an intention to treat bases. The attrition rate for secondary safety outcomes were 92.8% (39/42) for the TAC group and 87.2% for the IV CPA group.
Selective reporting (reporting bias)	Low risk	Study protocol available and prespecified outcomes were reported
Other bias	Low risk	Astellas Pharmaceutics supplied TAC but had no role in the design or conduct of the study or analysis or interpretation of results

Clark 1981

Methods	• Study design: open-label RCT • Study timeframe: from February 1978 • Duration of follow-up: 12 months
Participants	• Country: Canada • Setting: not reported • Inclusion criteria: Diagnosis of SLE (ACR criteria) and had increased DNA, low complement; presence of ANA; renal biopsy showing diffuse proliferative GN; CrCl > 30 mL/min at study entry • Number: treatment group 1 (6); treatment group 2 (6) • Mean age ± SD (years): not reported

Clark 1981 *(Continued)*

- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group 1
	  * Corticosteroids
	  * AZA
	• Treatment group 2
	  * Corticosteroids
	  * AZA
	  * Plasmapheresis

Outcomes	• Death • ESKD • Doubling of SCr • SCr • CrCl • Proteinuria
Notes	• Funding source: Physicians' Services Incorporated Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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	• Study design: parallel RCT • Study timeframe: not reported

Clark 1984 *(Continued)*

	• Duration of follow-up: 19 months
Participants	• Country: Canada. West Indies • Setting: multinational (3 sites) • Inclusion criteria: diagnosis of SLE (ACR criteria) and had at least one episode of ANA positivity; elevated DNA binding and complement depression; renal biopsy showing diffuse proliferative GN • Number (randomised): treatment group 1 (19); treatment group 2 (20) • Mean age ± SD (years): treatment group 1 (25 ± 2); treatment group 2 (26 ± 2) • Sex (M/F): treatment group 1 (1/18); treatment group 2 (5/15) • Exclusion criteria: CrCl < 30 mL/min or SCr > 3 mg/dL

Interventions	Induction therapy
	• Treatment group 1
	  * Steroids ± cytotoxics
	• Treatment group 2
	  * Conventional therapy
	  * PEX: 4 L within the first two weeks, thereafter one 4 L PEX every 3-4 weeks. In two centres patients received replacement with 5% human serum albumin and in one centre replacement was with plasma

Outcomes	• Death • ESKD • Doubling of SCr • SCr
Notes	• Funding source: Physicians' Services Incorporated Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	"Designated non-medical person at each Centre who removed a pre-folded slip of paper from a bowl"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all relevant outcomes are 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

Contreras 2004

Methods	• Study design: open-label, parallel RCT • Study timeframe: August 1996 and May 2003 • Duration of follow-up: 72 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: diagnosis of SLE (ACR criteria); ≥ 18 years; histologic diagnosis of proliferative lupus nephritis (WHO class III, IV, or Vb); classes III (12), IV (46) or Vb (1) • Number (randomised/analysed): treatment group 1 (19/19); treatment group 2 (20/20); treatment group 3 (20/20) • Mean age ± SD (years): treatment group 1 (33 ± 10); treatment group 2 (33 ± 12); treatment group 3 (32 ± 11) • Sex (M/F): treatment group 1 (1/19); treatment group 2 (2/18); treatment group 3 (1/19) • Exclusion criteria: CrCl that was consistently < 20 mL/min; any clinically significant infection; pregnancy; the receipt of more than seven doses of IV CPA, or the receipt of AZA for longer than 8 weeks

Interventions	Maintenance therapy: duration of therapy 1 to 3 years
	• Treatment group 1
	  * IV CPA: 0.5 to 1.0 g/m^2 every 3 months
	• Treatment group 2
	  * AZA: 1 to 3 mg/kg/d
	• Treatment group 3
	  * MMF: 500 to 3000 mg/d
	• All groups
	  * Induction therapy of 7 monthly boluses of IV CPA 0.5 to 1.0 g/m^2 and corticosteroids and maintenance therapy included prednisolone (up to 0.5 mg/kg/d)

Outcomes	• ESKD • Death • Doubling of SCr • Stable kidney function • Relapse: doubling of the UPCR (proteinuric) or an increase in SCr level of 50% or more for more than 1 month (nephritic) • Major infection • Herpes zoster virus infection • Malignancy • Ovarian failure
Notes	• Funding source: Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"After induction, participants were randomly assigned, in order of enrolment by means of sealed envelopes (stratified in two groups: blacks and other participants)." - consecutive sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelopes used

Contreras 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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	High risk	Roche pharmaceutical providing research nurse support and MMF 1999 to 2003. Authors received fees for lectures and a grant from Roche Pharmaceuticals.

CYCLOFA-LUNE 2010

Methods	• Study design: open-label, parallel RCT • Study timeframe: January 2002 to December 2006 • Duration of follow-up: median extended follow-up 7.7 years (range 5.0 to 10.3 years)
Participants	• Country: Czech Republic; Slovakia • Setting: multinational (8 sites) • Inclusion criteria: ACR criteria for SLE; biopsy-proven lupus nephritis (WHO or ISN/RPS criteria) and clinical activity as defined by presence of at least two of the following: abnormal proteinuria (more than 500 mg/24 h), abnormal microscopic haematuria, or C3 hypocomplementaemia • Number (analysed): treatment group 1 (21); treatment group 2 (19) • Mean age ± SD (years): treatment group 1 (30 ± 9); treatment group 2 (28 ± 5) • Sex (M/F): treatment group 1 (6/15); treatment group 2 (5/14) • 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, or active peptic ulcer

Interventions	Induction and maintenance therapy: duration of therapy was 9 months induction therapy and 9 months maintenance therapy
	• Treatment group 1
	  * Intermittent IV CPA: 10 mg/kg x 8 over 9 months followed by 4 or 5 oral pulses (10 mg/d in 6 to 8 week intervals)
	• Treatment group 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 groups
	  * 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	• Death • Renal relapse: signs of renal activity

CYCLOFA-LUNE 2010 *(Continued)*

	• Major infection • Herpes zoster virus • Ovarian failure • Bladder toxicity • Alopecia • Lymphopenia • Complete renal remission: SCr within the normal range with stable or improved values as compared with baseline (no more than 15% above baseline), AND inactive urinary sediment, AND normal range proteinuria (< 0.3 g/24 h) • Partial renal remission: SCr within the normal range with stable or improved values as compared with baseline (no more than 15% above baseline), AND at least 50% decrease in proteinuria to less than 3 g/d if nephrotic at baseline, or to 0.5 g/d if baseline non-nephrotic, AND either inactive urinary sediment or at least 25% improvement in C3 complement (patients with complete remission are counted within this less strict category as well • SCr • Proteinuria
Notes	• Funding source: IGA Ministry of Health Czech Republic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation 1:1, non-blocked methods for sequence generation not reported
Allocation concealment (selection bias)	Low risk	Central computerised system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

Decker 1975

Methods	• Study design: open-label, parallel RCT • Study timeframe: 1969 to 1981 • Duration of follow-up: median 7 years
Participants	• Country: USA

Decker 1975 *(Continued)*

- Setting: multicentre (number of sites not reported)
- Inclusion criteria: Diagnosis of SLE (ACR criteria); clinical or histologic evidence of active lupus GN (mostly proliferative lesions) (WHO classification criteria)
- Number (randomised/analysed): treatment group 1 (30/28); treatment group 2 (20/19); treatment group 3 (18/18); treatment group 4 (23/22); treatment group 5 (20/20)
- Age: median age 27 years (age for individual groups not reported)
- Sex (M/F): 15/92 (sex for individual groups not reported)
- Biopsy-proven lupus nephritis: (60/107)
- 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	Induction therapy: duration of therapy until 18 months of remission had been achieved or 4 years of protocol therapy
	• Treatment group 1
	  * Prednisolone alone: 1 mg/kg for 4 to 8 weeks, then tapering
	• Treatment group 2
	  * AZA: up to 4 mg/kg/d
	• Treatment group 3
	  * Oral CPA: up to 4 mg/kg/d
	• Treatment group 4
	  * CPA and AZA: up to 1 mg/kg/d of each
	• Treatment group 4
	  * IV pulse CPA: IV every 3 month 0.5 to 1.0 g/m^2
	• Additional treatment
	  * Groups 2 to 4 were also treated with low-dose prednisone (up to 0.5 mg/kg/d)

Outcomes	• Death • ESKD • Doubling of SCr • Toxicity • Stable kidney function • Herpes zoster virus infection • Major infection • Cancer • Premature ovarian failure • Haemorrhagic cystitis
Notes	• Funding source: NIH trial

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 of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Decker 1975 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	3.6% (4/111) of participants excluded as they did not complete 3 months of treatment
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	High risk	Patients were assigned to treatment groups 1, 2 and 3 from the beginning of the study (1969). Treatment groups 4 and 5 were introduced in January 1973. Pooling of multiple studies

Deng 2016

Methods	• Study design: parallel RCT • Study timeframe: not reported • Duration of follow-up: not reported
Participants	• Country: China • Setting: not reported • Inclusion criteria: biopsy-proven proliferative lupus nephritis • Number: 30 (numbers not available for groups) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * CPA: route of administration and dosage not reported
	• Treatment group 2
	  * Leflunomide: route of administration and dosage not reported
	• Both groups
	  * Prednisone: dosage not reported

Outcomes	• Adverse events • Proteinuria • Serum albumin
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

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

Deng 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all pre-specified outcomes found on the protocol are reported; data could not be meta-analysed
Other bias	High risk	Primary outcomes identified on clinicaltrials.gov page not reported. Focus on p-values in the results, with no reporting of the continuous or categorical data

Derksen 1988

Methods	• Study design: parallel RCT • Study timeframe: 1981 to 1985 • Duration of follow-up: 26 weeks
Participants	• Country: Netherlands • Setting: multicentre (5 sites) • Inclusion criteria: diagnosis of SLE (ARA criteria); presence of active lupus nephritis, defined by a decreased CrCl, an active urine sediment (> 5 RBC/HPF and cellular casts) and proteinuria > 0.5 g/24 h; biopsy-proven proliferative lupus nephritis (class III or IV WHO classification criteria); insufficient response of kidney function to treatment with corticosteroids alone given in a single daily dose of 1-1.5 mg/kg for at least 3 weeks • Number (randomised): treatment group 1 (11); treatment group 2 (9) • Mean age, range SD (years): treatment group 1 (28, 15 to 55); treatment group 2 (36, 18 to 60) • Sex (M/F): treatment group 1 (3/8); treatment group 2 (2/7) • Exclusion criteria: deterioration of kidney function could be explained by other causes, such as the use of NSAIDs, infection or hypotension; patients with active renal insufficiency with oliguria/anuria (dialysis indications), and patients with psychiatric manifestations

Interventions	Induction therapy: duration of therapy was 26 weeks
	• Treatment group 1
	  * Prednisone ± cytotoxics (oral AZA or CPA 2 mg/kg if kidney function and haematological functions permitted)
	• Treatment group 2
	  * PEX alone: short course
	• Both groups
	• Daily oral prednisone (1.5 mg/kg) until the time of randomisation, the dose was gradually reduced (a decrease in daily dose of 10 mg, once a week) until a daily dose of 1 mg/kg was reached

Outcomes	• Death • ESKD

Derksen 1988 *(Continued)*

	• CrCl
Notes	• Funding source: not reported

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 of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all expected outcomes are reported
Other bias	High risk	Pooling interventions in cytotoxic group

Donadio 1972

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: 3 years
Participants	• Country: USA • Setting: single centre • Inclusion criteria: histologic evidence of kidney disease; one or more of the following: serositis, arthralgia, and arthritis, skin rash consistent with SLE and haematological abnormalities that included leukopenia, thrombocytopenia or a circulating anticoagulant • Number (randomised): treatment group (7); treatment group (9) • Age range: 17 to 68 years • Sex (M/F): 2/14 • Exclusion criteria: received > 7.5 mg prednisone daily in the previous 6 months (except a dose of 20 mg daily for a maximum of 2 weeks); previous cytotoxic medication other than antimalarial treatment
Interventions	Induction therapy • Treatment group * Prednisone + AZA (2 mg/kg/body weight for 6 months); average duration of therapy was 26 months for AZA

Donadio 1972 *(Continued)*

	• Control group * Prednisone: 60 mg/d for 2 months, 40 mg/d by 3 months, 30 mg/d by 4 months, 25 mg/d by 5 months and 20 mg/d by 6 months
Outcomes	• Death • Complete remission • Relapse • Toxicity • CrCl • Proteinuria • Leucopenia (WCC < 3000/mL^3)
Notes	• Funding source: Mayo Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	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 1976

Methods	• Study design: open-label, parallel RCT • Study timeframe: commenced December 1971 • Duration of follow-up: 4 years
Participants	• Country: USA • Setting: single centre • Inclusion criteria: SLE fulfilled 4 or more criteria used for the classification of the disease; a positive LE-cell preparation or rosettes of neutrophils or nucleolysis; a positive antinuclear-antibody test in titres ≥ 1:32 or elevated levels of anti-nDNA; CrCl < 80 mL/min/1.73 m^2 or a reduction of 25% in the

Donadio 1976 *(Continued)*

	CrCl as compared with the initial clearance of a maximal period of three months; and adequate renal biopsy showing diffuse proliferative GN • Number (randomised): treatment group (24); control group (26) • Mean age, range (years): treatment group (30.2, 16 to 60); control group (32.3, 17 to 50) • Sex (M/F): treatment group (5/19); control group (4/22) • Exclusion criteria: Previous CPA or immunosuppressive drugs in the last 6 months
Interventions	Induction therapy • Treatment group * Oral CPA: 2 mg/kg/d for 6 months * Maintenance dose of prednisone to control other systemic manifestations • Control group * Prednisone: 60 mg/d tapered after 1 to 3 months
Outcomes	• ESKD • Death • Toxicity • Major infection • Treatment failure: ESKD or final CrCl increased by 25% • Relapse: reappearance of systematic features, reductions in CrCl, increased proteinuria and changes in anti-nDNA and CH50 levels • Current status on kidney function • Proteinuria • Avascular necrosis
Notes	• Funding source: Mayo Foundation and Constance Belden Memorial Fund

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	Low risk	All expected outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Doria 1994

Methods	• Study design: parallel RCT • Study timeframe: 1988 to 1993 • Duration of follow-up: every 4 weeks for 24 months and then every 8 weeks thereafter
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: SLE (1982 ACR criteria); biopsy-proven class IV lupus nephritis (WHO classification criteria); normal kidney function (SCr ≤ 1.2 mg/dL) • Number (randomised): treatment group 1 (7); treatment group 2 (5); control group (6) • Mean age, range (years): treatment group 1 (30, 20 to 55); treatment group 2 (23, 15 to 32); control group (25, 15 to 46) • Sex (M/F): 2/16 (not reported for individual groups) • Exclusion criteria: Pregnancy; aged < 15 and > 80 years; infections; insulin-dependent DM; history of malignancy; immunosuppressive therapy within a 6 month period prior to renal biopsy

Interventions	Induction therapy
	• Treatment group
	  * Standard therapy
	  * PEX: 3 x times weekly for 1 week then twice a week for 2 weeks then once a week for 2 months then once a fortnight for 3 months. 50% of the patient's plasma volume was removed and replaced with a 4% human albumin solution
	• Treatment group 2
	  * Standard therapy
	  * IV MP: 500 mg daily for 3 consecutive days
	• Control group
	  * Standard therapy
	  ☐ Prednisone: 2 mg/kg/d for 4 weeks with slow tapering (5 mg every 10 days)
	  ☐ AZA: 2 mg/kg/d

Outcomes	• Death • ESKD • Doubling of SCr • 24 h urinary protein • Partial remission • Complete remission • Herpes zoster virus • Leucopenia
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Doria 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Dyadyk 2001

Methods	• Study design: parallel RCT • Study timeframe: not reported • Duration of follow-up: 19 years
Participants	• Country: Ukraine • Setting: not reported • Inclusion criteria: diffuse proliferative lupus nephritis class IV (WHO classification criteria) • Number (randomised/analysed): treatment group 1 (21/21); treatment group 2 (38/38) • Mean age: 36 years (not reported for groups) • Sex (M/F): treatment group 1 (4/17); treatment group 2 (5/33) • Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group 1
	  * AZA: 1.5 to 2.0 mg/kg/d; mean total duration of therapy (18.9 months)
	• Treatment group 2
	  * CPA: 1.5 to 3.5 mg/kg/d; mean total duration of therapy (21.7 months)

Outcomes	• Death (all causes) • Complete remission • Partial remission
Notes	• Abstract-only publications • 5 and 10 year survival follow-up • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Dyadyk 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all relevant reported outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

El-Sehemy 2006

Methods	• Study design: parallel RCT • Study timeframe: commenced January 2004 • Duration of follow-up: 6 months
Participants	• Country: Egypt • Setting: single centre • Inclusion criteria: all SLE patients; class III (1), class IV (10), class Vc (5), class Va or b (4), class V (1), unclassified (1) • Number (randomised/analysed): treatment group 1 (7/7); treatment group 2 (7/7); treatment group 3 (8/8) • Age range (years): treatment group 1 (18 to 29); treatment group 2 (19 to 24); treatment group 3 (18 to 27) • Sex (M/F): all female • Exclusion criteria: uncontrolled infection; CNS manifestations; known neoplastic disease; intention to become pregnant; previous immunosuppressive drugs < 3 months prior to study

Interventions	Induction therapy: duration of therapy not reported
	• Treatment group 1
	  * CPA: 0.75 mg/m^2
	• Treatment group 2
	  * CSA: 1 to 2 mg/kg/d
	• Treatment group 3
	  * AZA: 1 to 2 mg/kg/d
	• All groups
	  * 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	• Major infection • Ovarian failure • Proteinuria

El-Sehemy 2006 *(Continued)*

	• CrCl
Notes	• Three participants from group 1 and one participant from group 3 shifted to group II due to side effects or no response • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected patient outcomes reported
Other bias	High risk	Baseline kidney function highly different between groups. Reported outcomes with patients transferred to different groups

El-Shafey 2010

Methods	• Study design: open label, RCT • Study timeframe: February 2006 to December 2008 • Duration of follow-up: 24 weeks
Participants	• Country: Egypt • Setting: single centre • Inclusion criteria: diagnosis of SLE (ACR criteria); newly diagnoses active proliferative class III or IV lupus nephritis (WHO classification criteria); ≥15 years • Number (randomised/analysed/completed 24 week induction phase): treatment group 1 (24/24/20); treatment group 2 (23/23/19) • Mean age ± SD (years): treatment group 1 (22.8 ± 5.8); treatment group 2 (23.8 ± 5.6) • Sex (M/F): treatment group 1 (1/23); treatment group 2 (1/22) • Exclusion criteria: eGFR < 30 mL/min, SCr > 200 µmol/L, WCC < 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	Induction therapy: duration of therapy was 6 months

El-Shafey 2010 *(Continued)*

- Treatment group 1
  - MMF: 1 g twice daily for 6 months
- Treatment group 2
  - IV CPA: 0.5 to 1.0 g/m^2 for 6 months, median monthly dose 0.75 g/m^2
- Both groups
  - 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	• Death (all causes) • ESKD • Remission: combined complete and partial remission at 6 months • Complete renal remission: normal SCr, proteinuria < 0.5 g/d and urine RBC < 5 per HPF, without RBC cast • Partial renal remission: improvement of 50% in all abnormal renal measurements without deterioration (within 20%) of any measurement • Major infection • Herpes zoster virus • Menstrual irregularities • Diarrhoea • Lymphopenia • SCr • eGFR • Proteinuria
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	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

Florez-Suarez 2004

Methods	• Study design: parallel RCT • Study timeframe: not reported • Duration of follow-up: 1year
Participants	• Country: Mexico • Setting: not reported • Inclusion criteria: lupus nephritis patients type IV and V • Number (randomised): 20 (numbers per group not reported) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy: duration of treatment was 12 months
	• Treatment group 1
	  * MMF: up to 2 g/d
	• Treatment group 2
	  * IV CPA: monthly (does not reported)
	• Both groups
	  * Prednisone

Outcomes	• Complete remission • Partial remission • Treatment failure • Death
Notes	• Abstract-only publication; authors contact - no reply • Funding source: Roche Mexico

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Data unable to be meta-analysed

Florez-Suarez 2004 *(Continued)*

Other bias	High risk	abstract-only publication; funded by Roche Mexico

Fries 1973

Methods	• Study design: open-label, RCT • Study timeframe: not reported • Duration of follow-up: 40 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: SLE with antinuclear antibodies; involvement of two or more organs • Number (randomised/lupus nephritis): treatment group (10/5); control group (12/5) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group
	  * CPA: adjusted on the basis of weekly WCC, attempting to maintain a WCC between 3500 and 4000 cells/cu mm
	• Control group
	  * Prednisone: 1 mg/kg/d

Outcomes	• Relapse • Failure or response of treatment
Notes	• Significant cross-over • Funding source: Clinical Research centre Grant RR-70 and Biotechnology Resources Branch of the National Institutes of Health RR00311-04

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Fries 1973 *(Continued)*

Selective reporting (reporting bias)	High risk	Not all relevant reported outcomes are reported
Other bias	High risk	Heavy cross-over between groups

Fu 1997

Methods	• Study design: parallel RCT • Study timeframe: July 1994 to December 1995 • Duration of follow-up: 1 year
Participants	• Country: Taiwan • Setting: single centre • Inclusion criteria: diagnosis of SLE (ACR 1982 revised criteria); class III-IV lupus nephritis proven by biopsy (WHO classification criteria) with heavy proteinuria and normal SCr • Number (randomised): treatment group 1 (20); treatment group 2 (20) • Mean age ± SD (years): treatment group 1 (10.2 ± 3.4); treatment group 2 (10.4 ± 3.1) • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Maintenance therapy: duration of treatment was 12 months
	• Treatment group 1
	  * Oral CPA: 2 mg/kg/d
	  * Prednisolone: 2 mg/kg/d
	• Treatment group 2
	  * CSA: 5 mg/kg/d every 12 h
	• Both groups
	  * 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	• Proteinuria • SCr • CrCl • Height velocity • Height SDS
Notes	• Funding source: not reported

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 random number table
Allocation concealment (selection bias)	Low risk	Used sealed, completely opaque, envelopes numbered in sequence according to a table of random numbers
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Fu 1997 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

Furie 2014

Methods	• Study design: double-blind, parallel RCT • Study timeframe: not reported • Duration of follow-up: 12 months
Participants	• Countries: North America, Europe, South America, Asia, Australia, India, South Africa, Turkey • Setting: multinational (85 sites) • Inclusion criteria: aged ≥ 18 years; diagnosis of SLE (ACR criteria); class III or IV GN (ISN/RPS 2003 criteria or WHO 1982 classification), complement C3 or C4 levels below the lower limit of normal or elevated anti-dsDNA antibody titres at the time of screening were further requirements for eligibility as were UPCR of ≥ 0.44 mg/mg (50 mg/mmol) at the time of screening and active urinary sediment (> 5 RBC or >8 WBC/HPF or cylinduria at time of screening or the current flare • Number (randomised/analysed): treatment group 1 (99/99); treatment group 2 (99/99); control group (100/100) • Mean age ± SD (years): treatment group 1 (30.5 ± 10.6); treatment group 2 (31 ± 9.5); control group (31.8 ± 9) • Sex (M/F): treatment group 1 (13/86); treatment group 2 (15/84); control group (19/81) • Exclusion criteria: evidence of severe, rapidly advancing kidney failure (i.e. increase in SCr levels of ≥ 1 mg/dL within 1 month prior to screening or a SCr level of > 3 mg/dL); evidence of severe unstable and or progressive central nervous system lupus; use of immunosuppressive or immunomodulatory agents during the study except for antimalarial agents and protocol defined MMF and glucocorticoids

Interventions	Induction therapy: duration of therapy was 12 months
	• Treatment group 1
	  * Abatacept 10/10 regimen: weight tiered (500 mg for patients weighing < 60 kg, 750 mg for patients 60–100 kg, 1,000 mg for patients >1 00 kg) on days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337
	• Treatment group 2
	• Abatacept 30/10 regimen: 30 mg/kg on days 1, 15, 29, and 57, followed by abatacept approximating 10 mg/kg (weight tiered: 500 mg for patients weighing <60 kg, 750 mg for patients 60–100 kg, 1,000 mg for patients >100 kg) on days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337
	• Control group
	  * Placebo: consisted of dextrose 5% in water or normal saline on days 1, 15, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337
	• All groups
	  * MMF (dosage based on race and prior treatment) and prednisone (or prednisone equivalent), followed by adjustment or taper

Furie 2014 *(Continued)*

Outcomes	• Death (all causes) • ESKD • Complete response: 1) eGFR 90% of screening level if normal at screening visit, or eGFR 90% of 6-month, pre-flare value if abnormal at screening, 2) UPCR 0.26 g/g (30 mg/mmol), and 3) inactive urinary sediment (RBC and WBC/HPF within normal limits of central laboratory assessments; no RBC or WBC casts) • Partial response: SCr level normal or 125% of baseline; UPCR 50% of baseline and 3.0 g/g (339 mg/mmol) if nephrotic, or 1.0 g/g (133 mg/mmol) if non-nephrotic; urinary sediment inactive or 50% reduction in RBC/HPF from baseline; for confirmation, assessed on day 337 and confirmed on day 365 • Major infection • Herpes zoster virus
Notes	• Funding source: Bristol Myers Squibb

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported, however patients were stratified according to prior treatment
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy placebo study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not all relevant reported outcomes are reported
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	High risk	Sponsor included in data analysis/authorship

Ginzler 1976

Methods	• Study design: cross-over RCT • Study timeframe: not reported • Duration of follow-up: 4 months then crossed over
Participants	• Country: USA • Setting: single centre • Inclusion criteria: diagnosis of SLE (ARA criteria); active kidney disease as manifested by either 1) the new appearance of hypocomplementaemia, azotaemia (SCr > 1.2 mg%), urinary protein excretion >200 mg/24 h; cellular casts or more than 10 RBC/HPF in the urine sediment, or hypertension, or 2) deterioration in renal status in a patient with previously known renal disease, including either the

Ginzler 1976 *(Continued)*

	new development of any of the above manifestations, or a 50% increase in SCr, or a 200% increase in urinary protein excretion; a renal biopsy demonstrating diffuse proliferative or membranous GN • Number (randomised): treatment group 1 (8); treatment group 2 (6) • Mean age ± SD (years): treatment group 1 (28.2 ± 8.5); treatment group 2 (25.8 ± 6.2) • Sex (M/F): not reported • Exclusion criteria: SCr > 3 mg/dL, previous exposure to cytotoxic drugs

Interventions	Induction therapy: duration of treatment was 4 months
	• Treatment group 1
	  * Oral AZA: 1.25 mg/kg/d
	  * CPA: 1.25 mg/kg/d
	• Treatment group 2
	  * AZA: 2.5 mg/kg/d
	• Both groups
	  * Prednisone prior to randomisation (minimum dose of 1 mg/kg/d for 3 weeks); steroid dose was tapered throughout the study by a maximum of 5 mg decrements at each clinic visit, in accordance with parameters of clinical disease activity

Outcomes	• Death • ESKD • Toxicity • Proteinuria • CrCl • Ovarian failure • Infection
Notes	• Funding source: Supported by a grant from Lupus Erythematosus Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with a cross-over to other treatment under certain conditions (predetermined therapeutic failures)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

Ginzler 1976 *(Continued)*

Other bias	High risk	Cross-over design and reporting of results, difficult to separate treatment effects

Ginzler 2005

Methods	• Study design: open-label, non-inferiority RCT • Study timeframe: December 1999 to October 2003 • Duration of follow-up: 24 weeks
Participants	• Country: USA • Setting: multicentre (19 sites) • Inclusion criteria: diagnosis of SLE (ACR criteria), 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 • Number (randomised/analysed): treatment group 1 (71/71); treatment group 2 (69/69) * 113 had diffuse proliferative lupus nephritis; 27 had pure membranous • Mean age ± SD (years): treatment group 1 (32.5 ± 10); treatment group 2 (31.0 ± 9.0) • Sex (M/F): treatment group 1 (10/61); treatment group 2 (4/65) • Ethnicity (Black/white/Hispanic/Asian/other): treatment group 1(43/12/10/6/0); treatment group 2 (36/12/18/2/1) • Exclusion criteria: CrCl < 30 mL/min, SCr > 3.0 mg/dL; severe co-existing conditions precluding immunosuppression or requiring IV antibiotics; prior treatment with MMF; treatment with IV CPA in last 12 months; treatment within last 30 days; pregnancy or lactation

Interventions	Induction therapy: duration of therapy was 24 weeks
	• Treatment group 1
	  * MMF: 0.5 g twice daily to increase to max 1 g 3 times/d
	• Treatment group 2
	  * IV CPA: 0.5 g/m^2 BSA increased to 1.0 g/m^2
	• Both groups
	  * Prednisone at a dose of 1 mg/kg/d, with tapering by 10 to 20% at 1 week or 2 week intervals, on the basis of clinical improvement
	  * The new appearance or worsening of manifestations of extrarenal disease could be treated with one 3-day pulse of IV MP or increased dose of prednisone to a maximum of 2 mg/kg/d

Outcomes	• Death • ESKD • Doubling of SCr • Relapse • Stable kidney function • Major infection • Herpes zoster • Ovarian failure • GI upset • Diarrhoea • Lymphopenia (< 800 lymphocytes/mm^3) • Complete remission in proteinuria • Partial remission in proteinuria • Complete renal remission: defined at 24 weeks as return to within 10% of normal values of SCr levels, proteinuria, and urine sediment

Ginzler 2005 *(Continued)*

	• Partial renal remission: defined at 24 weeks as improvement of 50% in all abnormal renal measurements, without worsening (within 10 percent) of any measurement • Treatment failure: patients in whom treatment failed included all those without complete or partial remission at 24 weeks, plus those who stopped treatment for any reason • SCr • Daily proteinuria
Notes	• 1 participant on MMF crossed-over to CPA and 2 participants on IV CPA crossed over to MMF • Funding source: FDA's Orphan Products Development program and a supplemental grant from Roche Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Due to early termination, primary outcome as per protocol not reported; Not all expected outcomes reported
Other bias	High risk	The study was terminated early and there was heavy cross-over between study arms. Funding provided by a supplemental grant from Roche laboratories

Gourley 1996

Methods	• Study design: open-label, parallel RCT • Study timeframe: from mid 1990 • Duration of follow-up: > 5 years
Participants	• Country: USA • Setting: single centre • Inclusion criteria: SLE; GN was defined as a sediment on 2 or more urinalysis that showed either 10 or more RBC/HPF or erythrocyte or leukocyte casts (without evidence of infection) or both plus biopsy-proven active proliferative lupus GN (within 3 months of study entry); 79/82 class III/IV on biopsy; 3/82 no biopsy • Number (randomised): treatment group 1 (27); treatment group 2 (28); control group (27) • Mean age (years): treatment group 1 (30); treatment group 2 (31); control group (30) • Sex (M/F): treatment group 1 (6/21); treatment group 2 (3/25); control group (5/22)

Gourley 1996 *(Continued)*

	• 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 DM; allergy to study medication

Interventions	Induction therapy
	• Treatment group 1
	  * IV CPA: 0.75 g/m^2 boluses monthly for 6 months then 3 monthly for at least 2 years
	• Treatment group 2
	  * IV MP: as per control group
	  * IV CPA: as per treatment group 1
	• Control group
	  * IV MP: 3 doses (1 g/m^2) over 3 consecutive days then one dose monthly for 12 months
	• All groups
	  * Initially given oral prednisone (0.5 mg/kg/d) for 4 weeks. The prednisone dose was then tapered by 5 mg every other day each week to the minimal dose required to control extrarenal disease or 0.25 mg/kg every other day, whichever was greater
	  * For severe extrarenal flares of lupus, patients were permitted to receive prednisone, 1.0 mg/kg per day for 2 weeks

Outcomes	• Death • ESKD • Doubling of SCr • Renal remission • Treatment failure: ≥ 10 RBC/HPF, cellular casts, proteinuria (>1 g of protein/d) • Relapse: reactivation of renal disease after 6 or more months of remission • One or more infections • Herpes zoster virus infection • Amenorrhoea • Avascular necrosis
Notes	• 2 participants lost to follow-up • Funding source: Arthritis Foundation

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)	Unclear risk	Using masked card but no description methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome data with the exception of adverse events, were collected in a blinded manner
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; participants at endpoints censored but considered in final analysis

Gourley 1996 *(Continued)*

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

Grootscholten 2006

Methods	• Study design: parallel RCT • Study timeframe: September 1995 to September 2001 • Duration of follow-up: 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). Median extended follow-up was 9.6 years (range 0.1 to 13.2 years)
Participants	• Country: Netherlands • Setting: multicentre (number of sites not reported) • Inclusion criteria: biopsy-proven lupus nephritis (PALGA), diagnosis of SLE (ACR criteria); 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 • Number (randomised/analysed): treatment group 1 (50/50); treatment group 2 (37/37) • Mean age, range (years): treatment group 1 (30, 24 to 47); treatment group 2 (33, 26 to 39) • Sex (M/F): treatment group 1 (6/44); treatment group 2 (9/28) • 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 treatment; 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	Induction and maintenance therapy
	• Treatment group 1
	  * IV CPA: 750 mg/m^2, 13 pulses in 2 years, oral prednisolone cumulative corticosteroid dose (11 g)
	• Treatment group 2
	  * Oral AZA: 2 mg/kg/d in 2 years, IV MP (3 x 3 pulses of 1000 mg) and oral prednisolone (initially 1 mg/kg/d for 4 weeks, 0.75 mg/kg/d for 4 weeks, 0.50 mg/kg/d for 4 weeks and thereafter tapered by 5mg every 4 weeks to a final dose of 10 mg daily after 6 months)
	• Both groups
	  * Switched to long-term AZA (2 mg/kg) plus prednisolone (10 mg/d) after 2 years

Outcomes	• Death • ESKD • Doubling of SCr • Deterioration of kidney function • major infection • Ovarian failure • Daily proteinuria • Renal relapse: could occur after week 12, and was defined as doubling of the lowest obtained SCr so far and/ or development of either a nephrotic syndrome (proteinuria > 3.5 g/d and serum albumin < 30 g/L), while the lowest protein excretion so far had been ≤ 2.0 g/d repeatedly, or proteinuria < 1.5 g/d without other causes, in a previously non-proteinuric patient
Notes	• 8/87 class III or Vc class IV or Vd 79/97 13/87 given previous cytotoxics IV CPA: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 • Funding source: Dutch Kidney Foundation, Dutch League against Rheumatism

Grootscholten 2006 *(Continued)*

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)	Unclear risk	Central office with computer program. Not sufficiently clear to determine risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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 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	• Study design: open-label, RCT • Study timeframe: not reported • Duration of follow-up: 2 years
Participants	• Country: USA • Setting: single centre • Inclusion criteria: SLE diagnosed using established specific criteria (positive antinuclear antibodies, a score of severe points or more on major-minor criteria scale; all patients also met the preliminary criteria for SLE (ARA); active life-threatening disease (severe nephritis, central nervous system involvement, haemolytic anaemia, thrombocytopenia, myocarditis, lupus crisis) • Number (randomised): treatment group (11); control group (13) • Mean age ± SD (years): treatment group (33.5 ± 13.2); control group (31.7 ± 13.9) • Sex (M/F): treatment group (2/9); control group (2/11) • Exclusion criteria: prior treatment with cytotoxic drugs; 20 mg prednisone/d during the preceding 6 weeks

Interventions	Induction therapy: duration of therapy was 24 months
	• treatment group
	  * Oral AZA: 3 to 4 mg/kg/d
	  * Prednisone: as per control group

Hahn 1975 *(Continued)*

	• Control group * Prednisone: daily oral dose of 40 to 60 mg was maintained for 4 to 6 months. After prednisone was maintained at 40 to 60 mg daily for 6 months in both groups, it was tapered slowly (by 5 mg increments every 2 weeks to a level of 30 mg daily, then by 2.5 mg increments every 2 weeks)
Outcomes	• Death • Toxicity • Major infection • Infection • Proteinuria • Remission of proteinuria • CrCl • SCr
Notes	• 2/24 lost to follow-up • Funding source: US Public Health Service grants AM17469 and AM05548 and Public Health Service Research grant FR-36 from the General Clinical Research centre Branch, Division of Research Facilities and Resources; and the Arthritis Foundation

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected clinical outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Hong 2007

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: 6 months
Participants	• Country: China • Setting: not reported

Hong 2007 *(Continued)*

- Inclusion criteria: diffuse proliferative lupus nephritis on renal biopsy; all > 2 g/d proteinuria and SCr < 3 mg/dL
- Number (randomised/analysed): treatment group 1 (13/13); treatment group 2 (12/12)
- Mean age ± SD: 30.7± 5.1 years
- Sex (M/F): 2/23
- Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group 1
	  * Oral FK506 (TAC): 0.1 mg/kg/d
	• Treatment group 2
	  * IV CPA: 0.5 to 0.75g/m^2 monthly
	• Both groups
	  * Prednisolone: 0.8 mg/kg/d

Outcomes	• Stable kidney function • No response • Infection • Complete remission (urinary protein excretion < 0.4 g/24 h, no active urinary sediment (urinary RBC < 10×10^4/mL), serum albumin > 35 g/L, SCr in normal ranges) • Partial remission (between complete remission and no response - referred to urinary protein excretion > 2 g or the reduction less than the baseline value, serum albumin < 30 g/L, or increment of SCr > 50% of the baseline value) • Proteinuria
Notes	• Abstract-only publication • Funding source: not reported

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all expected outcomes reported
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Houssiau 2002

Methods	• Study design: RCT • Study timeframe: September 1996 to September 2000 • Duration of follow-up: 10 years
Participants	• Country: Europe (countries not reported) • Setting: multinational (19 sites) • Inclusion criteria: diagnosis of SLE (ACR criteria); age ≥ 14 years; biopsy-proven proliferative lupus GN (WHO class III, IV, Vc, or Vd); proteinuria 500 mg/24 h; 69/90 class IV or Vc/Vd • Number (randomised): treatment group 1 (46); treatment group 2 (44) • Mean age ± SD (years): treatment group 1 (30 ± 11); treatment group 2 (33 ± 12) • Sex (M/F): treatment group 1 (3/43); treatment group 2 (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 neoplasia's; DM; severe toxicity or immunosuppressive drugs; anticipated poor compliance

Interventions	Induction and maintenance therapy
	• Treatment group 1
	  * High dose IV CPA: received 8 pulses within a year (6 monthly pulses followed by 2 quarterly pulses. The initial IV CPA dose was 0.5 g/m^2 of body surface area; subsequent doses were increased by 250 mg according to the WBC count nadir measured on day 14, with a maximum of 1,500 mg per pulse
	• Treatment group 2
	  * Low dose IV CPA: received 6 fortnightly IV CPA pulses at a fixed dose of 500 mg
	• Both groups
	  * All patients received 3 daily pulses of 750 mg of IV MP, followed by oral prednisolone (or equivalent) at an initial dosage of 0.5 mg/kg/d for 4 weeks. A dosage of 1 mg/kg/d was allowed in critically ill patients (those with renal impairment or severe extrarenal disease), glucocorticoid therapy (5–7.5 mg of prednisolone per day) was maintained at least until month 30 after inclusion; after 4 weeks, prednisolone (or equivalent) dosages were tapered by 2.5 mg every 2 weeks.
	  * Both treatment arms, AZA (2 mg/kg/d) was started 2 weeks after the last CPA injection and continued at least until month 30 after study inclusion

Outcomes	• Death • ESKD • Renal remission: defined as 10 RBC/HPF and a 24-hour urinary protein level < 1 g, in the absence of a doubling of the SCr level; and the number of severe flares • Treatment failure: defined as any of the following 3 features: 1. Absence of a primary response A. For patients with a baseline SCr ≥ 1.3 mg/dL but ≤ 2.6 mg/dL, absence of a primary response was defined as failure of the SCr to decrease to < 1.3 mg/dL at 6 months; B. For patients with a baseline SCr > 2.6 mg/dL, absence of a primary response was defined as failure of the SCr level to improve by 50% at 6 months; C. For patients with nephrotic syndrome at baseline (serum albumin level < 3.5 g/dL and 24-hour urinary protein level ≥ 3 g/d), but without renal impairment (SCr < 1.3 mg/dL), absence of a primary response was defined as the persistence of nephrotic syndrome at 6 months; 2. A glucocorticoid-resistant flare (defined as a severe flare that did not respond to a 1-month increase in the glucocorticoid dosage); 3. A doubling of the SCr over the lowest value reached at any time during the follow-up and confirmed on 2 consecutive visits 1 month apart • Doubling of SCr • Relapse: severe renal flare was defined as 1 of the following 3 features: renal impairment, increase in proteinuria, or severe systemic disease. Renal impairment was defined as an SLE-related increase of 33% in the SCr within a 1-month period; An increase in proteinuria defined as recurrence or appearance of nephrotic syndrome (albuminaemia ≤ 3.5 g/dL and proteinuria ≥ 3 g/24 h); In patients with low-grade proteinuria at baseline (≥ 0.5 g but ≤1 g in 24 h); a 3-fold increase in 24-hour urinary protein levels within a 3-month period was also considered a severe flare, provided that it was accompanied by microscopic haematuria and a 33% reduction of serum C3 levels within a 3-month period

Houssiau 2002 *(Continued)*

	• Toxicity • Proteinuria • Infection • Herpes zoster virus • Ovarian failure • Leucopenia: ≤ 4000/µL
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 • Funding source: supported by the European League against Rheumatism

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 of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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 by the European League Against Rheumatism. The study appears to be free of other sources of bias

Jayne 2013

Methods	• Study design: double-blind double-dummy RCT • Study timeframe: not reported • Duration of follow-up: 6 months
Participants	• Country: not reported • Setting: multicentre (number of sites not reported) • Inclusion criteria: active lupus nephritis • Number (randomised): treatment group 1 (16); treatment group 2 (16); control group (15) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Jayne 2013 *(Continued)*

Interventions	Induction therapy: duration of treatment was 6 months
	• Treatment group 1
	  * High-dose laquinimod: oral 1 mg/d
	• Treatment group 2
	  * Low-dose laquinimod: oral 0.5 mg/d
	• Control group
	  * Placebo
	• All groups
	  * All patients received MMF and prednisone (or equivalent)

Outcomes	• Death • Remission • Kidney function • Adverse events
Notes	• Abstract-only publication • Funding source: not reported

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 of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy placebo study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes were reported
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Kaballo 2016

Methods	• Study design: parallel RCT • Study timeframe: March 2008 to August 2011 • Duration of follow-up: 36 months
Participants	• Country: Sudan

Kaballo 2016 *(Continued)*

- Setting: multicentre (2 sites)
- Inclusion criteria: aged 12 to 75 years and have been diagnosed with SLE (ACR revised criteria); lupus nephritis criteria included persistent proteinuria > 0.5 g/d and presence of active urine sediment; renal biopsies were performed at presentation, only patients who had a histological diagnosis of severe proliferative Class III and IV and/or membranous Class V lupus nephritis (ISN/RPS 2003 classification) were enrolled
- Number (randomised): treatment group 1 (41); treatment group 2 (40)
- Mean age ± SD (years): treatment group 1 (27.1 ± 9.8); treatment group 2 (29.4 ± 11.6)
- Sex (M/F): treatment group 1 (3/38); treatment group 2 (3/37)
- Exclusion criteria: ESKD; malignancy; severe cardiovascular or liver disease; severe infection

Interventions	Maintenance therapy
	• Treatment group 1
	  * Oral MMF: 22 mg/kg/d, range 1000 to 3000 mg/d. The dosages remained unchanged within the 1st year, and then they were reduced by 25% in stable patients after the 1st year and continued for at least another year before further tapering
	• Treatment group 2
	  * Oral AZA: 2 mg/kg/d. The dosages remained unchanged within the 1st year, and then they were reduced by 25% in stable patients after the 1st year and continued for at least another year before further tapering
	• Both groups
	  * All patients underwent induction therapy using IV pulse CPA (500 mg/m^2 of body surface area with a maximum dose ≤ 500 mg) monthly for six months, plus 3 consecutive pulses of IV MP (15 mg/kg/d maximum 500 mg). All patients initially received oral prednisone (1 mg/kg)

Outcomes	• Death • ESKD • Complete remission: defined as reduction in proteinuria to ≤0.2 g/d with normal SCr • Partial remission: defined as a reduction of proteinuria from nephrotic range to a range between 0.2 and 2.0 g/d or reduction of proteinuria more than 50% with normal SCr • Relapse: patients in complete or partial remission, defined by an increase in SCr levels 50% or more over the last value besides a nephritic urinary sediment and generally increased proteinuria (nephritic flare) or by an increase in proteinuria without modification of SCr (proteinuric flare). Proteinuria had to increase by at least 2 g/d if the basal proteinuria was <3.0 g/d, or double if the patient had already nephrotic range proteinuria • Doubling of SCr • Major infection • Alopecia • Leucopenia • Nausea • Vomiting • Diarrhoea • Proteinuria
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients stratified by block randomisation (stratification factors were gender, age and weight)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Kaballo 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Trial registration was not reported, all expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kamanamool 2017

Methods	• Study design: open-label, parallel RCT • Study timeframe: 1 April 2012 to 31 March 2016 • Duration of follow-up: 12 months

Participants	• Country: Thailand
	• Setting: multicentre (number of sites not reported)
	• Inclusion criteria: patients with active, biopsy-proven lupus nephritis Class III, IV or V (ISN/RPS) 2003 criteria within 24 weeks of randomisation and who were ANA (ANA) or anti-double stranded DNA (anti-dsDNA) positive
	• Number (randomised/analysed): treatment group 1 (42/42); treatment group 2 (41/41)
	  * Treatment group 1: class III or IV (29), class V or III/IV + V (13)
	  * Treatment group 2: class III or IV (28), class V or III/IV + V (13)
	• Mean age ± SD (years): treatment group 1 (34.1 ± 11.1); treatment group 2 (31.7 ± 10.5)
	• Sex (M/F): treatment group 1 (1/40); treatment group 2 (3/38)
	• Exclusion criteria: Severe extra-renal manifestations; previous therapy with calcineurin inhibitor or MMF or CPA within the previous four months before randomisation; allergy to macrolide antibiotics; uncontrolled hypertension (SBP > 160 mm Hg or DBP > 100 mm Hg); severely deteriorated kidney function or rapid progressive crescentic GN; severe myocarditis or cardiomyopathy; requiring plasmapheresis or IVIG; severe infection or active TB; active hepatitis and evidence of chronic liver disease; HIV infection; MD; pregnancy; hypersensitivity or contraindication to MMF, mycophenolic acid, TAC, corticosteroids or any components of these drug products

Interventions	Induction therapy
	• Treatment group 1
	  * Oral MMF: initiated at a dose of 500 mg twice daily (patients > 50 kg and eGFR > 60 mL/min) for 2 weeks. It was then advanced to 750 mg twice daily in lupus nephritis patients weighing less than 50 kg, or 1000 mg twice daily in lupus nephritis patients weighing 50 kg or more. Dosage of MMF was prescribed according to the ACR recommendations, which suggest MMF 2 g/d for Asians
	• Treatment group 2
	  * Oral TAC: started at a dosage of 0.1 mg/kg/d divided into two daily doses at 12-hour intervals, and the dosage was titrated to achieve trough blood concentrations of 6–10 ng/mL in the first and second month and then 4–8 ng/mL thereafter

Kamanamool 2017 *(Continued)*

	• Both groups
	  * All patients received prednisone at a dose of 0.5 to 0.7 mg/kg/d (maximum 60 mg/d), with tapering by 5 to 10 mg/d every two weeks until a dose of 5 mg/d had been achieved, and this dosage was maintained until the end of 24 weeks
	  * All patients who had remission received AZA 1 to 2 mg/kg/d for 24 weeks as standard treatment. For patients who did not respond to the induction therapy, treatment depended on physician decision

Outcomes	• Death • Complete remission • SCr • Disease activity
Notes	• Funding source: Astellas Pharma (Thailand) Co., Ltd provided study drug and budget

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We stratified patients into two strata according to the classification of renal pathology (Class III–IV LN or Class V III/IV LN). Patients were randomly assigned 1:1 to a TAC group or an MMF group."
Allocation concealment (selection bias)	Low risk	To preserve the allocation concealment, the generation of blocks of four to six randomisation lists was electronically produced at Ramathibodi Hospital and web-based randomizations was used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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	"Astellas Pharma (Thailand) Co., Ltd. provided study drug and funded the study but had no role in study design, data collection, data analysis, data interpretation or conclusions." The study appears to be free of other sources of bias

Lewis 1992

Methods	• Study design: open-label, parallel RCT • Study timeframe: 1 April 1981 to 30 September 1986 • Duration of follow-up: mean follow-up 2.5 years with termination of study
Participants	• Country: USA • Setting: multicentre • Inclusion criteria: ≥ 16 years; SLE (ARA criteria); qualifying biopsy; 35 participants with class IV disease

Lewis 1992 *(Continued)*

- Number (randomised): treatment group 1 (40); treatment group 2 (46)
- Mean age ± SD (years): treatment group 1 (31 ± 11); treatment group 2 (33 ± 14)
- Sex (M/F): treatment group 1 (7/33); treatment group 2 (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	Induction therapy
	• Treatment group 1
	  * Oral CPA
	  * Corticosteroids
	  * PEX: 3 x weekly for 4 weeks
	• Treatment group 2
	  * Oral CPA
	  * Corticosteroids

Outcomes	• Death • ESKD • Remission: SCr ≤ 1.2 mg/dL and a 24-hour urinary protein of ≤ 0.2 g/d • Toxicity • Infection • Herpes zoster virus infection • SCr • Proteinuria
Notes	• Funding source: Public health service

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)	Low risk	Generated by Biostatistical Coordinating centre which issued treatment assignments by telephone after confirmation of patient eligibility
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; 1 patient lost-to follow-up
Selective reporting (reporting bias)	Low risk	Study protocol available and pre-specified outcomes were reported
Other bias	High risk	The study was terminated early

Li 2009c

Methods	• Study design: open-label, pilot RCT • Study timeframe: not reported • Duration of follow-up: 48 weeks
Participants	• Country: Hong Kong • Setting: single centre • Inclusion criteria: diagnosis of SLE (revised ACR criteria); biopsy-proven lupus nephritis class III or IV (WHO classification criteria), clinical activity index ≥ 6/24, proteinuria ≥ 1.5 g/24 h, albumin ≤ 35 g/L; 3/19 participants with class IV disease • Number (randomised/analysed): treatment group 1 (9/9); treatment group 2 (10/10) • Mean age ± SD (years): treatment group 1 (40.3 ± 13.9); treatment group 2 (39.6 ± 8.6) • Sex (M/F): treatment group 1 (0/9); treatment group 2 (1/9) • Exclusion criteria: severe infection in last 3 months; HIV; HBV or HCV; active TB; pregnancy; on oral/IV CPA, AZA or MMF within 8 weeks or prednisolone ≥ 0.5 mg/kg/d within 4 weeks; history of cancer; DM or kidney failure leading to dialysis

Interventions	Induction therapy
	• Treatment group 1
	  * RTX: 1000 mg, treatment repeated on day 15
	• Treatment group 2
	  * RTX: 1000 mg, 250 mg MP day 1, followed by IV CPA 750 mg, treatment repeated once on day 15
	• Both groups
	  * All participants received 250 mg IV MP on day 1, oral prednisolone 30 mg/d from day 2 to day 5, then 0.5 mg/kg for 4 weeks, then dose reduction 5 mg every 2 weeks
	  * Patients were pre-medicated with chlorpheniramine (10 mg IV) and paracetamol (1 g orally) 30 min before IV infusions
	  * All participants on ACEi before the study and continued on same dose

Outcomes	• Major infection • Herpes zoster virus infection • Complete response: if the baseline (at week 0) SLEDAI scores were greater than 0 and the follow-up score was equal to 0 • Partial response: if the baseline SLEDAI scores were greater than the follow-up score but the follow-up score was not equal to 0 • Treatment failure: worse disease activity • CrCl • Proteinuria
Notes	• Funding source: Roche provided the study drug

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
Allocation concealment (selection bias)	Low risk	Randomisation table kept by a third party
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Li 2009c *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected outcomes were reported
Other bias	Low 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 2012

Methods	• Study design: open-label, parallel RCT • Study timeframe: • Duration of follow-up:
Participants	• Country: China • Setting: single centre • Inclusion criteria: aged 8 to 65 years; diagnosis of SLE (1997 revised ARA criteria); biopsy-proven classes III, IV-S or IV-G, V, V + III or V + IV lupus nephritis (2003 ISN/ RPS classification criteria) 6 months before randomisation, chronic index ≤ 3 and urinary protein excretion of ≥ 1.0 g/24 h, and/or a recent deterioration in kidney function; 60 participants with classes III, IV and V disease; 35 participants with class IV disease • Number (randomised/analysed): treatment group 1 (20/20); treatment group 2 (20/20); treatment group 3 (20/20) • Median age, range (years): treatment group 1 (26.5, 16 to 62); treatment group 2 (29, 17 to 50); treatment group 3 (22, 17 to 64) • Sex (M/F): treatment group 1 (3/17); treatment group 2 (3/17); treatment group 3 (2/19) • Exclusion criteria: treatment with MMF, TAC, CSA or CPA within the previous year; SCr concentration > 5.0 mg/dL; life-threatening complications such as cerebral lupus, pancreatitis, GI haemorrhage, within 6 months or active peptic ulcer within 3 months, severe infection, severe cardiovascular disease, bone marrow insufficiency with cytopenia not attributable to SLE or poor drug compliance

Interventions	Induction therapy: duration of treatment was 6 months
	• Treatment group 1
	  * Oral MMF: 1.5 to 2.0 g/d
	• Treatment group 2
	  * Oral TAC: 0.08 to 0.1 mg/kg/d, target 12 hour trough 6 to 8 ng/mL
	• Treatment group 3
	  * IV CPA: 0.5 to 0.75 g/1.73 m^2
	• All groups
	  * All patients received 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	• Death • Stable kidney function • Major infection

Li 2012 *(Continued)*

	• Leucopenia • Complete renal remission: urinary protein excretion < 0.3 g/24 h with normal urine sediment, serum albumin concentration > 35 g/L and SCr above baseline values by ≤ 15% • Partial renal remission: urinary protein excretion between 0.3 to 2.9 g/24 h, having decreased by at least 50% from baseline values, with a serum albumin concentration of at least 30 g/L and relative stabilisation (± 30%) in SCr • Complete remission in proteinuria • Doubling of SCr • Proteinuria • Serum albumin
Notes	• Funding source: Shanghai Institutes of Health and Chinese National Natural Science Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

Liou 2007

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: 18 months
Participants	• Country: China • Setting: single centre • Inclusion criteria: biopsy-proven lupus nephritis • Number (randomised): treatment group 1 (19); treatment group 2 (21) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Liou 2007 *(Continued)*

Interventions	Induction and maintenance therapy: 6 months induction therapy and 12 months maintenance therapy
	• Treatment group 1
	  * Oral leflunomide: 30 mg/d; after 6 months of induction therapy, leflunomide was reduced to 20 mg/d
	• Treatment group 2
	  * IV CPA: 1g per month; after 6 months IV CPA was given 1g/3 months for maintenance therapy
	• Both groups
	  * All patients received prednisolone 0.8 to 1 mg/kg/d tapered to 10 mg/d

Outcomes	• Complete renal remission (not defined) • Herpes zoster virus infection • Proteinuria • Serum albumin • SCr
Notes	• Abstract-only publication • Only induction therapy (6 months) reported • Funding source: not reported

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all expected clinical outcomes are reported
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Liu 2015

Methods	• Study design: open-label, parallel RCT • Study timeframe: April 2009 to June 2011 • Duration of follow-up: 24 weeks

Liu 2015 *(Continued)*

Participants	• Country: China
	• Setting: multicentre (number of sites not reported)
	• Inclusion criteria: patients aged 18 to 65 years; diagnosis of SLE (ACR criteria); biopsy-proven class III, IV, V, III+V, and IV+V lupus nephritis (ISN/RPS 2003 classification criteria) within 6 months before study entry; proteinuria (≥1.5 g/d) with a SCr ≤ 3.0 mg/dL)
	• Number (randomised/analysed): treatment group 1 (181/175); treatment group 2 (181/181)
	  * Treatment group 1: class III (10), class IV (74), class V (32); class III+IV or IV+V (65)
	  * Treatment group 2: class III (9), class IV (76), class V (37); class III+IV or IV+V (52)
	• Median age, IQR (years): treatment group 1 (33.6, 24.2 to 41.5); treatment group 2 (30.3, 23.3 to 38.6)
	• Sex (M/F): treatment group 1 (20/161); treatment group 2 (13/168)
	• Exclusion criteria: treatment with MMF, CPA, TAC, or high-dose MP; current RRT; plasmapheresis, or IVIG within the 12 weeks before randomisation; abnormal liver function or serum glucose test results; and pathologic chronicity index > 3

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * IV CPA: initiated at a dose of 0.75 g/m^2 body surface area and then adjusted to a dose of 0.5 to 1.0 g/m^2 body surface area every 4 weeks for 6 doses
	• Treatment group 2
	  * Oral MMF: 0.5 g twice/d
	  * Oral TAC: 2 mg twice/d
	• Both groups
	  * IV MP pulse therapy (0.5 g/d) for 3 days, followed by oral prednisone (0.6 mg/kg/d) every morning for 4 weeks. The daily dose of prednisone was tapered by 5 mg/d every 2 weeks to 20 mg/d and then by 2.5 mg/d every 2 weeks to a maintenance dose of 10 mg/d

Outcomes	• Death • Complete remission: 24 h urinary protein excretion ≤ 0.4 g, the absence of active urine sediments, serum albumin level ≥ 35 g/L, and normal SCr • Partial remission: ≥ 50% reduction in proteinuria and urine protein < 3.5 g/24 h, serum albumin level ≥30 g/L, and normal or ≤ 25% increase in SCr level from baseline • Doubling of SCr • Major infection • Herpes zoster virus infection • Menstrual disorder • Avascular necrosis • Alopecia • Leucopenia • Upper GI symptoms • Diarrhoea
Notes	• Funding source: National Basic Research Program of China (973 Program, No. 2012CB517600, No. 2012CB517606), National Key Technology R&D Program (2011BAI10B04, 2013BAI09B04).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list, stratified by centre was created by Rundo International Pharmaceutical Research & Development (Shanghai) Co. Ltd. by using computer generated random-number sequences
Allocation concealment (selection bias)	Low risk	Sequentially numbered, concealed envelopes containing group assignment were provided to the investigators. After eligible patients provided written in-

Liu 2015 *(Continued)*

		formed consent, the envelopes were opened in sequence and patients were randomly assigned, in a 1:1 ratio, to the multi-target regimen or IV CPA
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were adjudicated by the Clinical Endpoints Committee, blinded to treatment regimen.
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear why 6 patients (3%) in the IV CPA group were not given therapy and not included in the analysis and why patients in the IV CPA group were seen at twice the follow-up rate then patients in the multi-target therapy group
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes were reported
Other bias	Low risk	This study appears to be free of other sources of bias

Loo 2010

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: 6 months
Participants	• Country: Malaysia • Setting: single centre • Inclusion criteria: aged ≥ 12 years; diagnosis of SLE (ARA 1982 criteria) and biopsy proven severe classes III or IV ± V lupus nephritis (ISN/RPS 2003 classification criteria) • Number (randomised/analysed): treatment group 1 (14/14); treatment group 2 (14/14) • Mean age ± SD (years): treatment group 1 (31.9 ± 11.6); treatment group 2 (30.2 ± 7.5) • Sex (M/F): treatment group 1 (4/10); treatment group 2 (0/14) • Ethnicity: treatment group 1 (Chinese (5), Malay (7), Indian (2)); treatment group 2 (Chinese (5), Malay (7), Indian (2)) • Exclusion criteria: not reported

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * PEX: 3 sessions (3L per session) following MP treatment. For PEX, the plasma removed was replaced with 2 litres of human albumin 5% and the balance with Hartman's solution
	• Treatment group 2
	  * Immunoadsorption: 3 sessions carried out on a daily or every other day basis for 3 days. Three litres of plasma or 1 plasma volume, whichever was greater was processed at each session
	• Both groups
	  * All patients received standard induction IV pulse MP at 250 mg/d for 3 days followed by PEX or immunoadsorption. Followed by IVIG 10 g/d for 3 days. Patients subsequently proceed to the consolidation phase with pulse IV CPA at 10 to 12 mg/kg/dose 2-weekly for 4 doses, then monthly for four more doses. Patients were then randomised to receive maintenance therapy with either oral CSA or MMF in conjunction with low dose steroid, for a further 12 to 18 months

Outcomes	• Relapse: nephrotic syndrome

Loo 2010 *(Continued)*

Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Consecutive enrolment
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all expected outcomes were reported
Other bias	High risk	Marked differences (demographics and clinical characteristics) between groups at baseline

Lui 1997

Methods	• Study design: parallel RCT • Study timeframe: not reported • Duration of follow-up: 12 months
Participants	• Country: Hong Kong • Setting: not reported • Inclusion criteria: class IV disease • Number (randomised/analysed): treatment group 1 (17/17); treatment group 2 (17/17) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group 1
	  * Oral CSA: 5 mg/kg/d, reduced to 2.5 mg/kg/d
	• Treatment group 2
	  * Oral CPA: 1 mg/kg/d
	• Both groups
	  * All patients received prednisolone (0.5 mg/kg/d) and AZA (1 mg/kg/d)

Lui 1997 *(Continued)*

Outcomes	• Failure to respond • Partial response • Complete response • Proteinuria • CrCl • Infection • Herpes zoster virus infection • Leucopenia • Amenorrhoea
Notes	• Abstract-only publication • Funding source: not reported

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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	Abstract-only publication; insufficient information to permit judgement

LUNAR 2012

Methods	• Study design: phase III, double-blind double-dummy RCT • Study timeframe: January 2006 to January 2008 • Duration of follow-up: 12 months
Participants	• Countries: USA, Latin America • Setting: multinational (52 sites) • Inclusion criteria: aged 16 to 75 years of age; diagnosis of SLE (ACR criteria); history of ANA positivity; diagnosis of class III or IV lupus nephritis (ISN/RPS 2003 Classification) with either active or active chronic disease; proteinuria (urine polymerase chain reaction > 1.0); If the biopsy was performed > 3 months before screening; an active urinary sediment (> 10 RBC/HPF or the presence of RBC casts) • Number (randomised/analysed): treatment group (72/72); control group (72/72)

LUNAR 2012 *(Continued)*

- Mean age ± SD (years): treatment group (31.8 ± 9.6); control group (29.4 ± 9.3)
- Sex (M/F): treatment group (9/63); control group (5/67)
- Exclusion criteria: active infection; recurrent or chronic infection,; CPA or CNI 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	Induction therapy: duration of therapy was 12 months
	• Treatment group
	  * IV RTX: 1000 mg (days 1, 15, 168, 182)
	• Control group
	  * Placebo
	• Both groups
	  * MMF: initial dosage of 1.5 g/d in 3 divided doses, and the dosage was increased to 3 g/d by week 4
	  * IV MP: 1,000 mg was administered 30–60 minutes prior to the administration of study drug on day 1 and again within 3 days.
	  * Oral prednisone: 0.75 mg/kg/d (maximum 60 mg) was administered until day 16 and tapered to 10 mg/d by week 16

Outcomes	• Death (all causes) • Stable creatinine • Major infection • Herpes zoster virus infection • Complete response: SCr ≤ 115% of baseline if it was normal at baseline; inactive urinary sediment (< 5 RBC/HPF and absence of RBC casts); and UPCR < 0.5 • Partial response: SCr ≤ 115% of baseline; RBCs/HPF ≤ 50% above baseline and no RBC casts; and at least a 50% decrease in the UPCR to < 1.0 (if the baseline UPCR was ≤ 3.0) or to ≤ 3.0 (if the baseline UPCR was > 3.0) • Treatment failure (if criteria for complete response or partial response were not met, for early termination from the study or inability to assess the end point due to missing data, or for initiation of a new immunosuppressant agent prior to week 52 • Complete response in proteinuria • Partial response in proteinuria • Serious adverse events • Nausea • Diarrhoea
Notes	• Funding source: Genentech and Biogen Idec

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy placebo study
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

LUNAR 2012 *(Continued)*
All outcomes

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	High risk	Some authors declared grants/research support from Genentech and Aspreva, and sponsor included in data analysis and authorship

MAINTAIN Nephritis 2010

Methods	• Study design: open-label, parallel RCT • Study timeframe: July 2002 and March 2006 • Duration of follow-up: median follow-up 53 months; extended median follow-up was 9.16 years (range 1.5 to 13 years)
Participants	• Country: European (countries not reported) • Setting: multinational (27 sites) • Inclusion criteria: SLE ≥ 14 years, diagnosis of SLE (ACR criteria), proteinuria ≥ 0.5 g/d, biopsy-proven lupus nephritis Class III, IV, Vc or Vd lupus nephritis (WHO classification criteria) • Number (randomised/analysed): treatment group 1 (52/52); treatment group 2 (53/53) • Mean age ± SD (years): treatment group 1 (33 ± 11); treatment group 2 (33 ± 10) • Sex (M/F): treatment group 1 (4/48); treatment group 2 (5/48) • Exclusion criteria: recent treatment with high dose corticosteroids or immunosuppressive drugs; non-lupus related renal disease (such as microthrombotic disease associated with antiphospholipid syndrome); pre-existing chronic kidney failure (defined as a SCr value above the upper normal value for the local laboratory) due to a previous episode of lupus nephritis or other cause; pregnancy or breast feeding; previous malignancy (except skin and cervical intraepithelial neoplasia's); DM; previously documented severe toxicity of immunosuppressants, anticipated non-compliance with the protocol

Interventions	Maintenance therapy
	• Treatment group 1
	  * AZA: 2 mg/kg/d
	• Treatment group 2
	  * MMF: 2 g/d
	• Both groups
	  * Induction therapy of 3 x 750 mg IV MP followed by oral glucocorticoids 0.5 mg/kg/d and 6 fortnightly pulses IV CPA 500 mg
	  * Maintenance treatment started in both groups at week 12

Outcomes	• Death • ESKD • Relapse: (i) recurrence or the development of nephrotic syndrome (serum albumin ≤ 3.5 g/dL and proteinuria ≥ 3 g/24 h); (ii) renal impairment (≥ 33% increase of SCr within a 1-month period directly attributed to lupus nephritis and confirmed 1 week later; flare referred to as 'renal impairment') or (iii) a threefold increase of 24 h proteinuria within a 3-month period accompanied by microscopic haematuria (defined as a number of RBC/HPF superior to upper normal limit for the local laboratory) and ≥ 33% reduction of serum C3 level within a 3-month period (this definition of renal flare was only applicable to those patients with low-grade baseline 24 h proteinuria (≥ 0.5 g and < 1 g); this type of renal flare is further referred to as 'proteinuria increase' • Time to renal flare

MAINTAIN Nephritis 2010 *(Continued)*

	• Doubling of SCr • Number of withdrawals due to toxicity • Number of treatment failures • Major infection • Herpes zoster virus infection • Avascular necrosis • Malignancy • Alopecia • Leucopenia • Kidney function over time • 24 hour proteinuria over time
Notes	• Funding source: no external funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by minimisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

Mehra 2018

Methods	• Study design: open-label, parallel RCT • Study timeframe: December 2015 to December 2016 • Duration of follow-up: 12 months
Participants	• Country: India • Setting: single centre • Inclusion criteria: diagnosis of SLE (ACR criteria); aged > 16 years; proteinuria ≥ 500 mg/24 h and/or urine routine microscopy showing active cellular casts/sediments (> 5 RBC/HPF and > 5 WBC/HPF and cellular casts); biopsy-proven proliferative class III, IV lupus GN (ISN/RPS) criteria

Mehra 2018 *(Continued)*

- Number (randomised/analysed): treatment group 1 (37/37); treatment group 2 (38/38)
  - Treatment group 1: class III (11), class IV (26); had crescents (14; 38%)
  - Treatment group 2: class III (17), class IV (21); had crescents (8; 21%)
- Mean age ± SD (years): not reported
- Sex (M/F): treatment group 1 (3/34); treatment group 2 (4/34)
- Exclusion criteria: ever treated previously with IV or oral cyclophosphamide, MMF, cyclosporine or steroids > 15 mg/d in the last 3 months; renal thrombotic microangiopathy, pre-existing chronic kidney failure, previous malignancy (except skin and cervical intraepithelial neoplasia); DM or coronary heart disease; previously documented severe toxicity to immunosuppressive drugs; patients with active acute or chronic infections; pregnancy

Interventions	Induction therapy
	• Treatment group 1
	  * High dose IV CPA: four weekly six cycles of 750 mg/m^2 with a maximum of 1.5 g per pulse.
	• Treatment group 2
	  * Low dose IV CPA: six fortnightly IV CPA cycles at a fixed dose of 500 mg
	• Both groups
	  * All participants received 3 daily pulses of 1 g IV MP followed by 1 mg/kg/d of prednisolone for 4 weeks tapered by 5 mg every 2 weeks to reach a dose of 5–7.5 mg/d until completion of 52 weeks. After completion of induction, oral AZA 2 mg/kg was started two weeks after the last CPA dose. For patients with AZA-related toxicity, the dosage was reduced to 1 mg/kg/d
	  * All patients received hydroxychloroquine during the study (5 to 6 mg/kg, 400 mg/d maximum) after normal baseline fundus evaluation
	  * Hypertension (DBP > 90 mm Hg) was treated with ACEi (unless contraindicated) and other appropriate drugs
	  * Atorvastatin was started for patients with LDL cholesterol > 100 mg/dL

Outcomes	• Death • Complete remission: UPCR < 0.5 g and normal GFR (> 90 mL/ min) or stable (< 10% deterioration from baseline if GFR was previously abnormal) kidney function and inactive urinary sediments. • Partial remission: ≥ 50% reduction in proteinuria to sub-nephrotic levels, normal GFR (> 90 mL/ min) or stable (< 10%) deterioration from baseline if GFR was previously abnormal • Renal relapse (not defined) • Treatment failure • Major infection • Herpes zoster virus infection • Ovarian failure • Bone toxicity: avascular necrosis • Alopecia • Leucopenia • GI disturbance • CrCl
Notes	• Funding source: Investigator initiated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised, using block randomization, eight blocks of 10 patients each with 1:1 random allocation was performed using a computer generated random number table."

