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Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients (Review)

Hahn D, Hodson EM, Hamiwka LA, Lee VWS, Chapman JR, Craig JC, Webster AC

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[Intervention Review]

Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients

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ABSTRACT

Background

Kidney transplantation is the therapy of choice for many patients with end-stage kidney disease (ESKD) with an improvement in survival rates and satisfactory short term graft survival. However, there has been little improvement in long-term survival. The place of target of rapamycin inhibitors (TOR-I) (sirolimus, everolimus), which have different modes of action from other commonly used immunosuppressive agents, in kidney transplantation remains uncertain. This is an update of a review first published in 2006.

Objectives

To evaluate the short and long-term benefits and harms of TOR-I (sirolimus and everolimus) when used in primary immunosuppressive regimens for kidney transplant recipients.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 20 September 2019 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register were identified through searches of CENTRAL, MEDLINE and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs in which drug regimens, containing TOR-I commenced within seven days of transplant, were compared to alternative drug regimens, were included without age restriction, dosage or language of report.

Data collection and analysis

Three authors independently assessed study eligibility, risk of bias, and extracted data. Results were reported as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) with 95% CI for continuous outcomes. Statistical analyses were performed using the random-effects model. The certainty of the evidence was assessed using GRADE

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Main results

Seventy studies (17,462 randomised participants) were included; eight studies included two comparisons to provide 78 comparisons. Outcomes were reported at six months to three years post transplant.

Risk of bias was judged to be low for sequence generation in 25 studies, for allocation concealment in 23 studies, performance bias in four studies, detection bias in 65 studies, attrition bias in 45 studies, selective reporting bias in 48 studies, and for other potential bias in three studies. Risk of bias was judged to be at high risk of bias for sequence generation in two studies, allocation concealment in two studies, performance bias in 61 studies, detection bias in one study, attrition bias in four studies, for selective reporting bias in 11 studies and for other potential risk of bias in 46 studies.

Compared with CNI and antimetabolite, TOR-I with antimetabolite probably makes little or no difference to death (RR 1.31, 95% CI 0.87 to 1.98; 19 studies) or malignancies (RR 0.86, 95% CI 0.50 to 1.48; 10 studies); probably increases graft loss censored for death (RR 1.32, 95% CI 0.96 to 1.81; 15 studies), biopsy-proven acute rejection (RR 1.60, 95% CI 1.25 to 2.04; 15 studies), need to change treatment (RR 2.42, 95% CI 1.88 to 3.11; 14 studies) and wound complications (RR 2.56, 95% CI 1.94 to 3.36; 12 studies) (moderate certainty evidence); but reduces CMV infection (RR 0.43, 95% CI 0.29 to 0.63; 13 studies) (high certainty evidence).

Compared with antimetabolites and CNI, TOR-I with CNI probably makes little or no difference to death (RR 1.06, 95% CI 0.84 to 1.33; 31 studies), graft loss censored for death (RR 1.09, 95% CI 0.82 to 1.45; 26 studies), biopsy-proven acute rejection (RR 0.95, 95% CI 0.81 to 1.12; 24 studies); and malignancies (RR 0.83, 95% CI 0.64 to 1.07; 17 studies); probably increases the need to change treatment (RR 1.56, 95% CI 1.28 to 1.90; 25 studies), and wound complications (RR 1.56, 95% CI 1.28 to 1.91; 17 studies); but probably reduces CMV infection (RR 0.44, 95% CI 0.34 to 0.58; 25 studies) (moderate certainty evidence).

Lower dose TOR-I and standard dose CNI compared with higher dose TOR-I and reduced dose CNI probably makes little or no difference to death (RR 1.07, 95% CI 0.64 to 1.78; 9 studies), graft loss censored for death (RR 1.09, 95% CI 0.54 to 2.20; 8 studies), biopsy-proven acute rejection (RR 0.87, 95% CI 0.67 to 1.13; 8 studies), and CMV infection (RR 1.42, 95% CI 0.78 to 2.60; 5 studies) (moderate certainty evidence); and may make little or no difference to wound complications (RR 0.95, 95% CI 0.53 to 1.71; 3 studies), malignancies (RR 1.04, 95% CI 0.36 to 3.04; 7 studies), and the need to change treatments (RR 1.18, 95% CI 0.58 to 2.42; 5 studies) (low certainty evidence).

Lower dose of TOR-I compared with higher doses probably makes little or no difference to death (RR 0.84, 95% CI 0.67 to 1.06; 13 studies), graft loss censored for death (RR 0.92, 95% CI 0.71 to 1.19; 12 studies), biopsy-proven acute rejection (RR 1.26, 95% CI 1.10 to 1.43; 11 studies), CMV infection (RR 0.87, 95% CI 0.63 to 1.21; 9 studies), wound complications (RR 0.92, 95% CI 0.66 to 1.29; 7 studies), and malignancy (RR 0.84, 95% CI 0.54 to 1.32; 10 studies) (moderate certainty evidence); and may make little or no difference to the need to change treatments (RR 0.91, 95% CI 0.78 to 1.05; 10 studies) (low certainty evidence).

It is uncertain whether sirolimus and everolimus differ in their effects on kidney function and lipid levels because the certainty of the evidence is very low based on a single small study with only three months of follow-up.

Authors' conclusions

In studies with follow-up to three years, TOR-I with an antimetabolite increases the risk of graft loss and acute rejection compared with CNI and an antimetabolite. TOR-I with CNI potentially offers an alternative to an antimetabolite with CNI as rates of graft loss and acute rejection are similar between interventions and TOR-I regimens are associated with a reduced risk of CMV infections. Wound complications and the need to change immunosuppressive medications are higher with TOR-I regimens. While further new studies are not required, longer-term follow-up data from participants in existing methodologically robust RCTs are needed to determine how useful immunosuppressive regimens, which include TOR-I, are in maintaining kidney transplant function and survival beyond three years.

PLAIN LANGUAGE SUMMARY

Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients

What is the issue?

Kidney transplantation is the treatment of choice for many patients with end-stage kidney disease. However, some kidney transplants do not work for long periods so it is important to find ways to improve long-term transplant function by choosing the best therapies to maintain kidney function and keep transplant recipients healthy with minimal side effects.

What did we do?

We reviewed 70 studies, with 17,462 randomised participants, which compared TOR-1 (everolimus or sirolimus) with other agents for initial immunosuppressive therapy for kidney transplant recipients.

What did we find?

We found that everolimus or sirolimus combined with cyclosporin or tacrolimus prevented kidney transplant failure and rejection as effectively as mycophenolate (an antimetabolite) with cyclosporin or tacrolimus in studies with follow-up from six months to three years.

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The risk for viral infections (CMV and BK) was lower with TOR-I. However, wound complications were more common with TOR-I and more people had to stop TOR-I and change to other immunosuppressive medications.

Conclusions

Although the results indicate that TOR-I were effective in preventing transplant failure and rejection in the short term, studies do not follow-up participants beyond six months to three years. Therefore, we do not need further studies but we do need much longer periods of follow-up of participants in existing studies to determine how useful these medications are for maintaining kidney transplant function in the longer term.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): main outcomes for primary immunosuppression in kidney transplant recipients

TOR-I versus CNI: outcomes up to 2 years (main outcomes) for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant services

Intervention: TOR-I
Comparison: CNI

Outcomes (up to 2 years for primary outcomes)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with CNI	Risk with TOR-I			
Death (all causes)	25 per 1,000	33 per 1,000 (22 to 50)	RR 1.31 (0.87 to 1.98)	3618 (19)	⊕⊕⊕⊖ MODERATE [1]
Graft loss censored for death	51 per 1,000	68 per 1,000 (49 to 93)	RR 1.32 (0.96 to 1.81)	3277 (14)	⊕⊕⊕⊖ MODERATE [1]
Biopsy-proven acute rejection	196 per 1,000	333 per 1,000 (258 to 429)	RR 1.70 (1.32 to 2.19)	3309 (15)	⊕⊕⊕⊖ MODERATE[1]
CMV infection	157 per 1,000	68 per 1,000 (46 to 99)	RR 0.43 (0.29 to 0.63)	2026 (13)	⊕⊕⊕⊕ HIGH
Adverse wound outcomes: all complications	77 per 1,000	198 per 1,000 (150 to 260)	RR 2.56 (1.94 to 3.36)	1679 (12)	⊕⊕⊕⊖ MODERATE [1]
All malignancies	24 per 1,000	20 per 1,000 (12 to 35)	RR 0.86 (0.50 to 1.48)	2584 (10)	⊕⊕⊕⊖ MODERATE [1]
Number needing to change treatment	132 per 1,000	320 per 1,000 (249 to 412)	RR 2.42 (1.88 to 3.11)	3148 (14)	⊕⊕⊕⊖ MODERATE [1]

*__The risk in the intervention group__ (and its 95% CI) 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; **CMV**: cytomegalovirus

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

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Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] few events leading to wide confidence intervals

Summary of findings 2. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes for primary immunosuppression in kidney transplant recipients

TOR-I versus CNI: outcomes up to two years (secondary outcomes) for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant services

Intervention: TOR-I
Comparison: CNI: outcomes up to two years (secondary outcomes)

Outcomes (up to 2 years for secondary outcomes)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with CNI	Risk with TOR-I			
New-onset diabetes mellitus	60 per 1,000	56 per 1,000 (42 to 76)	RR 0.93 (0.69 to 1.26)	2791 (13)	⊕⊕⊕⊖ MODERATE [1]
Lymphoma/PTLD	2 per 1,000	6 per 1,000 (2 to 19)	RR 2.47 (0.78 to 7.86)	2537 (8)	⊕⊕⊕⊖ MODERATE [1]
Tremor	204 per 1,000	51 per 1,000 (31 to 83)	RR 0.25 (0.15 to 0.41)	799 (6)	⊕⊕⊕⊕ HIGH
GFR (mL/min)	The mean GFR was 2.2 mL/min higher with TOR-I (1.29 lower to 5.68 higher) than CNI		--	2983 (15)	⊕⊕⊖⊖ LOW [2 3]
Cholesterol (mmol/L)	The mean cholesterol level was 0.77 mmol/L higher with TOR-I (0.45 higher to 1.09 higher) than CNI		--	579 (7)	⊕⊕⊖⊖ LOW [1 2]
Triglycerides (mmol/L)	The mean triglyceride level 0.57 mmol/L higher with TOR-I (0.28 higher to 0.86 higher) than CNI		--	843 (8)	⊕⊕⊖⊖ LOW [1 2]
Thrombocytopenia	38 per 1,000	200 per 1,000	RR 5.26	593 (4)	⊕⊕⊖⊖

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	(109 to 367)	(2.87 to 9.63)		LOW [1,2]

*__The risk in the intervention group__ (and its 95% CI) 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; **PTLD:** post-transplant lymphoproliferative disease; **GRF:** glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Small studies/ few events with wide confidence intervals
[2] Unexplained heterogeneity

Summary of findings 3. Target of rapamycin inhibitors (TOR-I) versus antimetabolites: primary outcomes for primary immunosuppression in kidney transplant recipients

TOR-I versus antimetabolites: outcomes up to 2 years (primary outcomes) for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant services
Intervention: TOR-I
Comparison: antimetabolites

Outcomes (up to 2 years for primary outcomes)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with antimetabolites	Risk with TOR-I			
Death (all causes)	29 per 1,000	31 per 1,000 (24 to 38)	RR 1.06 (0.84 to 1.33)	10,482 (31)	⊕⊕⊕⊖ MODERATE [1]
Graft loss (censored)	35 per 1,000	38 per 1,000 (29 to 51)	RR 1.09 (0.82 to 1.45)	8966 (26)	⊕⊕⊕⊖ MODERATE [1]
Biopsy-proven acute rejection	141 per 1,000	134 per 1,000 (113 to 158)	RR 0.95 (0.81 to 1.12)	10,101 (24)	⊕⊕⊕⊖ MODERATE [2]
CMV infection	136 per 1,000	59 per 1,000 (46 to 78)	RR 0.44 (0.34 to 0.58)	10,049 (26)	⊕⊕⊕⊖ MODERATE [2]

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Adverse wound outcomes: all complications	155 per 1,000	241 per 1,000 (199 to 297)	RR 1.56 (1.28 to 1.90)	6913 (17)	⊕⊕⊕⊖ MODERATE [2]
All malignancies	34 per 1,000	28 per 1,000 (22 to 36)	RR 0.83 (0.64 to 1.07)	8799 (17)	⊕⊕⊕⊖ MODERATE [1]
Number needing to change treatment	174 per 1,000	248 per 1,000 (203 to 302)	(RR 1.56, 1.28 to 1.90)	9747 (25)	⊕⊕⊕⊖ MODERATE [2]

*__The risk in the intervention group__ (and its 95% CI) 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; **CMV:** cytomegalovirus

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Few events leading to wide confidence intervals
[2] Significant heterogeneity present

Summary of findings 4. Target of rapamycin inhibitors (TOR-I) versus antimetabolites: secondary outcomes for primary immunosuppression in kidney transplant recipients

TOR-I compared to antimetabolites: outcomes to 2 years (secondary outcomes) for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant units
Intervention: TOR-I
Comparison: antimetabolites

Outcomes (up to 2 years for secondary outcomes)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with antimetabolites	Risk with TOR-I			
New-onset diabetes mellitus	85 per 1,000	103 per 1,000 (86 to 124)	RR 1.28, (1.07 to 1.54)	8728 (23)	⊕⊕⊕⊖ MODERATE [1]
BK virus infection	84 per 1,000	52 per 1,000 (42 to 64)	RR 0.62 (0.50 to 0.76)	5152 (12)	⊕⊕⊕⊕ HIGH

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GFR (mL/min)	The mean GFR was 2.89 mL/min lower with TOR-I (4.91 lower to 0.88 lower) than with antimetabolites		--	7099 (25)	⊕⊕⊕⊖ MODERATE [2]
Hypercholesterolaemia	102 per 1,000	187 per 1,000 (151 to 229)	RR 1.83 (1.48 to 2.25)	5725 (12)	⊕⊕⊖⊖ LOW [1 2]
Hypertriglyceridaemia	143 per 1,000	212 per 1,000 (180 to 249)	RR 1.48 (1.26 to 1.74)	4698 (9)	⊕⊕⊕⊖ MODERATE[1]
Leucopenia	123 per 1,000	50 per 1,000 (38 to 65)	RR 0.43 (0.33 to 0.56)	8396 (15)	⊕⊕⊖⊖ LOW [1 2]
Thrombocytopenia	33 per 1,000	65 per 1,000 (46 to 92)	RR 1.96 (1.38 to 2.79)	5028 (8)	⊕⊕⊖⊖ LOW [1 3]

*__The risk in the intervention group__ (and its 95% CI) 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; **GFR:** glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Funnel plot shows few studies reporting participants without events suggesting publication bias
[2] Significant heterogeneity between studies
[3] Few events with wide confidence intervals

Summary of findings 5. Variable target of rapamycin inhibitor (TOR-I) and calcineurin inhibitor (CNI): primary outcomes for primary immunosuppression in kidney transplant recipients

Variable TOR-I and CNI: primary outcomes for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant centres
Intervention: lower dose TOR-I and standard CNI
Comparison: higher dose TOR-I and reduced CNI

Outcomes (up to 2 years for primary outcomes)	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants	Certainty of the evidence

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	Risk with higher dose TOR-I	Risk with low dose TOR-I		(studies)	(GRADE)
Death (all causes)	39 per 1,000	41 per 1,000 (25 to 69)	RR 1.07 (0.64 to 1.78)	1501 (9)	⊕⊕⊕⊖ MODERATE [1]
Graft loss (censored)	36 per 1,000	39 per 1,000 (19 to 79)	RR 1.09 (0.54 to 2.20)	1385 (8)	⊕⊕⊕⊖ MODERATE [1]
Biopsy-proven acute rejection	155 per 1,000	135 per 1,000 (104 to 175)	RR 0.87 (0.67 to 1.13)	1381 (8)	⊕⊕⊕⊖ MODERATE [1]
CMV infection	40 per 1,000	57 per 1,000 (32 to 105)	RR 1.42 (0.78 to 2.60)	865 (5)	⊕⊕⊕⊖ MODERATE [2]
Adverse wound outcomes: all complications	135 per 1,000	128 per 1,000 (72 to 231)	RR 0.95 (0.53 to 1.71)	291 (3)	⊕⊕⊖⊖ LOW [3]
All malignancies	15 per 1,000	16 per 1,000 (5 to 46)	RR 1.04 (0.36 to 3.04)	1163 (7)	⊕⊕⊖⊖ LOW [1]
Number needing to change treatment	186 per 1,000	219 per 1,000 (108 to 450)	RR 1.18 (0.58 to 2.42)	734 (5)	⊕⊕⊖⊖ LOW [4]

*__The risk in the intervention group__ (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; **CMV:** cytomegalovirus

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Few events leading to wide confidence intervals
[2] Few events in only five studies; wide confidence intervals
[3] Only reported in three studies; wide confidence intervals
[4] Significant heterogeneity

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Summary of findings 6. Variable target of rapamycin inhibitor (TOR-I) and calcineurin inhibitor (CNI): secondary outcomes for primary immunosuppression in kidney transplant recipients

Variable TOR-I and CNI: secondary outcomes for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant centres
Intervention: lower dose TOR-I and standard CNI
Comparison: higher dose TOR-I and reduced CNI

Outcomes (up to 2 years for secondary outcomes)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with higher dose TOR-I	Risk with lower dose TOR-I			
New-onset diabetes mellitus: TAC	57 per 1,000	102 per 1,000 (56 to 183)	RR 1.79 (0.99 to 3.23)	580 (5)	⊕⊕⊖⊖ LOW [1,2]
New-onset diabetes mellitus: CSA	63 per 1,000	36 per 1,000 (17 to 75)	RR 0.57 (0.27 to 1.20)	606 (3)	⊕⊕⊖⊖ LOW [1,2]
GFR (mL/min)	The mean GFR was 5.96 mL/min lower with low dose TOR-I (9.54 lower to 2.38 lower) compared to higher dose TOR-I		--	1305 (7)	⊕⊕⊖⊖ LOW [1,3]
Hypercholesterolaemia	251 per 1,000	241 per 1,000 (188 to 307)	RR 0.96 (0.75 to 1.22)	734 (4)	⊕⊕⊕⊖ MODERATE [2]
Hypertriglyceridaemia	521 per 1,000	443 per 1,000 (380 to 526)	RR 0.85 (0.73 to 1.01)	734 (4)	⊕⊕⊕⊖ MODERATE [2]
Anaemia	339 per 1,000	315 per 1,000 (271 to 366)	RR 0.93 (0.80 to 1.08)	1074 (6)	⊕⊕⊕⊖ MODERATE [2]
Leucopenia	107 per 1,000	106 per 1,000 (75 to 150)	RR 0.99 (0.70 to 1.40)	1012 (5)	⊕⊕⊕⊖ MODERATE [2]

*__The risk in the intervention group__ (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; **TAC:** tacrolimus; **CSA:** cyclosporin; **GFR:** glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

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Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Few events leading to wide confidence intervals
[2] Over 50% of included studies have unclear sequence generation and allocation concealment
[3] Significant heterogeneity

Summary of findings 7. Low versus higher dose target of rapamycin inhibitor (TOR-I): primary outcomes for primary immunosuppression in kidney transplant recipients

Low versus higher dose TOR-I: primary outcomes for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant centres
Intervention: lower dose TOR-I
Comparison: higher dose TOR-I

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with higher dose TOR-I	Risk with lower dose TOR-I			
Death (all causes)	35 per 1,000	31 per 1,000 (22 to 44)	RR 0.89 (0.63 to 1.25)	3894 (13)	⊕⊕⊕⊖ MODERATE [1]
Total graft loss (with death)	85 per 1,000	72 per 1,000 (57 to 90)	RR 0.84 (0.67 to 1.06)	3476 (11)	⊕⊕⊕⊖ MODERATE [1]
Biopsy-proven acute rejection	179 per 1,000	226 per 1,000 (197 to 257)	RR 1.26 (1.10 to 1.43)	3731 (11)	⊕⊕⊕⊖ MODERATE [1]
CMV infection	49 per 1,000	43 per 1,000 (31 to 60)	RR 0.87 (0.63 to 1.21)	3099 (9)	⊕⊕⊕⊖ MODERATE [2]
All malignancy	29 per 1,000	24 per 1,000 (15 to 38)	RR 0.84 (0.54 to 1.32)	3175 (10)	⊕⊕⊕⊖ MODERATE [1]
Number needing to change treatment	325 per 1,000	296 per 1,000 (254 to 341)	RR 0.91 (0.78 to 1.05)	3652 (10)	⊕⊕⊖⊖ LOW [1 2]

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*The risk in the intervention group (and its 95% CI) 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; **CMV:** cytomegalovirus

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] few events leading to wide confidence intervals
[2] Significant heterogeneity

Summary of findings 8. Low versus higher dose target of rapamycin inhibitor (TOR- I): secondary outcomes for primary immunosuppression in kidney transplant recipients

Low versus higher dose TOR- I: secondary outcomes for primary immunosuppression in kidney transplant recipients

Patient or population: primary immunosuppression in kidney transplant recipients
Setting: kidney transplant centres
Intervention: low dose TOR-I
Comparison: higher dose TOR- I

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with higher dose TOR- I	Risk with low dose TOR-I			
Diabetes	119 per 1,000	82 per 1,000 (61 to 111)	RR 0.69 (0.51 to 0.93)	2125 (6)	⊕⊕⊕⊖ MODERATE [1]
Lymphoma/PTLD	9 per 1,000	6 per 1,000 (2 to 15)	RR 0.66 (0.25 to 1.73)	2792 (7)	⊕⊕⊕⊖ MODERATE [1]
Acne/rash	152 per 1,000	131 per 1,000 (95 to 185)	RR 0.86 (0.62 to 1.21)	2958 (6)	⊕⊕⊖⊖ LOW [1 2]
GRF (mL/min)	The mean GFR was 2.88 mL/min higher with low dose TOR-I (0.71 lower to 6.48 higher) compared to higher dose TOR-I		--	1863 (7)	⊕⊕⊖⊖ LOW [1 3]
Hypercholesterolaemia	266 per 1,000	232 per 1,000 (208 to 261)	RR 0.87 (0.78 to 0.98)	3250 (9)	⊕⊕⊕⊖

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					MODERATE [1]
Anaemia	294 per 1,000	238 per 1,000 (212 to 267)	RR 0.81 (0.72 to 0.91)	3179 (10)	⊕⊕⊖⊖ LOW [1 3]
Thrombocy-topenia	145 per 1,000	84 per 1,000 (64 to 109)	RR 0.58 (0.44 to 0.75)	2242 (9)	⊕⊕⊖⊖ LOW [1 3]

*__The risk in the intervention group__ (and its 95% CI) 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; **PTLD:** post-transplant lymphoproliferative disease; **GFR:** glomerular filtration rate

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] few events leading to wide confidence intervals
[2] unexplained heterogeneity
3 over 50% of included studies have unclear sequence generation and allocation concealment

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BACKGROUND

Description of the condition

Kidney transplantation is the treatment of choice for many patients with end-stage kidney disease (ESKD) providing improved patient survival rates (95% one-year survival) and satisfactory short-term graft survival. To maintain long-term graft survival our challenge is the need to suppress the host immune system. Immunosuppressive therapies used in kidney transplantation inhibit one or more steps in the allo-immune response that would otherwise result in rejection. Long-term graft survival beyond five years has shown little improvement since the 1970s. Transplant waiting lists continue to grow with demand exceeding organ availability. Strategies to increase donor organ availability and to prolong kidney allograft survival have become priorities in kidney transplantation (ANZDATA 2017; NHS Blood and Transplant 2019 "Taking Organ Transplantation to 2020 Strategy", USRDS 2018).

Description of the intervention

Standard immunosuppressive therapy consists of initial induction and maintenance regimens to prevent rejection. Most current immunosuppressive regimens in the immediate post-operative period typically involve three drug groups each directed to a site in the T-cell activation or proliferation cascade which are central to the rejection process: calcineurin inhibitors (CNI; e.g. cyclosporin, tacrolimus), antimetabolite agents (azathioprine (AZA), mycophenolate mofetil (MMF), mycophenolate sodium (MPS)) and corticosteroids (prednisolone) with 93% recipients in the USA, and 70% in Australia, being discharged from hospital after transplantation on these agents. Following the introduction of CNI (cyclosporin in the early 1980s and tacrolimus the 1990s), one-year graft survival improved to the current level at of over 90% though long-term graft survival ranges between 34% and 56% across different population groups in Europe and the USA (KDIGO 2009; Gondos 2013).

Target of rapamycin inhibitors (TOR-I) (sirolimus, everolimus) are immunosuppressive agents with a mode of action different from other commonly used immunosuppressive agents. Sirolimus is a macrocyclic lactone antibiotic produced from *Streptomyces hygroscopicus* initially discovered as an antifungal agent. The immunosuppressive properties were deemed an undesirable effect and led to the development of a useful drug. Everolimus is a derivative of sirolimus. Both bind to the same intracellular immunophilin as tacrolimus (FKBP12), but instead of inhibiting calcineurin, the drug-receptor complex then binds to proteins known as the "mammalian targets of rapamycin" (mTOR). This causes inhibition of a multifunctional serine-threonine kinase, preventing both DNA and protein synthesis resulting in arrest of the cell cycle (Hernandez 2011, Dumont 2001; Saunders 2001).

Based upon laboratory data, the early expectation was that TOR-I would provide synergistic immunosuppression when combined with CNI (Schuurman 1997; Stepkowski 1997). The absence of nephrotoxicity in animal models increased expectations of significant clinical benefit (Viklicky 2000). Clinical studies dispelled some of the early optimism as synergistic nephrotoxicity was demonstrated when either sirolimus or everolimus were combined with cyclosporin (Kahan-301 2000; MacDonald-302 2001; Vitko-201 2001). Since then studies have been undertaken to explore strategies that avoid this interaction and clarify other potential benefits such as vascular protection (Ponticelli 2004) and a reduction in malignancy (Stallone 2005), and the impact of harms such as hyperlipidaemia and wound complications. Nevertheless the ANZDATA 2017 report indicates that fewer than 1% of transplant recipients receive everolimus or sirolimus in the initial post transplant regimen and fewer than 4% receive TOR-I at one year post transplant.

How the intervention might work

The major cause of long-term graft loss is chronic allograft nephropathy a complex, multifactorial process characterised clinically by a progressive decline in graft function, proteinuria and hypertension, and pathologically characterised by interstitial fibrosis/tubular atrophy. Chronic allograft nephropathy is a consequence of immunological and non-immunological injury. Immunological factors include human leukocyte antigen (HLA) matching, episodes of acute rejection and suboptimal immunosuppression. Important non-immunological factors implicated are donor organ characteristics, delayed graft function, recipient-related factors, hypertension, hyperlipidaemia and viral infections. CNI are linked to nephrotoxicity contributing to long-term graft failure, hypertension, hyperlipidaemia, and new-onset diabetes mellitus. The TOR-I have increased treatment options that produce adequate immunosuppression, allow reduced CNI dose with a reduction in CNI-associated side effects and reduced incidence of viral infections (Hernandez 2011; Kumar 2017).

Why it is important to do this review

Despite being in use for many years, the place of these agents in kidney transplantation remains uncertain. The aim of this study was to identify and summarise the currently available evidence of the short and long-term benefits and harms of sirolimus and everolimus when used in primary immunosuppressive regimens for kidney transplant recipients. Since the review, which included 33 studies, was first published in 2006, an additional 37 studies have been identified. Their inclusion in the review should provide a more comprehensive assessment of the place of TOR-I in immunosuppressive regimens. In this update we have only added studies where participants were commenced on a TOR-I less than seven days from date of transplant. Studies in which participants commenced TOR-I after seven days will be considered in a subsequent systematic review.

OBJECTIVES

To evaluate the short and long-term benefits and harms of TOR-I (sirolimus and everolimus) when used in primary immunosuppressive regimens for kidney transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) where drug regimens containing sirolimus or everolimus were compared to an alternative drug regimen in the immediate post transplant period (less than seven days post transplant) were included.

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Types of participants

Inclusion criteria

All patients of all ages with ESKD, who were the recipient of a first or subsequent deceased donor or living donor kidney transplant, were included. There was no restriction by age of recipients, or dosage of immunosuppressive drugs.

Exclusion criteria

Studies in which participants commenced TOR-I agents seven days or more post transplant were excluded. Studies in which transplant recipients received another solid organ in addition to a kidney transplant (e.g. kidney and pancreas) were excluded.

Types of interventions

Sirolimus or everolimus, given in combination with any other immunosuppressive agents, at any stage in the intra-operative or immediate post-transplant period. All dosage regimens were included. Sirolimus and everolimus were considered together to estimate 'class effect'.

Types of outcome measures

The outcome measures relate to those used by transplant registries to assess patient and graft survival. Outcome events were reported at the end of follow up or at two to three years post transplant depending on data availability.

Primary outcomes

- Death (all causes)
- All-cause graft loss (death with functioning allograft or dependence on dialysis)
- Graft loss censored for death with functioning allograft
- All acute rejection and biopsy-proven acute rejection
- Incidence of cytomegalovirus (CMV) infections (all definitions), with diagnosis by culture, serology, antigen or antibody testing, or as specified by authors.
- All adverse wound outcomes and lymphocoele
- All malignancies
- Number needing to change treatment.

Secondary outcomes

- New-onset diabetes mellitus
- Lymphoma/post transplant lymphoproliferative disorder (PTLD)
- Number with BK virus infection (all definitions)
- Graft function (measured as absolute value or change in serum creatinine (SCr), glomerular filtration rate (GFR), creatinine clearance (CrCl)
- Incidence of treatment-related adverse reactions related to TOR-I (specifically anaemia, thrombocytopenia, leucopenia, hypercholesterolaemia, hypertriglyceridaemia) and/or to CNI.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 20 September 2019 through contact with the Information Specialist using search terms relevant to this review.

The Specialised Register contains studies identified from the following 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 Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

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

Searching other resources

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

Data collection and analysis

Selection of studies

The original review was undertaken by four authors (ACW, VWSL, JRC, JCC). The 2019 update was undertaken by three authors (LH, DH, EH) with support from ACW and VWSL. Disagreement about inclusion of studies in the review was resolved by discussion between authors.

Data extraction and management

Data extraction was performed independently by three authors (LH, DH, EH) using a standardised form. Where possible, authors of published work were contacted for clarification of unclear data.

Assessment of risk of bias in included studies

The following items were assessed independently 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?
  - 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)?

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- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Studies were grouped and analysed according to the following comparisons.

- TOR-I versus CNI
- TOR-I versus antimetabolite
- Variable dosages of TOR-I and/or CNI
- Low versus higher doses of TOR-I.

For dichotomous outcomes (e.g. death, graft loss, acute rejection) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used (e.g. SCr, GFR), the mean difference (MD) with 95% CI was used.

Where sufficient RCTs were identified, publication bias was investigated using funnel plots (Egger 1997).

Unit of analysis issues

No cross-over studies were identified for this review. If we had identified any cross-over studies, we would only have included data from the first period of treatment in cross-over studies (Higgins 2011).

Dealing with missing data

Any further information or clarification required from the authors was requested by written or electronic correspondence and relevant information obtained in this manner was included in the review. We aimed to analyse available data in meta-analyses using intention-to-treat (ITT) data. However, where only ITT data were available graphically or were not provided and additional information could not be obtained from the study authors, per-protocol (PP) data was used in analyses. We imputed standard deviations if necessary based on those from other studies included in meta-analyses.

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

The search strategy applied aimed to reduce publication bias caused by lack of publication of studies with negative results. We investigated for publication bias using funnel plots if there were sufficient studies of each comparison (Higgins 2011).

Data synthesis

Data were summarised using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen. Where there were multiple publications of the same study, all reports were reviewed to ensure that all details of methods and results were included.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity by assessing the P-value for subgroup differences provided in RevMan analyses. Subgroups, defined a priori, were publication type (abstract or full publication), study methodological quality (sequence generation and allocation concealment), CNI used (whether tacrolimus or cyclosporin), whether or no induction with antibody was included in the immunosuppressive co-interventions, the TOR-I used (whether sirolimus or everolimus) and the antimetabolite used (whether mycophenolate or azathioprine).

Sensitivity analysis

Sensitivity analyses tested decisions where inclusion of a study may have altered the results of the meta-analysis or when it may have led to heterogeneity.

'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 (Schunemann 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 (Schunemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

Primary outcomes

- Death
- Graft loss (censored for death)
- Biopsy-proven acute rejection
- CMV infection
- All adverse wound outcomes
- All malignancies
- Number needing to change treatment (for adverse effects, unsatisfactory response, other medical event. Does not include poor compliance, withdrawal of consent, death, graft loss, protocol violation, loss to follow up, non-medical events)

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Secondary outcomes

- New-onset diabetes mellitus
- Number with BK infection
- Glomerular filtration rate
- Number with hypercholesterolaemia
- Number with hypertriglyceridaemia
- Number with leucopenia
- Number with thrombocytopenia

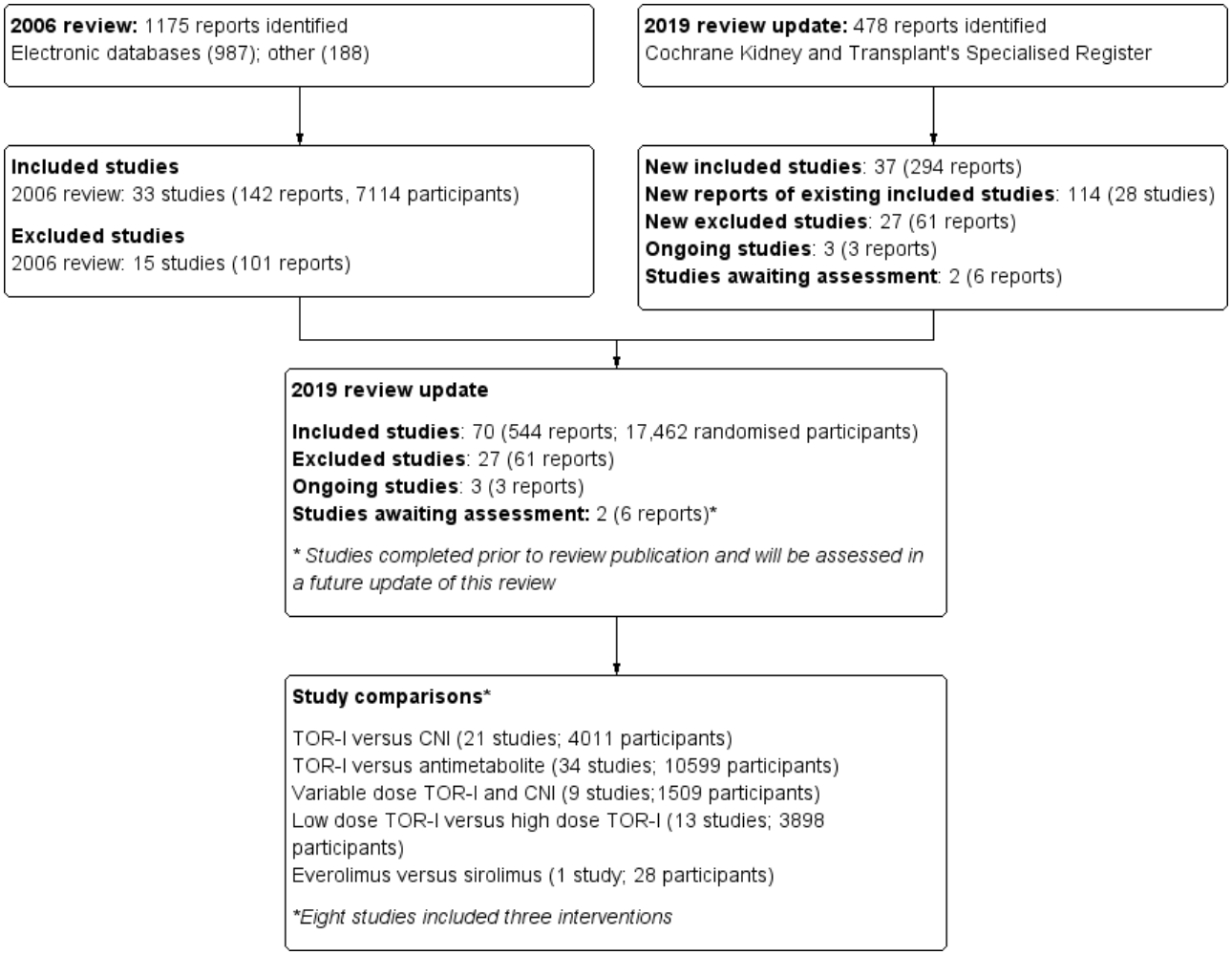
RESULTS

Description of studies

Results of the search

The initial review published in 2006 included 33 studies (142 reports). Further searches up to 30 September 2019 identified 37 new included studies (294 reports), 27 excluded studies (61 reports), and five ongoing studies (EVER TWIST 2013; Ferreira 2019; NCT02077556; NCT03468478; Traitanon 2019). Prior to publication of this review, two of these ongoing studies (Ferreira 2019; Traitanon 2019) were published and shall be included in a future update of this review (Figure 1).

Figure 1. Flow diagram.



Included studies

See Characteristics of included studies.

The 70 completed studies included 17,462 randomised participants; eight studies (Gelens 2006; Kahan-301 2000; Kandaswamy 2005; Kovarik-251 2001; ORION 2011; Tedesco-Silva 2010; Vitko-201 2001; Vitko-TERRA 2004) included three interventions so that 78 comparisons were included in the review. Twenty-two studies compared TOR-I (sirolimus or everolimus) with a CNI (tacrolimus or cyclosporin). Thirty-three studies compared TOR-I with an antimetabolite (MMF, MPS or AZA). Nine studies compared variable doses of TOR-I with variable doses of a CNI. Thirteen studies compared low doses with higher doses of TOR-I. One study compared everolimus with sirolimus (Rostaing 2001). Duration of follow-up ranged from six months to three years.

TOR-I versus calcineurin inhibitor

The 22 studies of TOR-I compared with a CNI included 4011 participants (CALFREE 2006; Cattaneo 2005; Durlik 2008; Durrbach 2008; EVEROLD 2014; Fernandes-Charpiot 2014; FIBRASIC 2009;

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Flechner 2013; Flechner-318 2002; Gelens 2006; Glotz 2010; Groth-207 1999; Kreis-210 2000; Lebranchu-132 2004; Martinez-Mier 2006; Morelon 2010; ORION 2011; Pescovitz 2007; Riad 2007; Schaefer 2006; Stegall 2003; SYMPHONY 2007).

One study (EVEROLD 2014) did not report the participant numbers in each group so 1523 participants were included in the TOR-I group and 2184 in the CNI group. All participants also received an antimetabolite.

TOR-I versus antimetabolite

The 33 studies of TOR-I compared with an antimetabolite included 10,599 participants (Anil Kumar 2005; Anil Kumar 2008; ATHENA 2016; AVESTA 2017; Bertoni 2011; Burke 2002; Ciancio 2016; Esmeraldo 2015; Favi 2009; Favi 2012; Gallon 2006; Gelens 2006; Gonwa-PSG 2003; Kahan-301 2000; Kandaswamy 2005; Kovarik-251 2001; Machado 2001; ORION 2011; Paoletti 2012; Qazi 2017; RECORD 2017; Sampaio 2008; Shetty 2015; Souza 2017; Spagnoletti 2017; Stallone 2004; Takahashi 2013a; Tedesco-Silva 2010; Tedesco-Silva 2015; TRANSFORM 2018; van Gurp 2010; Vitko-201 2001; Vitko-TERRA 2004).

Two studies (AVESTA 2017; Spagnoletti 2017) did not report the participant numbers in each group so 6123 participants were included in the TOR-I group and 4318 in the antimetabolite group. All study participants also received a CNI (tacrolimus or cyclosporin). Participants in the antimetabolite group received MMF or MPS except in two studies where azathioprine was administered (Kahan-301 2000; Machado 2001).

Variable doses of TOR-I and CNI

The nine studies comparing variable doses of TOR-I and CNI included 1509 participants with 744 in the higher dose TOR-I with reduced dose CNI group and 765 in the lower dose TOR-I with standard dose CNI group (Bertoni 2011; Cohen 2002; EVEREST 2009; Grinyo 2004; Kahan-203 1999; Kandaswamy 2005; MacDonald-302 2001; Russ 2003; Velosa-212 2001).

Lower versus higher doses of TOR-I

The thirteen studies of lower versus higher doses of TOR-I included 3898 participants with 1951 in the lower dose TOR-I group and 1947 participants in the higher dose TOR-I group (Hamdy 2005; Kahan-157 2001; Kahan-301 2000; Kovarik-2306 2004; Kovarik-251 2001; Kramer-2307 2003; MacDonald-302 2001; Pascual 2010; Tedesco-Silva 2003; Tedesco-Silva 2010; van Hooff 2003; Vitko-201 2001; Vitko-TERRA 2004).

Sirolimus versus everolimus

One study (28 participants) compared sirolimus (16 participants) with everolimus (12 participants) (Rostaing 2001).

Excluded studies

See Characteristics of excluded studies.

For the 2019 update, 27 studies (61 reports) were excluded. Seventeen studies were excluded because TOR-I was commenced seven days or more post transplant. TOR-I were commenced after day 14 in one study; the remaining 16 studies commenced TOR-I four weeks or more after study commencement. Six studies were excluded because they: 1) compared early with delayed administration of TOR-I (two studies); 2) studied steroid withdrawal (one study); 3) compared liquid with tablet formulation of sirolimus (one study); 4) studied the effect of increasing the dose of TOR-I at one year (one study); or 5) compared increased dose of TOR-I at three months as TAC ceased (one study). Three studies were excluded because it was unclear whether they were RCTS and one study was terminated because of inability to recruit participants.

Risk of bias in included studies

Risk of bias attributes are summarised for all studies in Figure 2 and Figure 3. Risk of bias attributes are reported for each of the five groups of comparisons below

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

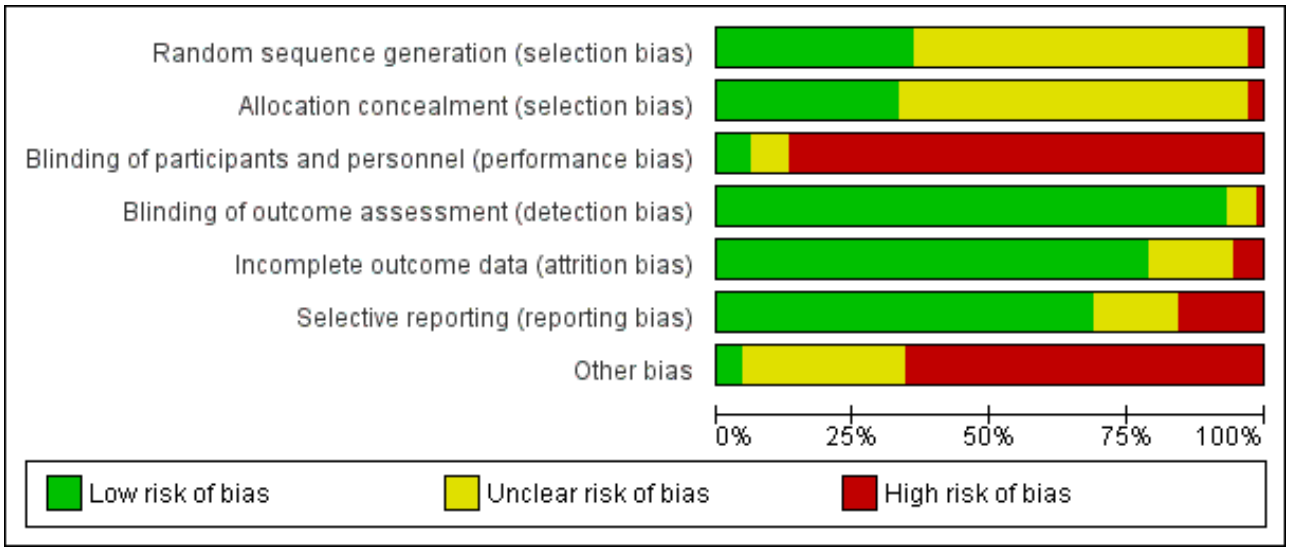

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Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

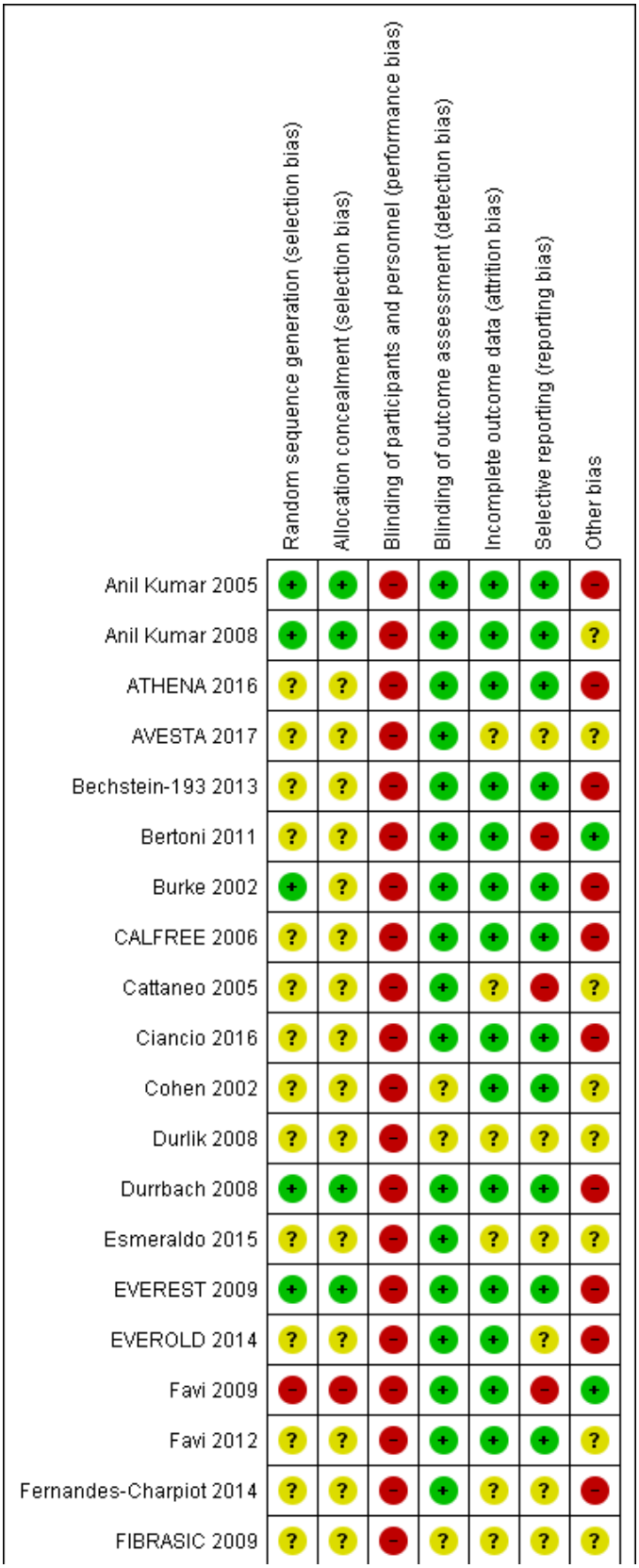

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Figure 3. (Continued)

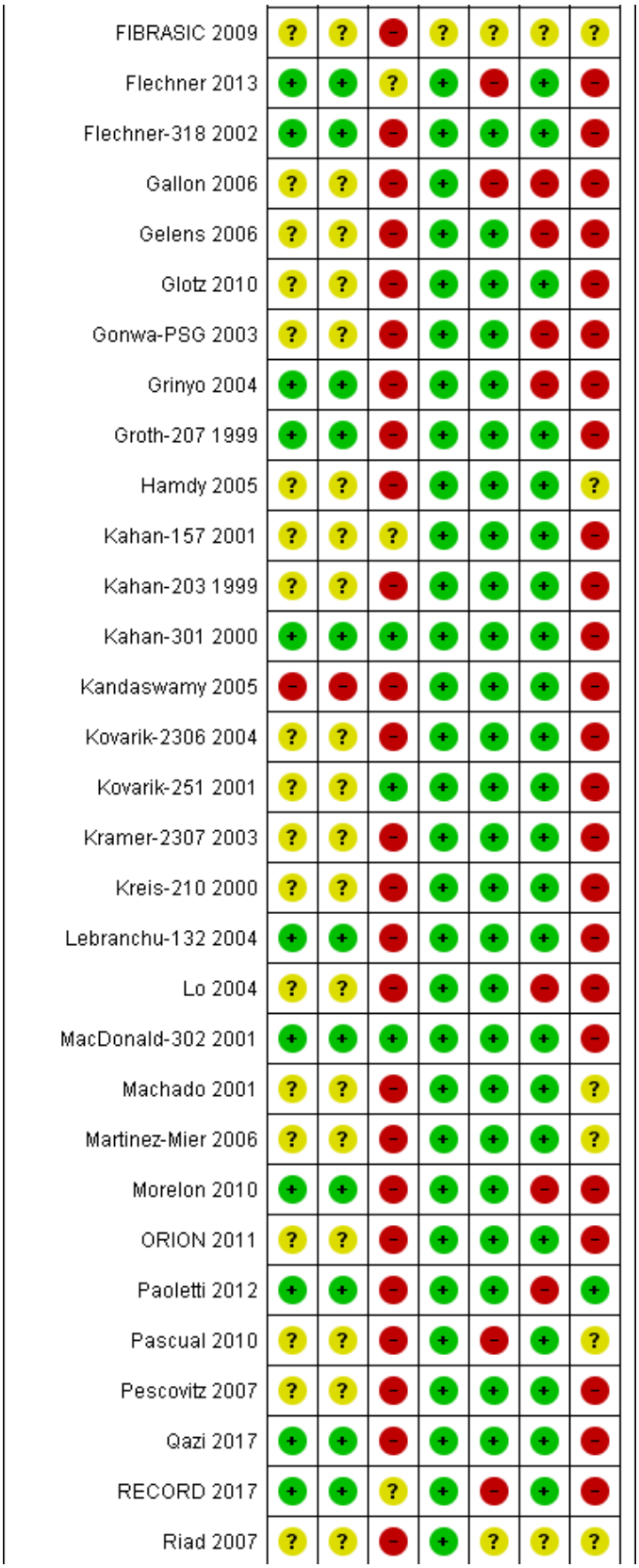

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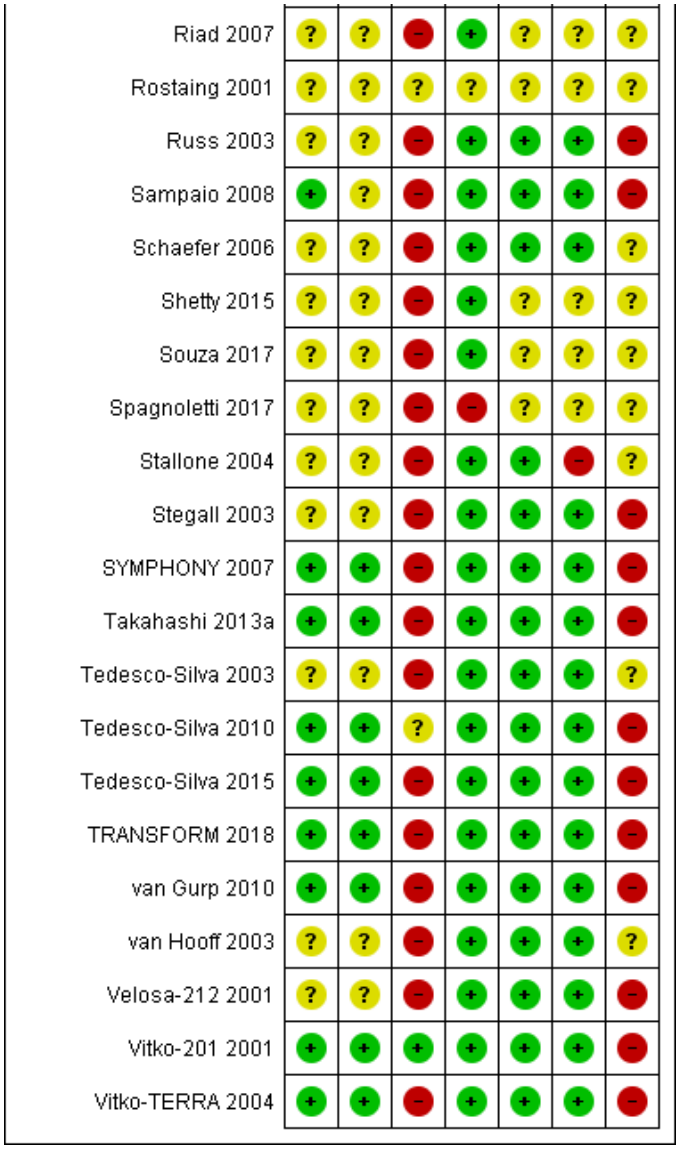
Figure 3. (Continued)



Allocation

TOR-1 versus calcineurin inhibitor

Of 22 studies, 14 were at low risk for sequence generation and allocation concealment. The remaining seven were at high risk of bias for both sequence generation and random allocation concealment.

TOR-I versus antimetabolite

Of 33 studies, 14 were at low risk of bias for sequence generation and 18 were at unclear risk. Twelve comparisons were at low risk of bias for allocation concealment and 20 studies were at unclear risk. Two comparisons were at high risk of sequence generation and allocation concealment (Favi 2009; Kandaswamy 2005).

Variable dosage of TOR-I and calcineurin inhibitor

Of nine studies, two comparisons were at low risk of bias for sequence generation and allocation concealment (EVEREST 2009; Grinyo 2004), one was at high risk of bias (Kandaswamy 2005) while six studies were at unclear risk.

Lower versus higher doses of TOR-1

Of 13 studies, five were at low risk of bias and the remaining eight studies were assessed as unclear for sequence generation and allocation concealment.

Sirolimus versus everolimus

Rostaing 2001 was judged to be at unclear risk of bias for both sequence generation and allocation concealment.

Blinding

TOR-1 versus calcineurin inhibitor

Twenty studies were at high risk of bias for performance bias and one study was assessed as unclear (Flechner 2013).

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All studies were assessed as at low risk for detection bias as the primary outcomes (GFR and/or biopsy-proven acute rejection) were laboratory based and unlikely to be influenced by detection bias.

TOR-I versus antimetabolite

Three studies were at low risk of performance bias (Kahan-301 2000; Kovarik-251 2001; Vitko-201 2001), 29 comparisons were at high risk and one comparison was at unclear risk (RECORD 2017).

In most comparisons, the primary outcomes were laboratory based so were considered unlikely to be influenced by detection bias. Thirty-two studies were at low risk and one study was at unclear risk of detection bias (Durlik 2008).

Variable dosage of TOR-I and calcineurin inhibitor

All nine studies were at high risk of performance bias.

In most comparisons, the primary outcomes were laboratory based so were considered unlikely to be influenced by detection bias. Eight studies were at low risk while one study (Cohen 2002) was at unclear risk of detection bias.

Lower versus higher doses of TOR-I

Four comparisons were assessed at low risk of performance bias (Kahan-301 2000; Kovarik-251 2001; MacDonald-302 2001; Vitko-201 2001), nine studies were at high risk of bias and two was assessed as at unclear risk (Kahan-157 2001; Tedesco-Silva 2010).

All studies were assessed at low risk of detection bias as the primary outcomes were laboratory based and unlikely to be influenced by detection bias.

Sirolimus versus everolimus

Rostaing 2001 was judged to be at unclear risk of bias for both performance and detection bias.

Incomplete outcome data

TOR-1 versus calcineurin inhibitor

Seventeen studies were considered at low risk of attrition bias, with four at unclear risk (Cattaneo 2005; Durlik 2008; FIBRASIC 2009; Riad 2007) and one at high risk of bias (Flechner 2013).

TOR-I versus antimetabolite

Twenty-six comparisons were considered to be at low risk of attrition bias while two were at high risk (Gallon 2006: RECORD 2017) and five were at unclear risk (AVESTA 2017; Esmeraldo 2015; Shetty 2015; Souza 2017; Spagnoletti 2017).

Variable dosage of TOR-I and CNI

Eight studies were considered to be at low risk of attrition bias while one study (Russ 2003) was at high risk.

Lower versus higher doses of TOR-I

Twelve studies were considered to be at low risk of attrition bias while one study was at high risk (Pascual 2010).

Sirolimus versus everolimus

Rostaing 2001 was judged to be at unclear risk of bias for attrition bias.

Selective reporting

TOR-1 versus calcineurin inhibitor

Fourteen studies were considered at low risk of bias for selective reporting, with three assessed as at high risk of bias (Cattaneo 2005; Gelens 2006; Morelon 2010) and the remaining five assessed as at unclear risk (Durlik 2008; EVEROLD 2014; Fernandes-Charpiot 2014; FIBRASIC 2009; Riad 2007).

TOR-I versus antimetabolite

Twenty-one studies were considered to be at low risk of attrition bias while seven were at high risk (Bertoni 2011; Favi 2009; Gallon 2006; Gelens 2006; Gonwa-PSG 2003; Paoletti 2012; Stallone 2004) and five studies were at unclear risk (AVESTA 2017; Esmeraldo 2015; Shetty 2015; Souza 2017; Spagnoletti 2017).

Variable dosage of TOR-I and calcineurin inhibitor

Nine studies were considered to be at low risk of reporting bias.

Lower versus higher doses of TOR-I

All 13 studies were considered to be at low risk of reporting bias

Sirolimus versus everolimus

Rostaing 2001 was judged to be at unclear risk of bias for selection bias.

Other potential sources of bias

TOR-1 versus CNI

Sixteen studies were industry funded studies and assessed as high risk of bias and the remaining six studies were assessed as unclear (Cattaneo 2005; Durlik 2008; FIBRASIC 2009; Martinez-Mier 2006; Riad 2007; Schaefer 2006).

TOR-I versus antimetabolite

Three studies were at low risk (Bertoni 2011; Favi 2009; Paoletti 2012) and 22 studies reporting on industry funded studies were considered to be at high risk of bias. Eight studies did not report funding sources and were considered to be at unclear risk of bias (Anil Kumar 2008; Esmeraldo 2015; Favi 2012; Machado 2001; Shetty 2015; Souza 2017; Spagnoletti 2017; Stallone 2004).

Variable dosage of TOR-I and CNI

Eight studies reporting on industry funded studies were considered to be at high risk while one study (Cohen 2002) was at unclear risk as it did not report funding sources.

Lower versus higher doses of TOR-I

Nine studies reported industry funding and were assessed at high risk of bias.

Sirolimus versus everolimus

Rostaing 2001 was judged to be at unclear risk of bias as it did not report funding sources.

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Effects of interventions

See: **Summary of findings for the main comparison** Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): main outcomes for primary immunosuppression in kidney transplant recipients; **Summary of findings 2** Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes for primary immunosuppression in kidney transplant recipients; **Summary of findings 3** Target of rapamycin inhibitors (TOR-I) versus antimetabolites: primary outcomes for primary immunosuppression in kidney transplant recipients; **Summary of findings 4** Target of rapamycin inhibitors (TOR-I) versus antimetabolites: secondary outcomes for primary immunosuppression in kidney transplant recipients; **Summary of findings 5** Variable target of rapamycin inhibitor (TOR-I) and calcineurin inhibitor (CNI): primary outcomes for primary immunosuppression in kidney transplant recipients; **Summary of findings 6** Variable target of rapamycin inhibitor (TOR-I) and calcineurin inhibitor (CNI): secondary outcomes for primary immunosuppression in kidney transplant recipients; **Summary of findings 7** Low versus higher dose target of rapamycin inhibitor (TOR-I): primary outcomes for primary immunosuppression in kidney transplant recipients; **Summary of findings 8** Low versus higher dose target of rapamycin inhibitor (TOR- I): secondary outcomes for primary immunosuppression in kidney transplant recipients

TOR-1 versus CNI

Primary outcomes

Up to two years post kidney transplant, TOR-I with an antimetabolite compared to a CNI with an antimetabolite:

- Probably makes little or no difference to death (Analysis 1.1 (19 studies, 3618 participants): RR 1.31, 95% CI 0.87 to 1.98; I^2 = 0%) (moderate certainty evidence).
- Probably increases graft loss uncensored for death (Analysis 1.2 (20 studies, 3619 participants): RR 1.41, 95% CI 1.11 to 1.80; I^2 = 0%) and censored for death (Analysis 1.3 (15 studies, 3277 participants): RR 1.32, 95% CI 0.96 to 1.81; I^2 = 0%) (moderate certainty of evidence). When graft loss was reported for subgroups according to CNI administered, TOR-I compared with tacrolimus probably slightly increases graft loss while TOR-I compared with cyclosporin probably makes little or no difference to graft loss uncensored for death (Analysis 1.2.1; Analysis 1.2.2) or censored for death (Analysis 1.3.1; Analysis 1.3.2).
- Probably increases all acute rejection (Analysis 1.4 (19 studies, 3019 participants): RR 1.58, 95% CI 1.30 to 1.91; I^2 = 21%) and biopsy-proven rejection (Analysis 1.5 (15 studies, 2708 participants): RR 1.60, 95% CI 1.25 to 2.04; I^2 = 35%) (moderate certainty evidence).
- Reduces the risk of CMV infection (Analysis 1.6 (13 studies, 2026 participants): RR 0.43, 95% CI 0.29 to 0.63; I^2 = 27%) (high certainty evidence).
- Probably increases the risk of all wound complications (Analysis 1.7.1 (12 studies, 1679 participants): RR 2.56, 95% CI 1.94 to 3.36; pI^2 = 0%) and of lymphocoele (Analysis 1.7.2 (8 studies, 2538): RR 2.29, 95% CI 1.73 to 3.02; I^2 = 0%) (moderate certainty evidence).
- Probably increases the need to change immunosuppressive therapy-related to adverse events (Analysis 1.9 (14 studies, 3148 participants): RR 2.42, 95% CI 1.88 to 3.11; I^2 = 52%) (moderate certainty evidence).
- Probably makes little or no difference to all malignancies (Analysis 1.8 (10 studies, 2584 participants): RR 0.86, 95% CI 0.50 to 1.48; I^2 = 0%) (moderate certainty evidence).
- A small substudy of SYMPHONY 2007 involving 156 participants found no difference in health-related quality of life between participants receiving TOR-I and those receiving CNI.