Mehra 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Fellow researcher had given random block and number to patients sequentially, who was unaware of treatment allocation and had no other role in the study."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected outcomes were reported and partial remission listed in protocol not reported.
Other bias	Low risk	The study appears to be free of other sources of bias

Mendonca 2017

Methods	• Study design: open-label, parallel RCT • Study timeframe: November 2014 to November 2015 • Duration of follow-up: 6 months

Participants	• Country: India
	• Setting: single centre
	• Inclusion criteria: SLE according to the SLICC 2012 and the ACR criteria; all biopsy-proven class III, IV or III/IV +V lupus nephritis was diagnosed based on biopsy findings as per the ISN/RPS
	• Number (randomised/analysed): treatment group 1 (18/17); treatment group 2 (23/23)
	  * Treatment group 1: class III (1); class IV (11); class V (2); class III+V or class IV+V (3)
	  * Treatment group 2: class III (1); class IV (15); class V (3); class III+V or class IV+V (4)
	• Mean age ± SD (years): treatment group 1 (26.0 ± 10.8); treatment group 2 (25.7 ± 10.3)
	• Sex (M/F): treatment group 1 (3/14); treatment group 2 (5/18)
	• Exclusion criteria: CKD stage-3 and above; crescentic lupus nephritis; pancreatitis, GI haemorrhage within six months or active peptic ulcer disease within last three months; ongoing infection; bone marrow insufficiency with cytopenias not attributable to SLE; and prior treatment with CPA or MM

Interventions	Induction therapy
	• Treatment group 1
	  * Oral MMF: twice daily, titrated from 750 mg twice daily in the 1st week, and 1.0 g twice daily in the 2nd week, to a target dosage of 1.5 g twice daily, if required, based on the disease activity and response. Reduction was permitted to 2 g/d in response to any adverse events
	• Treatment group 2
	  * Low dose IV CPA: Pulse CPA (750 mg/m^2), which was adjusted to 500 to 1000 mg/m^2 every 4 weeks to maintain a nadir leukocyte count of 2.5 to 4.0 × 10^9/L for a total of 6 pulses. A 25% decrease in dosage for age older than 60 years, and SCr > 3.4 mg/dL was followed
	• Both groups
	  * All participants had received unified concomitant corticosteroid therapy according to protocol that consisted of three doses of IV pulse MP 500 mg followed by oral prednisone (or equivalent) at an initial dose of 0.5 mg/kg/d. Prednisolone dosage was tapered by a decrease of 5 mg/d every

Mendonca 2017 *(Continued)*

	two weeks until a dose of 10 mg/day was achieved, and this dosage was maintained till the end of six months. * Doses of ACEi and/or ARB had been unchanged during the 6 month follow-up period * Target blood pressure was kept at 130/80 mm Hg * Hyperlipidaemia was treated using statins and/or fibric acid derivatives as required
Outcomes	• Death • Complete remission: urinary protein excretion < 0.3 g/24 h was accomplished with normal serum albumin levels and/or an improvement in the baseline SCr levels of > 50% • Partial remission: improvement of > 50% from baseline proteinuria, serum albumin levels of at least 30 g/L, and SCr level of ≥ 25% from baseline or stable SCr level within 25% of the baseline • Treatment failure • Major infection • Herpes zoster virus infection • Diarrhoea • Nausea • Vomiting • CrCl • SCr • Daily proteinuria
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	No protocol available, some expected outcomes not reported
Other bias	Low risk	The study appears to be free of other sources of bias

Mitwalli 2011

Methods	• Study design: double-blind, parallel RCT

Mitwalli 2011 *(Continued)*

- Study timeframe: December 1997 to January 2007
- Duration of follow-up: mean follow-up 6.77 ± 3.3 years

Participants	• Country: Saudi Arabia • Setting: single centre • Inclusion criteria: adult patients with newly diagnosed biopsy-proven lupus nephritis (WHO class IV) • Number (randomised/analysed): treatment group 1 (73/73); treatment group 2 (44/44) • Mean age ± SD (years): treatment group 1 (36.4 ± 12.7); treatment group 2 (30.3 ± 10.4) • Sex (M/F): treatment group 1 (12/61); treatment group 2 (5/39) • Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group 1
	  * IV CPA: 10 mg/kg monthly for 6 months then 2 monthly for 12 months
	• Treatment group 2
	  * IV CPA: 5 mg/kg monthly for 6 months then 2 monthly for 36 months
	• Both groups
	  * 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 both (groups)
	• Hydroxychloroquine: 200 mg/d for 24 months
	• AZA: 1 mg/kg/d for 24 months

Outcomes	• Death • Doubling of SCr • Stable kidney function • Major infection • Ovarian failure • Malignancy • Lymphopenia • Complete remission of proteinuria: < 0.3 g/24 h with normal serum albumin levels and/or an improvement in the baseline SCr levels of > 50% • Partial remission of proteinuria: > 50% reduction in proteinuria, serum albumin levels ≥ 30 g/L, and SCr ≥ 25% from baseline or stable SCr level within 25% of the baseline • SCr • Daily proteinuria
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study

Mitwalli 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded according to the protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All outcomes on clinicaltrials.gov are reported
Other bias	High risk	Marked differences in clinical characteristics between the groups - median cumulative dose of CPA between the groups, high rates of leucopenia in the low dose compared to the high dose CPA group at baseline

Mok 2016

Methods	• Study design: open-label, parallel RCT • Study timeframe: 2005 to 2012 • Duration of follow-up: median 30 months
Participants	• Countries: Hong Kong, China • Setting: multicentre (number of centres not reported) • Inclusion criteria: aged ≥ 18 years; diagnosis of SLE (ACR criteria); biopsy-proven active lupus class III/ IV/ V(ISN/RPS 2003 classification) within 4 weeks; SCr < 2.3 mg/dL • Number (randomised/analysed): treatment group 1 (74/74); treatment group 2 (76/76) • Mean age ± SD (years): treatment group 1 (36.2 ± 14); treatment group 2 (36.1 ± 13.1) • Sex (M/F): treatment group 1 (4/70); treatment group 2 (8/68) • Exclusion criteria: refusal to be randomised; preference for treatment with conventional regimens such as CPA; planning for pregnancy within 12 months after randomisation

Interventions	Induction therapy and maintenance therapy
	• Treatment group 1
	  * TAC: initial dosage 0.1 mg/kg/d in two divided doses, reduced to 0.06 mg/kg/d if clinical response was satisfactory at month in two divided doses for 6 months
	• Treatment group 2
	  * MMF: 2 g/d initially, augmented to up to 3 g/d if clinical response was suboptimal in two divided doses for 6 months
	• Both groups
	  * Prednisolone: 0.6 mg/kg/d for 6 weeks then tapered by 5 mg/d every week to < 10 mg/d. 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	• Death • ESKD • Doubling of SCr • Stable kidney function • Relapse • Major infection • Herpes zoster virus • Diarrhoea • Nausea

Mok 2016 *(Continued)*

- Complete renal remission: stabilisation (within 25%) or improvement in SCr with reduction of proteinuria to < 1 g/d (or UPCR < 1.0), resolution of urinary sediment abnormalities (urine RBC < 5/HPF and absence of cellular casts) and persistent improvement in C3 and anti-dsDNA levels
- Partial renal remission: stabilisation (within 25%) or improvement in SCr with persistent reduction of proteinuria (if nephrotic range at baseline, a ≥ 50% decrease in proteinuria but < 3 g/d (or UPCR < 3.0); if non-nephrotic at baseline, a decrease to ≤ 50% of the pre-treatment value but > 1 g/d (or UPCR > 1.0) and improvement in urinary sediment abnormalities (≥ 50% reduction in haematuria and urine RBC <10/HPF)
- Treatment failure: deterioration of SCr (> 25%), an increase in proteinuria, or a reduction in proteinuria but not to the extent of complete renal remission or partial renal remission)
- Renal flare: proteinuric flare - an increase in proteinuria to more than 2g/d (or UPCR >2.0), with or without deterioration in SCr (< 30%), after a complete remission; or doubling of proteinuria (or UPCR), with or without deterioration in SCr (<30%), in patients who achieved partial remission. Nephrotic flare - an increase or recurrence of active urinary sediments (RBC ≥10/HPF or active cellular casts) with a concomitant increase in proteinuria (or UPCR) or deterioration in SCr (≥30%) after excluding other causes (e.g. sepsis, over diuresis, nephrotoxic agents, renal vein thrombosis)
- Alopecia
- Proteinuria
- CrCl
- Serum albumin

Notes	• Funding source: no support from any organisation including industry (Roche and Astella)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by computer-generated blocks of four in a 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Central research assistant was responsible for treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

Moroni 2006

Methods	• Study design: open label, parallel RCT • Study timeframe (recruitment): March 1999 to March 2001

Moroni 2006 *(Continued)*

	• Duration of follow-up: a least 1 year follow-up, invited to continue to 4 years
Participants	• Country: Italy • Setting: multicentre • Inclusion criteria: aged at least 16 years; diagnosis of SLE (ACR criteria) and biopsy-proven class IV, Vc or Vd lupus nephritis with a chronicity index of ≤ 4 (WHO classification); patients with a new diagnosis of lupus nephritis or were experiencing a new flare of a previously quiescent disease were enrolled if they had active urine sediment (≥ 5 RBC/HPF); proteinuria > 1 g/d in case of new diagnosis or > 2 g if new renal flare; SCr < 4 mg/dL; after induction therapy those with no major extrarenal signs or symptoms of lupus requiring aggressive therapy; SCr ≤ 1.5 mg/dL, proteinuria > 0.5 g/d; CrCl > 60 mL/min; diastolic BP < 90 mm Hg with a maximum of two antihypertensive drugs and the oral prednisone dose ≤ 0.5 mg/kg/d • Number (randomised/analysed): treatment group 1 (36/36); treatment group 2 (33/33) • Mean age ± SD (years): treatment group 1 (31.7 ± 9.1); treatment group 2 (31.2 ± 11.7) • Sex (M/F): treatment group 1 (3/33); treatment group 2 (4/29) • Exclusion criteria: potential silent nephritis; renal diseases unrelated to SLE; treatment with CSA or AZA in the 6 months preceding the screening visit; cumulative CPA dose > 200 mg/kg; any contraindication to the study drugs; previous malignancy

Interventions	Maintenance therapy: duration of therapy was 24 months
	• Treatment group 1
	  * CSA: 4 mg/kg/d and reduced to maintenance dose (2.5 to 3.0 mg/kg/d) if proteinuria < 1 g/d, if proteinuria was higher the dose was reduced more slowly
	• Treatment group 2
	  * AZA: 2 mg/kg/d optional reduction at 1 month to 1.5 mg/kg/d if proteinuria < 1 g/d and SCr stable
	• Both groups
	  * Induction therapy: 3 x IV 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
	  * During maintenance therapy both groups received oral prednisone which had to be reduced from 0.5 to 0.2 mg/kg/d by the end of the 6 months, in the case of normal levels of SCr and proteinuria of < 0.5 g/d and in absence of extrarenal symptoms. A further reduction or complete withdrawal could be attempted at the investigators discretion

Outcomes	1. Death 2. ESKD 3. Major infection 4. Lymphopenia 5. GI disorders 6. Complete remission proteinuria 7. Proteinuria at 2 and 4 years 8. CrCl at 2 and 4 years 9. 24 hour proteinuria 10. Renal flare
Notes	• Funding source: educational grant from Novartis Pharma AG

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

Moroni 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded endpoint study
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	High risk	Sponsor included in data management and analysis: Novartis Pharma and authorship

Mulic-Bacic 2008

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: 24 weeks
Participants	• Country: Bosnia Herzegovina • Setting: not reported • Inclusion criteria: active lupus nephritis class III, IV or V (WHO classification criteria) • Number (randomised/analysed): treatment group 1 (20/20); treatment group 2 (25/25) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy: duration of therapy was 24 months
	• Treatment group 1
	  * MMF: 2 g/d for 6 months then 1 g/d for 18 months, administer orally
	• Treatment group 2
	  * IV CPA: 0.5 g/m^2 monthly
	• Both groups
	  * Prednisolone: 0.75 to 1 mg/kg/d with determined tapering

Outcomes	• Death • Stable kidney function • Complete remission proteinuria • Partial remission proteinuria • Complete remission: normalisation of abnormal renal measurements and maintenance of baseline normal measurements • Partial remission
Notes	• Abstract-only publication • Funding source: not reported

Mulic-Bacic 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected clinical outcomes reported and no protocol available; abstract-only publication
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

MyLupus 2011

Methods	• Study design: open-label, parallel RCT • Study timeframe: February 2007 to November 2009 • Duration of follow-up: 6 months
Participants	• Countries: France, Germany, Italy, Spain, UK, Hungary, Greece, Colombia, Taiwan • Setting: multinational (19 sites) • Inclusion criteria: aged ≥ 18 years, (i) diagnosis of SLE (ACR criteria); biopsy-proven (within previous 24 months) proliferative lupus nephritis (class III or IV) (ISN/RPS 2003 classification criteria); proteinuria defined as UPCR > 0.5 at screening and baseline; and clinical activity defined by one or more of the following: SCr > 1 mg/dL; microscopic haematuria (> 5 RBC/HPF) and presence of cellular casts • Number (randomised/analysed): treatment group 1 (42/42); treatment group 2 (39/39) • Mean age ± SD (years): treatment group 1 (32.2 ± 8.5); treatment group 2 (34.2 ± 10.7) • Sex (M/F): treatment group 1 (5/37); treatment group 2 (10/29) • Exclusion criteria: CrCl < 30 mL/min; IV glucocorticoids, oral or IV CPA or MMF during the previous 3 months; antibody therapy within the previous 6 months

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * Standard dose EC-MPS
	  * Prednisolone: 1 mg/kg/d
	• Treatment group 2
	• Reduced dose EC-MPS
	• Prednisolone: 0.5 mg/kg/d

MyLupus 2011 *(Continued)*

	• Both groups
	  * MP: 0.5 g IV/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	• Death • Infection • Herpes zoster virus infection • Vomiting • Diarrhoea • Complete remission: UPCR < 0.5 with normalised urine sediment and SCr within 10% of normal value • Partial remission: reduction in UPCR of 50% compared with baseline, and SCr improved or stable (i.e. within 10% of baseline value) • Renal flare: A mild SLE flare was diagnosed if SLE increased after partial or complete response, defined as the presence of 1 or 2 BILAG B scores and no A scores and intention by the investigator to increase the glucocorticoid dose; a moderate to severe SLE flare was diagnosed if increased lupus activity after partial or complete response resulted in 1 BILAG A score or 3 BILAG B scores • UPCR • Creatinine
Notes	• Funding source: Novartis Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	High risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected outcomes were reported
Other bias	High risk	Novartis Pharma AG funded. Sponsor involved in authorship, Disclosure of consulting fees from Novartis Pharma, Amgen, BMS and Roche

Nakamura 2002e

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported

Nakamura 2002e *(Continued)*

	• Duration of follow-up: 6 months
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: diagnosis of SLE (ACR criteria); biopsy-proven diffuse proliferative, class IV lupus nephritis (WHO classification criteria); oral corticosteroid with or without cytotoxic drugs for at least 6 months with treatment resistance • Number (randomised): treatment group 1 (10); treatment group 2 (10) • Mean age (years): treatment group 1 (30.5); treatment group 2 (29.5) • Sex (M/F): treatment group 1 (2/8); treatment group 2 (2/8) • Exclusion criteria: not reported

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * PEX: double filtration 1 to 2 weekly
	• Treatment group 2
	  * IV CPA: 0.75 to 1.0 g/m^2 once a month for 6 months
	• Both groups
	• Oral prednisone (or equivalent): 1 mg/kg/d tapered to the minimum dose needed to control extrarenal diseases

Outcomes	• Proteinuria • Urinary podocyte number
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Ong 2005

Methods	• Study design: open-label, parallel RCT • Study timeframe: January 2001 to December 2002 • Duration of follow-up: 6 months
Participants	• Country: Malaysia • Setting: multicentre (8 sites) • Inclusion criteria: aged > 16 years; diagnosis of SLE (ACR criteria); class III or IV lupus nephritis (WHO classification criteria) • Number (randomised/analysed): treatment group 1 (28/25); treatment group 2 (26/19) • Mean age ± SD (years): treatment group 1 (30.5 ± 8.7); treatment group 2 (31.3 ± 9.9) • Sex (M/F): treatment group 1 (3/23); treatment group 2 (4/15) • Exclusion criteria: SCr > 200 µmol/L, WCC < 3.5 x 10^9/L; 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 months

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * IV CPA: 0.75 to 1 g/m^2 monthly for 6 months
	• Treatment group 2
	  * MMF: 1 g orally twice daily for 6 months
	• Both groups
	  * Prednisolone: 60 mg/d for 4 to 6 weeks then tapering dose to 5 to 10 mg/d

Outcomes	• Death • ESKD • Stable kidney function • Major infection • Herpes zoster virus • Leucopenia (< 3.5 x 10^9/L) • Oligomenorrhoea • GI side effects • Complete renal remission: stabilisation or improvement in kidney function, RCC < 10, proteinuria < 3 g • Combined partial remission: stabilisation or improvement in kidney function, RCC < 10, proteinuria < 3 g if was > 3 g or at least 50% reduction or < 1.0 g if subnephrotic • Proteinuria
Notes	• Funding source: not reported; MMF supplied by Roche Malaysia

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)
Allocation concealment (selection bias)	Low risk	Randomisation performed centrally
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Ong 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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

Pal 2017

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: not reported
Participants	• Country: India • Setting: not reported • Inclusion criteria: lupus nephritis class III and IV or III/IV + V • Number (randomised/analysed): 58 (number per group not reported) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy: duration of therapy not reported
	• Treatment group 1
	  * Oral TAC: 0.75 mg/kg
	  * Oral AZA: 2 mg/kg
	• Treatment group 2
	  * IV CPA: 500 mg/m^2 monthly
	• Both groups
	  * MP: 3 pulsed doses and subsequently, prednisolone was given at doses of 0.5 mg/kg/d for the next 1 month and then tapered as tolerated to 10 mg or less by 3 months

Outcomes	• Complete renal remission • Partial renal remission • Daily proteinuria • Adverse events • Disease activity
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Pal 2017 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Likely to be an open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all expected outcomes have been reported
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Rathi 2016

Methods	• Study design: open-label, proof-of-concept RCT • Study timeframe: not reported • Duration of follow-up: 6 months
Participants	• Country: India • Setting: single centre • Inclusion criteria: aged 12 to 65 years; diagnosis of SLE (ACR criteria); biopsy-proven class III, IV, V, III +V, or IV+V lupus nephritis (ISN/RPS 2003 classification criteria) • Number (randomised/analysed): treatment group 1 (50/50); treatment group 2 (50/50) • Mean age ± SD (years): treatment group 1 (30.6 ± 9.5); treatment group 2 (28.3 ± 9.5) • Sex (M/F): treatment group 1 (5/45); treatment group 2 (3/47) • Exclusion criteria: crescentic lupus nephritis (> 50% crescents in biopsy); SCr of > 265 µmol/L; neurological or pulmonary lupus; ongoing infection; pregnancy; prior treatment with CPA or MMF

Interventions	Induction therapy
	• Treatment group 1
	  * IV CPA: 6 fixed doses 0.5 g administered fortnightly; duration of therapy was 3 months
	• Treatment group 2
	  * Oral MMF: initiated at a dose of 0.5 g twice a day and increased every 2 weeks to achieve a target dose of 1.5–3.0 g/d; duration of therapy was 6 months
	• Both groups
	• IV MP: 3 daily boluses (0.75 g each) at the beginning of treatment followed by oral prednisolone (1 mg/kg/d) for 8 weeks and subsequent tapering
	• Hydroxychloroquine: 6 mg/kg, single daily dose
	• ACEi or ARB
	Maintenance therapy
	• At the end of induction therapy patients received maintenance therapy AZA (2 mg/kg) and prednisolone (5 to 7.5 mg/d)

Rathi 2016 *(Continued)*

Outcomes	• Death • Complete remission: return to normal SCr along with proteinuria ≤ 0.5 g/d and inactive urine sediment • Partial remission: defined as treatment response, as a decrease in the UPCR to < 3 in subjects with a baseline ratio ≥ 3 or a decrease in UPCR by ≥ 50% in those with a baseline ratio < 3, along with stabilisation or improvement in SCr (a 24-week SCr level within 25% of baseline). • Herpes zoster virus infection • Ovarian failure • Alopecia • Leucopenia
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	Low risk	Study protocol available from Indian clinical trials registry and pre-specified outcomes were reported
Other bias	High risk	High dropout rate; baseline characteristics different between the two groups with UPCR significantly higher in the CPA group

Rovin 2016

Methods	• Study design: double-blind, parallel, proof-of-concept RCT • Study timeframe: not reported • Duration of follow-up: placebo mean 40.1 weeks; sirukumab mean 36.1 weeks
Participants	• Countries: 6 (countries not reported) • Setting: multinational (18 sites) • Inclusion criteria: adults (18 to 70 years); diagnosis of SLE (ACR or SLICC criteria), including seropositivity for ANA and/or anti-ds DNA autoantibodies; biopsy-proven (within 14 months of randomisation) Class III or IV lupus nephritis (ISN/RPS 2003 classification criteria), and persistently active (proteinuria > 0.5 g/d or at least one of the following criteria: haematuria (≥ 5 RBC/HPF), anti-dsDNA-positive test,

Rovin 2016 *(Continued)*

	or C3 or C4 complement levels below the lower limit of normal; plus disease despite standard-of-care induction and maintenance immunosuppressive treatment
	• Number (randomised/analysed): treatment group (21/21); control group (4/4)
	  * Treatment group: class III (7); class IV (14)
	  * Control group: class III (2); class IV (2)
	• Mean age ± SD (years): treatment group (30.6 ± 7.7); control group (37.8 ± 11.4)
	• Sex (M/F): treatment group (4/17); control group (0/4)
	• Exclusion criteria: received CPA within 3 months of randomisation; unless intolerant, patients were required to be on a stable dose of an ACEi and/or an ARB; poorly controlled hypertension (mean SBP >150 mm Hg) or a pattern of worsening or unstable kidney disease during the 8-week screening period

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group
	  * Sirukumab (IL-6 antibody): 10 mg/kg administered IV every 4 weeks
	• Control group
	  * Placebo: administered IV every 4 weeks
	• Both groups
	  * MMF (1 to 3 g/d; or the equivalent dose of mycophenolic acid/mycophenolate sodium) or AZA (1 to 3 mg/kg/d), with or without oral corticosteroids (≤ 20 mg/d prednisone or equivalent)

Outcomes	• Death • Major infection • Malignancy • Diarrhoea • Kidney function
Notes	• Funding source: Janssen Research & development LLC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes were reported
Other bias	High risk	Marked differences (demographics and clinical characteristics) between groups at baseline. Sponsor involved in authorship

Sabry 2009

Methods	• Study design: quasi-RCT • Study timeframe: not reported • Duration of follow-up: 1 year
Participants	• Country: Egypt • Setting: single centre • Inclusion criteria: ACR criteria for SLE; ≥ 18 years; biopsy-proven proliferative lupus nephritis (WHO class IV), urine protein > 0.5 g/d • Number (randomised/analysed): treatment group 1 (26/26); treatment group 2 (20/20) • Mean age ± SD (years): treatment group 1 (26.4 ± 9); treatment group 2 (25.7 ± 7) • Sex (M/F): treatment group 1 (4/22); treatment group 2 (2/18) • 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; DM, documented toxicity; anticipated poor compliance

Interventions	Induction therapy: duration of therapy was 12 months
	• Treatment group 1
	  * High dose CPA: 6 x monthly pulses + 2 x quarterly pulses. Initial dose (0.5 g/1.73 m^2) then dose increased by 250 mg according to WCC on day 14 with final increment to maximum dose of 1 g/1.73m^2
	• Treatment group 2
	  * Low dose CPA: 6 x monthly pulses + 2 x quarterly pulses fixed dose of 0.5 g/d
	• Both groups
	  * 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

Outcomes	• Death • ESKD • Doubling of SCr • Relapse: defined by a doubling of the urinary protein excretion or by an increase in the SCr level by 50% or more for more than 1 month • Treatment failure: defined as urinary protein excretion ≥ 3 g/24 h; and/or doubling of SCr or severe flare that was resistant to increased glucocorticoid dose; patients who did not meet complete or partial remission criteria were considered as having treatment failure • Major infection • Ovarian failure • Anaemia • Leucopenia • GI side effects • Proteinuria • SCr • Serum albumin
Notes	• Six participants with most severe form of lupus nephritis allocated to high-dose arm • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Sabry 2009 *(Continued)*

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 of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol available, all expected outcomes were reported
Other bias	Unclear risk	Differences in baseline characteristics between the groups (more severe proteinuria and lower serum albumin in high dose CPA

Sedhain 2016

Methods	• Study design: open-label, parallel RCT • Study timeframe: January 2014 to June 2015 • Duration of follow-up: 6 months
Participants	• Country: Nepal • Setting: single centre • Inclusion criteria: biopsy-proven proliferative lupus nephritis • Number (randomised/analysed): 49/42; treatment group 1 (21); treatment group 2 (21) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * MMF: administered orally daily
	• Treatment group 2
	  * IV CPA: administered monthly

Outcomes	• Complete remission: normal SCr and proteinuria ≤ 0.5 g/d • Partial remission • Treatment failure: no response to therapy • Proteinuria
Notes	• Abstract-only publication

Sedhain 2016 *(Continued)*

- Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to provide judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to provide judgement
Other bias	High risk	Characteristics of the six patients unable to complete the study period are not provided and these patients were not included in the analysis; abstract-only publication

Sesso 1994a

Methods	• Study design: parallel RCT • Study timeframe: September 1990 to December 1992 • Duration of follow-up: 15 months
Participants	• Country: Brazil • Setting: single centre • Inclusion criteria: aged ≥ 16 years; diagnosis of SLE (ARA criteria); severe lupus nephritis (defined as nephritic urine sediment or urinary protein of > 3.0 g/d and impaired kidney function (CrCl < 80 mL/min or a recent reduction of at least 30%); if CrCl was stable the patient had to have histology of diffuse proliferative GN (WHO classification criteria); 23/29 diffuse proliferative lupus nephritis • Number (randomised): treatment group 1 (14); treatment group 2 (15) • Mean age ± SE (years): treatment group 1 (30.0 ± 2.7); treatment group 2 (24.3 ± 1.5) • Sex (M/F): treatment group 1 (2/12); treatment group 2 (2/13) • Exclusion criteria: 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	Induction therapy: duration of therapy was 10 months • Treatment group 1 * IV CPA: 0.5 to 1.0 g/m^2, monthly pulse for 4 months, bimonthly for 4 months then quarterly for 6 months

Sesso 1994a *(Continued)*

	• Treatment group 2
	  * IV 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
	  * Low dose oral prednisolone: 0.5 mg/kg/d initially then tapered to control extra-renal manifestations

Outcomes	• Death • ESKD • Doubling of SCr • Bone toxicity • Bladder toxicity • Malignancy • Major infection • Proteinuria • Complete remission: improvement of SCr and of urine sediment or proteinuria • Partial remission: trend of improvement of SCr and of urine sediment or proteinuria • Relapse: worsening of urine sediment, proteinuria and kidney function after having reached initial improvement with therapy, requiring reinstitution of therapy
Notes	• 2 participants lost to follow-up • Funding source: Instituto Paulista de Estudos e Pesquisas em Nefrologia e Hipertensao

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	High risk	Proteinuria between groups at baseline was different

SIMPL 2014

Methods	• Study design: double-blind, pilot RCT

SIMPL 2014 *(Continued)*

- Study timeframe: not reported
- Duration of follow-up: 36 months

Participants	• Country: Canada
	• Setting: single-centre
	• Inclusion criteria: aged ≥ 18 years; had a history of SLE according to ACR criteria; class III or class IV or class III/IV + V lupus nephritis by the ISN/RPS classification criteria; must have had an index biopsy within the 3 years previous to study enrolment, and could have been induced with CPA, MMF or another immunosuppressant as seen as appropriate by their physician; to be in at least partial remission at the time of randomisation, defined as having a) 0.3 to 2.9 g/d proteinuria, b) serum albumin at least 30 g/L and c) stable kidney function), be receiving between 5 and 20 mg/d of prednisone and provide informed consent
	• Number (randomised/analysed): treatment group 1 (7/7); treatment group 2 (8/8)
	  * Treatment group 1: class III (1), class IV (6), class V (5)
	  * Treatment group 2: class III (3), class IV (4), class V (3)
	• Mean age ± SD (years): treatment group 1 (28.4 ± 5.6); treatment group 2 (39.2 ± 12.8)
	• Sex (M/F): treatment group 1 (0/7); treatment group 2 (2/6)
	• Exclusion criteria: pregnant; required prednisone for treatment of another medical condition other than SLE; were receiving or expected to receive RRT within the next 6 months

Interventions	Maintenance therapy: duration of therapy was 36 months
	• Treatment group 1
	  * Prednisone withdrawal: tapered the dose of prednisone contained in the capsules at a rate of 5 mg/d every 2 weeks until the dose was 10 mg/d, then by 2.5 mg/d every 2 weeks until the dose was 5 mg/d and then by 1 mg/d every 2 weeks until no prednisone and only placebo was contained in the capsules. A capsule containing placebo only was then continued for the duration of the study.
	• Treatment group 2
	  * Prednisone: Low-dose maintenance glucocorticoids were tapered from their steroid dose at the time of randomisation, if necessary, to a target dose of 7.5 mg/d using the same algorithm as the prednisone withdrawal group. Patients who were already on 5 to 7.5 mg/d of prednisone therapy were maintained on their current dose with no changes made to the dose
	• Both groups
	  * Hydroxychloroquine, and antihypertensives, NSAIDs and statins were left to the discretion of the patient's usual care providers. Vitamin D and calcium were recommended for all patients in the study as osteoporosis prophylaxis

Outcomes	• Relapse (composite of renal and major non-renal flare)
	  * Renal flare: defined as the occurrence of any one of the three following events: (1) Increased proteinuria, measured by either 24 hour urine collection or by a urine protein to creatinine ratio, by at least a) 1 g/d if the baseline proteinuria was less than 0.2 g/d or, b) 2 g/d if the baseline proteinuria was between 0.2 and 1 g/d (inclusive), or c) more than double the baseline proteinuria if the baseline proteinuria was greater than 1 g/d; (2) A sustained (i.e. for two consecutive measures) increase in SCr by at least 30% over baseline that was not due to institution of antihypertensive therapy or angiotensin converting enzyme inhibitor therapy and with new haematuria attributable to active SLE; (3) New sustained haematuria attributable to active SLE, and exclusive of menses, infection or medications, that was associated with an increase in proteinuria by at least 0.8 g/d)
	  * Major non-renal flare
	• Major infection
	• Quality of life: SF-36

Notes	• 2 participants lost to follow-up • Funding source: centre for Advancement of Health, Calgary

Risk of bias

Bias	Authors' judgement	Support for judgement

SIMPL 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Patients were randomly allocated to either the prednisone or placebo group using a random number list generated by an independent statistician. Randomization was blocked and stratified according to the duration of steroid treatment at the time of enrollment (≤12 months or >12 months) and remission status (partial or complete)."
Allocation concealment (selection bias)	Low risk	"Allocation was concealed using sealed, opaque, sequentially numbered envelopes maintained by an independent physician. When a participant was randomised, the independent physician faxed the study number and assigned treatment to the study pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study "Patients, investigators, care providers and data analysts remained blinded to study treatment throughout the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients, investigators, care providers and data analysts remained blinded to study treatment throughout the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	All prespecified outcomes are reported, but not all expected outcomes are reported
Other bias	High risk	Pilot study - underpowered

Steinberg 1971

Methods	• Study design: double-blind, parallel RCT • Study timeframe: not reported • Duration of follow-up: 10 weeks
Participants	• Country: USA • Setting: single centre • Inclusion criteria: diagnosis of SLE (ARA criteria); a positive lupus erythematosus cell test in the course of the disease; kidney disease unaccounted for by other pathological processes, with at least one of the following: RBC casts in a fresh centrifuged urine sediment; cellular casts and either haematuria (≥ 20 RBC/HPF) or pyuria (e≥ 20 WBC/HPF); proteinuria ≥ 1 g/24 h; CrCl < 50 mL/min; 8/15 diffuse proliferative lupus nephritis • Number (randomised/analysed): treatment group (7/9); control group (6/6) • Mean age, range (years): treatment group (23, 11 to 36); control group (23, 11 to 36) • Sex (M/F): treatment group (0/7); control group (2/6) • Exclusion criteria: major infection within the preceding 2 weeks; pregnancy; granulocyte count < 1500/mm^3, immunosuppressive therapy within 3 months; severe liver disease

Interventions	Induction therapy: duration of treatment was 10 weeks
	• Treatment group
	  * Oral CPA: initial dose of 3 mg/kg/d could be increased to 4 mg/kg/d after 2 weeks
	  * Prednisone: 30 mg/d
	• Control group
	  * Prednisone: 30 mg/d

Steinberg 1971 *(Continued)*

	• Both groups * Aspirin: 30 mg/d
Outcomes	• Death • Toxicity • Alopecia • Complete remission of proteinuria • Relapse: major SLE flare (criteria not reported) • Proteinuria • CrCl
Notes	• 2 participants crossed-over to CPA therapy following placebo treatment period and were included in the analysis for CPA • Funding source: Drug and placebo were supplied through the kindness of Dr Martin E. Vancif, Mead Johnson Laboratories, Evansville, Ind

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 study, the next sequential envelope was opened in the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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	High risk	Cross-over of two participants from the placebo to CPA arm were included in the analysis

Sun 2015

Methods	• Study design: open-label, parallel RCT • Study timeframe: September 2007 to February 2012 • Duration of follow-up: 6 months
Participants	• Country: China • Setting: single centre • Inclusion criteria: aged 14 to 60 years; SLEDAI ≥ 12; renal-biopsy-proven diffuse segment or global (IV-s of IV-G) lupus nephritis (ISN/RPS 2003 classification criteria)

Sun 2015 *(Continued)*

- Number (randomised/analysed): treatment group 1 (40/40); treatment group 2 (42/42)
- Mean age ± SD (years): treatment group 1 (33.3 ± 11); treatment group 2 (31.9 ± 8.7)
- Sex (M/F): treatment group 1 (3/37); treatment group 2 (4/38)
- Exclusion criteria: complicated by uncontrolled severe infections or neuropsychiatric SLE; abnormal liver or kidney function (defined as > 2 times of the normal values of transaminases or > 265.2 μmol/L of SCr level); patients with < 3×10^9/L of WBC or < 50×10^9/L of platelets; patients who received any cytotoxic or immunosuppressive drugs like CPA, TAC, MMF, or CSA within 3 months; pregnant or lactating women; patients with cerebrovascular disease, glucose metabolism disorder, or severe cardiopulmonary dysfunction

Interventions	Induction therapy: duration of therapy was 6 months
	• Treatment group 1
	  * IV CPA: monthly dose of 0.75 g/m^2
	• Treatment group 2
	  * IV CPA: monthly dose of 0.4 g/m^2
	  * Oral MMF: 1.0 g/d
	• Both groups
	• Prednisolone was started at a daily dose of 1.0 mg/kg for both groups, and then the dose was reduced gradually after 4 to 8 weeks until completion of the treatment

Outcomes	1. Death 2. Major infection 3. Leucopenia: WCC < 4000/mm^3 4. Complete remission: < 0.3 g/24 h proteinuria with ≥ 35 g/L of serum albumin and normal SCr level 5. Partial remission: proteinuria range 0.3 to 2.9 g/24 h with an albumin concentration of ≥ 30 g/L, stable or improved kidney function with reduction of proteinuria by > 50% 6. Serum albumin 7. Proteinuria
Notes	• Funding source: This study was in part supported by the Natural Science Foundation of Hunan Province (No. 13JJ3033)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data

Sun 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	No study protocol available but expected outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Wallace 1998

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: > 24 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: diagnosis of SLE (ACR criteria); aged ≥ 16 years; class III or IV lupus nephritis on renal biopsy and chronicity index < 6; 2/19 class IV • Number (randomised): treatment group 1 (9); treatment group 2 (9) • Mean age ± SD (years): treatment group 1 (33.0 ± 10.0); treatment group 2 (32.0 ± 14.0) • Sex (M/F): treatment group 1 (1/8); treatment group 2 (0/9) • Exclusion criteria: SCr > 3 mg/dL; renal biopsy chronicity index ≥ 6; pregnancy; < 16 years; immunosuppression in last 3 months

Interventions	Induction therapy: duration of treatment was 8 months
	• Treatment group 1
	  * PEX: 3 x daily preceding CPA
	  * IV CPA: (750 mg/m^2 x 6)
	• Treatment group 2
	• IV CPA: 750 mg/m^2 x 6 over 8 months
	• Both groups
	  * Prednisolone: 1 mg/kg/d for 6 weeks then tapering dose

Outcomes	• Death • ESKD • Complete remission: SCr < 1.4 mg/dL, a 24-h urine protein < 500 mg, absence of urinary casts; normal BP and serum albumin > 4.0 mg/dL • SCr • Serum albumin • Proteinuria
Notes	• 1 patient lost to follow-up • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Wallace 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Not all expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Yap 2017

Methods	• Study design: parallel RCT • Study timeframe: not reported • Duration of follow-up: 6 months
Participants	• Country: Hong Kong • Setting: not reported • Inclusion criteria: active lupus nephritis • Number (randomised): treatment group 1 (7); treatment group 2 (7) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Interventions	Induction therapy: duration of treatment was 6 months
	• Treatment group 1
	  * MMF: no details provided
	• Treatment group 2
	  * CPA: no details provided
	• Both groups
	  * Prednisone or prednisone equivalent: no details provided

Outcomes	• Immunological function
Notes	• Funding source: Bristol Myers Squibb

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Yap 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All 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)	High risk	Not all relevant clinical outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement; abstract-only publication

Yee 2004

Methods	• Study design: open label, parallel RCT • Study timeframe: June 1992 to May 1996 • Duration of follow-up: intended to be 5 to 10 years

Participants	• Countries: Austria, Czech Republic, Lithuania, Slovenia, Sweden, UK
	• Setting: multinational (8 sites)
	• Inclusion criteria: diagnosis of SLE (ACR criteria); biopsy-proven proliferative lupus nephritis (WHO classification criteria), aged 16 to 65 years
	• Number (randomised/analysed): treatment group 1 (16/13); treatment group 2 (16/16)
	  * Treatment group 1: class III (6), class IV (10)
	  * Treatment group 2: class III (5), class IV (8)
	• Mean age ± SD (years): treatment group 1 (42.4 ± 11.8); treatment group 2 (32.2 ± 11.7)
	• Sex (M/F): treatment group 1 (2/11); treatment group 2 (2/14)
	• Exclusion criteria: previous CPA or AZA in preceding 3 weeks; pure membranous or mesangial proliferative GN on biopsy; previous treatment with CPA for > 3 months; allergy to study drugs; previous malignancy; primary immunodeficiency (except complement components); non-lupus-related kidney disease

Interventions	Induction therapy: duration of treatment was 24 months
	• Treatment group 1
	  * Intermittent IV CPA: 10 mg/kg 3 x/wk, max 1 g for 4 doses, then orally (same dose split over 2/7) 4 weekly for 9 months and 6 weekly for 12 months
	  * IV 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
	• Treatment group 2
	  * Oral CPA: 2 mg/kg/d for 3 months then 1.5 mg/kg/d
	  * Oral prednisolone: 0.85 mg/kg/d (max dose 60 mg) reducing to 0.11 mg/kg/d by week 53
	• Both groups
	  * H2 receptor antagonist (ranitidine 150 mg at night or cimetidine 400 mg at night) and amphotericin lozenges (10 mg four times a day) as prophylaxis while on daily CPA and for two weeks with each pulse of CPA

Outcomes	• Death

Yee 2004 *(Continued)*

- ESKD
- Doubling of SCr
- Major infection
- Ovarian failure
- Malignancy
- Bladder toxicity
- Nausea/vomiting
- Treatment failure: failure to respond to treatment

Notes	• Study terminated after 4 years due to poor recruitment and high withdrawal rate • Funding source: European League Against Rheumatism (EULAR) Standing Committee on International Clinical Studies including Therapeutic Trials (ESCIST); Lupus UK; and the Swedish Medical Research Council (grant 13489).

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 of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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	High risk	Study was terminated after four years as patient recruitment was disappointing and many patients had been withdrawn; Many physicians became reluctant to enter patients because of concerns that the oral regimen was slower to work and more toxic than the pulse regimen, following development of severe neutropenia in the continuous group; This led to the premature termination of the study

Zhang 1995a

Methods	• Study design: open-label, parallel RCT • Study timeframe: not reported • Duration of follow-up: 12 to 39 months
Participants	• Country: China • Setting: single centre

Zhang 1995a *(Continued)*

- Inclusion criteria: biopsy-proven active lupus nephritis
- Number (randomised): 36 (numbers per group not reported)
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Induction therapy
	• Treatment group 1
	  * CPA: monthly pulse 0.5 to 0.8 g/m^2 until remission
	• Treatment group 2
	  * CPA: monthly pulse 0.5 to 0.8 g/m^2 for 1 year
	• Both groups
	  * Minimum necessary dose of steroids

Outcomes	• Remission • Relapse • Urinalysis • Serology
Notes	• Abstract-only publications • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All 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)	High risk	Data unable to be meta-analysed
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

ACEi - angiotensin-converting enzyme inhibitor; ACR - American College of Rheumatology; ANA - antinuclear antibody; ARA - American Rheumatology Association; ARB - angiotensin receptor blocker; AZA - azathioprine; BILAG - British Isles Lupus Assessment Group; CKD - chronic kidney disease; CMV - cytomegalovirus; CNI - calcineurin; CNS - central nervous system; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporin A; DM - diabetes mellitus; EC-MPS - enteric-coated mycophenolate sodium; eGFR - estimated glomerular filtration rate; ELNT - Euro-lupus nephritis treatment; ESKD - end-stage kidney disease; GI - gastrointestinal: GN - glomerulonephritis;

Hb - haemoglobin; HBV - hepatitis B virus; HCV - hepatitis C virus; HIV - human immunodeficiency virus; HPF - high power field; IA - immunoadsorption; ISN/RPS - International Society of Nephrology/Renal Pathology Society; IV - intravenous; IVIG - intravenous immunoglobulin; M/F - male/female; MMF - mycophenolate mofetil; MP - methylprednisolone; NSAID/s - nonsteroidal anti-inflammatory drug/s; PEX - plasma exchange or plasmapheresis; PALGA - Dutch Pathology Registry; RBC - red blood cell/s; RCC - red cell count; RCT - randomised controlled trial; RTX - rituximab; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; SDS - standard deviation score; SLE - systemic lupus erythematosus; SLEDAI - SLE Disease Activity Index; SLICC - Systemic Lupus Collaborating Clinics; TAC - tacrolimus; TB - tuberculosis; WHO - World Health Organization; ISN/RPS - International Society of Nephrology/ Renal Pathology Society; UPCR - urine protein-to-creatinine ratio; WBC - white blood cell/s; WCC - white cell count

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

Study	Reason for exclusion
Andrade-Ortega 2010	Wrong population: not biopsy-proven lupus nephritis
Antunes 2001	Wrong intervention: not comparing immunosuppression
ASPEN 2008	Wrong population: not biopsy-proven lupus nephritis
ATLAS 2016	Wrong population: diagnosis of biopsy-proven proliferative lupus nephritis at randomisation unclear
Austin 2009	Wrong population: not biopsy-proven lupus nephritis but membranous
Balow 1981	Wrong population: not biopsy-proven lupus nephritis
Balow 1984	No relevant outcomes
Ble 2011	Wrong intervention: not immunosuppressive intervention
Chanchairujira 2009	No relevant clinical outcomes
Clark 1993	Wrong population: not biopsy-proven lupus nephritis
Clark 2001a	Wrong population: not biopsy-proven lupus nephritis
CONTROL 2016	Wrong population: diagnosis of biopsy-proven proliferative lupus nephritis at randomisation was unclear
Davis 1999	Wrong population and intervention: not biopsy-proven lupus nephritis or comparing immunosuppression
Daza 2005	Wrong intervention: not comparing immunosuppression
Deng 2017a	Wrong intervention: not comparing immunosuppression
Feng 2014	Wrong population: not biopsy-proven lupus nephritis
Frutos 1997	Insufficient information to determine if the study is randomised
Hebert 1987	Wrong population: not biopsy-proven lupus nephritis
Khajehdehi 2012	Wrong intervention: not immunosuppressive intervention
Kuo 2001	Wrong intervention: not comparing immunosuppression
Li 2005	Insufficient information to determine if the study is randomised

Study	Reason for exclusion
Li 2014a	Wrong intervention: not immunosuppressive intervention
LJP 394-90-05 2003	Wrong population: not biopsy-proven lupus nephritis
LJP 394-90-09 2005	Wrong population: not biopsy-proven lupus nephritis
Lu 2002	Wrong population: not biopsy-proven lupus nephritis
Miyasaka 2009	Wrong population: included class II and class V lupus nephritis
NCT00001212	Wrong population: membranous lupus nephritis
NCT00404157	The study has been terminated
NCT00429377	The recruitment status of this study is unknown (registered 2007). The completion date of this study has passed and the status has not been verified in more than two years.
NCT00436438	Study terminated early for administrative reasons
NCT00539799	This study was withdrawn prior to enrolment, as the local pharmacy were unwilling to comply with the study protocol
NCT00659217	The recruitment status of this study is unknown (registered 2008). The completion date of this study has passed and the status has not been verified in more than two years
NCT01299922	This study was withdrawn prior to recruitment
NCT01342016	This study has been terminated due to safety concerns of active control drug
NCT01930890	Study was terminated because results from previous studies did not demonstrate sufficient efficacy
NCT02176486	Study was terminated, insufficient enrolment
Pierucci 1989	Wrong population: not comparing immunosuppression
Schaumann 1992	Unclear if biopsy-proven lupus nephritis
Su 2007	Wrong population: not biopsy-proven lupus nephritis
Sztejnbok 1971	Wrong population: not biopsy-proven lupus nephritis
Wallace 2006	Wrong population: not biopsy-proven lupus nephritis
Wang 2007	Wrong population: non-invasive necrotising vasculopathy-severe variant not usually responsive to standard therapy
Witte 1993	Unclear if biopsy-proven lupus nephritis
Yap 2012	Wrong population: not biopsy-proven lupus nephritis
Ye 2001	Wrong population: not biopsy-proven lupus nephritis
Yoshida 1996	Wrong intervention: not comparing immunosuppression

Study	Reason for exclusion
Zhang 2015c	Wrong population: biopsy-proven proliferative lupus nephritis were excluded
Zheng 2005a	Unclear if biopsy-proven lupus nephritis

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

2nd 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	Multicentre RCT
Participants	Adult, proliferative lupus nephritis, biopsy-proven, active urinary sediment, proteinuria
Interventions	6 months IV CPA induction followed by either 3 monthly IV CPA 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	

ChiCTR-TRC-09000587

Trial name or title	The intensive therapy of severe lupus nephritis: a multicenter, randomised, controlled prospective clinical trial
Methods	Multicentre, randomised controlled
Participants	Adult, SLE according to ACR criteria, renal biopsy-proven lupus nephritis: 24 hours proteinuria (≥ 3.0g/d or +++), erythrocyturia > 5/HPF, leucocyturia or cast (RBC, Hb, tubuli or mixed); SLEDAI score ≥10
Interventions	1. NIH IV CPA standard program (Induction period, follow-up once every four weeks; consolidation therapy: follow-up once every twelve weeks, maintenance therapy: follow-up once every twelve weeks. 2. Intensive group: mini-pulse of CPA, hydroxychloroquine and another immunosuppressive agent, such as MMF, leflunomide, AZA or methotrexate
Outcomes	Serum albumin, SCr, SLEDAI, liver function, adverse events
Starting date	September 2009
Contact information	Zhanguo Li, The department of rheumatology and immunology, People's Hospital, Peking university, Beijing, China
Notes	

ChiCTR-TRC-10000931

Trial name or title	Treatment of severe lupus nephritis with tacrolimus (FK 506) based immunosuppression
Methods	Multicentre RCT
Participants	Adult; SLE (ACR criteria); SLEDAI > 10 points; biopsy-proven lupus nephritis severe type III, IV type, V +III type and V+IV-type lupus nephritis (WHO2004 criteria), heavy-III, with severe segmental lesions that have loop necrosis or crescent formation of the III-type lupus nephritis); significant renal disease, proteinuria ≥ 2 g/24 h, with active urine sediment (urine RBC > 400,000/mL, tube urine, leukocytes in urine), SCr < 3mg/dL (265 µmol/L)
Interventions	Tacrolimus (0.5 mg and 1 mg)
Outcomes	Serum albumin, SCr, proteinuria, immunological function, renal biopsy, adverse events
Starting date	2009
Contact information	Changlin Mei, Shanghai Changzheng Hospital, Beijing China
Notes	Sponsor - Astellas Pharma China Inc.

CTRI/2016/01/006488

Trial name or title	Comparison of two steroid dose regimen in lupus nephritis: a randomised controlled trial
Methods	RCT
Participants	12 to 70 years of age, SLE (ACR criteria); biopsy-proven lupus nephritis (ISN/RPS class III, IV, III+V or IV+V)
Interventions	1. Low dose oral prednisolone (0.5 mg/kg/d) 2. Oral prednisolone (1 mg/kg/d) Patients in both groups will receive IV MP (750 mg) for 3 days, followed by oral prednisolone for a period of 8 weeks followed by a taper. All patients will receive MMF
Outcomes	Complete remission, partial remission, SELENA-SLEDAI, quality of life, immunological function, adverse events
Starting date	January 2016
Contact information	Krishan Lal Gupta, Department of nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
Notes	

CTRI/2017/05/008697

Trial name or title	Randomised controlled trial of multi-targetted therapy versus low-dose intravenous cyclophosphamide in the treatment of lupus nephritis
Methods	Parallel RCT

CTRI/2017/05/008697 *(Continued)*

Participants	Adults, SLE ACR criteria; lupus nephritis class III, IV, V, a combination of III+V or IV+V; SCr < 3.0 mg/dL
Interventions	1. MMF: 1 g/d in 2 divided doses and TAC 0.1 mg/kg/d to target a trough level of 4 to 7 ng/mL. MMF and TAC will be taken morning and evening, before meals, and with a glass of water 2. CPA: Euro-lupus Nephritis trial group regimen of six fortnightly IV infusions of a fixed dose of 500 mg CPA • All the patients will be given 3 IV infusion of MP (750 mg) followed by 1 mg/kg/d of oral prednisolone for a period of 8 weeks followed by taper to 7.5 mg/d at the end of 6 months • All the patients will be given maintenance treatment after completion of induction treatment, in the form of AZA (2 mg/kg) plus low-dose steroids
Outcomes	1. Decrease in 24 h proteinuria, defined as decrease in the UPCR to 3 in subjects with baseline nephrotic range proteinuria (≥ 3 UPCR) or decrease in the UPCR by ≥ 50% in subjects with subnephrotic proteinuria (3 UPCR) 2. Stabilization of SCr (i.e., a week 24 SCr level ± 25% of baseline) or improvement
Starting date	July 2016
Contact information	Krishan Lal Gupta, Department of Nephrology, Nehru Hospital, Post Graduate Institute of Medical Education and Research, Chandigarh, India
Notes	Follow-up: 6 months

ISRCTN66475575

Trial name or title	Enteric coat mycophenolate sodium versus intravenous cyclophosphamide for severe paediatric lupus nephritis
Methods	Multicentre RCT
Participants	Paediatric lupus nephritis
Interventions	1. EC-MPS (myfortic®): 720 to 860 mg/m^2/d, oral twice daily + oral steroid 2. CPA: 750 to 1000 mg/m^2/d (maximum dose 1000 mg/d), IV monthly for 6 months then every 3 months + oral steroid
Outcomes	1. Death 2. ESKD 3. Complete remission 4. Partial remission 5. Relapse (renal and non-renal) 6. Disease activity: SLEDAI 7. Infection 8. GI symptoms
Starting date	July 2009
Contact information	Wattana Chartapisak, Department of Pediatrics, Chiang Mai, Thailand
Notes	

NCT00302549

Trial name or title	To compare the efficacy and safety of FK506 vs IVC in the treatment of class III-IV lupus nephritis
Methods	Multicentre RCT
Participants	Adult (18 to 65 years) female patients with SLE according to ACR criteria, SLEDAI > 10; biopsy-proven class III or IV lupus nephritis according to the WHO classification criteria within 3 month and have significant active pathological lesion; proteinuria ≥ 2 g/24 h, and an active urine sediment (haematuria with white cells and casts in urine)
Interventions	1. TAC: 0.1 mg/kg/d 2. IV CPA
Outcomes	Safety and efficacy
Starting date	May 2004
Contact information	Lei-shi Li, Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, Jiangsu, China
Notes	Study was registered over 10 years ago and it is unlikely the study will be published

NCT00705367

Trial name or title	A single centre, randomised, placebo-controlled, double blind, parallel group study to evaluate the tolerability of a single dose of Abatacept 30 mg/kg via intravenous infusion in Chinese SLE subjects with lupus nephritis
Methods	Single-centre, double blind and open-label extension RCT
Participants	Adult; ≥ 18 years of age; SLE and with lupus nephritis currently stable for the last 3 months without change in treatment for lupus nephritis; stable renal disease; no flaring of other organ systems in a minimum of the last 3 months
Interventions	1. Abatacept: IV 30 mg/kg, single dose at day 1 and IV 10 mg/kg on days 15 and 29 followed by doses every 4 weeks until the end of the study 2. Placebo: IV
Outcomes	1. Death 2. Adverse events 3. Clinical characteristics: e.g. blood pressure, heart rate
Starting date	August 2008
Contact information	Bristol-Myers Squibb
Notes	Study includes short-term follow-up period and long-term extension period

NCT00881309

Trial name or title	To compare the efficacy and safety of tripterygium vs azathioprine in the maintenance therapy for lupus nephritis
Methods	RCT
Participants	Adults, class III-V lupus nephritis (biopsy-proven)
Interventions	Induction with MMF, CPA, TAC or multi-target therapy followed by randomisation to either AZA maintenance therapy or tripterygium 90 mg once/d
Outcomes	Complete remission
Starting date	March 2009
Contact information	Weixin Hu, Nanjing University School of Medicine, China
Notes	

NCT01056237

Trial name or title	Long-term study of multi-target therapy as maintenance treatment for lupus nephritis
Methods	Open-label RCT
Participants	Adults (18 to 65 years); SLE; diagnosed class Ⅲ, Ⅳ, Ⅳ+Ⅴ, Ⅲ+Ⅴ or Ⅴ lupus nephritis (ISN/RPS 2003 criteria) by renal biopsy; all patients had received induction therapy for 6 months with multi-therapy (FK506 + MMF) or IV CPA pulses. Patients were recruited when received partial remission or complete remission after 6 months induction therapy
Interventions	1. Multi-target therapy: TAC (1 to 3 mg/d) and MMF (0.5 to 0.75 g/d) 2. AZA: 1.0 to 2.0 mg/kg/d
Outcomes	Safety and efficacy
Starting date	February 2010
Contact information	Zhi-Hong Liu, Nanjing University School of Medicine
Notes	18 month duration

NCT01172002

Trial name or title	Leflunomide versus AZA for maintenance therapy of lupus nephritis
Methods	Open-label RCT
Participants	Adults, biopsy-proven proliferative lupus nephritis
Interventions	Leflunomide versus AZA (maintenance therapy)
Outcomes	Lupus nephritis flare

NCT01172002 *(Continued)*

Starting date	March 2010
Contact information	Bao Chun De, Renji Hospital
Notes	

NCT01284725

Trial name or title	Weaning of Immunosuppression in Nephritis of Lupus
Methods	Open-label RCT
Participants	Adult, biopsy-proven proliferative lupus nephritis
Interventions	Immunosuppressive treatment discontinuation versus continuation of MMF or AZA
Outcomes	Discontinuation of maintenance immunosuppressive therapy
Starting date	January 2011
Contact information	Noemie Jourde Chiche, Assistance Publique hôpitaux de Marseille
Notes	

NCT01639339

Trial name or title	A phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of Belimumab plus standard of care versus placebo plus standard of care in adult subjects with active lupus nephritis
Methods	Double-blind, placebo controlled RCT
Participants	Adult, diagnosis of SLE (ACR criteria), biopsy-proven lupus nephritis, clinically active lupus nephritis, autoantibody positive
Interventions	Belimumab versus placebo and standard therapy
Outcomes	Renal response, complete renal response, adverse events
Starting date	July 2012
Contact information	GlaxoSmithKline
Notes	

NCT01714817

Trial name or title	A phase 3 randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of BMS-188667 (Abatacept) or placebo on a background of mycophenolate mofetil and corticosteroids in the treatment of subjects with active class III or IV lupus nephritis

NCT01714817 *(Continued)*

Methods	Double-blind RCT
Participants	Age > 16 years; biopsy-proven class III or IV lupus nephritis within 12 months; UPCR ≥ 1; SCr ≤ 3 mg/dL (i.e., ≤ 265 µmol/L); active disease within 3 months - based on one of the following (1) worsening of lupus nephritis - UPCR ≥ 3 (2) active urine sediment (3) biopsy within 3 months indicating active class III or IV Inclusion criteria for the long-term extension period: achieved complete or partial renal response after completing 2 years of double-blind treatment
Interventions	1. BMS-188667 + MMF + Prednisone: BMS-188667 30 mg/kg injection by IV on days 1, 15, 29, and 57, followed by a weight-tiered dose approximating 10 mg/kg injection by IV every 4 weeks, MMF 1.5 g tablet by mouth and prednisone up to 60 mg tablet by mouth daily for 104 weeks 2. Placebo matching with BMS-188667 injection by IV on Days 1, 15, 29, and 57, followed by every 4 weeks, MMF 1.5 g tablet by mouth and prednisone up to 60 mg tablet by mouth daily for 104 weeks
Outcomes	Renal response
Starting date	January 2013
Contact information	Bristol-Myers Squibb
Notes	

NCT01845740

Trial name or title	A phase Ib study of milatuzumab administered subcutaneously in patients with active systemic lupus Erythematosus
Methods	Double-blind RCT
Participants	Adult ≥ 18 years; SLE (ACR criteria); positive ANA (titre ≥ 1:80); at least 1 BILAG A or 2 BILAG B scores in any organ/body system and ≥ 6 SELENA-SLEDAI score; receiving at least 5.0 mg/d oral prednisone (or equivalent) at stable doses for at least 4 weeks prior to study entry If receiving immunosuppressives or antimalarial agents, at stable doses for at least 4 weeks prior to study entry
Interventions	1. High dose milatuzumab SC 250 mg 2. Low dose milatuzumab SC 150 mg 3. Placebo SC
Outcomes	Safety and efficacy
Starting date	January 2015
Contact information	Heather Horne, Cedars Sinai Medical Center-Wallace Rheumatic Study centre, California, United States of America
Notes	

NCT01861561

Trial name or title	Efficacy and infectious complications of induction therapy with low-dose versus high-dose intravenous cyclophosphamide for proliferative lupus nephritis in children

NCT01861561 *(Continued)*

Methods	Open-label RCT
Participants	Children (≤ 15 years), diagnosis of SLE (ACR 1997 criteria), biopsy-proven class III or IV lupus nephritis (ISN/RPS 2003 classification criteria)
Interventions	High-dose IV CPA versus low-dose IV CPA (induction therapy)
Outcomes	Complete renal response, partial renal response, infection, quality of life, disease activity
Starting date	May 2013
Contact information	Nuntawan Piyaphanee, Siriraj Hospital, Thailand
Notes	

NCT02226341

Trial name or title	Open-label prospective randomised study to determine the efficacy and safety of two dosing regimens of ACTHar in the treatment of proliferative lupus nephritis
Methods	Open-label RCT
Participants	≥ 16 years, diagnosis of SLE (ACR/SLICC criteria), biopsy-proven class III or IV ±V lupus nephritis (ISN/RPS 2003 classification criteria)
Interventions	CellCept daily & ACTHar gel biweekly versus CellCept daily & ACTHar gel every other day
Outcomes	Complete response, partial response, renal flares, adverse events, cortisol levels, urinary lymphocytes
Starting date	October 2014
Contact information	Anca D Askanase, Columbia University, USA
Notes	

NCT02256150

Trial name or title	A multi-center, randomised, controlled, open-label clinical study to evaluate the efficacy and safety of mizoribine in comparison with cyclophosphamide in the treatment of lupus nephritis
Methods	Open-label RCT
Participants	Adult, diagnosis of SLE (ACR 1997 criteria), biopsy-proven class III, III+V, IV, IV+V or V (ISN/RPS 2003 classification criteria), proteinuria > 1 g/d, SLEDAI > 8, patient body weight 40-80kg at screening
Interventions	Mizoribine versus CPA
Outcomes	Complete remission, partial remission, treatment failure, ESKD, doubling of SCr, SCr, eGFR, C3, anti-dsDNA, anti-phospholipid, anti-Sm, SLEDAI
Starting date	November 2014

NCT02256150 *(Continued)*

Contact information	Asahi Kasei Pharma Corporation
Notes	

NCT02260934

Trial name or title	Rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis (IT-N055AI)
Methods	Open-label RCT
Participants	Adult, diagnosis of SLE (ACR criteria), biopsy-proven proliferative lupus nephritis (ISN/RPS classification criteria), > 5 RBC/HPF in absence of menses and infection, > WBC/HPF in absence of infection or cellular casts, UPCR > 1
Interventions	RTX, CPA and belimumab versus RTX and CPA
Outcomes	Major infection, hypogammaglobulinaemia, complete response, partial response, treatment failure, relapse anti-dsDNA, C3 and C4, death, leucopenia, ovarian failure, malignancy, thrombocytopenia, adverse advents
Starting date	October 2014
Contact information	Betty Diamond, Feinstein Institute for Medical Research: centre for Autoimmune and Musculoskeletal Diseases, USA
Notes	

NCT02457221

Trial name or title	A phase III, randomised, open, parallel-controlled, multi-center study to compare the efficacy and safety of tacrolimus capsules and cyclophosphamide injection in treatment of lupus nephritis
Methods	Open-label RCT
Participants	18-60 years, 18.5 ≤ BMI < 27, diagnosis of SLE (ACR 1997 criteria), biopsy-proven class III, IV, V, III+V, IV+V lupus nephritis (ISN/RPS 2003 classification criteria) within 24 weeks of study entry, proteinuria > 1.5 g/d, SCr < 3 mg/dL
Interventions	TAC versus CPA (induction therapy)
Outcomes	Complete remission, partial remission, proteinuria, serum albumin, SCr, eGFR, anti-dsDNA and ANA, SLEDAI, C3 and C4, renal biopsy active index and chronic index
Starting date	March 2015
Contact information	Astellas Pharma China, Inc.
Notes	

NCT02547922

Trial name or title	A multicentre, randomised, double-blind, placebo-controlled, phase 2 study evaluating the efficacy and safety of Anifrolumab in adult subjects with active proliferative lupus nephritis
Methods	Double-blind RCT
Participants	18 to 70 years, fulfil four or more of the ACR 1982 criteria which must include positive ANA, elevated anti-dsDNA, anti-Smith; biopsy-proven class III±V, IV±V, UPCR 1g/d, eGFR ≥ 35 mL/min/1.73 m^2, women of childbearing potential must have negative serum beta-hCG
Interventions	High-dose anifrolumab, low-dose anifrolumab versus placebo
Outcomes	Complete renal response, partial renal response, eGFR, proteinuria, urine sediment, adverse events
Starting date	November 2015
Contact information	AstraZeneca Clinical Study Information centre
Notes	

NCT02550652

Trial name or title	A randomised, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of Obinutuzumab in patients with ISN/RPS 2003 Class III or IV lupus nephritis
Methods	Double-blind, placebo-controlled RCT
Participants	Age 18-75 years, diagnosis of SLE (ACR criteria), biopsy-proven class III or IV lupus nephritis (ISN/RPS 2003 classification criteria), proteinuria UPCR > 1.0 g, premenopausal female participants agree to refraining from getting pregnant 18 months, male participants agree to use contraception for 12 month
Interventions	Obinutuzumab versus placebo
Outcomes	Complete renal response, partial renal response, anti-dsDNA, C3 and C4, disease activity, immune cells (CD-19 B-cells, T-cells, neutrophil), adverse events
Starting date	November, 2015
Contact information	Hoffmann-La Roche
Notes	

NCT02630628

Trial name or title	A randomised open-label study to evaluate the efficacy and safety of tacrolimus and corticosteroids in comparison with mycophenolate mofetil and corticosteroids in subjects with class III/IV ±V Lupus nephritis
Methods	Open-label RCT

NCT02630628 *(Continued)*

Participants	Adult, biopsy-proven lupus nephritis Class III/IV±V (ISN/RPS 2003 classification criteria), positive anti-dsDNA, UPCR > 1.0 g or 24 h urine protein > 1.0 g/d at baseline), with or without haematuria, new or flaring patients
Interventions	TAC versus MMF
Outcomes	Renal response
Starting date	September 2015
Contact information	Tak-Mao Daniel Chan, The University of Hong Kong
Notes	

NCT02770170

Trial name or title	A double-blind, randomised, placebo-controlled trial evaluating the effect of BI 655064 administered as sub-cutaneous injections, on renal response after one year treatment in patients with lupus nephritis
Methods	Double-blind, placebo-controlled RCT
Participants	18-70 years, diagnosis of SLE (ACR criteria), biopsy-proven class III or IV lupus nephritis (ISN/RPS 2003 classification criteria), proteinuria ≥ 1.0 g/d (UPCR ≥ 100 mg/mmol)
Interventions	BI 655064 (anti-CD-40 antibody) versus placebo
Outcomes	Complete renal response, partial response
Starting date	January 2016
Contact information	Boehringer Ingelheim
Notes	

NCT02936375

Trial name or title	Iguratimod as treatment for active lupus nephritis
Methods	Open-label RCT
Participants	Diagnosis of SLE (ACR criteria), biopsy-proven class III, IV, V, III+IV or IV+V active lupus nephritis, proteinuria 1g/d, body weight ≥ 40 kg, SLEDAI-2K ≥ 8, agreement of contraception
Interventions	Iguratimod versus CPA and AZA
Outcomes	Renal remission, renal flare, adverse events, disease activity (SLEDAI-2K, BILAG), patient general assessment
Starting date	March 2017
Contact information	Chunde Bao, RenJi Hospital

NCT02936375 *(Continued)*

Notes	

NCT02954939

Trial name or title	The effect of mycophenolate mofetil and cyclophosphamide on the lymphocyte subsets in patients With proliferative Lupus nephritis
Methods	Open-label RCT
Participants	18 to 80 years , biopsy-proven class III or IV±V lupus nephritis lupus nephritis (ISN/RPS 2003 classification criteria), active lupus nephritis indicated by proteinuria >1 g/d and/or rise in SCr by 15%
Interventions	MMF (induction and maintenance therapy) versus CPA (induction therapy) and AZA (maintenance therapy)
Outcomes	Lymphocyte subset profile (CD8+ T cells, CD4+ Th1, Th2, Th17 & Treg), Naïve & memory B cells, plasma cells, serum cytokine profile (IL-2, IL-5, IL-6, IL-7, IL-10, IL-17, IL-21, IL-23, IFN-alpha, IFN-gamma, TGF-beta)
Starting date	March 2012
Contact information	Desmond Yap, Queen Mary Hospital, Hong Kong
Notes	

NCT03021499

Trial name or title	A randomised, controlled double-blind study comparing the efficacy and safety of voclosporin (23.7 mg twice daily) with placebo in achieving renal response in subjects with active lupus nephritis
Methods	Double-blind RCT
Participants	Subjects with evidence of active nephritis, defined as follows: Kidney biopsy result within 2 years prior to screening indicating Class III, IV-S, IV-G (alone or in combination with Class V), or Class V lupus nephritis with a doubling or greater increase of UPCR within the last 6 months to a minimum of ≥ 1.5 mg/mg for Class III/IV or to a minimum of ≥ 2 mg/mg for Class V at screening. Biopsy results over 6 months prior to screening must be reviewed with a medical monitor to confirm eligibility. Or kidney biopsy result within 6 months prior to screening indicating Class III, IV-S or IV-G (alone or in combination with Class V) lupus nephritis with a UPCR of ≥ 1.5 mg/mg at screening. Or kidney biopsy result within 6 months prior to screening indicating Class V lupus nephritis and a UPCR of ≥ 2 mg/mg at screening. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.
Interventions	1. Voclosporin oral, 23.7 mg BID 2. Voclosporin placebo, oral, 3 capsules BID
Outcomes	1. Renal response 2. Partial renal response 3. kidney function 4. Disease activity - SELENA-SLEDAI 5. Quality of life

NCT03021499 *(Continued)*

Starting date	May 2017
Contact information	Mary Anne Dooley, University of North Carolina
Notes	Sponsor - Aurinia Pharmaceuticals Inc.

NCT03214731

Trial name or title	Efficacy and safety of artesunate plus standard of care in active lupus nephritis (AURORA)
Methods	Multicentre, double-blind RCT
Participants	14 to 65 years; SLE (ACR criteria); renal biopsy within 6 months prior to randomisation with a histological diagnosis (ISN/RPS 2003 classification of lupus nephritis) - class III, IV, V, III+V and IV+V (excluding Class III(C), IV-S(C), and IV-G(C)); class IV or IV+V lupus nephritis: proteinuria ≥ 1 g/24 h (or UPCR ≥ 1.0) or SCr > 1.3 mg/dL, with active urinary sediment (> 5 RBC/HPF or > 5 WBC/HPF (or within the reference range of the laboratory) in absence of menses and genitourinary tract infection, or presence of cellular casts (RBC or WBC casts)); Class III, III+V or V lupus nephritis: proteinuria ≥ 2 g/24 h (or UPCR ≥ 2.0) or SCr > 1.3 mg/dL; Provision of written informed consent by subject or guardian
Interventions	1. High-dose artesunate: 50 mg 2. Low-dose artesunate: 25 mg 3. Placebo • All patients received standard of care
Outcomes	1. Complete remission 2. Partial remission
Starting date	September 2017
Contact information	Xue Qing Yu, The 1st Affiliated Hospital, Sun Yet-sen University, Guangzhou, Guangdong, China
Notes	

PER-062-15

Trial name or title	A multicentre, randomised, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of two doses of anifrolumab in adult subjects with active systemic lupus erythematosus
Methods	Multicentre, double-blind RCT
Participants	Aged 18 - 70 years; weight ≥ 40.0 kg; adequate peripheral venous access; SLE (ACR criteria); currently receiving at least 1 of the following: (a) a dose of oral prednisone (≤ 40 mg/d) for a minimum of 2 weeks, the dose of oral prednisone the subject is taking must be stable for a minimum of 2 weeks prior to Week 0 (Day 1) (b) Any of the following medications administered for a minimum of 12 weeks prior to signing the informed consent, and at a stable dose for a minimum of 8 weeks prior to Day 1.
Interventions	1. High-dose anifrolumab (MEDI-546) - 150 mg IV administration 2. Low-dose anifrolumab (MEDI-546) - 300 mg IV administration 3. Placebo IV

PER-062-15 *(Continued)*

	• Investigational product will be administered every 4 weeks from Week 0 to Week 48 for a total of 13 doses.
Outcomes	1. SLE Responder Index 2. Disease activity - SLEDAI, BILAG 3. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity 4. Immunological function
Starting date	May 2015
Contact information	Luis Fernando Bellatin Vargas, Hogar Clínica, San Juan De Dios-Arequipa
Notes	

RING 2015

Trial name or title	RING, an investigator-initiated trial aimed at testing the efficacy of rituximab in refractory lupus nephritis: Rationale, trial design and call for participation (abstract)
Methods	RCT
Participants	SLE, age > 15 years old, ISN/RPS Class III, IV or V lupus nephritis (biopsy within 24 months), refractory lupus nephritis with previous treatment with Euro-lupus/NIH CPA or AZA or MMF, maximum 10 mg prednisolone/d, UPCR > 1 (mg/mg), and female patients on contraception
Interventions	1. RTX 2. Standard of care
Outcomes	Complete response (UPCR ≤ 0.5 (expressed in mg/mg) measured in a 24 h urine collection; and eGFR ≥ 60 mL/min or, if < 60 mL/min at screening, not fallen by > 20% compared to screening; and no increase of glucocorticoids throughout the study (except for two limited courses as per protocol; vide infra); and no introduction of another immunosuppressant.)
Starting date	August 2012
Contact information	Frédéric A. Houssiau, Université Catholique de Louvain, Belgium
Notes	

RITUXILUP 2013

Trial name or title	Phase 3 open label randomised multicentre controlled trial of rituximab and mycophenolate mofetil without oral steroids for the treatment of lupus nephritis
Methods	Open-label RCT
Participants	12 to 75 years, biopsy-proven lupus nephritis (ISN/RPS 2003 classification criteria), active lupus nephritis UPCR > 1000 mg/mmol, not planning pregnancy during study period
Interventions	RTX versus prednisolone

RITUXILUP 2013 *(Continued)*

Outcomes	Complete renal response, major infections, serious adverse and adverse events, disease activity scores, renal flare, serum C3, C4, anti-dsDNA, quality of life
Starting date	April 2015
Contact information	Liz Lightstone, Hammersmith Hospital, Imperial College Healthcare NHS Trust, United Kingdom
Notes	

ACEi - angiotensin-converting enzyme inhibitor; ACR - American College of Rheumatology; ARA - American Rheumatology Association; ARB - angiotensin receptor blocker; AZA - azathioprine; BILAG - British Isles Lupus Assessment Group; CKD - chronic kidney disease; CMV - cytomegalovirus; CNI - calcineurin; CNS - central nervous system; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporin A; DM - diabetes mellitus; EC-MPS - enteric-coated mycophenolate sodium; eGFR - estimated glomerular filtration rate; ELNT - Euro-lupus nephritis treatment; ESKD - end-stage kidney disease; ESR - erythrocyte sedimentation rate; GI - gastrointestinal: GN - glomerulonephritis; HBV - hepatitis B virus; HCV - hepatitis C virus; HIV - human immunodeficiency virus; HPF - high power field; IA - immunoadsorption; ISN/RPS - International Society of Nephrology/Renal Pathology Society; IV - intravenous; IVIG - intravenous immunoglobulin; M/F - male/female; MMF - mycophenolate mofetil; MP - methylprednisolone; NSAID/s - nonsteroidal anti-inflammatory drug/s; PEX - plasma exchange or plasmapheresis; PLAGA - Dutch Pathology Registry; RBC - red blood cell/s; RCC - red cell count; RCT - randomised controlled trial; RTX - rituximab; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; SELENA - Safety of Estrogens in Lupus Erythematosus National Assessment; SLE - systemic lupus erythematosus; SLEDAI - SLE Disease Activity Index; SLICC - Systemic Lupus Collaborating Clinics; TAC - tacrolimus; TB - tuberculosis; WHO - World Health Organization; ISN/RPS - International Society of Nephrology/ Renal Pathology Society; UPCR - urine protein-to-creatinine ratio; WBC - white blood cell/s; WCC - white cell count

DATA AND ANALYSES

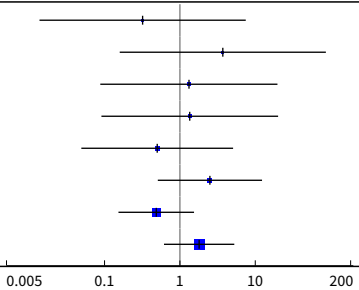
Comparison 1. Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	8	826	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.61, 2.06]
2 Remission	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete renal remission: MMF versus IV CPA	9	868	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.97, 1.42]
2.2 Partial renal remission: MMF versus IV CPA	9	868	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.18]
2.3 Complete remission in proteinuria: MMF versus IV CPA	6	686	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.85, 1.58]
2.4 Partial remission in proteinuria: MMF versus IV CPA	6	744	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.18]
3 Adverse renal outcomes	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD	3	231	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.27, 1.84]
3.2 Renal relapse	1	140	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.39, 2.44]

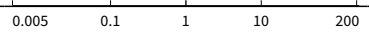
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Doubling of serum creatinine	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Stable kidney function	6	641	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.94, 1.17]
5 Ovarian failure	3	539	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.06, 2.18]
6 Menstrual irregularities	2	87	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.59]
7 Infection	7	1452	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.81, 1.58]
7.1 Major infection	6	699	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.54]
7.2 Herpes zoster virus	6	753	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.78, 2.46]
8 Malignancy	1	364	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.11, 3.86]
9 Leucopenia	6	753	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.33, 1.08]
10 Bladder toxicity	1	364	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.95]
11 Alopecia	3	622	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.19, 0.46]
12 Gastrointestinal (GI) adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Diarrhoea	4	609	Risk Ratio (M-H, Random, 95% CI)	2.42 [1.64, 3.58]
12.2 Vomiting	3	562	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.97]
12.3 Nausea	3	562	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.23, 0.98]
12.4 GI upset	3	569	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
13 Daily proteinuria	4	271	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.43, 0.26]
14 Serum creatinine	6	759	Mean Difference (IV, Random, 95% CI)	2.14 [-3.09, 7.37]

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

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
El-Shafey 2010	0/24	1/23		3.77%	0.32[0.01,7.48]
Mulic-Bacic 2008	1/20	0/25		3.77%	3.71[0.16,86.55]
Ong 2005	1/19	1/25		5.1%	1.32[0.09,19.71]
Mendonca 2017	1/17	1/23		5.13%	1.35[0.09,20.13]
Li 2012	1/20	2/20		6.95%	0.5[0.05,5.08]
Rathi 2016	5/50	2/50		14.75%	2.5[0.51,12.29]
Ginzler 2005	4/71	8/69		28.1%	0.49[0.15,1.54]
ALMS 2007	9/185	5/185		32.42%	1.8[0.61,5.27]

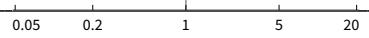


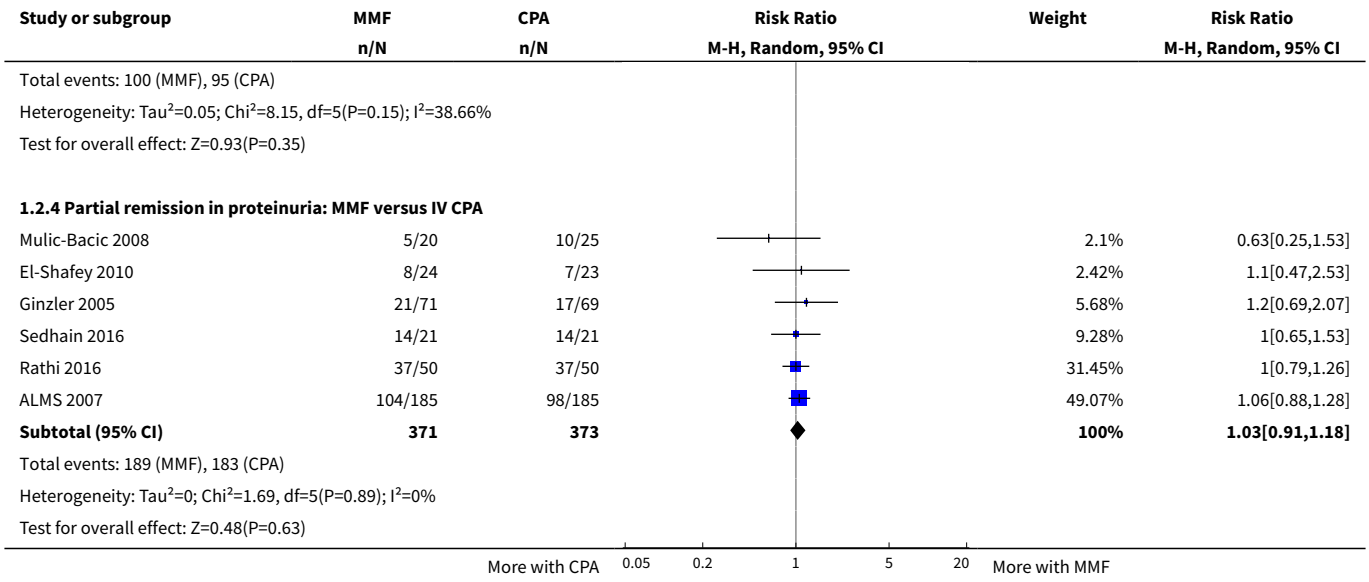
Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**406**	**420**		**100%**	**1.12[0.61,2.06]**
Total events: 22 (MMF), 20 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=5.4, df=7(P=0.61); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					



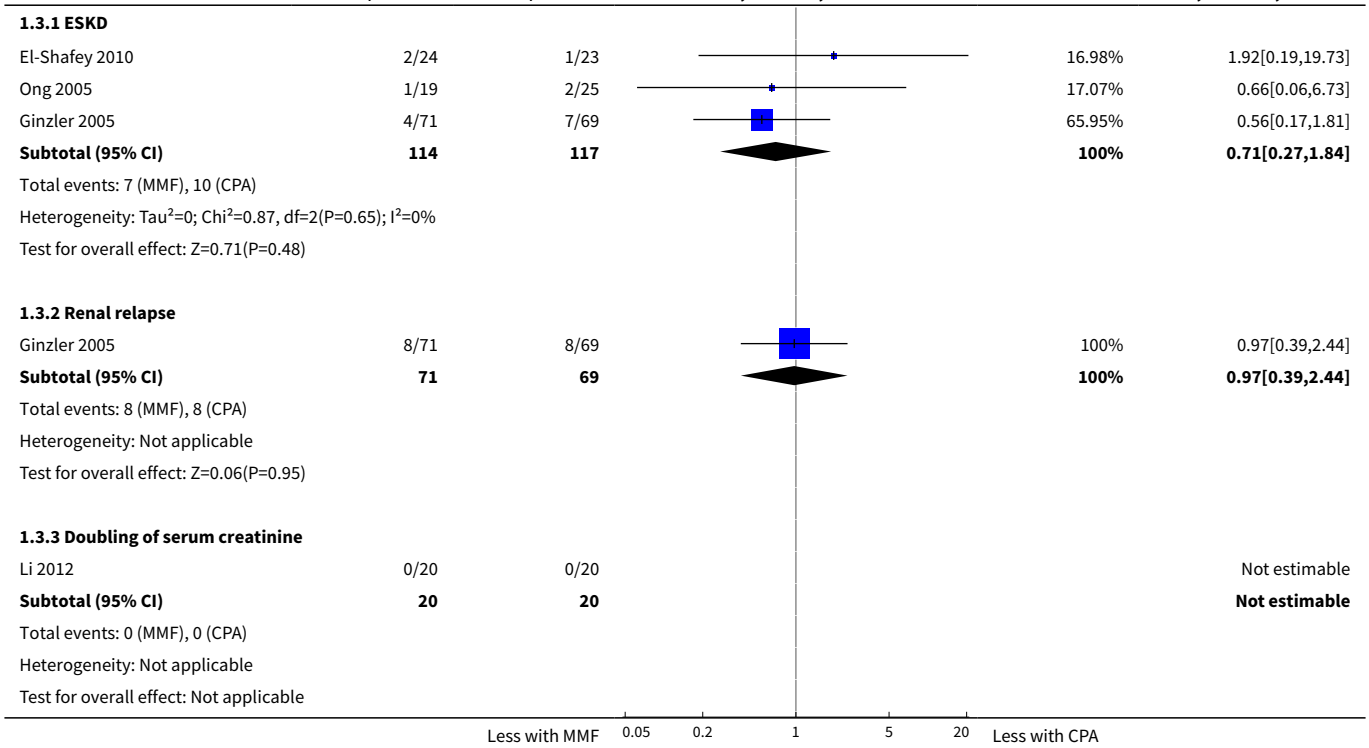
Analysis 1.2. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 2 Remission.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Complete renal remission: MMF versus IV CPA					
Ong 2005	5/19	3/25		2.22%	2.19[0.6,8.06]
Ginzler 2005	16/71	4/69		3.44%	3.89[1.37,11.05]
El-Shafey 2010	6/24	5/23		3.47%	1.15[0.41,3.25]
Li 2012	9/20	6/20		5.5%	1.5[0.66,3.43]
ALMS 2007	16/185	15/185		8.26%	1.07[0.54,2.09]
Mendonca 2017	9/17	11/23		9.81%	1.11[0.6,2.06]
Mulic-Bacic 2008	14/20	15/25		20.34%	1.17[0.76,1.79]
Sedhain 2016	14/21	14/21		20.54%	1[0.65,1.53]
Rathi 2016	27/50	25/50		26.41%	1.08[0.74,1.57]
Subtotal (95% CI)	**427**	**441**		**100%**	**1.17[0.97,1.42]**
Total events: 116 (MMF), 98 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=7.69, df=8(P=0.46); I^2=0%					
Test for overall effect: Z=1.6(P=0.11)					
1.2.2 Partial renal remission: MMF versus IV CPA					
Sedhain 2016	6/21	4/21		1.62%	1.5[0.49,4.56]
Li 2012	6/20	6/20		2.23%	1[0.39,2.58]
Mulic-Bacic 2008	5/20	10/25		2.47%	0.63[0.25,1.53]
El-Shafey 2010	8/24	7/23		2.84%	1.1[0.47,2.53]
Mendonca 2017	6/17	9/23		2.96%	0.9[0.4,2.05]
Ong 2005	6/19	10/25		2.99%	0.79[0.35,1.79]
Ginzler 2005	21/71	17/69		6.67%	1.2[0.69,2.07]
Rathi 2016	37/50	37/50		36.98%	1[0.79,1.26]
ALMS 2007	88/185	83/185		41.24%	1.06[0.85,1.32]
Subtotal (95% CI)	**427**	**441**		**100%**	**1.02[0.89,1.18]**
Total events: 183 (MMF), 183 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=2.59, df=8(P=0.96); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					
1.2.3 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 2012	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-Bacic 2008	14/20	15/25		24.45%	1.17[0.76,1.79]
ALMS 2007	44/185	50/185		29.08%	0.88[0.62,1.25]
Subtotal (95% CI)	**339**	**347**		**100%**	**1.16[0.85,1.58]**

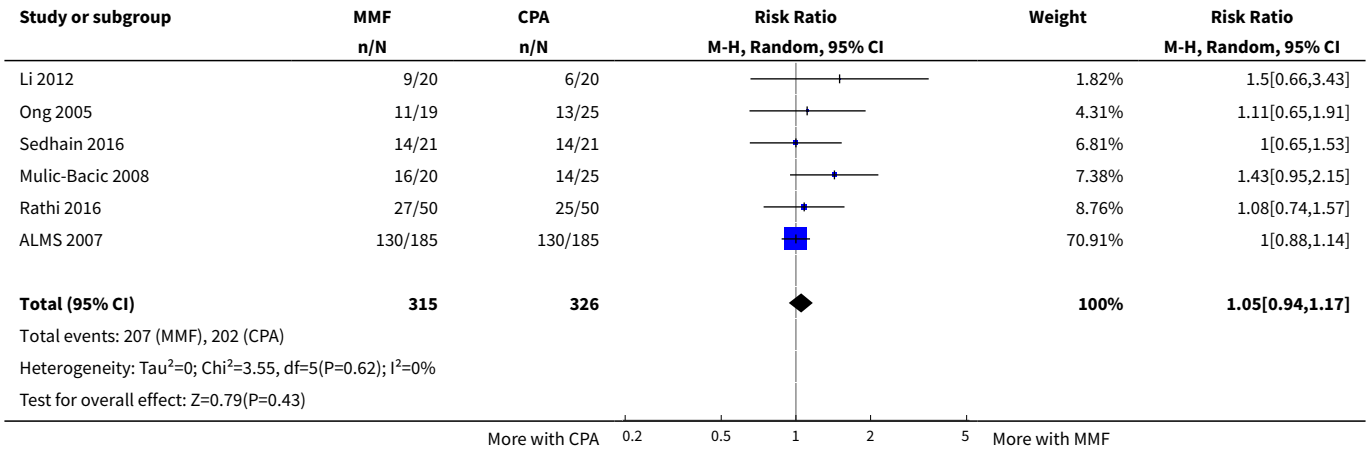




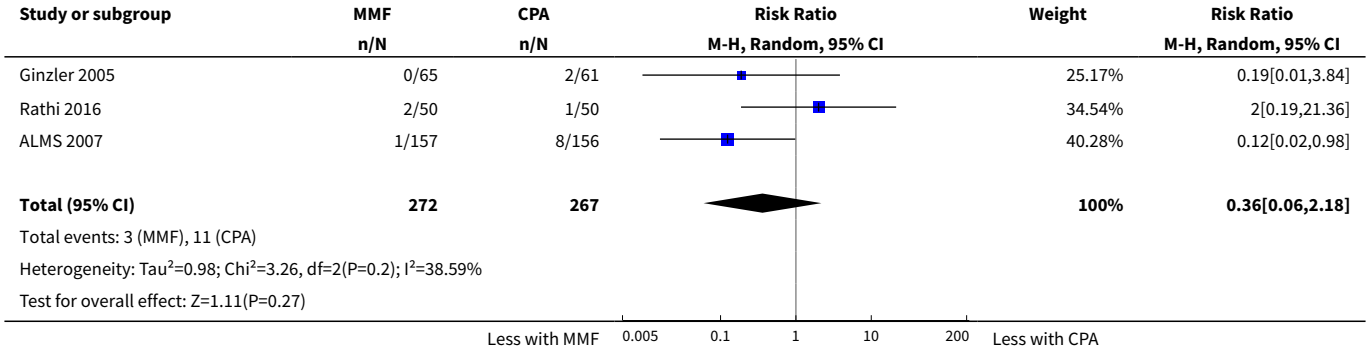
Analysis 1.3. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 3 Adverse renal outcomes.