Outcomes were downgraded for imprecision (Summary of findings for the main comparison).

Secondary outcomes

All outcomes were assessed by GRADE as shown in the results below but only the seven most important outcomes (**bold**) are included in Summary of findings 2,

TOR-I with an antimetabolite compared with CNI with an antimetabolite:

- Probably makes little or no difference in the risk of new-onset diabetes mellitus (Analysis 2.1 (15 studies, 2791 participants): RR 0.93, 95% CI 0.69 to 1.26; I^2 = 0%) regardless of CNI used (Analysis 2.1.1; Analysis 2.1.2) (**moderate certainty of evidence**).
- Probably makes little or no difference to the risk for lymphoma/PTLD (Analysis 2.2 (8 studies, 2537 participants): RR 2.47, 95% CI 0.78 to 7.86; I^2 = 0%) (**moderate certainty of evidence**).
- May make little or no difference to the risk for BK virus infection (Analysis 2.3 (3 studies, 386 participants): RR 0.46, 95% CI 0.16 to 1.29; I^2 = 0%) (low certainty evidence).
- Reduces the risk of adverse cosmetic outcomes including tremor (Analysis 2.4.1 (6 studies, 799 participants): RR 0.25, 95% CI 0.15 to 0.41; I^2 = 0%) (**high certainty evidence**) and may make little or no difference to hirsutism (Analysis 2.4 (1 study, 78 participants): RR 0.24, 95% CI 0.03 to 2.03; I^2 = 0%) (low certainty evidence).
- Probably slightly reduces serum creatinine (Analysis 2.6 (10 studies, 672 participants): MD -10.64 µmol/L, 95% CI -19.19 to -2.10; I^2 = 34%) and may increase GFR (Analysis 2.5 (15 studies, 2983 participants: MD 2.20 mL/min, 95% CI -1.29 to 5.68; I^2 = 74%) (**low certainty evidence**).
- It is uncertain whether TOR-I increases the number of participants with elevated cholesterol levels (Analysis 2.7.1 (4 studies, 1877 participants): RR 1.74, 95% CI 1.17 to 2.59; I^2 = 51%) because the evidence is very uncertain but may increase the number of participants with elevated triglyceride levels (Analysis 2.7.2 (5 studies, 1922 participants): RR 1.72, 95% CI 1.20 to 2.46; I^2 = 39%) (low certainty evidence).
- May increase the mean levels of cholesterol (Analysis 2.8.1 (7 studies, 579 participants): MD 0.77 mmol/L, 95% CI 0.45 to 1.09; I^2 = 56%) (**low certainty evidence**) and may increase the mean levels of triglycerides (Analysis 2.8.2 (8 studies, 853 participants): MD 0.57 mmol/L, 95% CI 0.28 to 0.86; I^2 = 63%).
- May increase the number of participants with anaemia (Analysis 2.9.1 (6 studies, 2216 participants): RR 1.47, 95% CI 1.28 to 1.70; I^2 = 0%) (**low certainty evidence**), leucopenia (Analysis 2.9.2 (5 studies, 1922 participants): RR 1.52, 95% CI 0.95 to 2.44; I^2 = 50%) or thrombocytopenia (Analysis 2.9.3 (4 studies, 592 participants): RR 5.26, 95% CI 2.87 to 9.63; I^2 = 0%) (low certainty evidence).

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Outcomes were downgraded for heterogeneity and imprecision (Summary of findings 2).

Longer term follow-up

Two studies (Flechner-318 2002; Lebranchu-132 2004) reported outcomes at five and three years respectively. TOR-I compared with CNI may make little or no difference to the number dying (Analysis 6.1), the number with graft loss (overall (Analysis 3.2) and censored for death with a functioning graft (Analysis 3.3)) and malignancies (Analysis 3.4). It is uncertain whether TOR-I compared with CNI increases GFR because the certainty of the evidence is very low (Analysis 3.5 (2 studies, 163 participants): MD 13.51 mL/min, 95% CI 6.94 to 20.08; I^2 = 65%)

TOR-I versus antimetabolite

Primary outcomes

Up to two years post kidney transplant, TOR-I with CNI compared with an antimetabolite with CNI (Summary of findings 3):

- Probably makes little or no difference to death (Analysis 4.1 (31 studies, 10,482 participants): RR 1.06, 95% CI 0.84 to 1.33; I^2 = 0%) (moderate certainty evidence).
- Probably makes little or no difference to graft loss (uncensored) (Analysis 4.2 (27 studies, 7626 participants): RR 1.14, 95% CI 0.93 to 1.40; I^2 = 8%) or graft loss (censored for death) (Analysis 4.3 (26 studies, 8966 participants): RR 1.09, 95% CI 0.82 to 1.45; I^2 = 25%) (moderate certainty evidence).
- Probably makes little or no difference to all acute rejection (Analysis 4.4 (31 studies, 10,075 participants): RR 0.90, 95% CI 0.79 to 1.02; I^2 = 35%) or to biopsy-proven acute rejection (Analysis 4.5 (24 studies, 10,101 participants): RR 0.95, 95% CI 0.81 to 1.12; I^2 = 51%) (moderate certainty evidence). In sensitivity analyses for both outcomes, heterogeneity was reduced below 30% by exclusion of ATHENA 2016 and Qazi 2017. These studies showed reduced biopsy-proven acute rejection with TOR-I in contrast to other studies, which showed no differences. Subgroup analysis demonstrated that TOR-I with reduced dose CNI, compared with antimetabolite and CNI, probably makes little or no difference to the number with biopsy-proven acute rejection (Analysis 4.5)
- Probably reduces the risk of CMV infection (Analysis 4.6 (26 studies, 10,049 participants): RR 0.44, 95% CI 0.34 to 0.58; I^2 = 68%) (moderate certainty evidence). Heterogeneity of the results may have been due to different reporting of CMV infection and/or disease in different studies.
- Probably increases the risk of all wound complications (Analysis 4.7.1 (17 studies, 6913 participants): RR 1.56, 95% CI 1.28 to 1.91; I^2 = 59%) and the risk of lymphocoele (Analysis 4.7.2 (16 studies, 8415 participants): RR 1.55, 95% CI 1.32 to 1.81; I^2 = 0%) (moderate certainty evidence). Heterogeneity in the risk of all wound complications was reduced by exclusion of ATHENA 2016.
- Probably makes little or no difference to the risk of malignancies (Analysis 4.8 (17 studies, 8799 participants): RR 0.83, 95% CI 0.64 to 1.07; I^2 = 7%) (moderate certainty evidence).
- Probably increases the need to change immunosuppressive treatment because of adverse effects (Analysis 4.9 (25 studies, 9747 participants): RR 1.56, 95% CI 1.28 to 1.90; I^2 = 71%) (moderate certainty evidence). Heterogeneity between studies was reduced by exclusion of Anil Kumar 2008, Kahan-301 2000 and Tedesco-Silva 2015,which found that TOR-I were not associated with an increase in the need to change immunosuppressive therapy.

Outcomes were downgraded for imprecision or heterogeneity (Summary of findings 3).

Secondary outcomes

All outcomes were assessed by GRADE as shown in the results below but only the seven most important outcomes (**bold**) are included in Summary of findings 4,

TOR-I with CNI compared with an antimetabolite with CNI:

- Probably increases the risk of new-onset diabetes mellitus (Analysis 5.1 (23 studies, 8728 participants): RR 1.28, 95% CI 1.07 to 1.54; I^2 = 22%) (**moderate certainty evidence**).
- Probably makes little or no difference to the risk of PTLD (Analysis 5.2 (14 studies, 5415 participants): RR 1.52, 95% CI 0.62 to 3.72; I^2 = 0%) (moderate certainty evidence).
- Reduces the risk of BK virus infection (Analysis 5.3 (12 studies, 5152 participants): RR 0.62, 95% CI 0.50 to 0.76; I^2 = 0%) (**high certainty evidence**).
- May make little or no difference to GFR overall (Analysis 5.5 (25 studies, 8099 participants): MD -2.89 mL/min, 95% CI -4.91 to -0.88; I^2 = 70%) (**low certainty evidence**). Subgroup analysis demonstrated that TOR-I with reduced dose CNI, compared with antimetabolite and CNI, may make little or no difference to GFR (Analysis 5.5.1 (8 studies, 3954 participants): MD 1.58 mL/min (95% CI -1.12 to 4.28; I^2 = 60%). However TOR-I with standard dose CNI, compared with antimetabolite and CNI, may lead to a reduction in GFR (Analysis 5.5.2 (17 studies, 4145 participants): MD -5.45 mL/min, 95% CI -7.55 to -3.35; I^2 = 49%).
- May increase the number of participants with elevated cholesterol levels (Analysis 5.7.1 (12 studies, 5725 participants): RR 1.83, 95% CI 1.48 to 2.25; I^2 = 46%) (**low certainty evidence**) and may increase the number with elevated triglyceride levels (Analysis 5.7.2 (9 studies, 4698 participants): RR 1.48, 95% CI 1.26 to 1.74; I^2 = 26%) (low certainty evidence).
- May increase mean levels of cholesterol Analysis 5.8.1 (14 studies, 5176 participants): MD 0.57 mmol/L, 95% CI 0.43 to 0.71; I^2 = 60%) and triglycerides (Analysis 5.8.2 (13 studies, 5099 participants): MD 0.40 mmol/L, 95% CI 0.29 to 0.51; I^2 = 53%) (low certainty evidence).
- May make little or no difference to the number of participants with anaemia (Analysis 5.9.1 (15 studies, 8595 participants): RR 1.06, 95% CI 0.92 to 1.23; I^2 = 67%) or to haemoglobin levels (Analysis 5.10.1 (6 studies, 1035 participants): MD -0.38 g/dL, 95% CI -0.63 to -0.12; I^2 = 15%) (low certainty evidence).
- May reduce the number of participants with leucopenia (Analysis 5.9.2) or may increase the number of participants with thrombocytopenia (Analysis 5.9.3) (low certainty evidence). It is uncertain whether TOR-I compared with antimetabolite makes any difference to white blood or platelet counts (Analysis 5.10.2; Analysis 5.10.3) because the certainty of the evidence is very low.
- May reduce the number of participants with tremor (Analysis 5.4.1 (5 studies, 3803 participants): RR 0.87, 95% CI 0.66 to 1.15; I^2 = 62%) and the number with gingival hyperplasia (Analysis 5.4.2

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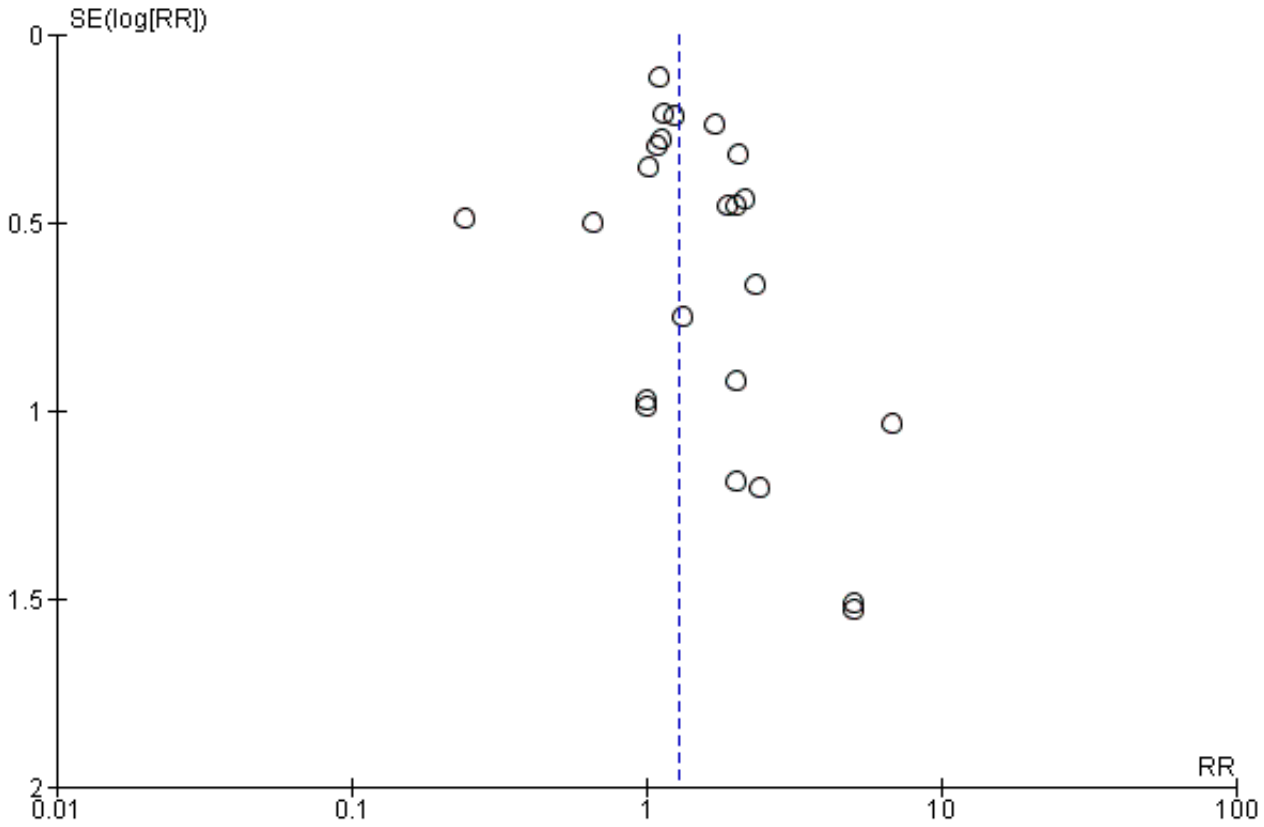
(2 studies, 903 participants): RR 0.30, 95% CI 0.15 to 0.60; I^2 = 0%) but increase the number with acne/rash (Analysis 5.4.4 (5 studies, 2022 participants): RR 1.74, 95% CI 1.08 to 2.81; I^2 = 67%) (low certainty evidence).

- It is uncertain whether TOR-I compared with antimetabolite makes any difference to the number of participants with hirsutism (Analysis 5.4,3) because the certainty of the evidence is very low.

Outcomes were downgraded for heterogeneity, imprecision and publication bias (Figure 4) (Summary of findings 4).

Figure 4. Funnel plot of comparison: 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, outcome: 5.1 New-onset diabetes mellitus.



Longer term follow-up

Five studies (Burke 2002; Gallon 2006; Kandaswamy 2005; Takahashi 2013a; Tedesco-Silva 2010) reported outcomes at five to eight years post-transplant. Limited data from single centres were available for these meta-analyses for the multicentre studies of Takahashi 2013a and Tedesco-Silva 2010. TOR-I compared with antimetabolite may make little or no difference to the number dying (Analysis 6.1), the number with graft loss overall (Analysis 6.2) and censored for death with a functioning graft (Analysis 6.3) and with malignancies (Analysis 6.4). It is uncertain whether TOR-I compared with antimetabolites influences GFR (Analysis 6.5). There was significant heterogeneity in the analyses for all outcomes except death. In sensitivity analyses removal of Gallon 2006 abolished the heterogeneity.

Variable doses of TOR-I and CNI

Primary outcomes

Lower dose TOR-I and standard dose CNI compared with higher dose TOR-I and reduced dose CNI:

- Probably makes little or no difference to death (all causes) (Analysis 7.1 (9 studies, 1501 participants): RR 1.07, 95% CI 0.64 to 1.78; I^2 = 0%) (moderate certainty evidence).
- Probably makes little of no difference to all graft loss (Analysis 7.2 (8 studies, 1385 participants): RR 1.09, 95% CI 0.68 to 1.75; I^2 = 21%) and graft loss censored for death (Analysis 7.3 (8 studies, 1385 participants): RR 1.09, 95% CI 0.54 to 2.20; I^2 = 25%) (moderate certainty evidence).
- Probably makes little or no difference to all acute rejection (Analysis 7.4 (9 studies, 1509 participants): RR 0.84, 95% CI 0.67 to 1.07; I^2 = 0%) and biopsy-proven acute rejection (Analysis 7.5 (8 studies, 1381 participants): RR 0.87, 95% CI 0.67 to 1.13; I^2 = 0%) (moderate certainty evidence).
- May make little or no difference to CMV infection (Analysis 7.6 (5 studies, 865 participants): RR 1.42, 95% CI 0.78 to 2.60; I^2 = 0%) (low certainty evidence).
- May make little or no difference to all wound complications (Analysis 7.7.1 (3 studies, 291 participants): RR 0.95, 95% CI 0.53 to 1.71; I^2 = 0%) or lymphocoele Analysis 7.7.2 (3 studies,

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702 participants): RR 0.86, 95% CI 0.45 to 1.63; I^2 = 46%) (low certainty evidence).
- May make little or no difference to malignancies (Analysis 7.8 (7 studies, 1163 participants): RR 1.04, 95% CI 0.36 to 3.04; I^2 = 0%) (low certainty evidence).
- May make little of no difference to the number of participants needing to change treatment (Analysis 7.9 (5 studies, 734 participants): RR 1.18, 95% CI 0.58 to 2.42; I^2 = 76%) (low certainty evidence).

Outcomes were downgraded for risk of bias issues, imprecision or heterogeneity (Summary of findings 5).

Secondary outcomes

All outcomes were assessed by GRADE as shown in the results below but only the seven most important outcomes (**bold**) are included in Summary of findings 6

Lower dose TOR-I and standard dose CNI compared with higher dose TOR-I and reduced dose CNI"

- May make little or no difference to the risk of new-onset diabetes mellitus whether participants also received tacrolimus (Analysis 8.1.1 (5 studies, 580 participants): RR 1.79, 95% CI 0.99 to 3.23; I^2 = 0%) or cyclosporin (Analysis 8.1.2 (3 studies, 606 participants): RR 0.57, 95% CI 0.27 to 1.20; I^2 = 0%) (**low certainty evidence**).
- May make little or no difference to the risk of lymphoma/PTLD (Analysis 8.2 (7 studies, 1298 participants): RR 0.68, 95% CI 0.15 to 3.07; I^2 = 0%).
- May slightly reduce GFR (Analysis 8.4 (7 studies, 1305 participants): MD -5.96 mL/min, 95% CI -9.54 to -2.38; I^2 = 48%) (**low certainty evidence**) or serum creatinine (Analysis 8.5 (9 studies, 1368 participants). MD 1.53 µmol/L, 95% CI -8.82 to 11.89; I^2 = 69%) (low certainty evidence).
- Probably makes little or no difference to the number of participants with increased cholesterol (Analysis 8.6.1 (4 studies, 734 participants). RR 0.96, 95% CI 0.75 to 1.22; I^2 = 0%) or triglyceride levels (Analysis 8.6.2 (4 studies, 734 participants): RR 0.85, 95% CI 0.73 to 1.01; I^2 = 16%) (**moderate certainty of evidence**).
- Probably makes little or no difference in the number with anaemia (Analysis 8.8.1 (6 studies, 1074 participants): RR 0.93, 95% CI 0.80 to 1.08; I^2 = 0%) (**moderate certainty evidence**).
- Probably makes little or no difference to the number of participants with leucopenia (Analysis 8.8.2 (5 studies, 1012 participants): RR 0.99, 95% CI 0.70 to 1.40; I^2 = 0%) (**moderate certainty evidence**) or thrombocytopenia (Analysis 8.8.3 (5 studies, 888 participants): RR 0.67, 95% CI 0.43 to 1.07; I^2 = 0%) (moderate certainty evidence).
- It is uncertain whether variable levels of TOR-I and CNI makes any difference to the number of participants with hirsutism (Analysis 8.3.1); gum hypertrophy (Analysis 8.3.2); mean levels of creatinine (Analysis 8.5), cholesterol (Analysis 8.7.1) and triglycerides (Analysis 8.7.2); or to mean levels of haemoglobin (Analysis 8.9.1), white blood count (Analysis 8.9.2), or platelet count (Analysis 8.9.3) because the certainty of the evidence is very low.

Outcomes were downgraded for risk of bias issues, heterogeneity and imprecision (Summary of findings 6).

Lower versus higher dose of TOR-I

Primary outcomes

Up to two years post kidney transplant, lower dose TOR-I with CNI versus higher dose TOR-I with CNI:

- Probably makes little or no difference to death (Analysis 9.1 (13 studies, 3894 participants): RR 0.89, 95% CI 0.63 to 1.25; I^2 = 0%) (moderate certainty evidence).
- Probably makes little or no difference to overall graft loss (Analysis 9.2 (11 studies, 3476 participants): RR 0.84, 95% CI 0.67 to 1.06; I^2 = 0%) and graft loss censored for death (Analysis 9.3 (12 studies, 3863 participants): RR 0.92, 95% CI 0.71 to 1.19; I^2 = 0%) (moderate certainty evidence).
- Probably slightly increases the risk of acute rejection (Analysis 9.4 (13 studies, 3898 participants): RR 1.25, 95% CI 1.10 to 1.42; I^2 = 0%) and biopsy-proven acute rejection (Analysis 9.5 (11 studies, 3731 participants): RR 1.26, 95% CI 1.10 to 1.43; I^2 = 0%) (moderate certainly evidence).
- Probably makes little or no difference to the risk of CMV infection (Analysis 9.6 (9 studies, 2099 participants): RR 0.87, 95% CI 0.63 to 1.21; I^2 = 0%) (moderate certainty evidence).
- Probably makes little or no difference to the risk of malignancy (Analysis 9.7 (10 studies, 3175 participants): RR 0.84, 95% CI 0.54 to 1.32; I^2 = 0%) (moderate certainty evidence).
- Probably makes little or no difference to the risk of all wound complications (Analysis 9.8.1 (7 studies, 2792 participants): RR 0.92, 95% CI 0.66 to 1.29; I^2 = 61%) or lymphocoele (Analysis 9.8.2 (10 studies, 3302 participants): RR 0.81, 95% CI 0.63 to 1.04; I^2 = 29%) (moderate certainty evidence).
- May make little or no difference to the need for treatment change (Analysis 9.9 (10 studies, 3652 participants): RR 0.91, 95% CI 0.78 to 1.05; I^2 = 52%) (low certainty evidence).

Outcomes were downgraded for heterogeneity or imprecision (Summary of findings 7).

Secondary outcomes

All outcomes were assessed by GRADE as shown in the results below but only the seven most important outcomes (**bold**) are included in Summary of findings 8.

Lower dose TOR-I and standard dose CNI compared with higher dose TOR-I and reduced dose CNI:

- Probably reduces the risk of new-onset diabetes mellitus (Analysis 10.1 (6 studies, 2125 participants): RR 0.69, 95% CI 0.51 to 0.93; I^2 = 16%) (**moderate certainty evidence**).
- Probably makes little or no difference to the risk of lymphoma (Analysis 10.2 (7 studies, 2792 participants): RR 0.66, 95% CI 0.25 to 1.73; I^2 = 0%) (**moderate certainty evidence**).
- May make little or no difference to the risk of adverse outcomes including tremor (Analysis 10.3.1 (1 study, 387 participants): RR 0.90, 95% CI 0.63 to 1.29), gum hyperplasia (Analysis 10.3.2 (2 studies, 622 participants): RR 1.45, 95% CI 0.48 to 4.42; I^2 = 0%) or acne/rash (Analysis 10.3.4 (6 studies, 2408 participants): RR 0.86, 95% CI 0.62 to 1.21; I^2 = 71%) (low certainty evidence) though it may reduce the risk of hirsutism (Analysis 10.3.3 (2 studies, 1102

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participants): RR 0.50, 95% CI 0.30 to 0.85; I^2 = 5%) (**low certainty evidence**).

- May make little or no difference to GFR (Analysis 10.4 (7 studies, 1863 participants): MD 2.88 mL/min, 95% CI -0.71 to 6.48; I^2 = 70%) (**low certainty evidence**) or to serum creatinine (Analysis 10.5 (5 studies, 1951 participants): MD -2.21 µmol/L, 95% CI -13.68 to 9.26; I^2 = 65% (low certainty evidence).
- Probably makes little or no difference to the number of participants with hypercholesterolaemia (Analysis 10.6.1 (9 studies, 3250 participants): RR 0.87, 95% CI 0.78 to 0.98; I^2 = 0%) (**moderate certainty evidence**), hypertriglyceridaemia (Analysis 10.6.2 (5 studies, 1064 participants): RR 0.71, 95% CI 0.47 to 1.07; I^2 = 0%) (moderate certainty evidence), mean cholesterol (Analysis 10.7.1 (5 studies, 1041 participants): MD -0.13 mmol/L, 95% CI -0.35 to 0.08; I^2 = 0%) or mean triglycerides (Analysis 10.7.2 (4 studies, 1041 participants): MD -0.37 mmol/L, 95% CI -0.72 to -0.03; I^2 = 22%) (moderate certainty evidence).
- May make little or no difference to the number of participants with anaemia (Analysis 10.8.1) (**low certainty evidence**), leucopenia (Analysis 10.8.2) (low certainty evidence), or thrombocytopenia (Analysis 10.8.3) (**low certainty evidence**).

Outcomes were downgraded for heterogeneity, imprecision and risk of bias related to sequence generation or allocation.(Summary of findings 8).

Comparative efficacy of sirolimus versus everolimus

Only one small study (28 recipients), reported as an abstract, compared sirolimus (mean dose 1.94 mg/d) to everolimus (mean dose 2.37 mg/d), with cyclosporin (mean dose 203 mg/d and 223 mg/d respectively) and prednisolone co-interventions (Rostaing 2001). Preliminary results for limited outcomes at three months showed higher GFR (Analysis 11.2: MD -17.00 mL/min, 95% CI -28.98 to -5.02) and lower mean SCr (Analysis 11.1: MD 33.00 µmol/L, 95% CI 2.00 to 64.00) for everolimus-treated patients, but lower total cholesterol (Analysis 11.3.1: MD -1.00 mmol/L, 95% CI -1.18 to -0.82) and triglycerides (Analysis 11.3.2: MD -0.30 mmol/L, 95% CI -0.44 to -0.16) for sirolimus-treated patients. In view of the small patient numbers, limited outcomes and short follow-up, it is uncertain whether sirolimus and everolimus differ in their effects on these outcomes.

Subgroup analyses

Stratified analysis was performed for the most commonly reported outcome, all acute rejection, to examine whether key study design features modified the overall results.

For studies of TOR-I versus CNI, P-values were greater than 0.05 for all analyses indicating no differences in the risk of acute rejection for the subgroups analysed (Analysis 12.1, Analysis 12.2, Analysis 12.3, Analysis 12.4) (Table 1). Only one study used everolimus and one study used azathioprine so different TOR-I and antimetabolites could not be assessed.

For studies comparing TOR-I with antimetabolite, P-values were greater than 0.05 for all analyses indicating no differences in the risk of acute rejection for the subgroups analysed (Analysis 13.1, Analysis 13.2, Analysis 13.3, Analysis 13.4; Analysis 13.5; Analysis 13.6) (Table 1).

For studies evaluating variable doses of TOR-I in combination with variable doses of CNI, P-values were greater than 0.05 for all analyses indicating no difference in the risk of acute rejection for the subgroups analysed (Analysis 14.1; Analysis 14.2; Analysis 14.3; Analysis 14.4; Analysis 14.5). (Table 2). All studies used mycophenolate mofetil or mycophenolate sodium so different antimetabolites could not be assessed.

For studies comparing low with higher doses of TOR-I, P-values were greater than 0.05 for all analyses indicating no difference in the risk of acute rejection for the subgroups analysed (Analysis 15.1; Analysis 15.2; Analysis 15.3; Analysis 15.4; Analysis 15.5). (Table 2). All studies used mycophenolate mofetil or mycophenolate sodium so different antimetabolites could not be assessed.

DISCUSSION

Summary of main results

Seventy studies (544 reports) with 17,462 participants were included in this review; 33 studies were included in the original review published in 2006 and 37 were added for the 2019 update. The studies were divided into four groups of comparisons. Data on outcomes in deceased donor and living donor transplant recipients was not reported separately in the included studies.

TOR-I compared with CNI

Twenty-one studies compared TOR-I with CNI with both groups receiving antimetabolites. For outcomes for up to three years, TOR-I compared with CNI probably makes little or no difference to death, graft loss and the number with malignancies but it probably increases the risk of biopsy-proven acute rejection compared with CNI (all moderate certainty evidence). TOR-I reduces the risk of CMV infection (high certainty evidence) but it probably increases the risk of wound complications and the number of participants who need to change immunosuppressive medications (moderate certainty evidence). Subgroup analyses of study methodology and design features for the outcome of all acute rejection identified no differences between groups (Table 1).

The outcomes in the 2019 review update are compared with those in the 2006 review in Table 3. In this update, the risk for all acute rejection and BPAR were increased with TOR-I and the risk for CMV disease was reduced while these risks did not differ in the 2006 review.

TOR-I compared with antimetabolite

Thirty-four studies compared TOR-I with antimetabolite with both groups receiving CNI. For outcomes for up to three years, TOR-I compared with antimetabolite probably makes little or no difference to death, graft loss, biopsy-proven acute rejection, and the risk for malignancies (all moderate certainty evidence). TOR-I probably reduces the risk of CMV infection (moderate certainty evidence) and the risk for BK virus infection (high certainty evidence). It probably increases the risk of wound complication and the number of participants who need to change immunosuppressive medications (moderate certainty evidence). Subgroup analyses of study methodology and design features for the outcome of all acute rejection identified no differences (Table 1).

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The outcomes in the 2019 review update are compared with those in the 2006 review in Table 4. In this update, no differences were identified in the risk for all acute rejection and BPAR while the risks were lower with TOR-I compared with antimetabolite in the 2006 review.

Variable TOR-I and CNI

Nine studies compared a lower TOR-I with standard CNI regimen with a higher TOR-I with reduced CNI regimen. For outcomes to two years the lower TOR-I regimen probably made little or no difference to death, graft loss, biopsy-proven acute rejection, and CMV infection (moderate certainty evidence). The lower TOR-I regimen may make little or no difference to the number of wound complications, the number with malignancies and the number needing to change immunosuppressive regimens (low certainty evidence). Subgroup analyses of study methodology and design features for the outcome of all acute rejection identified no differences (Table 2).

The outcomes in the 2019 review update are compared with those in the 2006 review in Table 5. In this update, no differences were identified in the risk for all acute rejection and BPAR while the risks were lower with TOR-I compared with antimetabolite in the 2006 review.

Low compared with higher doses of TOR-I

Thirteen studies compared a lower TOR-I with a higher TOR-I dose regimen. For outcomes to two years, the lower TOR-I dose probably makes little or no difference to death, graft loss, biopsy-proven acute rejection, CMV infection or the number with malignancies (moderate certainty evidence). Lower TOR-I dose compared with a higher dose probably reduces the number of participants with wound complications. It may make little or no difference to the number of participants needing to change immunosuppressive regimens (low certainty evidence). Subgroup analyses of study methodology and design features for the outcome of all acute rejection did not identify any differences (Table 2).

The outcomes in the 2019 review update are compared with those in the 2006 review in Table 6. In this update, the risk for hypercholesterolaemia was increased with higher doses of TOR-I while no difference was identified in the 2006 review.

Overall completeness and applicability of evidence

Most studies did not report on outcomes beyond three years. To determine efficacy outcomes in these short-term studies, the primary outcome was frequently a composite of outcomes and the studies were designed as non-inferiority studies. For example, Qazi 2017 used a composite efficacy endpoint of biopsy-proven acute rejection, graft loss, death and loss to follow up rather than individual components. In other studies, eGFR was the primary outcome of the study with or without biopsy-proven acute rejection. In the large study TRANSFORM 2018, the triallists used a composite primary outcome of the number of participants with eGFR < 50 mL/min calculated from the MDRD formula or with treated biopsy-proven acute rejection at 12 months. Because of the short duration of studies, outcomes of death or graft loss are unlikely to differ between treatment groups. Any identified differences between treatments are likely to be adverse effects of treatment. Therefore, the more important outcomes in short-term studies are adverse effects such as wound complications, CMV, lipid abnormalities and the number needing to change immunosuppressive medication. In the comparisons, these outcomes were reported less commonly than the outcomes of death, graft loss or biopsy-proven acute rejection. For example, in the comparison of TOR-I compared with CNI, CMV infection was reported in 13/21 studies while in the comparison of TOR-I compared with antimetabolite, CMV infection was reported in 24/34 studies.

Although this review included 70 studies, many studies did not report on outcomes important to participants including cosmetic complications and tremor. Health-related quality of life was only reported in a substudy of 156 participants of the SYMPHONY 2007. Because few studies reported separately on cardiovascular death or reported the number of cardiovascular events, we were not able to include an assessment of these outcomes in this review.

Quality of the evidence

Most studies did not report on how the sequence generation was derived or whether there was adequate allocation concealment. However, where these items were reported, they were generally at low risk of bias. Most studies were open label with only four studies being at low risk of performance bias. Almost all studies were considered at low risk of detection bias because the primary outcome was laboratory based and unlikely to be influenced by lack of blinding. Most studies were at low risk of incomplete outcome reporting or selective reporting though these quality outcomes were unclear in some studies available only in abstract form. Many studies were industry funded and considered at high risk for other bias.

GRADE assessment was used for 14 outcomes reported in summary of findings tables. In the comparisons of TOR-I versus CNI and TOR-I versus antimetabolite, GRADE assessment concluded that there was moderate certainty evidence for all primary outcomes except for CMV infection (high certainty evidence) in the TOR-I versus CNI comparison. In the comparisons of variable TOR-I and CNI and low versus higher TOR-I, GRADE assessment concluded that there was also moderate certainty evidence for most primary outcomes. Outcomes were downgraded for imprecision and heterogeneity. GRADE assessment for secondary outcomes was more likely to be considered low or very low particularly for laboratory outcomes. Outcomes were downgraded for imprecision, heterogeneity, publication bias and risk of bias for sequence generation and allocation concealment.

Potential biases in the review process

For this update a comprehensive search of the Cochrane Kidney and Transplant's Specialised Register was performed, which reduced the likelihood that eligible published studies were omitted from the review. Eligible studies published after the last search date of 20 September 2019 or published in congress proceedings not routinely searched could have been missed. Twelve studies were available in abstract form and provided limited information on study methods and results. Inclusion of these studies could be a source of bias.

The review was completed independently by at least two authors, who participated in all steps of the update. This limited the risk of errors in determining study eligibility, data extraction, risk of bias assessment and data synthesis. Some outcomes were reported in

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only a few studies which increased the risk of bias. In particular, adverse effects important to participants such as cosmetic effects and tremor were reported in few studies. The authors determined the outcomes that they considered were the most important for a review of TOR-I medications in kidney transplant recipients and did not report every outcome reported in each study. Therefore, some outcomes considered of importance by others could have been excluded from the review.

Agreements and disagreements with other studies or reviews

Recent systematic reviews of RCTs have evaluated TOR-I in kidney transplant recipients. Reviews included studies in which participants were converted to TOR-I weeks to months after kidney transplant as well as those commencing TOR-I at transplant while our review only included studies in which TOR-I was commenced at transplant or within six days of transplant. Kumar 2017 examined the role of TOR-I as an alternative to CNI and included 20 RCTs. Ten of these were also included in this review while the other 10 studies concerned later conversion to TOR-I regimens. As in this review they identified an increased risk of acute rejection among participants receiving de novo TOR-I compared with those receiving CNI but no difference in deaths or graft loss. Similarly, another review (Mallet 2017) including 24 RCTs (11 included in our review) found an increased risk of acute rejection in participants receiving de novo TOR-I compared with those receiving CNI but no difference in participants, who received TOR-I and reduced dose CNI compared with mycophenolic acid (MPA) and standard dose CNI. Wound complications were higher in all groups receiving TOR-I as in our review but graft loss did not differ between groups.

Mallet 2017 also examined the risk of CMV and BK virus infections in kidney transplant recipients receiving TOR-I. Among studies comparing TOR-I with CNI and studies comparing TOR-I and a reduced dose of CNI with MPA and standard dose CNI, CMV infection was reduced by 46% and 57% respectively. In equivalent analyses in this review, CMV infection was reduced by 57% and 58% respectively. Mallet 2017 found no difference in the number of patients with BK virus in studies comparing TOR-I with CNI (12 studies) or those comparing TOR-I with reduced dose CNI with standard dose CNI and MPA (two studies). In our review with additional studies, the risk for BK virus infection was reduced in participants receiving TOR-I compared with participants receiving MPA (high certainty evidence). However, in our review, it was unclear whether TOR-I compared with CNI reduced the number with BK virus infection because few studies addressed this outcome (very low certainty evidence).

AUTHORS' CONCLUSIONS

Implications for practice

Data included in this review show that TOR-I combined with an antimetabolite increases the risk for acute rejection compared with CNI combined with an antimetabolite suggesting that as initial immunosuppression for kidney transplant recipients, TOR-I should be given with a CNI rather than with an antimetabolite alone. More recent data confirm that TOR-I with CNI may offer a satisfactory alternative to an antimetabolite with CNI as rates of acute rejection are similar between interventions and TOR-I regimens are associated with a reduced risk of CMV and BK infections though wound complications and the need to change immunosuppressive medications are higher with TOR-I regimens. In addition, TOR-I regimens using a reduced dose of CNI compared with antimetabolite regimens result in similar GFR outcomes. However, most studies do not provide follow up beyond six months to three years. In the absence of long-term data particularly on graft survival, we are limited to reporting on the short-term outcomes including acute rejection, GFR and CMV disease and the adverse effects of each regimen and are unable to report on long term patient survival (particularly associated with cardiovascular disease and malignancy) and graft survival.

Implications for research

SYMPHONY 2007, which randomised 1645 participants, confirmed that TOR-I with an antimetabolite was inferior in terms of acute rejection rates to CNI with an antimetabolite so that few further studies evaluated this comparison. Similarly following the publication of TRANSFORM 2018, which enrolled 2037 participants and confirmed the relative efficacies of TOR-I with reduced dose CNI and mycophenolate sodium with standard dose CNI, there appears to be no requirement for further short-term studies comparing de novo use of TOR-I. There should be longer term follow-up of participants in the TRANSFORM 2018 and other large studies to provide longer term information about graft loss and graft function and help to assess the value of the outcomes of acute rejection and GFR reported for short follow up periods. Linkage to registry data can be used to provide longer follow up data on participants in RCTs. For example in a recent publication, Ying 2018 linked data from the Australian trial participants in four RCTs evaluating everolimus with registry data to determine the outcomes of incident cancers and cancer-related deaths.

To date studies have generally excluded sensitised recipients with PRA levels > 20%. Further studies are required in this group of transplant recipients.

This systematic review did not include studies where a TOR-I was added to the immunosuppressive regimen a week or more post-transplant. Further reviews are required to investigate the relative efficacies and adverse effects of TOR-I when introduced later after transplant.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anil Kumar 2005

Methods	• Design: open-label parallel RCT • Duration: October 2001 to June 2004 • Follow up: 12 months
Participants	• Setting: single centre transplant unit • Country: USA • Kidney transplant recipients aged ≥ 18 years, HIV negative, PRA < 10% • Number (group 1/group 2): 150 (75/75) • Mean age ± SD (years): group 1 (55.0 ± 12.0); group 2 (49.0 ± 13.7) • Sex (M/F): group 1 (51/49); group 2 (54/46) • Exclusions: not reported
Interventions	Co-interventions • Basiliximab, MP • TAC: 0.2 mg/kg/d from day 1 for level 10 to 18 ng/mL, then maintenance Treatment group 1 • SRL: 2 mg/d from day 4 for trough level 6 to 10 ng/mL Treatment group 2 • MMF: 2 g/d from day 1
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr • CAN • Haematological adverse effects

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Anil Kumar 2005 *(Continued)*

	• Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was determined using the First Generator Plan (www.randomization.com)
Allocation concealment (selection bias)	Low risk	Randomisation sequence was determined using the First Generator Plan (www.randomization.com)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/personnel reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary endpoint was acute rejection diagnosed on biopsy by pathologist without knowledge of the patient's clinical diagnosis
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for. Complete follow-up to 6 months
Selective reporting (reporting bias)	Low risk	Expected primary outcomes reported
Other bias	High risk	This clinical study was supported by an unrestricted financial grant from Fujisawa Healthcare and clinical revenue of Division of Transplantation, Drexel University College of Medicine

Anil Kumar 2008

Methods	• Design: parallel RCT • Duration: June 2000 to October 2004 • Follow up: 4 years or more
Participants	• Setting: single centre; Drexel University College of Medicine and Hahnemann University Hospital • Country: USA • First kidney transplant; recipients > 20 years, LD or DD donors • Number (group 1/group 2/group 3/ group 4): 200 (50/50/50/50) • Mean age ± SD (years): group 1 (51 ± 14); group 2 (56 ± 13); group 3 (48 ± 14); group 4 (59 ± 12) • Sex (M/F): group 1 (35/15); group 2 (37/13); group 3 (34/16); group 4 (34/16) • Exclusions: < 20 years; unable to sign an informed consent form; were HIV or HBV positive
Interventions	Treatment group 1 (MMF/CSA) • CSA: as above • MMF: 2 g/d for trough levels 1 to 3 µg/mL of MPA Treatment group 2 (SRL/CSA)

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Anil Kumar 2008 *(Continued)*

- CSA: as above
- SRL: 2mg/d from day 4 for levels 5 to 10 ng/mL.

Treatment group 3 (MMF/TAC)

- TAC: as above
- MMF: 2 g/d for trough levels 1 to 3 µg/mL of MPA

Treatment group 4 (SRL/TAC)

- TAC: as above
- SRL: 2 mg/d from day 4 for levels 5 to 10 ng/mL

Co-interventions

- Basiliximab
- MP (2 doses) and no further steroids
- CSA: 3 mg/kg/d for C2 blood levels of 1000 to 1200 ng/mL at 1 month and 700 ng/mL by 1 year
- TAC: 0.02 mg/kg for trough levels 15 to 18 ng/mL by day 4 till 1 month, then 10 ng/mL by 1 year

Outcomes	• Death • Acute rejection • Graft loss • CMV infection • DGF
Notes	• NOTE: for the analysis, groups 2 and 4 (SRL/CNI) were compared with 1 and 3 (MMF/CNI) • Significantly younger recipients in TAC/MMF group and significantly older recipients in the TAC/SRL group. Significantly older donors in the CSA/SRL group and significantly younger in the TAC/MMF group. Significantly more diabetes in recipients of the CSA/SRL and TAC/SRL groups. Significantly less cold ischaemia time in CSA/MMF group and significantly longer cold ischaemia time in the TAC/SRL group. Significantly fewer males in the CSA/SRL donor group and significantly more males in the TAC/SRL donor group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was determined using the First Generator Plan (http://www.randomization.com)
Allocation concealment (selection bias)	Low risk	Patients allocated using the First Generator Plan (http://www.randomization.com)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/personnel reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes of death, graft loss, biopsy-confirmed acute rejection were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All surviving patients completed 4 years of follow up; analysed in groups to which randomised

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Anil Kumar 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	Expected outcomes reported for all four treatment groups
Other bias	Unclear risk	Funding source not reported

ATHENA 2016

Methods	• Design: open-label RCT • Duration: December 2012 to March 2016 • Follow up: 12 months
Participants	• Setting: multicentre • Country: Germany (15 sites); France (12 sites) • Kidney transplant recipients (first or second LD or DD) • Number (group 1/group 2/group 3): 612 (208/199/205) • Mean age ± SD (years): group 1 (54.3 ± 13.5); group 2 (55.1 ± 12.6); group 3 (55.3 ± 12.1) • Gender (M/F): group 1 (138/70); group 2 (133/66): group 3 (140/65) • Exclusions: ABO-incompatible transplant; pre-existing donor-specific antibodies; cold ischaemia time ≥ 30 hours; multi-organ transplant; PRA > 20%; malignancy in previous 5 years (except skin, kidney, thyroid); pregnant/nursing mother or refusal to take contraception; thrombocytopenia; leucopenia; uncontrolled hypercholesterolaemia; hypertriglyceridaemia
Interventions	Treatment group 1 (EVL/TAC) • EVL: C0 target: 3 to 8 ng/mL (M1 to M12) • TAC: 4 to 8 ng/mL (M1 to M3); 3 to 5 ng/mL (M3 to M5) Treatment group 2 (EVL/CSA) • EVL: C0 target: 3 to 8 ng/mL (M1 to M12) • CSA: 75 to 125 ng/mL (M1 to M3); 50 to 100 ng/mL (M3 to M12) Treatment group 3 (MPA/TAC) • TAC: 4 to 8 ng/mL (M1 to M3); 3 to 5 ng/mL (M3 to M5) • MPA: 1.44 g/d mycophenolate sodium or 2 g/d of MMF Co-interventions • Corticosteroids/basiliximab in each group
Outcomes	• Death (all causes) • Graft loss • BPAR • Infections: CMV, BK • Adverse events
Notes	• Comparisons: TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "validated system to ensure an unbiased treatment assignment in a 1:1:1 ratio"

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ATHENA 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "validated system to ensure an unbiased treatment assignment in a 1:1:1 ratio"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is GFR and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	655 randomised; 43 did not receive medication. ITT population 612/safety population 612
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	High risk	The study was funded by Novartis Pharma GmbH, Nürnberg, Germany

AVESTA 2017

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 13 months
Participants	• Setting: single centre • Country: Iran • 60 kidney transplant recipients of LD or DD organs aged 18 to 65 years • Age and gender: not reported • Exclusions: not reported
Interventions	Treatment group 1 (EVL/rCSA) • EVL: 0.75 mg twice/day 3 to 8 ng/mL • CSA: 3 to 5 mg/kg 100 to 200 ng/mL (M1); 75 to 100 ng/mL (M2 to M3); 50 to 100 ng/mL (M4); 25 to 50 ng/mL (M6 to M12) Treatment group 2 (MPA/sCNI) • MMF: 1 g twice/d (CSA patients) • MMF: 500 mg twice/d (TAC patients) • TAC: 0.1 mg/kg, 7 to 10 ng/mL to M3 • CSA: 7.5 mg/kg, 150 to 300 ng/mL to M3 Co-interventions • Corticosteroids in each group
Outcomes	• BPAR • CMV and BK virus • GFR
Notes	• Abstract only available

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AVESTA 2017 *(Continued)*

- Patient numbers in each group not reported so data cannot be entered in meta-analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Eligible patients randomised 1:1 prior to transplantation
Allocation concealment (selection bias)	Unclear risk	Eligible patients randomised 1:1 prior to transplantation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information provided to suggest study was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was GFR so unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data to permit judgement - abstract only
Selective reporting (reporting bias)	Unclear risk	Insufficient data to permit judgement - abstract only
Other bias	Unclear risk	Insufficient data to permit judgement - abstract only

Bechstein-193 2013

Methods	• Design: open-label parallel RCT • Duration: completed in June 2002 • Follow up: 6 months
Participants	• Setting: kidney transplant services • Country: 13 European centres; European Rapamune Tacrolimus Study Group • Kidney transplant recipients (first or second DD grafts) aged ≥ 18 years • Number (group 1/group 2): 128 (63/65) • Mean age ± SD (years): group 1 (47.9 ± 13.3); group 2 (44.6 ± 14.8) • Sex (M/F): group 1 (45/18); group 2 (38/27) • Exclusions: planned antibody induction; multi-organ transplant; HIV, HBV or HCV; cancer in last 5 years; WBC ≤ 3000/mm^3 or platelet count ≤ 100,000/mm^3; hypersensitivity to study drugs; other investigational drug; PRA > 50%; cold ischaemia time > 12 hours; donor after cardiac death
Interventions	Treatment group 1 (rTAC; high dose SRL) • SRL: 15 mg x 3 days, then 5 mg/d adjusted for levels 8 to 15 ng/mL > 3 months • TAC: within 7 days after transplant; 0.05 mg/kg twice/d; adjusted to trough levels 3 to 7 ng/mL from M1 Treatment group 2 (sTAC; low dose SRL) • SRL: 15 mg x 3 days, then 5 mg/d adjusted to maintain 24-hour to trough levels 5 to 10 ng/mL from M1 • TAC: 0.05 mg/kg twice/d adjusted for trough levels 8 to 12 ng/mL > 3 months

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Bechstein-193 2013 *(Continued)*

	Co-interventions • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr • CMV infection • Malignancy • Haematological adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: variable dose of TOR-I and CNI • Doses of SRL/TAC are those post amendment needed because of high incidence of acute rejection in rTAC group due to insufficient blood levels of TAC and SRL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random assignment 1:1; no further information
Allocation concealment (selection bias)	Unclear risk	Random assignment 1:1; no further information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is laboratory based (CrCl) and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	Expected primary outcomes reported
Other bias	High risk	At the time of this study, Anthony J. Zygmunt was an employee of Wyeth Research

Bertoni 2011

Methods	• Design: parallel group RCT • Duration: not reported • Follow up: 12 months

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Bertoni 2011 *(Continued)*

Participants	• Setting: single centre study • Country: Italy • Kidney transplant recipients • Number (group 1/group 2): 106 (50/56) • Mean age ± SD (years): group 1 (49.7 ± 12.1); group 2 (45.7 ± 12.8) • Sex (MF): not reported • Exclusions: donor and recipient age > 65 years; PRA > 50%; retransplants; combined transplants; FSGS as primary disease, BMI > 25
Interventions	Treatment group 1 (sCSA/MMF) • MPA (EC-MPS): 1440 mg/d • CSA: starting at 6 mg/kg/d for C2 levels 500 to 700 ng/mL Treatment group 2 (rCSA/EVL) • EVL: 8 to 12 ng/mL initially then 3 to 8 ng/mL • CSA: starting at 4 mg/kg/d for C2 levels 250 to 300 ng/mL Co-interventions • Basiliximab • Corticosteroids
Outcomes	• Death (all causes) • Graft loss with death censored • CrCl • Biochemical adverse effects • Cosmetic/lifestyle adverse effects
Notes	• Comparison: TORI-I versus antimetabolite

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	Low risk	Primary outcomes (graft loss, BPAR) unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	High risk	No report on wound complications

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Bertoni 2011 *(Continued)*

Other bias	Low risk	Quote: "no financial support"

Burke 2002

Methods	• Design: parallel RCT • Duration: May 2000 to December 2001 • Follow up: 36 months
Participants	• Setting: single centre study • Country: USA • Kidney transplant recipients aged 14 to 78 years; DD and non-HLA identical LD • Number (group 1/group 2/group 3): 150 (50/50/50) • Mean age ± SD (years): group 1 (50 ± 13); group 2 (47 ± 16); group 3 (44 ± 16) • Sex (M/F): group 1 (35/15); group 2 (32/18); group 3 (32/18) • Exclusions: not reported
Interventions	Treatment group 1 (SRL/TAC) • SRL: 4 mg/d for level 8 ng/mL • TAC: 0.2 g/kg/d for levels 10ng/mL; 6 to 8 ng/mL by 3 to 6 months; 6 ng/mL by 12 months Treatment group 2 (MMF/TAC) • MMF: 2 g/d • TAC: 0.2 g/kg/d for level 10ng/mL, 8 ng/mL by 12 months Treatment group 3 (SRL/CS) • SRL: 4 mg/d for level 8 ng/mL • CSA: 10 mg/kg/d for levels 200 to 250 ng/mL, 150 to 200 ng/mL at 12 months Baseline immunosuppression • Daclizumab • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • CMV infection • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: TOR-I versus antimetabolite; groups 1 and 3 combined and compared with group 2
Risk of bias	

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Burke 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation scheme; equally divided into three groups
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	Low risk	Primary outcomes were laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	National Institutes of Health (grant R01DK25243-25), Miami Veterans Affairs Medical Center research support, Astellas Pharma US, Roche Laboratories, and Wyeth

CALFREE 2006

Methods	• Design: open-label RCT • Duration: January 2001 to July 2004 • Follow up: 6 months
Participants	• Setting: single centre • Country: Switzerland • Kidney transplant recipients aged 15 to 75 years • Number (group 1/group 2): 127 (63/64) • Mean age ± SD (years): group 1 (48 ± 14.4); group 2 (49.5 ± 14.4) • Sex (M/F): group 1 (44/19); group 2 (41/23) • Exclusions: HLA identical grafts; high immunological risk; positive cross match or ABO incompatibility; graft from a donor > 68 years; cold ischaemia time > 36 hours
Interventions	Treatment group 1 • SRL: 30 mg/d on days 0, 1, 2. Then 16 mg/d for trough level 10 to 2 0ng/mL (M1 to 3) then trough levels of 8 to 15 ng/mL (M4 to 6) Treatment group 2 • CSA: initial dose 600 mg/d for trough level 250 to 300 ng/mL for 3 months and then 150 to 250 ng/mL Co-interventions • MMF: 2 g/d

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CALFREE 2006 *(Continued)*

	• MP or prednisolone: initial dose 0.5 mg/kg, maintenance 5 mg/day stopped at 6 months
Outcomes	• Kidney function • Adverse events • Rejection
Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "127 patients were randomly assigned before transplant..(in a masked fashion)"
Allocation concealment (selection bias)	Unclear risk	Quote: "127 patients were randomly assigned before transplant..(in a masked fashion)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome (kidney function) was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/127 (3%) did not complete follow up
Selective reporting (reporting bias)	Low risk	Expected outcomes (graft function, rejection, death, adverse effects) reported
Other bias	High risk	Sponsored by Wyeth

Cattaneo 2005

Methods	• Design: parallel RCT • Duration: not reported • Follow up: 12 months
Participants	• Setting: single centre • Country: Italy • Primary kidney transplant recipients • Number (group 1/group 2): 21 (11/10) • Mean age ± SD (years): group 1 (47.5 ± 16.0); group 2 (42.3 ± 13.2) • Sex (M/F): group 1 (7/4); group 2 (5/5) • Exclusions: unclear
Interventions	Treatment group 1 • SRL: 4 mg and then adjusted to level 5 to 10 ng/mL Treatment group 2

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Cattaneo 2005 *(Continued)*

	• CSA: 1 to 2 mg/kg/d and adjusted to initial level 120 to 220 ng/mL; maintenance 70 to 120 ng/mL Co-interventions • MMF: 1g/d • Alemtuzumab: 30 mg • MP: 200 mg IV intraoperatively • Prednisolone: 250 mg on day 1, 125 mg on day 2
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with functioning graft • Acute rejection • CrCl • Infection • CMV • Biochemical adverse effect • Surgical adverse effect • Cosmetic/lifestyle adverse effect
Notes	• Comparison: TORI versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They were allocated to one of the following two study groups according to a randomization design"
Allocation concealment (selection bias)	Unclear risk	Quote: "They were allocated to one of the following two study groups according to a randomization design"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was MPA levels & these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all patients randomised were included in analyses
Selective reporting (reporting bias)	High risk	Only GFR and SCr reported
Other bias	Unclear risk	No report on funding

Ciancio 2016

Methods	• Design: parallel RCT • Duration: 11/2011 to 1/2014

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Ciancio 2016 *(Continued)*

	• Follow up: 12 months
Participants	• Setting: single centre • Country: USA • Participants: DD and non-haplotype identical living related donor transplants aged 30 to 70 years • Number (group 1/group 2): 30 (15/15) • Mean age ± SD (years): group 1 (49.9 ± 2.7); group 2 (48.5 ± 2.9) • Sex (M/F): group 1 (12/3); group 2 (11/4) • Exclusions: DGF
Interventions	Treatment group 1 (EVL/sTAC) • EVL: 0.75 mg twice/day within 24-hour post transplant, then adjusted to 3 to 8 ng/mL • TAC: 0.1 mg/kg twice/d when SCr < 4 mg/dL for trough 5 to 8 ng/mL till 7 to 10 days postoperatively Treatment group 2 (MPS/sTAC) • MPS: 720 mg orally twice/d • TAC 0.1 mg/kg twice/d when SCr < 4 mg/dL for trough 5 to 8 ng/mL till 7 to 10 days post operatively Co-interventions • Basiliximab • Prednisone
Outcomes	• Death (all causes) • Graft loss • Acute rejection • CMV • NODM
Notes	• Comparison: TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be open-label RCT but no other data provided
Allocation concealment (selection bias)	Unclear risk	Said to be open-label RCT but no other data provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was Biopsy proven rejection & unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for

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Ciancio 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Novartis educational grant CRAD001AUS103T

Cohen 2002

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 1 year
Participants	• Setting: multicentre study (US Rapamune-CSA Study Group) • Country: USA • Kidney transplant recipients; de novo DD or LD transplants • Number (group 1/group 2): 309 randomised; 296 (154/142) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: African Americans
Interventions	Treatment group 1 (rSRL/sCSA) • SRL: levels 5 to 15 ng/mL (doses not reported) • CSA: levels 150 to 300 ng/mL (doses not reported) Treatment group 2 (sSRL/rCSA) • SRL: levels 10 to 20 ng/mL (doses not reported) • CSA: levels 50 to125 ng/mL (doses not reported) Baseline immunosuppression • Steroids (prednisone or prednisolone)
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • CAN • Infection • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: variable dose of TOR-I and CNI • Abstracts only available

Risk of bias

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Cohen 2002 *(Continued)*

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	Primary outcome unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% participants did not complete 1 year follow-up
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Durlik 2008

Methods	• Design: parallel RCT • Duration: not reported • Follow up: 36 months
Participants	• Setting: multicentre study • Country: Poland • High risk DD kidney transplant recipients; aged 15 to 55 years; high immunologic risk was defined as retransplantation or PRA > 25% • Number (group 1/group 2): 62 (40/22) • Age range: 15-55 years • Sex (M/F): 30/32 • Exclusions: not reported
Interventions	Treatment group 1 (TAC, MMF) • ATG • MMF • TAC • Corticosteroids Treatment group 2 (TAC, SRL) • ATG • SRL • TAC • Corticosteroids

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Durlik 2008 *(Continued)*

	Co-interventions • Not reported
Outcomes	• GFR estimated from Cockcroft-Gault formula • DGF
Notes	• Compare M-TOR versus antimetabolite

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	Insufficient information to permit judgement

Durrbach 2008

Methods	• Design: open-label RCT • Duration: 2002 to 2004 • Follow up: 6 months
Participants	• Setting: multicentre pilot study • Country: France • Kidney transplant recipients of extended criteria donors • Number (group 1/group 2): 72 randomised; 69 transplanted (33/36) • Mean age ± SD (years): group 1 (52.6 ± 11.2); group 2 (57.1 ± 8.9) • Sex (M/F): not reported • Exclusions: positive crossmatch; peak PRA > 50%; dual kidney allograft; donation after cardiac death
Interventions	Treatment group 1 • SRL: 15 mg in first 2 days post transplant & 10 mg daily for initial target 10 to 20 ng/mL; maintenance 10 to 20 ng/mL

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Durrbach 2008 *(Continued)*

	Treatment group 2 • CSA: 6 mg/kg/d for initial target 150 to 300 ng/mL at 3 months; 75 to 200 ng/mL at 6 months Baseline immunosuppression • Steroids (prednisone or prednisolone) • MMF • ATG
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • SCr
Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised
Allocation concealment (selection bias)	Low risk	Centrally randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were patient/graft survival and these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All prespecified primary outcomes reported
Other bias	High risk	Funded by Wyeth. EUDRACT trial number: 0468E1-100969

Esmeraldo 2015

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 24 months
Participants	• Setting: single centre • Country: Brazil • First kidney transplant recipients low risk PRA < 50%

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Esmeraldo 2015 *(Continued)*

- Number (group 1/group 2): 115 (59/56)
- Mean age ± SD: 44 ± 14 years
- Sex (M/F): 92/23
- Exclusions: not reported

Interventions	Treatment group 1 (EVL/sTAC) • EVL: 1.5 mg twice/day for 3 to 8 ng/mL • TAC: dose for levels of 4 to 7 ng/mL Treatment group 2 (MPS/sTAC) • MPS: 720 mg twice/d • TAC: dose for levels of 4 to 7 ng/mL Co-interventions • Corticosteroids in each group: steroid-free by day 7 • ATG induction • No CMV prophylaxis
Outcomes	• Graft loss • Total acute rejection • CMV infection • GFR
Notes	• Abstract only available • Comparison: TOR-I vs antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised 1:1 within 24 hours post transplant. No further information
Allocation concealment (selection bias)	Unclear risk	Randomised 1:1 within 24 hours post transplant. No further information
Blinding of participants and personnel (performance bias) All outcomes	High risk	open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was CMV infection diagnosed by lab tests routinely done to 6 months and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Said to be ITT population
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement - abstract only
Other bias	Unclear risk	Insufficient information to permit judgement - abstract only

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EVEREST 2009

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 6 months with observational extension to 12 months
Participants	• Setting: national multi-centre study • Country: Italy (19 centres) • Single kidney transplant from a DD or non-HLA identical LD • Number (group 1/group 2): 285 (142/143) • Mean age ± SD (years): group 1 (45.8 ± 10.6); group 2 (45.4 ± 11.7) • Gender (M/F): group 1 (93/49); group 2 (89/54) • Exclusions: pregnancy; PRA ≥ 50%; previous transplant failed within 1 year; diagnosis of FSGS or primary hyperoxaluria; chronic active hepatitis; HIV positivity; plasma cholesterol levels ≥ 9.1 mmol/dL or triglyceride levels ≥ 5.6 mmol/L
Interventions	Treatment group 1 (rEVL/sCSA) • EVL 0.75 mg twice/d adjusted to maintain a blood level of 3 to 8 ng/mL until the end of month 6 • CSA: 2 mg/kg twice/d adjusted to maintain a blood level of C2 of 500 to 700 ng/mL within day 5 and until the end of month 2, then reduced to reach 350 to 500 ng/mL within month 6. C2 levels until month 12 were 350 to 450 ng/mL. Treatment group 2 (sEVL/rCSA) • EVL: 0.75 mg twice/d adjusted to maintain a blood level of 8 to 12 ng/mL until the end of month 6 • CSA: 2 mg/kg twice/d adjusted to maintain a blood level of C2 of 250 to 400 ng/mL within day 5 and until the end of month 2, then reduced to reach 200 to 400 ng/mL within month 4. C2 levels were maintained at 150 to 300 ng/mL thereafter Co-interventions • Basiliximab: 20 mg IV on days 0 and 4 after transplantation • IV MP: 500 mg on day 0 and 40 mg on day 1 • Oral prednisone: 20 mg/d until day 7, then 5 mg/d until day 45
Outcomes	• CrCl • Death • BPAR • Graft loss • CMV infection • DGF • Treated adverse reactions • eGFR
Notes	• Comparison is low dose TOR-I with high CNI versus high dose TOR-I with low CNI • No BK data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization codes were generated at Novartis Farma SpA (Origgio, Varese, Italy), using a validated computer method"