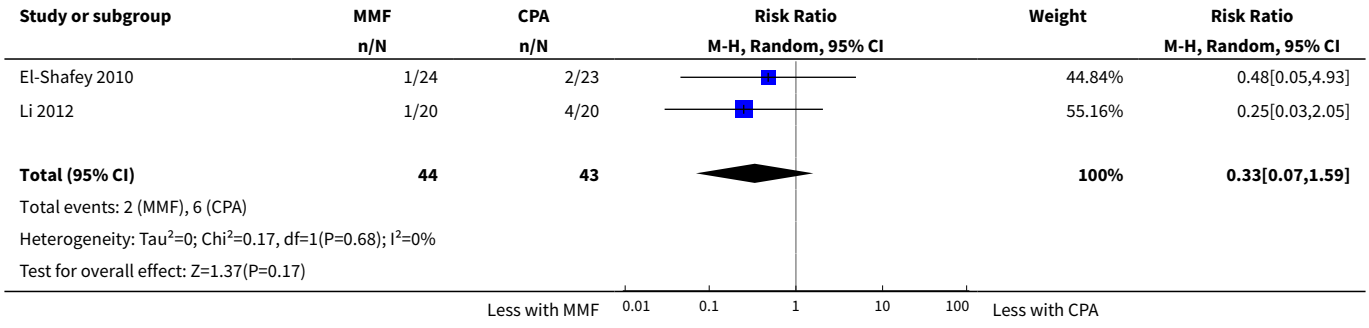
Analysis 1.4. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 4 Stable kidney function.



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

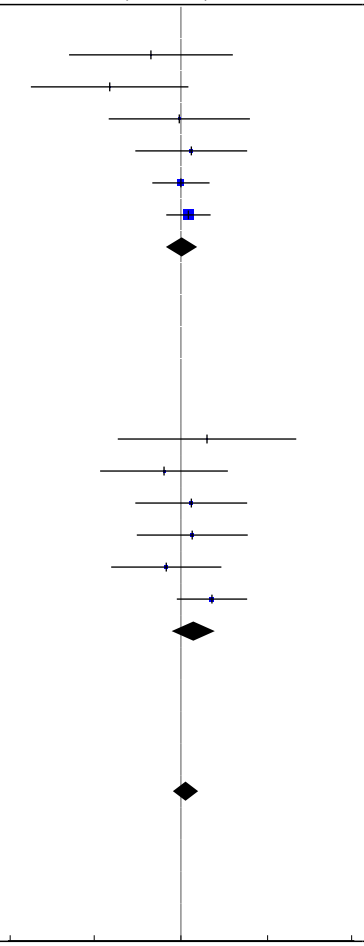


Analysis 1.6. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 6 Menstrual irregularities.



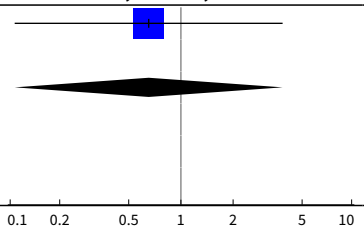
Analysis 1.7. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 7 Infection.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Major infection					
Mendonca 2017	1/17	3/23		2.39%	0.45[0.05,3.97]
Ginzler 2005	1/83	6/75		2.58%	0.15[0.02,1.22]
El-Shafey 2010	2/24	2/23		3.21%	0.96[0.15,6.25]
Ong 2005	3/19	3/25		5.12%	1.32[0.3,5.81]
Li 2012	8/20	8/20		19.6%	1[0.47,2.14]
ALMS 2007	22/185	18/185		32.6%	1.22[0.68,2.2]
Subtotal (95% CI)	**348**	**351**		**65.51%**	**1.02[0.67,1.54]**
Total events: 37 (MMF), 40 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=4.33, df=5(P=0.5); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					
1.7.2 Herpes zoster virus					
Rathi 2016	2/50	1/50		2.01%	2[0.19,21.36]
El-Shafey 2010	2/24	3/23		3.93%	0.64[0.12,3.48]
Ong 2005	3/19	3/25		5.12%	1.32[0.3,5.81]
Mendonca 2017	3/17	3/23		5.21%	1.35[0.31,5.9]
Ginzler 2005	3/83	4/75		5.27%	0.68[0.16,2.93]
ALMS 2007	14/184	6/180		12.95%	2.28[0.9,5.81]
Subtotal (95% CI)	**377**	**376**		**34.49%**	**1.39[0.78,2.46]**
Total events: 27 (MMF), 20 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=2.92, df=5(P=0.71); I^2=0%					
Test for overall effect: Z=1.12(P=0.26)					
Total (95% CI)	**725**	**727**		**100%**	**1.13[0.81,1.58]**
Total events: 64 (MMF), 60 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=7.91, df=11(P=0.72); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
Test for subgroup differences: Chi^2=0.74, df=1 (P=0.39), I^2=0%					



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

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ALMS 2007	2/184	3/180		100%	0.65[0.11,3.86]
Total (95% CI)	**184**	**180**		**100%**	**0.65[0.11,3.86]**
Total events: 2 (MMF), 3 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					

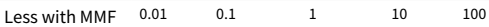


Analysis 1.9. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 9 Leucopenia.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Li 2012	1/20	1/20		4.3%	1[0.07,14.9]
El-Shafey 2010	4/24	3/23		12.2%	1.28[0.32,5.1]
Rathi 2016	7/50	5/50		16.4%	1.4[0.48,4.12]
Ginzler 2005	5/83	14/75		18.23%	0.32[0.12,0.85]
Ong 2005	7/19	13/25		23.76%	0.71[0.35,1.43]
ALMS 2007	11/184	38/180		25.11%	0.28[0.15,0.54]
Total (95% CI)	**380**	**373**		**100%**	**0.59[0.33,1.08]**
Total events: 35 (MMF), 74 (CPA)					
Heterogeneity: Tau^2=0.26; Chi^2=10.41, df=5(P=0.06); I^2=51.98%					
Test for overall effect: Z=1.7(P=0.09)					

Analysis 1.10. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 10 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
ALMS 2007	0/184	1/180		100%	0.33[0.01,7.95]
Total (95% CI)	**184**	**180**		**100%**	**0.33[0.01,7.95]**
Total events: 0 (MMF), 1 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					

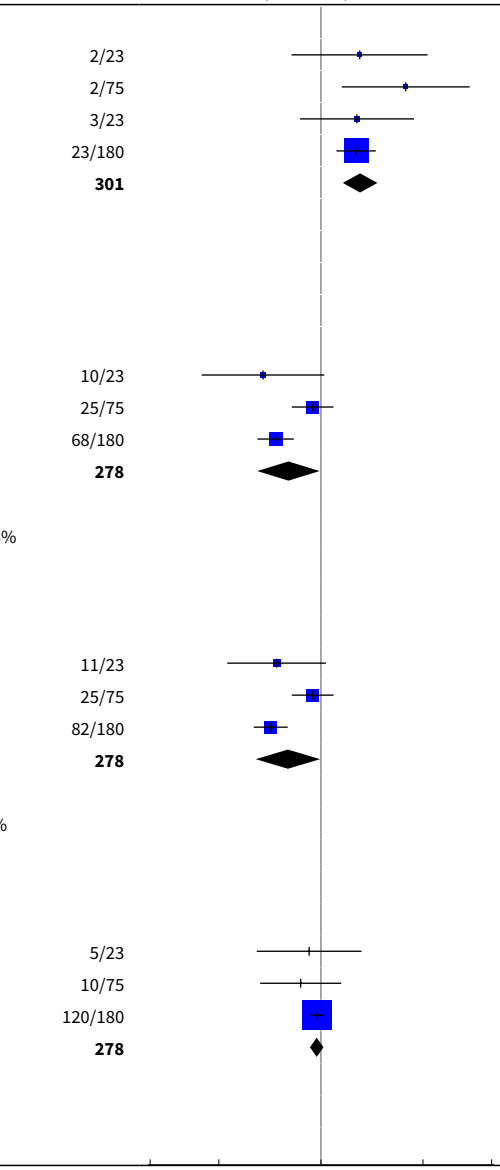


Analysis 1.11. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 11 Alopecia.

Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Rathi 2016	0/50	1/50		1.99%	0.33[0.01,7.99]
Ginzler 2005	0/83	8/75		2.49%	0.05[0,0.91]
ALMS 2007	20/184	64/180		95.52%	0.31[0.19,0.48]
Total (95% CI)	**317**	**305**		**100%**	**0.29[0.19,0.46]**
Total events: 20 (MMF), 73 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=1.5, df=2(P=0.47); I^2=0%					
Test for overall effect: Z=5.37(P<0.0001)					

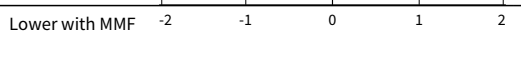
Analysis 1.12. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 12 Gastrointestinal (GI) adverse events.

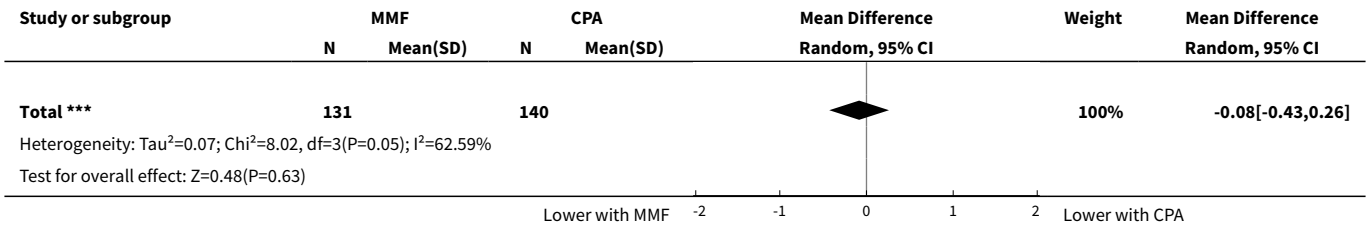
Study or subgroup	MMF n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Diarrhoea					
El-Shafey 2010	5/24	2/23		6.47%	2.4[0.52,11.14]
Ginzler 2005	15/83	2/75		7.35%	6.78[1.6,28.66]
Mendonca 2017	5/17	3/23		9.23%	2.25[0.62,8.17]
ALMS 2007	52/184	23/180		76.94%	2.21[1.42,3.45]
Subtotal (95% CI)	**308**	**301**		**100%**	**2.42[1.64,3.58]**
Total events: 77 (MMF), 30 (CPA)					
Heterogeneity: Tau²=0; Chi²=2.2, df=3(P=0.53); I²=0%					
Test for overall effect: Z=4.43(P<0.0001)					
1.12.2 Vomiting					
Mendonca 2017	2/17	10/23		16.98%	0.27[0.07,1.08]
Ginzler 2005	23/83	25/75		40.55%	0.83[0.52,1.33]
ALMS 2007	25/184	68/180		42.48%	0.36[0.24,0.54]
Subtotal (95% CI)	**284**	**278**		**100%**	**0.48[0.24,0.97]**
Total events: 50 (MMF), 103 (CPA)					
Heterogeneity: Tau²=0.26; Chi²=7.83, df=2(P=0.02); I²=74.45%					
Test for overall effect: Z=2.04(P=0.04)					
1.12.3 Nausea					
Mendonca 2017	3/17	11/23		21.92%	0.37[0.12,1.12]
Ginzler 2005	23/83	25/75		37.94%	0.83[0.52,1.33]
ALMS 2007	27/184	82/180		40.15%	0.32[0.22,0.47]
Subtotal (95% CI)	**284**	**278**		**100%**	**0.48[0.23,0.98]**
Total events: 53 (MMF), 118 (CPA)					
Heterogeneity: Tau²=0.3; Chi²=9.62, df=2(P=0.01); I²=79.21%					
Test for overall effect: Z=2.01(P=0.04)					
1.12.4 GI upset					
El-Shafey 2010	4/24	5/23		1.62%	0.77[0.23,2.5]
Ginzler 2005	7/83	10/75		2.72%	0.63[0.25,1.58]
ALMS 2007	113/184	120/180		95.65%	0.92[0.79,1.07]
Subtotal (95% CI)	**291**	**278**		**100%**	**0.91[0.78,1.06]**
Total events: 124 (MMF), 135 (CPA)					
Heterogeneity: Tau²=0; Chi²=0.76, df=2(P=0.68); I²=0%					
Test for overall effect: Z=1.24(P=0.22)					



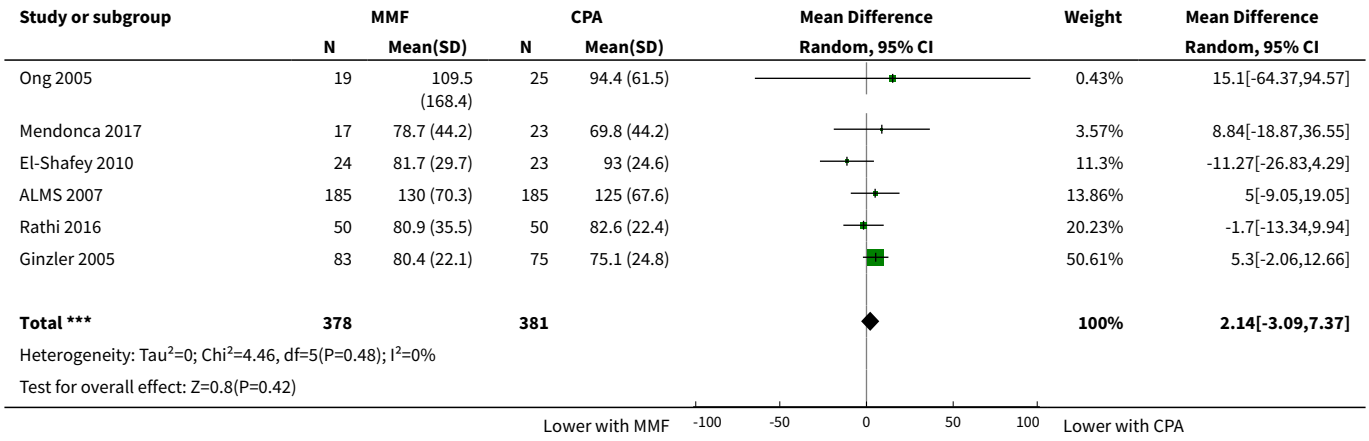
Analysis 1.13. Comparison 1 Mycophenolate mofetil (MMF) versus IV cyclophosphamide (CPA), Outcome 13 Daily proteinuria.

Study or subgroup	MMF N	MMF Mean(SD)	CPA N	CPA Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ginzler 2005	71	2 (2.8)	69	1.5 (1.3)		15.18%	0.57[-0.14,1.28]
Ong 2005	19	1.1 (0.6)	25	1.9 (1.5)		17.21%	-0.8[-1.45,-0.15]
Mendonca 2017	17	0.5 (0.3)	23	0.5 (0.6)		33.71%	-0.06[-0.34,0.22]
El-Shafey 2010	24	0.7 (0.5)	23	0.7 (0.5)		33.9%	-0.04[-0.32,0.24]





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

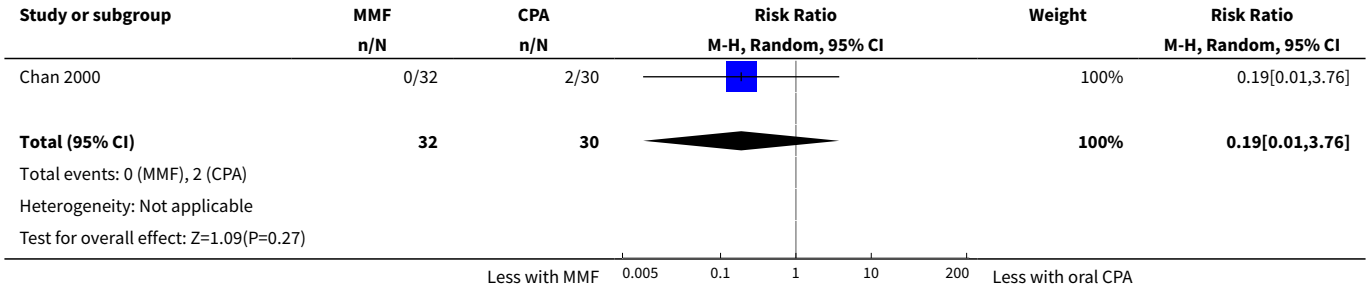


Comparison 2. Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA)

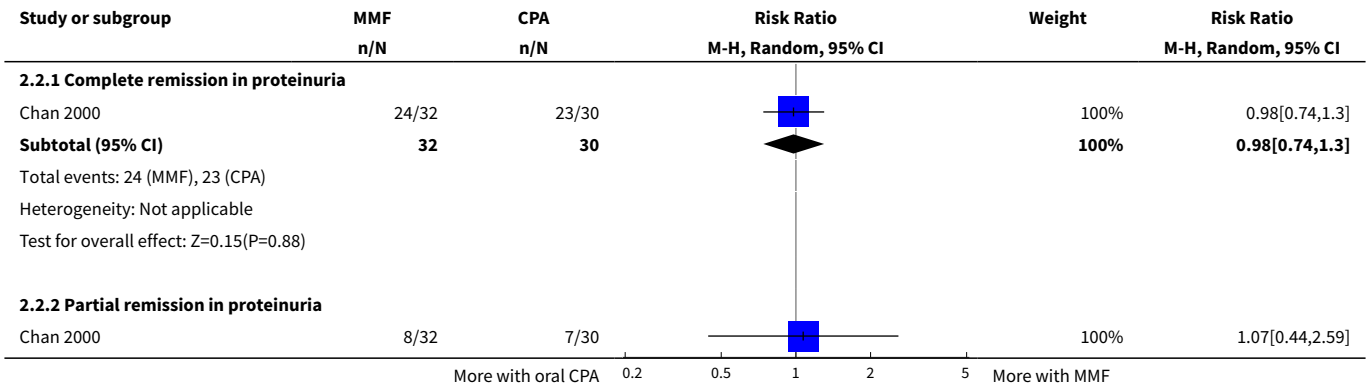
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	62	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.76]
2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete remission in proteinuria	1	62	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.30]
2.2 Partial remission in proteinuria	1	62	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.44, 2.59]
3 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD	1	62	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.76]
3.2 Renal relapse	1	62	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.55, 2.37]
3.3 Doubling of serum creatinine	1	62	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.11, 3.48]

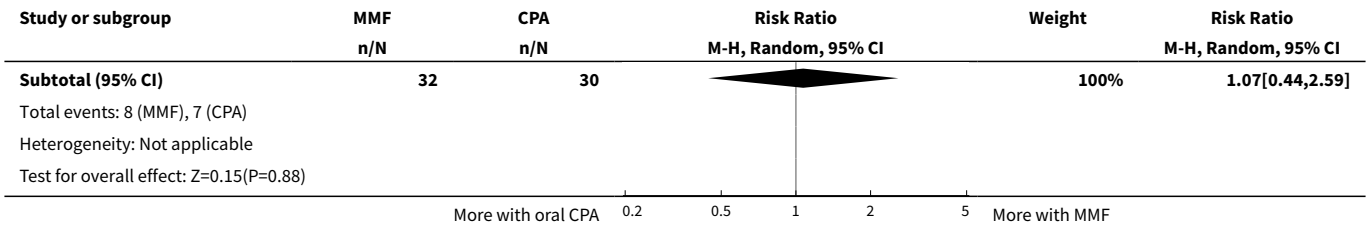
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Ovarian failure	1	53	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.73]
5 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Major infection	1	62	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.05, 0.89]
5.2 Herpes zoster virus	1	62	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.79]
6 Leucopenia	1	62	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 0.92]
7 Bone toxicity	1	62	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Alopecia	1	62	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.81]
9 Gastrointestinal (GI) adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 GI upset	1	62	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.31, 25.58]
10 Daily proteinuria	1	42	Mean Difference (IV, Random, 95% CI)	0.3 [-0.19, 0.79]

Analysis 2.1. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 1 Death.

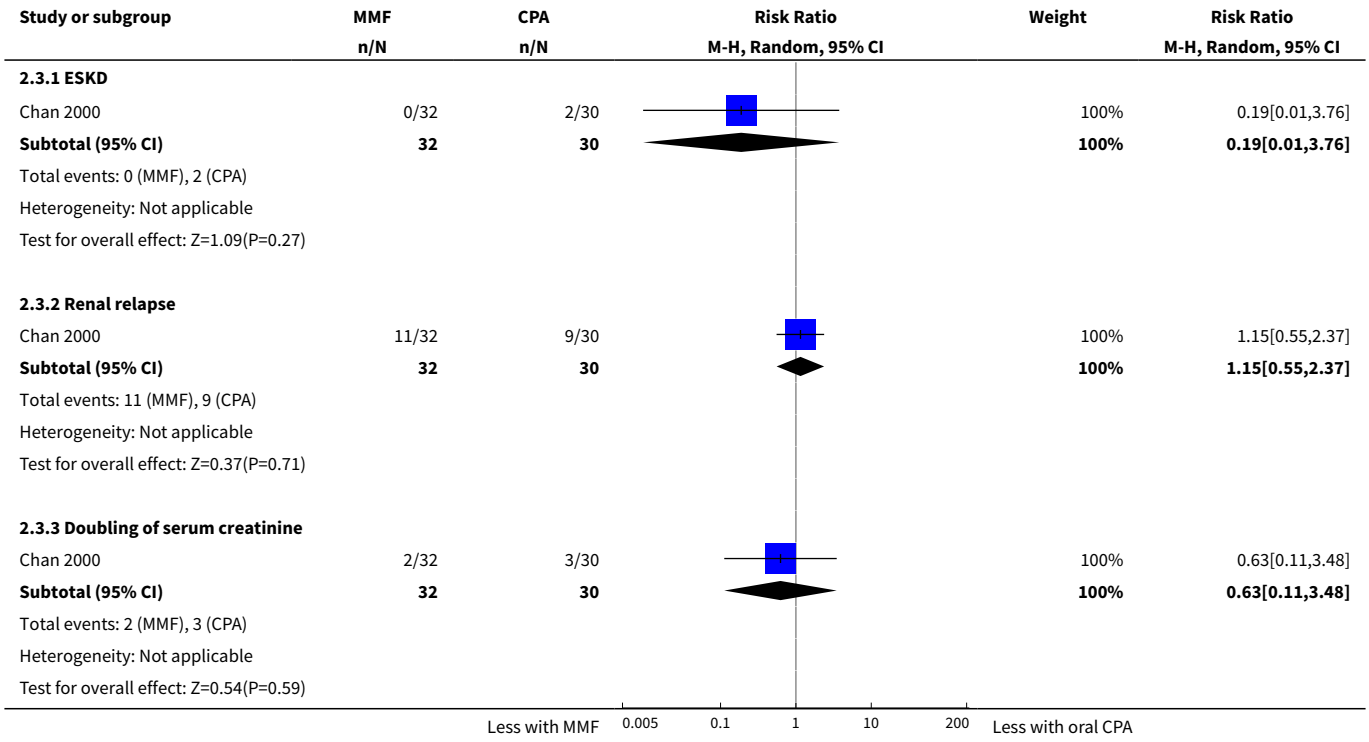


Analysis 2.2. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 2 Remission.

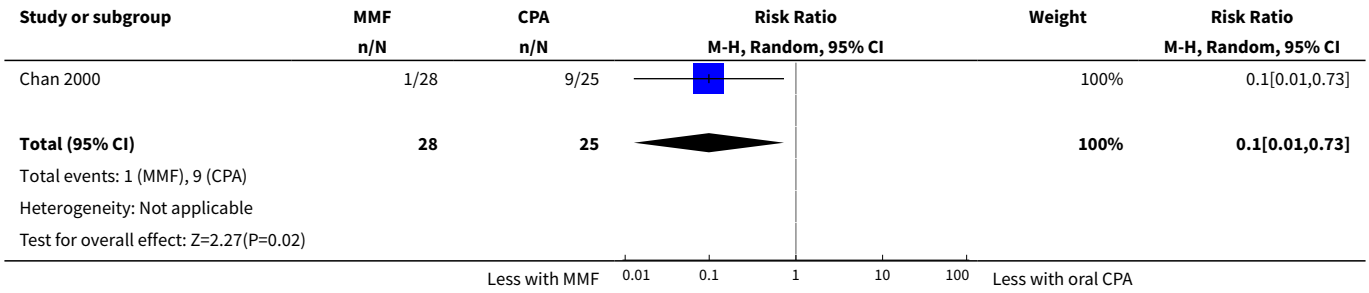




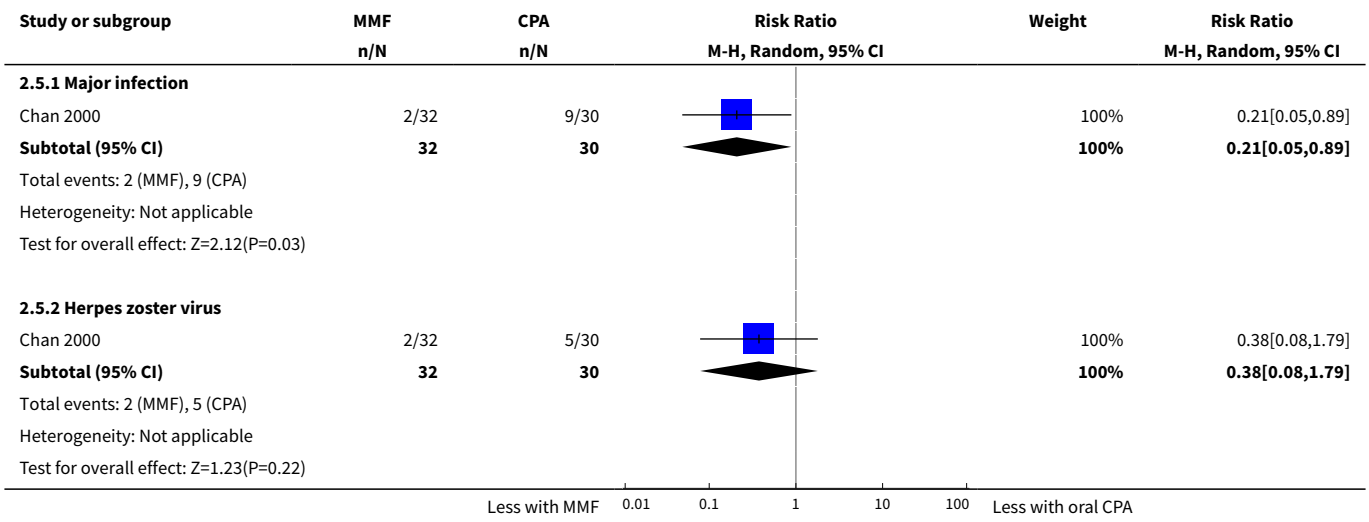
Analysis 2.3. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 3 Adverse renal outcomes.



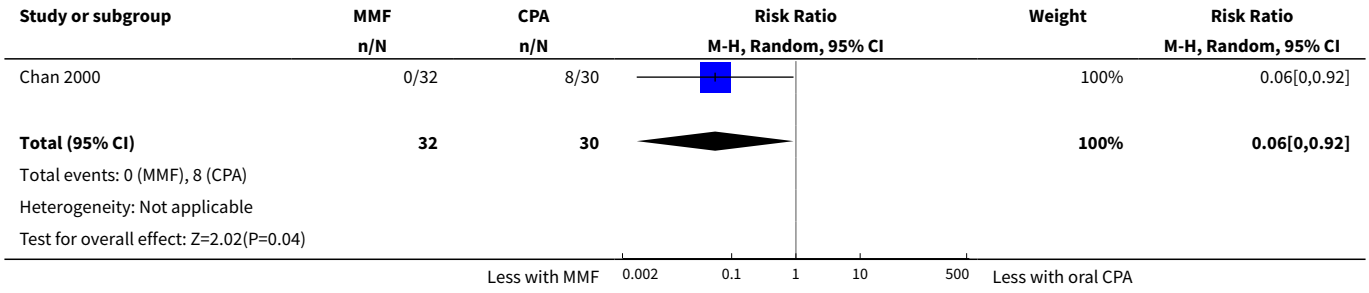
Analysis 2.4. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 4 Ovarian failure.



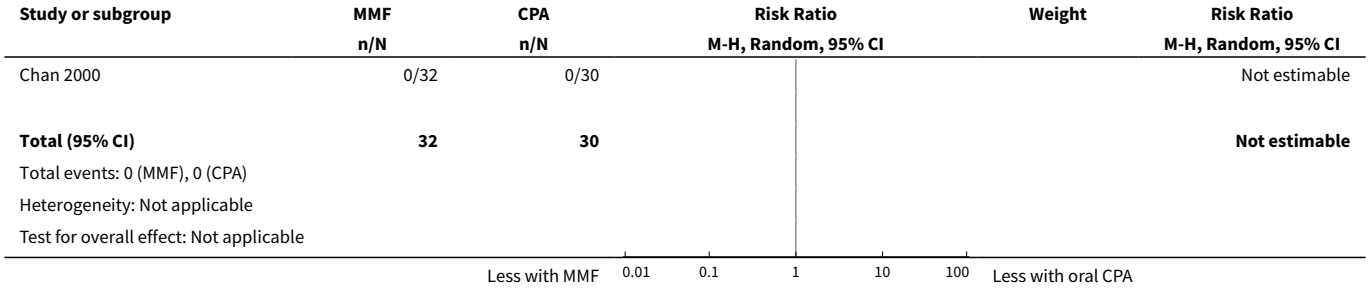
Analysis 2.5. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 5 Infection.



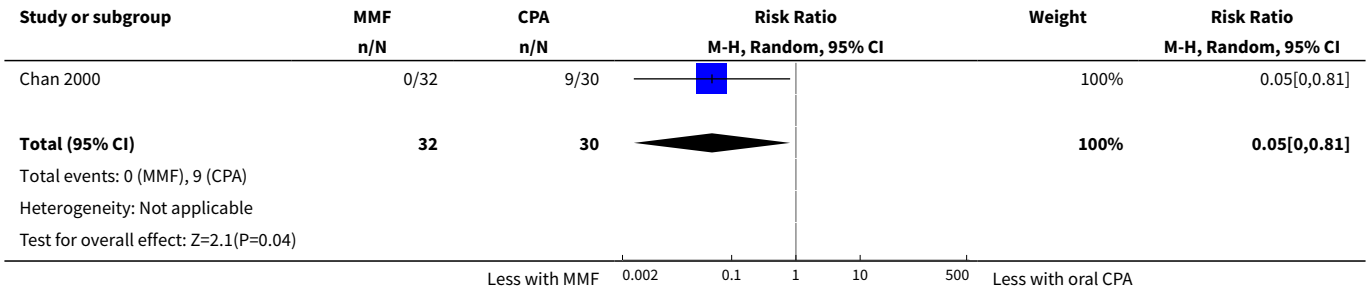
Analysis 2.6. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 6 Leucopenia.



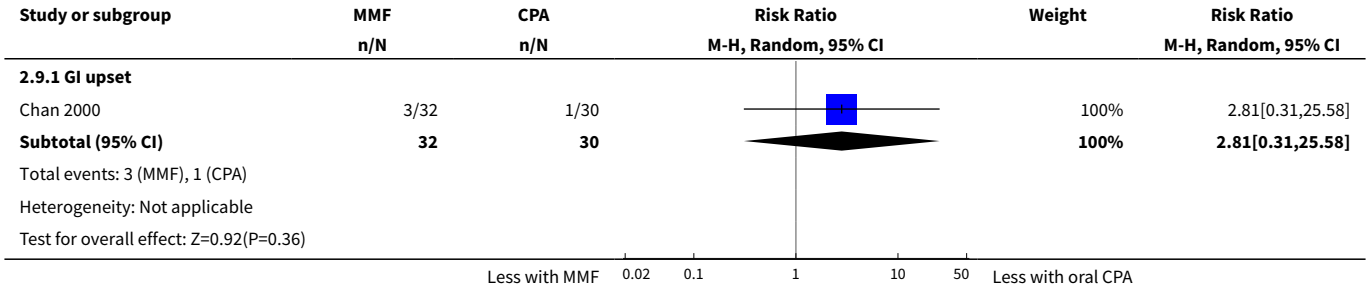
Analysis 2.7. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 7 Bone toxicity.



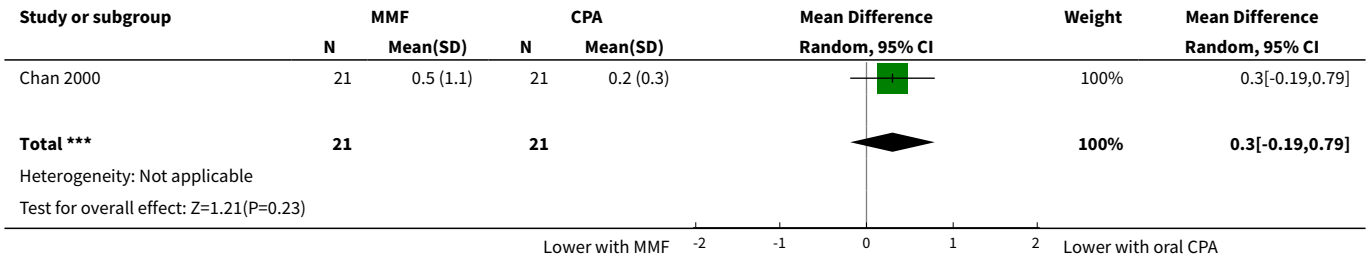
Analysis 2.8. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 8 Alopecia.



Analysis 2.9. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 9 Gastrointestinal (GI) adverse events.



Analysis 2.10. Comparison 2 Mycophenolate mofetil (MMF) versus oral cyclophosphamide (CPA), Outcome 10 Daily proteinuria.



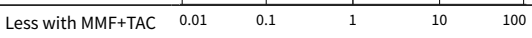
Comparison 3. Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	402	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

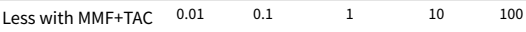
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Complete renal remission	2	402	Risk Ratio (M-H, Random, 95% CI)	2.38 [1.07, 5.30]
2.2 Partial renal remission	2	402	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.78, 1.28]
2.3 Complete remission in proteinuria	2	402	Risk Ratio (M-H, Random, 95% CI)	2.38 [1.07, 5.30]
2.4 Partial remission in proteinuria	2	402	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.26]
3 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Doubling of serum creatinine	2	402	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.10, 9.23]
4 Stable kidney function	2	402	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.40, 2.26]
5 Ovarian failure	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Menstrual irregularities	1	323	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.35]
7 Infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Major infection	2	402	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.11, 24.44]
7.2 Herpes zoster virus	2	402	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.22, 2.94]
8 Leucopenia	2	402	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.44]
9 Bone toxicity	1	362	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 73.16]
10 Alopecia	2	402	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.36, 1.72]
11 Gastrointestinal (GI) adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Diarrhoea	1	362	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.92, 5.94]
11.2 GI upset	2	402	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.10, 0.41]
12 Daily proteinuria	1	40	Mean Difference (IV, Random, 95% CI)	-1.69 [-2.81, -0.57]

Analysis 3.1. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 1 Death.

Study or subgroup	MMF+TAC n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bao 2008	0/20	0/20			Not estimable
Liu 2015	0/181	0/181			Not estimable

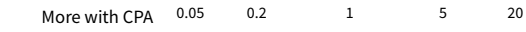


Study or subgroup	MMF+TAC n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**201**	**201**			**Not estimable**
Total events: 0 (MMF+TAC), 0 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



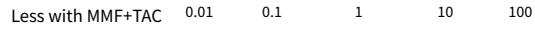
Analysis 3.2. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 2 Remission.

Study or subgroup	MMF+TAC n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Complete renal remission					
Bao 2008	13/20	3/20		31.46%	4.33[1.45,12.91]
Liu 2015	83/181	46/181		68.54%	1.8[1.34,2.42]
Subtotal (95% CI)	**201**	**201**		**100%**	**2.38[1.07,5.3]**
Total events: 96 (MMF+TAC), 49 (CPA)					
Heterogeneity: Tau^2=0.22; Chi^2=2.33, df=1(P=0.13); I^2=57.07%					
Test for overall effect: Z=2.12(P=0.03)					
3.2.2 Partial renal remission					
Bao 2008	8/20	8/20		10.91%	1[0.47,2.14]
Liu 2015	68/181	68/181		89.09%	1[0.77,1.3]
Subtotal (95% CI)	**201**	**201**		**100%**	**1[0.78,1.28]**
Total events: 76 (MMF+TAC), 76 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Not applicable					
3.2.3 Complete remission in proteinuria					
Bao 2008	13/20	3/20		31.46%	4.33[1.45,12.91]
Liu 2015	83/181	46/181		68.54%	1.8[1.34,2.42]
Subtotal (95% CI)	**201**	**201**		**100%**	**2.38[1.07,5.3]**
Total events: 96 (MMF+TAC), 49 (CPA)					
Heterogeneity: Tau^2=0.22; Chi^2=2.33, df=1(P=0.13); I^2=57.07%					
Test for overall effect: Z=2.12(P=0.03)					
3.2.4 Partial remission in proteinuria					
Bao 2008	6/20	8/20		8.74%	0.75[0.32,1.77]
Liu 2015	68/181	68/181		91.26%	1[0.77,1.3]
Subtotal (95% CI)	**201**	**201**		**100%**	**0.98[0.76,1.26]**
Total events: 74 (MMF+TAC), 76 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.39, df=1(P=0.53); I^2=0%					
Test for overall effect: Z=0.19(P=0.85)					



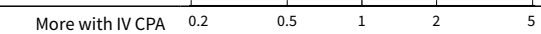
Analysis 3.3. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 3 Adverse renal outcomes.

Study or subgroup	MMF+TAC n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Doubling of serum creatinine					
Liu 2015	1/181	0/181		49.19%	3[0.12,73.16]
Bao 2008	0/20	1/20		50.81%	0.33[0.01,7.72]
Subtotal (95% CI)	**201**	**201**		**100%**	**0.98[0.1,9.23]**
Total events: 1 (MMF+TAC), 1 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=0.02(P=0.99)					



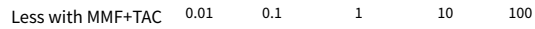
Analysis 3.4. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 4 Stable kidney function.

Study or subgroup	MMF+TAC n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bao 2008	19/20	11/20		34.31%	1.73[1.15,2.6]
Liu 2015	83/181	46/181		65.69%	1.8[1.34,2.42]
Total (95% CI)	**201**	**201**		**100%**	**1.78[1.4,2.26]**
Total events: 102 (MMF+TAC), 57 (CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=4.71(P<0.0001)					



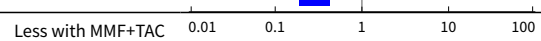
Analysis 3.5. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 5 Ovarian failure.

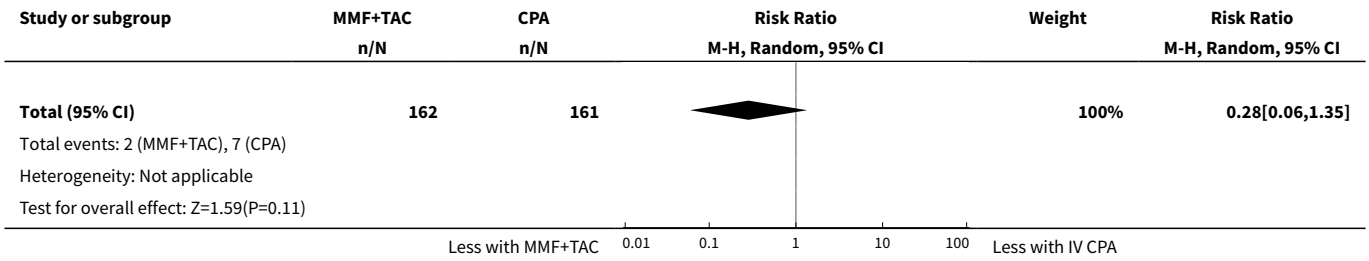
Study or subgroup	MMF+TAC n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bao 2008	0/16	0/18			Not estimable
Total (95% CI)	**16**	**18**			**Not estimable**
Total events: 0 (MMF+TAC), 0 (CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



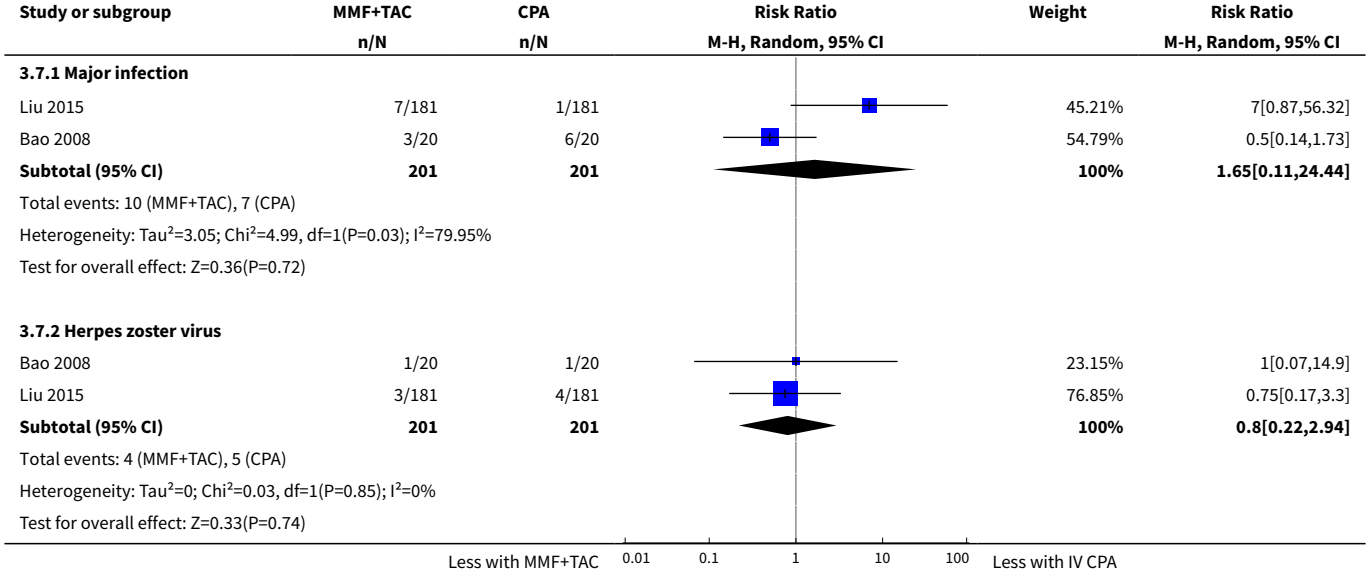
Analysis 3.6. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 6 Menstrual irregularities.

Study or subgroup	MMF+TAC n/N	CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Liu 2015	2/162	7/161		100%	0.28[0.06,1.35]

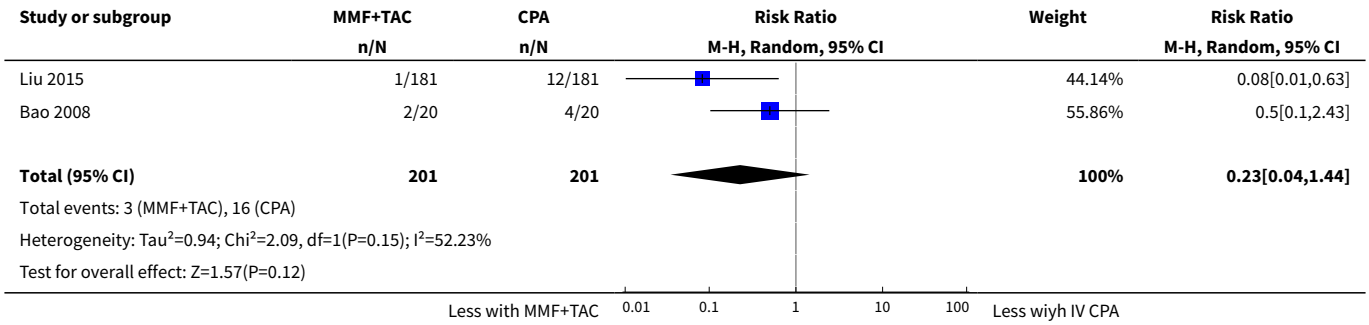




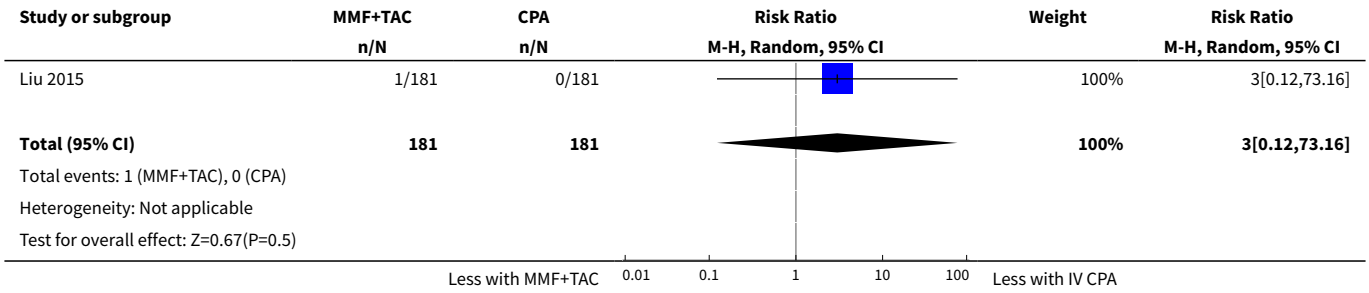
Analysis 3.7. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 7 Infection.



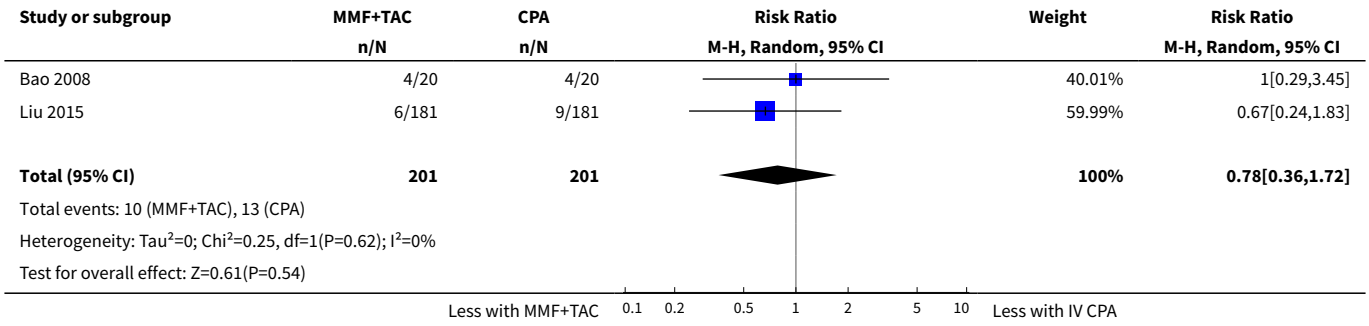
Analysis 3.8. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 8 Leucopenia.



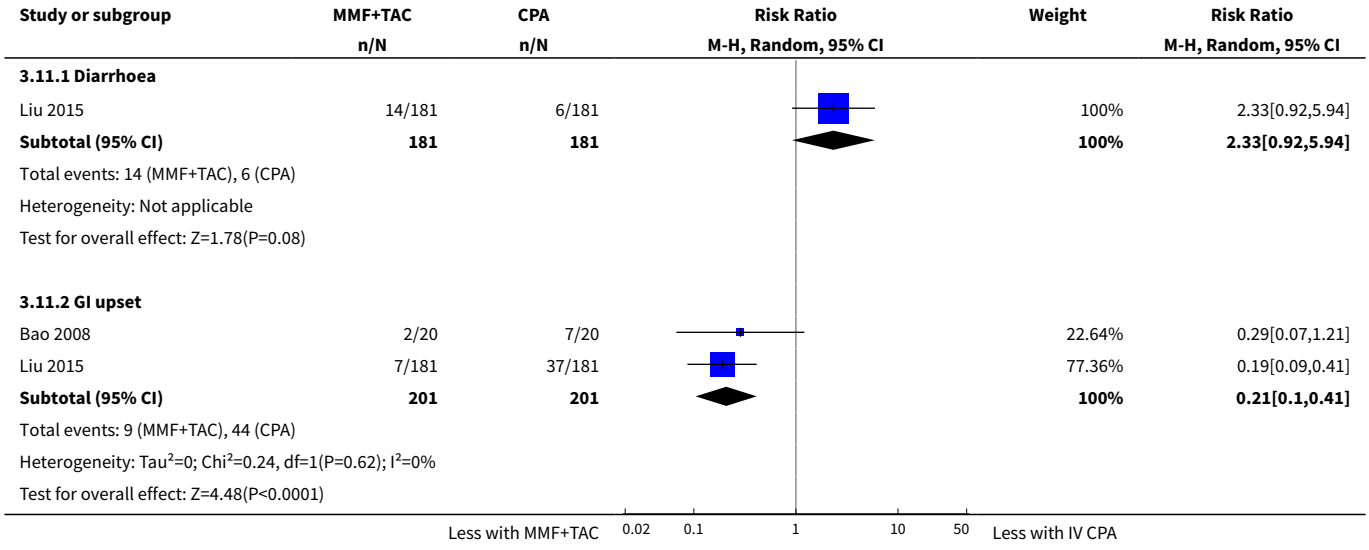
Analysis 3.9. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 9 Bone toxicity.



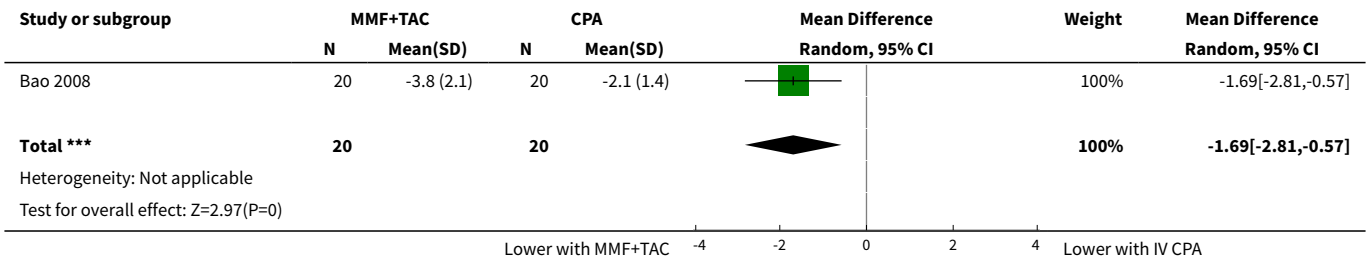
Analysis 3.10. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 10 Alopecia.



Analysis 3.11. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 11 Gastrointestinal (GI) adverse events.



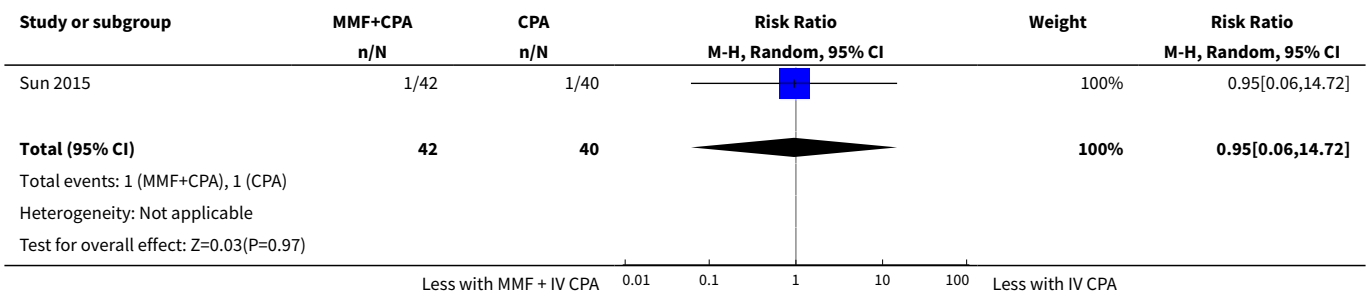
Analysis 3.12. Comparison 3 Mycophenolate mofetil (MMF) + tacrolimus (TAC) versus IV cyclophosphamide (CPA), Outcome 12 Daily proteinuria.



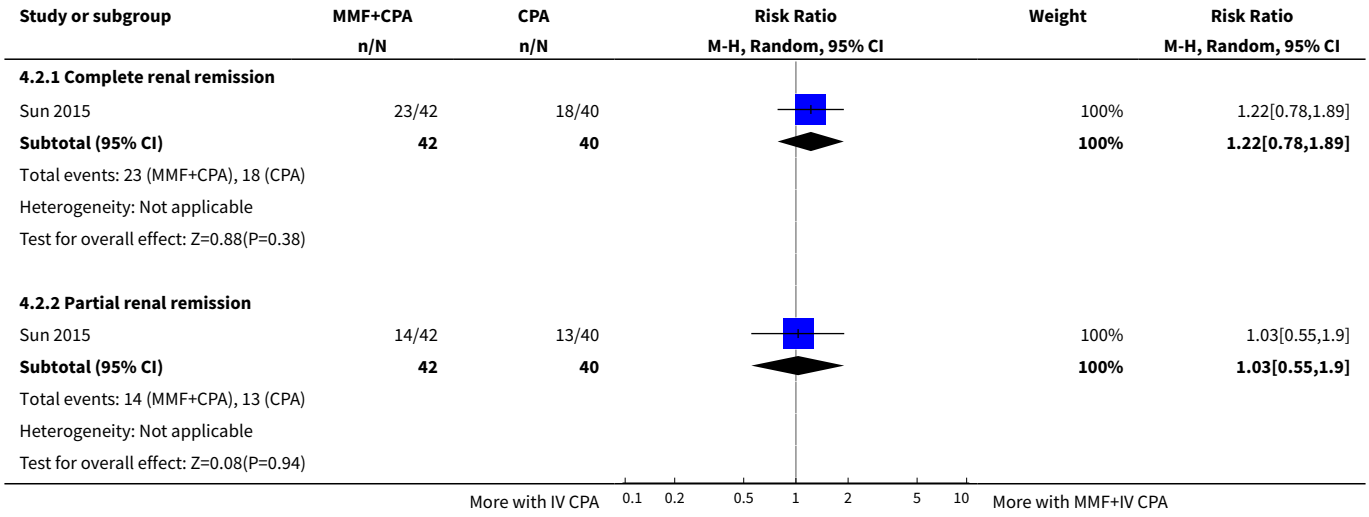
Comparison 4. Mycophenolate mofetil (MMF) + IV cyclophosphamide (CPA) versus IV CPA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	82	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.06, 14.72]
2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete renal remission	1	82	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.78, 1.89]
2.2 Partial renal remission	1	82	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.55, 1.90]
3 Menstrual irregularities	1	75	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.16, 1.48]
4 Infection	1	82	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.14, 0.93]
4.1 Major infection	1	82	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.14, 0.93]
5 Leucopenia	1	82	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.11, 3.60]
6 Daily proteinuria	1	77	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.12, 0.04]

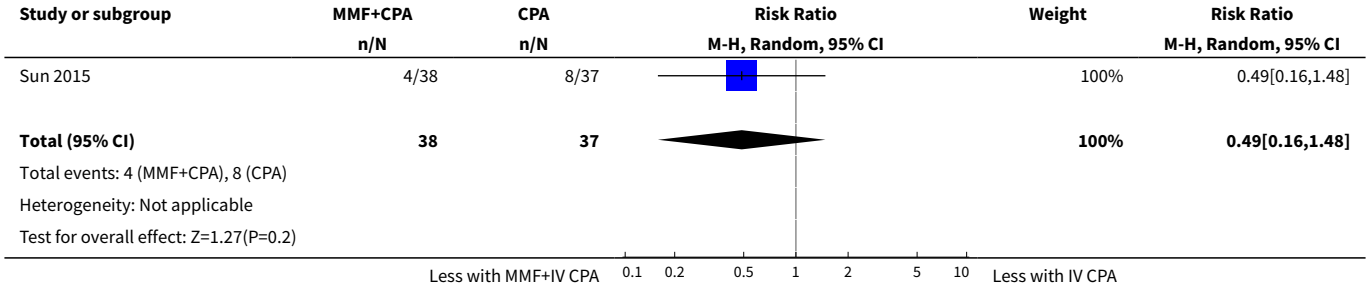
Analysis 4.1. Comparison 4 Mycophenolate mofetil (MMF) + IV cyclophosphamide (CPA) versus IV CPA, Outcome 1 Death.



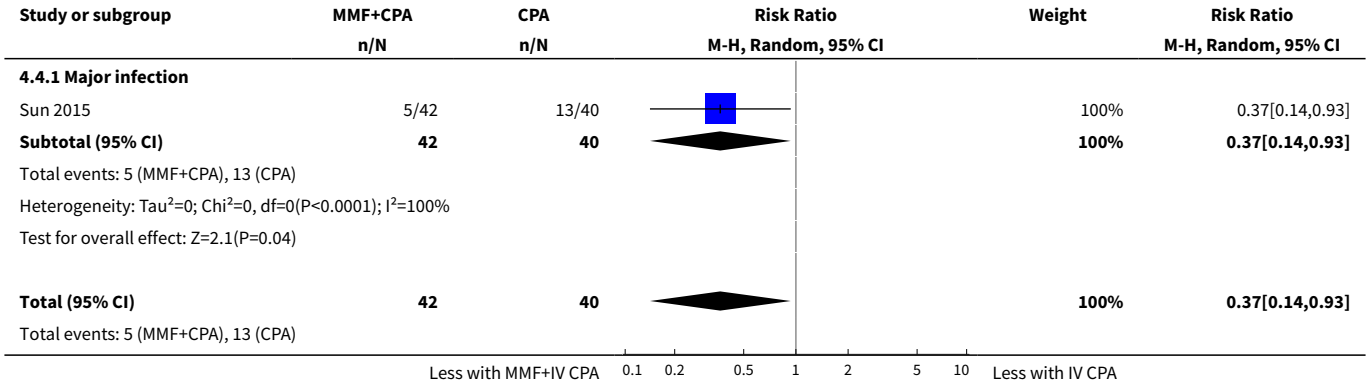
Analysis 4.2. Comparison 4 Mycophenolate mofetil (MMF) + IV cyclophosphamide (CPA) versus IV CPA, Outcome 2 Remission.

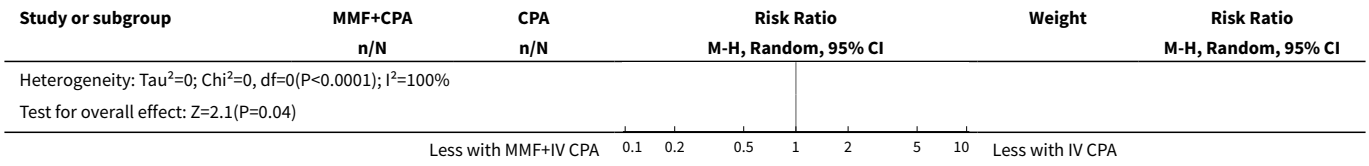


Analysis 4.3. Comparison 4 Mycophenolate mofetil (MMF) + IV cyclophosphamide (CPA) versus IV CPA, Outcome 3 Menstrual irregularities.

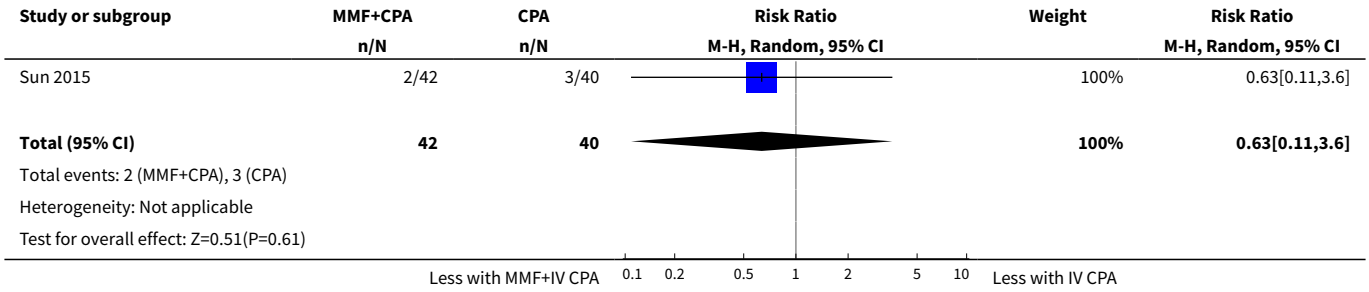


Analysis 4.4. Comparison 4 Mycophenolate mofetil (MMF) + IV cyclophosphamide (CPA) versus IV CPA, Outcome 4 Infection.

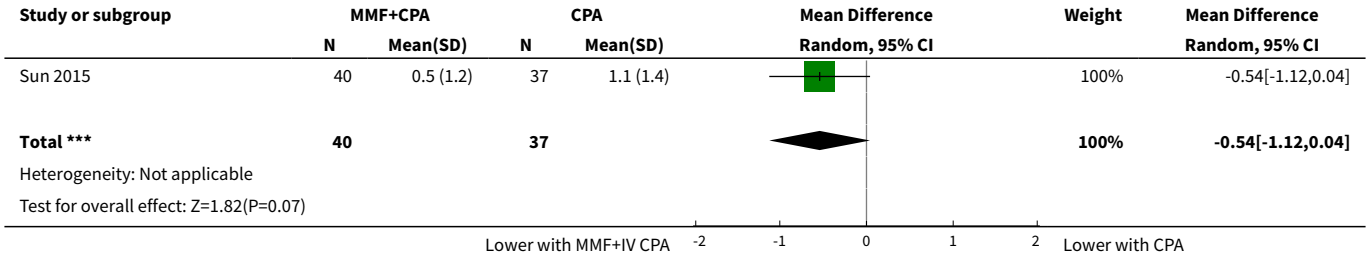




Analysis 4.5. Comparison 4 Mycophenolate mofetil (MMF) + IV cyclophosphamide (CPA) versus IV CPA, Outcome 5 Leucopenia.



Analysis 4.6. Comparison 4 Mycophenolate mofetil (MMF) + IV cyclophosphamide (CPA) versus IV CPA, Outcome 6 Daily proteinuria.



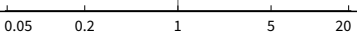
Comparison 5. Mycophenolate mofetil (MMF) versus tacrolimus (TAC)

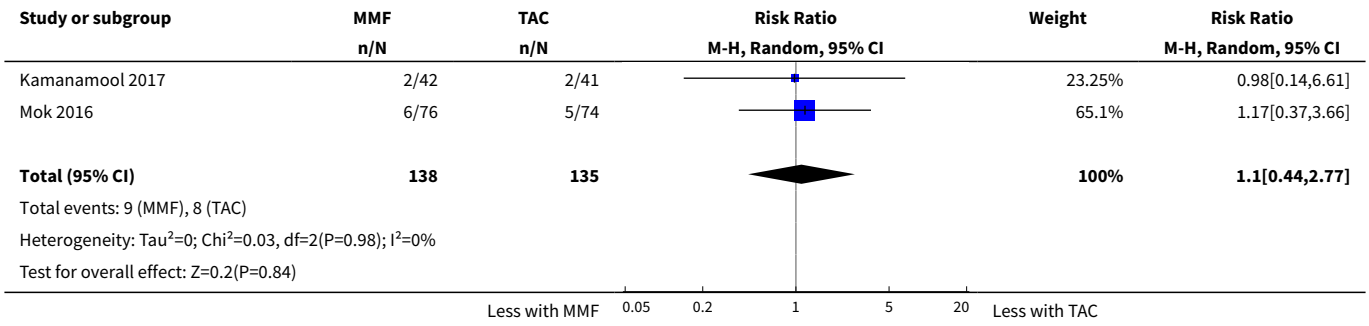
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3	273	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.44, 2.77]
2 Remission	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete renal remission	3	273	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.83, 1.26]
2.2 Partial renal remission	2	190	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.51, 1.36]
2.3 Complete remission in proteinuria	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.50, 1.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Partial remission in proteinuria	2	190	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.03]
3 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD	1	150	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.51, 2.91]
3.2 Renal relapse	1	150	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.93]
3.3 Renal relapse (nephritic flare)	1	152	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.36, 1.28]
3.4 Renal relapse (proteinuric flare)	1	150	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.12]
3.5 Deterioration in kidney function	1	150	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.27, 1.09]
4 Stable kidney function	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.50, 1.98]
5 Menstrual irregularities	1	40	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.52]
6 Infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Major infection	2	190	Risk Ratio (M-H, Random, 95% CI)	2.14 [0.93, 4.92]
6.2 Herpes zoster virus	1	150	Risk Ratio (M-H, Random, 95% CI)	6.82 [1.60, 28.96]
7 Leucopenia	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.90]
8 Alopecia	1	150	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.31]
9 Daily proteinuria (at 24 weeks)	1	150	Mean Difference (IV, Random, 95% CI)	0.18 [-0.25, 0.61]
10 Disease activity	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Renal SLEDAI	2	233	Mean Difference (IV, Random, 95% CI)	-0.21 [-2.05, 1.63]
10.2 Extrarenal SLEDAI	2	233	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.74, 0.22]
11 Serum creatinine	1	83	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.16, 0.14]
12 Creatinine clearance	1	40	Mean Difference (IV, Random, 95% CI)	-1.93 [-7.77, 3.91]

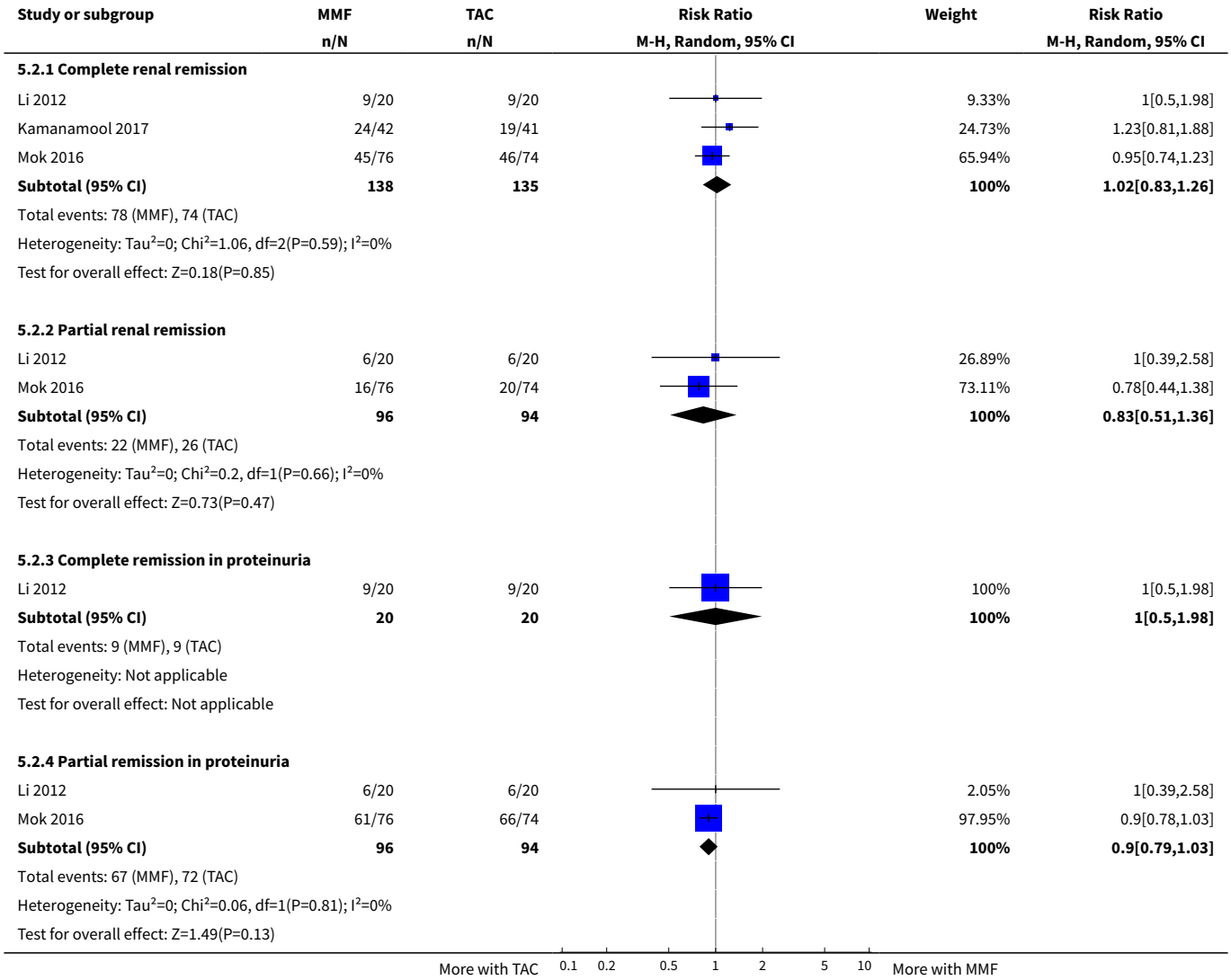
Analysis 5.1. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 1 Death.