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EVEREST 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Each center was assigned an adequate number of sealed envelops, each of them labeled with a unique patient number, that were opened after transplantation immediately before the administration of the first EVL dose"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were CrCl estimated from Cockcroft and Gault equation and the proportion of patients with BPAR. Unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis conducted. All participants accounted for
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in methods are reported
Other bias	High risk	Sponsored by Novartis. Several authors also had affiliations or were authors of Novartis

EVEROLD 2014

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 1 year
Participants	• Setting: national multi-centre study • Country: France • Participants: 1st or 2nd single transplantation of a recipient > 60 years, donor > 60 years, low immunological risk (PRA < 30%) • Number: 304 enrolled; 285 analysed • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: LD; 3rd transplantation; PRA > 30%
Interventions	Treatment group 1 • CSA: 6 to 8 mg/kg/d adjusted for C2 levels • MMF: 3 g/d • IL2 induction Treatment group 2 • EVL: 4 to 6 mg/d from day 5 • MMF: 3 g/d • ATG induction Treatment group 3 • Switch to EVL at week 7 • CSA till end of week 6 • IL2 induction

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EVEROLD 2014 *(Continued)*

	• MMF Co-interventions • Steroids
Outcomes	• Patient survival • Graft loss • DGF • BPAR • GFR (MDRD) • Discontinuation • Adverse events
Notes	• M-TOR versus CNI (compared groups 1 and 2) • No information on numbers in each group so data could not be entered into meta-analyses • No response from email to authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised but no other information provided.
Allocation concealment (selection bias)	Unclear risk	Said to be randomised but no other information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes unlikely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported on 94% of participants.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement - abstract only
Other bias	High risk	Novartis, Roche, Genzyme listed on clinical trials as sponsors

Favi 2009

Methods	• Design: open-label RCT • Duration: May 2004 to August 2006 • Follow up: 3 years
Participants	• Setting: single centre transplant unit • Country: Italy • Recipients of DD transplants

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Favi 2009 *(Continued)*

- Number (group 1/group 2): 60 (30/30)
- Mean age ± SD (years): group 1 (44 ± 11); group 2 (45 ± 10)
- Sex (M/F): group 1 (15/15); group 2 (18/12)
- Exclusions: PRA > 50%; cold ischaemia time > 24 hours

Interventions	Treatment group 1 (EVL/sCSA) • EVL; start dose 0.75 mg twice/d then dosed to maintain a trough level of 3 to 12 ng/mL • CSA: start dose 400 mg twice/d and then dosed to maintain a C2 level of 350 to 700 ng/mL Treatment group 2 (MMF/sTAC) • TAC: dosed to maintain a trough level of 8 to 10 ng/mL by month 3 and 5 to 8 ng/mL thereafter • MMF: 1 g twice daily Co-interventions • Basiliximab • Corticosteroids
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • BPAR • CrCl • Biochemical adverse effects
Notes	• Comparison: TOR-I versus antimetabolite • CSA and TAC were considered comparable across the groups as CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "consecutively assigned 1:1 to one of the two immunosuppressive regimens"
Allocation concealment (selection bias)	High risk	Quote: "consecutively assigned 1:1 to one of the two immunosuppressive regimens"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed follow-up
Selective reporting (reporting bias)	High risk	Adverse effects incompletely reported
Other bias	Low risk	This study was partially supported by UCSC grant MIUR 2007

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Favi 2012

Methods	• Design: phase 2 RCT • Duration: not reported • Follow up: 1 year
Participants	• Setting: single centre • Country: Italy • DD kidney transplant recipients • Number (group 1/group 2): 42 (21/21) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: not reported

Interventions	Treatment group 1
	• ER-TAC: dose not reported
	• EVL: dose not reported
	Treatment group 2
	• ER-TAC: dose not reported
	• MMF: dose not reported
	Co-interventions
	• Induction therapy
	  * Basiliximab: 20 mg IV on day 0 and day 4
	  * Thymoglobulin: 50 mg/d day 0 to day 3
	  * MP: 500 mg IV day 0, and 125 mg until day 3. Oral therapy commenced day 4

Outcomes	• Death (all causes) • Graft loss • BPAR • Adverse effects
Notes	• Comparison: TOR-I versus antimetabolite • Abstract only

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	Not blinded and lack of blinding likely to influence performance bias
Blinding of outcome assessment (detection bias)	Low risk	Primary outcomes were death, graft loss, BPAR and lack of blinding likely to influence outcome assessment

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Favi 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients (5%) lost to follow-up
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Fernandes-Charpiot 2014

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 12 months
Participants	• Setting: single centre transplant service • Country: Brazil • Kidney transplant recipients of extended criteria or standard criteria DD kidneys • Number (group 1/group 2): 68 (33/35) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: not reported
Interventions	Treatment group 1 (EVL/MPS) • EVL: doses not reported • MPS: doses not reported Treatment group 2 (TAC/MPS) • TAC: doses not reported • MPS: doses not reported Co-interventions • IL2 • Steroids
Outcomes	• Death (all causes) • Graft loss • Acute rejection • CMV
Notes	• Comparison: TOR-1 versus CNI • Abstract only available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised but no details provided

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Fernandes-Charpiot 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Said to be randomised but no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement - abstract only
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement - abstract only
Other bias	High risk	Novartis Research Support listed in disclosures

FIBRASIC 2009

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 12 months
Participants	• Setting: multicentre (4 centres) • Country: Belgium • De novo Kidney transplant recipients • Number (group 1/group 2): 45 (24/21) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: not reported
Interventions	Treatment group 1 (SRL/MMF) • SRL: doses not reported • MMF: doses not reported Treatment group 2 (CSA/MMF) • CSA: doses not reported • MMF: doses not reported Co-interventions • IL2 • Steroids
Outcomes	• GFR
Notes	• Comparison: TOR-1 versus CNI • Abstract only available

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FIBRASIC 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be a RCT but no details provided.
Allocation concealment (selection bias)	Unclear risk	Said to be a RCT but no details provided
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 - abstract only
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement - abstract only
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement - abstract only
Other bias	Unclear risk	Insufficient information to permit judgement - abstract only

Flechner 2013

Methods	• Design: parallel RCT; 2:1 randomisation • Study duration: June 2005 - June 2006: study recruitment stopped after about 12 months by data monitoring committee because of a high rate of acute rejection • Duration of follow-up: 206 patients completed 6 months follow-up. Originally planned for 2-year follow-up
Participants	• Setting: multicentre transplant services • Countries: USA, Spain, Australia, Canada, Turkey, Hungary, South Africa, Italy, Greece, Argentina, Chile, UK, Sweden • De novo kidney transplant recipients aged > 13 years; DD, LD (non HLA identical); WBC ≥ 4000 mm^3; platelets ≥ 100,000 mm^3; cholesterol ≤ 300 mg/dL, triglycerides ≤ 350 mg/dL • Number (group 1/group 2): ITT population (randomised and received transplant) 475 (314/161); safety population 471 (received at least one dose of medication) • Mean age ± SD (years): group 1 (42.9 ± 14.2); group 2 (42.7 ± 11.8) • Sex (M/F): group 1 (218/96); group 2 (116/45) • Exclusions: donor organ with cold ischaemic time > 30 hours or those from non-heart beating donors
Interventions	Treatment group 1 • SRL: 10 to 15 mg within 48 hours of transplant then 4 to 8 mg/d for levels ≥ 10 ng/mL; doses for levels to week 13, 10 to 15 ng/mL; weeks 14 to 26, 8 to 12 ng/mL; weeks 27 to 104, 5 to 12 ng/mL • After 6 months (Amendment 2), SRL loading dose of 15 mg x 2 & 10 mg daily until whole-blood SRL trough levels were 10.0 ng/mL or more; to week 26, 10 to 15 ng/mL; weeks 27 to 104, 8 to 15 ng/mL Treatment group 2

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Flechner 2013 *(Continued)*

	• CSA 6 to 8 mg/kg/dose; adjusted for levels to week 13, 150 to 300 ng/mL; weeks 14 to 26, 50 to 200 ng/mL; weeks 27 to 104, 50 to 150 ng/mL Co interventions • Basiliximab: 20 mg on day of transplant and day 4 • MMF: 2 g/d started within 48 hours • MP/prednisolone
Outcomes	• Graft survival • Patient survival • BPAR • GFR
Notes	• Comparison: TOR-1 versus CNI • Note study terminated prematurely due to high rate of acute rejection in the SRL group. 127 patients receiving SRL and 79 receiving CSA completed 6 months of treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned (2:1) by a computerized randomisation/enrolment system
Allocation concealment (selection bias)	Low risk	Patients were randomly assigned (2:1) by a computerized randomisation/enrolment system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were BPAR and GFR; unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Study terminated prematurely because of increased risk of rejection in SRL group
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Wyeth. Authors were employees/received funding from drug companies

Flechner-318 2002

Methods	• Design: open-label RCT • Duration: March 2000 to June 2001 • Follow up: 5 years
Participants	• Setting: single centre • Country: USA

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Flechner-318 2002 *(Continued)*

- Kidney transplant only recipients
- Number (group 1/group 2): 61 (31/30)
- Mean age, range (years): group 1 (48.4, 22 to 66); group 2 (46.7, 21 to 70)
- Sex (M/F): group 1 (21/10); group 2 (19/11)
- Exclusions: prior transplantation; HLA identical siblings; treatment for cancer; weight > 105 kg; total cholesterol > 350 mg/dL; triglycerides > 400 mg/dL; WBC < 3000/mm^3 or platelets < 75,000/mm^3

Interventions	Treatment group 1 • SRL: 15 mg within 48 hours of surgery; then 5 mg/d & then according to levels. Target 10 to 12 ng/mL till 6 months and then maintenance 5 to 10 ng/mL Treatment group 2 • CSA: 6 to 8 mg/d commenced when SCr below 4 mg/dL or by day 8; initial target 200 to 250 ng/mL; maintenance 200 to 250 ng/mL Co-interventions • Basiliximab • MMF: 2 g/d • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • CMV infection • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	Comparison: TOR-I versus CNI. 3 switched from Cyclosporin - 1 severe hirsutism and gum hypertrophy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised via computer-generated cards"
Allocation concealment (selection bias)	Low risk	Quote "randomised via computer-generated cards"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes of kidney function and number of acute rejection episodes between group were laboratory based and unlikely to be influenced by lack of blinding

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Flechner-318 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported (death, graft loss, rejection)
Other bias	High risk	Sponsored by Wyeth

Gallon 2006

Methods	• Design: open-label RCT • Duration: October 2000 to September 2001 • Follow up: mean of 8.6 years
Participants	• Setting: single centre transplant service • Country: USA • Kidney transplant recipients aged 30 to 70 years • Number (group 1/group 2): 90 (46/44); analysis on only 82 (37/45) patients • Mean age ± SD (years): group 1 (46.3 ± 12.6); group 2 (42.3 ± 11.9) • Sex (M/F): group 1 (22/15); group 2 (28/17) • Exclusions: paediatric recipients; receiving ABO incompatible or a positive donor-recipient cross match kidney; multi-organ transplants; kidney from a non-heart beating donor; known sensitivity to TAC, SRL or MMF; pregnant; HIV positive
Interventions	Treatment group 1 • SRL: started on postoperative day 1 at 3 mg/d; target 24-h trough levels 7 to 10 ng/mL Treatment group 2 • MMF: started on postoperative day 1 at 2 g/d Co-interventions • TAC: levels 8 to 10 ng/mL to 3 months; 7 to 9 ng/mL to 6 months; 6 to 8 ng/mL thereafter • Basiliximab • MP: till day 2
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl
Notes	• Comparison: TOR-I versus antimetabolite • The primary efficacy end-point was the 3-year graft survival rates. Outcome data also available for 8.6 years follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement

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Gallon 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Said to be randomised but no information provided
Allocation concealment (selection bias)	Unclear risk	Said to be randomised but no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was graft loss by 3 years & unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	82/94 (87%) randomised were analysed - per protocol analysis only
Selective reporting (reporting bias)	High risk	Limited information on adverse effects
Other bias	High risk	Partly funded by Astellas-USA

Gelens 2006

Methods	• Design: open-label RCT • Duration: not reported • Follow up: median follow up 9.2 months
Participants	• Setting: single centre • Country: Netherlands • Kidney transplant recipients • Number (group 1/group 2/group 3): 54 (18/18/18) • Median age (years): group 1 (59.3); group 2 (47.6); group 3 (57.1) • Sex (M/F): group 1 (13/5); group 2 (12/6); group 3 (11/7) • Exclusions: graft from a HLA identical sibling; patients with a high immunological risk (PRA > 85%); previous graft survival < 1 year due to rejection
Interventions	Treatment group 1 • SRL: initial 3 mg/d (pre-op and day 1); maintenance 1 mg/d (fixed dose) • TAC: 0.1 mg/d • Daclizumab: 1 mg/kg IV before reperfusion and on day 14 Treatment group 2 • TAC: 0.1 mg/day for levels 15 to 20 g/L for weeks 1 and 2; 10 to 15 g/L for weeks 3 and 4; thereafter 5 to 8 g/L • MMF: 2 g/d Treatment group 3 • High dose SRL: initial 15 mg/d (pre-op and day 1); maintenance 5 mg/d. Subsequent doses adjusted by trough levels target range: < 6 months, 10 to 15 µg/L; > 6 months, 5 to 10 µg/L

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Gelens 2006 *(Continued)*

	• MMF: 2 g/d Co-interventions • MP: 125 mg MP day 0 and day 1
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection
Notes	• Comparisons: group 1 versus 2 (SRL vs MMF); group 3 versus 2 (SRL versus TAC) • Study ceased after interim analysis of 54 participants showed higher rejection rate in SRL/MMF group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	12-month, open label, prospective, parallel group, randomised (1-1-1), single-centre study; no other information provided
Allocation concealment (selection bias)	Unclear risk	12-month, open label, prospective, parallel group, randomised (1-1-1), single-centre study; no other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death/graft loss and these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients included in analyses
Selective reporting (reporting bias)	High risk	Reported on death, graft loss, rejection-free survival. Inadequate reporting of adverse effects
Other bias	High risk	Sponsored by Roche, Astellas (Fujisawa Beneleux)

Glotz 2010

Methods	• Design: open-label RCT • Duration: June 2002 to January 2005 • Follow up: 12 months
Participants	• Setting: multicentre study • Country: Belgium and France • Kidney transplant patients aged 18 to 65 years with PRA < 50%; 1st or 2nd kidney transplant • Number (group 1/group 2): 141 (71/70) • Mean age ± SD (years): group 1 (48.5 ± 9.5); group 2 (46.7 ± 10.6) • Sex (M/F): group 1 (45/26); group 2 (43/27)

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Glotz 2010 *(Continued)*

	• Exclusions: lost prior transplants in the 6 months post-transplant for immunologic reasons; double kidney graft or multiple organ transplants; antibodies to the hepatitis C or B core antigen with evidence of active disease; liver dysfunction during 3 months pre-transplant; LD grafts; prolonged ischaemia time, donor age < 5 or > 65 years
Interventions	Treatment group 1 • SRL: 2 loading doses of 15 mg within 48 hours of transplant; 10 mg/d for 5 days, and then adjusted to targeted trough levels; initial target 12 to 20 ng/mL, maintenance 12 to 20 ng/mL • Thymoglobulin • MMF: 1.5 g/d • Prednisolone Treatment group 2 • TAC: 0.15 mg/kg/d for trough levels of 10 ng/mL (range, 8 to 12 ng/mL) for 3 months then 7 ng/mL (range 5 to 9 ng/mL) from 4 to 12 months • MMF 1.5 g/d • Prednisolone Co-interventions • Not reported
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects
Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Open-label randomised study. No further information provided
Allocation concealment (selection bias)	Unclear risk	Open-label randomised study. No further information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death, graft loss & these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	141/149 included in ITT analysis

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Glotz 2010 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Reported expected outcomes
Other bias	High risk	Wyeth Research, Paris, France

Gonwa-PSG 2003

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 12 months
Participants	• Setting: multicentre study (27 centres) • Country: USA • Kidney transplant recipients > 18 years, DD or non-HLA identical LRD • Number (group 1/group 2): 361 (185/176) • Mean age ± SD (years): group 1 (45.3 ± 12.4); group 2 (47.8 ± 12.3) • Sex (M/F): group 1 (124/61); group 2 (123/53) • Exclusions: non-heart beating donor or from a HLA identical living donor; extra-renal solid-organ transplants or bone-marrow-stem cell transplants; known sensitivity to TAC, SRL or MMF; those who were treated with investigational immunosuppressive agents; pregnant; HIV positive
Interventions	Treatment group 1 • SRL: initial dose 6 mg within 48 hours of transplant; then 2 mg/d; trough levels 4 to 12 ng/mL Treatment group 2 • MMF: 2 g/d Co-interventions • TAC: 0.15 to 0.20 mg/kg/d in 2 divided doses to achieve trough levels of initial 8 to 16 ng/mL; maintenance 5 to 15 ng/mL • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • BPAR • Steroid-resistant rejection • CrCl • SCr • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects
Notes	• Comparison: TOR-I versus antimetabolite • Prograf Study Group
Risk of bias	

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Gonwa-PSG 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised 1:1 to receive corticosteroids and either TAC plus SRL or TAC plus MMF. No other information
Allocation concealment (selection bias)	Unclear risk	Patients were randomised 1:1 to receive corticosteroids and either TAC plus SRL or TAC plus MMF. No other information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death, graft survival and these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	High risk	Limited information on adverse effects. No information on wound complications
Other bias	High risk	Sponsored by Fujisawa

Grinyo 2004

Methods	• Design: open-label RCT • Duration: 7 December 2000 to 21 January 2002 • Follow up: 2 years
Participants	• Setting: multicentre study (7 centres) • Country: Spain • Kidney transplant recipients aged 9 to 65 years • Number (group 1/group 2): 87 (43/44) • Mean age ± SD (years): group 1 (47.4 ± 11.2); group 2 (45.2 ± 13.5) • Sex (M/F): group 1 (30/13); group 2 (31/13) • Exclusions: infection with HIV; PRA > 50%; donors younger < 9 or > 65 years; cold Ischaemic time >36 hours; non heart-beating donors; infection with either HBV or HCV with impairment in liver function tests
Interventions	Treatment group 1 • Low dose-SRL: 6 mg on day 1 and then 2 mg/d to achieve trough levels 4 to 8 ng/mL • sTAC: 0.1 mg/d for trough levels 8 to 12 ng/mL for 3 months then 5 to 10 ng/mL Treatment group 2 • High-dose SRL: 15 mg on day 1 and then 5 mg/d to achieve levels 8 to 16 ng/mL • rTAC: 0.05 mg/kg/d for levels 3 to 8 ng/mL; TAC withdrawn from 4 months onwards in patients with stable kidney function, no rejection in previous 3 weeks & stable SRL levels Co-interventions

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Grinyo 2004 *(Continued)*

	• Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl (primary outcome) • SCr • Haematological adverse effects • Biochemical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: variable dose of TOR-I and CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated in a 1:1 proportion to one of two groups using computer-generated randomisation envelopes prepared by Wyeth without stratification
Allocation concealment (selection bias)	Low risk	Patients were randomly allocated in a 1:1 proportion to one of two groups using computer-generated randomisation envelopes prepared by Wyeth without stratification
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was kidney function: Laboratory outcome unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	High risk	No information on wound complications & limited information on other adverse effects
Other bias	High risk	Assistance provided by Wyeth

Groth-207 1999

Methods	• Design: open-label RCT • Duration: January 1996 to November 1996 • Follow up: 1 year
Participants	• Setting: international multicentre study (Sirolimus European Renal Transplant Study Group - Study 1) • Country: Sweden, Spain, UK, France (11 centres) • DD kidney transplant recipients. Kidney functioning within 24 hours of transplant

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Groth-207 1999 *(Continued)*

- Number (group 1/group 2): 83 (41/42)
- Mean age ± SD (years): group 1 (45.74 ± 10.86); group 2 (41.67 ± 11.85)
- Sex (M/F): group 1 (29/12); group 2 (25/17)
- Exclusions: evidence of systemic infection; an unstable disease state; significant cardiac abnormality; history of malignancy; an active GI disorder; pregnant women; PRA ≥ 70%; induction with antibody preparations; treatment with anticonvulsants or CCB or known hypersensitivity to macrolide antibiotics; AZA or CSA

Interventions	Treatment group 1 • SRL: 16 to 24 mg/m^2/d loading dose, followed by 8 to 12 mg/m^2/d until day 7 to 10; dose adjusted initial target 30 ng/mL for 2 months then for maintenance target 15 ng/mL Treatment group 2 • CSA: 10 mg/kg/d and then adjusted for trough levels of 200 to 400 ng/mL for 2 months, and 100 to 200 ng/mL after Co-interventions • AZA: 2 mg/kg/d • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer based randomisation
Allocation concealment (selection bias)	Low risk	Central computer based randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

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Groth-207 1999 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death, graft loss and biopsy confirmed acute rejection. These unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data addressed (ITT analysis)
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Supported by Wyeth-Ayerst

Hamdy 2005

Methods	• Design: parallel RCT • Duration: May 2001 to January 2003 • Follow up: 2 years
Participants	• Setting: Single centre study • Country: Egypt • Living donor kidney transplant recipients • Number (group 1/group 2): 132 (65/67) • Mean age ± SD (years): group 1 (32.3 ± 10.3); group 2 (31.8 ± 8.6) • Sex (M/F): group 1 (52/13); group 2 (47/20) • Exclusions: requiring 2nd kidney transplantation; patients < 18 years; cases with pre-transplant chemistries demonstrating a total serum cholesterol > 300 mg/dL; triglycerides > than 400 mg/dL; WBC < 4000/mm^3 or platelets < 150,000/mm^3; pre-transplant positive lymphocytotoxic cross-match test; > 50% DR mismatch
Interventions	Treatment group 1 • SRL: 10 mg/d within 24 hours of transplant and for 3 days; then 5 mg/day for levels 6 to 12 ng/mL • TAC: 0.03 mg/kg/d started on day 3 if CrCl > 50 mL/min targeting a 12-h whole blood trough level of 3 to 7 ng/mL. Treatment group 2 • SRL: 10 mg daily within 24 hours of transplant for levels of 10 to 15 ng/mL • MMF 2 g/d Co-interventions • Basiliximab • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • BPAR • GFR • Infection (no CMV) • Surgical adverse events • Biochemical adverse events

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Hamdy 2005 *(Continued)*

Notes	• Comparison: low dose versus high dose TOR-1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A prospective, randomised controlled trial where they were divided into two groups"
Allocation concealment (selection bias)	Unclear risk	Quote: "A prospective, randomised controlled trial where they were divided into two groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death and graft survival and these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	No report of funding

Kahan-157 2001

Methods	• Design: parallel RCT (RADB157 Study Group) • Duration: 12 months • Follow up: 12 months but results at 6 months available
Participants	• Setting: multicentre • Countries: USA, Canada, Germany, UK (8 centres) • De novo Kidney transplant recipients aged 16 to 65 years • Number (group 1/group 2/group 3): 103 (34/34/35) • Mean age ± SD (years): group 1 (43.6 ± 10.71); group 2 (44.2 ± 12.59); group 3 (46.1 ± 11.79) • Sex (M/F): group 1 (22/12); group 2 (19/15); group 3 (25/10) • Exclusions: cholesterol > 350 mg/dL; triglycerides > 750 mg/dL; WBC < 4 x 10^9/L; absolute neutrophil count < 2 x 10^9/L; platelet count < 100 x 10^9/L; severe systemic infections; malignancy; coagulopathy; cold ischaemia time < 40 hours; antibody induction; investigational drug within previous 4 weeks
Interventions	Treatment group 1 • EVL: 1 mg/d stated within 48 hours of transplant Treatment group 2 • EVL: 2 mg/d started within 48 hours of transplant Treatment group 3

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Kahan-157 2001 *(Continued)*

	• EVL: 4 mg/d started within 48 hours of transplant Co-interventions • CSA: levels initial 150 to 400 ng/mL, maintenance 75 to 300 ng/mL • Corticosteroids tapering to a minimum dose of 5 mg/d for at least 6 months
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects
Notes	• Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Said to be double-blinded but no information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death, graft survival and BPAR and these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Reported expected outcomes
Other bias	High risk	Sponsored by Novartis. Study authors employed by Novartis

Kahan-203 1999

Methods	• Design: single-blind RCT (Rapamune Study Group) • Duration: unclear

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Kahan-203 1999 *(Continued)*

	• Follow up: 1 year
Participants	• Setting: multicentre study • Country: USA, Canada, Germany. 18 centres • Kidney transplant recipients; DD or unrelated LRD; 18 to 65 years • Number (group 1,2, 3, 4, 5, 6): 149 (25/20/27/26/24/27) • Mean age ± SD (years): Group 1 (42.7 ± 13.1); group 2 (43.4 ± 9.4); group 3 (47.9 ± 9.0); group 4 (42.9 ± 15.8); group 5 (44.0 ± 13.1); group 6 (44.9 ± 13.0) • Sex (M/F): group 1 (15/10); group 2 (14/6); group 3 (20/7); group 4 (12/14); group 5 (16/8); group 6 (15/12) • Exclusions: WBC ≤ 4000 mm^3; Hb ≤ 70 g/L; platelets ≤ 150,000 mm^3; triglycerides ≤ 4.4 mmol/L, induction with ATG/ALG
Interventions	Treatment group 1 • Placebo • Full dose CSA: levels 200 to 350 ng/mL initially, tapering to 200 to 300 ng/mL and then 150 to 250 ng/mL from 4 to12 months Treatment group 2 • SRL: 1 mg/d • Full dose CSA Treatment group 3 • SRL: 3 mg/d • Full dose CSA Treatment group 4 • SRL: 1 mg/d • Reduced dose CSA: levels 100 to 175 ng/mL initially, tapering to 100 to 150 ng/mL and then 75 to 125 ng/mL from 4 to 12 months Treatment group 5 • SRL: 3 mg/d • Reduced dose CSA Treatment group 6 • SRL: 5 mg/d • Reduced dose CSA Co-interventions • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Acute rejection • SCr • Infection • CMV infection • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects

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Kahan-203 1999 *(Continued)*

Notes	• Comparison: variable dose of TOR-I and CNI (combine groups 2+3 and compared with 4+5+6)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised but no further information provided
Allocation concealment (selection bias)	Unclear risk	Said to be randomised but no further information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blind study. Patients not investigators blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death, graft survival and BPAR and these unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients appear to be accounted for; 149/151 received study drug and reported
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Wyeth-Ayerst

Kahan-301 2000

Methods	• Design: parallel RCT (USA Rapamune Study Group) • Duration: June 1996 to September 1997 • Follow up: 12 months
Participants	• Setting: national multicentre study (38 centres) • Country: USA • De novo kidney transplant recipients aged ≥ 13 years and weighing ≥ 40 kg • Number (group 1/group 2/group 3): 719 (284/274/161) • Mean age ± SD (years): group 1 (44.9 ± 13.6); group 2 (46.8 ± 13.0); group 3 (45.6 ± 13.0) • Sex (M/F): group 1 (208/76); group 2 (236/38); group 3 (118/43) • Exclusions: evidence of systemic infection; angina; MI in the previous 6 months or continuing maintenance therapy for life-threatening arrhythmia; WBC < 4 x 10^9; platelets < 100 x 10^9; cholesterol > 9.05 mmol/L; triglyceride > 5.65 mmol/L
Interventions	Treatment group 1 • SRL: initial dose 2 mg/d Treatment group 2 • SRL: initial dose 5 mg/d Treatment group 3

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Kahan-301 2000 *(Continued)*

	• AZA: 2 to 3 mg/kg/d Baseline immunosuppression • CSA: initial 200 to 350 ng/mL; maintenance 150 to 250 ng/mL • Prednisolone
Outcomes	• Composite endpoint • Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: TOR-I versus antimetabolite (data in 2 TOR-I groups combined) • Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated randomisation schedule"
Allocation concealment (selection bias)	Low risk	Study drugs assigned after transplant by computer generated randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Drug Study code could only be broken in event of emergency"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Drug Study code could only be broken in event of emergency"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in ITT analyses
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Funded by Wyeth-Ayerst

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Kandaswamy 2005

Methods	• Design: open-label RCT • Duration: March 2001 to April 2006 • Mean follow-up: minimum 12 months; ~7 (5.5–8.5) years (median/IQR)
Participants	• Setting: transplant unit; single centre • Country: USA • Number (group 1/group 2/group 3): 440 (151/149/140) • Median age, range (years): group 1 (50.4, 39.9 to 58.7); group 2 (48.1, 36.7 to 59.4); group 3 (48.6, 41.4 to 58.1) • Sex (M/F): group 1 (97/54); group 2 (88/61); group 3 (83/57) • Exclusions: taking maintenance prednisone within 3 months pretransplant
Interventions	Treatment group 1 • CSA: 8 mg/kg/d and adjusted for levels of 150 to 200 µg/L • MMF: 2g/d Treatment group 2 • TAC: 0.6 mg/d and adjusted for level of 8 to 12 µg/L • SRL: 1 mg pre-operatively; postoperative 2 mg/d and adjusted to levels of 3 to 7 µg/L Treatment group 3 • rTAC: 0.03 mg/kg and adjusted for levels of 3 to 7 µg/L • SRL: 1 mg of SRL pre-operatively; postoperative 5 mg/d and adjusted to achieve levels of 8 to 12 ng/mL Baseline immunosuppression • ATG: 5 doses • Prednisolone: 5 days only
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • GFR • CMV infection • Malignancy
Notes	• Comparison: TOR-I versus antimetabolite (Group 2+3 versus group 1) • Comparison: variable dose of TOR-I and CNI (group 2 versus group 3)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised by non-blinded card pull
Allocation concealment (selection bias)	High risk	Randomised by non-blinded card pull

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Kandaswamy 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were death, graft loss and biopsy confirmed acute rejection. These unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Each arm analysed according to ITT
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Funded by Fujisawa and Genzyme

Kovarik-2306 2004

Methods	• Design: open-label RCT (RAD 2306 International Study Group) • Duration: not reported • Follow up: 1 year RCT with 2 year further observations
Participants	• Setting: multicentre study • Countries: Brazil, Spain, Italy, Poland, Canada, USA, Venezuela • Number (group 1/group 2): 237 (112/125); 222 non-Black recipients randomised • Mean age ± SD (years): group 1 (42.5 ± 12.3); group 2 (42.8 ± 12.8) • Sex (% M): group 1 (63%); group 2 (54%) • Exclusions: unclear
Interventions	Treatment group 1 • EVL: 1.5 mg/d to maintain trough levels ≥ 3 ng/mL Treatment group 2 • EVL: 3 mg/d to maintain trough levels ≥ 3 ng/mL Co-interventions • CSA: initial dose 8 mg/kg/d for C2 levels 1000 to 1400 ng/mL (weeks 1 to 4); 700 to 900 ng/mL (weeks 5 to 8); 550 to 650 ng/mL (weeks 9 to 12); C2 350 to 450 ng/mL for months 4-12 • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • eGFR (Nankivell formula) • Infection • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects

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Kovarik-2306 2004 *(Continued)*

	• Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• All 15 Black participants were enrolled in EVL 3 mg/d group but included in analyses • Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective, multicenter, randomised study. No other information provided
Allocation concealment (selection bias)	Unclear risk	Prospective, multicenter, randomised study. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary endpoint was GFR and creatinine measured in central laboratory. Unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Novartis

Kovarik-251 2001

Methods	• Design: parallel group RCT (B251) • Duration: recruitment commenced in July 1998 • Follow up: 3 years
Participants	• Setting: multicentre study • Country: 44 centres in USA (33), Canada (3), Argentina (2), Brazil (2) • Participants aged 16 to 65 years receiving DD or LD (not haplo-identical) • Number (group 1/group 2/group 3): 583 (193/194/196) • Mean age, range (years): group 1 (43.3, 16 to 71); group 2 (43.7, 19 to 70); group 3 (43.4, 16 to 68) • Sex (M/F): group 1 (110/83); group 2 (123/71); group 3 (132/64) • Exclusions: recipients of donor organs with cold ischaemia > 40 hours;, patients with DGF > 48 hours post-transplantation; LD haplo-identical grafts; multiple solid-organ transplants; previous transplants; donor-specific transfusion; ABO-incompatible; or T-cell cross–match-positive donor organs; hypersensitivity to EVL; liver disease; HBV, HCV, HIV infection; significant mental illness; cardiac disease; severe uncontrolled hypercholesterolaemia; low WBC, neutrophil or platelet counts; severe systemic infection; malignancy; coagulopathy
Interventions	Treatment group 1

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Kovarik-251 2001 *(Continued)*

	• EVL: initial dose 1.5 mg/d; after amendment, dose altered for trough ≥ 3 ng/mL Treatment group 2 • EVL: initial dose 3 mg/d; after amendment, dose altered for trough ≥ 3 ng/mL Treatment group 3 • MMF: 2 g/d Co-interventions • CSA: initial 150 to 400 ng/mL; maintenance 100 to 300 ng/mL; after amendment trough levels 50 to 75 ng/mL in EVL groups only • Prednisolone
Outcomes	• Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • Haematological adverse effects • Biochemical adverse effects
Notes	• Comparison: TOR-I versus antimetabolite • Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was 1:1:1. No other information provided
Allocation concealment (selection bias)	Unclear risk	Randomisation was 1:1:1. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind double-dummy for 1 year; then open label, when amendment protocol introduced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind double-dummy for 1 year; then open label, when amendment protocol introduced
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Novartis, some authors employed by Novartis

Kramer-2307 2003

Methods	• Design: open-label RCT (RAD 2307 International Study Group) • Duration: not reported

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Kramer-2307 2003 *(Continued)*

	• Follow up: 12 months with 24 month extension (203 of 256 enrolled for second year)
Participants	• Setting: multicentre study • Countries: Australia, Colombia, Germany, France, Czech Republic, Argentina, USA, Italy, Norway, Switzerland • Adult de novo kidney transplant recipients (DD, LD) • Number (group 1/group 2): 256 (117/139); 243 non-Black recipients randomised • Mean age ± SD (years): group 1 (43.9 ± 12.7); group 2 (46.3 ± 11.8) • Sex (M/F): group 1 (81/36); group 2 (87/52) • Exclusions: HLA matched LD recipient
Interventions	Treatment group 1 • EVL: initial dose 1.5 mg/d for trough levels ≥ 3 ng/mL Treatment group 2 • EVL: initial dose 3 mg/d for trough levels ≥ 3 ng/mL Co-interventions • Basiliximab • CSA: initial C2 levels 500 to 700 ng/mL (0 to 8 weeks); C2 levels 350 to 450 ng/mL week 9 to month 12. • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • eGFR (Nankivell formula) • SCr • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• All 13 Black recipients received 3 mg/day of everolimus but were included in analyses • Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective, multicenter, randomised study. No other information provided
Allocation concealment (selection bias)	Unclear risk	Prospective, multicenter, randomised study. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

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Kramer-2307 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary endpoint was GFR and creatinine measured in central laboratory. Unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Supported by Novartis Pharma AG

Kreis-210 2000

Methods	• Design: open-label RCT • Duration: January 1997 to December 1997 • Follow-up: 12 months
Participants	• Setting: multicentre study (14) (Sirolimus European Renal Transplant Study Group - study 2) • Country: France, Sweden, Belgium, Spain, Germany • Aged 18 to 60 years; first DD transplant; WBC > 4.0 x 10^9/L, Hb > 70 g/L, platelets > 150 x 10^9/L, fasting triglycerides < 4.5 mmol/L • Number (group 1/group 2): 78 (40/38) • Mean age ± SD (years): group 1 (43.5 ± 10.9); group 2 (42.9 ± 11.4) • Sex (M/F): group 1 (28/12); group 2 (27/11) • Exclusions: evidence of a systemic infection; active liver disease; unstable disease state; significant cardiac abnormality; history of malignancy; active GI disorder; pregnant; PRA ≥ 70%
Interventions	Treatment group 1 • SRL: 24 mg/m^2 before transplantation; 2 doses of 24 mg/m^2 on days 1, 2 then 12 mg/m^2; doses for trough levels of 30 ng/mL for 2 months; 5 ng/mL thereafter Treatment group 2 • CSA: dose for initial target 200 to 400 ng/mL; maintenance 100 to 200 ng/mL Co-interventions • MMF: 2 g/d • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • CMV infection • Malignancy

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Kreis-210 2000 *(Continued)*

- Haematological adverse effects
- Biochemical adverse effects
- Surgical adverse effects
- Cosmetic/life style adverse effects

Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Open-label, parallel group, multicenter RCT. No other information provided
Allocation concealment (selection bias)	Unclear risk	Open-label, parallel group, multicenter RCT. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of participants or personnel but primary outcome was laboratory based and is unlikely to influence blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All primary outcomes mentioned
Other bias	High risk	Funded by Wyeth-Ayerst Research, Paris, France

Lebranchu-132 2004

Methods	• Design: open-label RCT • Duration: April 2002 to September 2003 • Follow up: 12 months
Participants	• Setting: transplant services • Country: France (13 centres) • Transplant recipients of DD grafts • Number (group 1/group 2): 145 (71/74) • Mean age ± SD (years): group 1 (45.6 ± 10.3); group 2 (45.1 ± 12.4) • Sex (M/F): group 1 (44/27); group 2 (45/29) • Exclusions: < 18 years; cold ischaemia time ≥ 36 hours; donor age ≥ 65 years; LD graft; graft from a non-heart beating donor; PRA > 80%, multiple organ transplants and any chronic disease requiring steroid therapy
Interventions	Treatment group 1 • SRL: 15 mg x 2 days; 10 mg/d and adapted for trough levels 10 to 15 ng/mL; maintenance 10 to 15 ng/mL

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Lebranchu-132 2004 *(Continued)*

	Treatment group 2 • CSA: 6 to 8 mg/kg/d for target 150 to 250 ng/mL from 4th month 75 to 150 ng/mL Co-interventions • ATG • MMF: 1 to 2 g/d • Prednisolone stopped at 6 months
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • CMV infection • Malignancy • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned prior to transplantation by computer-generated selection
Allocation concealment (selection bias)	Low risk	Patients were randomly assigned prior to transplantation by computer-generated selection
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of participants or personnel reported but primary outcome laboratory based and unlikely to influence judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Wyeth

Lo 2004

Methods	• Design: parallel RCT • Duration: November 2000 to October 2001 • Follow up: 6 months

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Lo 2004 *(Continued)*

Participants	• Setting: unclear • Country: USA • Kidney transplant recipients (DD) • Number (group 1/group 2): 39 (16/23) • Mean age (years): group 1 (46); group 2 (49) • Sex (M/F): group 1 (10/6); group 2 (13/10) • Exclusions: evidence of active infection; those receiving multiple organ transplants; patients with a WBC < 4000/mm^3; platelet count ≤ 100,000/mm^3; triglycerides ≥ 400 mg/dL; total cholesterol ≥ 300 mg/dL
Interventions	Treatment group 1 • SRL: started within 48 hrs of transplant; 4 mg/d for 2 days, then 2 mg/d for levels 5 to 10 ng/mL • sTAC: within 48 hrs of transplant to achieve tacrolimus levels 10 to 15 ng/mL Treatment group 2 • SRL: started within 48 hours; 10 mg/d for 2 days; 5 mg/d to achieve SRL levels 10 to 15 ng/mL • rTAC: dose within 48 hours to achieve levels 5 to 10 ng/mL Co-interventions • ATG • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • SCr • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects
Notes	• Comparison: variable dose of TOR-I and CNI • The primary endpoint of the study was a composite of patient death, graft lost, or BPAR at 6 months post-transplantation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective, randomised, comparative pilot study. No details provided
Allocation concealment (selection bias)	Unclear risk	Prospective, randomised, comparative pilot study. No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

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Lo 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary endpoint of the study was a composite of patient death, graft lost, or biopsy-confirmed AR at 6 months post-transplantation; unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed 6 months of study
Selective reporting (reporting bias)	High risk	Limited information on adverse effects
Other bias	High risk	Sponsored by Wyeth and SangStat

MacDonald-302 2001

Methods	• Design: parallel RCT (Rapamune Global Study Group) • Duration: October 1996 to September 1997 • Follow up: 12 months
Participants	• Setting: multicentre study (34 centres) • Country: Canada, USA, Australia, Italy, Sweden, France, Spain • Kidney transplant recipient first graft, DD or non-HLA identical LD • Number (group 1/group 2/group 3): 576 (227/219/130) • Mean age ± SD (years): group 1 (45.6 ± 12.3); group 2 (45.1 ± 12.2) • Sex (M/F): group 1 (147/80); group 2 (149/70); group 3 (91/39) • Exclusions: systemic infection; history of cardiac abnormalities or malignancy; received an investigational agent within 4 weeks of study entry; fasting cholesterol > 9.1 mmol/L and/or fasting triglycerides > 5.6 mmol/L
Interventions	Treatment group 1 • SRL: 6 mg for one dose and then 2 mg/d Treatment group 2 • SRL: 15 mg for one dose and then 5 mg/d Treatment group 3 • Placebo Co-interventions • CSA: 12-hour trough levels 200 to 400 ng/mL for 1 month; 200 to 300 ng/mL for months 2 and 3 then 150 to 250 ng/mL • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • CMV infection

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MacDonald-302 2001 *(Continued)*

	• Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: low dose versus higher dose TOR-I • Comparison: TOR-I versus placebo/no treatment (not included in review)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly assigned to one of three treatment groups in a 2:2:1 ratio. A computerized system was used to randomise and stratify patients by centre and donor source (living or cadaver)
Allocation concealment (selection bias)	Low risk	A computerized system was used to randomise and stratify patients by centre and donor source (living or cadaver)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and investigators blinded to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients and investigators blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Wyeth-Ayerst

Machado 2001

Methods	• Design: open-label RCT • Duration: June 1999 to February 2000 • Follow up: 12 months
Participants	• Setting: Single centre study • Country: Brazil • Primary one-haplotype LRD kidney allografts aged ≥ 13 years • Number (group 1/group 2): 70 (35/35) • Mean age ± SD (years): group 1 (35.8 ± 10.5); group 2 (32.7 ± 10.4) • Sex (M/F): group 1 (23/12); group 2 (23/12) • Exclusions: WBC < 4.0 x 10^9/L, platelets < 100 x 10^9/L; fasting cholesterol > 350 mg/dL; fasting triglyceride < 500 mg/dL; systemic infection; significant cardiac abnormality; malignancy in last 10 years; immunosuppressives per transplant; requiring antibody induction

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Machado 2001 *(Continued)*

Interventions	Treatment group 1 • SRL: initial dose 6 mg/dose, then 2 mg/d Treatment group 2 • AZA: 1.5 to 2 mg/kg/d Co-interventions • CSA: 8 to 10 mg/d for initial levels 200 to 400 ng/mL; maintenance 150 to 250 ng/mL after month 2. Doses/levels kept lower in SRL group • MP/prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • BPAR • SCr
Notes	• Comparison: TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised. No other information provided
Allocation concealment (selection bias)	Unclear risk	Said to be randomised. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants/personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes of graft loss, BPAR and death unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Martinez-Mier 2006

Methods	• Design: open-label RCT • Duration: May 2004 to January 2005 • Follow up: 12 months

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Martinez-Mier 2006 *(Continued)*

Participants	• Setting: single centre • Country: Mexico • Kidney transplant recipients: all LD • Number (group 1/group 2): 41 (20/21) • Mean age ± SD (years): group 1 (29.6 ± 7.6); group 2 (31.2 ± 9.21) • Sex (M/F): group 1 (12/8); group 2 (12/9) • Exclusions: evidence of systemic infection; HLA identical donor; prior treatment for cancer; pregnancy; weight > 105 kg; hypersensitivity to macrolide antibiotics; total cholesterol > 300 mg/dL; triglycerides > 400 mg/dL; WBC < 3000/mm^3, or platelets < 75,000/mm^3
Interventions	Treatment group 1 • SRL: 10 mg single dose then 3 mg/m^2 for levels 10 to 15 ng/mL for 3 months and then 5 to 10 ng/mL Treatment group 2 • CSA: 4 to 8 mg/kg for levels 150 to 300 ng/mL for 6 months and then 100 to 200 ng/mL Co-interventions • MMF: dose 2g/d • Basiliximab: 20 mg intraoperatively and at day 4 • MP: 1g IV intraoperatively • Prednisolone: initial dose 20 mg; 5 mg at 6 months
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr • CAN • Infection • CMV • Surgical adverse effects • Haematological adverse effects • Biochemical adverse effects • Cosmetic/lifestyle adverse effects
Notes	• Comparison: TOR-I versus CNI

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

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Martinez-Mier 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All prespecified outcomes mentioned
Other bias	Unclear risk	Insufficient information to permit judgement

Morelon 2010

Methods	• Design: RCT • Duration: not reported • Mean follow-up: 12 months
Participants	• Setting: single centre • Country: France • Kidney transplant recipients aged 18 to 65 years; PRA < 20%; negative cross-match; WBC > 4; platelets > 150; triglyceride < 4.5 mmol/L; cold ischaemia < 24 hours • Number (group 1/group 2): 19 (9/10) • Mean age ± SD (years): group 1 (42.6 ± 8.8); group 2 (51.1± 8.2) • Sex (M/F): group 1 (5/4); group 2 (1/9) • Exclusions: multiorgan transplant; previous malignancy; positive for HIV, HBV, HCV; infection at transplant; previous immunosuppression
Interventions	Treatment group 1 • SRL 15 mg/d on days 0 and 1; 10 mg/d on day 2; 5 mg/d on day 3 for levels 10 to 15 ng/mL • MMF: 2 g/d Treatment group 2 (CSA) • CSA: 5 mg/kg for target 125 to 225 ng/mL • MMF: 2g/d Co-interventions • Prednisone
Outcomes	• Death (all causes) • Acute rejection • Graft loss • Adverse effects • T cell parameters
Notes	• Comparison: SRL versus CSA

Risk of bias

Bias	Authors' judgement	Support for judgement

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Morelon 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomised using sealed envelopes
Allocation concealment (selection bias)	Low risk	Randomised using sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes of death/graft loss/AR unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	High risk	not all prespecified outcomes mentioned, limited information on adverse events
Other bias	High risk	Funded by Genzyme

ORION 2011

Methods	• Design: open-label RCT (Sirolimus ORION Study Group) • Duration: March 2004 to May 2005 • Follow up: 2 years
Participants	• Setting: multinational (65 centres) • Country: USA, Germany, UK, Australia, Spain, Italy, Switzerland, Canada, Poland, France, Belgium • Kidney transplant recipients aged ≥18 years, primary or secondary kidney allograft from LD or DD • Number (group 1/group 2/group 3): 450 (155/155/140); analysed 443 (152/152/139) • Mean age ± SD (years): group 1 (47.9 ± 13.3); group 2 (50.4 ± 13.0); group 3 (48.4 ± 13.2) • Sex (M/F): group 1 (109/43); group 2 (110/44); group 3 (81/58) • Exclusions: multiple organ transplants; BMI > 32 kg/m^2; WBC ≤ 3000/mm^3; platelets ≤ 100,000/mm^3; fasting triglycerides ≥ 400 mg/dL; fasting total cholesterol ≥ 300 mg/dL; cold ischaemia time > 30 hours
Interventions	Treatment group 1 • SRL: 15 mg then 5 mg/d for levels 8 to 15 ng/mL to week 13; adjusted to 12 to 20 ng/mL after TAC elimination • TAC: 0.2 mg/kg/d for levels 6 to 15 ng/mL to week 13, then dose decreased by 25%/week Treatment group 2 • SRL: 15 mg then 5 mg/d for levels 10 to 15 ng/mL to week 13; 8 to 15 ng/mL to week 26; then 5 to 15 ng/mL. Amended to 10 to 15 ng/mL to week 26, then 8 to 15 ng/mL • MMF: 2 g/d Treatment group 3 • TAC: 0.2 mg/kg/d for levels 8 to 15 ng/mL to week 26, then 5 to 15 ng/mL • MMF: 2 g/d

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ORION 2011 *(Continued)*

	Co-interventions • Daclizumab
Outcomes	• Death (all causes) • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr
Notes	• Contributes data to 2 separate comparisons: group 1 versus 3 (SRL versus MMF); group 2 versus 3 (SRL versus TAC) • Two years after study initiation (June 2006), group 2 patients (139) were discontinued from assigned therapy by the sponsor because of a higher-than-anticipated BPAR rate. 68/139 had follow up at 2 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" 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	Low risk	Primary outcomes was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for. Efficacy/safety analyses based on ITT comprising all patients, who were transplanted and received ≥ 1 dose of treatment medications. 1.6% excluded
Selective reporting (reporting bias)	Low risk	Primary endpoints mentioned
Other bias	High risk	Study sponsored by Wyeth and several investigators were employees of Wyeth at the time of the study

Paoletti 2012

Methods	• Design: open-label RCT • Duration: 1 August 2008 to 31 December 2009 • Mean follow-up: 12 months
Participants	• Setting: single centre • Country: Italy • Kidney transplant recipient ages 18 to 70 years undergoing single graft DD graft • Number (group 1/group 2): 30 (10/20)

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Paoletti 2012 *(Continued)*

- Mean age, range (years): group 1 (47, 32 to 67); group 2 (51, 28 to 65)
- Sex (M/F): group 1 (7/3); group 2 (14/6)
- Exclusions: diabetes; dual kidney transplant; LRD transplant; kidney donated after cardiac death; cardiac valvular abnormalities at time of enrolment

Interventions	Treatment group 1 • EVL: to achieve trough levels between 3 to 8ng/mL • rCSA: to achieve trough levels between 75 to 125 ng/mL in the first 2 months and 50 to 100 ng/mL thereafter Treatment group 2 • MMF: dose not reported • sCSA: to achieve trough levels between 150 to 300 ng/mL in the first 2 months, and 125 to 250 ng/mL thereafter Co-interventions • Antihypertensives (excluding ACE or ARB) administered to both groups to achieve BP ≤ 130/80 mmHg • IL2 • Steroids
Outcomes	• Death • Graft loss • BPAR • Diabetes • Lipids
Notes	• Comparison: TOR-1 and anti-metabolite (MMF)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated block; 1:2 randomisation was adopted
Allocation concealment (selection bias)	Low risk	Allocation was implemented using sequentially numbered, opaque sealed envelopes that were kept by an employee of the Regione Liguria Transplant Coordination Office who was not involved in the clinical study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Kidney outcomes unlikely to be influenced by lack of blinding. Primary outcome (cardiac) was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop-outs in of the groups, and all patients completed the 1-year observation period
Selective reporting (reporting bias)	High risk	Reporting of adverse events incomplete

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Paoletti 2012 *(Continued)*

Other bias	Low risk	The Italian National Health Service (Servizio Sanitario Nazionale) (Italy) and San Martino University Hospital (Azienda Ospedaliera Universitaria San Martino), Genoa (Italy)

Pascual 2010

Methods	• Design: open-label RCT • Duration: not reported • Mean follow-up: 6 months (3 withdrawn group 1; 5 in group 2)
Participants	• Setting: multicentre, (5 centres) • Country: Spain • Patients suffering from ESKD who were candidates for primary kidney transplant or re-transplant (except if the original graft was lost due to immunologic causes within the previous 12 months) from an ABO-compatible donor • Number (group 1/group 2): 35 (15/20) • Mean age ± SD (years): group 1 (44 ± 11.2); group 2 (46.2 ± 10.2) • Sex (M/F): group 1 (10/5); group 2 (14/6) • Exclusions: DGF; graft from a heart-arrest donor or from a donor's kidney with cold ischaemia time > 30 hours; thrombocytopenia; leukopenia; significant liver disease or liver cirrhosis
Interventions	Treatment group 1 • Low-dose EVL: 0.75 mg/twice/d unchanged to day 42; then levels of 3 to 8 ng/mL • sTAC: 0.075 mg/kg twice/d for levels 10 to 25 ng/mL to 14 days; 5 to 10 after 14 days Treatment group 2 • High-dose EVL: 1.5 mg twice/d unchanged to day 42; then levels of 3 to 8 ng/mL • sTAC: 0.075 mg/kg twice/d for levels 10 to 25 ng/mL to 14 days; 5 to 10 after 14 days Co-interventions • MP: 500 mg day 0, 125 mg day 1 • Prednisone 20 mg day 2, tapered to a maintenance dose of 5 mg from day 42 to study end
Outcomes	• PK1 profiles of EVR and TAC • Acute rejection • Graft loss
Notes	• Comparison: EVL low dose versus EVL high dose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised; insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open-label study

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Pascual 2010 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome lab based and unlikely to influence blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	8/35 withdrawn (22%)
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes mentioned
Other bias	Unclear risk	Insufficient information to permit judgement

Pescovitz 2007

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 6 months
Participants	• Setting: multicentre (6 centres) • Country: USA • Kidney transplant recipients aged 18 to 75 years able to take oral medications • Number (group 1/group 2): 45 (30/15) • Median age, range (years): group 1 (49.0, 21 to 70); group 2 (47.0, 28 to 64) • Sex (M/F): group 1 (16/14); group 2 (12/3) • Exclusions: HLA identical; PRA > 20%; HIV +ve; HepB surface antigen +ve; WBC < 2.5 x 10^9; platelets <100 x 10^9; Hb < 6 g/dL; hyperlipidaemia in previous year; African-Americans GI disorders likely to impair absorption; previous cancers; previous treatment with daclizumab
Interventions	Treatment group 1 • SRL: 15 mg/d for days 1 to 3; then 10 mg/day to 10 to 25 ng/mL at 2 months; maintenance 8 to 15 ng/mL Treatment group 2 • CSA: administered according to centre practice Co-interventions • Daclizumab • MMF: 2 g/d • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr • Malignancy • Biochemical adverse effects

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Pescovitz 2007 *(Continued)*

Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Enrolled 2:1 before transplant. No other information provided
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	Low risk	Primary outcomes BPAR, death, graft loss unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Roche

Qazi 2017

Methods	• Design: open-label RCT • Duration: January 2010 to February 2012 • Mean Follow up: 12 months
Participants	• Setting: multicentre (52 centres) • Country: USA (50); Canada (2) • Participants aged 18 to 70 years; kidney from a DD (including expanded criteria donor and DD after cardiac death) or living-unrelated or related non-HLA identical • Number (group 1/group 2): 613 (309/304); 3 withdrew consent from group 1 • Mean age ± SD (years): group 1 (50.0 ± 13.3); group 2 (48.4 ± 12.9) • Sex (M/F): group 1 (205/101); group 2 (202/102); data did not include patients who withdrew consent • Exclusions: cold ischaemic time > 30 hours; ABO-incompatible or T-cell/B-cell cross-match positive transplants; recipients with platelet count < 100,000/mm^3, neutrophil count < 1500/mm^3, or WBC < 3000/mm^3; malignancy within past 2 years; HIV, hepatitis B or C infections; other systemic infections < 30 days before transplantation
Interventions	Treatment group 1 • EVL: 1.5 mg within 24 hours; dose adjusted for target C0: 3 to 8 ng/mL from day 5 • rTAC: C0 from day 3 onwards 4 to 7 ng/mL; 3 to 6 ng/mL at month 2; 2 to 5 ng/mL at month 6 Treatment group 2

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Qazi 2017 *(Continued)*

	• MMF: 1000 mg twice/d • sTAC: levels from day 3 to maintain target range 8 to 12 ng/mL; 7 to 10ng/mL at month 2; 5 to 8 ng/mL at month 6 Co-interventions • Prednisone • Ganciclovir or valganciclovir for CMV prophylaxis • Pneumocystic prophylaxis
Outcomes	• Primary endpoint was composite efficacy endpoint (BPAR, graft loss, death, loss to follow-up) • BPAR • Graft loss • Death • GFR (calculated) • Adverse effects • CMV
Notes	• Non-inferiority study • Comparison EVL versus MMF

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Novartis Drug supply Management generated a randomization list, using a validated system with a fixed-block design that automated treatment-arm randomization in the specified ratio'
Allocation concealment (selection bias)	Low risk	Investigators received treatment allocation cards with sequential randomisation numbers and treatment group information
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 measures were unlikely to be influenced by lack of blinding (death, graft loss, BPAR)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients only excluded from everolimus group
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Funded by Novartis

RECORD 2017

Methods	• Design: open-label RCT • Duration: 28 August 2012 to 23 February 2015.

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RECORD 2017 *(Continued)*

	• Follow up: 12 months
Participants	• Setting: multicentre (7 centres) • Countries: Korea • Kidney transplant recipients DD or LRD; > 20 years • Number (group 1/group 2): 151 (76/75) • Mean age ± SD (years): group 1 (46.1 ± 13.0); group 2 (46.0 ± 10.8) • Sex (M/F): group 1 (57/21); group 2 (53/22) • Exclusions: multi-organ recipients or a kidney donated after cardiac death; ATG induction; desensitisation pre-transplantation; identical HLA matching between donor and recipient; cold ischaemic time of > 30 hours; leukocyte count < 2500/L, neutrophil count < 1500/L or platelet count < 100,000/L; recipient with HBV or HCV infection; history of any cancer, except successfully treated localized non-melanoma skin cancer; ABO-incompatible transplants.
Interventions	Treatment group 1 • SRL: 2 mg within 24 hours of reperfusion; levels 3 to 5 ng/mL • ER-TAC: LRD 0.2 mg/kg 2 days before transplant. DD 0.1 mg /kg on day of transplant. Levels 3 to 12 ng/mL 1st month, then 3 to 8 ng/mL; commenced within 48 hours of transplant Treatment group 2 • MMF: 500 mg within 24 hours of reperfusion; 1000 mg to 2000 mg/d • ER-TAC: LRD 0.2 mg/kg 2 days before transplant. DD 0.1 mg /kg on day of transplant. Levels 3 to 12 ng/mL 1st month, then 3 to 8 ng/mL; commenced within 48 hours of transplant Co-interventions • Basiliximab: 20 mg • Prednisolone
Outcomes	• Efficacy failure • BPAR • Graft loss • Patient death/patient loss to follow-up • eGFR (MDRD) • Overall survival and graft survival
Notes	• Comparison TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was centrally released by an electronic case report form before transplantation. Randomization code was generated and performed using a block designed stratified by each site"
Allocation concealment (selection bias)	Low risk	Quote: "randomization was centrally released by an electronic case report form before transplantation. Randomization code was generated and performed using a block designed stratified by each site"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All blinded before randomisation

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RECORD 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome BPAR, graft loss and patient death and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	All patients accounted for but greater than 10% not analysed
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes mentioned
Other bias	High risk	Pharma funded study. Funded by Astellas

Riad 2007

Methods	• Design: open-label RCT • Duration: 2003 to 2005 • Mean Follow up: 3 years
Participants	• Setting: multicentre (2 centres) • Country: UK • Kidney transplant recipients • Number (group 1/group 2): 80 (39/41) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: not reported
Interventions	Treatment group 1 • Cyclosporin • MMF • Prednisone Treatment group 2 • Daclizumab induction • SRL • MMF • Prednisone Co-interventions • Not reported
Outcomes	• Comparison of kidney function at 6 and 12 months post-transplant using Cockcroft-Gault formula • Patient and graft survival • BPAR
Notes	• Comparison: TOR-I compared with CNI

Risk of bias

Bias	Authors' judgement	Support for judgement

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Riad 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Said to be randomised; 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	Low risk	Primary outcome lab based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients accounted for
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Rostaing 2001

Methods	• Design: parallel RCT • Duration: not reported • Follow up: 3 months
Participants	• Setting: single centre • Country: France • Kidney transplant recipients: DD transplants • Number (group 1/group 2): 28 (16/12) • Mean age ± SD (years): group 1 (43 ± 3); group 2 (41 ± 3) • Sex (M/F): not reported • Exclusions: unclear
Interventions	Treatment group 1 • SRL: mean dose 1.94 ± 0.19 mg/d Treatment group 2 • EVL: mean dose 2.37 ± 0.22 mg/d Co-interventions • CSA • Prednisone
Outcomes	• CrCl • Biochemical adverse effects
Notes	• Comparison: SRL versus EVL

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Rostaing 2001 *(Continued)*

- Abstract only

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	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)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Russ 2003

Methods	• Design: open-label RCT (Australian Rapamune-Tacrolimus Study Group) • Duration: not reported • Follow up: 6 months
Participants	• Setting: multicentre (7 centres) • Country: Australia • Adult kidney transplant recipients; 1st or 2nd DD graft or non-HLA identical LD • Number (group 1/group 2): 64 (33/31) • Mean age ± SD (years): group 1 (43.9 ± 12.1); group 2 (46.9 ± 12.2) • Sex (MF): group 1 (20/13); group 2 (21/10) • Exclusions: sensitized patients with PRA > 50% and recipients of regrafts who had lost their first graft because of rejection within the first 6 months
Interventions	Treatment group 1 • High-SRL: adjusted for target levels 10 to 15 ng/mL • rTAC: adjusted for target levels 3 to 7 ng/mL Treatment group 2 • Low-SRL: adjusted for target levels 5 to 10 ng/mL • sTAC: adjusted for target levels 10 to 15 ng/mL Co-interventions

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Russ 2003 *(Continued)*

	• Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr • Malignancy
Notes	• Comparison: variable dose of TOR-I and CNI

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	Low risk	Outcomes laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funded by Wyeth

Sampaio 2008

Methods	• Design: open-label RCT • Duration: 12 August 2003 to 04 March 2005 • Mean follow-up: 12 months
Participants	• Setting: single centre • Country: Brazil • Participants: first kidney allograft, DD or LRD • Number (group 1/group 2): 100 (50/50) • Mean age ± SD (years): group 1 (42.6 ± 14.2); group 2 (37.4 ± 10.3) • Sex (M/F): group 1 (38/12); group 2 (31/19)