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 2012	1/20	1/20		11.65%	1[0.07,14.9]

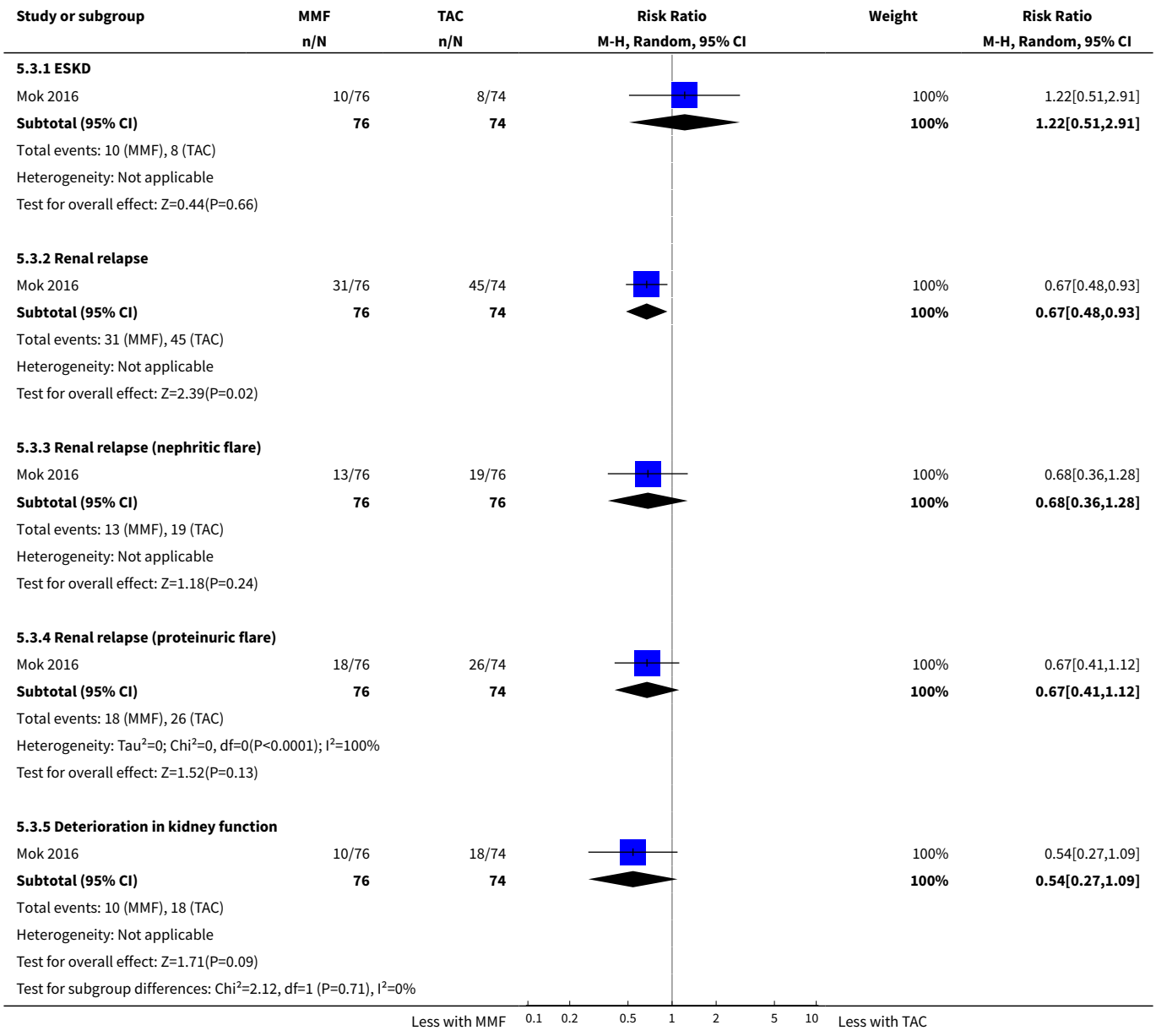




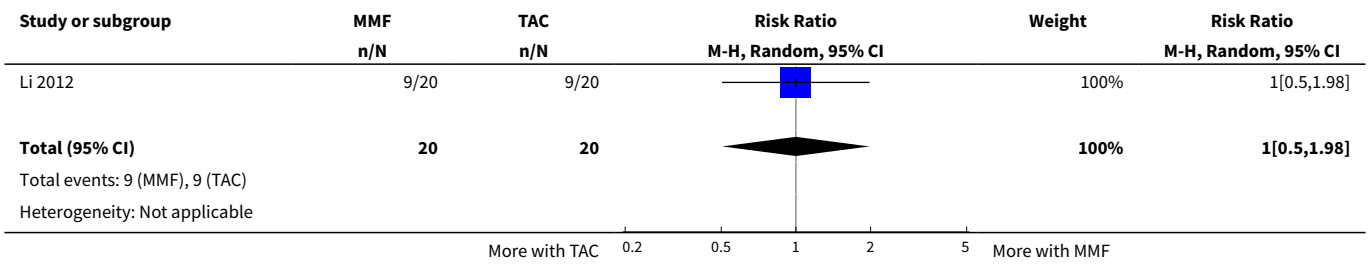
Analysis 5.2. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 2 Remission.

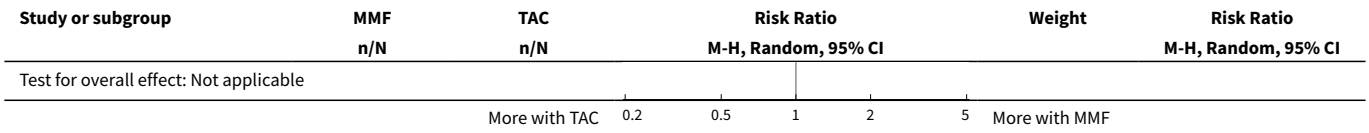


Analysis 5.3. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 3 Adverse renal outcomes.

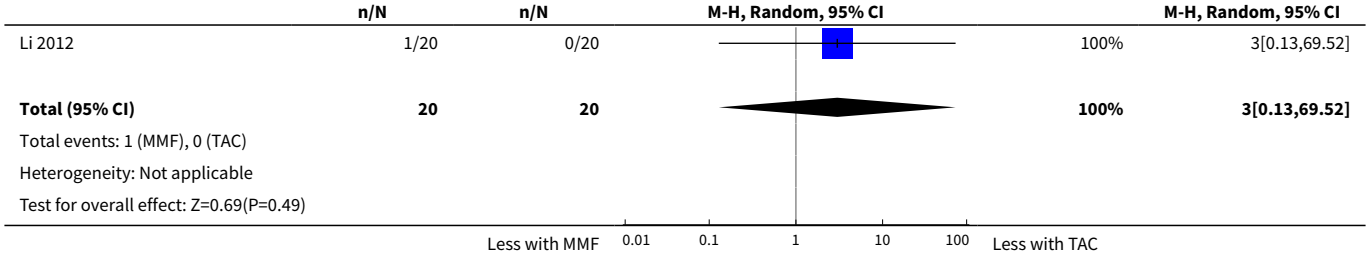


Analysis 5.4. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 4 Stable kidney function.

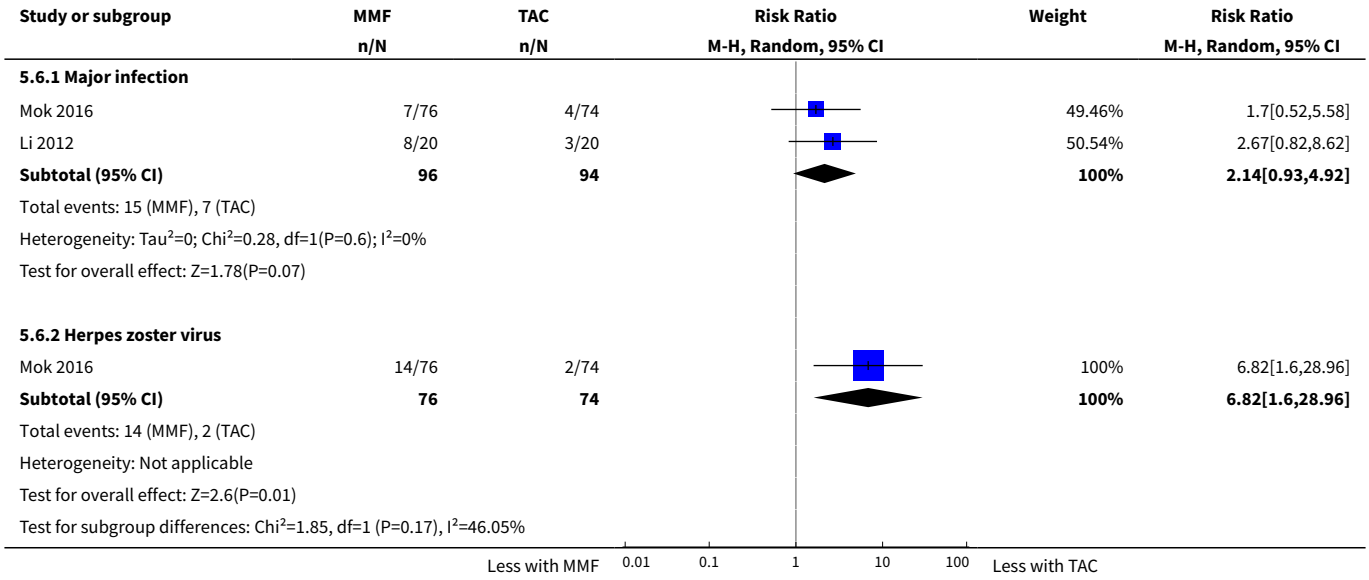




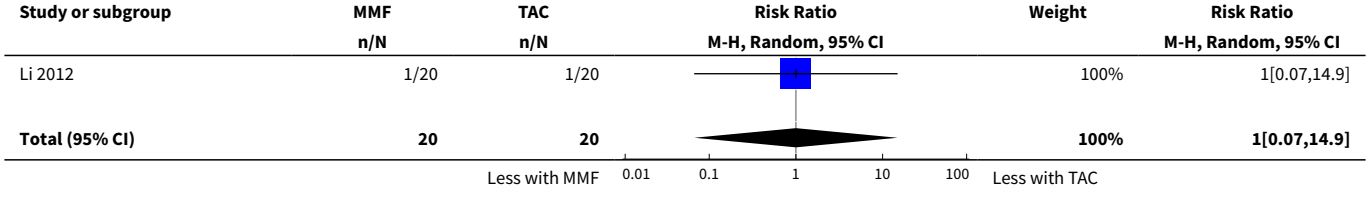
Analysis 5.5. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 5 Menstrual irregularities.

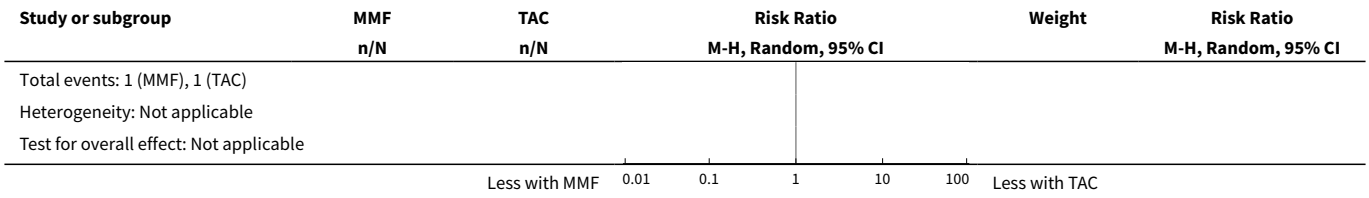


Analysis 5.6. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 6 Infection.

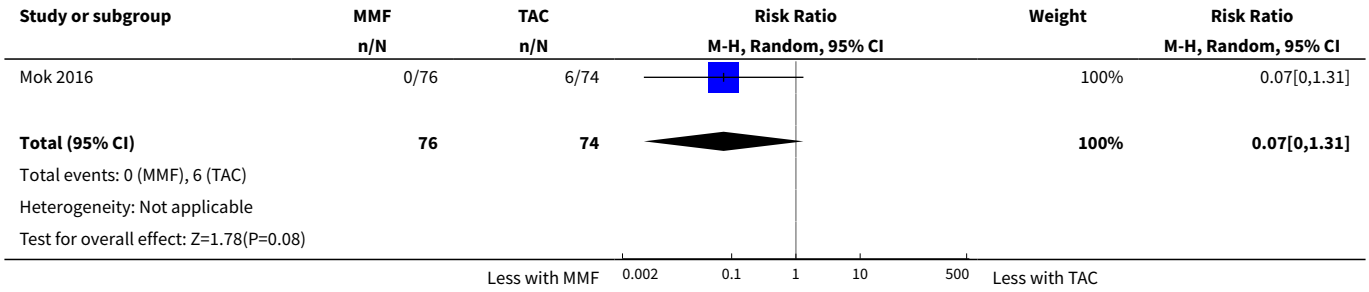


Analysis 5.7. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 7 Leucopenia.

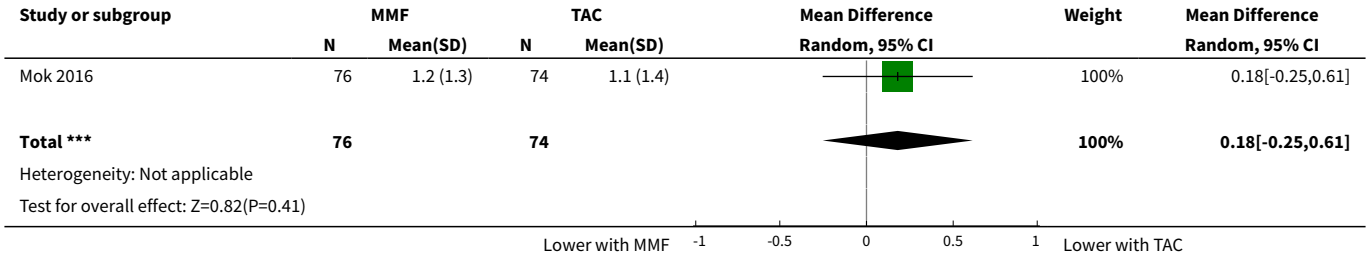




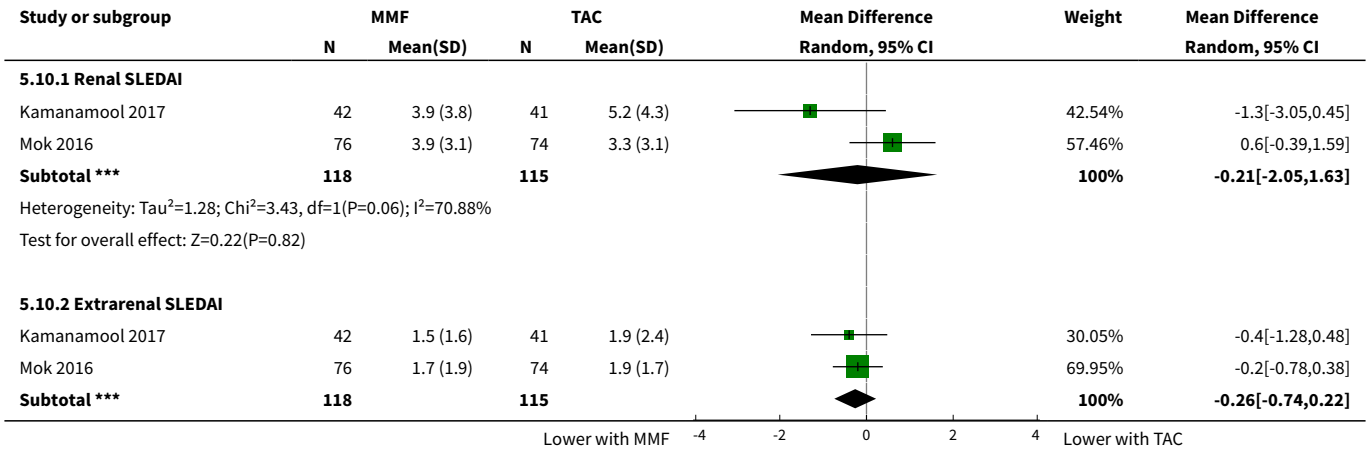
Analysis 5.8. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 8 Alopecia.

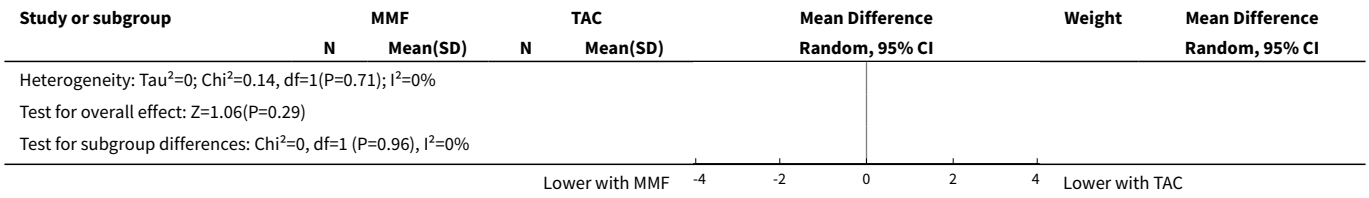


Analysis 5.9. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 9 Daily proteinuria (at 24 weeks).

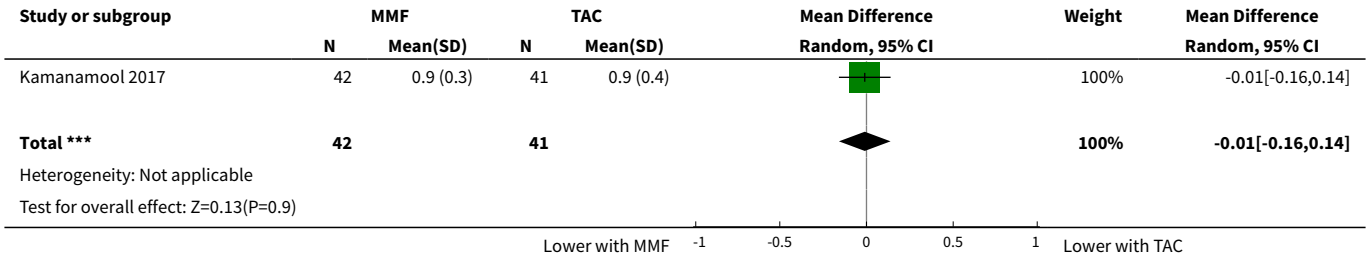


Analysis 5.10. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 10 Disease activity.

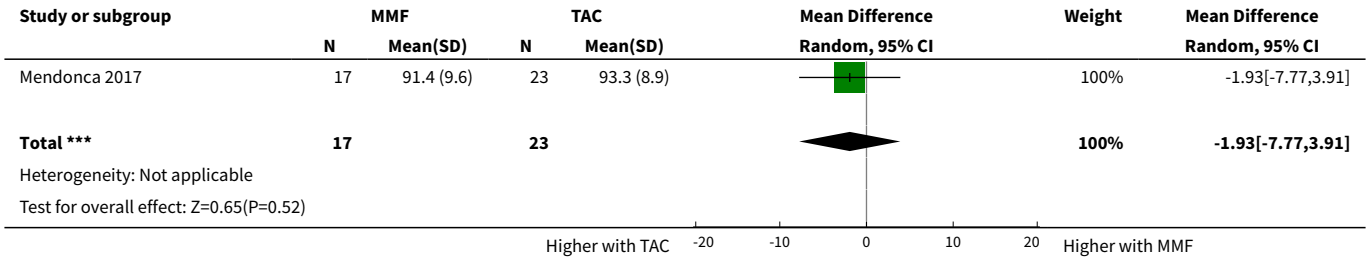




Analysis 5.11. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 11 Serum creatinine.



Analysis 5.12. Comparison 5 Mycophenolate mofetil (MMF) versus tacrolimus (TAC), Outcome 12 Creatinine clearance.



Comparison 6. Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA)

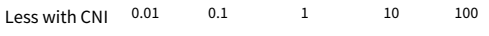
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Death	3	153	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.06, 2.69]
1.2 Death: extended follow-up	1	38	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Remission	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete renal remission	4	178	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.94, 1.93]
2.2 Partial renal remission	4	178	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.61, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Complete remission in proteinuria	3	105	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.08, 2.70]
3 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD: extended follow-up	1	38	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.85]
3.2 Doubling of serum creatinine	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.72]
3.3 Doubling of serum creatinine: extended follow-up	1	38	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.16, 6.38]
4 Stable kidney function	4	186	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.61, 2.00]
5 Ovarian failure	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Ovarian failure	2	113	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.18]
5.2 Premature ovarian failure: extended follow-up	1	27	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.02]
6 Menstrual irregularities	2	54	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.04, 4.05]
7 Infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Major infection	3	138	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.33, 1.63]
7.2 Herpes zoster virus	2	113	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.38, 5.20]
8 Malignancy: extended follow-up	1	38	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.26, 97.70]
9 Leucopenia	3	153	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.13, 1.49]
10 Alopecia	2	113	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.02, 1.76]
11 Gastrointestinal (GI) adverse events	1	73	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.12, 1.01]
12 Daily proteinuria	2	156	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.67, -0.07]
12.1 At 9 months	1	40	Mean Difference (IV, Random, 95% CI)	-0.83 [-1.37, -0.29]
12.2 At 12 months	1	38	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.43, -0.11]
12.3 At 18 months	1	40	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.26, 0.26]
12.4 Extended follow-up	1	38	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.49, 0.29]
13 Creatinine clearance	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 At 6 months	1	150	Mean Difference (IV, Random, 95% CI)	11.70 [1.61, 21.79]
13.2 At 9 months	1	40	Mean Difference (IV, Random, 95% CI)	14.90 [1.35, 28.45]
13.3 At 12 months	1	38	Mean Difference (IV, Random, 95% CI)	-15.70 [-23.71, -7.69]
13.4 At 18 months	1	40	Mean Difference (IV, Random, 95% CI)	-1.40 [-17.25, 14.45]
14 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 At 9 months	1	40	Mean Difference (IV, Random, 95% CI)	12.70 [1.88, 23.52]
14.2 At 18 months	1	40	Mean Difference (IV, Random, 95% CI)	2.70 [-11.50, 16.90]
14.3 Extended follow-up	1	38	Mean Difference (IV, Random, 95% CI)	-8.0 [-20.35, 4.35]

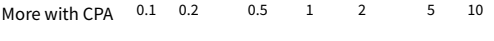
Analysis 6.1. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 1 Death.

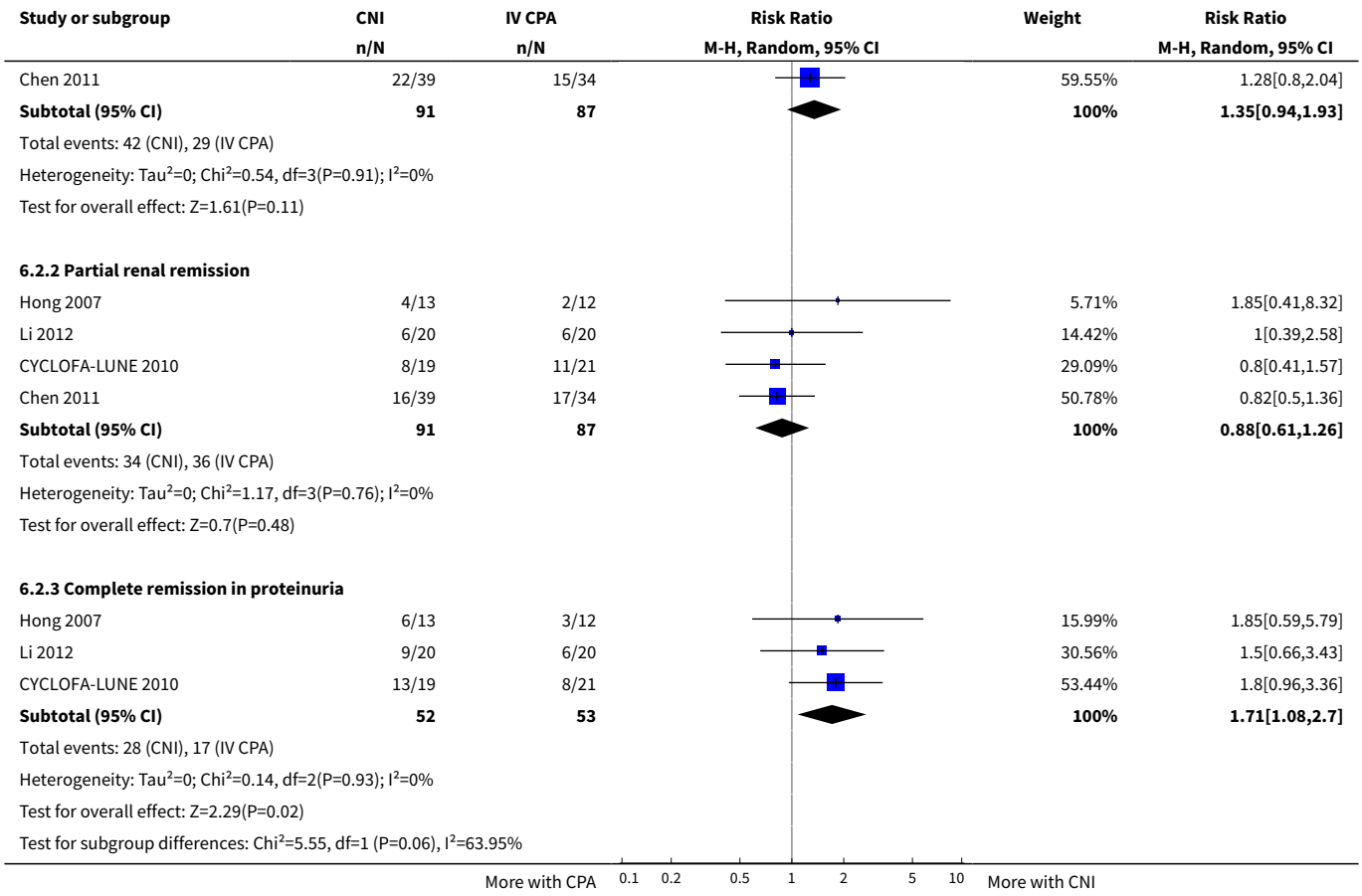
Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Death					
CYCLOFA-LUNE 2010	0/19	0/21			Not estimable
Chen 2011	0/39	1/34		34.89%	0.29[0.01,6.93]
Li 2012	1/20	2/20		65.11%	0.5[0.05,5.08]
Subtotal (95% CI)	**78**	**75**		**100%**	**0.41[0.06,2.69]**
Total events: 1 (CNI), 3 (IV CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=0.92(P=0.36)					
6.1.2 Death: extended follow-up					
CYCLOFA-LUNE 2010	0/19	0/19			Not estimable
Subtotal (95% CI)	**19**	**19**			**Not estimable**
Total events: 0 (CNI), 0 (IV CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					



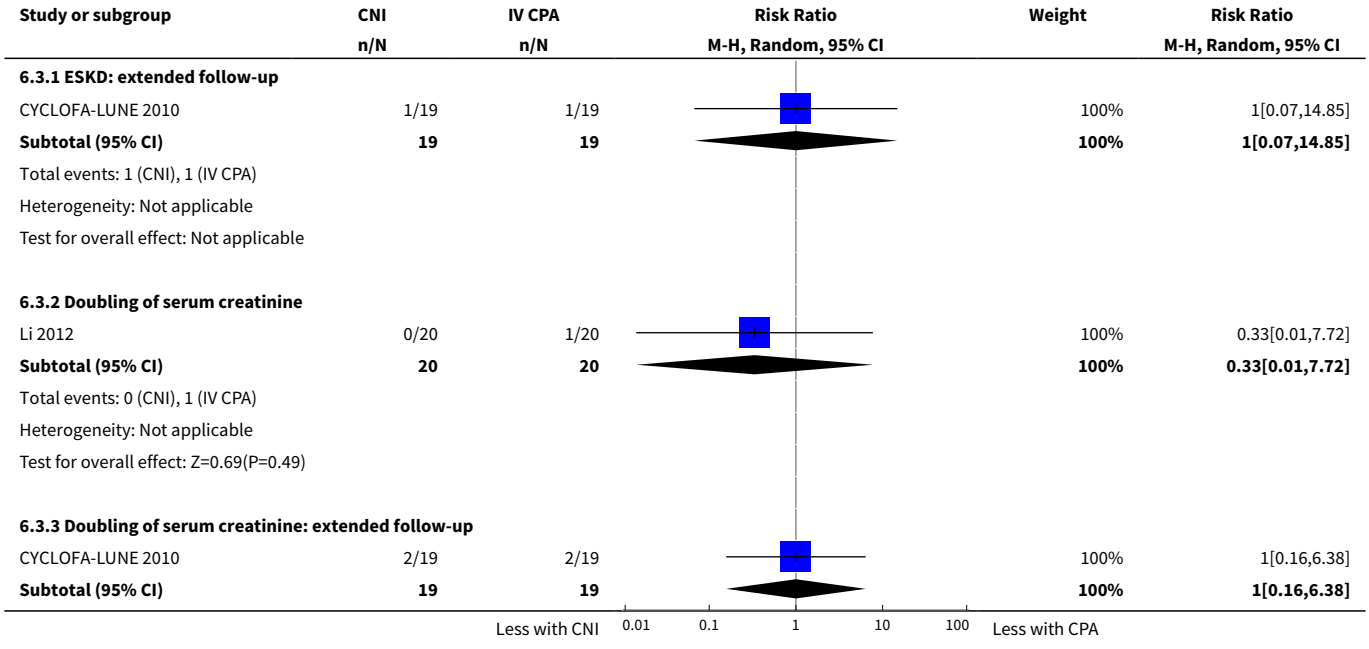
Analysis 6.2. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 2 Remission.

Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Complete renal remission					
Hong 2007	6/13	3/12		10%	1.85[0.59,5.79]
CYCLOFA-LUNE 2010	5/19	5/21		11.34%	1.11[0.38,3.23]
Li 2012	9/20	6/20		19.11%	1.5[0.66,3.43]

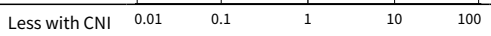




Analysis 6.3. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 3 Adverse renal outcomes.

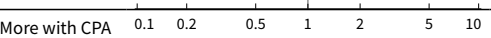


Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 2 (CNI), 2 (IV CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



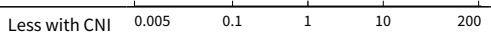
Analysis 6.4. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 4 Stable kidney function.

Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hong 2007	6/13	3/12		15.98%	1.85[0.59,5.79]
Li 2012	9/20	6/20		22.31%	1.5[0.66,3.43]
CYCLOFA-LUNE 2010	9/19	18/21		30.66%	0.55[0.33,0.92]
Chen 2011	22/42	15/39		31.05%	1.36[0.83,2.22]
Total (95% CI)	**94**	**92**		**100%**	**1.11[0.61,2]**
Total events: 46 (CNI), 42 (IV CPA)					
Heterogeneity: Tau^2=0.23; Chi^2=9.11, df=3(P=0.03); I^2=67.06%					
Test for overall effect: Z=0.34(P=0.73)					

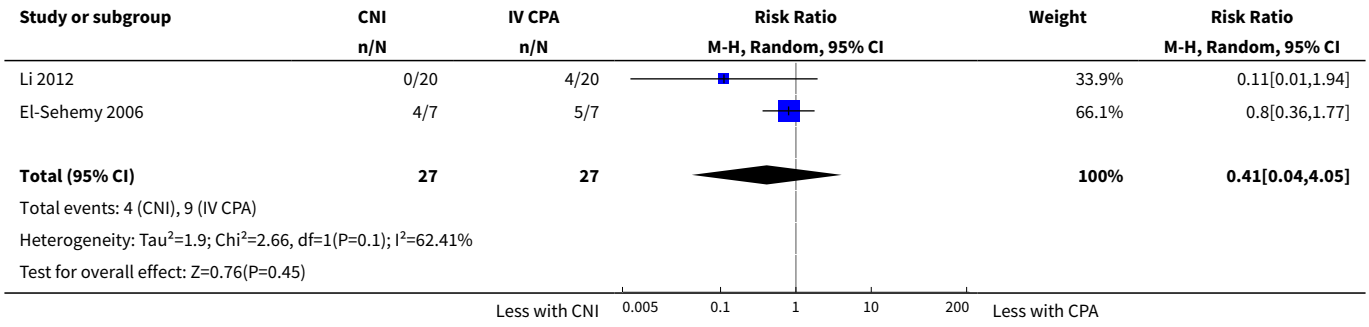


Analysis 6.5. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 5 Ovarian failure.

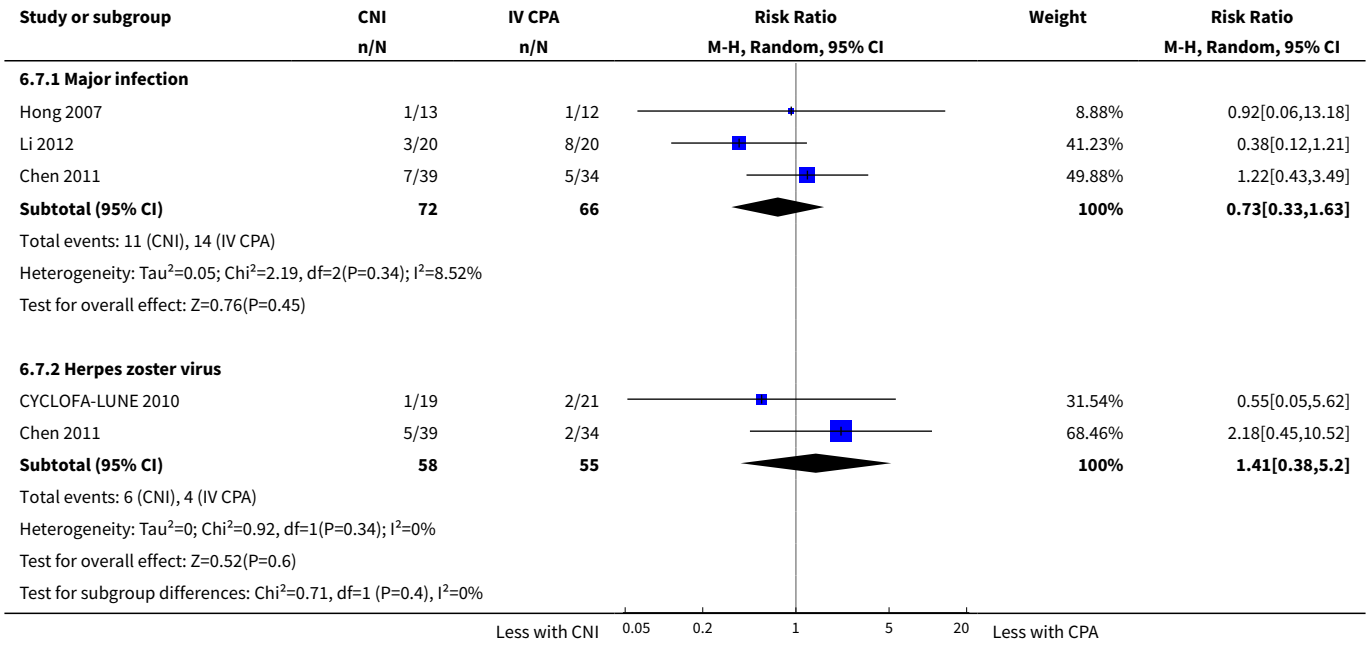
Study or subgroup	CNI n/N	IV CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 Ovarian failure					
CYCLOFA-LUNE 2010	0/19	1/21		47.71%	0.37[0.02,8.5]
Chen 2011	0/39	2/34		52.29%	0.18[0.01,3.52]
Subtotal (95% CI)	**58**	**55**		**100%**	**0.25[0.03,2.18]**
Total events: 0 (CNI), 3 (IV CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%					
Test for overall effect: Z=1.25(P=0.21)					
6.5.2 Premature ovarian failure: extended follow-up					
CYCLOFA-LUNE 2010	0/14	1/13		100%	0.31[0.01,7.02]
Subtotal (95% CI)	**14**	**13**		**100%**	**0.31[0.01,7.02]**
Total events: 0 (CNI), 1 (IV CPA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.46)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.91), I^2=0%					



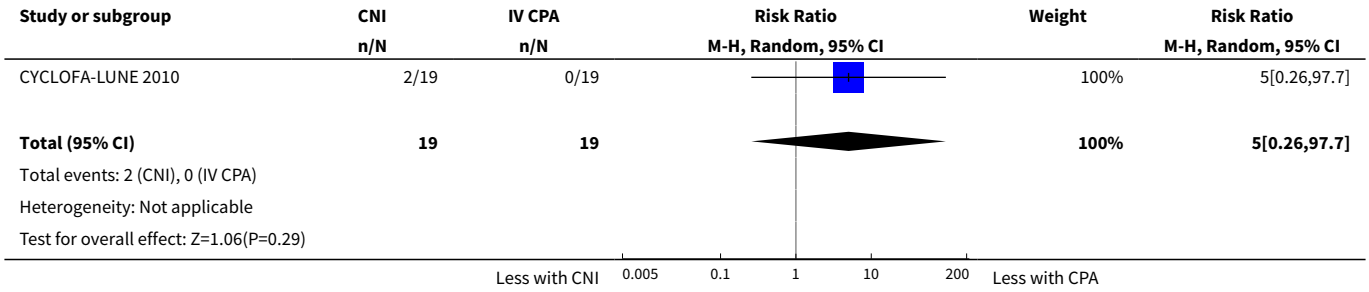
Analysis 6.6. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 6 Menstrual irregularities.



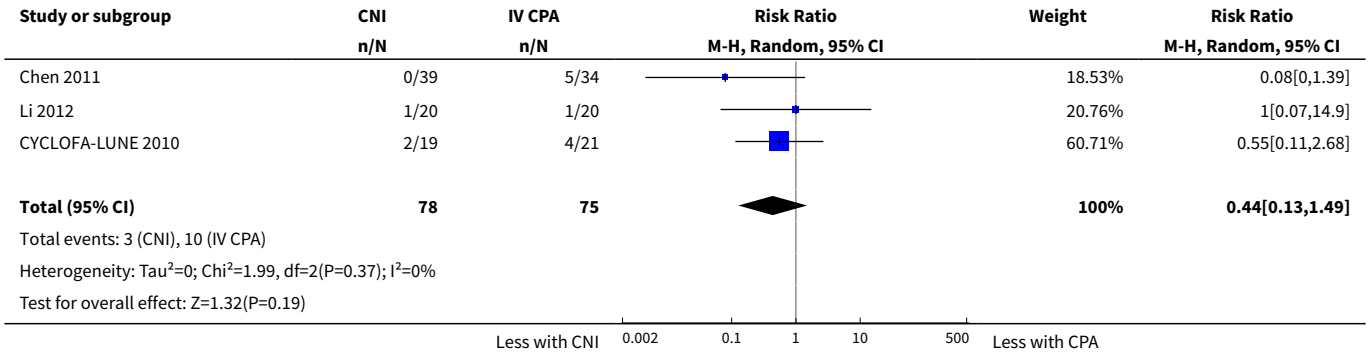
Analysis 6.7. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 7 Infection.



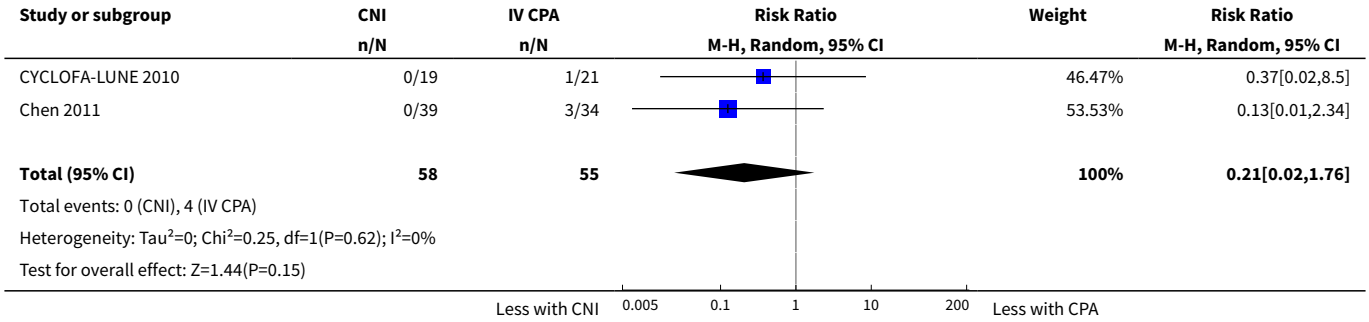
Analysis 6.8. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 8 Malignancy: extended follow-up.



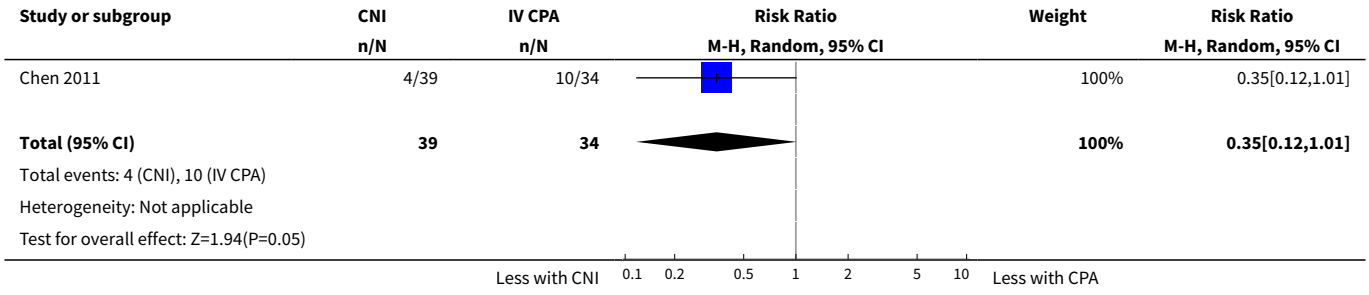
Analysis 6.9. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 9 Leucopenia.



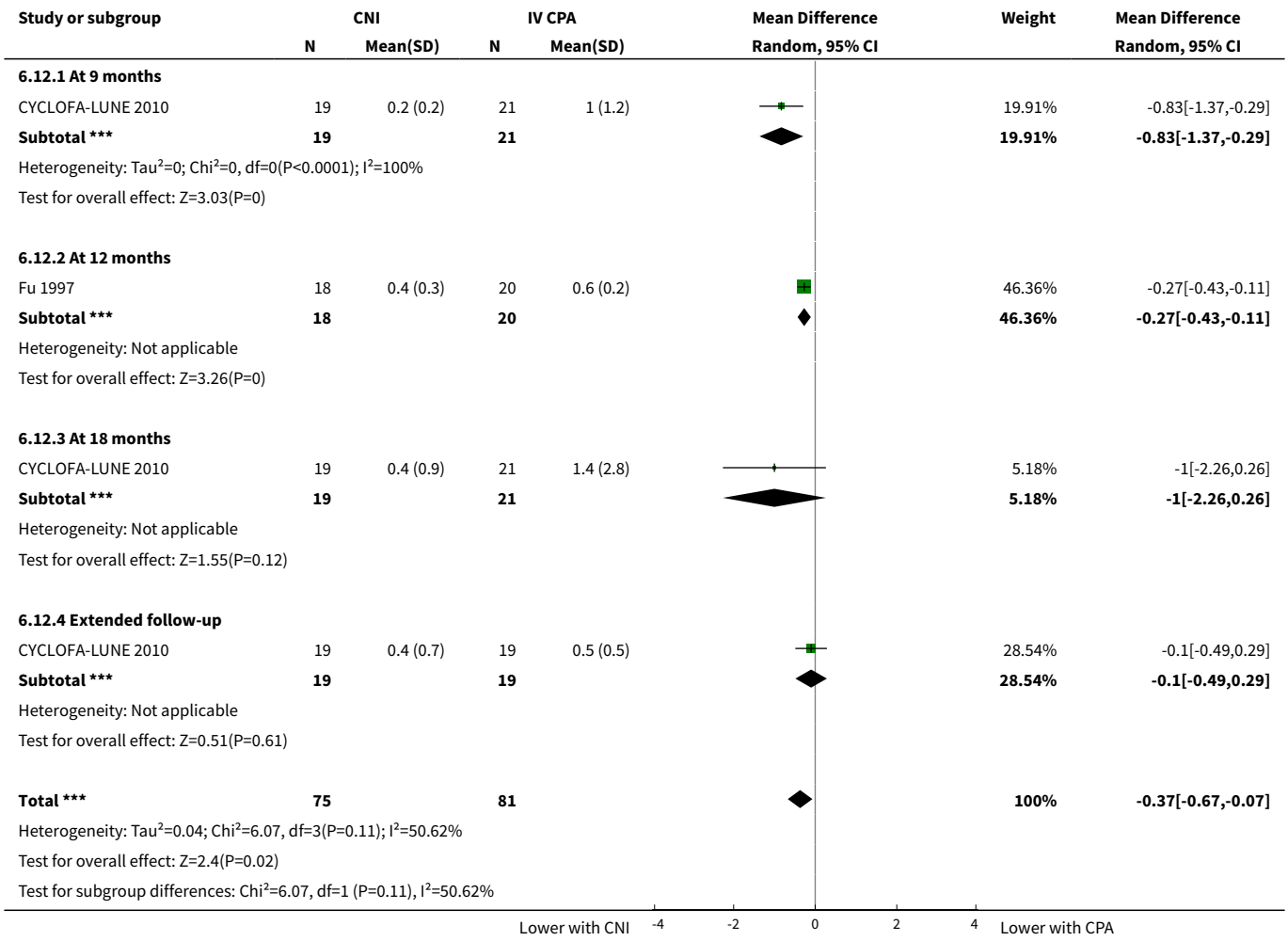
Analysis 6.10. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 10 Alopecia.



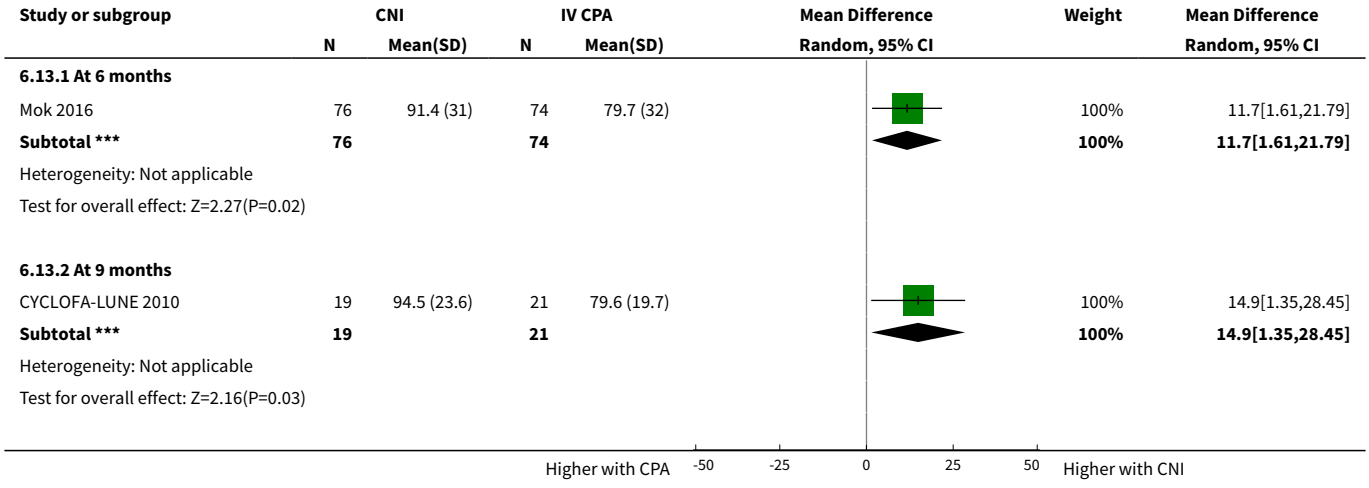
Analysis 6.11. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 11 Gastrointestinal (GI) adverse events.

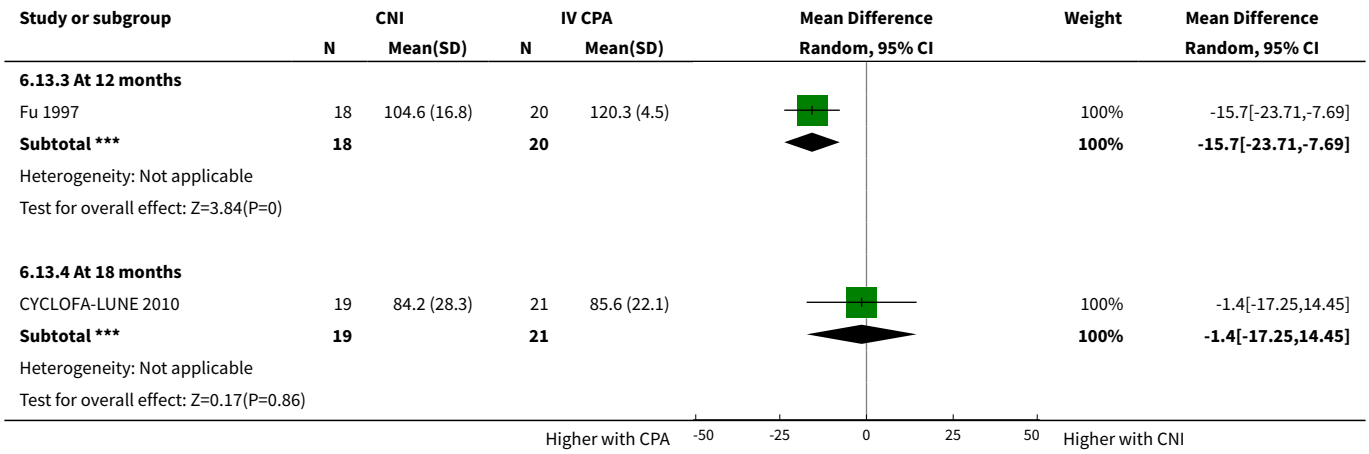


Analysis 6.12. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 12 Daily proteinuria.

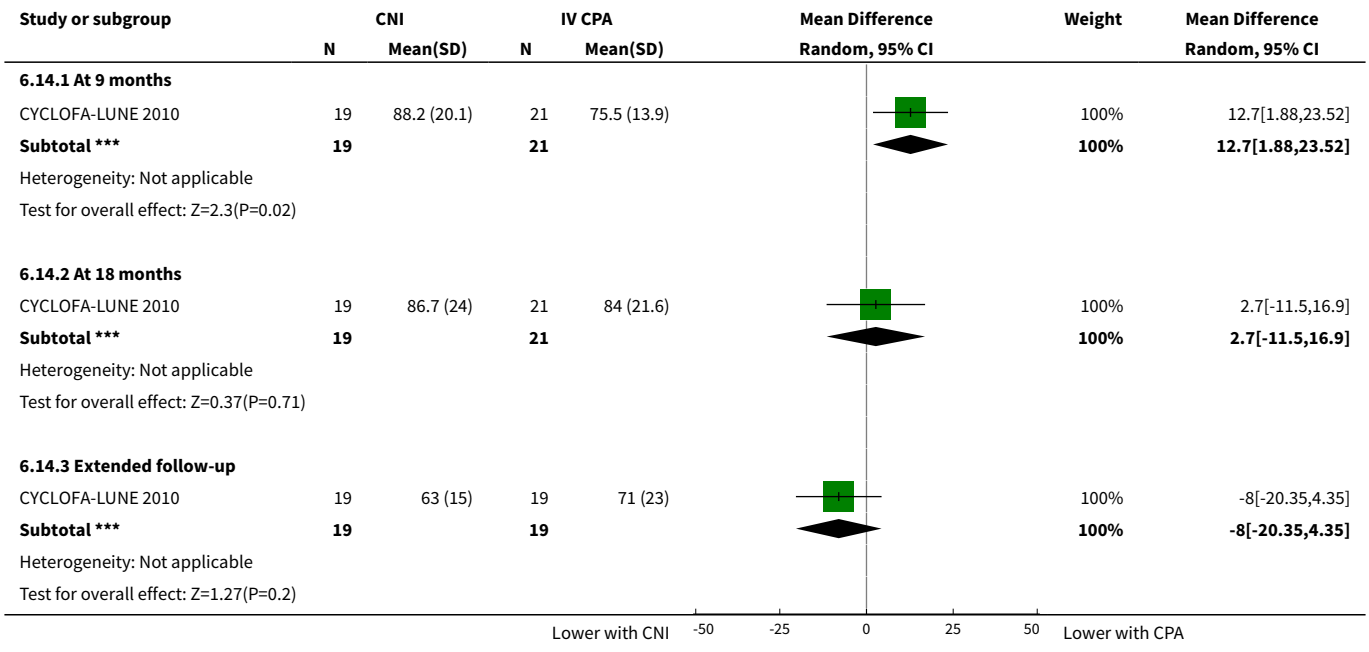


Analysis 6.13. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 13 Creatinine clearance.





Analysis 6.14. Comparison 6 Calcineurin inhibitors (CNI) versus IV cyclophosphamide (CPA), Outcome 14 Serum creatinine.

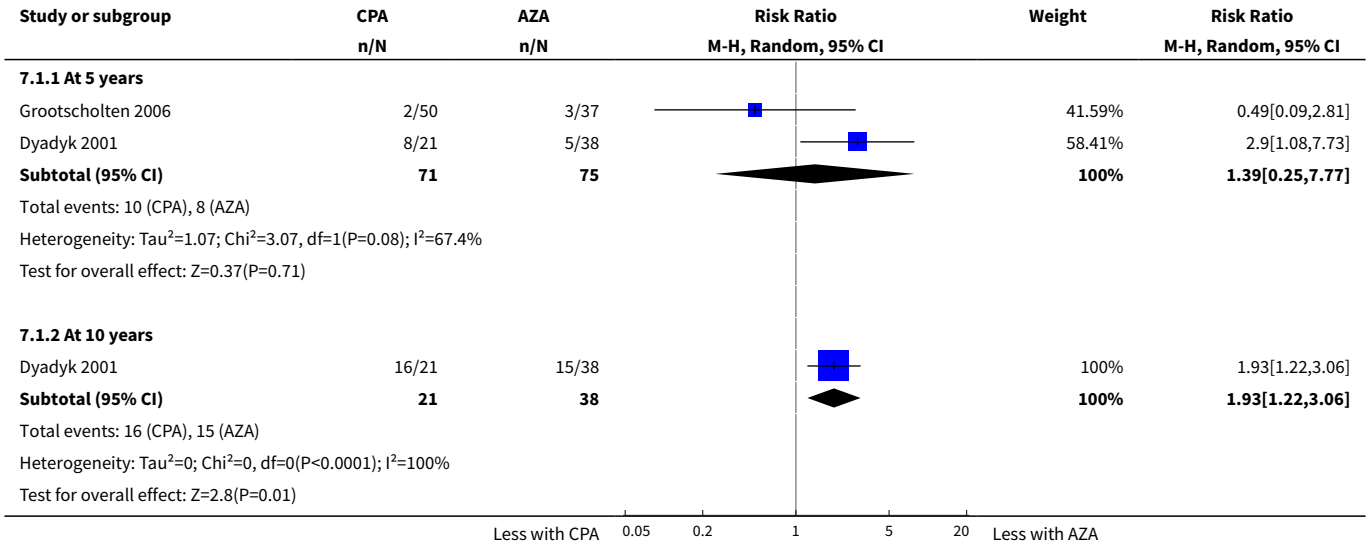


Comparison 7. Cyclophosphamide (CPA) versus azathioprine (AZA)

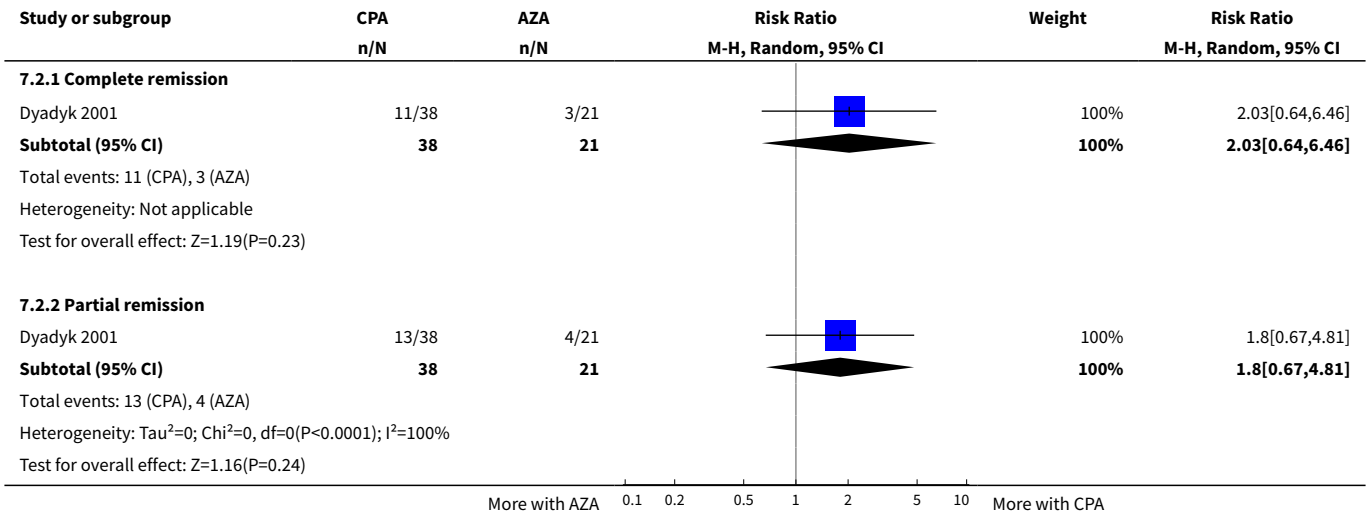
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At 5 years	2	146	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.25, 7.77]
1.2 At 10 years	1	59	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.22, 3.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Remission in proteinuria	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete remission	1	59	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.64, 6.46]
2.2 Partial remission	1	59	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.67, 4.81]
3 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD	2	144	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.15, 1.07]
3.2 ESKD at 9.6 years (median)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.15, 6.82]
3.3 Renal relapse	1	87	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.64]
3.4 Renal relapse at 9.6 years (median)	1	87	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.10, 0.67]
3.5 Doubling of serum creatinine	2	144	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.95]
3.6 Deterioration of kidney function	1	30	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.18, 2.42]
4 Stable kidney function	1	57	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.86, 2.01]
5 Ovarian failure	2	126	Risk Ratio (M-H, Random, 95% CI)	2.11 [0.59, 7.53]
6 Menstrual irregularities	1	15	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.69, 5.23]
7 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Major infection	1	57	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.27, 5.86]
7.2 Herpes zoster virus	1	57	Risk Ratio (M-H, Random, 95% CI)	2.75 [0.68, 11.18]
8 Malignancy	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 CPA versus AZA	2	144	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.13, 2.63]
8.2 10 year follow-up	1	87	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.11, 5.01]
9 Bone toxicity	1	87	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Bladder toxicity	2	144	Risk Ratio (M-H, Random, 95% CI)	3.59 [0.19, 66.14]

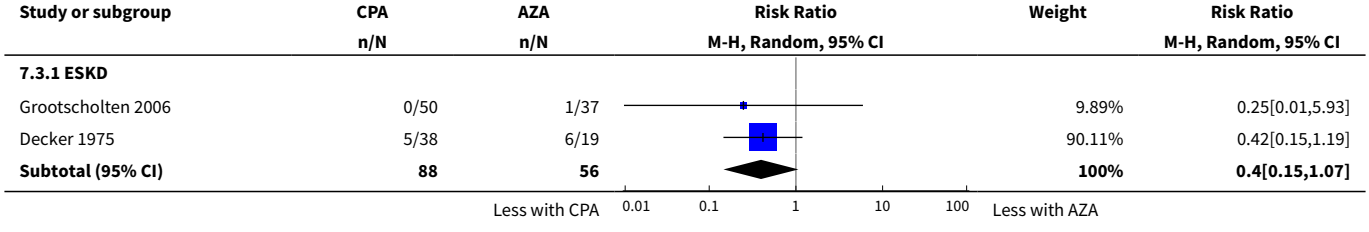
Analysis 7.1. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 1 Death.

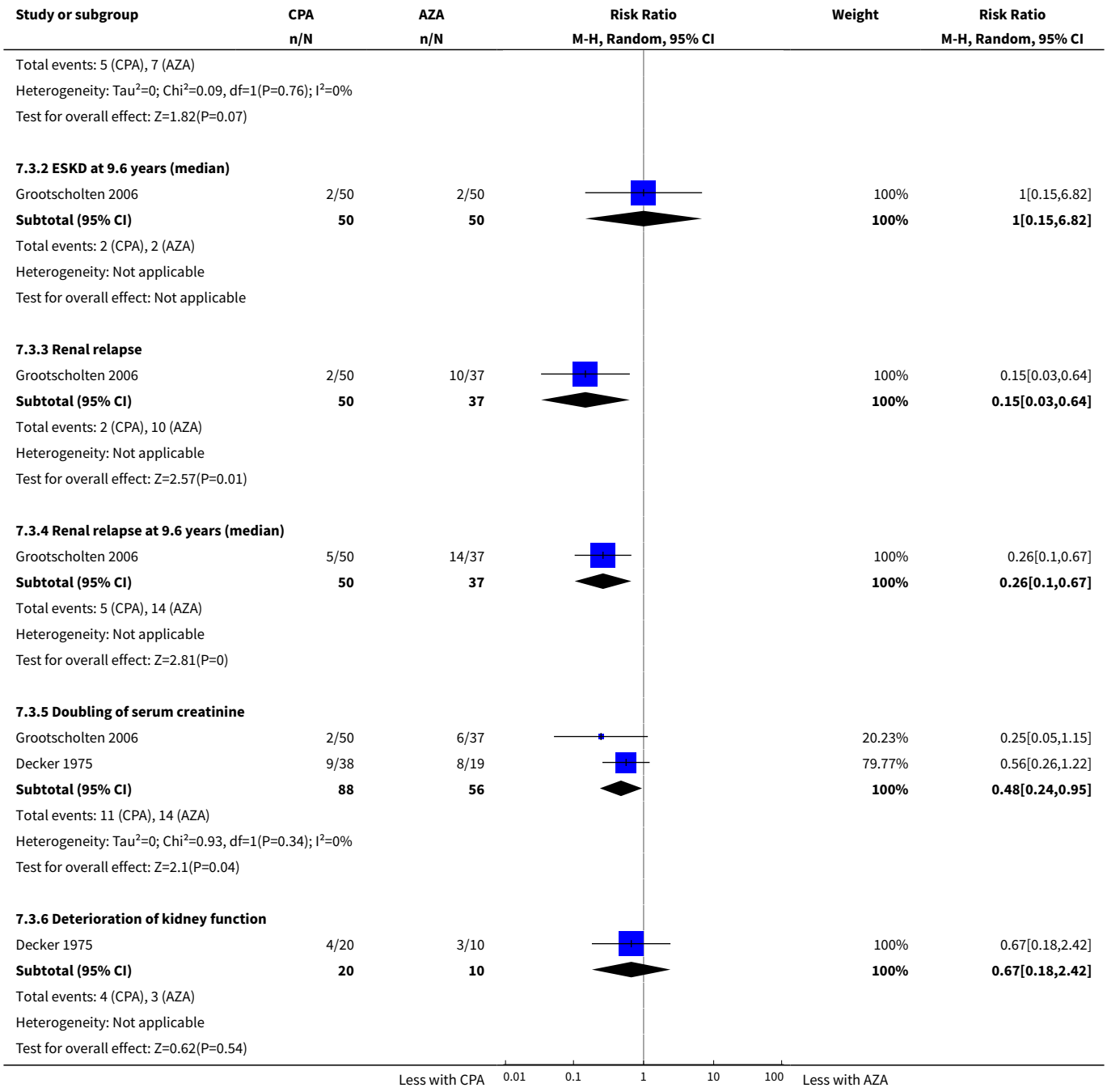


Analysis 7.2. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 2 Remission in proteinuria.

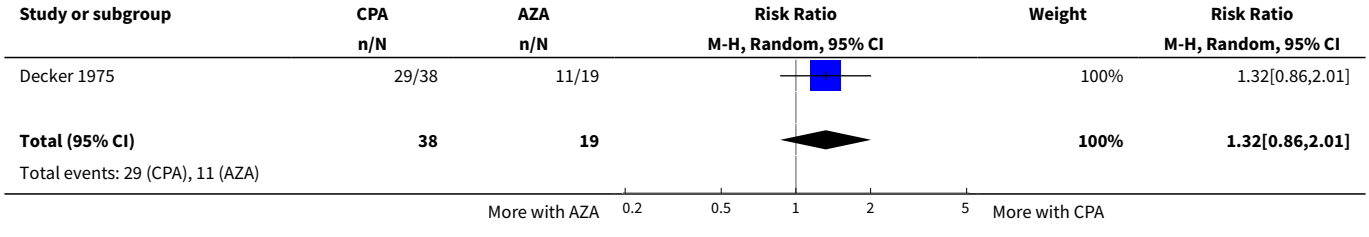


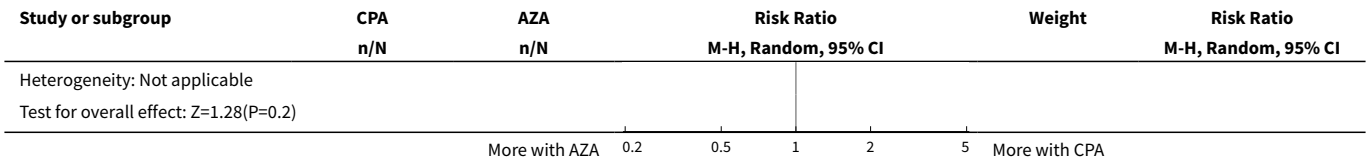
Analysis 7.3. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 3 Adverse renal outcomes.



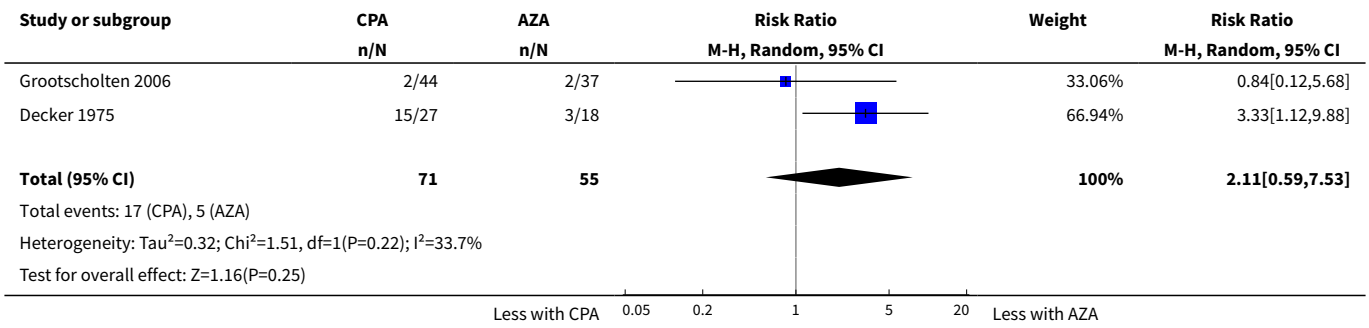


Analysis 7.4. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 4 Stable kidney function.

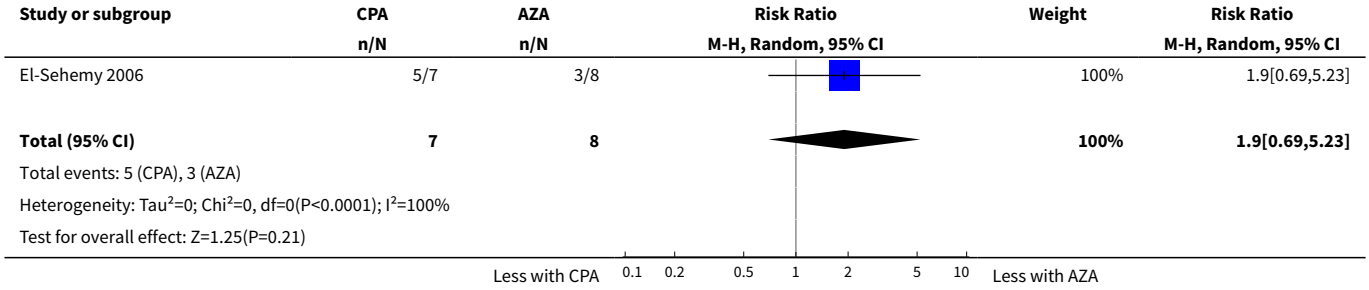




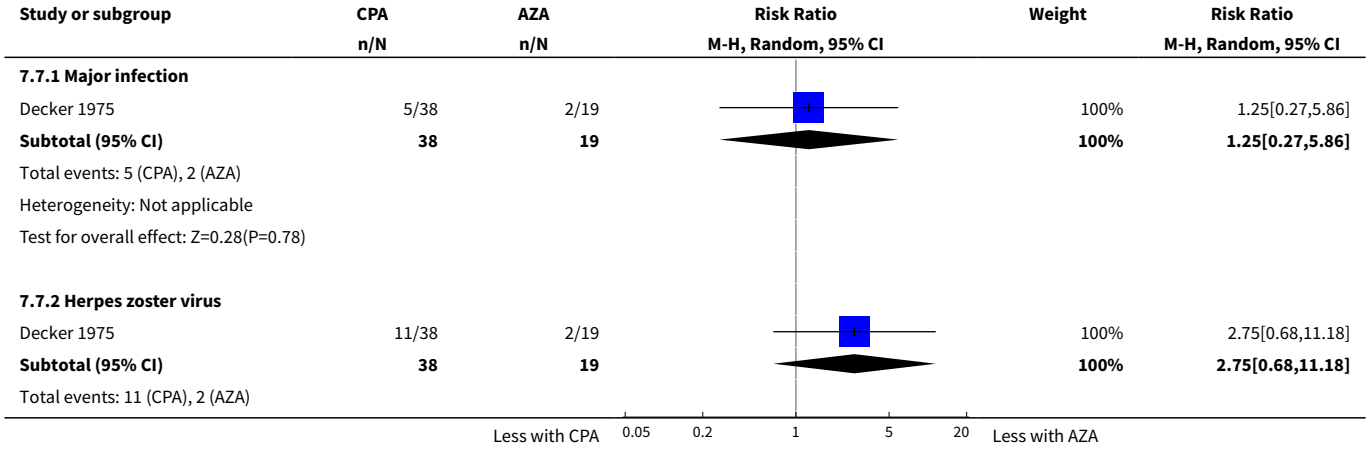
Analysis 7.5. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 5 Ovarian failure.



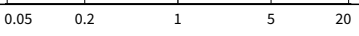
Analysis 7.6. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 6 Menstrual irregularities.



Analysis 7.7. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 7 Infection.

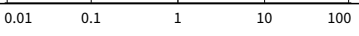


Study or subgroup	CPA n/N	AZA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					
Test for subgroup differences: Chi²=0.55, df=1 (P=0.46), I²=0%					



Analysis 7.8. Comparison 7 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
7.8.1 CPA versus AZA					
Grootscholten 2006	0/50	1/37		22.35%	0.25[0.01,5.93]
Decker 1975	3/38	2/19		77.65%	0.75[0.14,4.12]
Subtotal (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)					
7.8.2 10 year follow-up					
Grootscholten 2006	2/50	2/37		100%	0.74[0.11,5.01]
Subtotal (95% CI)	**50**	**37**		**100%**	**0.74[0.11,5.01]**
Total events: 2 (CPA), 2 (AZA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					
Test for subgroup differences: Chi²=0.04, df=1 (P=0.85), I²=0%					

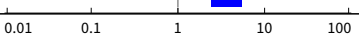


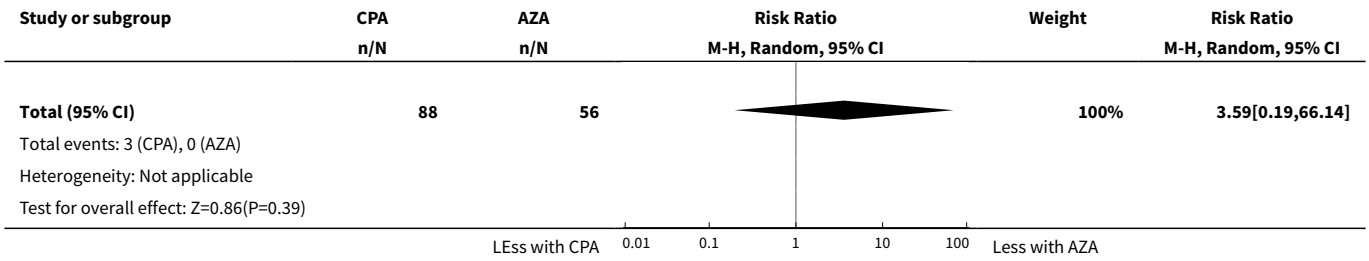
Analysis 7.9. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 9 Bone toxicity.