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Sampaio 2008 *(Continued)*

	• Exclusions: recipients of a kidney from non-heart beating or ABO incompatible donors or with a positive crossmatch
Interventions	Treatment group 1 • MMF: 2 g/d • sTAC: 0.1 to 0.15 mg/ kg/d with levels 15 to 20 ng/mL (day 0 to 15); 10 to 15 ng/mL (days 15 to 30); 8 to 12 ng/mL (days 30 to 90); 5 to 10 ng/mL (> 90 days) Treatment group 2 (SRL/sTAC) • SRL: 15 mg stat, 5 mg/d to day 7 and then 2 mg/d first year • sTAC: 0.1 to 0.15 mg/ kg/d with levels 15 to 20 ng/mL (day 0 to 15); 10 to 15 ng/mL (days 15 to 30); 8 to 12 ng/mL (days 30 to 90); 5 to 10 ng/mL (> 90 days) Co-interventions • Corticosteroids • Pneumocystis prophylaxis • No induction therapy
Outcomes	• Composite end point - first occurrence of BPAR, graft loss, death • Incidence of BPAR, severity of AR • Use of ATG graft loss, death and patient and graft survival censored for death • Safety outcomes: infections, malignancy, diabetes, hypercholesterolaemia • Kidney function: Cockcroft-Gault formulae
Notes	• Comparison: TOR-1 versus MMF

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised 1:1 using a computer generated sequence number"
Allocation concealment (selection bias)	Unclear risk	Randomisation was computer generated but unclear whether sequence was known to investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All studies pre-specified outcomes mentioned
Other bias	High risk	Grant sponsored by Jansen-Cilag

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Schaefer 2006

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 12 months
Participants	• Setting: single centre • Country: USA • Primary kidney transplant recipients: DD or non-HLA identical LD • Number (group 1/group 2): 80 (41/39) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: not reported
Interventions	Treatment group 1 • SRL: 5mg/d from day 3; target levels 8 to 12 ng/mL Treatment group 2 • TAC: 0.15mg/kg/d; target levels 8 to 12 ng/mL Co-interventions • MMF: 2g/d • MP/prednisolone • ATG: 4 doses
Outcomes	• Death (all causes) • Graft loss censored for death • Acute rejection • SCr • Infection • Biochemical adverse effects • Cosmetic/lifestyle adverse effects
Notes	• Comparison: TOR-I versus CNI

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	Low risk	Outcomes unlikely to be influenced by lack of blinding

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Schaefer 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Prespecified outcomes mentioned
Other bias	Unclear risk	Insufficient information to permit judgement

Shetty 2015

Methods	• Design: open-label RCT • Duration: not reported • Mean follow-up: 12 months
Participants	• Setting: single centre • Country: USA • Adult LRD kidney transplant recipients • Number (group 1/group 2): 39 (19/20) • Mean age ± SD (years): group 1 (47 ± 16); group 2 (50 ± 14) • Sex (M/F): not reported • Exclusions: not reported
Interventions	Treatment group 1 • EVL: levels 3 to 8 ng/mL • rTAC: levels 4 to 7 ng/mL to 2 months, 3 to 5 ng/mL from 3 to 6 months; 2 to 5 ng/mL after 6 months • Steroid free Treatment group 2 • sTAC: levels 8 to 10 ng/mL to 2 months, 6 to 8 ng/mL from 2 to 6 months; 4 to 8 ng/mL after 6 months • MMF: dose not reported • Steroid free Co-interventions • Alemtuzumab induction
Outcomes	• Graft survival • Graft function - eGFR • Rejection • Adverse events
Notes	• Comparison: TOR-1 versus MMF

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomised; insufficient information to permit judgement

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Shetty 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Said to be randomised; 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	Low risk	Primary outcomes lab based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement; abstract only
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement, abstract only
Other bias	Unclear risk	Insufficient information to permit judgement; abstract only

Souza 2017

Methods	• Design: RCT • Duration: not reported • Mean follow-up: 319 ± 21 days
Participants	• Setting: not reported • Country: Brazil • Kidney transplant recipients, sensitized patients (PRA > 30%) • Number (group 1/group 2): randomised (14/16); analysed (12/15) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: not reported
Interventions	Treatment group 1 (dosage not reported) • EVL • MMF • TAC • Corticosteroids Treatment group 2 (dosage not reported) • MMF • TAC • Corticosteroids Co-interventions • ATG • Corticosteroids
Outcomes	• Death • Graft loss

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Souza 2017 *(Continued)*

- Acute rejection
- CMV infection

Notes	• Abstract only • Quadruple therapy versus triple therapy EVL/MMF/TAC/steroids versus MMF/TAC/steroids (TOR - I + antimetabolite versus antimetabolite) • Included in TOR-I versus antimetabolite group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Single centre, prospective, randomised, controlled pilot study
Allocation concealment (selection bias)	Unclear risk	Single centre, prospective, randomised, controlled pilot study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes were CMV diagnosis and BPAR; unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Spagnoletti 2017

Methods	• Design: open-label RCT • Duration: not reported • Mean Follow up: 12 months
Participants	• Setting: multicentre (6 centres) • Country: Italy • Patients > 18 years, receiving a DD kidney, first kidney transplant were randomised on day 1 LRD kidney transplant recipients • Number (group 1/group 2): 98; group numbers not reported • Mean age ± SD (years) not reported • Sex (M/F): not reported • Exclusions: not reported
Interventions	Treatment group 1 (dosage/levels not reported) • EVL • TAC

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Spagnoletti 2017 *(Continued)*

	Treatment group 2 (dosage/levels not reported) • MMF • TAC • Steroid free Co-interventions • ATG induction • Steroid free by day 5
Outcomes	• 12- month composite endpoint including: incidence of clinical + BPAR, graft survival, percentage of patients with SCr >1.8 mg/mL, percentage of patients with failed steroid withdrawal, percentage of patients converted from the assigned therapy * The occurrence of at least one of these conditions was considered treatment failure
Notes	• Study terminated after 98 enrolled as end-point reached • Abstract only with no additional information so data could not be added to meta-analyses

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	High risk	Primary outcome composite outcome - included clinical rejection, need to change medication
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgment; abstract only
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment; abstract only
Other bias	Unclear risk	insufficient information to permit judgment; abstract only

Stallone 2004

Methods	• Design: open-label RCT • Duration: enrolment from January 2000 • Follow up: 12 months
Participants	• Setting: single centre • Country: Italy • Kidney transplant recipients

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Stallone 2004 *(Continued)*

- Number (group 1/group 2): 90 (42/48)
- Mean age ± SD (years): group 1 (50.4 ± 7.8); group 2 (51.8 ± 6.3)
- Sex (M/F): not reported
- Exclusions: not reported

Interventions	Treatment group 1 • SRL: 15 mg, then 5 mg/d for trough levels 6 to 10 ng/mL • CSA: 4 to 7 mg/kg/d for C2 levels 600 to 800 ng/mL; for DGF, CSA 3 to 5 mg/kg/d for C2 levels 400 to 600 ng/mL Treatment group 2 • MMF: 2 g/d • CSA: 10 mg/kg/d for C2 levels 1200 to 1400 ng/mL; for DGF, CSA C2 levels 800 to 1000 ng/mL Co-interventions • Basiliximab • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr
Notes	• Comparison: TOR-I versus antimetabolite

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	Low risk	Outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recipients accounted for
Selective reporting (reporting bias)	High risk	No report of adverse effects
Other bias	Unclear risk	Insufficient information to permit judgement

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Stegall 2003

Methods	• Design: open-label RCT • Duration: April 2001 to January 2004 • Follow up: mean follow-up 33 months (13 to 47 months)
Participants	• Setting: single centre • Country: USA • Kidney transplant recipients; 81% LD, 19% DD • Number (group 1/group 2): 165 (81/84) • Mean age, range (years): group 1 (50, 22 to 73); group 2 (48, 19 to 80) • Sex (M/F): group 1 (45/36); group 2 (44/40) • Exclusions: multiple organ transplants; paediatric recipients; expected to receive a pancreas after kidney transplantation; receiving an ABO incomparable or positive cross match transplant; pre transplant fasting serum cholesterol > 350 mg/dL or fasting serum triglyceride level > 500 mg/dL; after 12 months patients with BMI > 32 kg/m^2 excluded because of high risk of wound problems in SRL group
Interventions	Treatment group 1 • SRL: 10 mg/d for 2 days; 5 mg/d, initial target 10 to 20 ng/mL to 4 months; then 6 to 15 ng/mL Treatment group 2 • TAC: 6 mg/d from day 4: initial target level 12 to 15 ng/mL; 8 to 10 ng/mL in months 1 to 4; then 6 to 8 ng/mL Co-interventions • ATG: 5 doses • MMF: 1.5 g/d • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • GFR • SCr • CMV infection • Adverse effects
Notes	• Comparison: TOR-I versus CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A prospective, randomised trial". No other information provided
Allocation concealment (selection bias)	Unclear risk	Quote: "A prospective, randomised trial". No other information provided
Blinding of participants and personnel (performance bias)	High risk	Open-label study

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Stegall 2003 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three (1.8%) excluded from final analysis as did not receive transplants
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	This study was supported in part by research contracts from Wyeth Research, Philadelphia, PA, Genzyme Corporation, Cambridge, MA, and Roche Laboratories Inc., Nutley, NJ

SYMPHONY 2007

Methods	• Design: open-label RCT • Duration: November 2002 to November 2004 • Follow up: 1 year
Participants	• Setting: international multicentre (83 centres in 15 countries) • Country: Turkey, Germany, Spain, Switzerland, Sweden, Belgium, USA, Canada, Israel, Czech Republic, Australia, Austria, Brazil, Poland, Mexico • 1st or 2nd LD or DD transplant; aged 18 to 75 years • Number (randomised/analysed): 1645/1589. group 1 (410/390); group 2 (413/399); group 3 (411/401); group 4 (411/399) • Mean age ± SD (years): group 1 (45.9 ± 13.8); group 2 (47.2 ± 13.5); group 3 (45.4 ± 14.7); group 4 (44.9 ± 14.5) • Sex (M/F): group 1 (255/155); group 2 (274/139); group 3 (270/141); group 4 (274/137) • Exclusions: history of malignancy, PRA >20%, transplants of kidneys with >30 hr of cold ischaemia, non-heart beating donor, need for other immunosuppressive therapy, active liver disease, history of cancer, active peptic ulcer, severe anaemia, leucopenia, thrombocytopenia, previous treatment with daclizumab/basiliximab
Interventions	Treatment group 1 • sCSA: 6 to 10 mg/kg/d for trough levels 150 to 300 ng/mL months 0 to 3; then 100 to 200 ng/mL Treatment group 2 • rCSA: 2 to 4 mg/kg/d for trough levels 50 to 100 ng/mL Treatment group 3 • rTAC: 0.1 mg/kg/d for trough levels 3 to 7 ng/mL Treatment group 4 • rSRL: 9 mg/d for 3 days, then 3 mg/d for trough level 4 to 8 ng/mL Co-interventions • Daclizumab • MMF

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SYMPHONY 2007 *(Continued)*

	• Steroids
Outcomes	• eGFR at 12 months (primary outcome) • Death • Acute rejection • Graft loss • DGF • Infections • Malignancy • Adverse reactions
Notes	• Comparison is TOR-I versus CNI by comparing group 4 with 1, 2 and 3 combined • ITT group received transplant and treatment. ITT results reported for all outcomes except infections and adverse reactions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients underwent randomisation... with the use of a centralized interactive voice response system (ClinIT)"
Allocation concealment (selection bias)	Low risk	Quote: "Patients underwent randomisation... with the use of a centralized interactive voice response system (ClinIT)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was eGFR; laboratory outcome so unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% randomised patients not included in ITT analyses
Selective reporting (reporting bias)	Low risk	Expected outcomes for this review (death, graft loss and acute rejection) have been reported. No protocol but outcomes specified in methods reported in results
Other bias	High risk	Funding for the study was provided by Hoffmann-La Roche

Takahashi 2013a

Methods	• Design: open-label RCT • Duration: February 2008 to August 2010 • Mean follow-up: 12 months
Participants	• Setting: multicentre (22 centres) • Country: Japan • Patients 18 to 65 years, primary kidney transplant • Number (group 1/group 2): 122 (61/61)

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Takahashi 2013a *(Continued)*

- Mean age ± SD (years): group 1 (42.5 ± 14.13); group 2 (38.6 ± 11.36)
- Sex (M/F): group 1 (46/15); group 2 (37/24)
- Exclusions: no evidence of graft function within 24 hours of transplantation; cold ischaemia time > 24 hours; donor age > 65 years; patients of multiorgan, ABO-incompatible, positive T-cell cross-match or HLA identical LRD transplants; recent anti-HLA class I PRA > 20% by complement-dependent cytotoxicity-based assay or > 50% by flow cytometry or ELISA

Interventions	Treatment group 1 • EVL: 1.5 mg (targeted C0 3 to 8 ng/mL) • rCSA: C0 100 to 200 ng/mL; 75 to 150 ng/mL from month 2; 50 to 100 ng/mL from month 4; 25 to 50 ng/mL from month 6 Treatment group 2 • MMF: 2 g/d • sCSA: 200 to 300 ng/mL; 100 to 250 ng/mL from month 2 Co-interventions • Steroids • Basiliximab • CMV prophylaxis
Outcomes	• Efficacy failure: composite of BPAR, graft loss, death or LTFY at 12 months • Kidney function at 12 months eGFR determined by MDRD formula • Adverse events
Notes	• Comparison TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by donor type deceased/living; randomised 1:1. Independent clinical research company using a validated system that automated the random assignment of treatment arms to randomisation numbers
Allocation concealment (selection bias)	Low risk	Randomisation list was produced by an independent clinical research organization using a validated system that automated the random assignment of treatment arms to randomisation numbers
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome is GFR. Lab measure unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT and less than 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

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Takahashi 2013a *(Continued)*

Other bias	High risk	Author list includes Novartis employees

Tedesco-Silva 2003

Methods	• Design: open-label RCT • Duration: January 2000 to January 2002 • Follow up: 12 months
Participants	• Setting: single centre • Country: Brazil • Kidney transplant recipients of Black ethnicity; ≥ 13 years; DD or non HLA identical LD; -ve T-cell cross-match; WBC ≥ 4 x 10^9/L, platelet count ≥ 100 x 10^9/L; fasting cholesterol ≤ 350 mg/dL; triglycerides ≤ 500 mg/dL • Number (group 1/group 2): 70 (34/36) • Mean age ± SD (years): group 1 (33.1 ± 10.9); group 2 (35.6 ± 12.3) • Sex (M/F): group 1 (22/12); group 2 (25/9) • Exclusions: evidence of systemic infection; a history of clinically significant cardiac abnormalities or malignancy within 10 years of enrolment into the study; PRA ≥ 50%; immunosuppression; antibody induction; recent investigational drug; HbSAg +ve
Interventions	Treatment group 1 • SRL: 15 mg then 5 mg/d till day 7; adjusted to levels 8 to 12 ng/mL Treatment group 2 • SRL: 15 mg then 5 mg/d till day 7; adjusted to levels 15 to 20 ng/mL Co-interventions • CSA: 8 to 10 mg/kg for trough levels 200 to 300 ng/mL for 2 weeks; 100 to 200 ng/mL for 2 weeks; then 100 to 150 ng/mL • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: low dose versus higher dose TOR-I

Risk of bias

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Tedesco-Silva 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective, 12-month, randomised, two-arm, concentration-controlled study. Randomised 7 days after transplant
Allocation concealment (selection bias)	Unclear risk	Prospective, 12-month, randomised, two-arm, concentration-controlled study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Tedesco-Silva 2010

Methods	• Design: open-label RCT (A2309 study) • Duration: not reported • Follow up: 2 years
Participants	• Setting: multicentre • Country: Argentina, Australia, Brazil, Hong Kong, Italy, Korea, New Zealand, Slovakia, South Africa, Sweden, Taiwan, Turkey, UK, USA, • Primary kidney transplant recipients aged 18 to 70 years • Number (group 1/group 2/group 3): 833 (277/279/277) • Mean age ± SD (years): group 1 (45.7 ± 12.7); group 2 (45.3 ± 13.4); group 3 (47.2 ± 12.7) • Sex (M/F): group 1 (177/100); group 2 (191/88); group 3 (189/88) • Exclusions: kidney donated after cardiac death or with a cold ischaemia time > 40 hours; donor age > 65 years; recipients of multiorgan or ABO incompatible or positive T-cell crossmatch or HLA identical living related donor transplants or PRA > 20%
Interventions	Treatment group 1 • EVL: initial dose 1.5 mg/d for levels 3 to 8 ng/mL • rCSA: trough levels 25 to 50 ng/mL from 6 to 24 months Treatment group 2 • Everolimus: initial dose 3 mg/d for levels 6 to 12 mg/mL • rCSA: trough levels 25 to 50 ng/mL from 6 to 24 months Treatment group 3 • MPS: 1.44 g/d

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Tedesco-Silva 2010 *(Continued)*

	• sCSA: trough levels 100 to 250 ng/mL from 6 to 24 months Co-interventions • Basiliximab induction: 20 mg within 2 hours of transplantation and at day 4 • Corticosteroids
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects
Notes	• Comparison: TOR-I versus antimetabolite • Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned a randomisation number, which was linked to one of the three treatment groups, using an interactive voice-response system. The randomisation scheme was reviewed and approved by the Biostatistics Quality Assurance Group
Allocation concealment (selection bias)	Low risk	Patients were assigned a randomisation number, which was linked to one of the three treatment groups, using an interactive voice-response system. The randomisation scheme was reviewed and approved by the Biostatistics Quality Assurance Group
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label RCT
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Funded by Novartis. Authors received money from drug companies

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Tedesco-Silva 2015

Methods	• Design: open-label RCT • Duration: 11 July 2011 to 4 May 2013 • Mean Follow up: 12 months
Participants	• Setting: single centre • Country: Brazil • Adult recipients, low/moderate immunological risk; ABO compatible; first transplant, LD or DD • Number (group 1/group 2/group 3): 288 (85/102/101) evaluated • Mean age ± SD (years): group 1 (43.7 ± 13.6); group 2 (45.1 ± 14.0); group 3 (44.8 ± 12.2) • Sex (M/F): group 1 (54/31); group 2 (68/34); group 3 (68/33) • Exclusions: HLA identical or expanded criteria DD; positive cytotoxic cross-match or PRA ≥ 50%, class I or class II
Interventions	Treatment group 1 • rATG: single dose 3 mg/kg • EVL: 3 mg/d for levels 4 to 8 ng/mL • TAC: 0.1 mg/kg/d for levels 3 to 5 ng/mL Treatment group 2 • Basiliximab: 2 doses • EVL: 3 mg/d for levels 4 to 8 ng/mL • sTAC: 0.2 mg/kg/d for trough 3 to 8 ng/mL for 3 months then 3 to 5 ng/mL Treatment group 3 • Basiliximab: 2 doses • MPS: 1440 mg/d • sTAC: 0.2 mg/kg/d for trough 6 to 8 ng/mL Co-interventions • No CMV prophylaxis: weekly monitoring of CMV viral replication (pp65CMV Ag) for 6 months • Corticosteroids
Outcomes	• Cumulative incidence of CMV infection • BPAR • Graft loss • Death
Notes	• Comparison: EVL/basiliximab versus mycophenolate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation sequence, stratified living/deceased donor, randomised 1:1
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelops. Transplant surgeons were blinded to treatment allocation
Blinding of participants and personnel (performance bias)	High risk	Open-label study

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Tedesco-Silva 2015 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based & unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	High risk	Investigator-initiated study that was partially supported by Novartis

TRANSFORM 2018

Methods	• Design: open-label RCT • Duration: December 2013 to January 2016 • Follow up: 12 months
Participants	• Setting: multicentre (186 centres) • Countries: 42 countries (Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Chile, Colombia, Croatia, Czech, Egypt, France, Germany, Greece, India, Israel, Italy, Japan, Korea, Kuwait, Lebanon, Malaysia, Mexico, Netherlands, Norway, Philippines, Poland, Portugal, Russia, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, USA) • Participants: de novo kidney transplant recipients, LD or DD • Number (group 1/group 2): 2037 (1022/1015) • Mean age ± SD (years): group 1 (49.3 ± 14.1); group 2 (49.3 ± 14.5) • Sex (M/F): group 1 (710/315): group 2 (707/308) • Exclusions: HLA identical or expanded criteria DD; positive cytotoxic cross-match or PRA ≥ 50%; HCV infection in donor/recipient; cold ischaemia time > 30 hours
Interventions	Treatment group 1 (EVL/rCNI) • EVL: 1.5 mg twice/day for TAC recipients & 0.75 mg twice/day for CSA recipients. • rTAC: 4 to 7 ng/mL day 0 to month 2; 2-5 ng/mL month 3 to 6; 2 to 4 ng/mL month 7 to 24 (913 recipients received TAC) • rCSA: 100 to 150 ng/mL day 0 to month 2; 50 to 100 ng/mL month 3 to 6; 25 to 50 ng/mL month 7 to 24 (100 received CSA) Treatment group 2 (MPA/sCNI) • MPS 1.44 g/d or MMF 2 g/d • TAC: 8 to 12 ng/mL day 0 to month 2; 6 to 10 ng/mL month 3 to 6; 5 to 8 ng/mL month 7 to 24 (916 recipients received TAC) • CSA: 200 to 300 ng/mL day 0 to month 2; 150 to 200 ng/mL month 3 to 6; 100 to 200 ng/mL month 7 to 24 (95 received CSA) Co-interventions • No CMV prophylaxis: weekly monitoring of CMV viral replication (pp65CMV Ag) for 6 months • Corticosteroids • Basiliximab or ATG

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TRANSFORM 2018 *(Continued)*

Outcomes	• Number with eGFR < 50 ml/min (MDRD) or treated BPAR at 12 months • Composite of number with treated BPAR, graft loss, or death at 12 months • Death • Graft loss • Acute rejection (total and biopsy proven) • CMV infection, wound complications • Adverse effects
Notes	• Comparison: TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization sequence, stratified within treatment groups by donor type (living, deceased standard criteria, or deceased expanded criteria) and by the type of CNI (CsA or tacrolimus), was generated by a computer program and implemented by telephone-based interactive response technology."
Allocation concealment (selection bias)	Low risk	Quote: "A randomization sequence, stratified within treatment groups by donor type (living, deceased standard criteria, or deceased expanded criteria) and by the type of CNI (CsA or tacrolimus), was generated by a computer program and implemented by telephone-based interactive response technology."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcomes (GFR, BPAR) were laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Pharma funded by Novartis

van Gurp 2010

Methods	• Design: phase III, open-label RCT • Duration: October 2004 to July 2006 • Mean follow-up: 6 months
Participants	• Setting: multicentre (51 centres) • Country: 13 European countries • Participants: 18 to 60 years old, primary kidney transplant or re-transplantation (unless graft lost due to rejection at less than 12 months); DD or LD • Number (group 1/group 2): 634 (318/316) • Mean age ± SD (years): group 1 (44.3 ± 11.3); group 2 (44.9 ± 11.1)

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van Gurp 2010 *(Continued)*

- Sex (M/F): group 1 (204/114); group 2 (204/112)
- Exclusions: high immunological risk defined as PRA > 50% in the previous 6 months; previous graft survival < 1 year due to immunological reasons; increased liver function tests; patient or donor HIV positive; previous recipient of another organ transplant; intolerance to study drugs; additional immunosuppressives; malignancy; hypercholesterolaemia > 350 mg/dL; uncontrolled infection

Interventions	Treatment group 1 • sTAC: 0.1 mg/kg twice/d (first dose prior to surgery). Trough levels days 0 to 14, 10 to 15 ng/mL. Days 15 to 42, 4 to 6 ng/mL and days 43 to 183, 4 to 6 ng/mL • SRL: loading dose 6 mg with postoperative dose of TAC, followed by maintenance doses of 2 mg for 28 days and 1 mg thereafter Treatment group 2 (MMF/sTAC) • sTAC: 0.1 mg/kg twice/d (first dose prior to surgery). Trough levels days 0 to 14, 10 to 15 ng/mL. Days 15 to 42, 8 to 12 ng/mL and days 43 to 183, 5 to 10 ng/mL • MMF: loading dose 1g pre-transplant, followed by daily dose of 2 g for first 14 days then 1 g daily thereafter Co-interventions • Adjuvant corticosteroids 100 to 500 mg bolus perioperatively, then 125 mg bolus on day 1. Thereafter steroids were tapered steadily from 20 mg on day 2 to 5 mg by day 90 and discontinued on day 91 • Cotrimoxazole prophylaxis for *Pneumocystis carinii* • Ganciclovir for CMV prophylaxis
Outcomes	• Kidney function calculated form Cockcroft-Gault formula • Incidence and time to BPAR; patient survival; graft survival; adverse effects; kidney dysfunction; diabetes mellitus; hypertension; hypercholesterolaemia
Notes	• Comparison: TOR-I versus antimetabolite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation 1:1, stratified by centre before first dose of medication. Sealed randomisation envelopes were supplied by study sponsor
Allocation concealment (selection bias)	Low risk	Sealed randomisation envelopes were supplied by study sponsor
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded and primary outcome (GFR) was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes mentioned or reported

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van Gurp 2010 *(Continued)*

Other bias	High risk	Funded by Astelllas Pharma Europe, involved in study design, analysis of data and preparation of manuscript

van Hooff 2003

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 6 months
Participants	• Setting: multicentre (5 centres) • Country: Netherlands, Belgium, Poland • Kidney transplant recipients ≥ 18 years • Number (group 1/group 2/group 3/group 4): 104 (28/25/25/26) • Mean age (years): group 1 (48.4); group 2 (43.6); group 3 (48.9); group 4 (47.0) • Sex (M/F): group 1 (16/12); group 2 (13/12); group 3 (18/7); group 4 (16/10) • Exclusions: PRA > 50%, previous graft lost < 1 year for immunological reasons; liver disease; cholesterol > 350 mg/dL; triglycerides > 500 mg/dL; poorly controlled diabetes, WBC < 3000 cells/L; platelets < 100,000/L; malignancy; infections; intolerance of study drugs
Interventions	Treatment/control group 1 • TAC (as above) • Prednisolone Treatment group 2 • SRL: 0.5 mg/d, continued Treatment group 3 • SRL: 1 mg/d, continued Treatment group 4 • SRL: 2 mg/d, continued Co-interventions • TAC: 0.2 mg/kg/d for levels 5 to 20 ng/mL to day 14; 5 to 15 ng/mL to day 42; then 5 to 15 ng/mL • Prednisolone
Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects

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van Hooff 2003 *(Continued)*

	• Cosmetic/life style adverse effects
Notes	• Comparison: low dose (groups 1 and 2) versus higher dose (group 4) TOR-I • Comparison: TOR-I versus placebo/no treatment • Data not included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective RCT. No other information provided
Allocation concealment (selection bias)	Unclear risk	Prospective RCT. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/106 (1.9%) not transplanted and excluded from analysis
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Velosa-212 2001

Methods	• Design: phase II, open-label RCT (Sirolimus Renal Function Study Group) • Duration: not reported • Follow up: 1 year
Participants	• Setting: multicentre (17 centres) • Country: USA, Spain, Italy • Primary kidney transplant recipients; ≥13 years, weight ≥ 40 kg, DD grafts, WBC ≥ 4000/mm^3, platelets ≥ 100,000/mm^3, triglycerides ≤ 500 mg/dL, cholesterol ≤ 350 mg/dL; good kidney function postoperatively • Number (group 1/group 2): 197 (97/100). 49 enrolled but not randomised because of ATN-DGF, which resolved later than day 7 • Mean age ± SD (years): group 1 (44.9 ± 12.9); group 2 (45.2 ± 11.6) • Sex (M/F): group 1 (55/42); group 2 (58/42) • Exclusions: systemic infection; chronic antiarrhythmic therapy for ventricular arrhythmia; other cardiac abnormalities precluding surgery; history of malignancy within the last 10 years; use of any investigational during within 4 weeks of SRL administration; current use of immunosuppressive agents
Interventions	Treatment group 1

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Velosa-212 2001 *(Continued)*

	• SRL: 6 mg loading dose, then fixed dose 2 mg/d • sCSA: levels 200 to 400 ng/mL for month 1; 200 to 350 ng/mL for month 2; 200 to 300 ng/mL for month 3; 150 to 250 ng/mL for months 4 to 12 Treatment group 2 • SRL: 20 mg/d for 3 days, 10 mg/d for days 4 to 9 then adjusted for levels 10 to 20 ng/mL day 10 to month 12 • rCSA: for level 100 to 175 ng/mL for month 1; then 100 to 150 ng/mL. CSA withdrawn considered after 2 months if kidney function stable and no acute rejection episodes Co-interventions • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • SCr • Malignancy • Haematological adverse effects • Biochemical adverse effects • Cosmetic/life style adverse effects
Notes	• Comparison: variable dose TOR-I and CNI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised assigned to two groups. No other information provided
Allocation concealment (selection bias)	Unclear risk	Patients were randomised assigned to two groups. No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Funded by Wyeth

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Vitko-201 2001

Methods	• Design: parallel RCT (RAD B201 Study group) • Duration: August 1988 to August 1999 • Follow up: 3 years
Participants	• Setting: multicentre (54 centres) • Country: Australia, Austria, Belgium, Czech Republic, France, Germany, Italy, Netherlands, Norway, Russia, South Africa, Switzerland, UK • De novo kidney transplant recipients aged 18 to 68 years; LD or DD, ischaemia time < 40 hours • Number (group 1/group 2/group 3): 588 ITT population (194/198/196) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusions: multiple organ transplants; +ve T-cell crossmatch; induction therapy before study entry; hypersensitivity to study drugs; non-protocol immunosuppressive drugs, treatments, investigational drugs within 1 month before randomisation or baseline; liver disease; HIV; severe cardiac disease; severe uncontrolled hyperlipidaemia
Interventions	Treatment group 1 • EVL: initial dose 1.5 mg/d Treatment group 2 • EVL: initial dose 3 mg/d Treatment group 3 • MMF: 2 g/d Co-interventions • CSA: initial 150 to 400 ng/mL; maintenance 100 to 300 ng/mL • Prednisolone
Outcomes	• Death (all causes) • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • CrCl • SCr • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects
Notes	• Comparison: TOR-I versus antimetabolite (combine groups 1 & 2) • Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised according to a computer-generated schedule that ensured equal distribution among the three treatment groups within each centre

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Vitko-201 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	Patients were randomised according to a computer-generated schedule that ensured equal distribution among the three treatment groups within each centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy for 12 months
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double dummy for 12 months
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Supported by Novartis

Vitko-TERRA 2004

Methods	• Design: open-label RCT • Duration: not reported • Follow up: 6 months
Participants	• Setting: multicentre (75 centres) • Country: 15 European countries, Australia • Kidney transplant recipients ≥ 18 years, 1st or 2nd grafts (unless immunological reason for previous graft loss) • Number (group 1/group 2/group 3): 677 (325/325/327) • Mean age ± SD (years): group 1 (44.6 ± 12.9); group 2 (47.3 ± 12.4); group 3 (46.0 ± 11.7) • Sex (M/F): group 1 (211/114); group 2 (195/130); group 3 (219/108) • Exclusions: PRA > 85%; liver disease; infection; severe cholesterolaemia; donor kidney ischaemia time > 40 hours; non-heart beating donor; HBV, HCV or HIV +ve donor; malignancy; GI disorders; intolerance to study drugs
Interventions	Treatment group 1 • SRL: single dose 1.5 mg then 0.5 mg/d then adjusted for levels Treatment group 2 • SRL: single dose 6 mg then 2 mg/d then adjusted for levels Treatment group 3 • MMF: 1 g/d Co-interventions • TAC: 0.2 mg/kg/d for levels 8 to 16 ng/mL (days 0 to 14) then 5 to 15 ng/mL • Prednisolone