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
Total (95% CI)	**50**	**37**			**Not estimable**
Total events: 0 (CPA), 0 (AZA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 7.10. Comparison 7 Cyclophosphamide (CPA) versus azathioprine (AZA), Outcome 10 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
Decker 1975	3/38	0/19		100%	3.59[0.19,66.14]

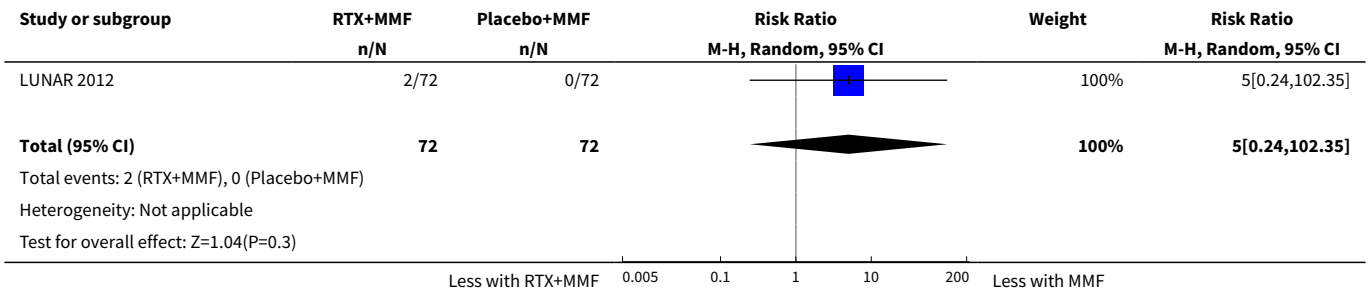




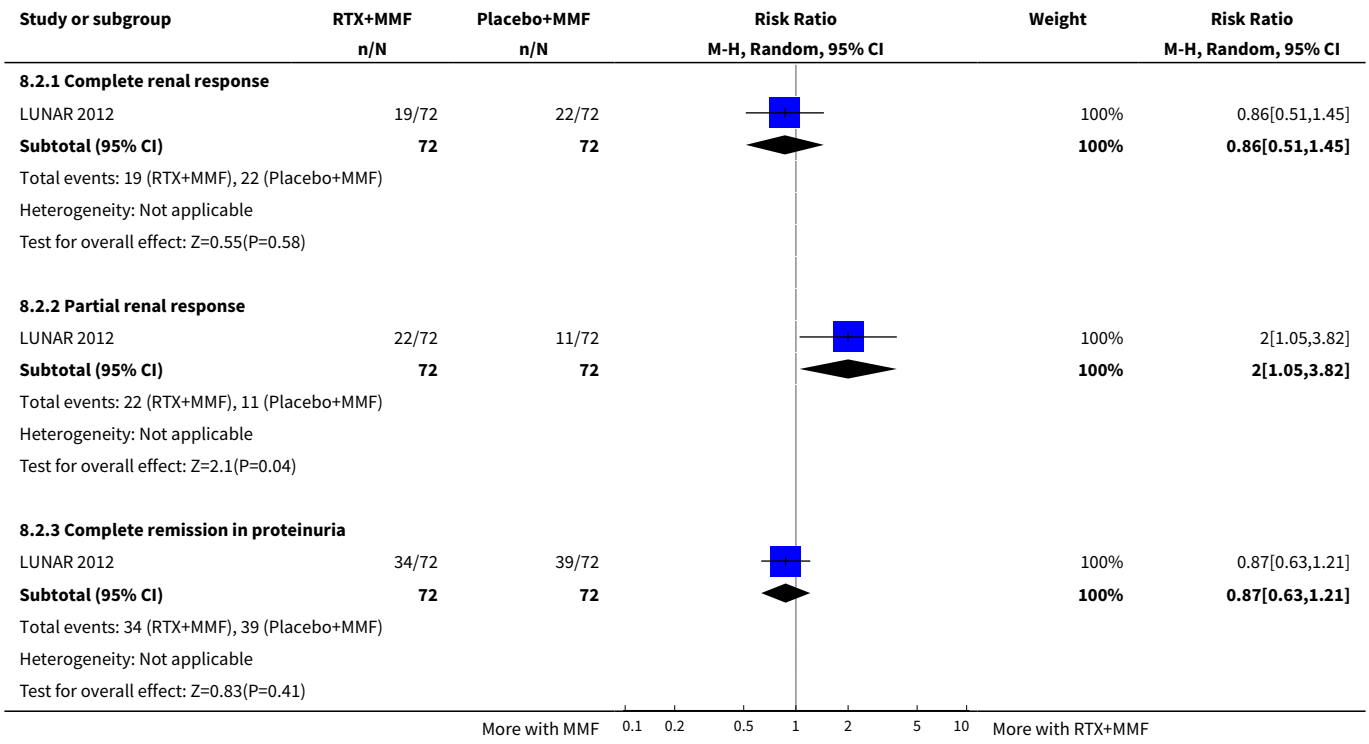
Comparison 8. Rituximab (RTX) + mycophenolate mofetil (MMF) versus placebo + MMF

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	144	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.24, 102.35]
2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete renal response	1	144	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.51, 1.45]
2.2 Partial renal response	1	144	Risk Ratio (M-H, Random, 95% CI)	2.0 [1.05, 3.82]
2.3 Complete remission in proteinuria	1	144	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.21]
3 Stable kidney function	1	144	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.90, 1.71]
4 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Major infection	1	144	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.48, 2.08]
4.2 Herpes zoster virus	1	144	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.36, 1.85]
5 Leucopenia	1	144	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.85, 10.63]

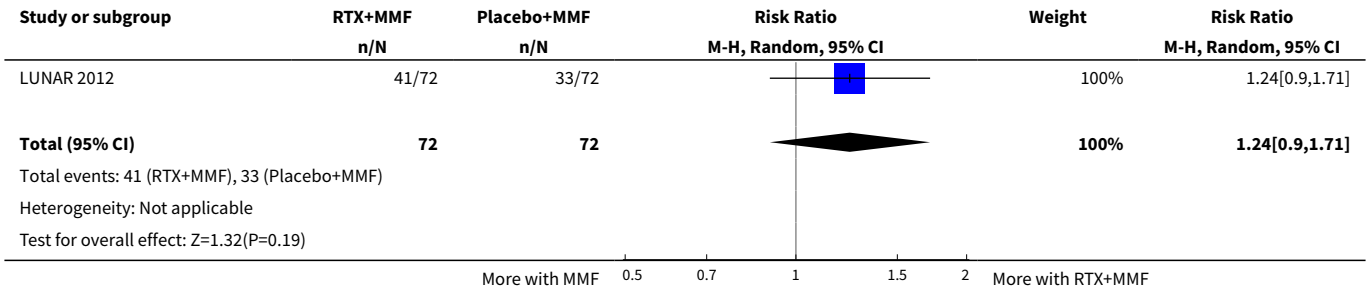
Analysis 8.1. Comparison 8 Rituximab (RTX) + mycophenolate mofetil (MMF) versus placebo + MMF, Outcome 1 Death.



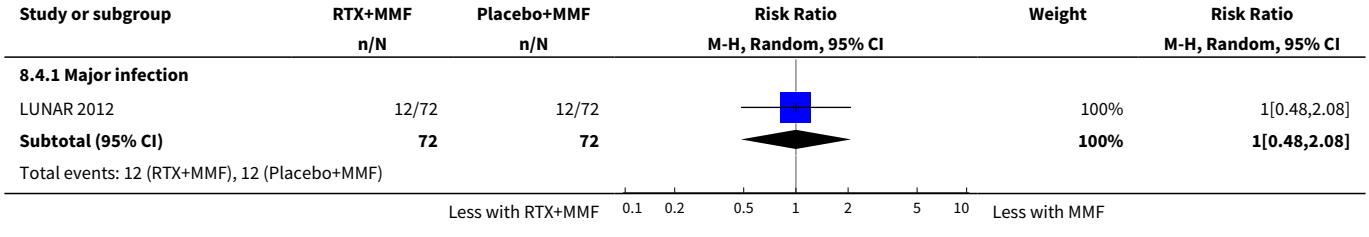
Analysis 8.2. Comparison 8 Rituximab (RTX) + mycophenolate mofetil (MMF) versus placebo + MMF, Outcome 2 Remission.

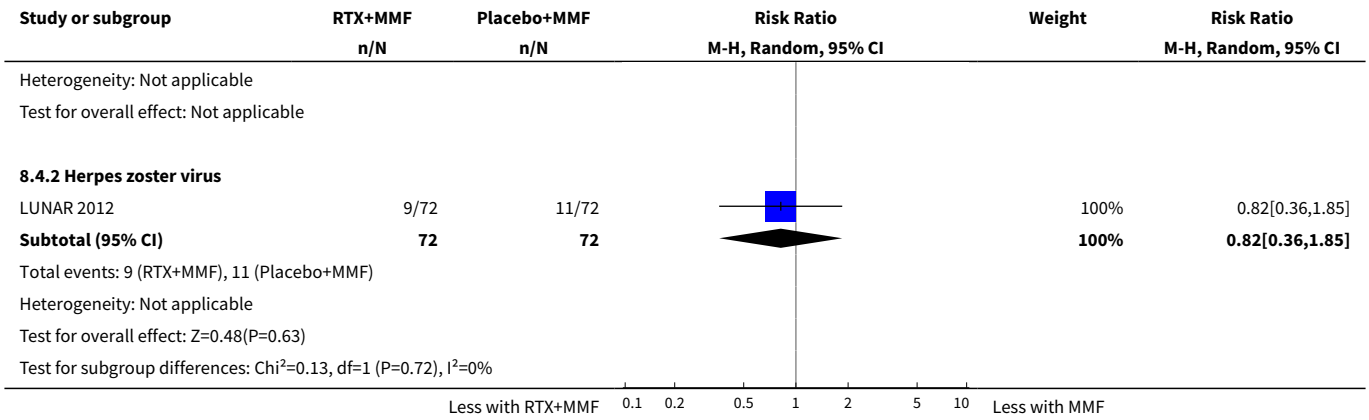


Analysis 8.3. Comparison 8 Rituximab (RTX) + mycophenolate mofetil (MMF) versus placebo + MMF, Outcome 3 Stable kidney function.

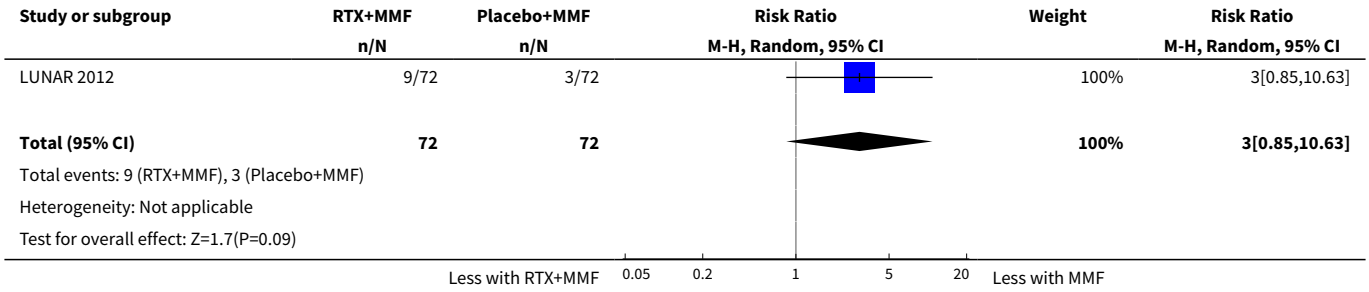


Analysis 8.4. Comparison 8 Rituximab (RTX) + mycophenolate mofetil (MMF) versus placebo + MMF, Outcome 4 Infection.





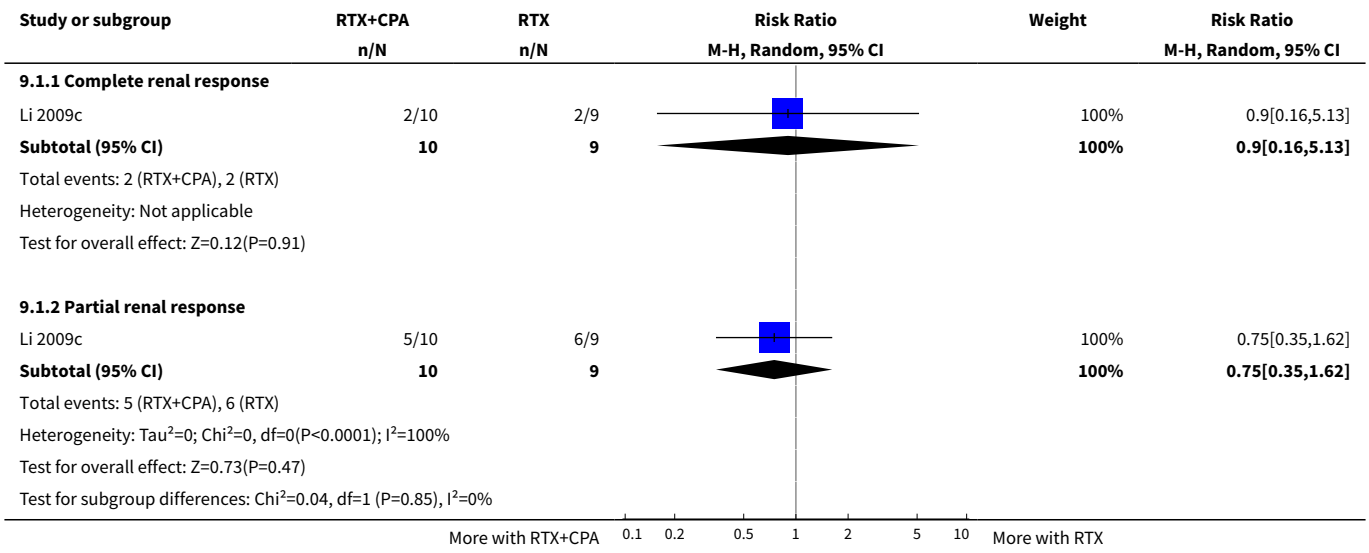
Analysis 8.5. Comparison 8 Rituximab (RTX) + mycophenolate mofetil (MMF) versus placebo + MMF, Outcome 5 Leucopenia.



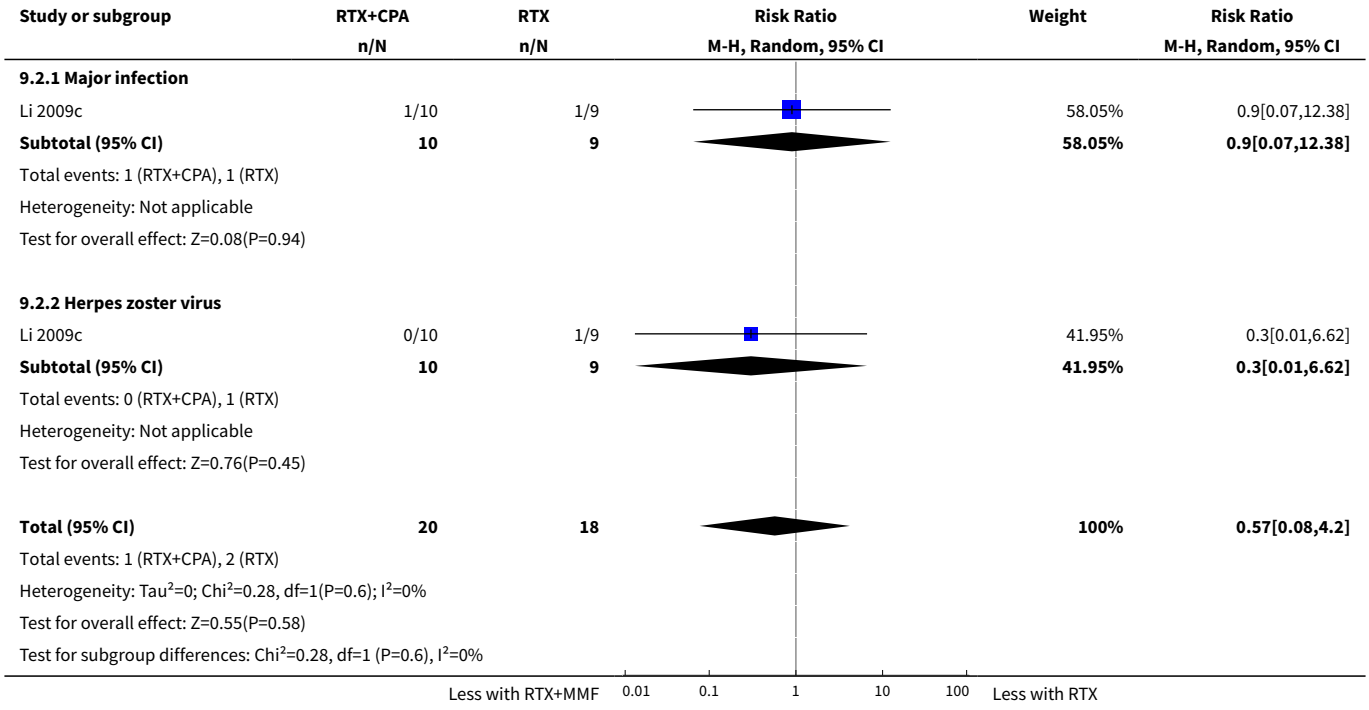
Comparison 9. Rituximab (RTX) + cyclophosphamide (CPA) versus RTX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Complete renal response	1	19	Risk Ratio (M-H, Random, 95% CI)	0.9 [0.16, 5.13]
1.2 Partial renal response	1	19	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.35, 1.62]
2 Infection	1	38	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.08, 4.20]
2.1 Major infection	1	19	Risk Ratio (M-H, Random, 95% CI)	0.9 [0.07, 12.38]
2.2 Herpes zoster virus	1	19	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 6.62]
3 Daily proteinuria	1	19	Mean Difference (IV, Random, 95% CI)	-0.30 [-2.29, 1.69]
4 Creatinine clearance	1	19	Mean Difference (IV, Random, 95% CI)	-17.20 [-50.66, 16.26]
5 Serum creatinine	1	19	Mean Difference (IV, Random, 95% CI)	35.00 [-27.14, 97.14]

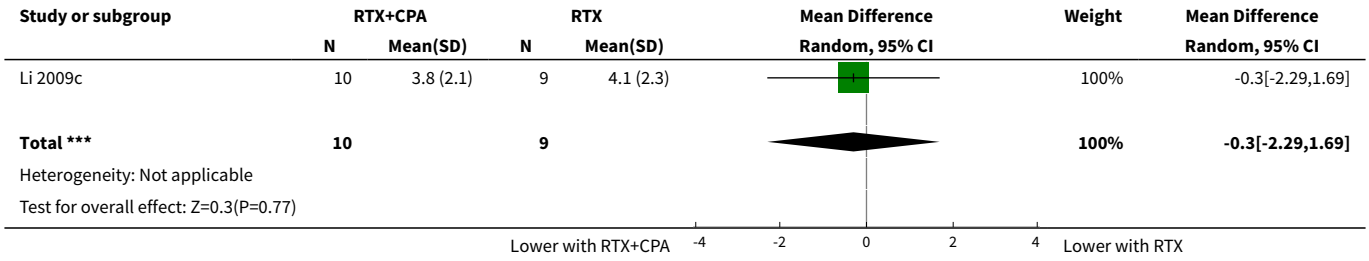
Analysis 9.1. Comparison 9 Rituximab (RTX) + cyclophosphamide (CPA) versus RTX, Outcome 1 Remission.



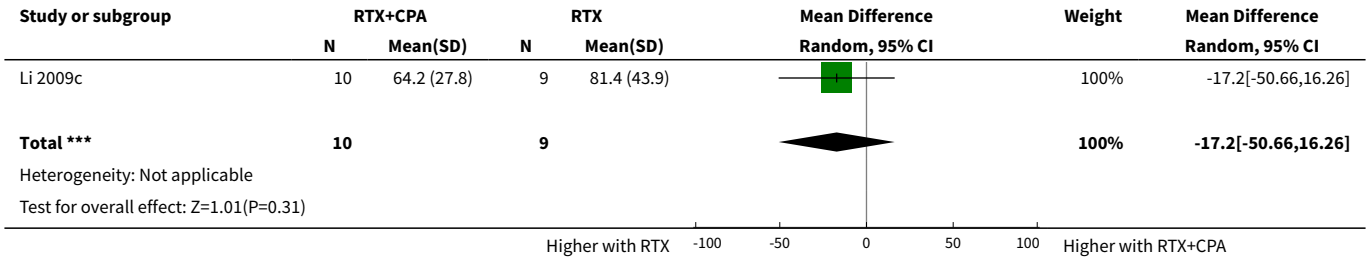
Analysis 9.2. Comparison 9 Rituximab (RTX) + cyclophosphamide (CPA) versus RTX, Outcome 2 Infection.



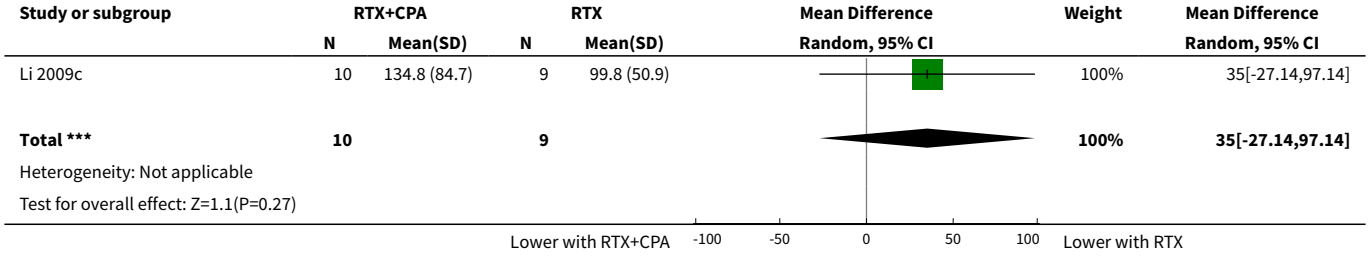
Analysis 9.3. Comparison 9 Rituximab (RTX) + cyclophosphamide (CPA) versus RTX, Outcome 3 Daily proteinuria.



Analysis 9.4. Comparison 9 Rituximab (RTX) + cyclophosphamide (CPA) versus RTX, Outcome 4 Creatinine clearance.



Analysis 9.5. Comparison 9 Rituximab (RTX) + cyclophosphamide (CPA) versus RTX, Outcome 5 Serum creatinine.



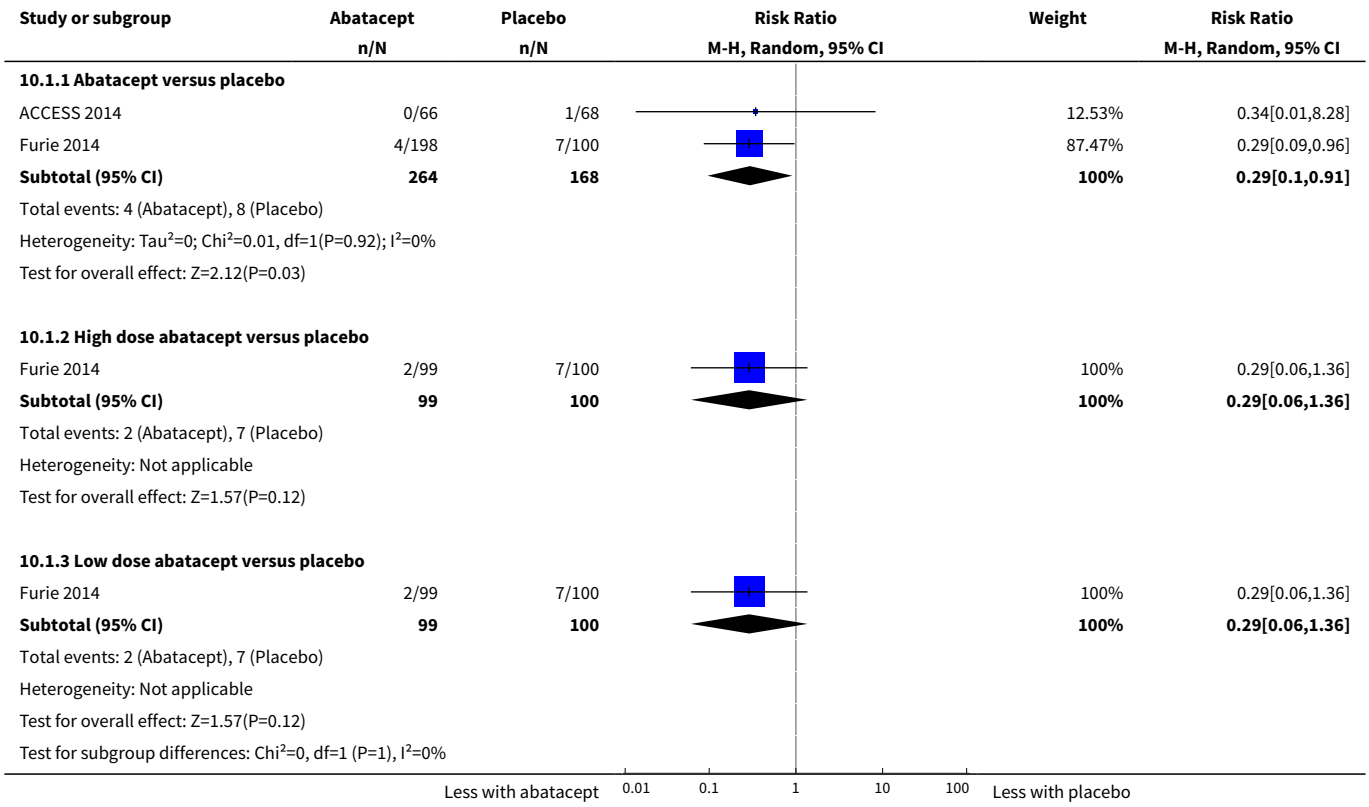
Comparison 10. Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Abatacept versus placebo	2	432	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.10, 0.91]
1.2 High dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.06, 1.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Low dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.06, 1.36]
2 Remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete remission: abatacept versus placebo	2	432	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.74, 1.71]
2.2 Complete remission: high dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.46, 2.83]
2.3 Complete remission: low dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.58, 3.31]
2.4 Partial remission: abatacept versus placebo	2	432	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.58, 1.33]
2.5 Partial remission: high dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.51, 2.01]
2.6 Partial remission: low dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.29, 1.43]
3 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD: Abatacept versus placebo	1	298	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.21, 3.45]
3.2 ESKD: high dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.21, 4.88]
3.3 ESKD: low dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.11, 3.94]
3.4 Renal relapse: abatacept versus placebo	1	134	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.22, 4.92]
4 Major Infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Abatacept versus placebo	2	432	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.81, 2.04]
4.2 High dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.78, 2.40]
4.3 Low dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.59, 1.95]
5 Herpes zoster virus	1		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 Abatacept versus placebo	1	298	Risk Ratio (M-H, Random, 95% CI)	9.64 [0.57, 164.02]
5.2 High dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	7.07 [0.37, 135.11]
5.3 Low dose abatacept versus placebo	1	199	Risk Ratio (M-H, Random, 95% CI)	13.13 [0.75, 229.99]
6 Health-related quality of life	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Physical component	1	134	Mean Difference (IV, Random, 95% CI)	0.0 [-3.73, 3.73]
6.2 Mental component	1	134	Mean Difference (IV, Random, 95% CI)	-0.60 [-4.50, 3.30]
7 Disease activity (BILAG)	1	134	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.23, 0.43]

Analysis 10.1. Comparison 10 Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS, Outcome 1 Death.

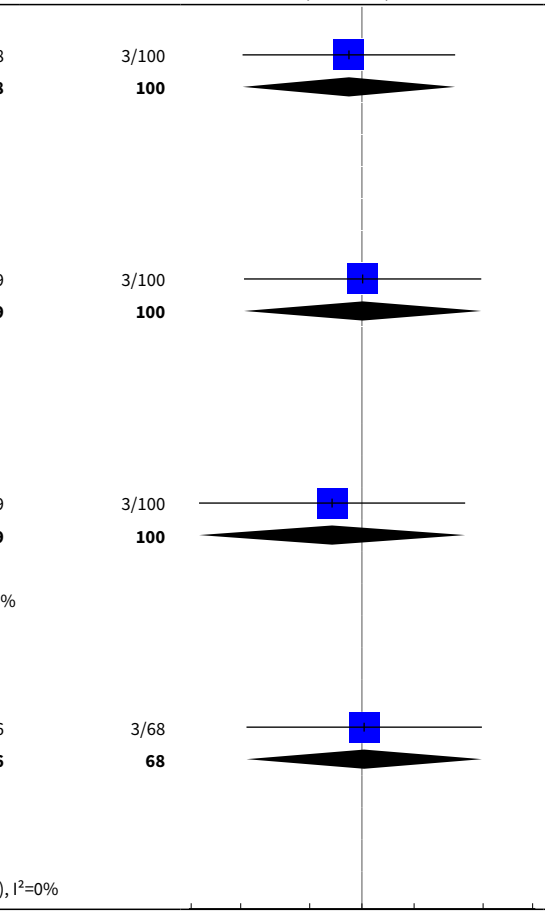


Analysis 10.2. Comparison 10 Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS, Outcome 2 Remission.

Study or subgroup	Abatacept n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.2.1 Complete remission: abatacept versus placebo					
Furie 2014	20/198	8/100		28.33%	1.26[0.58,2.77]
ACCESS 2014	22/66	21/68		71.67%	1.08[0.66,1.77]
Subtotal (95% CI)	**264**	**168**		**100%**	**1.13[0.74,1.71]**
Total events: 42 (Abatacept), 29 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					
10.2.2 Complete remission: high dose abatacept versus placebo					
Furie 2014	9/99	8/100		100%	1.14[0.46,2.83]
Subtotal (95% CI)	**99**	**100**		**100%**	**1.14[0.46,2.83]**
Total events: 9 (Abatacept), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					
10.2.3 Complete remission: low dose abatacept versus placebo					
Furie 2014	11/99	8/100		100%	1.39[0.58,3.31]
Subtotal (95% CI)	**99**	**100**		**100%**	**1.39[0.58,3.31]**
Total events: 11 (Abatacept), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.74(P=0.46)					
10.2.4 Partial remission: abatacept versus placebo					
Furie 2014	23/198	14/100		44.97%	0.83[0.45,1.54]
ACCESS 2014	17/66	19/68		55.03%	0.92[0.53,1.61]
Subtotal (95% CI)	**264**	**168**		**100%**	**0.88[0.58,1.33]**
Total events: 40 (Abatacept), 33 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
10.2.5 Partial remission: high dose abatacept versus placebo					
Furie 2014	14/99	14/100		100%	1.01[0.51,2.01]
Subtotal (95% CI)	**99**	**100**		**100%**	**1.01[0.51,2.01]**
Total events: 14 (Abatacept), 14 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.98)					
10.2.6 Partial remission: low dose abatacept versus placebo					
Furie 2014	9/99	14/100		100%	0.65[0.29,1.43]
Subtotal (95% CI)	**99**	**100**		**100%**	**0.65[0.29,1.43]**
Total events: 9 (Abatacept), 14 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.07(P=0.28)					
Test for subgroup differences: Chi^2=2.46, df=1 (P=0.78), I^2=0%					

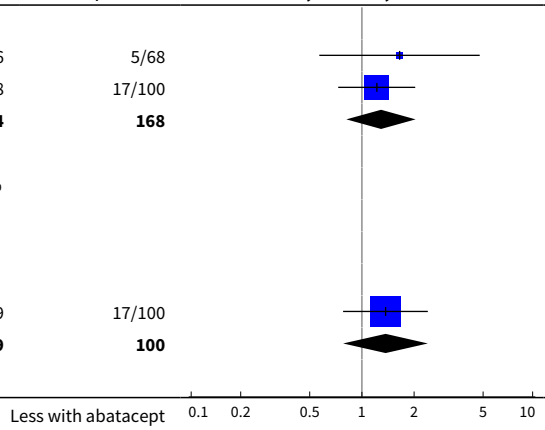
Analysis 10.3. Comparison 10 Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS, Outcome 3 Adverse renal outcomes.

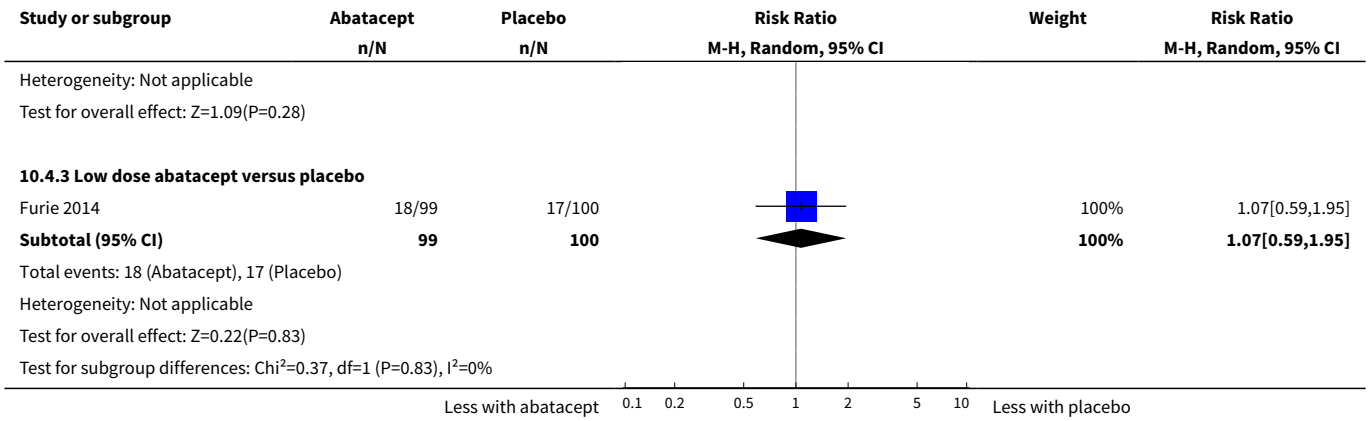
Study or subgroup	Abatacept n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.3.1 ESKD: Abatacept versus placebo					
Furie 2014	5/198	3/100		100%	0.84[0.21,3.45]
Subtotal (95% CI)	**198**	**100**		**100%**	**0.84[0.21,3.45]**
Total events: 5 (Abatacept), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
10.3.2 ESKD: high dose abatacept versus placebo					
Furie 2014	3/99	3/100		100%	1.01[0.21,4.88]
Subtotal (95% CI)	**99**	**100**		**100%**	**1.01[0.21,4.88]**
Total events: 3 (Abatacept), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
10.3.3 ESKD: low dose abatacept versus placebo					
Furie 2014	2/99	3/100		100%	0.67[0.11,3.94]
Subtotal (95% CI)	**99**	**100**		**100%**	**0.67[0.11,3.94]**
Total events: 2 (Abatacept), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.44(P=0.66)					
10.3.4 Renal relapse: abatacept versus placebo					
ACCESS 2014	3/66	3/68		100%	1.03[0.22,4.92]
Subtotal (95% CI)	**66**	**68**		**100%**	**1.03[0.22,4.92]**
Total events: 3 (Abatacept), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.98), I^2=0%					



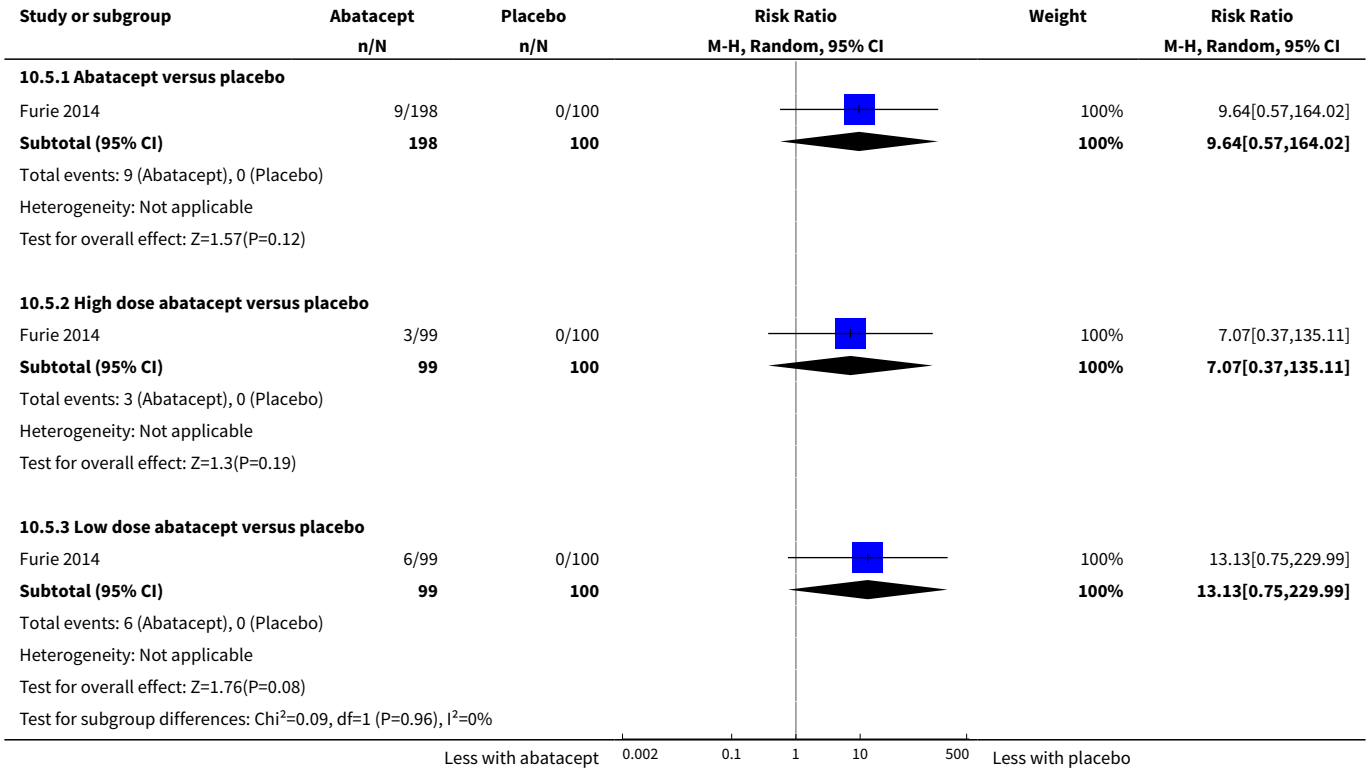
Analysis 10.4. Comparison 10 Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS, Outcome 4 Major Infection.

Study or subgroup	Abatacept n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.4.1 Abatacept versus placebo					
ACCESS 2014	8/66	5/68		18.76%	1.65[0.57,4.78]
Furie 2014	41/198	17/100		81.24%	1.22[0.73,2.03]
Subtotal (95% CI)	**264**	**168**		**100%**	**1.29[0.81,2.04]**
Total events: 49 (Abatacept), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					
10.4.2 High dose abatacept versus placebo					
Furie 2014	23/99	17/100		100%	1.37[0.78,2.4]
Subtotal (95% CI)	**99**	**100**		**100%**	**1.37[0.78,2.4]**
Total events: 23 (Abatacept), 17 (Placebo)					

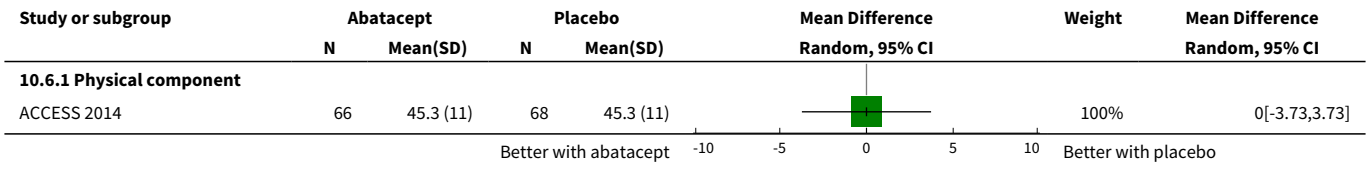


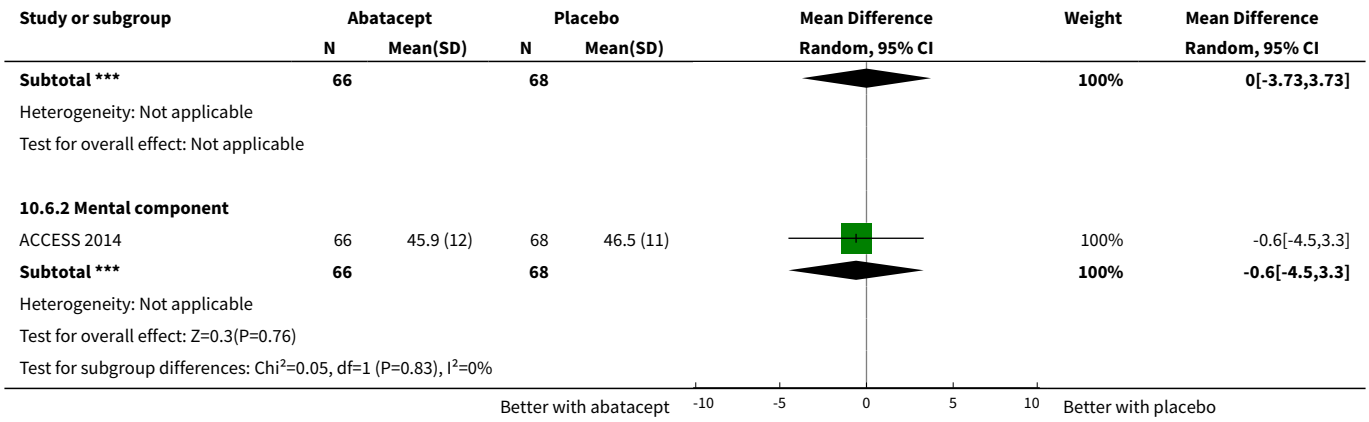


Analysis 10.5. Comparison 10 Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS, Outcome 5 Herpes zoster virus.

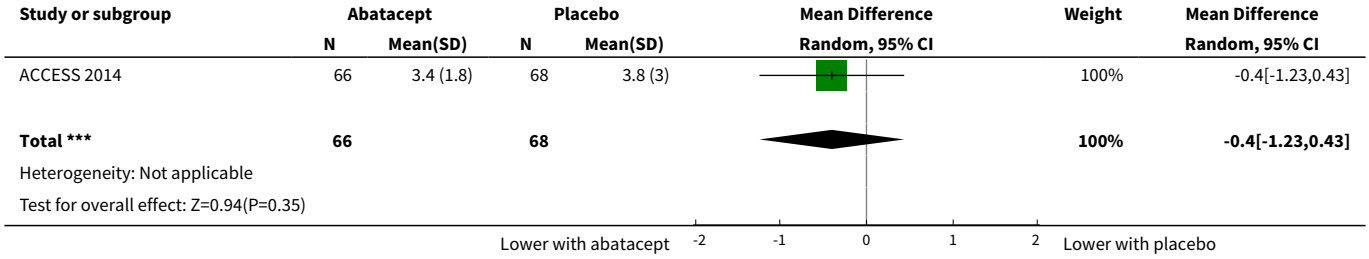


Analysis 10.6. Comparison 10 Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS, Outcome 6 Health-related quality of life.





Analysis 10.7. Comparison 10 Abatacept + other immunosuppressive agent (IS) + versus placebo + other IS, Outcome 7 Disease activity (BILAG).

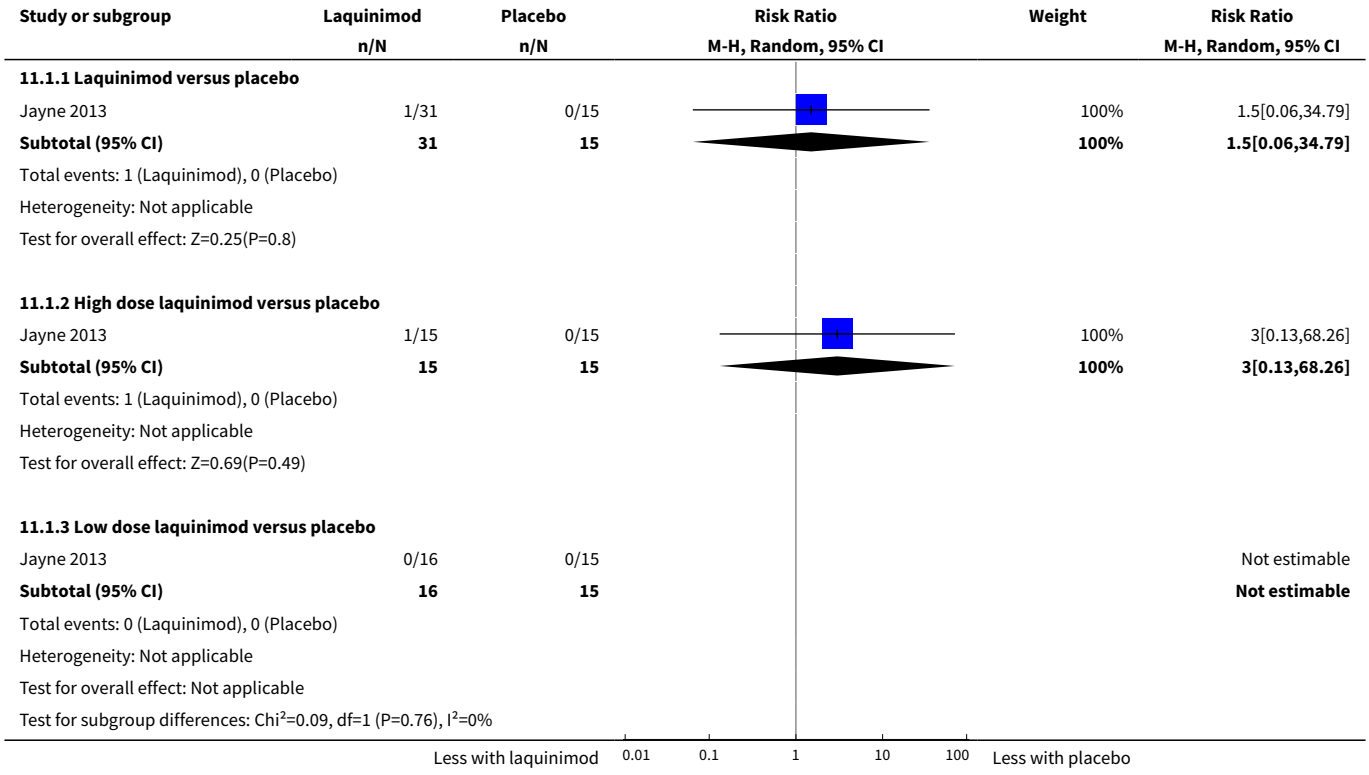


Comparison 11. Laquinimod + other immunosuppressive agent (IS) versus placebo + other IS

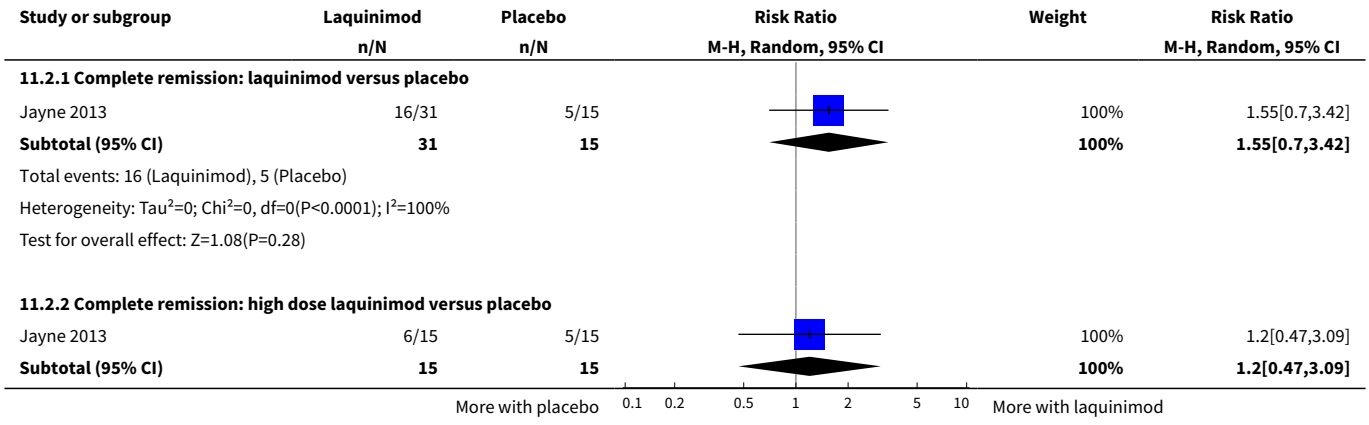
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Laquinimod versus placebo	1	46	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.06, 34.79]
1.2 High dose laquinimod versus placebo	1	30	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 68.26]
1.3 Low dose laquinimod versus placebo	1	31	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete remission: laquinimod versus placebo	1	46	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.70, 3.42]
2.2 Complete remission: high dose laquinimod versus placebo	1	30	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.47, 3.09]

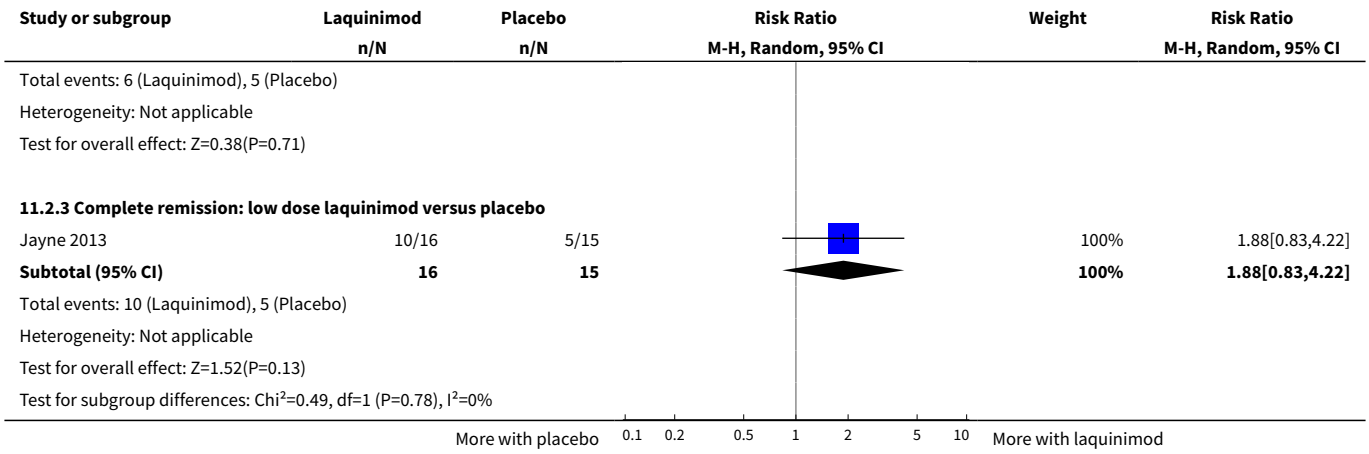
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Complete remission: low dose laquinimod versus placebo	1	31	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.83, 4.22]

Analysis 11.1. Comparison 11 Laquinimod + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 1 Death.



Analysis 11.2. Comparison 11 Laquinimod + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 2 Complete remission.



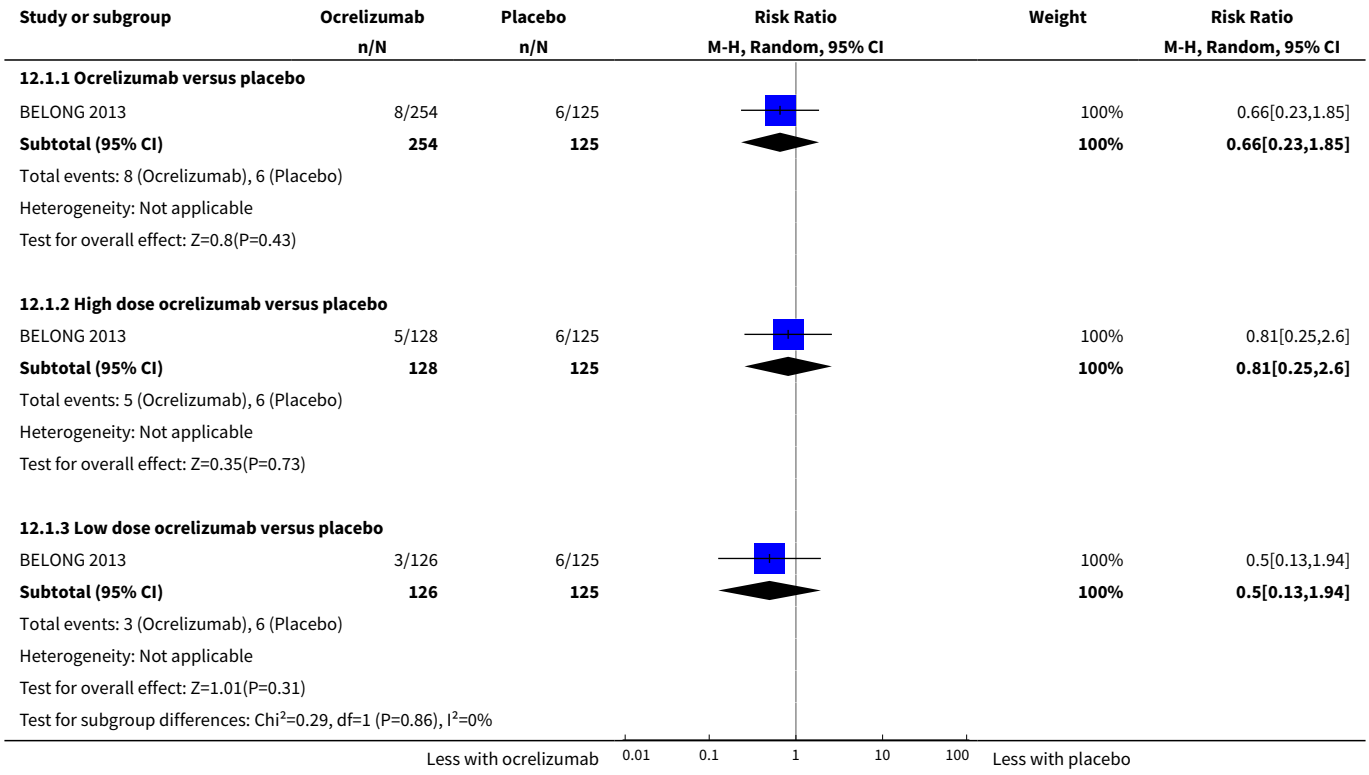


Comparison 12. Ocrelizumab + other immunosuppressive agent (IS) versus placebo + other IS

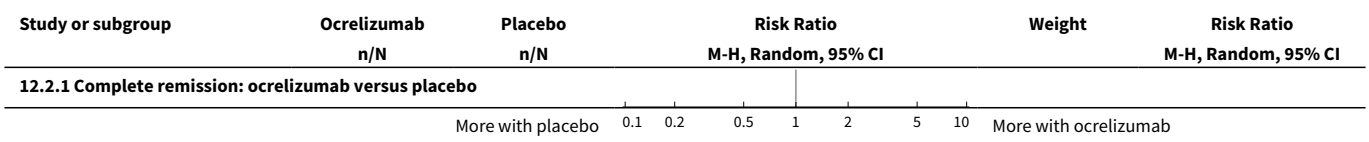
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Ocrelizumab versus placebo	1	379	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.23, 1.85]
1.2 High dose ocrelizumab versus placebo	1	253	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.25, 2.60]
1.3 Low dose ocrelizumab versus placebo	1	251	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.13, 1.94]
2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete remission: ocrelizumab versus placebo	1	223	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.74, 1.56]
2.2 Complete remission: high dose ocrelizumab versus placebo	1	148	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.44]
2.3 Complete remission: low dose ocrelizumab versus placebo	1	150	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.82, 1.85]
2.4 Partial remission: ocrelizumab versus placebo	1	223	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.89, 2.49]
2.5 Partial remission: high dose ocrelizumab versus placebo	1	148	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.03, 3.08]
2.6 Partial remission: low dose ocrelizumab versus placebo	1	150	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.65, 2.20]

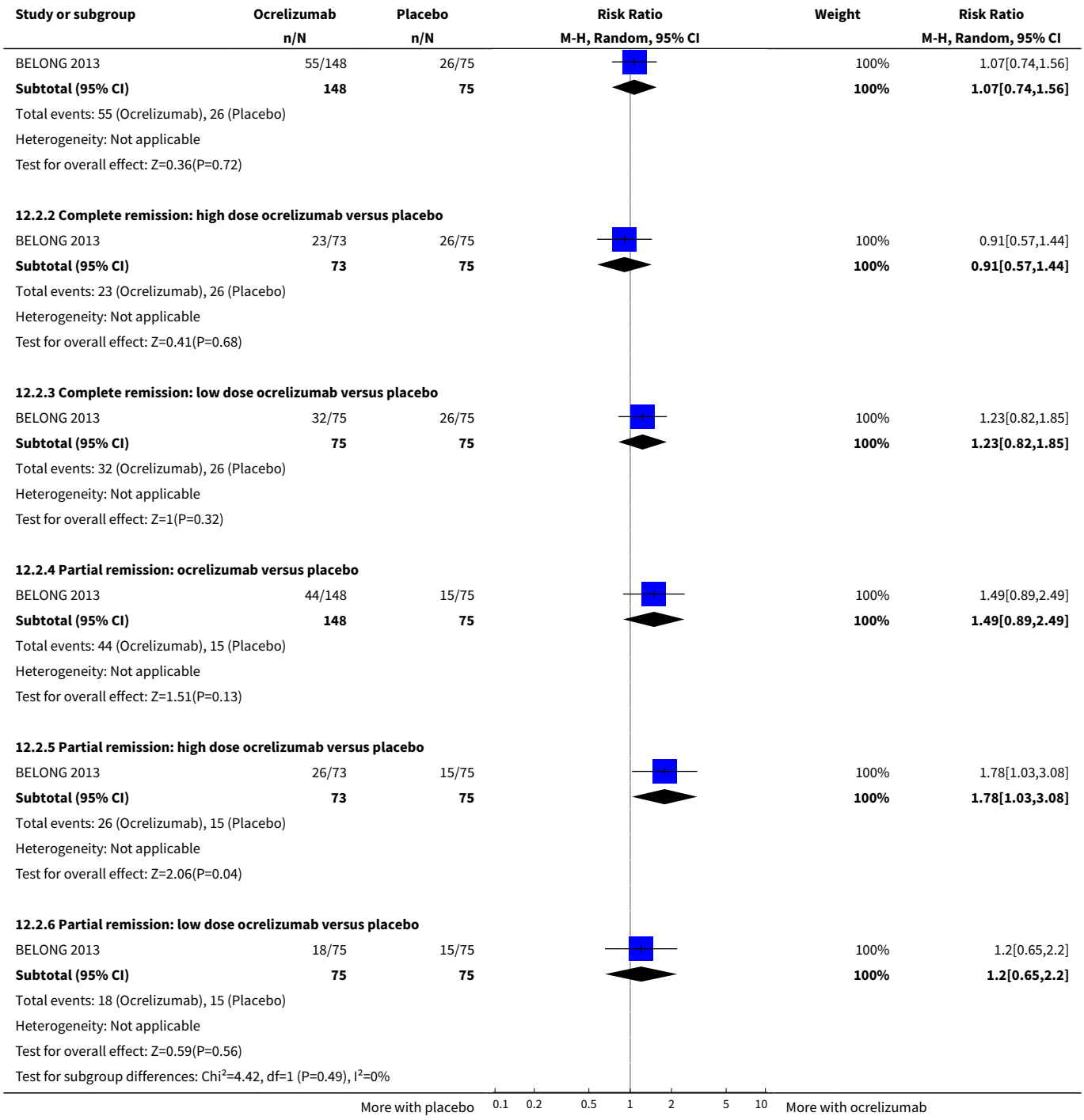
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Major Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Ocrelizumab versus placebo	1	378	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.95, 1.36]
3.2 High dose ocrelizumab versus placebo	1	252	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.85, 1.30]
3.3 Low dose ocrelizumab versus placebo	1	251	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.00, 1.48]

Analysis 12.1. Comparison 12 Ocrelizumab + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 1 Death.

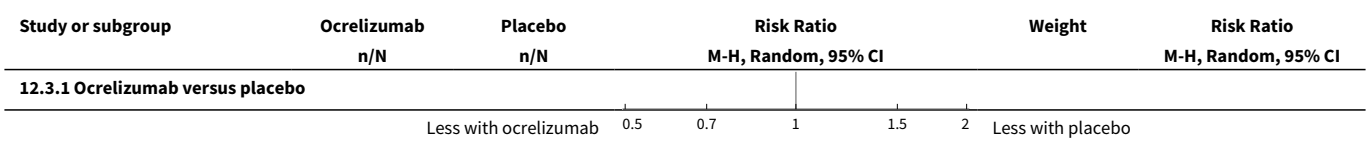


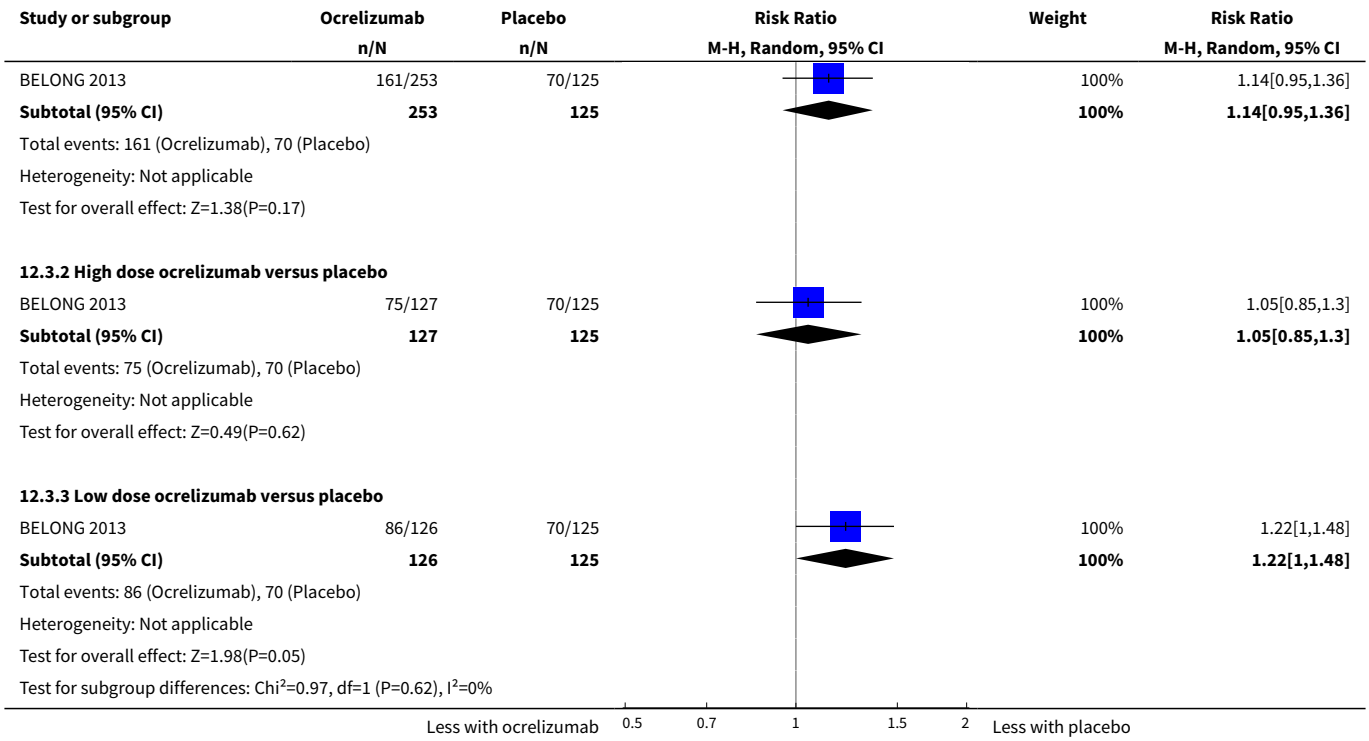
Analysis 12.2. Comparison 12 Ocrelizumab + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 2 Remission.





Analysis 12.3. Comparison 12 Ocrelizumab + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 3 Major Infection.

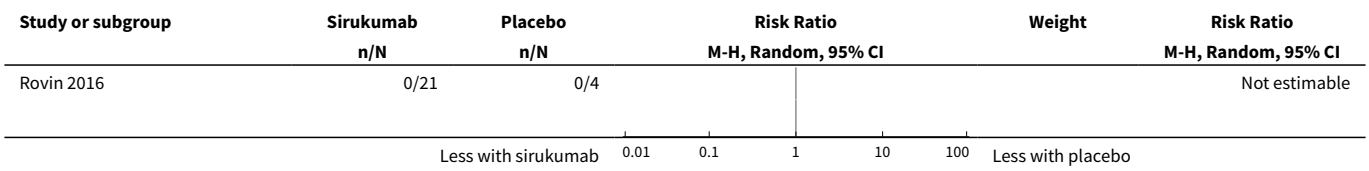


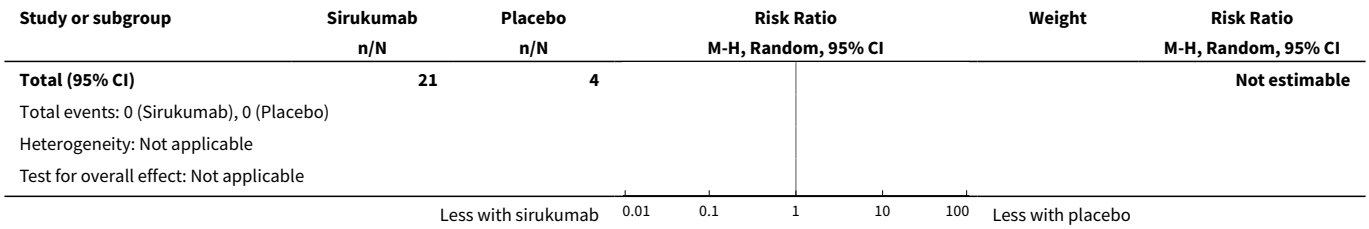


Comparison 13. Sirukumab + other immunosuppressive agent (IS) versus placebo + other IS

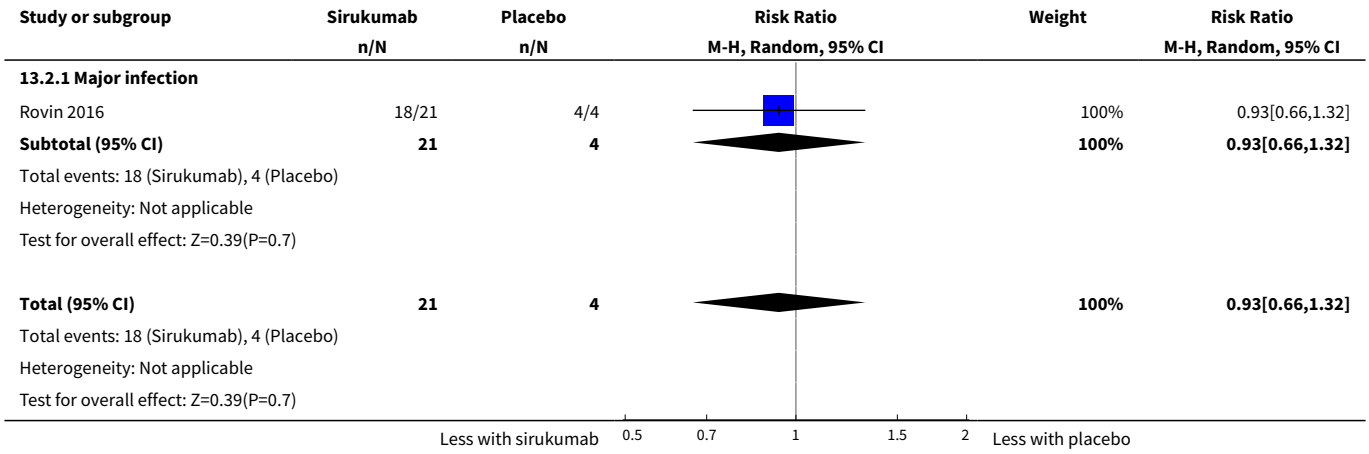
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	25	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Infection	1	25	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.66, 1.32]
2.1 Major infection	1	25	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.66, 1.32]
3 Malignancy	1	25	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Gastrointestinal (GI) adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Diarrhoea	1	25	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.10, 26.15]

Analysis 13.1. Comparison 13 Sirukumab + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 1 Death.

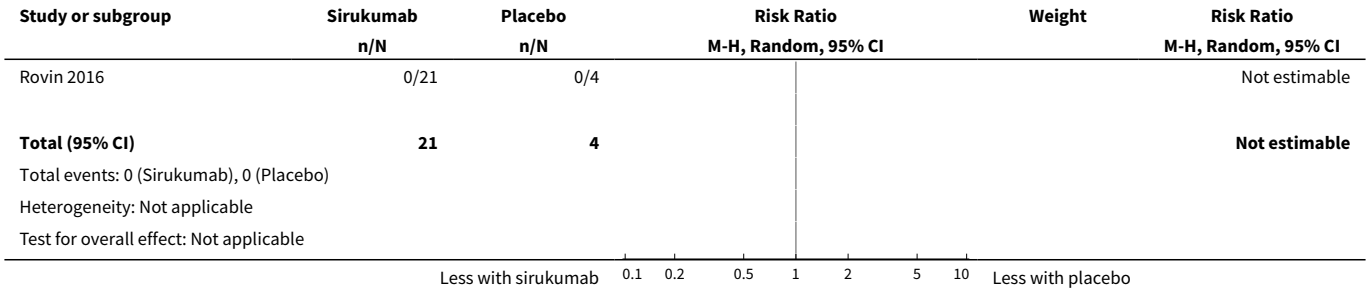




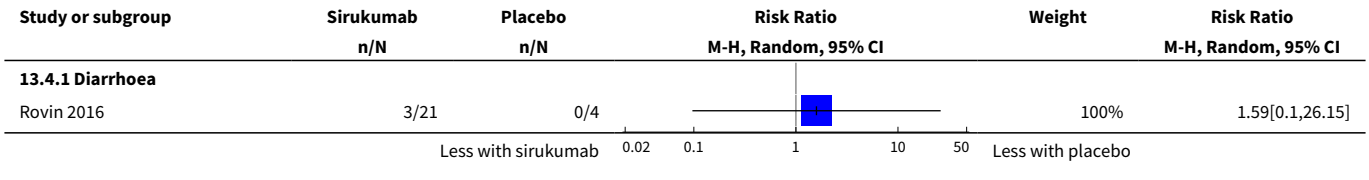
Analysis 13.2. Comparison 13 Sirukumab + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 2 Infection.

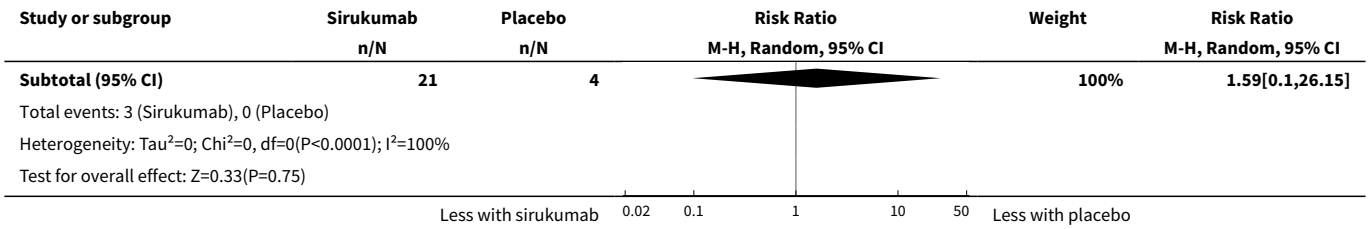


Analysis 13.3. Comparison 13 Sirukumab + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 3 Malignancy.



Analysis 13.4. Comparison 13 Sirukumab + other immunosuppressive agent (IS) versus placebo + other IS, Outcome 4 Gastrointestinal (GI) adverse events.

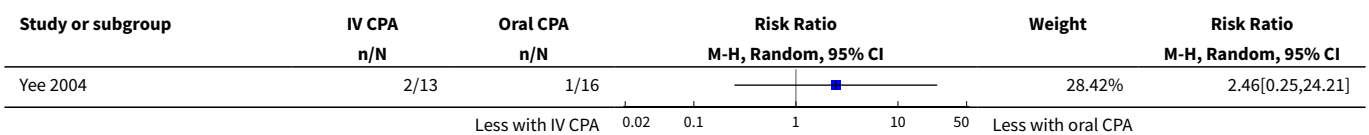


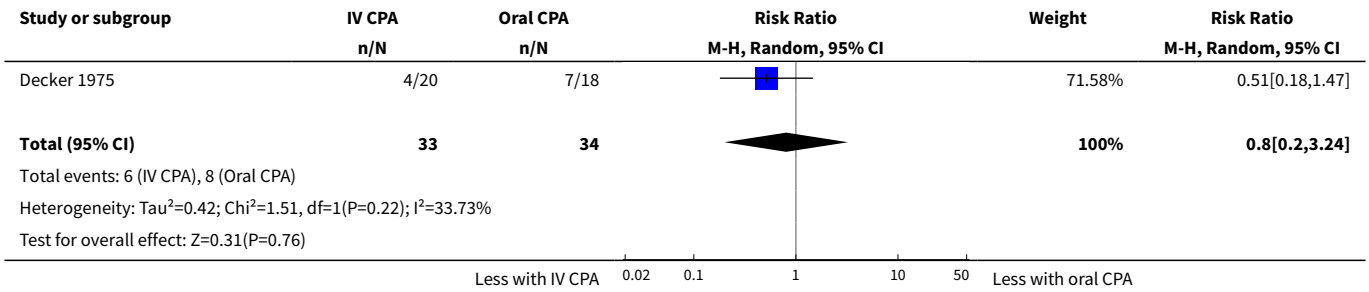


Comparison 14. IV versus oral cyclophosphamide (CPA)

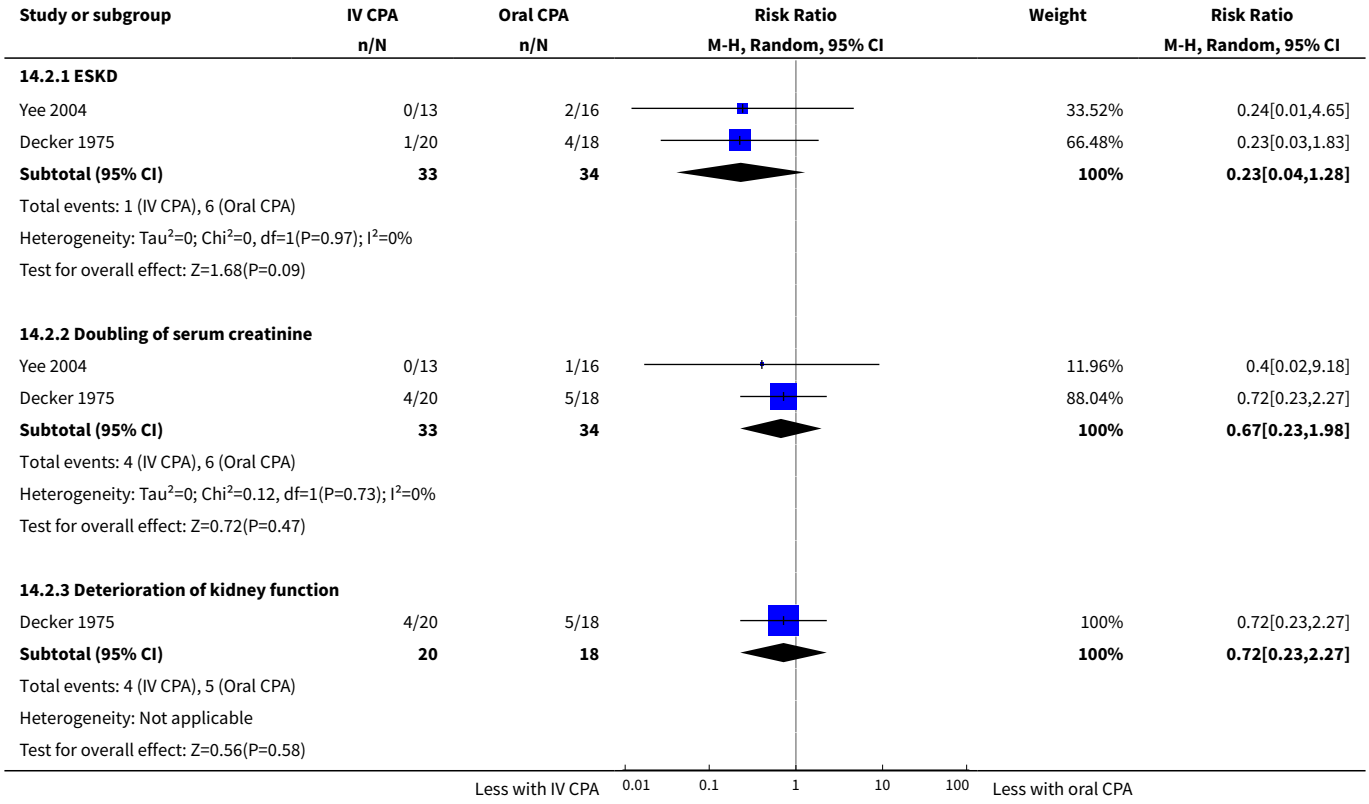
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	67	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.20, 3.24]
2 Adverse renal outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 ESKD	2	67	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.28]
2.2 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	38	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.77, 1.59]
4 Ovarian failure	2	56	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.37, 1.30]
5 Infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Major infection	2	67	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.47, 2.90]
5.2 Herpes zoster virus	1	38	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.28, 2.04]
6 Malignancy	2	67	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.41, 4.96]
7 Bladder toxicity	2	67	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.83]
8 Gastrointestinal (GI) adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 GI upset	1	29	Risk Ratio (M-H, Random, 95% CI)	3.69 [0.43, 31.43]

Analysis 14.1. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 1 Death.

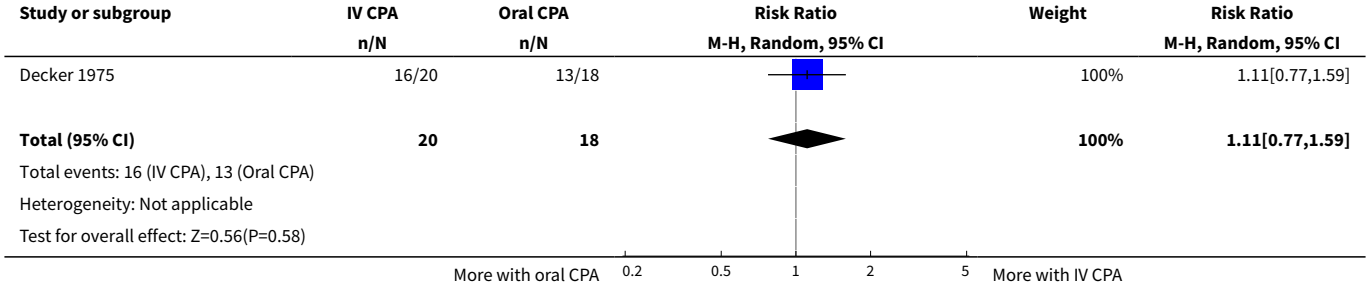




Analysis 14.2. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 2 Adverse renal outcomes.

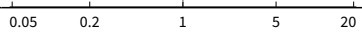


Analysis 14.3. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 3 Stable kidney function.



Analysis 14.4. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 4 Ovarian failure.

Study or subgroup	IV CPA n/N	Oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Decker 1975	8/17	7/10		94.46%	0.67[0.35,1.28]
Yee 2004	1/13	1/16		5.54%	1.23[0.08,17.83]
Total (95% CI)	**30**	**26**		**100%**	**0.7[0.37,1.3]**
Total events: 9 (IV CPA), 8 (Oral CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=1.13(P=0.26)					



Less with IV CPA — Less with oral CPA

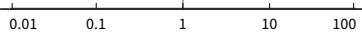
Analysis 14.5. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 5 Infection.

Study or subgroup	IV CPA n/N	Oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
14.5.1 Major infection					
Decker 1975	2/20	3/18		29.91%	0.6[0.11,3.19]
Yee 2004	5/13	4/16		70.09%	1.54[0.52,4.59]
Subtotal (95% CI)	**33**	**34**		**100%**	**1.16[0.47,2.9]**
Total events: 7 (IV CPA), 7 (Oral CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.87, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					
14.5.2 Herpes zoster virus					
Decker 1975	5/20	6/18		100%	0.75[0.28,2.04]
Subtotal (95% CI)	**20**	**18**		**100%**	**0.75[0.28,2.04]**
Total events: 5 (IV CPA), 6 (Oral CPA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.56(P=0.57)					

Less with IV CPA — Less with oral CPA

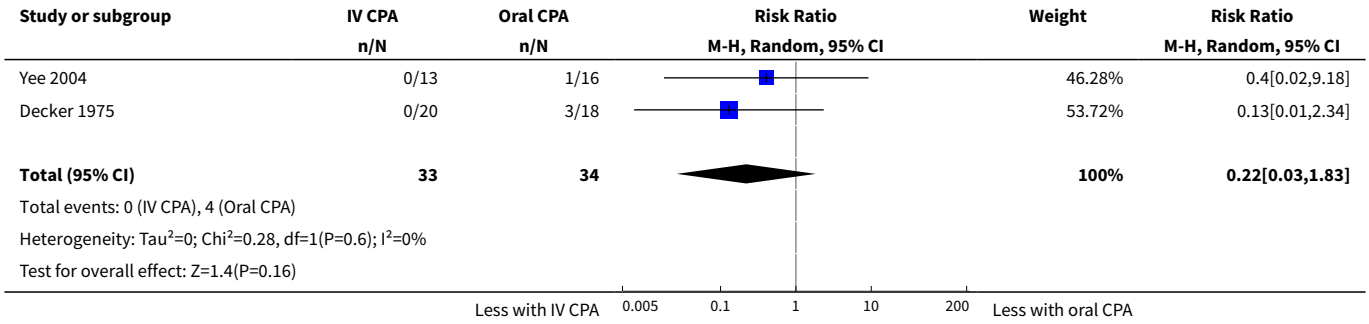
Analysis 14.6. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 6 Malignancy.

Study or subgroup	IV CPA n/N	Oral CPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Yee 2004	1/13	0/16		15.85%	3.64[0.16,82.62]
Decker 1975	4/20	3/18		84.15%	1.2[0.31,4.65]
Total (95% CI)	**33**	**34**		**100%**	**1.43[0.41,4.96]**
Total events: 5 (IV CPA), 3 (Oral CPA)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					

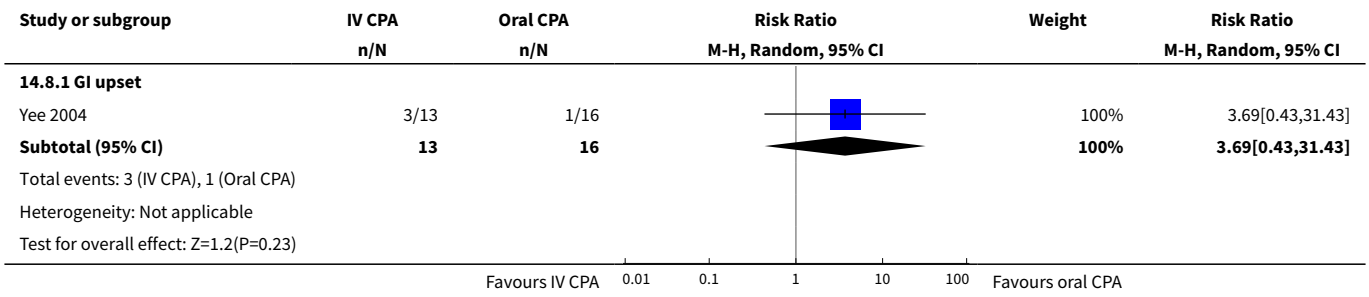


Less with IV CPA — Less with oral CPA

Analysis 14.7. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 7 Bladder toxicity.



Analysis 14.8. Comparison 14 IV versus oral cyclophosphamide (CPA), Outcome 8 Gastrointestinal (GI) adverse events.

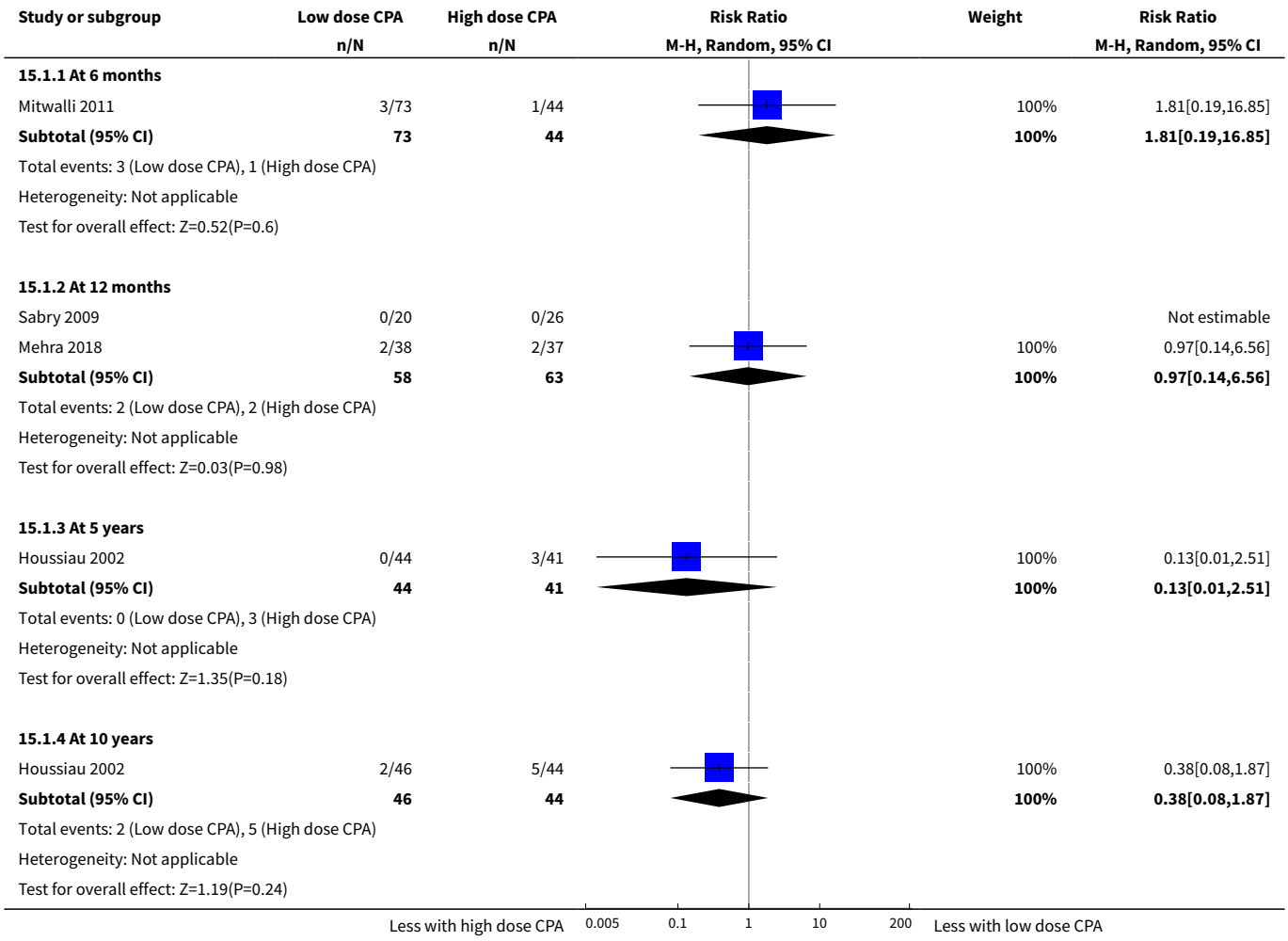


Comparison 15. Low versus high dose cyclophosphamide (CPA)

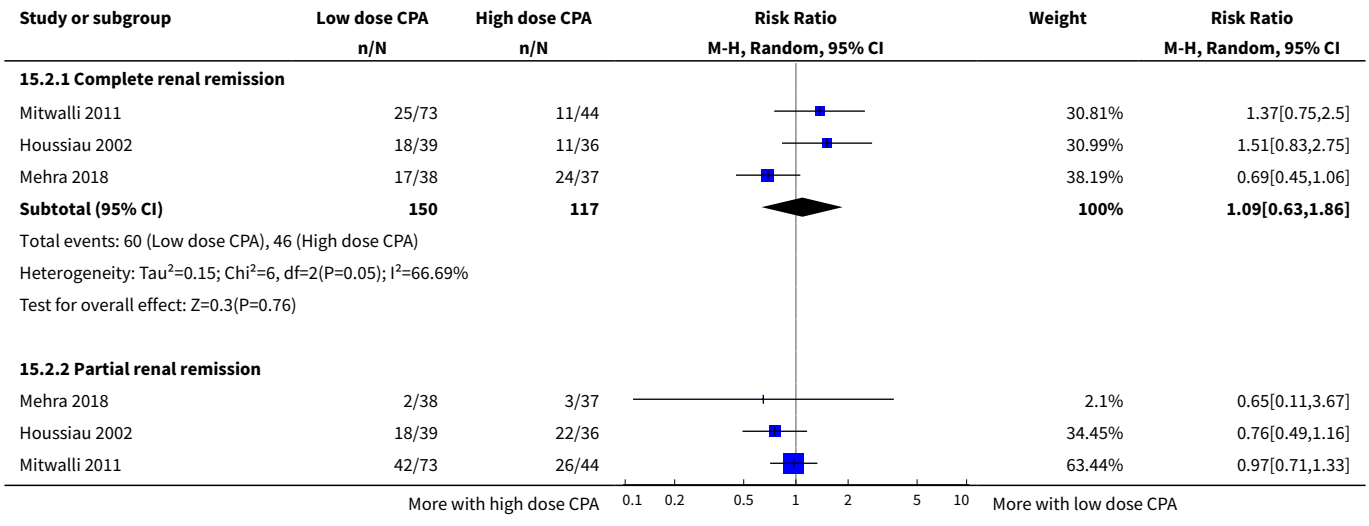
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At 6 months	1	117	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.19, 16.85]
1.2 At 12 months	2	121	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.14, 6.56]
1.3 At 5 years	1	85	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.51]
1.4 At 10 years	1	90	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.87]
2 Remission	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete renal remission	3	267	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.63, 1.86]
2.2 Partial renal remission	3	267	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.14]
3 Adverse renal outcomes	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

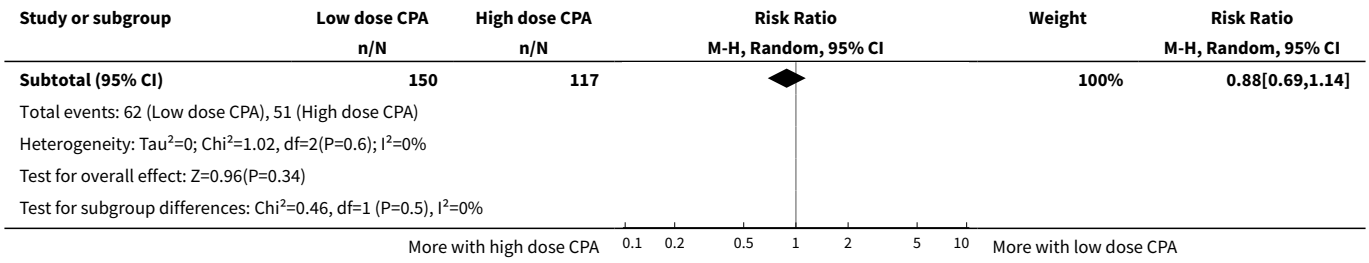
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 ESKD	2	135	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.05, 5.20]
3.2 ESKD at 5 years	1	85	Risk Ratio (M-H, Random, 95% CI)	2.80 [0.30, 25.81]
3.3 ESKD at 10 years	1	90	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.37, 9.92]
3.4 Renal relapse	3	211	Risk Ratio (M-H, Random, 95% CI)	2.75 [0.47, 15.98]
3.5 Doubling of serum creatinine	2	135	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.02]
3.6 Doubling of serum creatinine at 5 years	1	85	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 1.04]
3.7 Doubling of serum creatinine at 10 years	1	90	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.26, 2.42]
4 Stable kidney function	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 At 3 years	1	89	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.50, 1.03]
4.2 At 5 years	1	85	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.20]
5 Ovarian failure	4	299	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.70, 4.31]
6 Infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Major infection	4	327	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.83, 2.49]
6.2 Herpes zoster virus	3	281	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.41, 6.05]
7 Malignancy	2	206	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.09, 23.31]
8 Leucopenia	3	281	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.13, 5.15]
9 Bone toxicity	2	164	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.48, 18.02]
10 Alopecia	1	75	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.25]
11 Gastrointestinal (GI) adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 GI disturbance	1	75	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.94]
12 Daily proteinuria	3	242	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.65, 0.46]
13 Creatinine clearance	1	117	Mean Difference (IV, Random, 95% CI)	-12.60 [-23.63, -1.57]
14 Serum creatinine	3	247	Mean Difference (IV, Random, 95% CI)	2.85 [-7.61, 13.31]
15 Disease activity (SLEDAI)	1	75	Mean Difference (IV, Random, 95% CI)	-1.50 [-3.04, 0.04]

Analysis 15.1. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 1 Death.

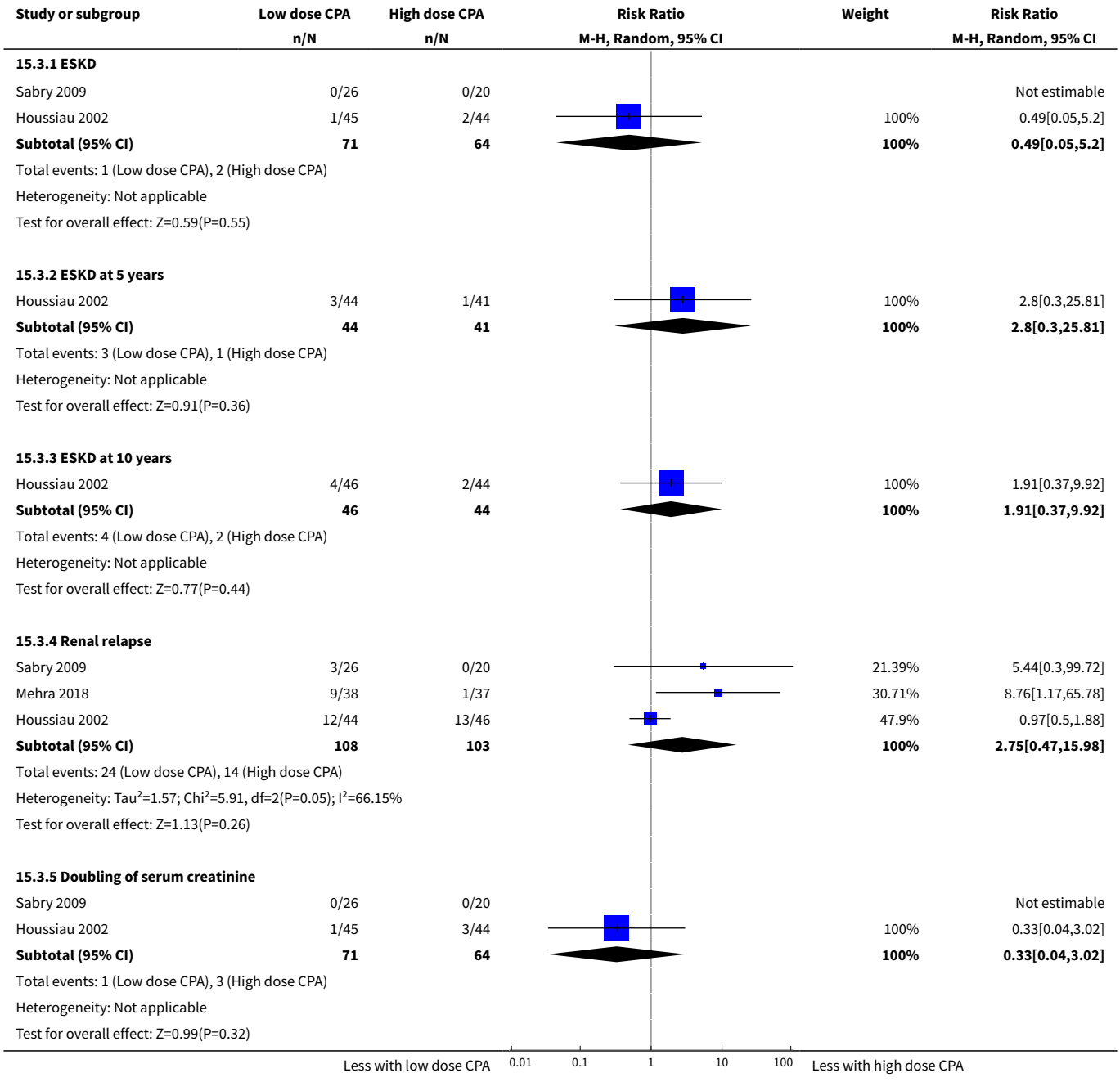


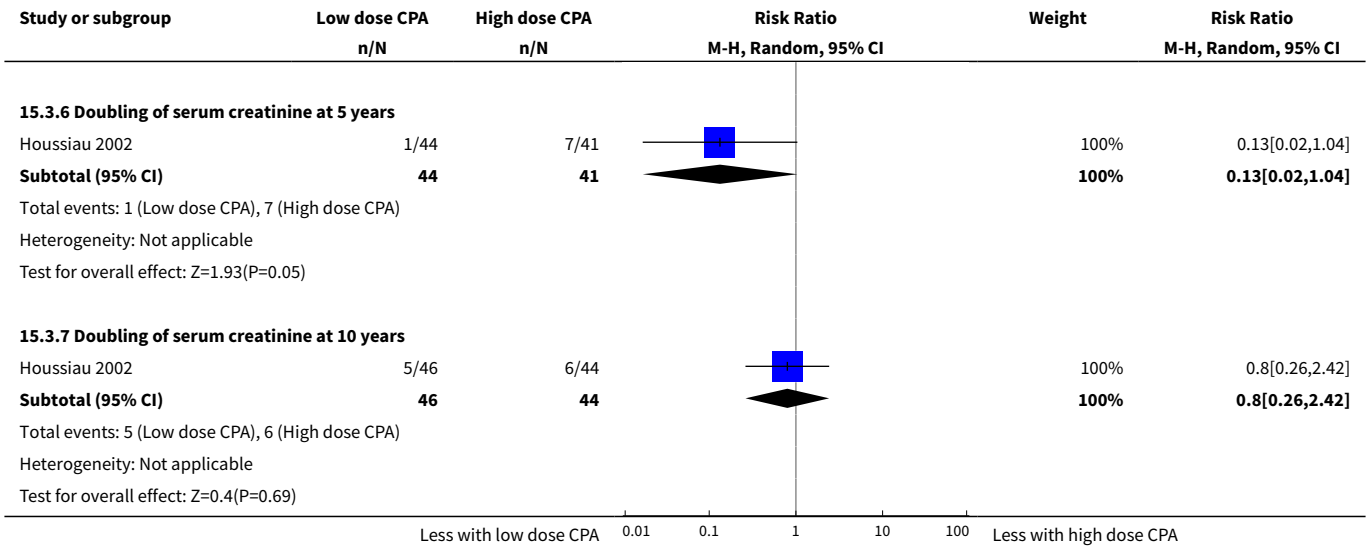
Analysis 15.2. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 2 Remission.



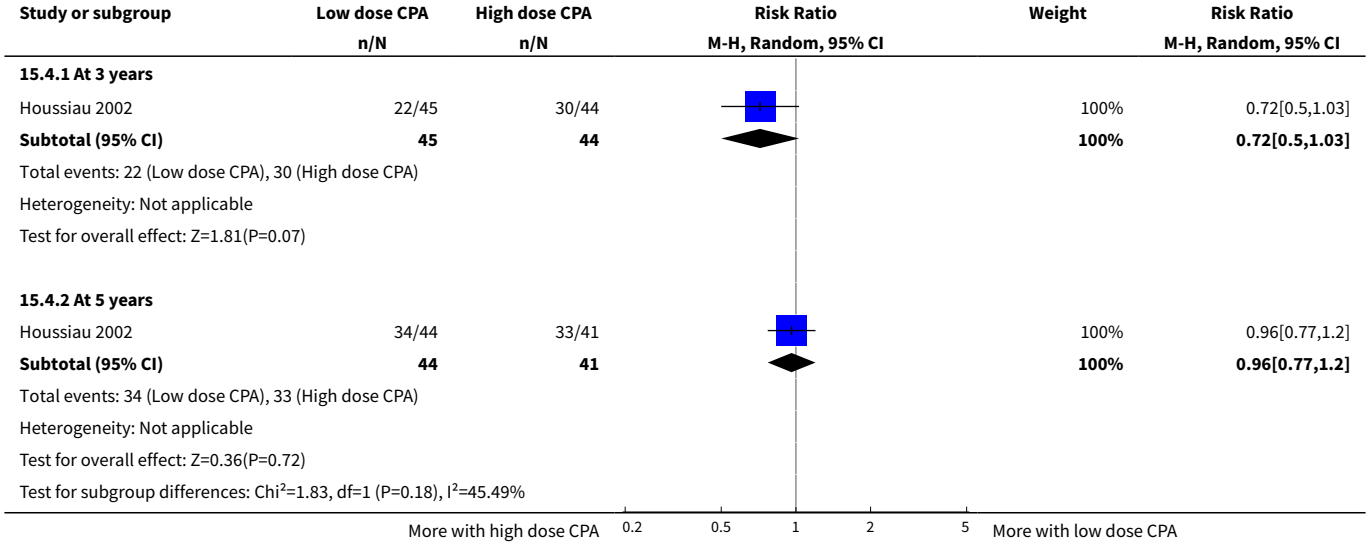


Analysis 15.3. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 3 Adverse renal outcomes.

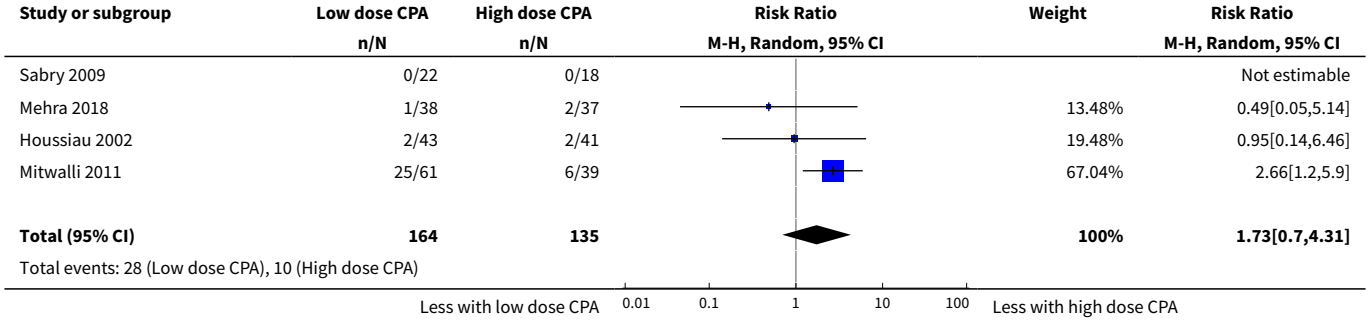


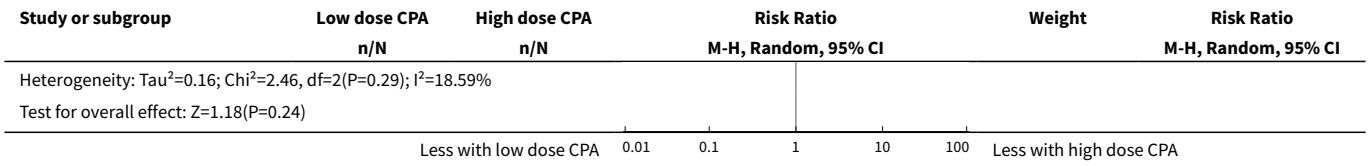


Analysis 15.4. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 4 Stable kidney function.

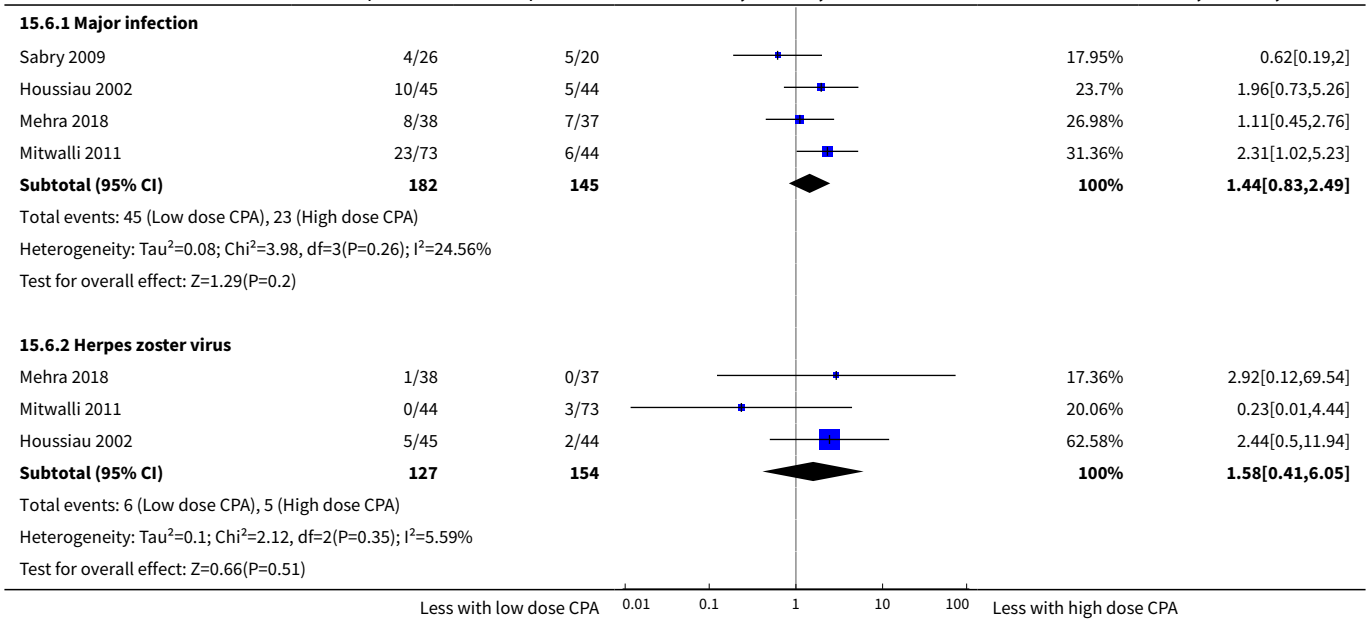


Analysis 15.5. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 5 Ovarian failure.

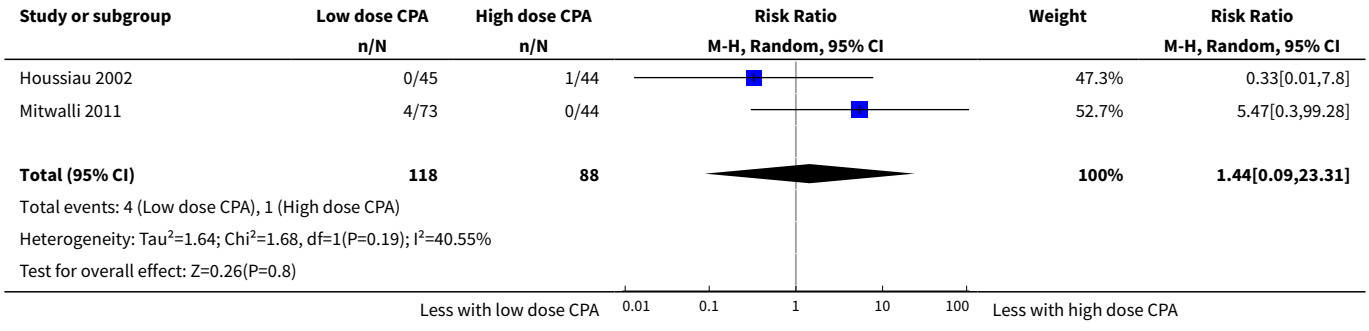




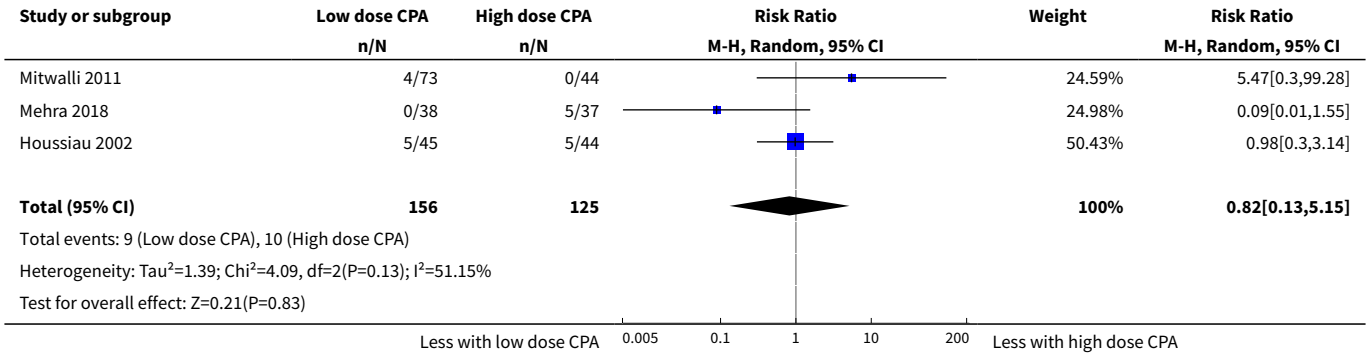
Analysis 15.6. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 6 Infection.



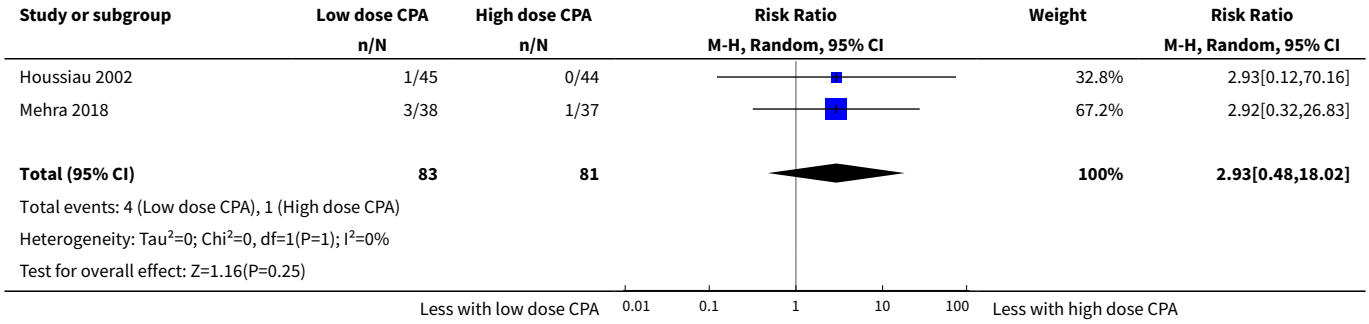
Analysis 15.7. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 7 Malignancy.



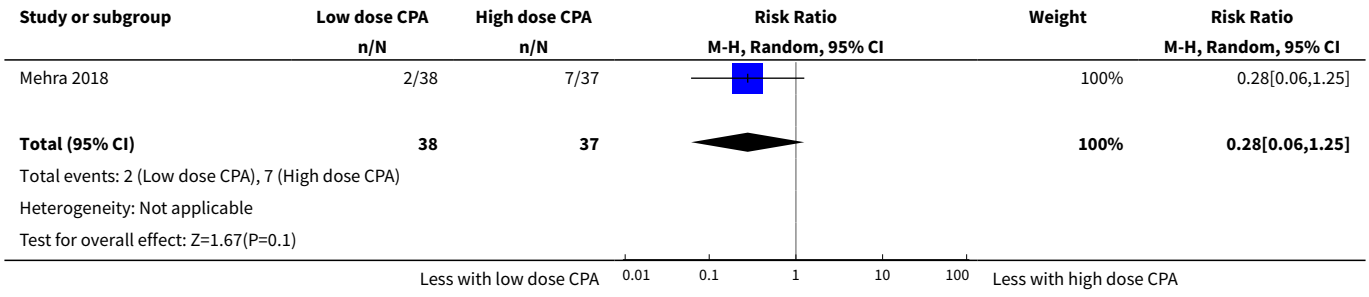
Analysis 15.8. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 8 Leucopenia.



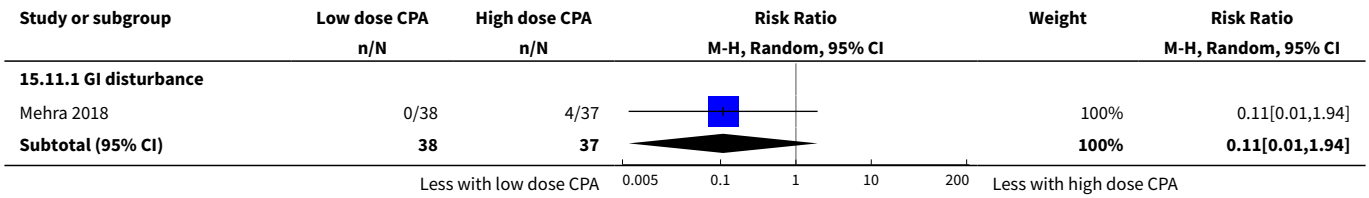
Analysis 15.9. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 9 Bone toxicity.

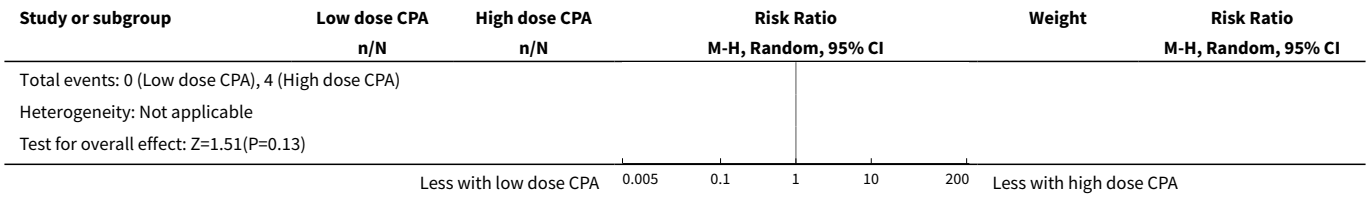


Analysis 15.10. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 10 Alopecia.

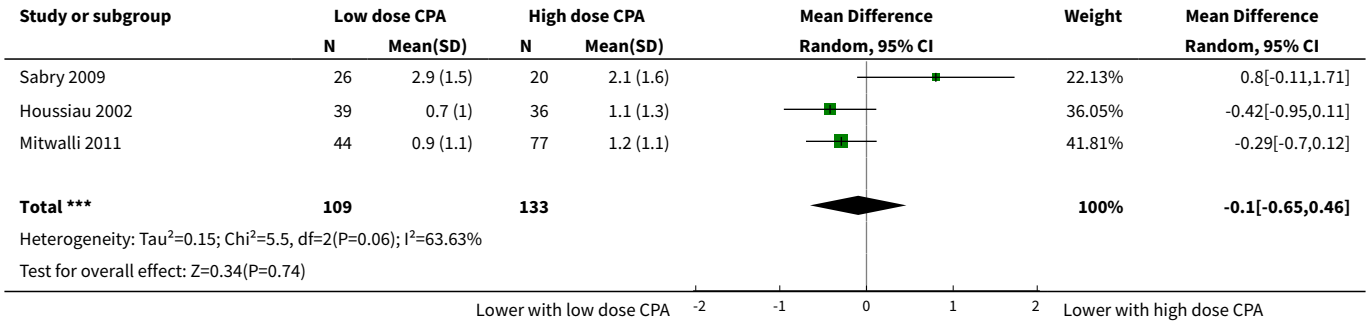


Analysis 15.11. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 11 Gastrointestinal (GI) adverse events.

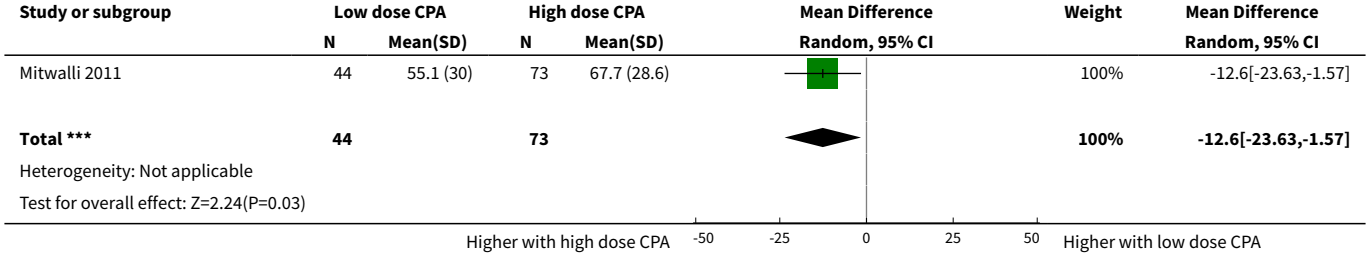




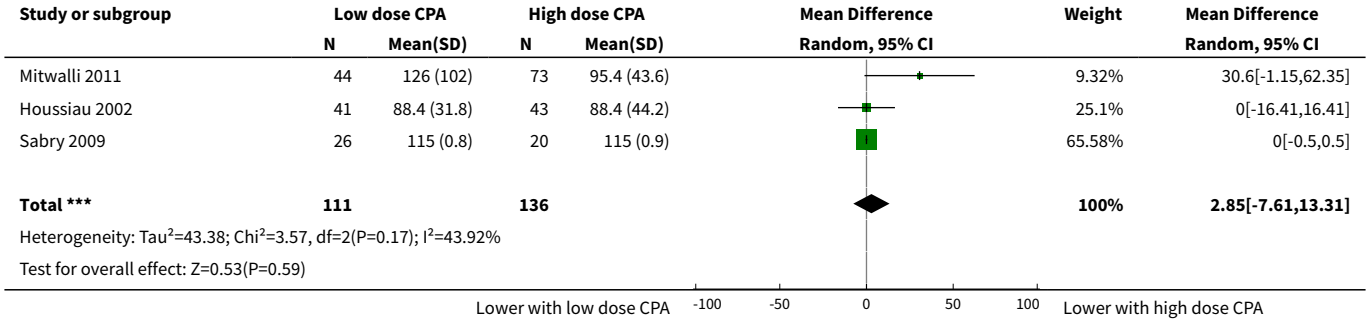
Analysis 15.12. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 12 Daily proteinuria.



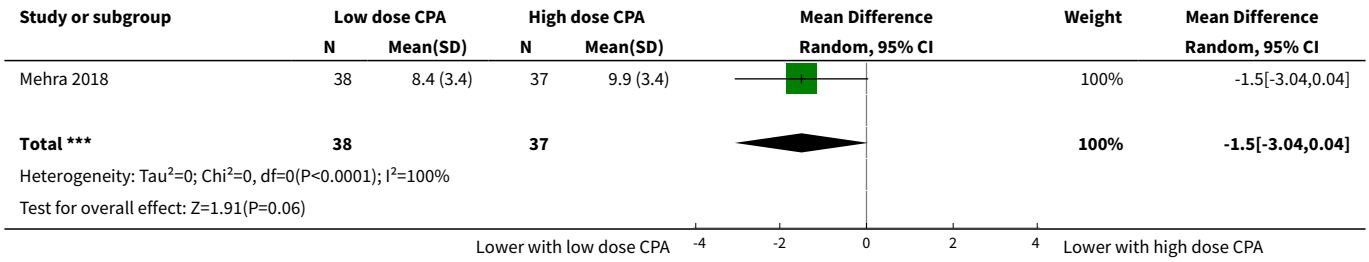
Analysis 15.13. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 13 Creatinine clearance.



Analysis 15.14. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 14 Serum creatinine.



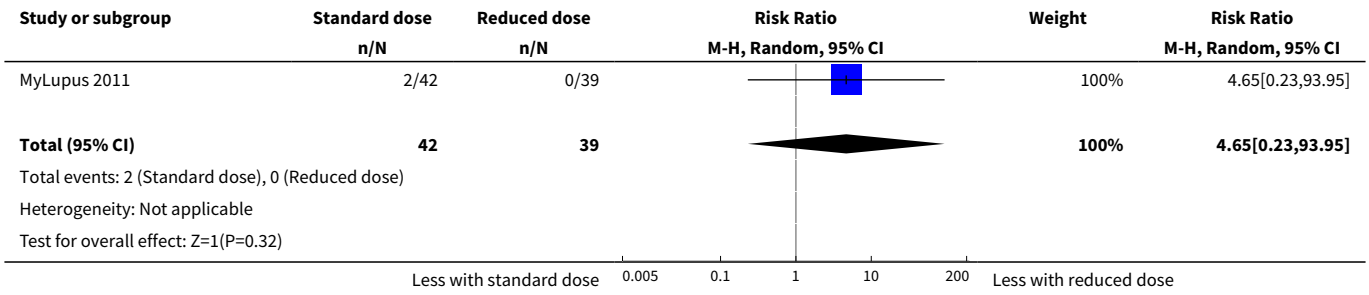
Analysis 15.15. Comparison 15 Low versus high dose cyclophosphamide (CPA), Outcome 15 Disease activity (SLEDAI).



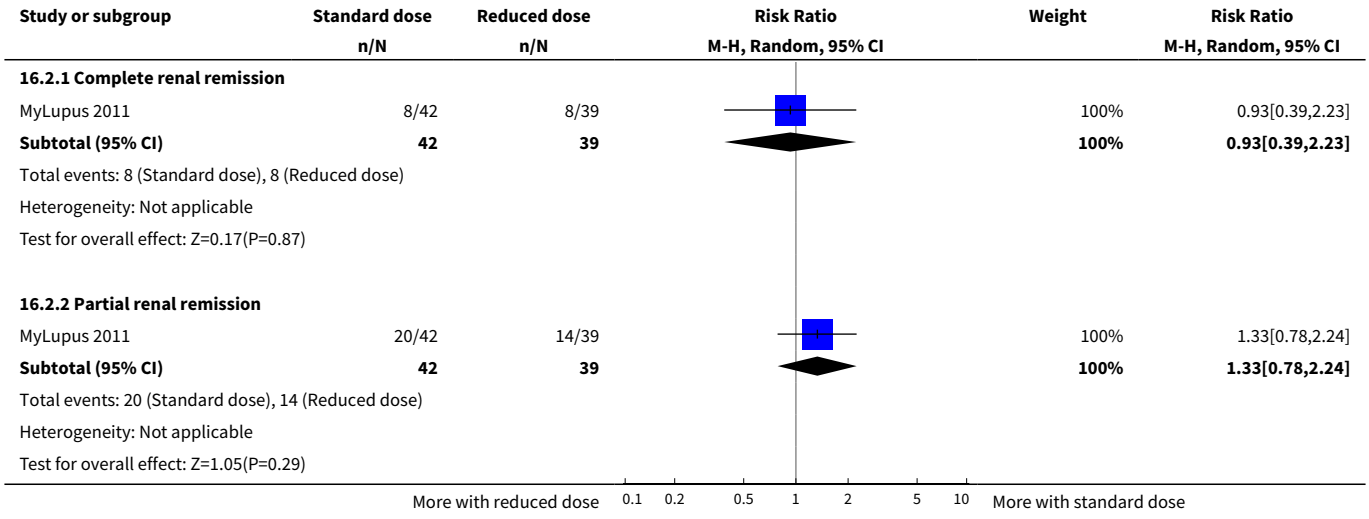
Comparison 16. Standard versus reduced dose oral corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	81	Risk Ratio (M-H, Random, 95% CI)	4.65 [0.23, 93.95]
2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Complete renal remission	1	81	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.39, 2.23]
2.2 Partial renal remission	1	81	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.78, 2.24]
3 Relapse	1	50	Risk Ratio (M-H, Random, 95% CI)	2.38 [0.10, 55.72]
4 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Major infection	1	81	Risk Ratio (M-H, Random, 95% CI)	4.64 [0.57, 38.00]
4.2 Herpes zoster virus	1	81	Risk Ratio (M-H, Random, 95% CI)	13.95 [0.82, 236.48]
5 Gastrointestinal (GI) adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Diarrhoea	1	81	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.51, 2.64]
5.2 Vomiting	1	81	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.25, 3.46]
5.3 Nausea	1	81	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.30, 25.67]
6 Creatinine clearance	1	74	Mean Difference (IV, Random, 95% CI)	-5.80 [-21.08, 9.48]
7 Serum creatinine	1	81	Mean Difference (IV, Random, 95% CI)	-2.40 [-15.98, 11.18]

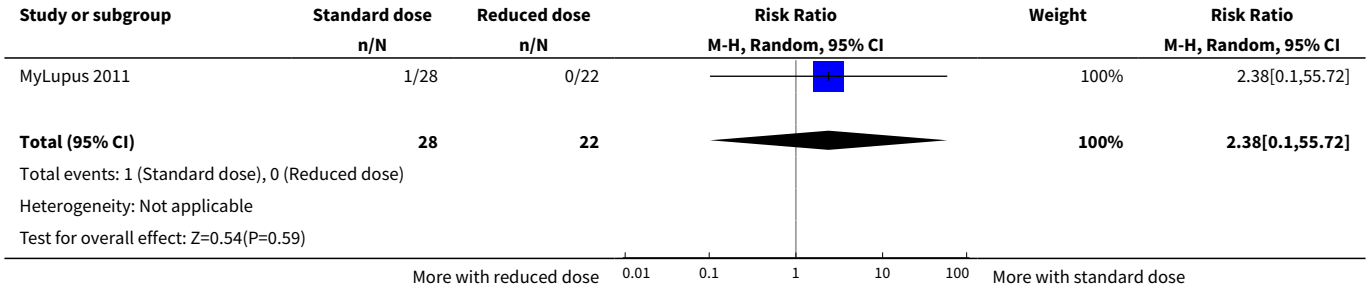
Analysis 16.1. Comparison 16 Standard versus reduced dose oral corticosteroids, Outcome 1 Death.



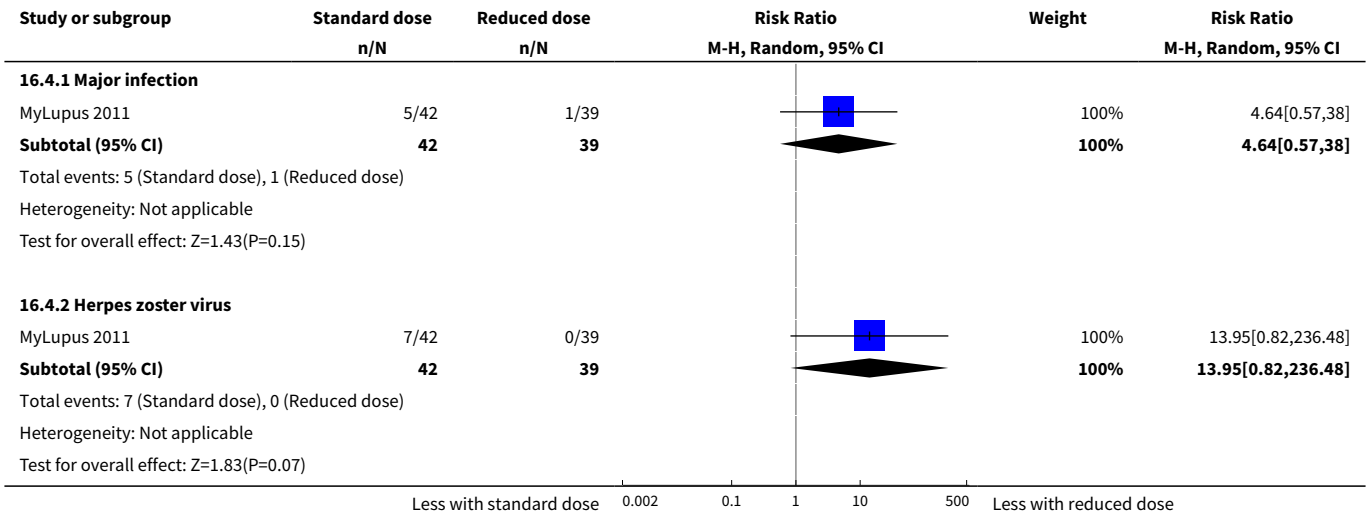
Analysis 16.2. Comparison 16 Standard versus reduced dose oral corticosteroids, Outcome 2 Remission.



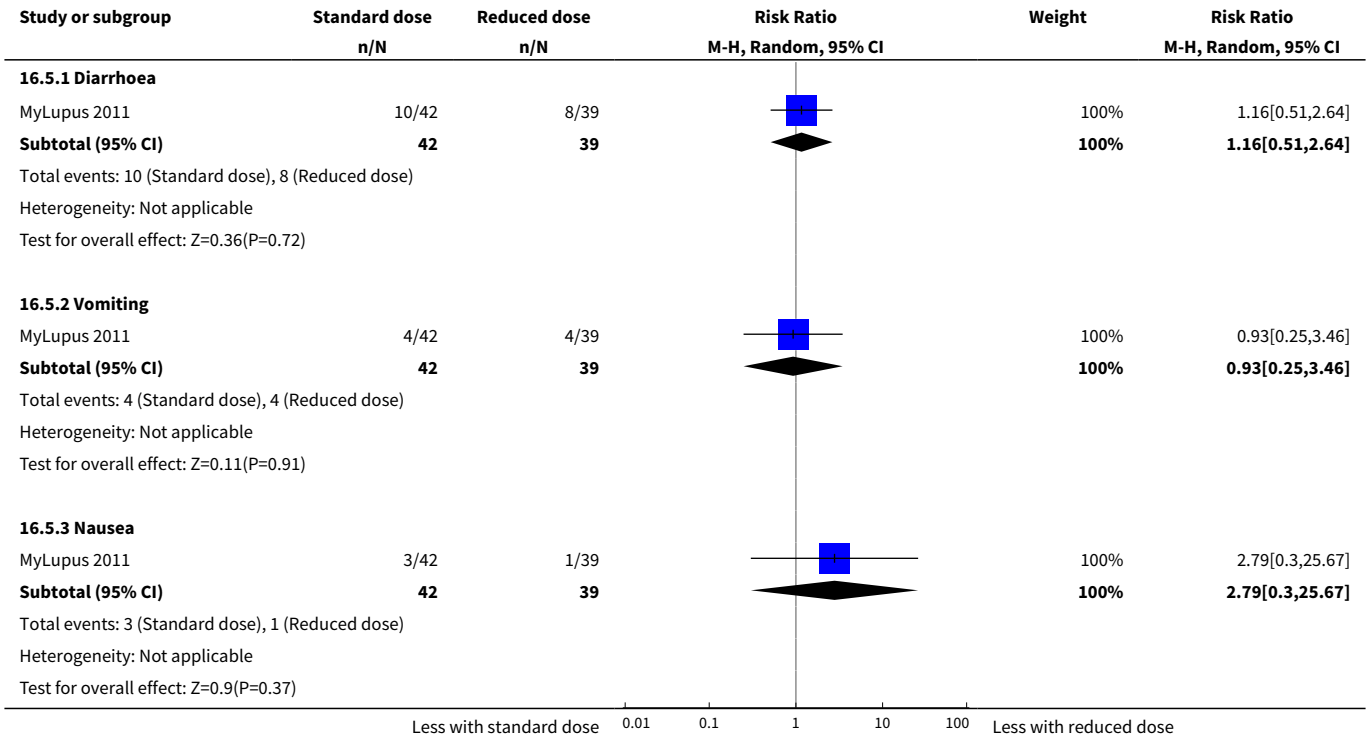
Analysis 16.3. Comparison 16 Standard versus reduced dose oral corticosteroids, Outcome 3 Relapse.



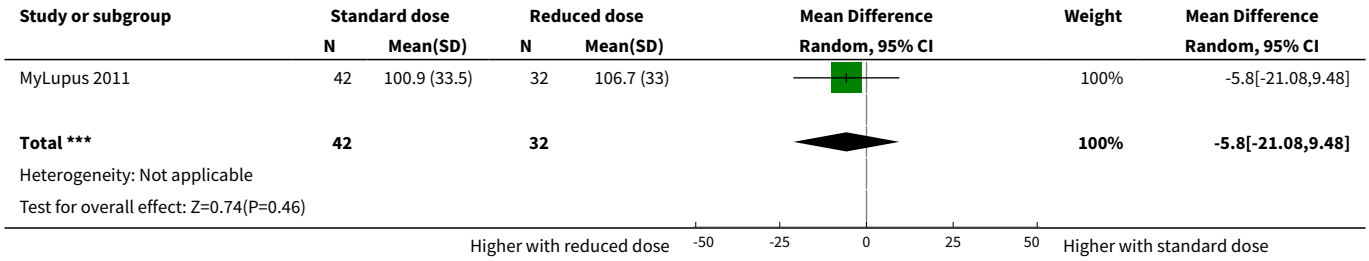
Analysis 16.4. Comparison 16 Standard versus reduced dose oral corticosteroids, Outcome 4 Infection.



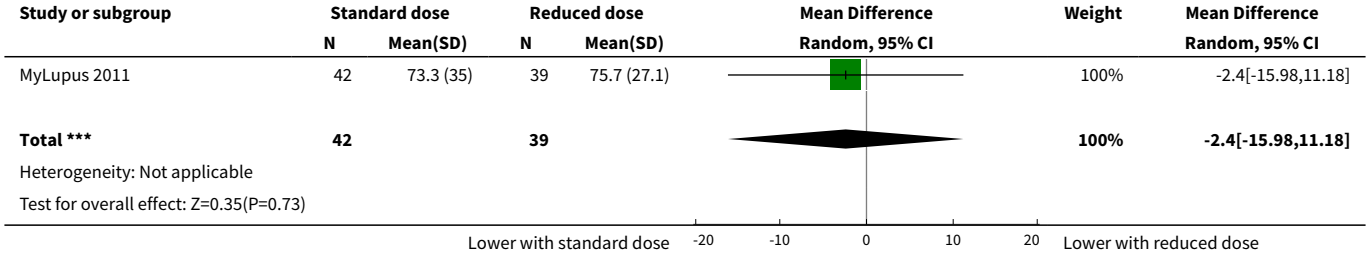
Analysis 16.5. Comparison 16 Standard versus reduced dose oral corticosteroids, Outcome 5 Gastrointestinal (GI) adverse events.



Analysis 16.6. Comparison 16 Standard versus reduced dose oral corticosteroids, Outcome 6 Creatinine clearance.



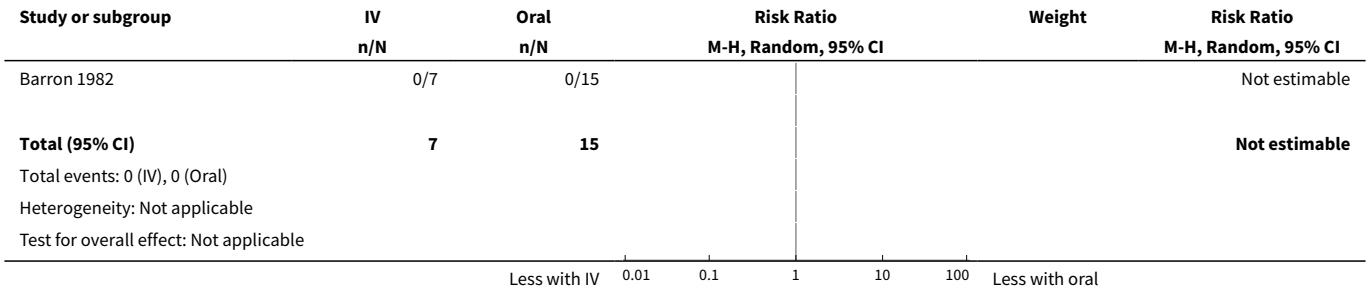
Analysis 16.7. Comparison 16 Standard versus reduced dose oral corticosteroids, Outcome 7 Serum creatinine.



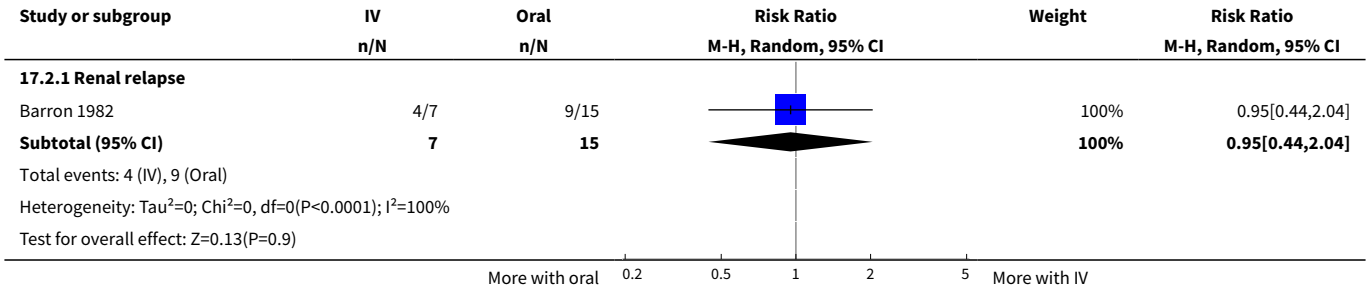
Comparison 17. IV versus oral corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	22	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Renal relapse	1	22	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.44, 2.04]

Analysis 17.1. Comparison 17 IV versus oral corticosteroids, Outcome 1 Death.



Analysis 17.2. Comparison 17 IV versus oral corticosteroids, Outcome 2 Adverse renal outcomes.



Comparison 18. Cyclophosphamide (CPA) + corticosteroids versus corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	5	226	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.53, 1.82]
2 Complete remission of proteinuria	1	13	Risk Ratio (M-H, Random, 95% CI)	2.63 [0.13, 54.64]
3 Adverse renal outcomes	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD	5	278	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.39, 1.03]
3.2 Renal relapse	2	84	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.08, 0.62]
3.3 Doubling serum creatinine	4	228	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.88]
4 Deterioration of kidney function	5	179	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.52, 1.18]
5 Stable kidney function	5	278	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.00, 1.45]
6 Ovarian failure	3	147	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.10, 4.34]
7 Infection	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Major infection	6	291	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.50, 1.51]
7.2 Herpes zoster virus	3	199	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.63, 4.99]
8 Malignancy	2	117	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.07, 9.90]
9 Bone toxicity	3	197	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.40, 1.75]
10 Bladder toxicity	2	65	Risk Ratio (M-H, Random, 95% CI)	2.66 [0.33, 21.68]
11 Daily proteinuria	3	92	Mean Difference (IV, Random, 95% CI)	0.15 [-0.23, 0.54]
12 Serum creatinine	1	29	Mean Difference (IV, Random, 95% CI)	-52.0 [-111.39, 7.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Creatinine clearance	2	63	Mean Difference (IV, Random, 95% CI)	12.23 [-0.13, 24.58]

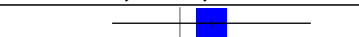
Analysis 18.1. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 1 Death.

Study or subgroup	CPA+steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
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 1994a	2/14	3/15		13.35%	0.71[0.14,3.66]
Donadio 1976	5/24	5/26		26.74%	1.08[0.36,3.28]
Decker 1975	11/38	6/14		46.74%	0.68[0.31,1.48]
Total (95% CI)	**138**	**88**		**100%**	**0.98[0.53,1.82]**
Total events: 29 (CPA+steroid), 15 (Steroid)					
Heterogeneity: Tau^2=0.05; Chi^2=4.43, df=4(P=0.35); I^2=9.69%					
Test for overall effect: Z=0.07(P=0.94)					

Less with CPA+steroid — Less with steroid

Analysis 18.2. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 2 Complete remission of proteinuria.

Study or subgroup	CPA+steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Steinberg 1971	1/7	0/6		100%	2.63[0.13,54.64]
Total (95% CI)	**7**	**6**		**100%**	**2.63[0.13,54.64]**
Total events: 1 (CPA+steroid), 0 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.53)					

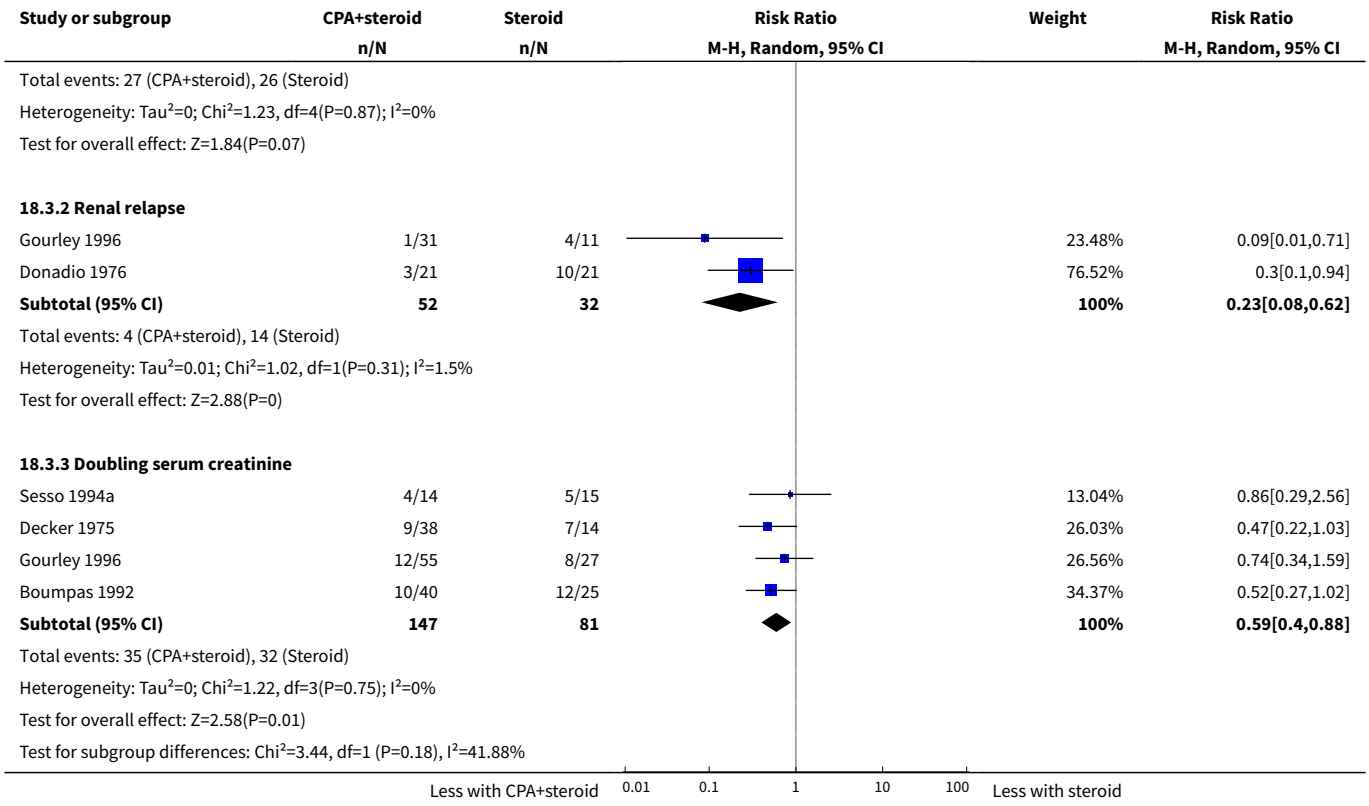


More with steroid — More with CPA+steroid

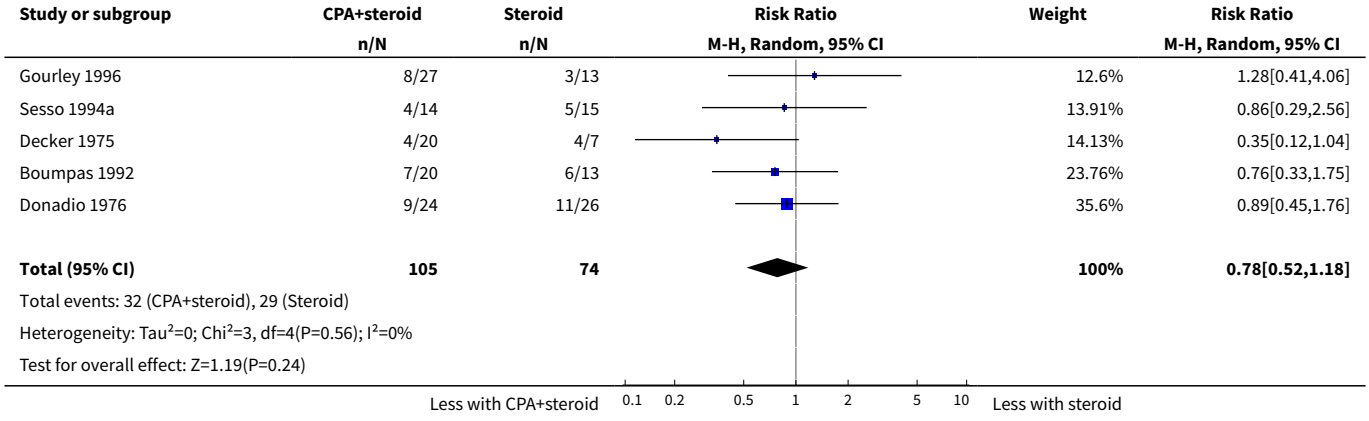
Analysis 18.3. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 3 Adverse renal outcomes.

Study or subgroup	CPA+steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
18.3.1 ESKD					
Sesso 1994a	2/14	3/15		8.82%	0.71[0.14,3.66]
Donadio 1976	4/24	6/26		18.23%	0.72[0.23,2.25]
Decker 1975	5/38	5/14		20.3%	0.37[0.13,1.08]
Boumpas 1992	7/40	6/25		25.09%	0.73[0.28,1.92]
Gourley 1996	9/55	6/27		27.56%	0.74[0.29,1.86]
Subtotal (95% CI)	**171**	**107**		**100%**	**0.63[0.39,1.03]**

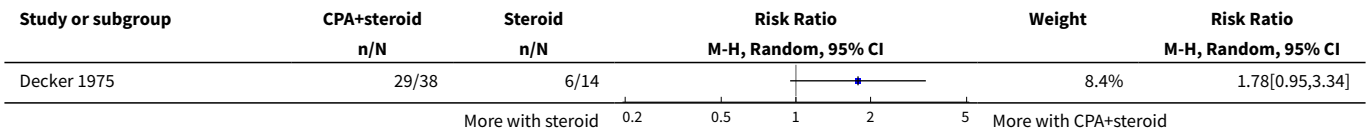
Less with CPA+steroid — Less with steroid

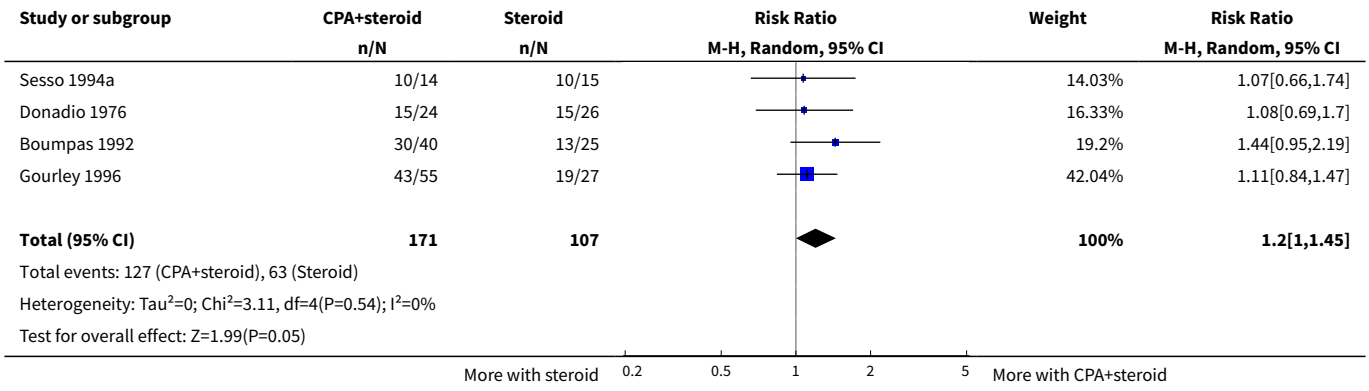


Analysis 18.4. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 4 Deterioration of kidney function.

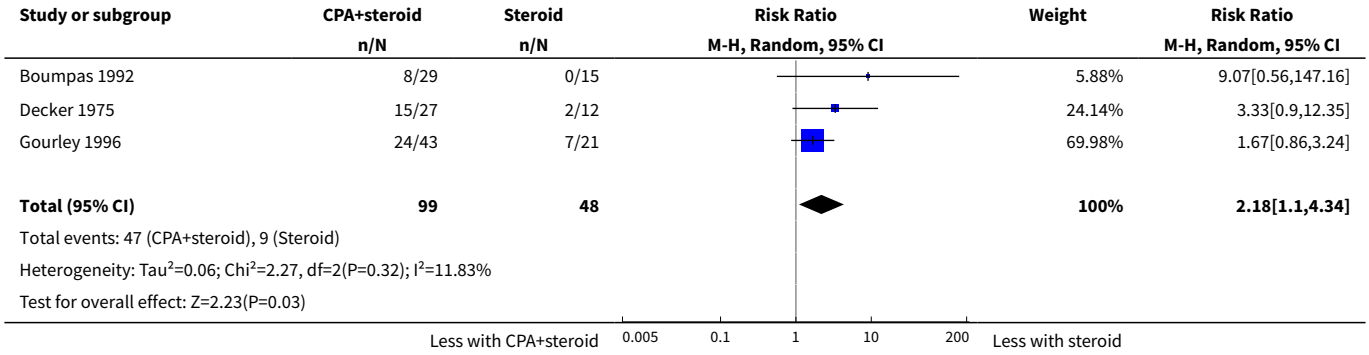


Analysis 18.5. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 5 Stable kidney function.

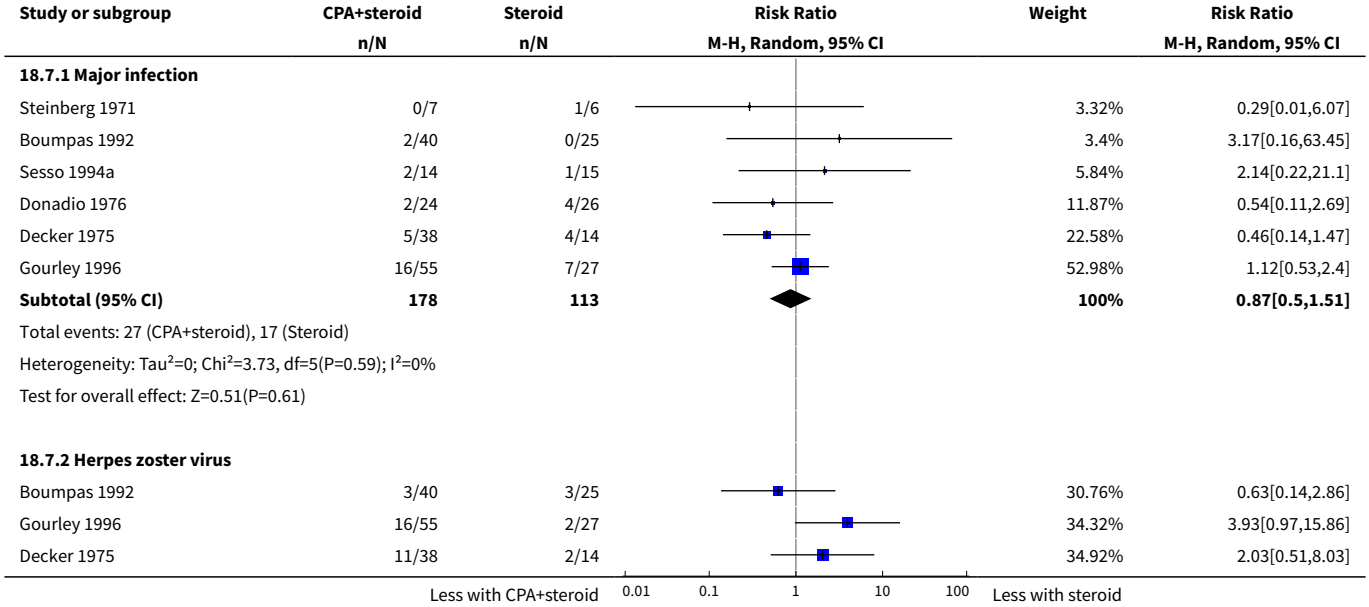


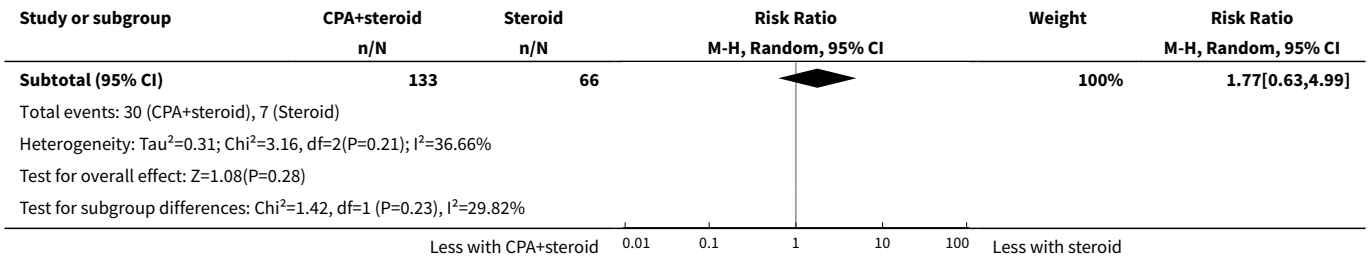


Analysis 18.6. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 6 Ovarian failure.

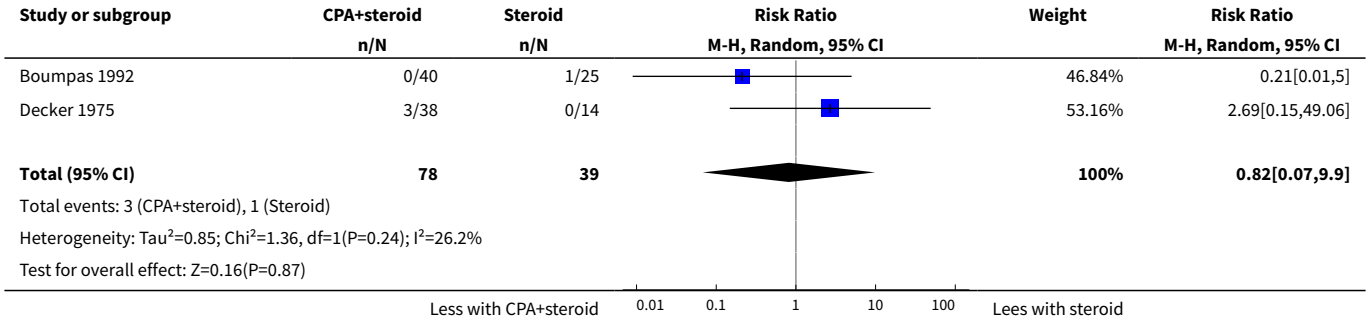


Analysis 18.7. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 7 Infection.

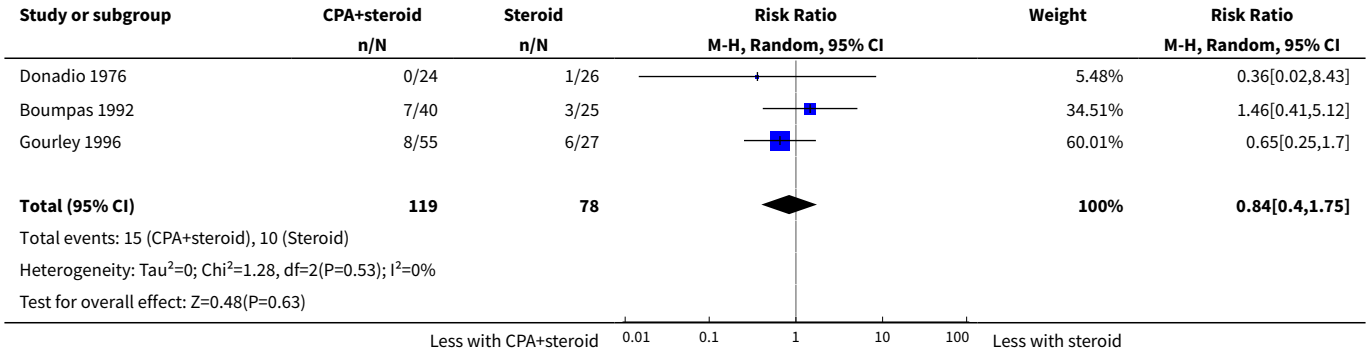




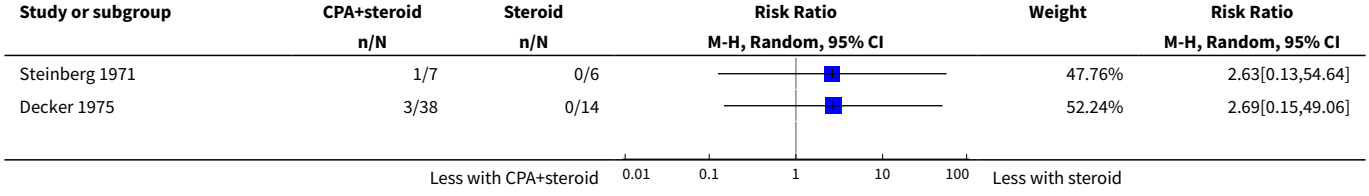
Analysis 18.8. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 8 Malignancy.

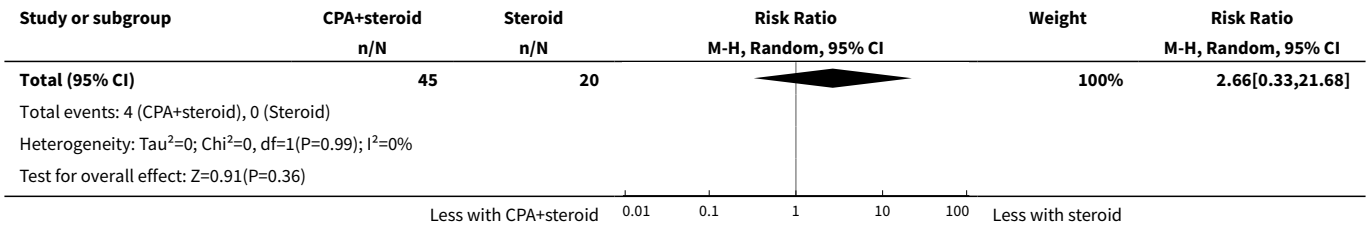


Analysis 18.9. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 9 Bone toxicity.

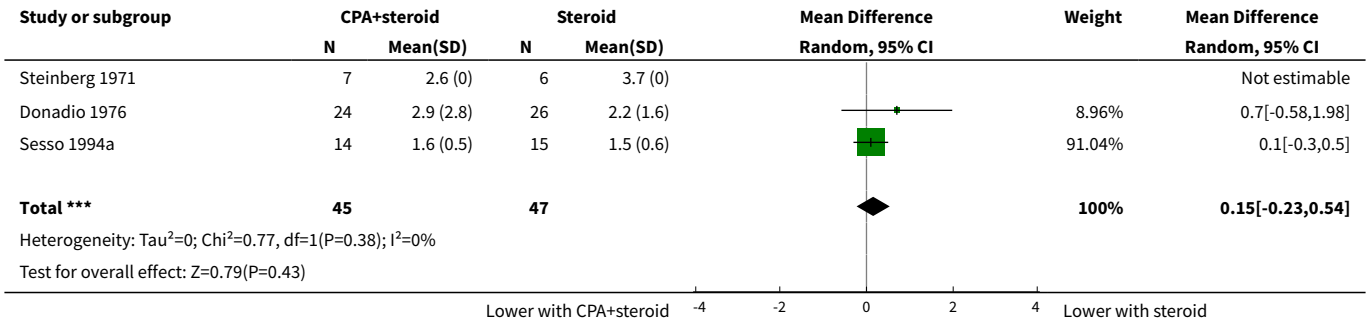


Analysis 18.10. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 10 Bladder toxicity.

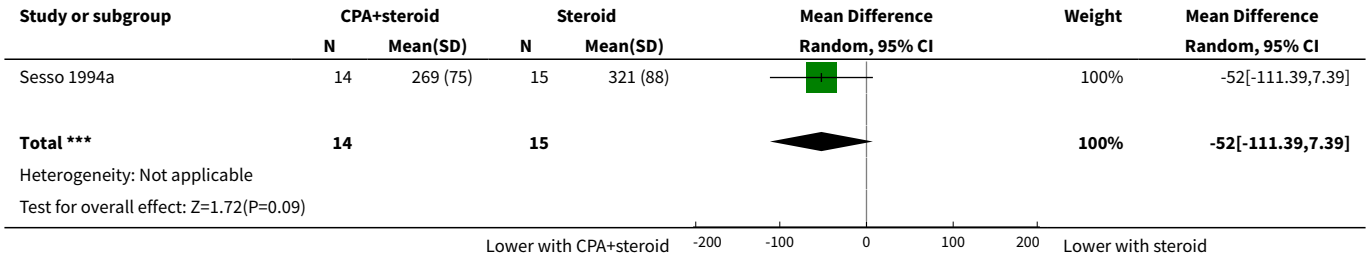




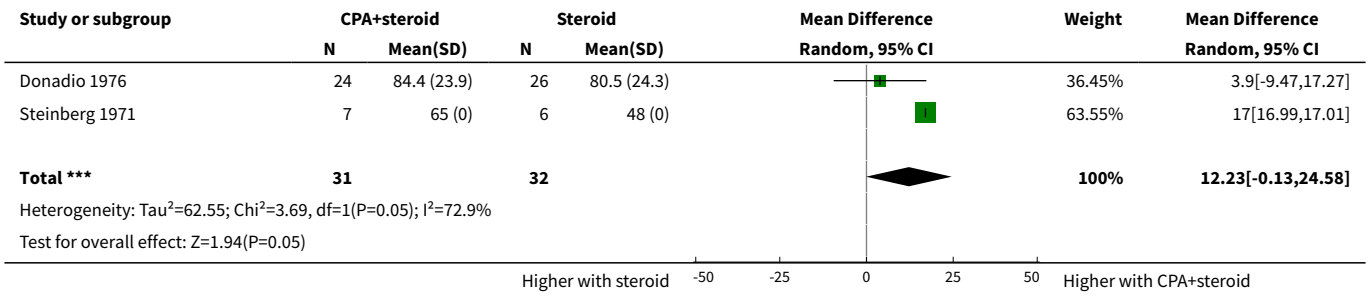
Analysis 18.11. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 11 Daily proteinuria.



Analysis 18.12. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 12 Serum creatinine.



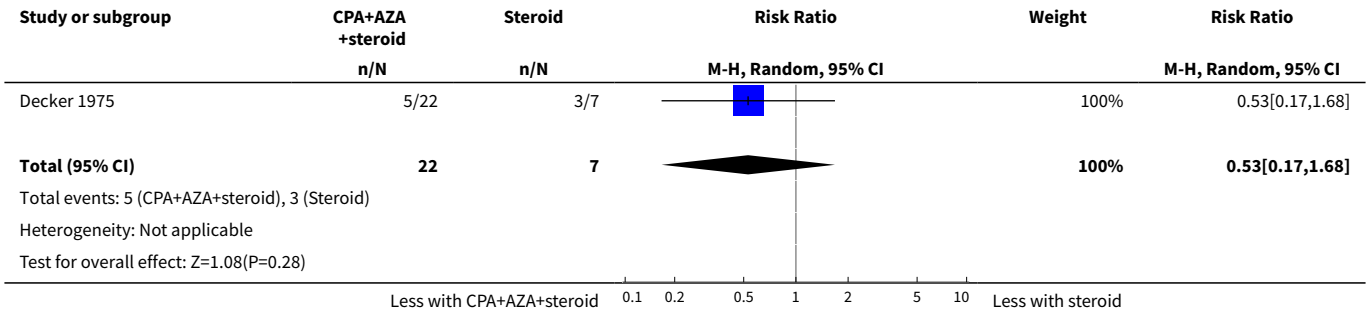
Analysis 18.13. Comparison 18 Cyclophosphamide (CPA) + corticosteroids versus corticosteroids, Outcome 13 Creatinine clearance.



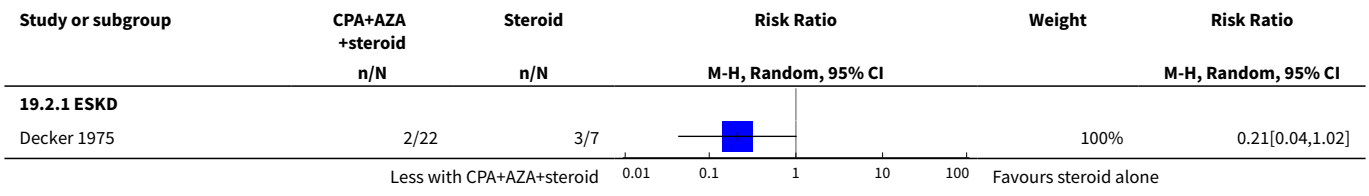
Comparison 19. Cyclophosphamide (CPA) + azathioprine (AZA) + corticosteroids versus corticosteroids alone

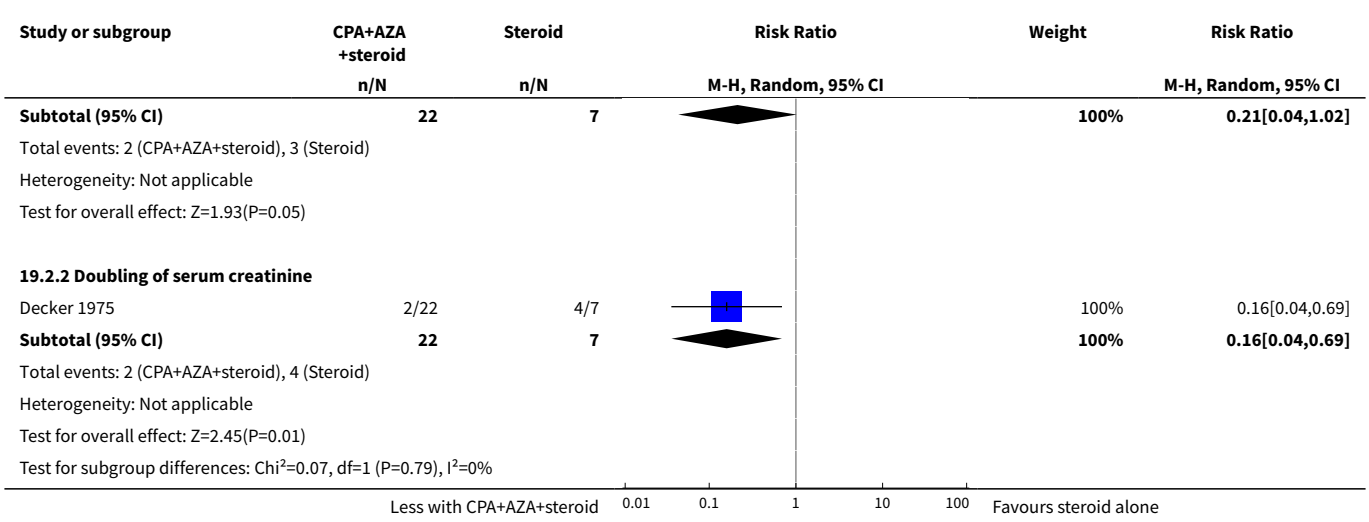
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	29	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.17, 1.68]
2 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 ESKD	1	29	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.04, 1.02]
2.2 Doubling of serum creatinine	1	29	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.04, 0.69]
3 Stable kidney function	1	29	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.83, 3.06]
4 Ovarian failure	1	27	Risk Ratio (M-H, Random, 95% CI)	7.32 [0.49, 108.96]
5 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Major infection	1	29	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.10, 2.30]
5.2 Herpes zoster virus	1	29	Risk Ratio (M-H, Random, 95% CI)	5.22 [0.33, 81.40]
6 Bladder toxicity	1	29	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.14, 42.17]

Analysis 19.1. Comparison 19 Cyclophosphamide (CPA) + azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 1 Death.

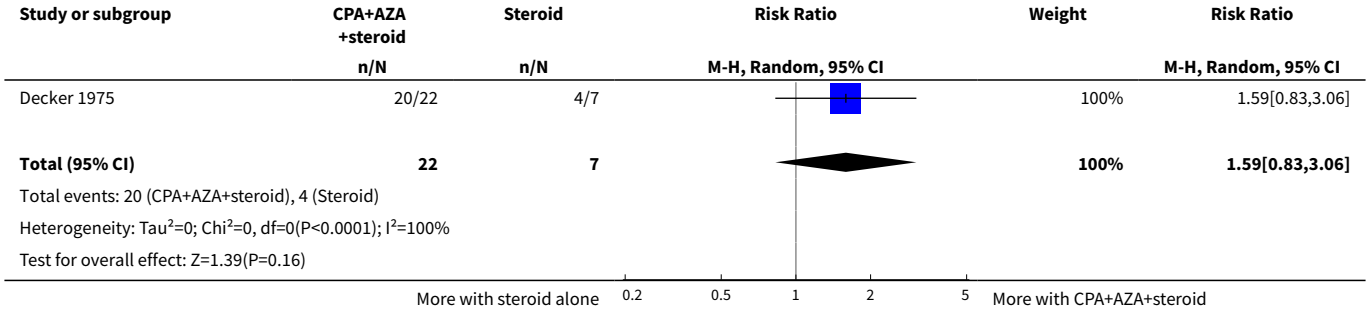


Analysis 19.2. Comparison 19 Cyclophosphamide (CPA) + azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 2 Adverse renal outcomes.

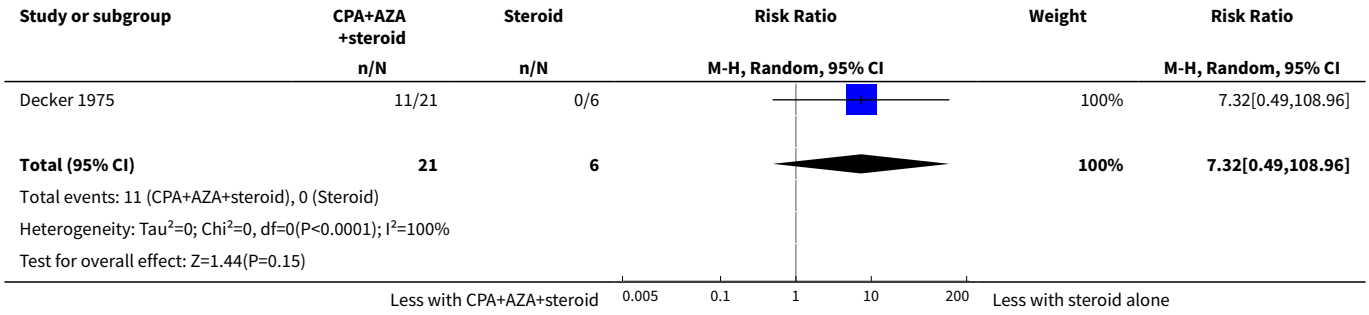




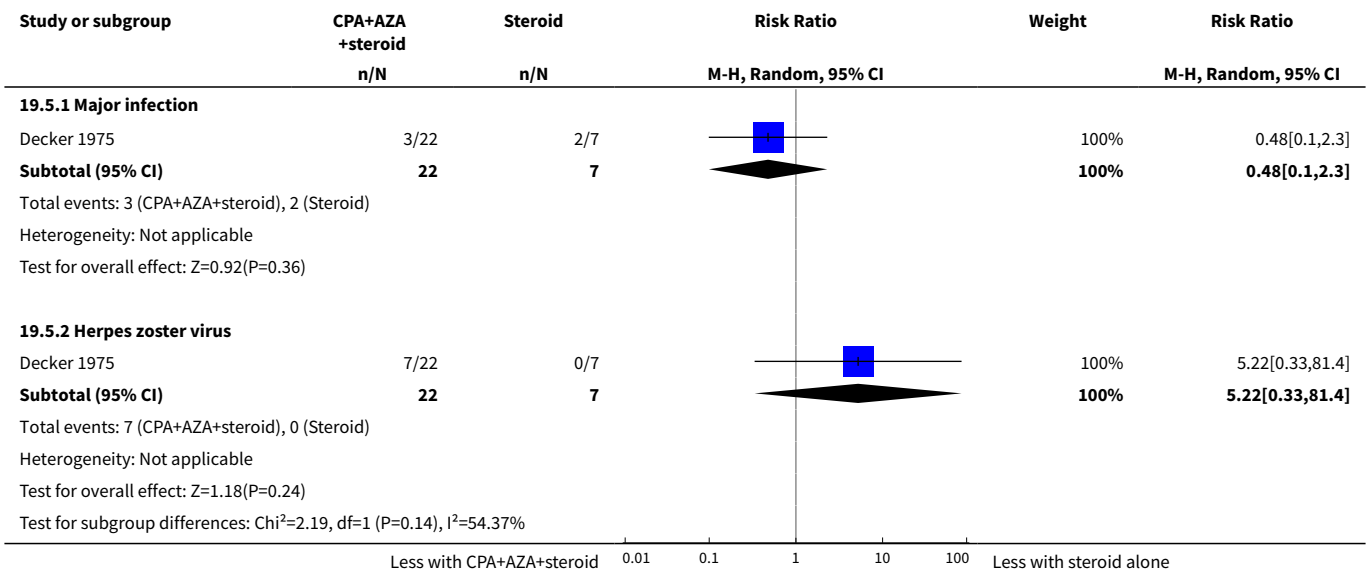
Analysis 19.3. Comparison 19 Cyclophosphamide (CPA) + azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 3 Stable kidney function.



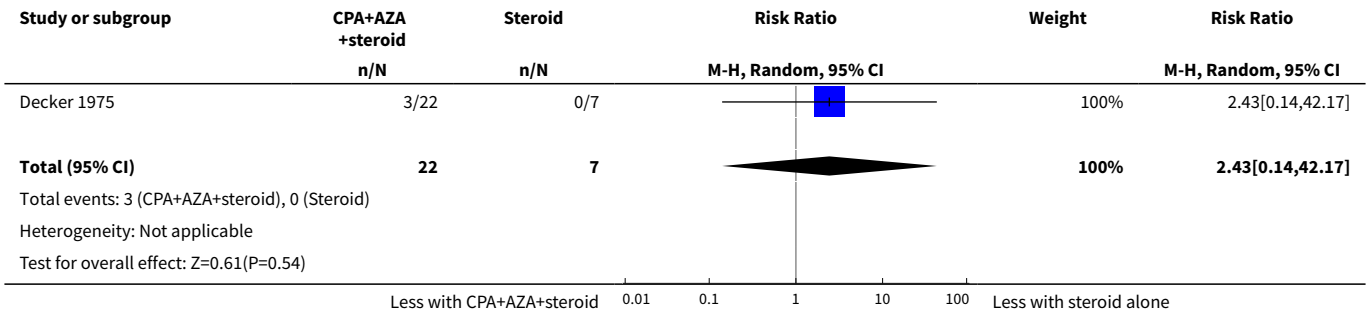
Analysis 19.4. Comparison 19 Cyclophosphamide (CPA) + azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 4 Ovarian failure.



Analysis 19.5. Comparison 19 Cyclophosphamide (CPA) + azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 5 Infection.



Analysis 19.6. Comparison 19 Cyclophosphamide (CPA) + azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 6 Bladder toxicity.



Comparison 20. Azathioprine (AZA) + corticosteroids versus corticosteroids alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3	78	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 0.99]
2 Complete remission of proteinuria	2	37	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.54, 1.69]
3 Adverse renal outcomes	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 ESKD	2	54	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.17, 2.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Renal relapse	1	16	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.22, 2.74]
3.3 Doubling of serum creatinine	1	26	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.36, 2.68]
4 Stable kidney function	1	26	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.48, 2.14]
5 Ovarian failure	1	24	Risk Ratio (M-H, Random, 95% CI)	2.58 [0.15, 43.86]
6 Infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Herpes zoster virus	2	42	Risk Ratio (M-H, Random, 95% CI)	3.56 [0.46, 27.79]
7 Malignancy	1	26	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.11, 37.22]
8 Bone toxicity	1	24	Risk Ratio (M-H, Random, 95% CI)	3.55 [0.43, 29.42]
9 Creatinine clearance	1	24	Mean Difference (IV, Random, 95% CI)	5.0 [-3.14, 13.14]

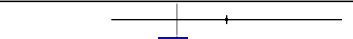
Analysis 20.1. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 1 Death.

Study or subgroup	AZA+steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hahn 1975	2/11	4/13		11.24%	0.59[0.13,2.64]
Decker 1975	7/19	3/7		23.31%	0.86[0.3,2.43]
Cade 1973	6/13	13/15		65.44%	0.53[0.29,0.99]
Total (95% CI)	**43**	**35**		**100%**	**0.6[0.36,0.99]**
Total events: 15 (AZA+steroid), 20 (Steroid)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=2(P=0.74); I^2=0%					
Test for overall effect: Z=1.98(P=0.05)					

Less with AZA+steroid — Less with steroid alone

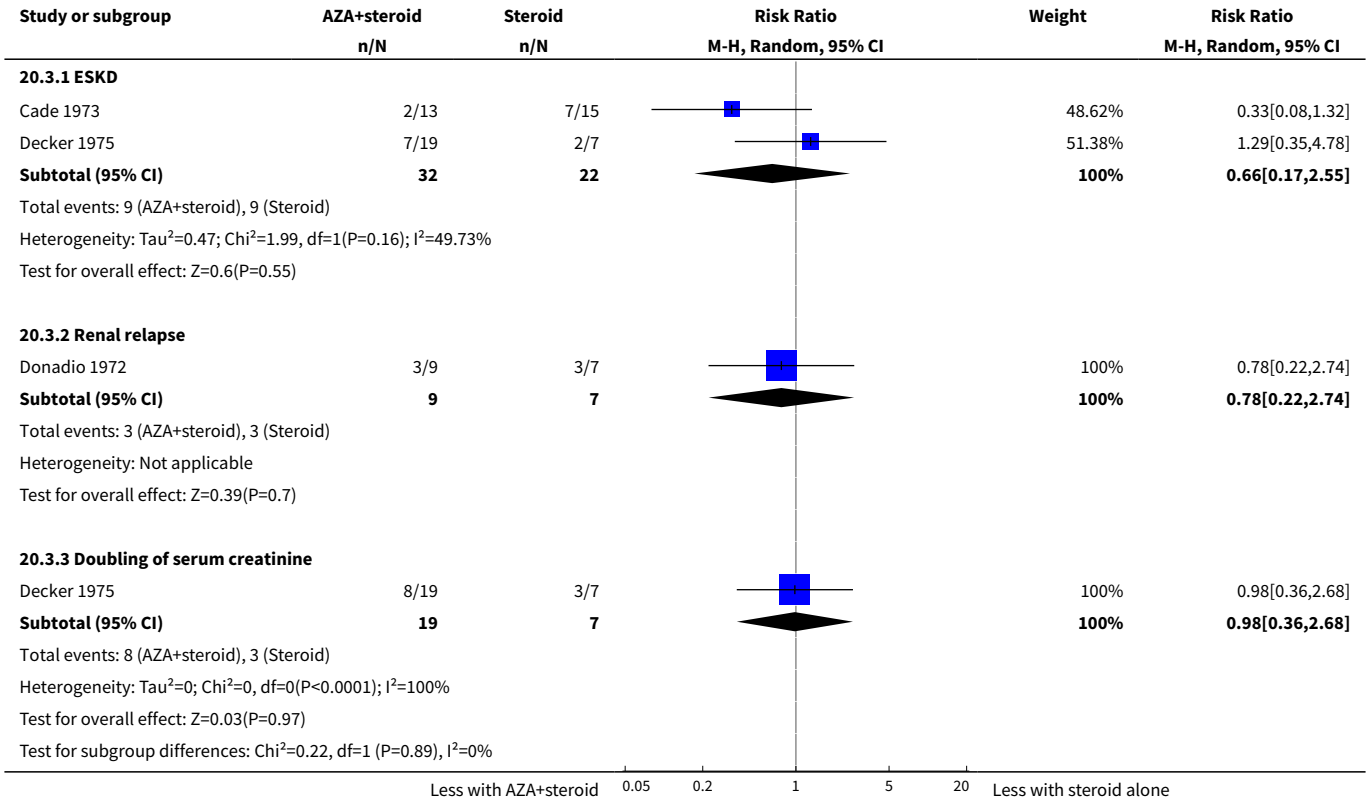
Analysis 20.2. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 2 Complete remission of proteinuria.

Study or subgroup	AZA+steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Donadio 1972	1/7	0/9		3.43%	3.75[0.18,80.19]
Hahn 1975	8/11	8/10		96.57%	0.91[0.56,1.46]
Total (95% CI)	**18**	**19**		**100%**	**0.95[0.54,1.69]**
Total events: 9 (AZA+steroid), 8 (Steroid)					
Heterogeneity: Tau^2=0.03; Chi^2=1.02, df=1(P=0.31); I^2=2.25%					
Test for overall effect: Z=0.16(P=0.87)					

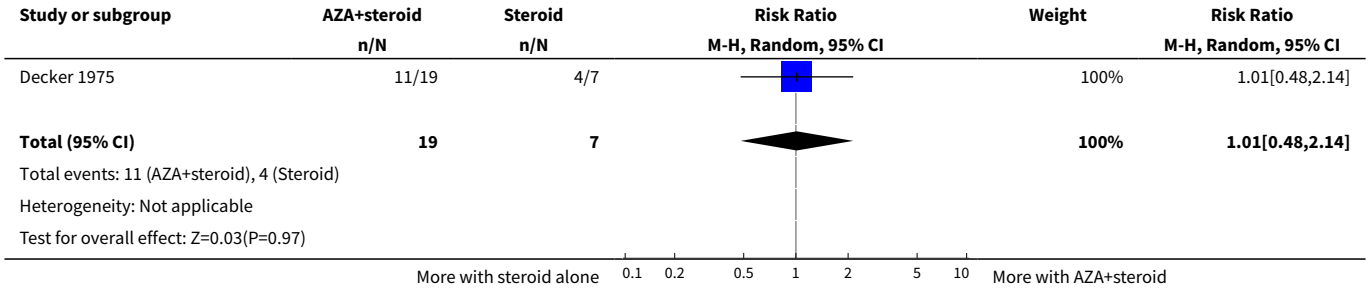


More with steroid alone — More with AZA+steroid

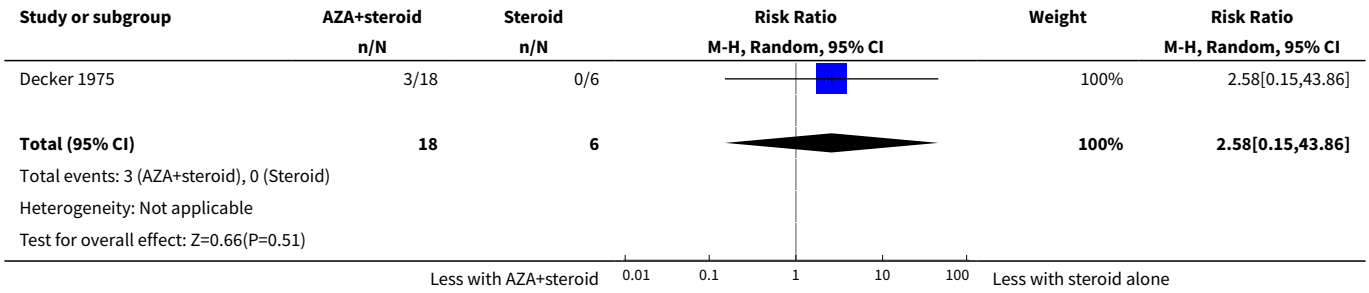
Analysis 20.3. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 3 Adverse renal outcomes.



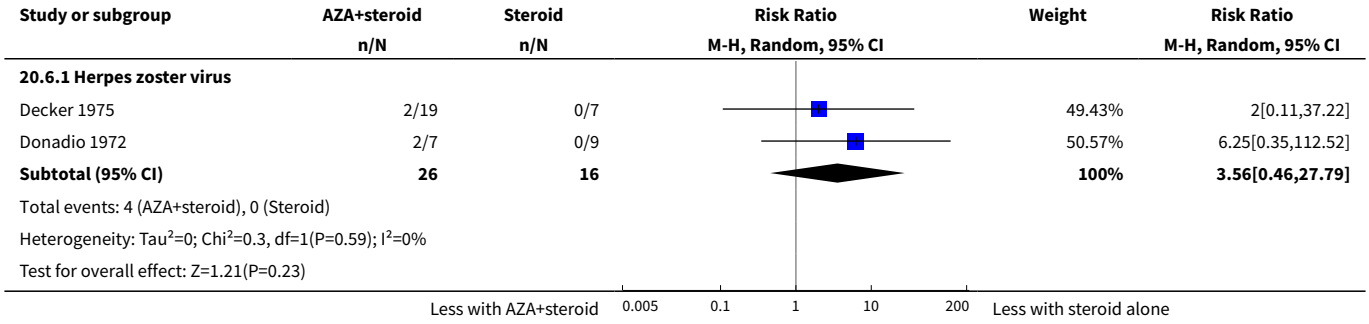
Analysis 20.4. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 4 Stable kidney function.



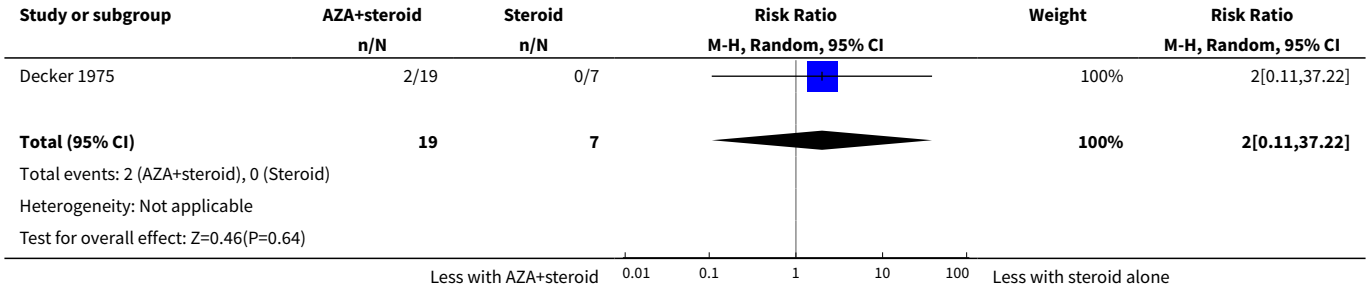
Analysis 20.5. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 5 Ovarian failure.



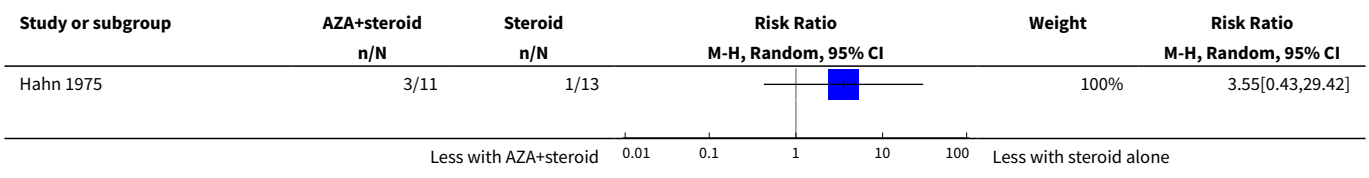
Analysis 20.6. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 6 Infection.

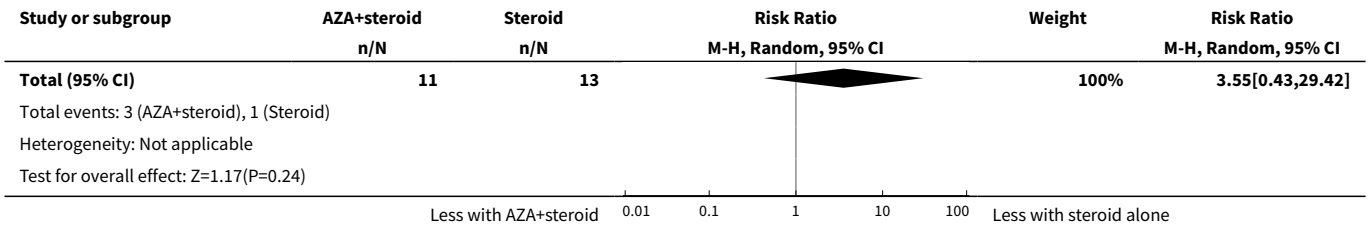


Analysis 20.7. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 7 Malignancy.

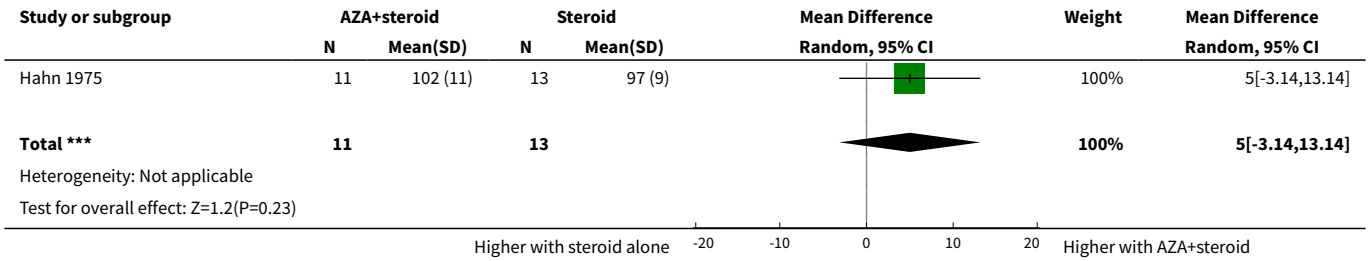


Analysis 20.8. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 8 Bone toxicity.





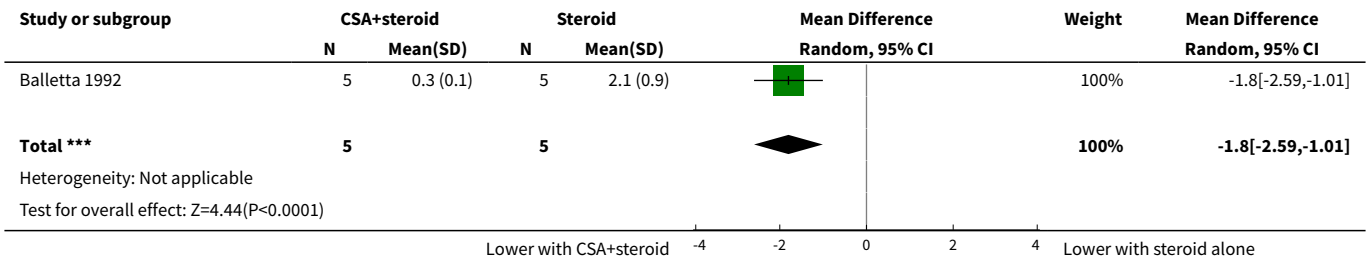
Analysis 20.9. Comparison 20 Azathioprine (AZA) + corticosteroids versus corticosteroids alone, Outcome 9 Creatinine clearance.



Comparison 21. Cyclosporin (CSA) + corticosteroids versus corticosteroids alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Daily proteinuria	1	10	Mean Difference (IV, Random, 95% CI)	-1.8 [-2.59, -1.01]
2 Serum creatinine	1	10	Mean Difference (IV, Random, 95% CI)	-31.90 [-73.63, 9.83]
3 Creatinine clearance	1	10	Mean Difference (IV, Random, 95% CI)	-42.5 [-85.02, 0.02]

Analysis 21.1. Comparison 21 Cyclosporin (CSA) + corticosteroids versus corticosteroids alone, Outcome 1 Daily proteinuria.



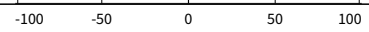
Analysis 21.2. Comparison 21 Cyclosporin (CSA) + corticosteroids versus corticosteroids alone, Outcome 2 Serum creatinine.

Study or subgroup	CSA+steroid N	CSA+steroid Mean(SD)	Steroid N	Steroid Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Balletta 1992	5	91.9 (17.7)	5	123.8 (44.2)		100%	-31.9[-73.63,9.83]
Total ***	**5**		**5**			**100%**	**-31.9[-73.63,9.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.5(P=0.13)							

Lower with CSA+steroid — Lower with steroid

Analysis 21.3. Comparison 21 Cyclosporin (CSA) + corticosteroids versus corticosteroids alone, Outcome 3 Creatinine clearance.

Study or subgroup	CSA+steroid N	CSA+steroid Mean(SD)	Steroid N	Steroid Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Balletta 1992	5	81.3 (20)	5	123.8 (44.2)		100%	-42.5[-85.02,0.02]
Total ***	**5**		**5**			**100%**	**-42.5[-85.02,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.96(P=0.05)							



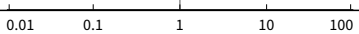
Higher with steroid alone — Higher with CSA+steroid

Comparison 22. Misoprostol + corticosteroids versus corticosteroids alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Doubling of serum creatinine	1	14	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 22.1. Comparison 22 Misoprostol + corticosteroids versus corticosteroids alone, Outcome 1 Adverse renal outcomes.

Study or subgroup	Misoprostol+steroid n/N	Steroid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
22.1.1 Doubling of serum creatinine					
Belmont 1995	0/7	0/7			Not estimable
Subtotal (95% CI)	**7**	**7**			**Not estimable**
Total events: 0 (Misoprostol+steroid), 0 (Steroid)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

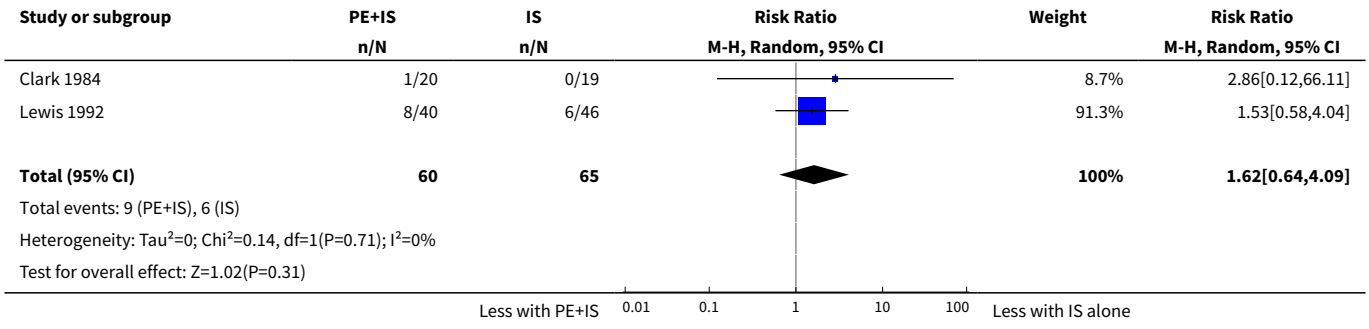


Less with misoprostol+steroid — Less with steroid alone

Comparison 23. Plasma exchange (PE) + immunosuppression (IS) versus IS alone

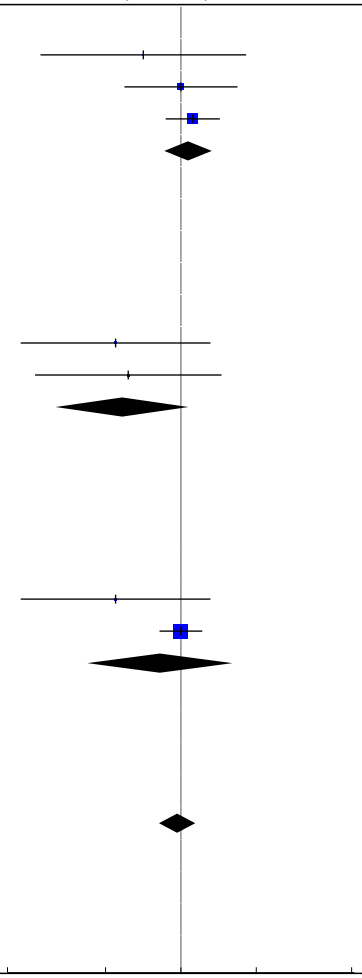
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	125	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.64, 4.09]
2 Adverse renal outcomes	4	251	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.51, 1.55]
2.1 ESKD	3	143	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.60, 2.57]
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 Leucopenia	1	18	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.20, 34.07]
6 Daily proteinuria	2	30	Mean Difference (IV, Random, 95% CI)	-0.56 [-5.23, 4.11]
7 Serum creatinine	3	69	Mean Difference (IV, Random, 95% CI)	-17.90 [-23.41, -12.39]
8 Creatinine clearance	1	12	Mean Difference (IV, Random, 95% CI)	26.0 [-17.60, 69.60]
9 Disease activity (SLAM)	1	18	Mean Difference (IV, Random, 95% CI)	0.67 [-3.47, 4.81]

Analysis 23.1. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 1 Death.



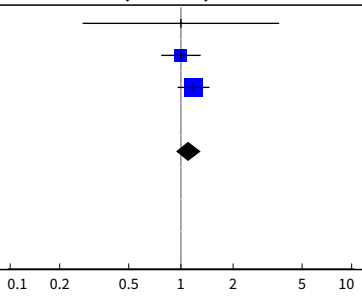
Analysis 23.2. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 2 Adverse renal outcomes.

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
23.2.1 ESKD					
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)					
23.2.2 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)					
23.2.3 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%					

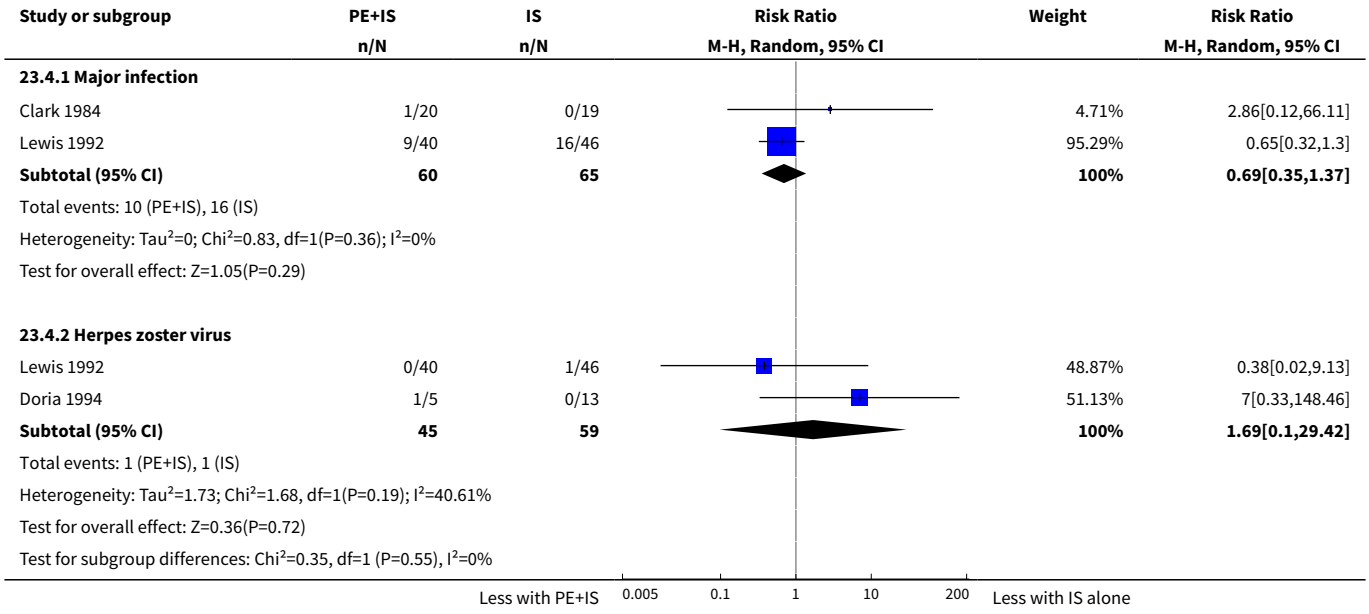


Analysis 23.3. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 3 Stable kidney function.

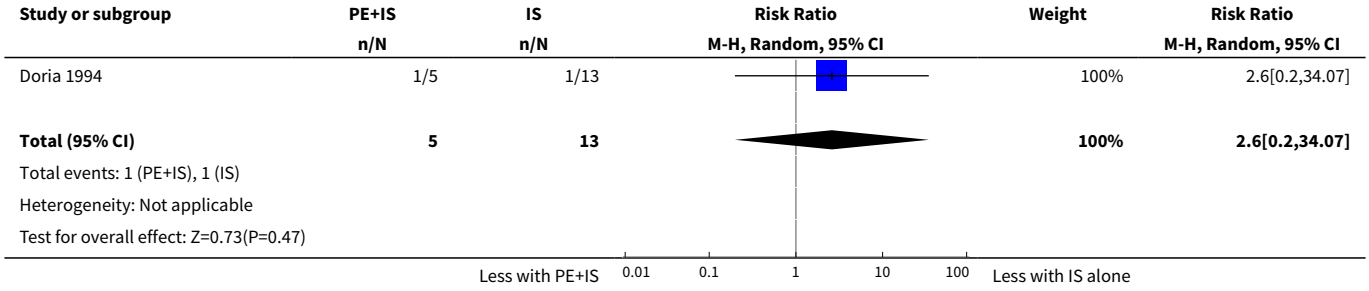
Study or subgroup	PE+IS n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Wallace 1998	3/9	3/9		1.57%	1[0.27,3.69]
Doria 1994	5/5	13/13		39.18%	1[0.77,1.3]
Clark 1984	20/20	16/19		59.25%	1.18[0.96,1.46]
Total (95% CI)	**34**	**41**		**100%**	**1.1[0.94,1.3]**
Total events: 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)					



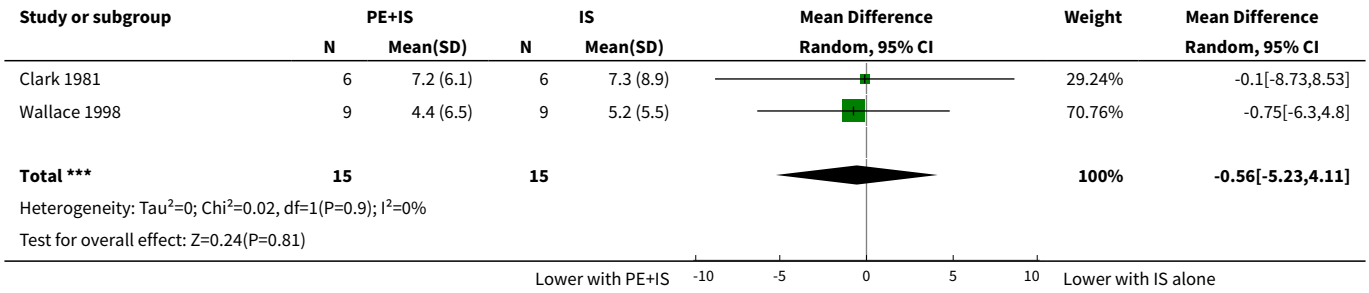
Analysis 23.4. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 4 Infection.



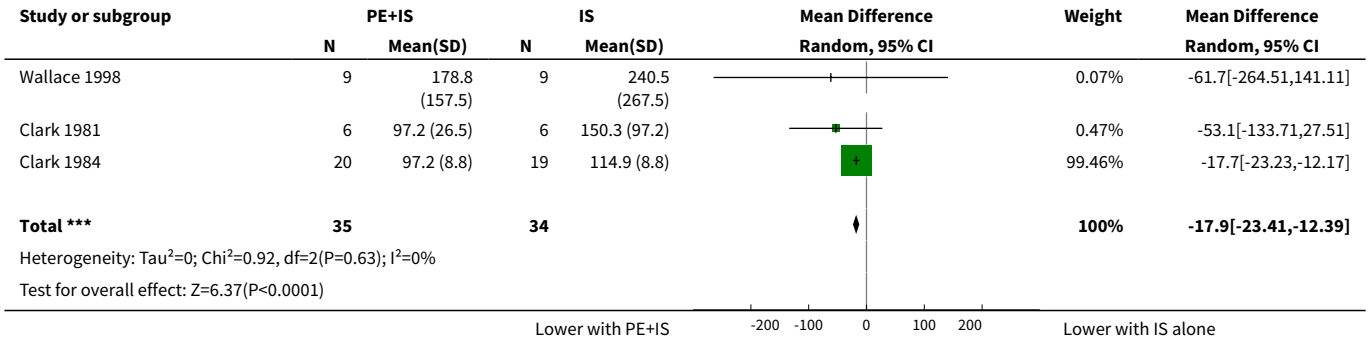
Analysis 23.5. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 5 Leucopenia.



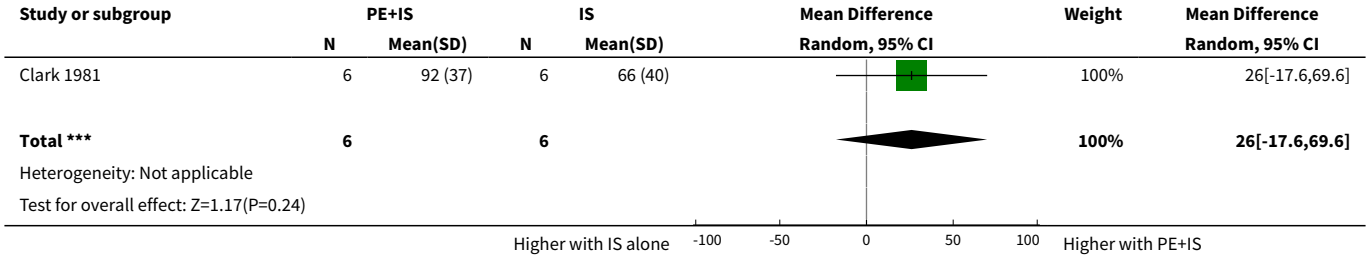
Analysis 23.6. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 6 Daily proteinuria.



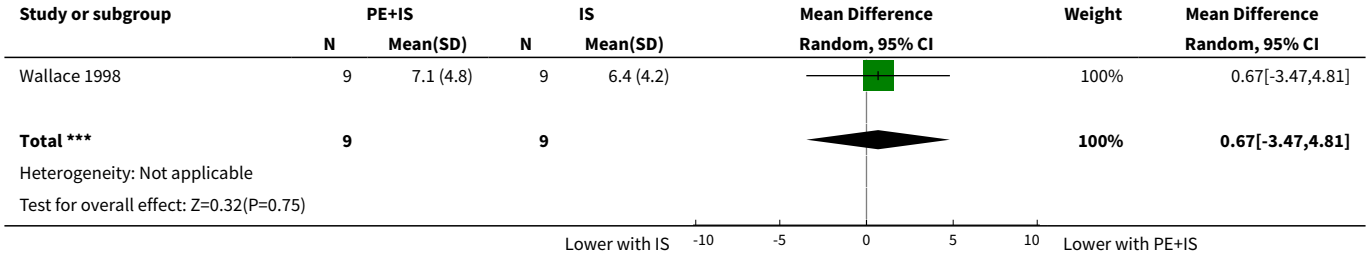
Analysis 23.7. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 7 Serum creatinine.



Analysis 23.8. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 8 Creatinine clearance.



Analysis 23.9. Comparison 23 Plasma exchange (PE) + immunosuppression (IS) versus IS alone, Outcome 9 Disease activity (SLAM).



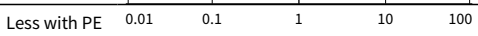
Comparison 24. Plasma exchange (PE) versus immunosuppression (IS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 ESKD	1	20	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.01, 4.44]
2 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Major infection	1	20	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.02, 8.78]
2.2 Herpes zoster virus	1	20	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.01, 4.44]
3 Leucopenia	1	20	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.01, 4.44]
4 Alopecia	1	20	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Daily proteinuria	1	20	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.45, 0.25]
6 Creatinine clearance	1	20	Mean Difference (IV, Random, 95% CI)	15.30 [-5.40, 36.00]

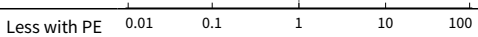
Analysis 24.1. Comparison 24 Plasma exchange (PE) versus immunosuppression (IS), Outcome 1 Adverse renal outcomes.

Study or subgroup	PE n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
24.1.1 ESKD					
Derksen 1988	0/9	2/11		100%	0.24[0.01,4.44]
Subtotal (95% CI)	**9**	**11**		**100%**	**0.24[0.01,4.44]**
Total events: 0 (PE), 2 (IS)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.96(P=0.34)					

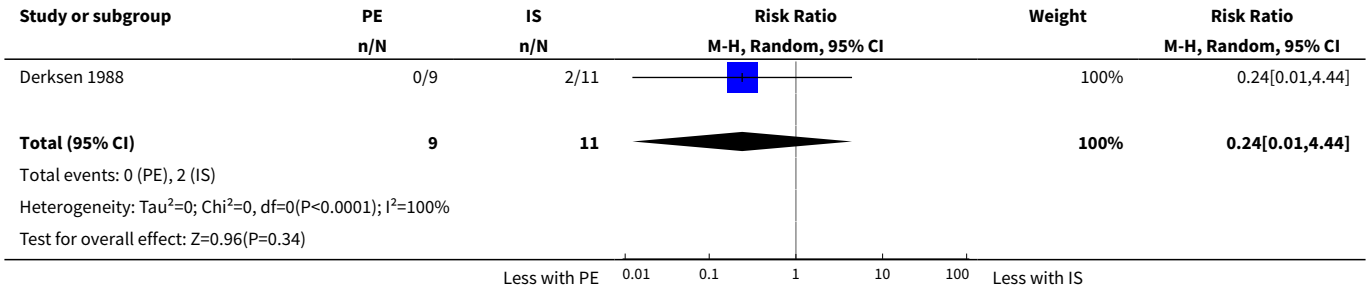


Analysis 24.2. Comparison 24 Plasma exchange (PE) versus immunosuppression (IS), Outcome 2 Infection.

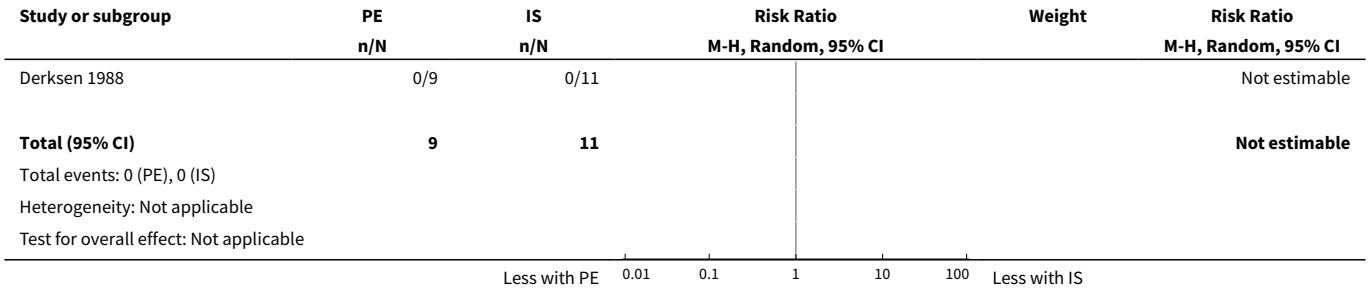
Study or subgroup	PE n/N	IS n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
24.2.1 Major infection					
Derksen 1988	0/9	1/11		100%	0.4[0.02,8.78]
Subtotal (95% CI)	**9**	**11**		**100%**	**0.4[0.02,8.78]**
Total events: 0 (PE), 1 (IS)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					
24.2.2 Herpes zoster virus					
Derksen 1988	0/9	2/11		100%	0.24[0.01,4.44]
Subtotal (95% CI)	**9**	**11**		**100%**	**0.24[0.01,4.44]**
Total events: 0 (PE), 2 (IS)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.96(P=0.34)					



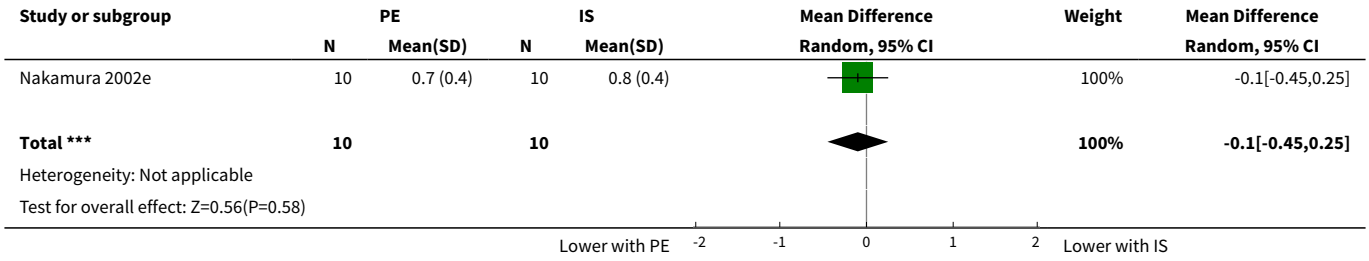
Analysis 24.3. Comparison 24 Plasma exchange (PE) versus immunosuppression (IS), Outcome 3 Leucopenia.



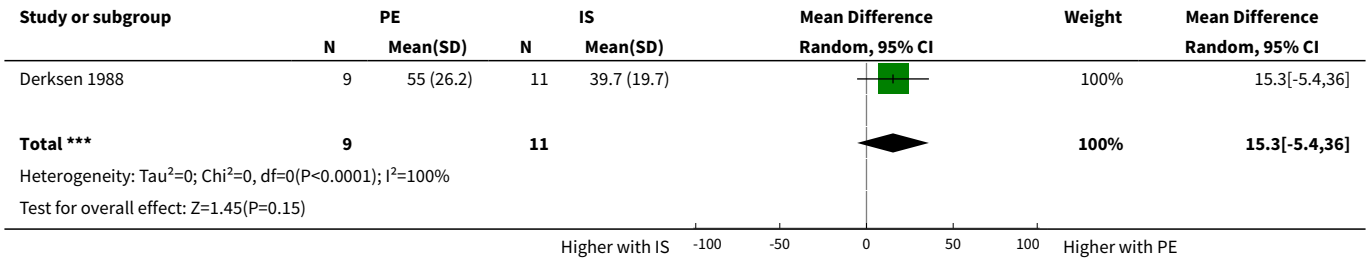
Analysis 24.4. Comparison 24 Plasma exchange (PE) versus immunosuppression (IS), Outcome 4 Alopecia.



Analysis 24.5. Comparison 24 Plasma exchange (PE) versus immunosuppression (IS), Outcome 5 Daily proteinuria.



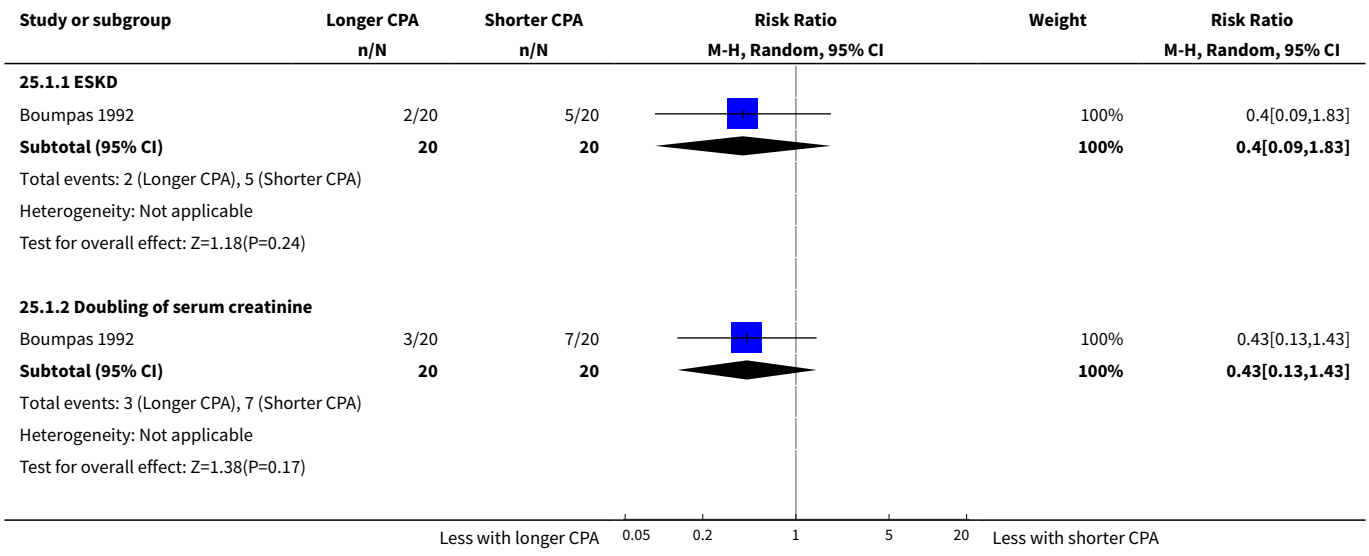
Analysis 24.6. Comparison 24 Plasma exchange (PE) versus immunosuppression (IS), Outcome 6 Creatinine clearance.

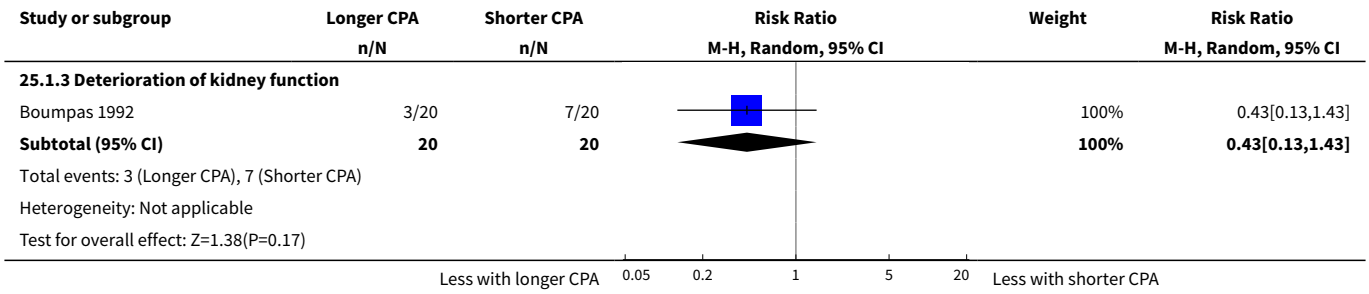


Comparison 25. Long versus short duration cyclophosphamide (CPA)

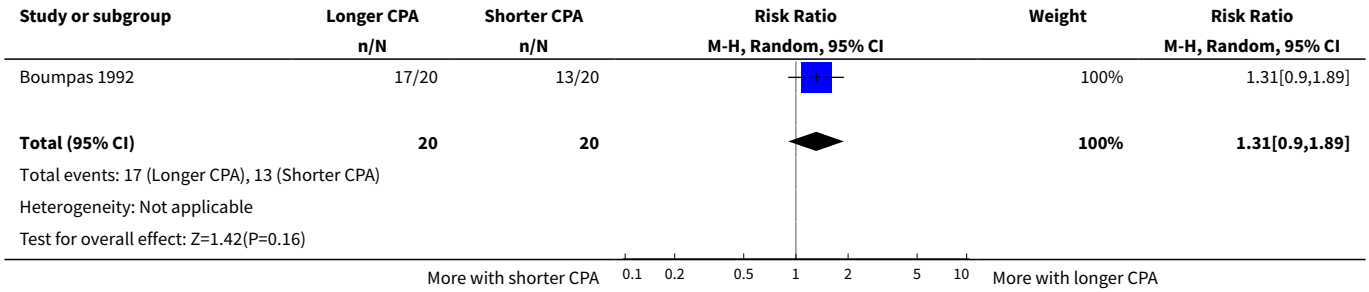
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 ESKD	1	40	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.09, 1.83]
1.2 Doubling of serum creatinine	1	40	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.13, 1.43]
1.3 Deterioration of kidney function	1	40	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.13, 1.43]
2 Stable kidney function	1	40	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.90, 1.89]
3 Ovarian failure	1	29	Risk Ratio (M-H, Random, 95% CI)	2.05 [0.60, 7.02]
4 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Major infection	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 14.90]
4.2 Herpes zoster virus	1	40	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.08]
5 Malignancy	1	40	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.52]
6 Bone toxicity	1	40	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.34, 5.21]
7 Bladder toxicity	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 25.1. Comparison 25 Long versus short duration cyclophosphamide (CPA), Outcome 1 Adverse renal outcomes.

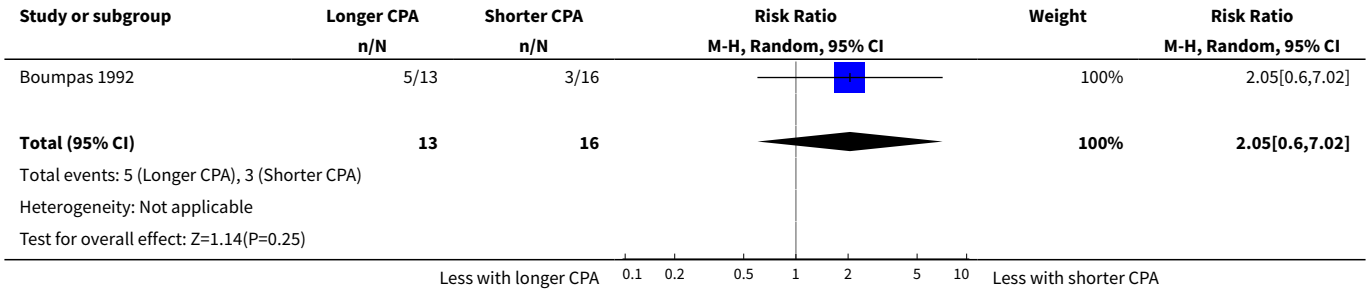




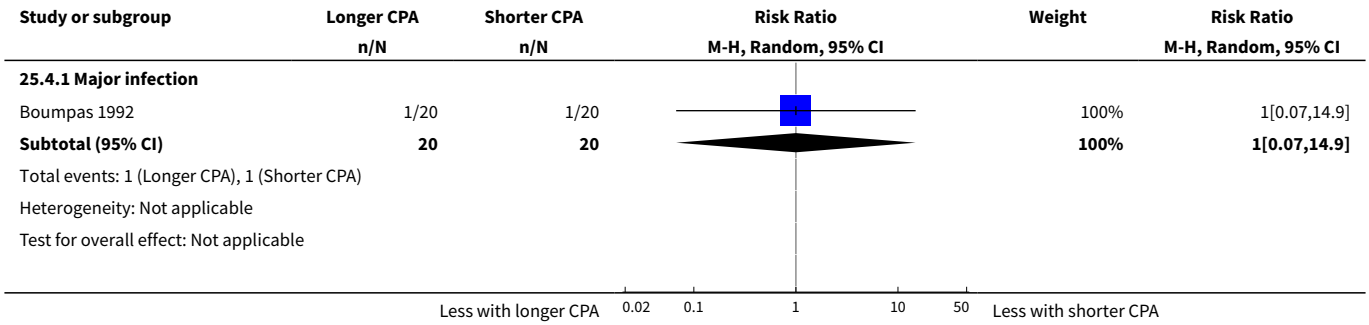
Analysis 25.2. Comparison 25 Long versus short duration cyclophosphamide (CPA), Outcome 2 Stable kidney function.

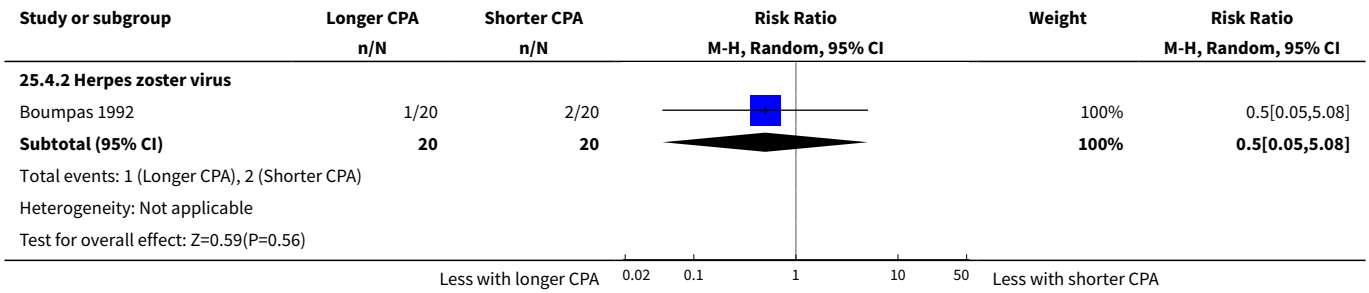


Analysis 25.3. Comparison 25 Long versus short duration cyclophosphamide (CPA), Outcome 3 Ovarian failure.

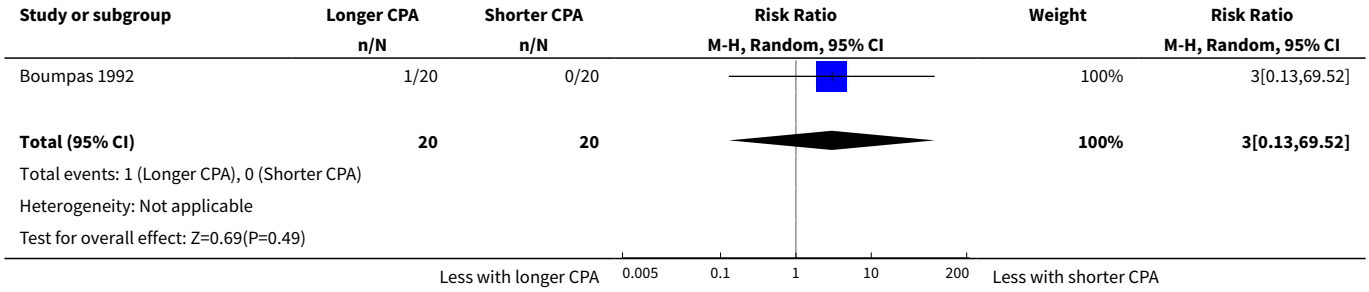


Analysis 25.4. Comparison 25 Long versus short duration cyclophosphamide (CPA), Outcome 4 Infection.

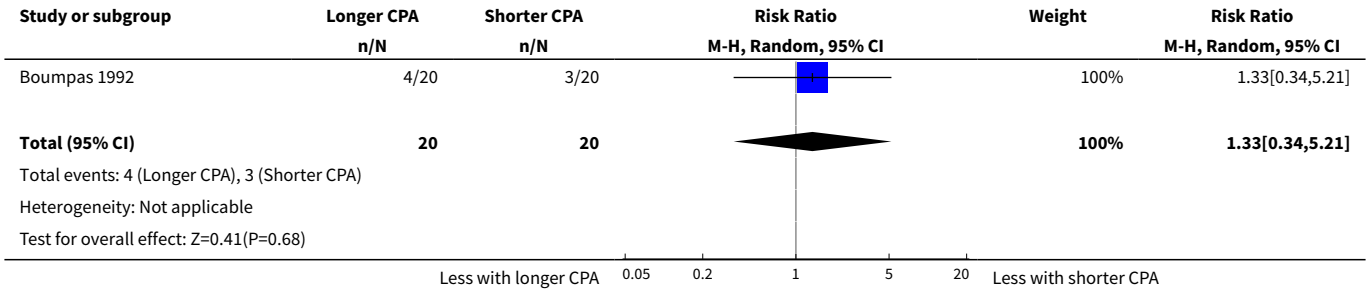




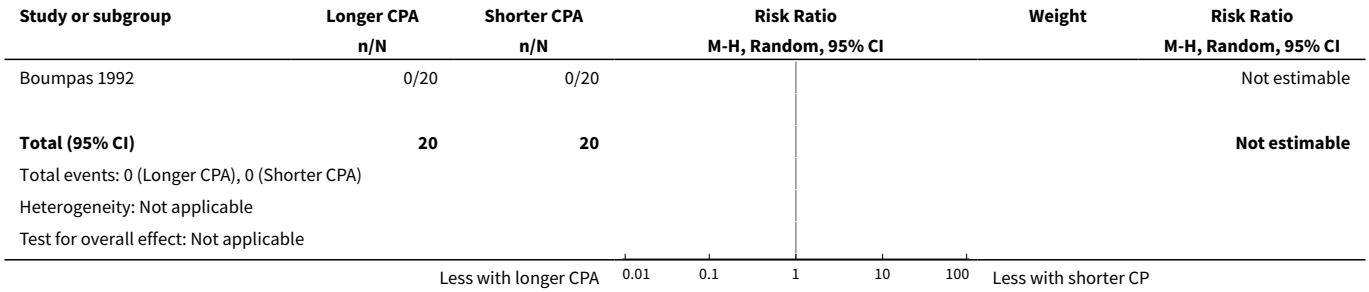
Analysis 25.5. Comparison 25 Long versus short duration cyclophosphamide (CPA), Outcome 5 Malignancy.



Analysis 25.6. Comparison 25 Long versus short duration cyclophosphamide (CPA), Outcome 6 Bone toxicity.



Analysis 25.7. Comparison 25 Long versus short duration cyclophosphamide (CPA), Outcome 7 Bladder toxicity.



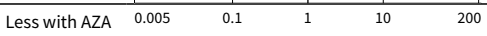
Comparison 26. Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At end of treatment duration or follow-up	4	451	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.34, 3.87]
1.2 At 10 years	1	87	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.11, 3.54]
2 Renal relapse	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 At end of treatment duration or follow-up	4	452	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.20, 2.55]
2.2 At 10 years	1	87	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.69, 1.69]
3 End-stage kidney disease	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 At end of treatment duration or follow-up	4	452	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.52, 5.54]
3.2 At 10 years	1	87	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.03, 2.88]
4 Doubling of serum creatinine	4	452	Risk Ratio (M-H, Random, 95% CI)	2.19 [1.03, 4.66]
5 Ovarian failure	2	177	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.17, 3.42]
6 Infection	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Major infection	3	412	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.60, 1.96]
6.2 Herpes zoster virus	1	105	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.36, 4.48]
7 Malignancy	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 At end of treatment duration or follow-up	3	370	Risk Ratio (M-H, Random, 95% CI)	4.04 [0.45, 36.07]
7.2 At 10 years	1	87	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.18, 19.84]
8 Leucopenia	3	412	Risk Ratio (M-H, Random, 95% CI)	5.61 [1.68, 18.72]
9 Bone toxicity	1	105	Risk Ratio (M-H, Random, 95% CI)	3.06 [0.13, 73.36]
10 Alopecia	3	412	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.46, 1.95]
11 Gastrointestinal (GI) adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 GI symptoms	1	105	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.41, 2.51]
11.2 Nausea	2	307	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.65, 1.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Diarrhoea	2	307	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.31, 1.73]
11.4 Vomiting	2	307	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.18, 3.62]
12 Daily proteinuria	1	81	Mean Difference (IV, Random, 95% CI)	0.40 [-0.53, 1.33]

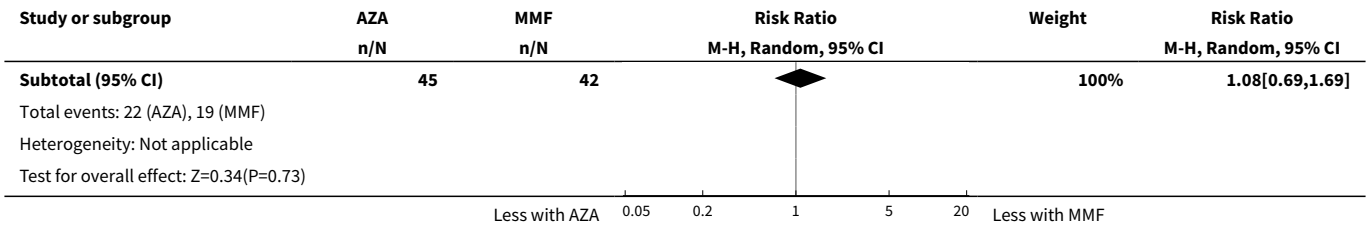
Analysis 26.1. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 1 Death.

Study or subgroup	AZA n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
26.1.1 At end of treatment duration or follow-up					
ALMS 2007	1/111	0/115		14.42%	3.11[0.13,75.47]
Contreras 2004	0/19	1/20		14.87%	0.35[0.02,8.1]
MAINTAIN Nephritis 2010	0/52	2/53		16.17%	0.2[0.01,4.14]
Kaballo 2016	4/40	2/41		54.53%	2.05[0.4,10.57]
Subtotal (95% CI)	**222**	**229**		**100%**	**1.15[0.34,3.87]**
Total events: 5 (AZA), 5 (MMF)					
Heterogeneity: Tau^2=0; Chi^2=2.7, df=3(P=0.44); I^2=0%					
Test for overall effect: Z=0.23(P=0.82)					
26.1.2 At 10 years					
MAINTAIN Nephritis 2010	2/45	3/42		100%	0.62[0.11,3.54]
Subtotal (95% CI)	**45**	**42**		**100%**	**0.62[0.11,3.54]**
Total events: 2 (AZA), 3 (MMF)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.59)					

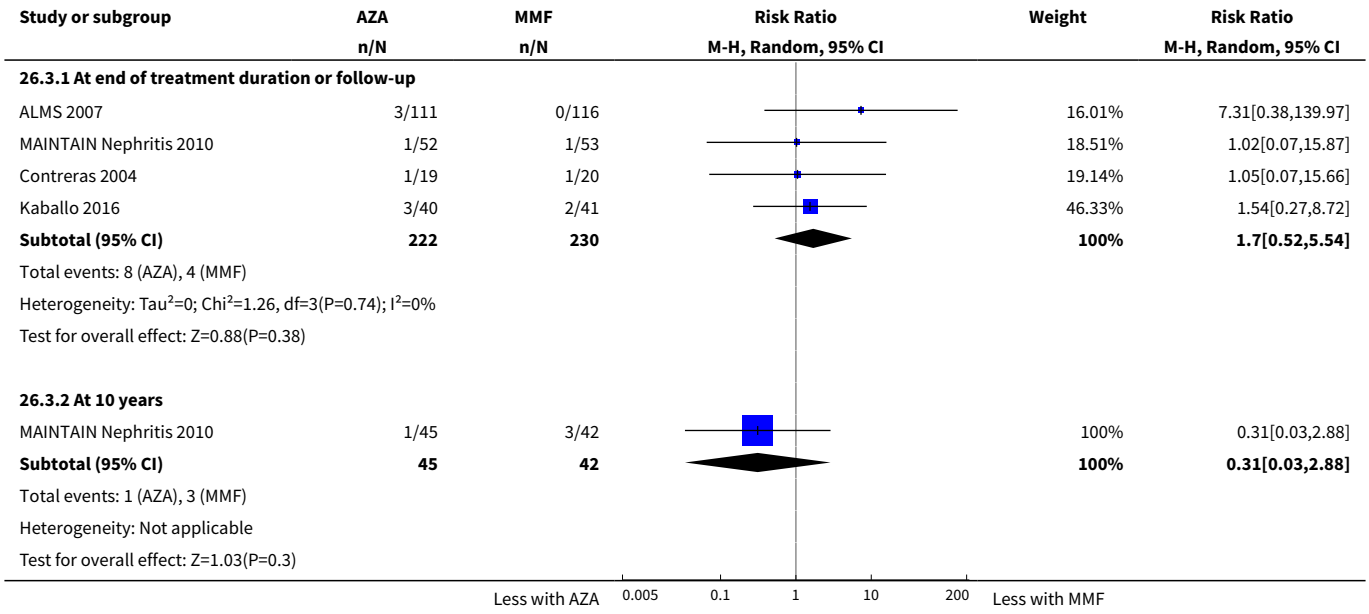


Analysis 26.2. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 2 Renal relapse.

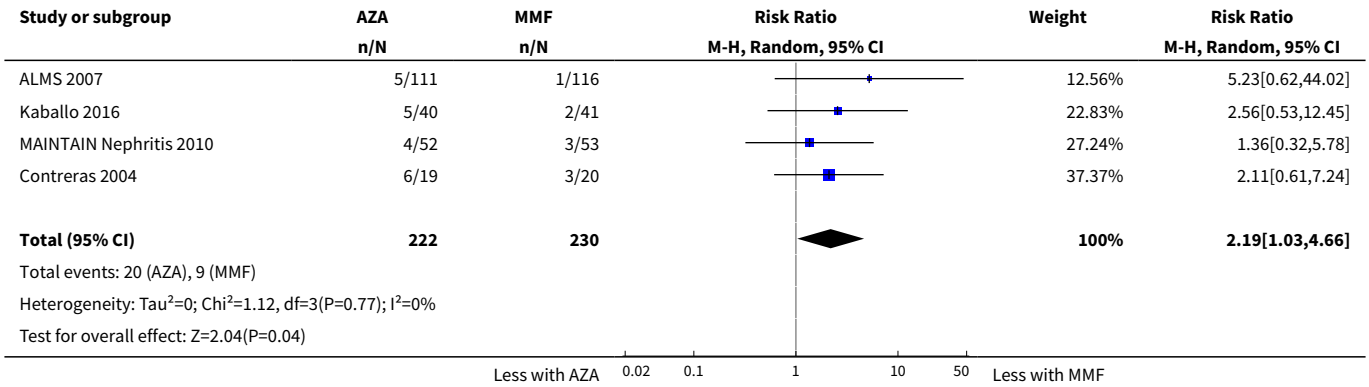
Study or subgroup	AZA n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
26.2.1 At end of treatment duration or follow-up					
Kaballo 2016	4/40	4/41		8.17%	1.02[0.28,3.82]
Contreras 2004	6/19	3/20		9.27%	2.11[0.61,7.24]
MAINTAIN Nephritis 2010	13/52	10/53		26.52%	1.33[0.64,2.75]
ALMS 2007	36/111	18/116		56.04%	2.09[1.26,3.45]
Subtotal (95% CI)	**222**	**230**		**100%**	**1.75[1.2,2.55]**
Total events: 59 (AZA), 35 (MMF)					
Heterogeneity: Tau^2=0; Chi^2=1.76, df=3(P=0.62); I^2=0%					
Test for overall effect: Z=2.91(P=0)					
26.2.2 At 10 years					
MAINTAIN Nephritis 2010	22/45	19/42		100%	1.08[0.69,1.69]



Analysis 26.3. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 3 End-stage kidney disease.



Analysis 26.4. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 4 Doubling of serum creatinine.

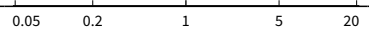


Analysis 26.5. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 5 Ovarian failure.

Study or subgroup	AZA n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
MAINTAIN Nephritis 2010	1/48	2/48		39.46%	0.5[0.05,5.33]
Kaballo 2016	2/40	2/41		60.54%	1.02[0.15,6.93]
Total (95% CI)	**88**	**89**		**100%**	**0.77[0.17,3.42]**
Total events: 3 (AZA), 4 (MMF)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.64); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					

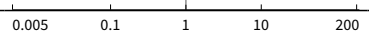
Analysis 26.6. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 6 Infection.

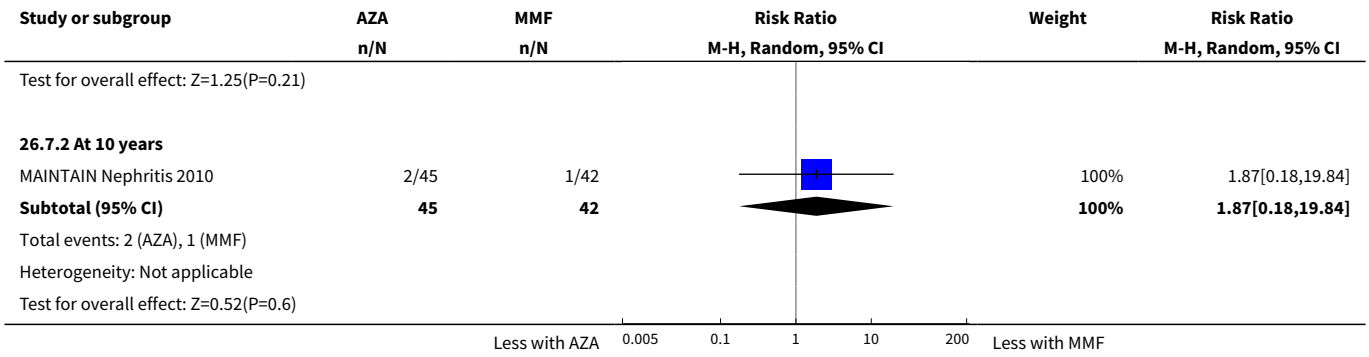
Study or subgroup	AZA n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
26.6.1 Major infection					
Kaballo 2016	1/40	1/41		4.72%	1.02[0.07,15.83]
MAINTAIN Nephritis 2010	6/52	7/53		33.93%	0.87[0.31,2.43]
ALMS 2007	13/111	11/115		61.35%	1.22[0.57,2.62]
Subtotal (95% CI)	**203**	**209**		**100%**	**1.08[0.6,1.96]**
Total events: 20 (AZA), 19 (MMF)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=2(P=0.87); I^2=0%					
Test for overall effect: Z=0.26(P=0.79)					
26.6.2 Herpes zoster virus					
MAINTAIN Nephritis 2010	5/52	4/53		100%	1.27[0.36,4.48]
Subtotal (95% CI)	**52**	**53**		**100%**	**1.27[0.36,4.48]**
Total events: 5 (AZA), 4 (MMF)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.71)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%					



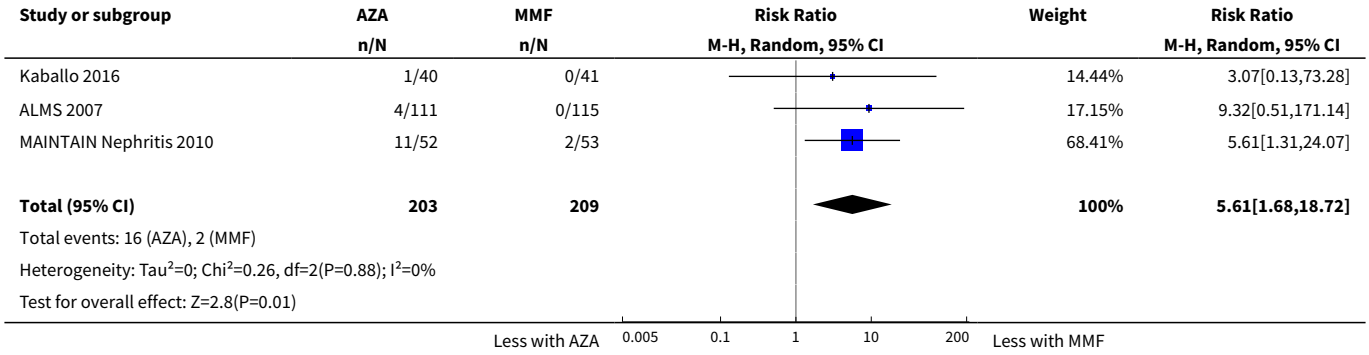
Analysis 26.7. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 7 Malignancy.

Study or subgroup	AZA n/N	MMF n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
26.7.1 At end of treatment duration or follow-up					
Contreras 2004	0/19	0/20			Not estimable
ALMS 2007	1/111	0/115		47.14%	3.11[0.13,75.47]
MAINTAIN Nephritis 2010	2/52	0/53		52.86%	5.09[0.25,103.62]
Subtotal (95% CI)	**182**	**188**		**100%**	**4.04[0.45,36.07]**
Total events: 3 (AZA), 0 (MMF)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					

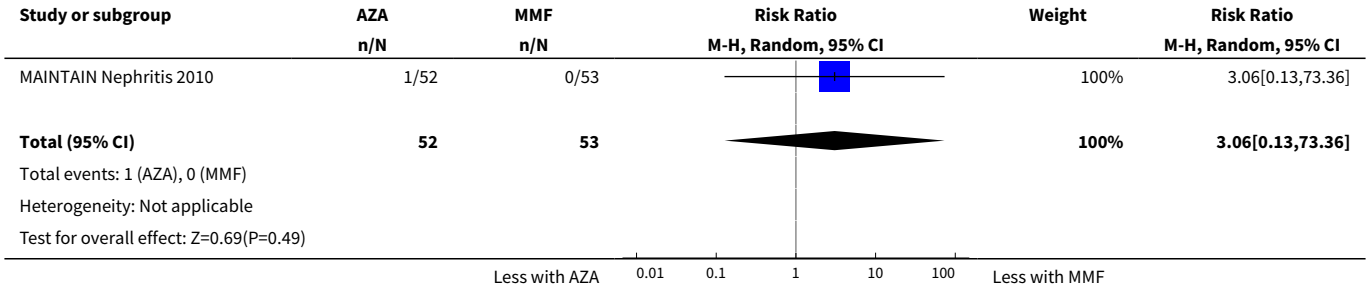




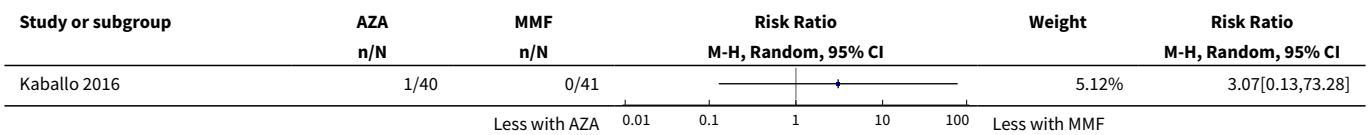
Analysis 26.8. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 8 Leucopenia.

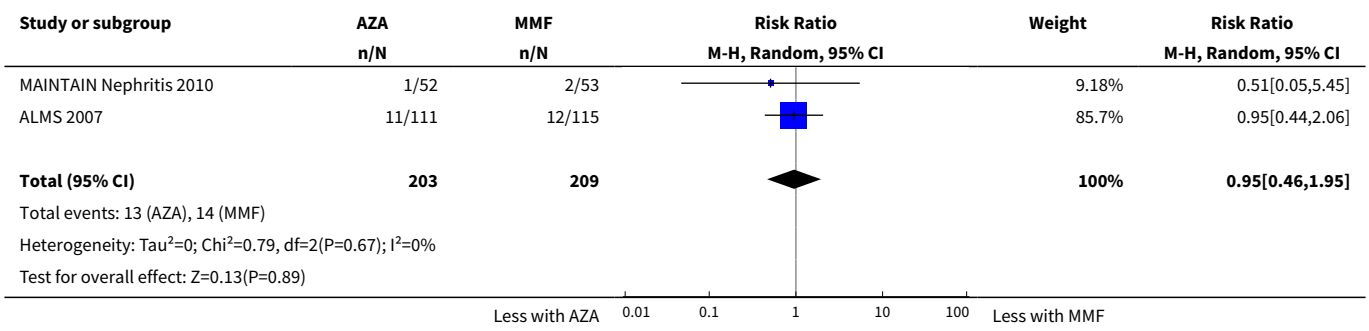


Analysis 26.9. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 9 Bone toxicity.

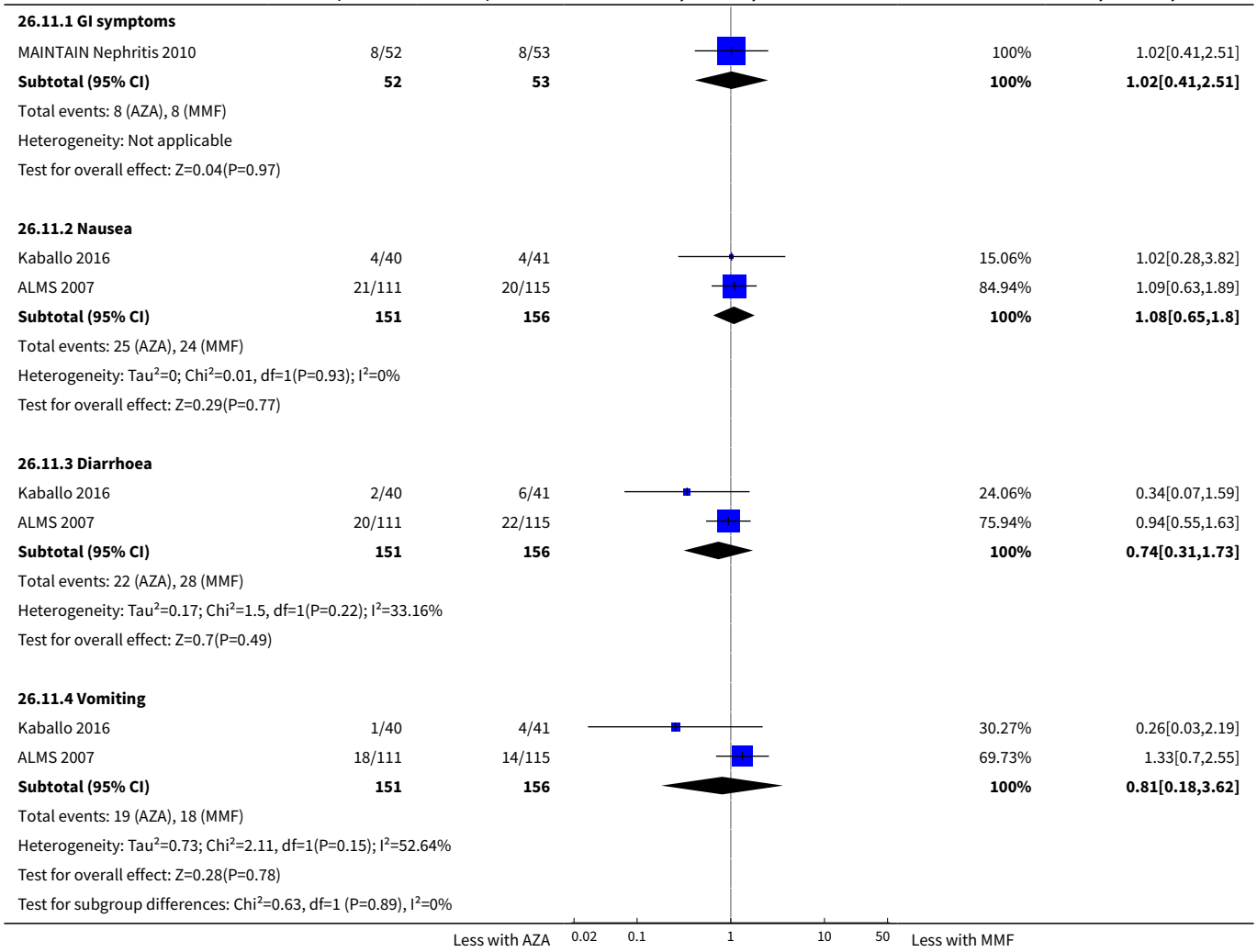


Analysis 26.10. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 10 Alopecia.

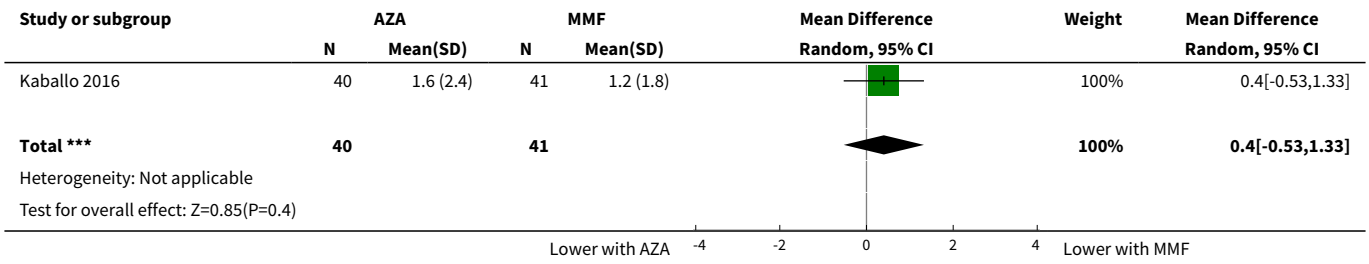




Analysis 26.11. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 11 Gastrointestinal (GI) adverse events.



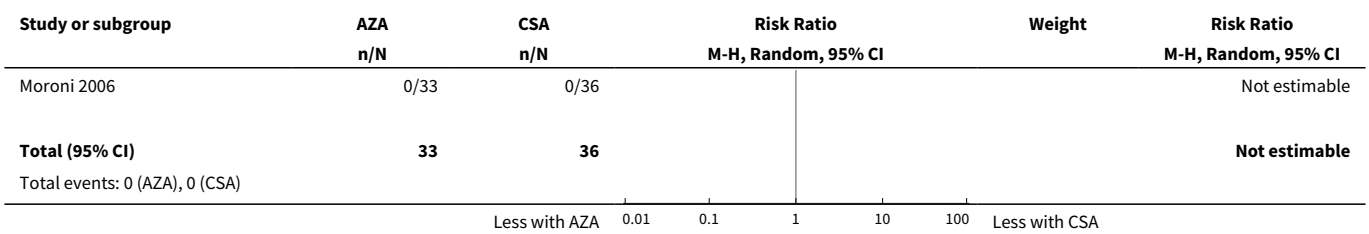
Analysis 26.12. Comparison 26 Maintenance: azathioprine (AZA) versus mycophenolate mofetil (MMF), Outcome 12 Daily proteinuria.

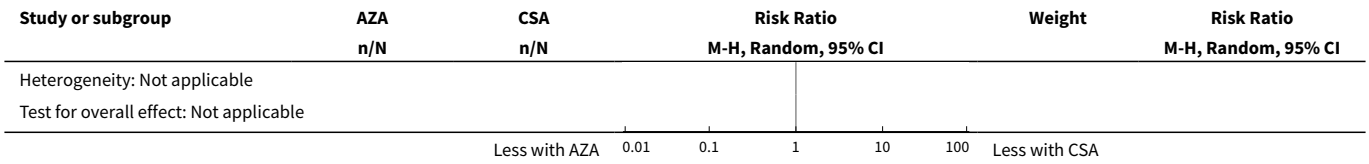


Comparison 27. Maintenance: azathioprine (AZA) versus cyclosporin (CSA)

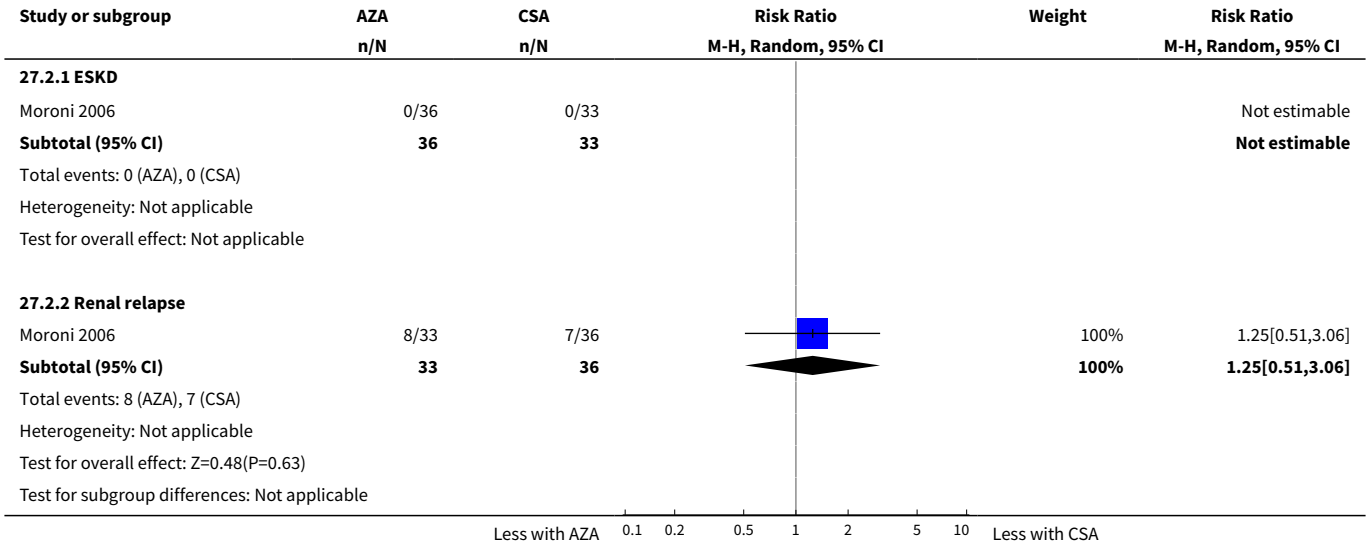
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 ESKD	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Renal relapse	1	69	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.51, 3.06]
3 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Major infection	1	69	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.01, 4.73]
4 Leucopenia	1	69	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.95, 7.86]
5 Gastrointestinal (GI) adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 GI disturbance	1	69	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.09, 0.97]
6 Daily proteinuria	1	69	Mean Difference (IV, Random, 95% CI)	0.15 [-0.23, 0.53]
7 Disease activity (SLEDAI)	1	69	Mean Difference (IV, Random, 95% CI)	-3.20 [-5.77, -0.63]

Analysis 27.1. Comparison 27 Maintenance: azathioprine (AZA) versus cyclosporin (CSA), Outcome 1 Death.

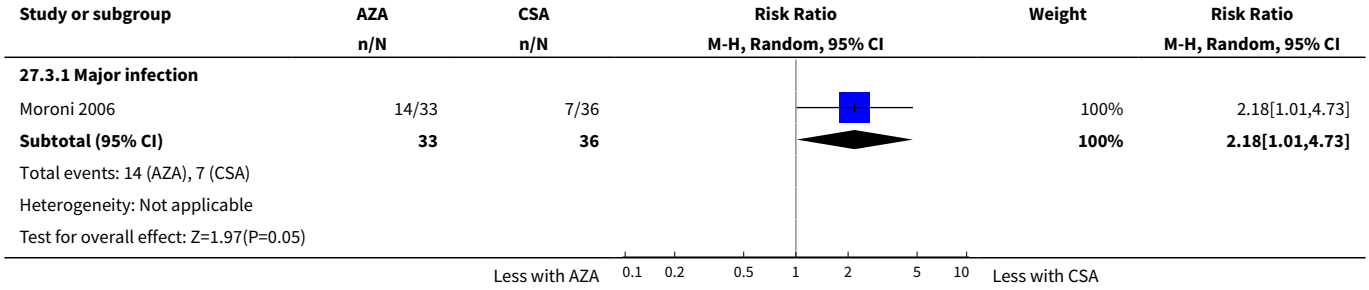




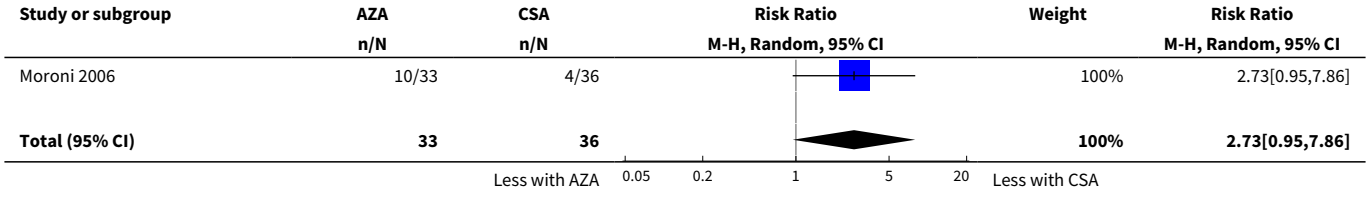
Analysis 27.2. Comparison 27 Maintenance: azathioprine (AZA) versus cyclosporin (CSA), Outcome 2 Adverse renal outcomes.

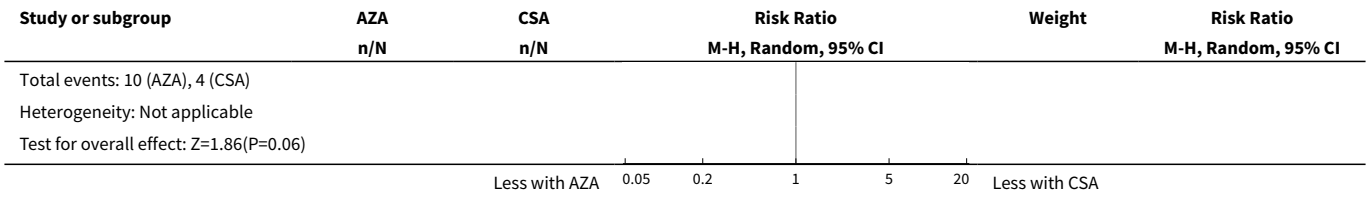


Analysis 27.3. Comparison 27 Maintenance: azathioprine (AZA) versus cyclosporin (CSA), Outcome 3 Infection.

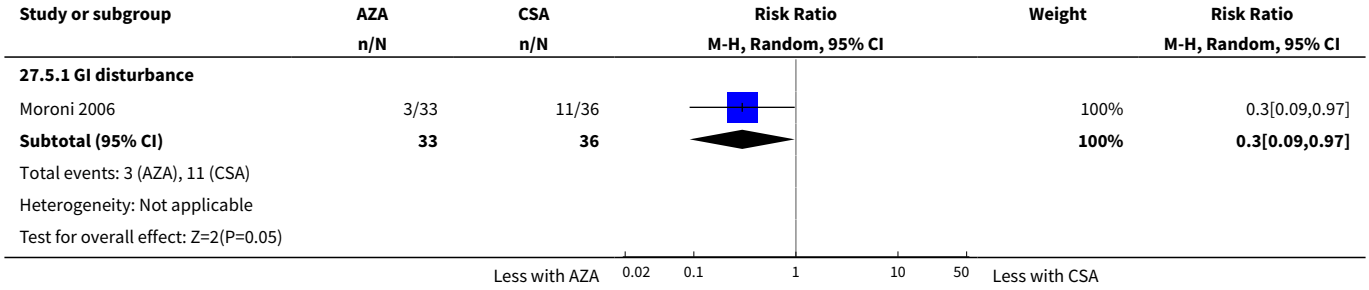


Analysis 27.4. Comparison 27 Maintenance: azathioprine (AZA) versus cyclosporin (CSA), Outcome 4 Leucopenia.

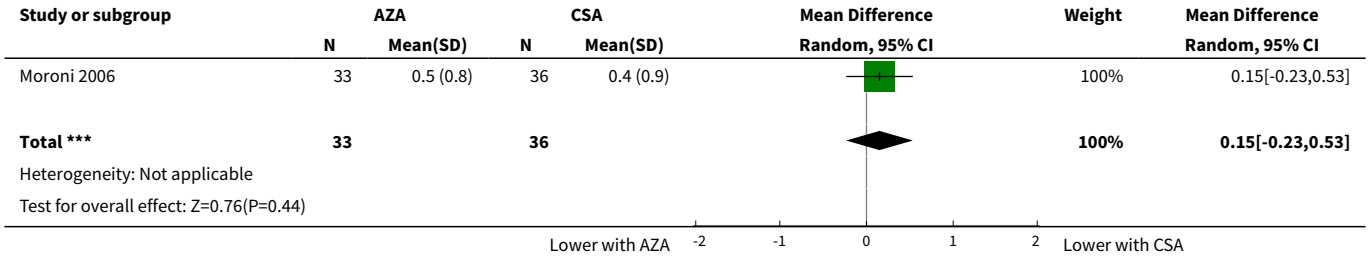




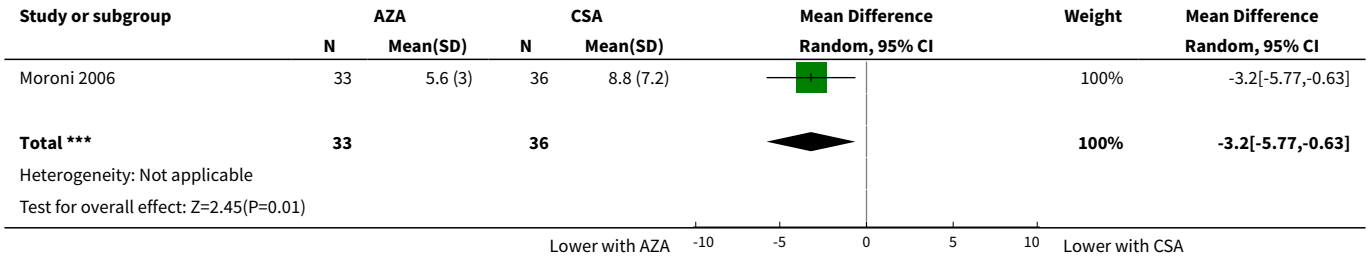
Analysis 27.5. Comparison 27 Maintenance: azathioprine (AZA) versus cyclosporin (CSA), Outcome 5 Gastrointestinal (GI) adverse events.



Analysis 27.6. Comparison 27 Maintenance: azathioprine (AZA) versus cyclosporin (CSA), Outcome 6 Daily proteinuria.



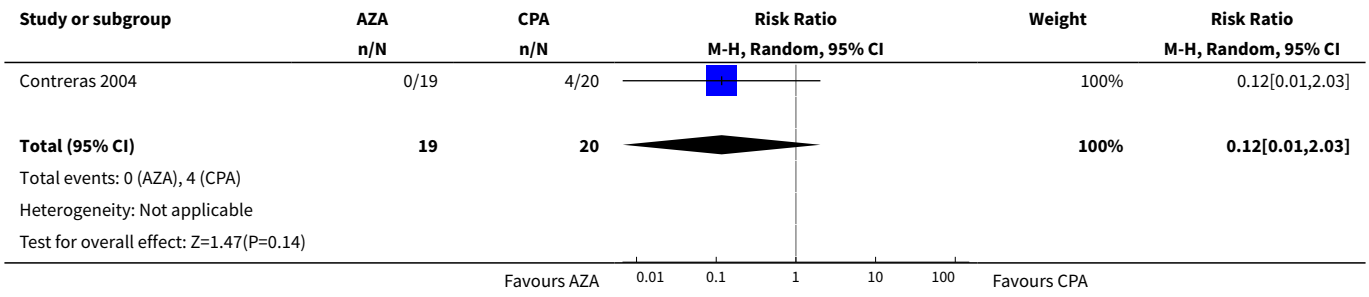
Analysis 27.7. Comparison 27 Maintenance: azathioprine (AZA) versus cyclosporin (CSA), Outcome 7 Disease activity (SLEDAI).



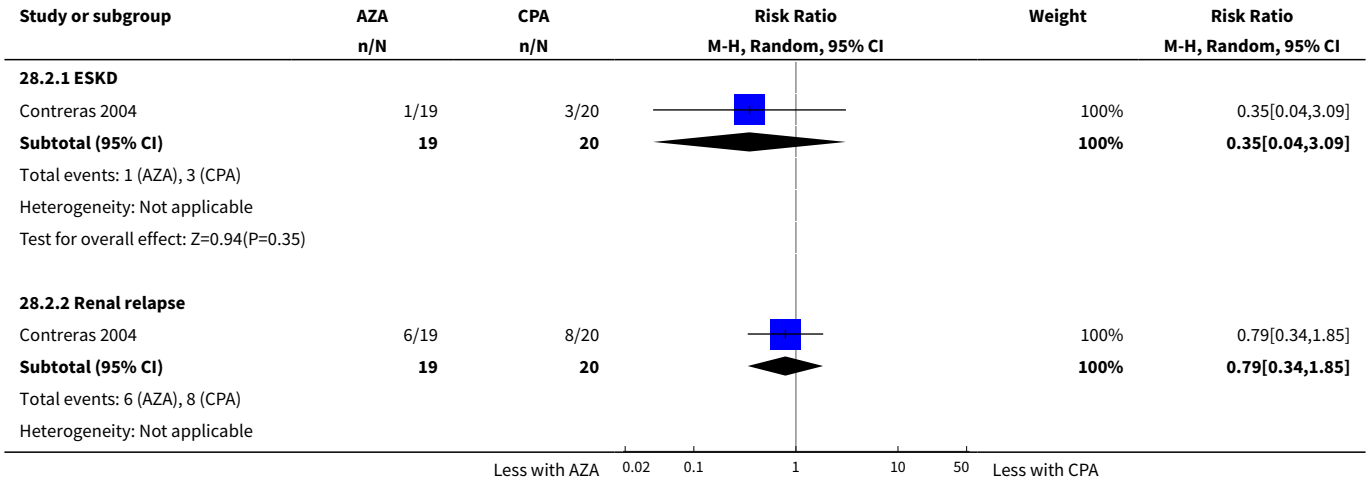
Comparison 28. Maintenance: azathioprine (AZA) versus cyclophosphamide (CPA)

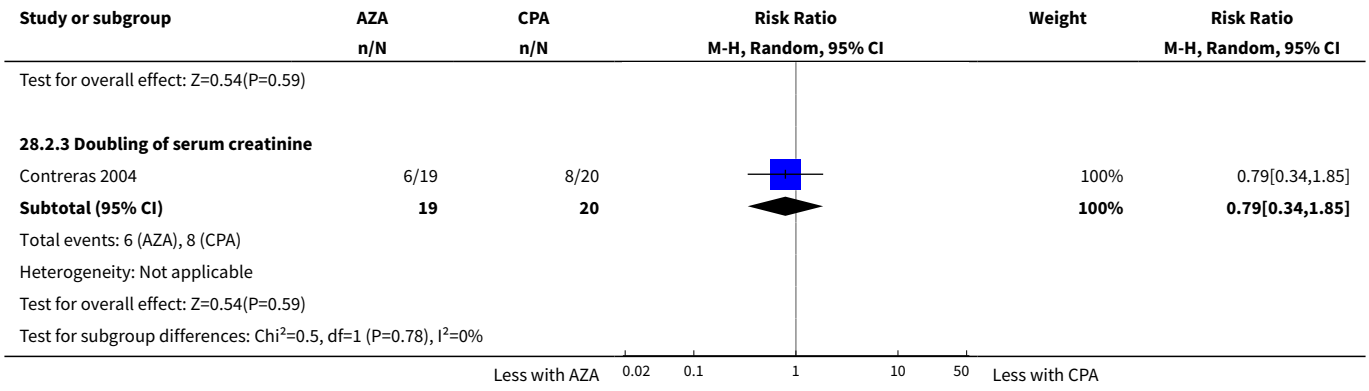
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	39	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.03]
2 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 ESKD	1	39	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.09]
2.2 Renal relapse	1	39	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.34, 1.85]
2.3 Doubling of serum creatinine	1	39	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.34, 1.85]
3 Bladder toxicity	1	39	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Creatinine clearance	1	38	Mean Difference (IV, Random, 95% CI)	-15.70 [-23.71, -7.69]

Analysis 28.1. Comparison 28 Maintenance: azathioprine (AZA) versus cyclophosphamide (CPA), Outcome 1 Death.

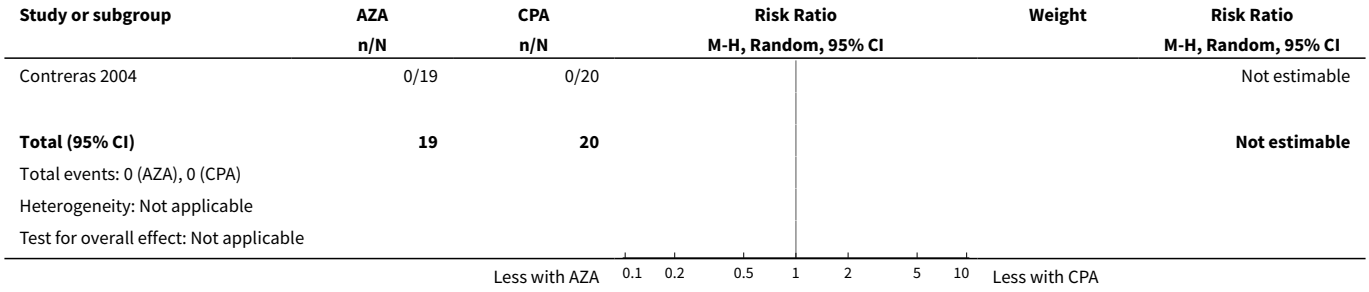


Analysis 28.2. Comparison 28 Maintenance: azathioprine (AZA) versus cyclophosphamide (CPA), Outcome 2 Adverse renal outcomes.

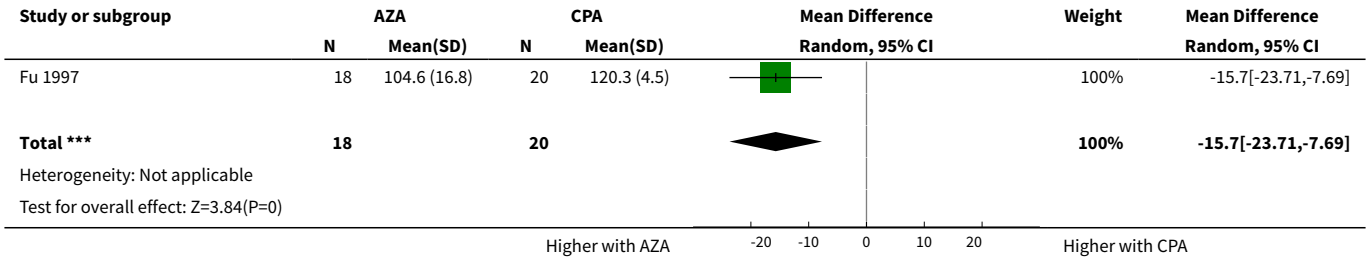




Analysis 28.3. Comparison 28 Maintenance: azathioprine (AZA) versus cyclophosphamide (CPA), Outcome 3 Bladder toxicity.



Analysis 28.4. Comparison 28 Maintenance: azathioprine (AZA) versus cyclophosphamide (CPA), Outcome 4 Creatinine clearance.

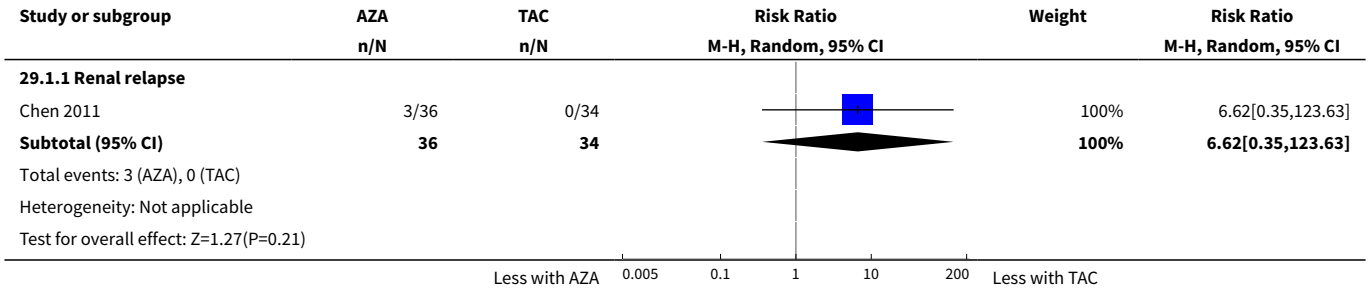


Comparison 29. Maintenance: azathioprine (AZA) versus tacrolimus (TAC)

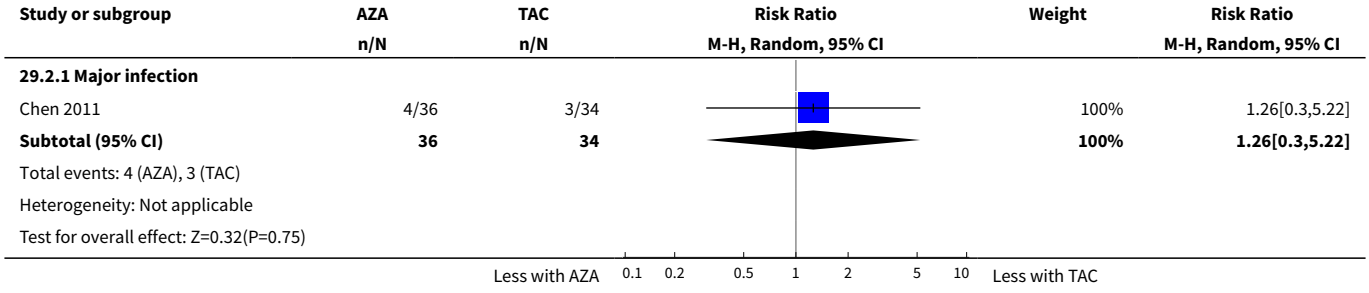
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse renal outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Renal relapse	1	70	Risk Ratio (M-H, Random, 95% CI)	6.62 [0.35, 123.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Major infection	1	70	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.30, 5.22]
3 Gastrointestinal (GI) adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 GI disturbance	1	70	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.18, 19.89]

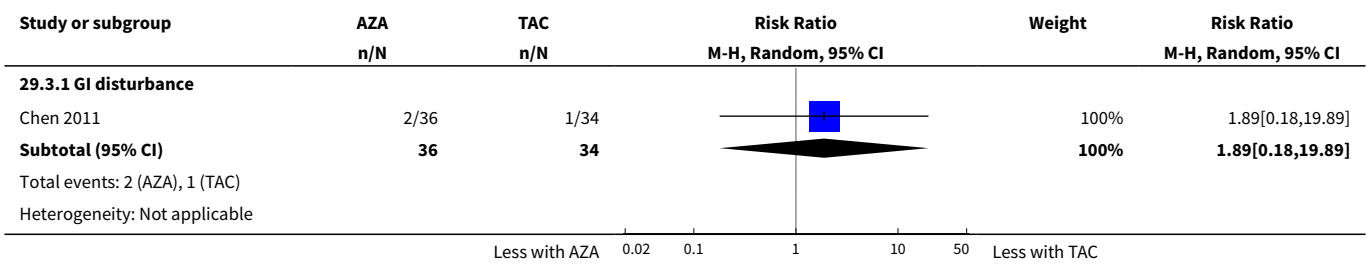
Analysis 29.1. Comparison 29 Maintenance: azathioprine (AZA) versus tacrolimus (TAC), Outcome 1 Adverse renal outcomes.

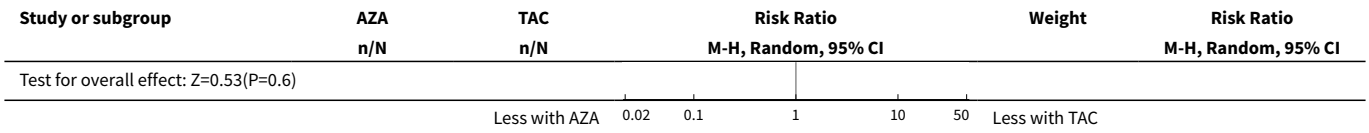


Analysis 29.2. Comparison 29 Maintenance: azathioprine (AZA) versus tacrolimus (TAC), Outcome 2 Infection.



Analysis 29.3. Comparison 29 Maintenance: azathioprine (AZA) versus tacrolimus (TAC), Outcome 3 Gastrointestinal (GI) adverse events.

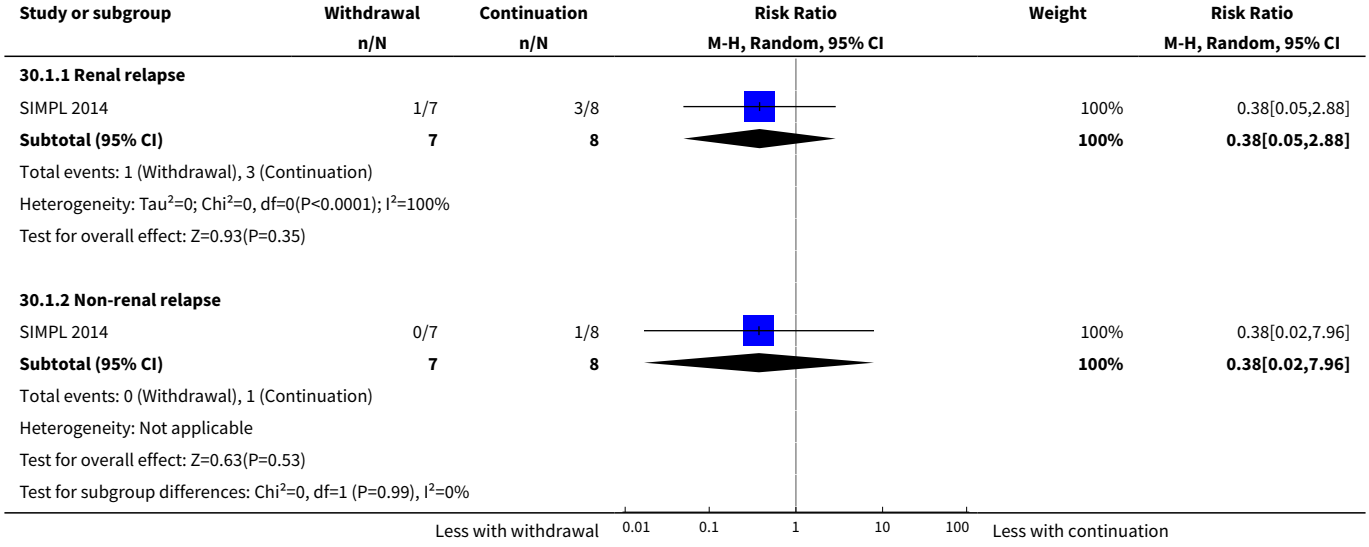




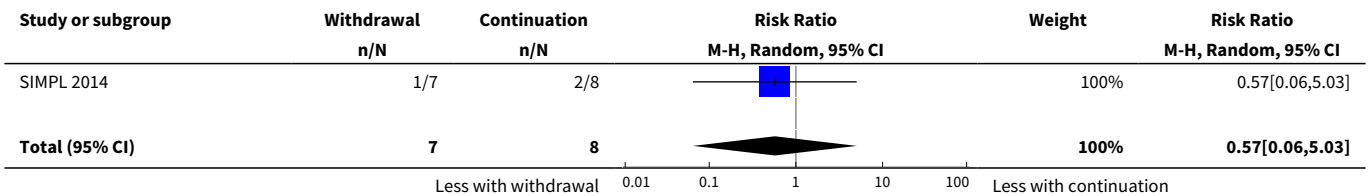
Comparison 30. Maintenance: prednisone withdrawal versus prednisone continuation

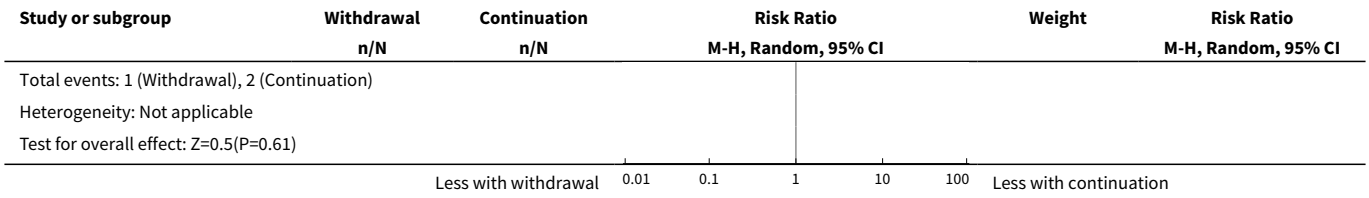
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Renal relapse	1	15	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.05, 2.88]
1.2 Non-renal relapse	1	15	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.02, 7.96]
2 Major infection	1	15	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.06, 5.03]

Analysis 30.1. Comparison 30 Maintenance: prednisone withdrawal versus prednisone continuation, Outcome 1 Relapse.



Analysis 30.2. Comparison 30 Maintenance: prednisone withdrawal versus prednisone continuation, Outcome 2 Major infection.

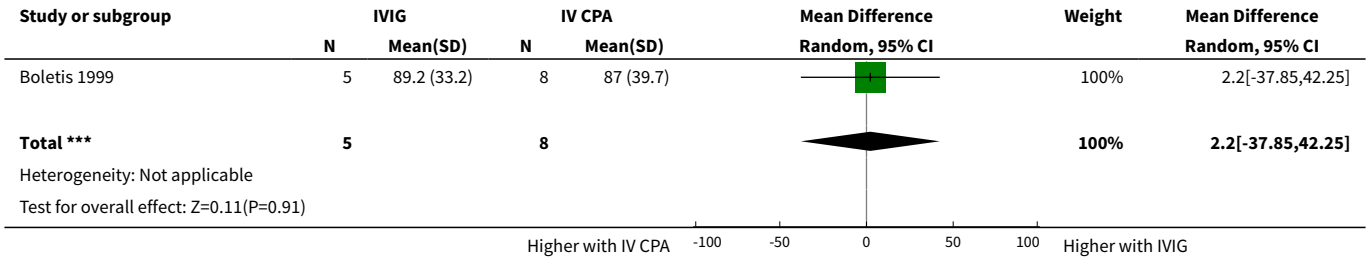




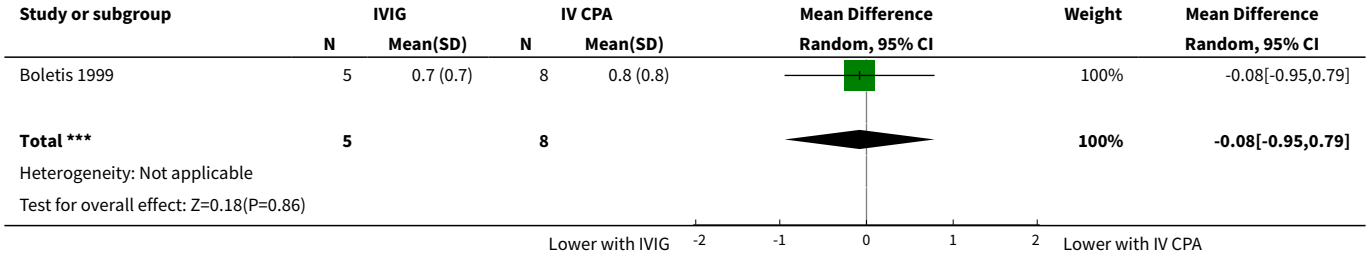
Comparison 31. Maintenance: intravenous immunoglobulin (IVIG) versus intravenous cyclophosphamide (IV CPA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine clearance	1	13	Mean Difference (IV, Random, 95% CI)	2.20 [-37.85, 42.25]
2 Daily proteinuria	1	13	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.95, 0.79]
3 Serum creatinine	1	14	Mean Difference (IV, Random, 95% CI)	-35.40 [-128.90, 58.10]

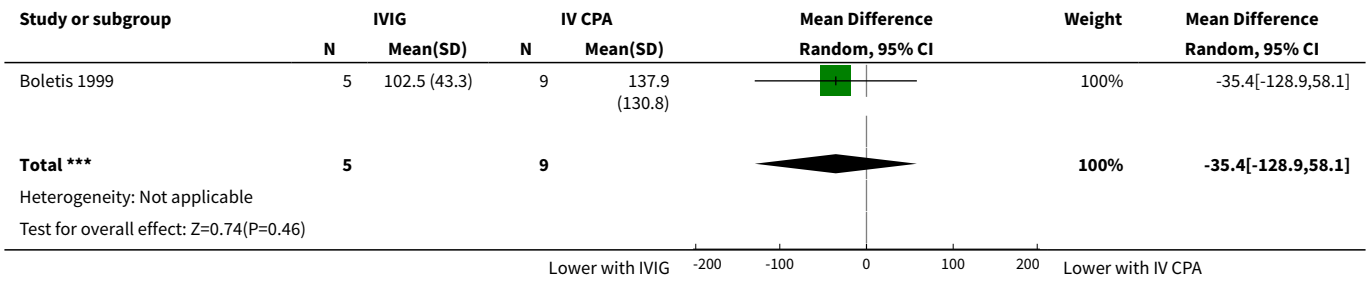
Analysis 31.1. Comparison 31 Maintenance: intravenous immunoglobulin (IVIG) versus intravenous cyclophosphamide (IV CPA), Outcome 1 Creatinine clearance.



Analysis 31.2. Comparison 31 Maintenance: intravenous immunoglobulin (IVIG) versus intravenous cyclophosphamide (IV CPA), Outcome 2 Daily proteinuria.



Analysis 31.3. Comparison 31 Maintenance: intravenous immunoglobulin (IVIG) versus intravenous cyclophosphamide (IV CPA), Outcome 3 Serum creatinine.



ADDITIONAL TABLES

Table 1. Description of health-related quality of life outcomes

Study ID	Comparison	Therapy	Measure	Time point	Description of results
ACCESS 2014	Abatacept versus placebo	Induction	SF-36 physical and mental component (mean ± SD)	6 months	• In the abatacept group after 6 months of therapy the physical component score increased from 39 ± 11 to 45.3 ± 11. In the placebo + standard of care therapy group after 6 months of therapy, the physical component score increased from 39 ± 10 to 46.5 ± 11 • In the abatacept group after 6 months of therapy the mental component score increased from 40 ± 13 to 45.9 ± 12. In the placebo + standard of care group after 6 months of therapy, the mental component score increased from 40 ± 13 to 46.5 ± 11
Furie 2014	Abatacept versus placebo	Induction	SF-36 (adjusted mean change ± SE)	12 months	• In the high dose abatacept group after 12 months of therapy the adjusted mean ± SE of SF-36 scores were: physical component 4.2 ± 0.91, mental component 2.5 ± 1.0, physical functioning 2.6 ± 0.96, role-physical 4.2 ± 1.2, bodily pain 4.5 ± 1.1, general health 4.7 ± 0.9, vitality 3.9 ± 0.98, social functioning 4.0 ± 1.0, role-emotional 1.6 ± 1.3, and mental health 3.1 ± 1.1 • In the low dose abatacept group after 12 months of therapy, the adjusted mean ± SE of SF-36 scores were: physical component, 5.0 ± 0.91, mental component 4.7 ± 1.0, physical functioning 4.2 ± 0.95, role-physical 6.9 ± 1.2, bodily pain 4.6 ± 1.0, general health 4.4 ± 0.89, vitality 4.6 ± 0.97, social functioning 6.1 ± 1.0, role-emotional 5.6 ± 1.3, and mental health 4.0 ± 1.1. In the placebo + standard of care group after 12 months of therapy, the adjusted mean ± SE of SF-36 scores were: physical component 3.8 ± 0.9, mental component 4.4 ± 1.0, physical functioning 2.8 ± 0.94, role-phys-

Table 1. Description of health-related quality of life outcomes *(Continued)*

					ical 5.3 ± 1.2, bodily pain 4.3 ± 1.0, general health 4.0 ± 0.88, vitality 4.8 ± 0.96, social functioning 5.1 ± 1.0, role-emotional 4.7 ± 1.3, and mental health 3.2 ± 1.1
LUNAR 2012	Rituximab versus placebo	Induction	SF-36 - physical functioning (mean change ± SD)	12 months	• In the rituximab group after 12 months of therapy the SF-36 physical functioning score increased by 4.8 ± 10.4 • In the placebo + standard of care therapy group, after 12 months of therapy the SF-36 physical functioning score increased by 5.7 ± 9.4

Table 2. Description of fatigue outcomes

Study ID	Comparison	Therapy	Measure	Time point	Description of results
Furie 2014	Abatacept versus placebo	Induction	Fatigue VAS (adjusted mean change ± SE)	6 months	• In the high dose abatacept group after 6 months of therapy the fatigue VAS decreased by 12.2 ± 2.7 • In the low dose abatacept group after 6 months of therapy the fatigue VAS decreased by 12.3 ± 2.7 • In the placebo + standard of care group after 6 months of therapy the fatigue VAS decreased by 11.1 ± 2.7
			Fatigue severity score (adjusted mean change ± SE)		• In the high dose abatacept group after 6 months of therapy the fatigue VAS decreased by 12.2 ± 2.7 • In the low dose abatacept group after 6 months of therapy the fatigue VAS decreased by 12.3 ± 2.7 • In the placebo + standard of care group after 6 months of therapy the fatigue VAS decreased by 11.1 ± 2.7

VAS - visual analogue scale

Table 3. Description of disease activity outcomes

Study ID	Comparison	Measure	Time point	Description of results
Induction therapy				
ACCESS 2014	Abatacept versus placebo	BILAG (mean ± SD)	6 months	• In the placebo + standard of care therapy group after 6 months of therapy the BILAG scores were 3.4 ± 1.8 • In the abatacept group after 6 months of therapy the BILAG scores were 3.8 ± 3.0
ALMS 2007	MMF versus IV CPA	SLEDAI (mean change ± SD)	6 months	• In the IV CPA group after 6 months of therapy the SLEDAI scores decreased by 6.6 ± 8.0

Table 3. Description of disease activity outcomes *(Continued)*

				• In the MMF group after 6 months of therapy the SLEDAI scores decreased by 6.2 ± 10.1 • The mean difference between the groups was 0.41 (95% CI -1.48 to 2.30)
Deng 2016	Leflunomide versus CPA	SLEDAI	6 months	"SLEDAI scores were reduced"
El-Shafey 2010	MMF versus IV CPA	SLAM (mean change ± SD)	6 months	• In the IV CPA group after 6 months of therapy SLAM scores decreased by 22.1 ± 7.72 • In the MMF group after 6 months of therapy SLAM scores decreased by 17.84 ± 7.25
Grootscholten 2006	IV CPA versus AZA	SLEDAI	24 months	"SLEDAI and VAS scores did not differ between groups and decreased significantly and paralleled each other (r = 0.673, P<0.01)"
Hong 2007	TAC versus IC CPA	SLEDAI	6 months	"SLEDAI level of FK506 (TAC) group is better than that of CPA group, (P<0.05)"
Houssiau 2002	High CPA versus low CPA	ECLAM	12 months	"ECLAM score significantly improved in both groups during the first year of follow-up. No significant difference was noted between patients in the low-dose and high-dose IV CYC groups for any of the parameters examined (P>0.05)"
Kamanamool 2017	MMF versus TAC	SLEDAI-2K (mean ± SD)	12 months	• In the MMF group, mean SLEDAI-2K was decreased from 11.6 ± 4.8 to 6.3 ± 3.9 after 6 months therapy, and 5.4 ± 4.4 after 12 months • In the TAC group, mean SLEDAI-2K was decreased from 9.0 ± 3.7 to 6.3 ± 5.1 after 6 months and to 7.1 ± 5.4 after 12 months • The results showed a similar pattern with respect to renal SLEDAI and modified SLEDAI
Li 2009c	Rituximab versus rituximab + CPA	SLEDAI (mean ± SD)	12 months	• The overall SLEDAI of both groups at baseline was 9.2 ± 3.4, this decreased to 2.5 ± 2.5 after 12 months of therapy • There was significant improvements in SLEDAI in both groups
Li 2012	MMF versus TAC versus IV CPA	SLEDAI (mean ± SD)	6 months	• In all three groups (IV CPA, MMF, TAC) after 6 months of therapy the SLEDAI across all three groups was 7.7 ± 4.7. In all three groups the SLEDAI scores decreased
Liu 2015	MMF + TAC versus IV CPA	SLEDAI (mean change ± SD)	6 months	• In the IV CPA group after 6 months of therapy SLEDAI decreased by 11.01 ± 6.07 • In the MMF+TAC group after 6 months of therapy SLEDAI decreased by 8.55 ± 5.05
Loo 2010	PEX versus IA	SLEDAI	6 months	"The SLEDAI gap between the study groups remained the same throughout the study. The improvements in SLEDAI score of both groups were also significantly demonstrated."
LUNAR 2012	Rituximab versus placebo	BILAG (Time adjusted area un-	12 months	• In the rituximab group after 12 months of therapy SLEDAI decreased to 8.49 ± 5.79

Table 3. Description of disease activity outcomes *(Continued)*

		der the curve minus baseline mean ± SD)		• In the placebo + standard of care group after 12 months of therapy SLEDAI decreased to 8.58 ± 5.14
Mehra 2018	High-dose CPA versus low-dose CPA	Renal SLEDAI	6 months	At 24 weeks, renal SLEDAI were similar between high-dose and low-dose cyclophosphamide
Mok 2016	MMF versus TAC	Renal SLEDAI (mean ± SD)	6 months	• In the MMF group after 6 months of therapy renal SLEDAI scores were 3.9 ± 3.1 • In the tacrolimus group after 6 months of therapy renal SLEDAI scores were 3.3 ± 3.1
		Extrarenal SLEDAI (mean ± SD)		• In the MMF group after 6 months of therapy extrarenal SLEDAI scores were 1.7 ± 1.9 • In the tacrolimus group after 6 months of therapy extrarenal SLEDAI scores were 1.9 ± 1.7
MyLupus 2011	Standard dose PRED versus reduced dose PRED	Global BILAG (mean ± SD)	6 months	For both groups (reduced dose and standard dose corticosteroids) at the end of 6 months of treatment global BILAG reduced from 14 ± 5.4 to 5.0 ± 3.8 (P < 0.001)
		SLEDAI (mean ± SD)		For both groups (reduced dose and standard dose corticosteroids) at the end of 6 months of treatment SLEDAI reduced from16.2 ± 6.9 to 6.2 ± 5.1 (P < 0.001)
Ong 2005	MMF versus IV CPA	SLEDAI (mean change ± SD)	6 months	• In the IV CPA group after 6 months of therapy SLEDAI decreased by 6.8 ± 6.6 • In the MMF group after 6 months of therapy SLEDAI decreased by -7.2 ± 7.7
Rathi 2016	MMF versus IV CPA	SLEDAI	6 months	"SLEDAI improved significantly in both the groups over the study period, and there were no differences between the treatment groups."
Rovin 2016	Sirukumab versus placebo	SLEDAI-2K	6 months	"Eighteen patients (14 in the sirukumab group and 4 in the placebo group) had a SLEDAI-2K RI-50 response at any time through week 24."
		Physician's and patients global assessment of disease activity		"Neither the patient's nor the physician's global assessment scores of disease activity showed notable improvement over time in either treatment group (data not shown)."
Wallace 1998	PE versus standard of care	SLAM (mean ± SD)	12 months	• In the standard of care group after 12 months of therapy SLAM scores were 6.44 ± 4.16 • In the PEX group after 12 months of therapy SLAM scores were 7.11 ± 4.78
Maintenance therapy				
MAINTAIN Nephritis 2010	AZA versus MMF	SLEDAI	36 months	"SLEDAI and ECLAM scores decreased similarly in both groups"
		ECLAM		

Table 3. Description of disease activity outcomes *(Continued)*

Moroni 2006	AZA versus CSA	SLEDAI (mean ± SD)	24 months	• In the AZA group after 24 months of therapy SLEDAI scores were 5.6 ± 3.0 • In the CSA group after 24 months of therapy SLEDAI scores were 8.8 ± 7.2

AZA - azathioprine; BILAG - British Isles Lupus Assessment Group; CPA - cyclophosphamide; CSA - cyclosporin; ECLAM - European Consensus Lupus Activity Measurement; IA - immunoadsorption; MMF - mycophenolate mofetil; IV - intravenous; PE - plasma exchange; PEX - plasmapheresis; PRED - corticosteroid; SLAM - Systemic Lupus Activity Measure; SLEDAI - Systemic Lupus Erythematosus Disease Activity Index; TAC - tacrolimus

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).

(Continued)

	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.
	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 can-

(Continued)

	not 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
20 June 2018	New citation required and conclusions have changed	New studies incorporated
20 June 2018	New search has been performed	Review updated; 26 new studies added

HISTORY

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

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

Each author individually contributed the following:

- David J Tunnicliffe: conduct data analysis, author
- Suetonia C Palmer: conduct data analysis, author
- Lorna Henderson: 2012 update design, analysis, reading drafts and co-author
- Philip Masson: 2012 update design, analysis, reading drafts and co-author
- Jonathan C Craig: reading drafts and co-author
- Allison Tong: reading drafts and co-author
- Davinder Singh-Grewal: reading drafts and co-author

- Robert Flanc: original design and author
- Matthew Roberts: original design and author
- Angela Webster: 2012 update design, analysis, reading drafts and co-author
- Giovanni FM Strippoli: conduct data analysis, reading drafts, original design and author

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Cochrane Kidney and Transplant, Australia.

External sources

- Cochrane Review Support Programme 2017, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced quality assessment checklist.

NOTES

The numbering of comparisons for induction therapy in the data and analyses section is reflected throughout the main text.

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