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Vitko-TERRA 2004 *(Continued)*

Outcomes	• Death (all causes) • Cause-specific death • Graft loss censored for death • Graft loss or death with a functioning graft • Acute rejection • Steroid-resistant rejection • CrCl • SCr • Infection • CMV infection • Malignancy • Haematological adverse effects • Biochemical adverse effects • Surgical adverse effects
Notes	• Comparison: TOR-I versus antimetabolite • Comparison: low dose versus higher dose TOR-I

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was 1:1:1 and was performed locally at each centre using sealed randomisation envelopes supplied by the study sponsor
Allocation concealment (selection bias)	Low risk	Randomisation was 1:1:1 and was performed locally at each centre using sealed randomisation envelopes supplied by the study sponsor
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Fujiawa

ARB - angiotensin receptor blocker; ATN - acute tubular necrosis; ACEi - angiotensin-converting enzyme inhibitor; ALG - antilymphocyte globulin; ATG - antithymocyte globulin; AZA - azathioprine; BMI - body mass index; BP - blood pressure; BPAR - biopsy-proven acute rejection; CAN - chronic allograft nephropathy; CCB - calcium channel blockers; CMV - cytomegalovirus; CNI - calcineurin inhibitor; CrCl - creatinine clearance; CSA - cyclosporin; DD - deceased donor; ER - extended release; ESKD - end-stage kidney disease; EVL - everolimus; FSGS - focal segmental glomerulosclerosis; (e)GFR - (estimated) glomerular filtration rate; GI - gastrointestinal; Hb - haemoglobin; HbSAg - hepatitis B surface antigen; HBV - hepatitis B virus; HCV - hepatitis C virus; HIV - human immunodeficiency virus; HLA - human leukocyte antigen; IL2 - interleukin 2; ITT - intention-to-treat; IV - intravenous(ly); LD - living donor; LRD - living-related donor; M/F- male/female; MI - myocardial infarction; MMF - mycophenolate mofetil; MP - methylprednisolone; MPA - mycophenolic acid; MPS - mycophenolate sodium; NODM - new-onset diabetes mellitus; PRA - panel reactive antibodies; r - reduced dose (rCSA; rTAC); RCT - randomised controlled trial; s -

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standard dose (sCSA; sTAC); SCr - serum creatinine; SD - standard deviation; SRL - sirolimus; TAC - tacrolimus; TOR-I - target of rapamycin inhibitor; WBC - white blood cells

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

Study	Reason for exclusion
ADHERE 2017	SRL not started till day 28 post transplant
Barsoum 2007	Cannot compare SRL with MMF till 3 months or more post transplant
CALLISTO 2009	Compared SRL commenced at transplant with SRL commenced at week 5
Carmellini 2010	TOR-I use in stable transplant patients (> 6 months); not primary immunosuppression
CENTRAL 2012	Patient randomised at week 7
CERTITEM 2015	Randomised at 3 months based on protocol biopsy at 3 months. Therefore not primary Immuno-suppression
Citterio 2004	Unclear if this is a RCT
Cruzado 2016	Switch to EVL as secondary immunosuppression more than 1 year post transplant
EVIDENCE 2014	Study of non-inferiority of steroid withdrawal
Fior 2015	Unclear if this is a RCT
Libetta 2007	Patients selected into study at 3 months; unclear whether RCT
Libetta 2015	Late conversion to SRL
Mathew 2006	Compares same dose of SRL using oral solution or tablets
Nafar 2012	Quasi-RCT comparing TOR-I with CNI but TOR-I not commenced till 3 months post transplant
NCT00005113	Paediatric study terminated due to inability to recruit sufficient patients
NCT00965094	Patients not randomised until month 3
nEVEROLD 2017	Conversion to TOR-I at 1 month
NEVERWOUND 2014	Compares immediate with delayed administration of EVL
Novoa 2011	Patients not randomised till 3 months
Oh 2012	EVL commenced at 1 month post transplant
Pretagostini 2016	EVL commenced at 1 month post transplant
Rivelli 2014	Both groups received SRL; dose increased in one group at 3 months when TAC ceased
SOCRATES 2014	EVL not commenced till 14 days post transplant
Tamashiro 2017	Late conversion at 3 months to TOR-I; not clear whether this is an RCT
van Gelder 2003	Conversion to TOR-I at 12 months

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Study	Reason for exclusion
Wojciechowski 2017	Late conversion to TOR-I after diagnosis of BK viruria
Wyrley-Birch 2009	Randomisation between pairs of recipients of kidneys from same donor not groups of recipients

CNI - calcineurin inhibitor; EVL - everolimus; MMF - mycophenolate mofetil; RCT - randomised controlled trial; SRL - sirolimus; TAC - tacrolimus; TOR-I - target of rapamycin inhibitor

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

Ferreira 2019

Methods	Single centre RCT enrolling adult recipients of ECD donors
Participants	171 enrolled
Interventions	All receive single dose of 1 gm methylprednisolone & then oral prednisone & induction with 4 doses of ATG Group 1 • EVL from day 1 and TAC from day 8 Group 2 • MPA from day 1 and TAC from day 8
Outcomes	• The primary endpoint was the cumulative incidence of first CMV infection/disease during the first year after transplantation • Other outcomes treatment failure, BPAR
Notes	The institution “Hospital do Rim” have received research grants from Novartis and Sanofi to conduct this study

Traitanon 2019

Methods	RCT enrolling adults 18 to 70 years; recipients of living donor transplants; PRA < 20%; patients with ESKD from primary FSGS excluded
Participants	88 enrolled by June 2014
Interventions	Group • Standard dose TAC + MMF Group 2 • Reduced dose TAC + EVL
Outcomes	Change in transplant function Change in T cell and B cell immune response
Notes	Study supported by Novartis

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ATG - antithymocyte globulin; BPAR - biopsy-proven acute rejection; CMV - cytomegalovirus; ECD - extended criteria donors; ESKD - end-stage kidney disease; EVL - everolimus; FSGS - focal segmental glomerulosclerosis; MMF - mycophenolate mofetil; MPA - mycophenolic acid; PRA - panel reactive antibodies; RCT - randomised controlled trial; TAC - tacrolimus

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

EVER TWIST 2013

Trial name or title	EVER TWIST study
Methods	Open-label RCT enrolling de novo kidney transplant recipients
Participants	31 enrolled by 2013
Interventions	Group A • Induction with MP/ATG. Then TAC, EVL, MPS (till 6 months), MP (till 1 month) Group B • Induction with ATG. Then TAC, MPS, MP
Outcomes	Immunological data
Starting date	Not reported
Contact information	Dr Carmelo Libetta
Notes	

NCT02077556

Trial name or title	The effect of everolimus on the pharmacokinetics of tacrolimus in renal transplant patients, and the effect of ABCB1, CYP3A4, CYP3A5, POR genetic polymorphism on the two drugs
Methods	RCT; parallel assignment; open-label
Participants	70 adult recipients (20 to 65 years) of de novo kidney transplants; aspartate aminotransferase/alanine aminotransferase within 2 times the upper limit of normal range
Interventions	Group 1 • EVL: 1 mg orally every 12 hours from post operation day 1 to achieve trough concentrations of 3 to 8 ng/mL • TAC: 0.05 to 0.075 mg/kg orally every 12 hours from post operation day 1 to achieve trough concentrations of 8 to 12 ng/mL • Also MP, prednisolone Group 2 • MMF: 10 to 15 mg/kg orally every 12 hours from post operation day 1 • TAC: 0.05 to 0.075 mg/kg orally every 12 hours from post operation day 1 to achieve trough concentrations of 8 to 12 ng/mL • Also MP, prednisolone
Outcomes	Pharmacokinetic profiles (8 to 10 days post transplant); acute rejection (within 2 weeks)

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NCT02077556 *(Continued)*

Starting date	April 2014; Estimated study completion date January 2018
Contact information	Fe-Lin Lin Wu; flwu@ntu.edu.tw. Taiwan
Notes	Duration of follow-up not reported but only clinical outcome to be reported is acute rejection within 2 weeks of transplant. Primary outcomes are pharmacological as aim of study is to investigate for drug interactions

NCT03468478

Trial name or title	Comparison of the efficacy and safety of sirolimus versus everolimus versus mycophenolate in kidney transplantation (SEM)
Methods	RCT; parallel assignment; open label
Participants	400 adult recipients (18 years and older) of their first living or deceased donor kidney transplant. Patients with FSGS/history of nephrotic syndrome excluded
Interventions	Group 1 (SRL + rTAC) • SRL: 3 mg daily (blood level 4 to 8 ng/mL) • TAC 0.05 mg twice daily (blood level 3 to 5 ng/mL) Group 2 (EVL + rTAC) • EVL: 1.5 mg twice daily (blood level 4 to 8 ng/mL) • TAC: 0.05 mg twice daily (blood level 3 to 5 ng/mL) Group 3 (MMF + sTAC) • MMF: 1 g twice/day or MPS 720 mg twice/d • TAC: 0.1 mg twice daily (blood level not reported)
Outcomes	Incidence of CMV disease or infection by 12 months; no other outcomes provided
Starting date	June 16, 2017; expected completion date June 18, 2021
Contact information	Helio Tedesco Silva Jr, Hospital do Rim e Hipertensão, Brazil
Notes	

ATG - antithymocyte globulin; CMV - cytomegalovirus; ESKD - end-stage kidney disease; EVL - everolimus; FSGS - focal segmental glomerulosclerosis; MMF - mycophenolate mofetil; MP - methylprednisolone; MPS - mycophenolate sodium; PRA - panel reactive antibodies; RCT - randomised controlled trial; reduced dose - r (rCSA, rTAC); SRL - sirolimus; standard dose - s (sCSA, sTAC); TAC - tacrolimus

DATA AND ANALYSES

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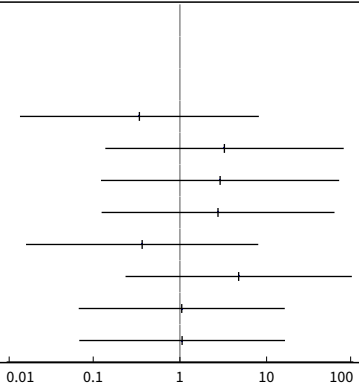
Comparison 1. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	19	3618	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.87, 1.98]
2 Total graft loss including death	19	3619	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.11, 1.80]
2.1 Tacrolimus	7	1386	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.25, 2.56]
2.2 Cyclosporin	13	2233	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.83, 1.61]
3 Graft loss censored for death	14	3277	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.96, 1.81]
3.1 Tacrolimus	5	1238	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.17, 3.25]
3.2 Cyclosporin	10	2039	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.68, 1.54]
4 All acute rejection	19	3016	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.31, 1.92]
5 Biopsy-proven acute rejection	15	2708	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.25, 2.04]
6 CMV infection	13	2026	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.29, 0.63]
7 Adverse wound outcomes	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 All complications	12	1679	Risk Ratio (M-H, Random, 95% CI)	2.56 [1.94, 3.36]
7.2 Lymphocoele	8	2538	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.73, 3.02]
8 All malignancies	10	2584	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.50, 1.48]
9 Number needing to change treatment	14	3148	Risk Ratio (M-H, Random, 95% CI)	2.42 [1.88, 3.11]

Analysis 1.1. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 1 Death (all causes).

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pescovitz 2007	0/30	0/15			Not estimable
Gelens 2006	0/18	0/18			Not estimable
Martinez-Mier 2006	0/20	0/21			Not estimable
Groth-207 1999	0/41	1/42		1.68%	0.34[0.01,8.14]
Durrbach 2008	1/33	0/36		1.68%	3.26[0.14,77.46]
Flechner-318 2002	1/31	0/30		1.69%	2.91[0.12,68.66]
Cattaneo 2005	1/11	0/10		1.76%	2.75[0.12,60.7]
Morelon 2010	0/9	1/10		1.77%	0.37[0.02,8.01]
Schaefer 2006	2/41	0/39		1.87%	4.76[0.24,96.16]
Riad 2007	1/39	1/41		2.25%	1.05[0.07,16.23]
Fernandes-Charpiot 2014	1/33	1/35		2.26%	1.06[0.07,16.27]



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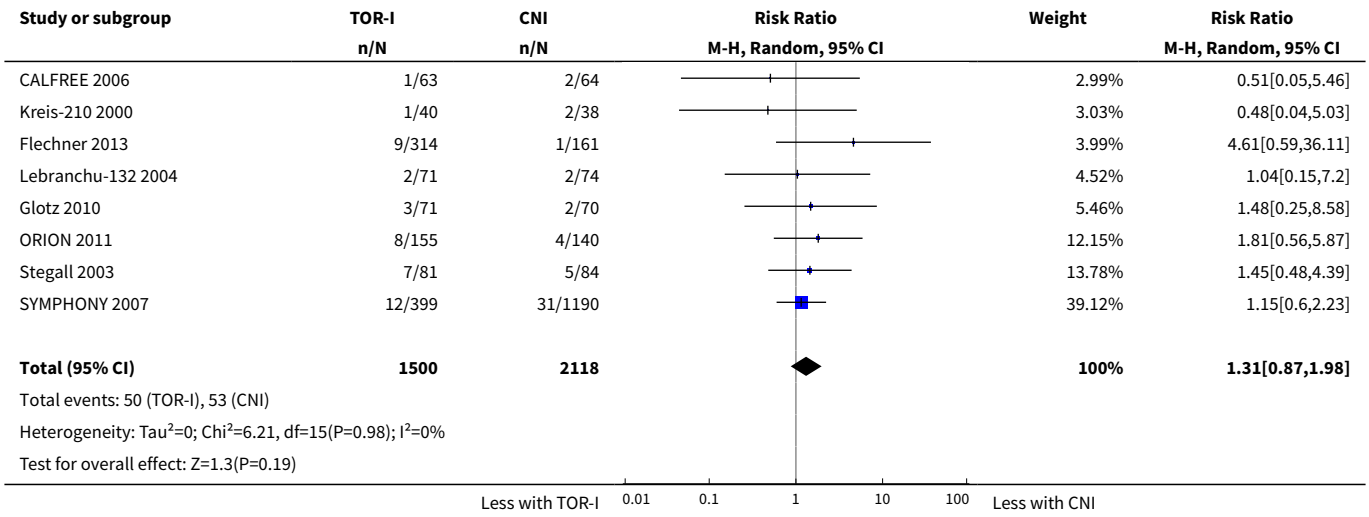
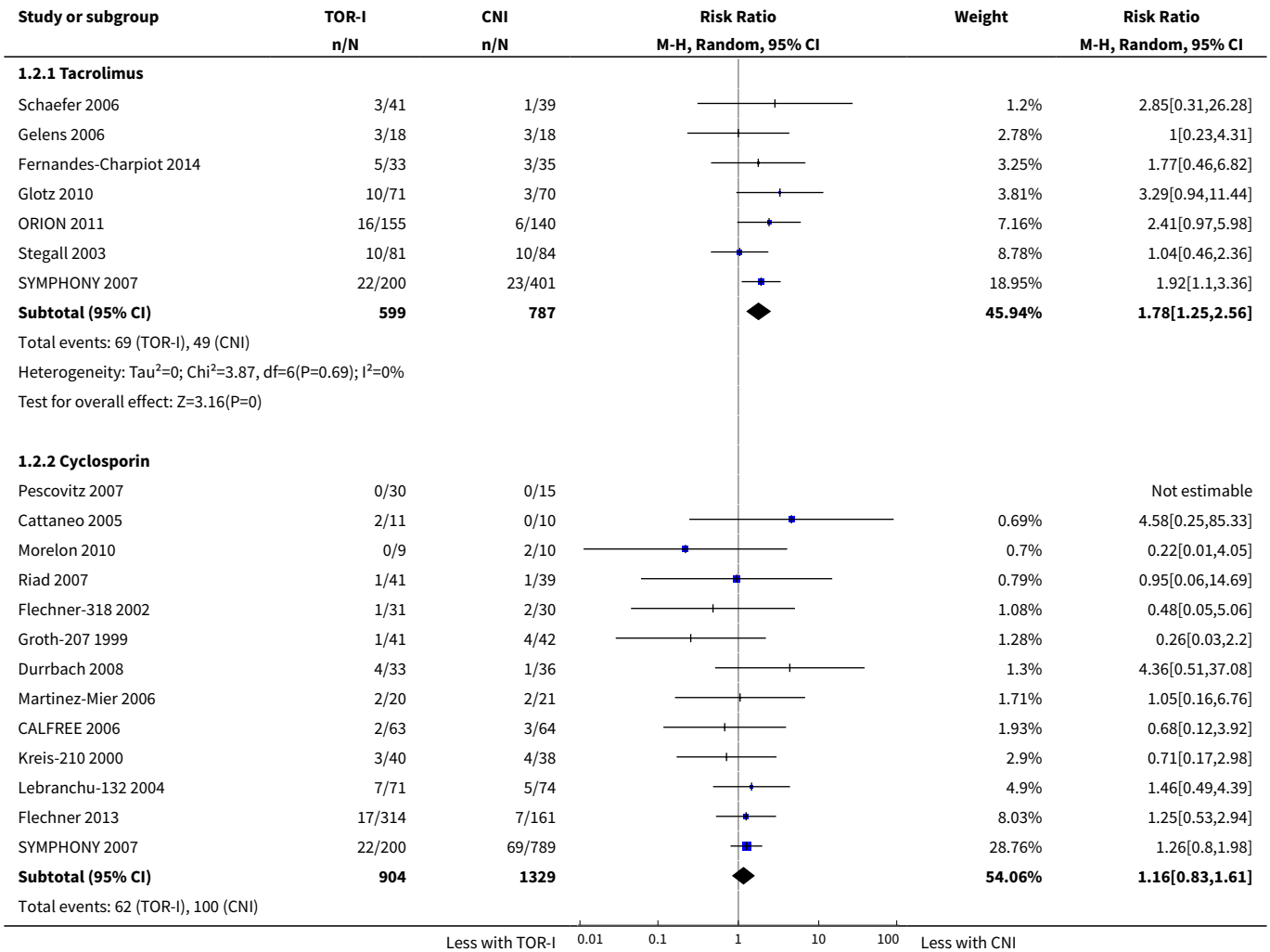


Analysis 1.2. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 2 Total graft loss including death.



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Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=7.16, df=11(P=0.79); I²=0%					
Test for overall effect: Z=0.86(P=0.39)					
Total (95% CI)	**1503**	**2116**		**100%**	**1.41[1.11,1.8]**
Total events: 131 (TOR-I), 149 (CNI)					
Heterogeneity: Tau²=0; Chi²=14.03, df=18(P=0.73); I²=0%					
Test for overall effect: Z=2.78(P=0.01)					
Test for subgroup differences: Chi²=3.02, df=1 (P=0.08), I²=66.87%					

Analysis 1.3. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 3 Graft loss censored for death.

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Tacrolimus					
Glotz 2010	7/71	1/70		2.33%	6.9[0.87,54.64]
ORION 2011	8/155	2/140		4.25%	3.61[0.78,16.73]
Gelens 2006	3/18	3/18		4.68%	1[0.23,4.31]
Stegall 2003	5/81	5/84		6.92%	1.04[0.31,3.45]
SYMPHONY 2007	16/200	15/401		21.37%	2.14[1.08,4.24]
Subtotal (95% CI)	**525**	**713**		**39.56%**	**1.95[1.17,3.25]**
Total events: 39 (TOR-I), 26 (CNI)					
Heterogeneity: Tau²=0.01; Chi²=4.06, df=4(P=0.4); I²=1.58%					
Test for overall effect: Z=2.56(P=0.01)					
1.3.2 Cyclosporin					
Cattaneo 2005	1/11	0/10		1.04%	2.75[0.12,60.7]
Morelon 2010	0/9	1/10		1.05%	0.37[0.02,8.01]
Flechner-318 2002	0/31	2/30		1.11%	0.19[0.01,3.88]
CALFREE 2006	1/63	1/64		1.32%	1.02[0.06,15.89]
Martinez-Mier 2006	2/20	1/21		1.85%	2.1[0.21,21.39]
Groth-207 1999	1/41	3/42		2.02%	0.34[0.04,3.15]
Kreis-210 2000	2/40	2/38		2.74%	0.95[0.14,6.41]
Lebranchu-132 2004	5/71	3/74		5.14%	1.74[0.43,7]
Flechner 2013	8/314	6/161		9.21%	0.68[0.24,1.94]
SYMPHONY 2007	16/200	55/789		34.94%	1.15[0.67,1.96]
Subtotal (95% CI)	**800**	**1239**		**60.44%**	**1.02[0.68,1.54]**
Total events: 36 (TOR-I), 74 (CNI)					
Heterogeneity: Tau²=0; Chi²=4.64, df=9(P=0.86); I²=0%					
Test for overall effect: Z=0.11(P=0.91)					
Total (95% CI)	**1325**	**1952**		**100%**	**1.32[0.96,1.81]**
Total events: 75 (TOR-I), 100 (CNI)					
Heterogeneity: Tau²=0; Chi²=12.46, df=14(P=0.57); I²=0%					
Test for overall effect: Z=1.73(P=0.08)					
Test for subgroup differences: Chi²=3.75, df=1 (P=0.05), I²=73.31%					

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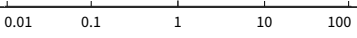
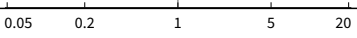
Analysis 1.4. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 4 All acute rejection.

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Morelon 2010	1/9	1/10		0.52%	1.11[0.08,15.28]
Cattaneo 2005	2/11	1/10		0.71%	1.82[0.19,17.12]
Martinez-Mier 2006	3/20	1/21		0.75%	3.15[0.36,27.83]
Schaefer 2006	5/41	1/39		0.8%	4.76[0.58,38.91]
Durrbach 2008	4/33	3/36		1.7%	1.45[0.35,6.02]
Pescovitz 2007	12/30	2/15		1.84%	3[0.77,11.72]
Fernandes-Charpiot 2014	7/33	4/35		2.6%	1.86[0.6,5.76]
Flechner-318 2002	4/31	7/30		2.65%	0.55[0.18,1.7]
Lebranchu-132 2004	9/71	6/74		3.38%	1.56[0.59,4.17]
Gelens 2006	9/18	5/18		4.11%	1.8[0.75,4.32]
Kreis-210 2000	11/40	7/38		4.45%	1.49[0.65,3.45]
Glotz 2010	12/71	9/70		4.83%	1.31[0.59,2.92]
Riad 2007	16/41	8/39		5.65%	1.9[0.92,3.93]
Flechner 2013	60/314	8/161		5.84%	3.85[1.89,7.84]
Stegall 2003	15/80	12/82		6.1%	1.28[0.64,2.56]
ORION 2011	43/156	13/140		8.13%	2.97[1.67,5.29]
Groth-207 1999	17/41	16/42		9.2%	1.09[0.64,1.85]
CALFREE 2006	29/63	23/64		12.43%	1.28[0.84,1.95]
SYMPHONY 2007	87/200	246/789		24.33%	1.4[1.15,1.69]
Total (95% CI)	**1303**	**1713**		**100%**	**1.59[1.31,1.92]**
Total events: 346 (TOR-I), 373 (CNI)					
Heterogeneity: Tau^2=0.03; Chi^2=22.44, df=18(P=0.21); I^2=19.8%					
Test for overall effect: Z=4.75(P<0.0001)					



Analysis 1.5. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 5 Biopsy-proven acute rejection.

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Morelon 2010	1/9	1/10		0.85%	1.11[0.08,15.28]
Durrbach 2008	4/33	3/36		2.67%	1.45[0.35,6.02]
Pescovitz 2007	12/30	2/15		2.87%	3[0.77,11.72]
Fernandes-Charpiot 2014	7/33	4/35		3.94%	1.86[0.6,5.76]
Flechner-318 2002	4/31	7/30		4.01%	0.55[0.18,1.7]
Stegall 2003	6/64	7/59		4.59%	0.79[0.28,2.22]
Lebranchu-132 2004	9/71	6/74		4.98%	1.56[0.59,4.17]
Gelens 2006	9/18	5/18		5.92%	1.8[0.75,4.32]
Glotz 2010	10/71	9/70		6.32%	1.1[0.47,2.53]
Kreis-210 2000	11/40	7/38		6.33%	1.49[0.65,3.45]
Riad 2007	16/41	8/39		7.72%	1.9[0.92,3.93]
Flechner 2013	60/314	8/161		7.93%	3.85[1.89,7.84]
ORION 2011	43/156	13/140		10.28%	2.97[1.67,5.29]
Groth-207 1999	17/41	16/42		11.27%	1.09[0.64,1.85]
SYMPHONY 2007	80/200	225/789		20.32%	1.4[1.15,1.72]



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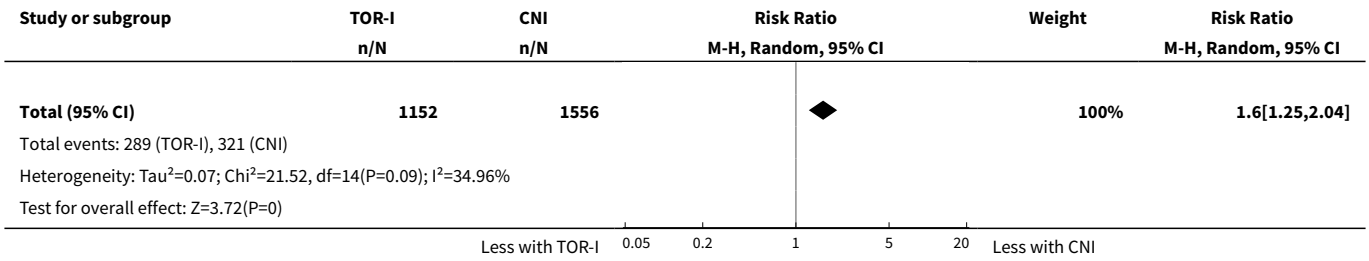
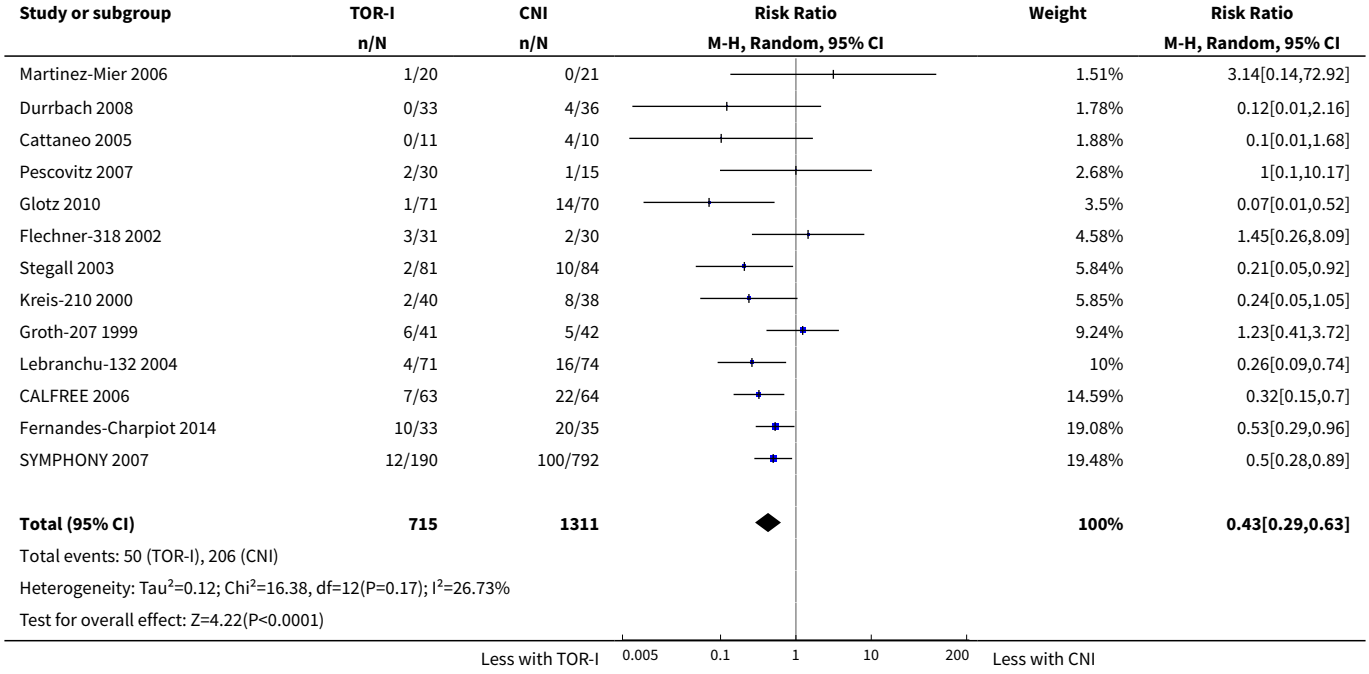
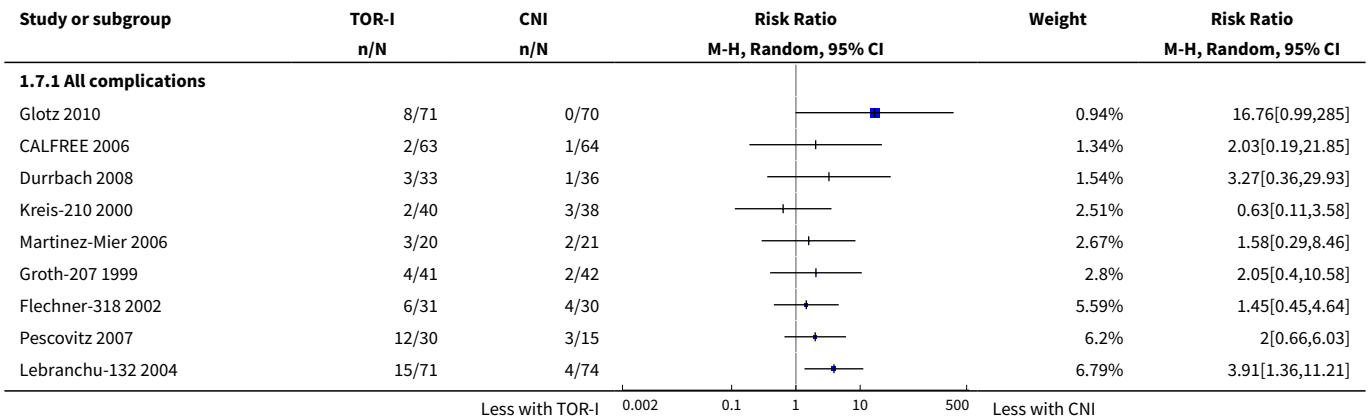


Analysis 1.6. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 6 CMV infection.



Analysis 1.7. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 7 Adverse wound outcomes.



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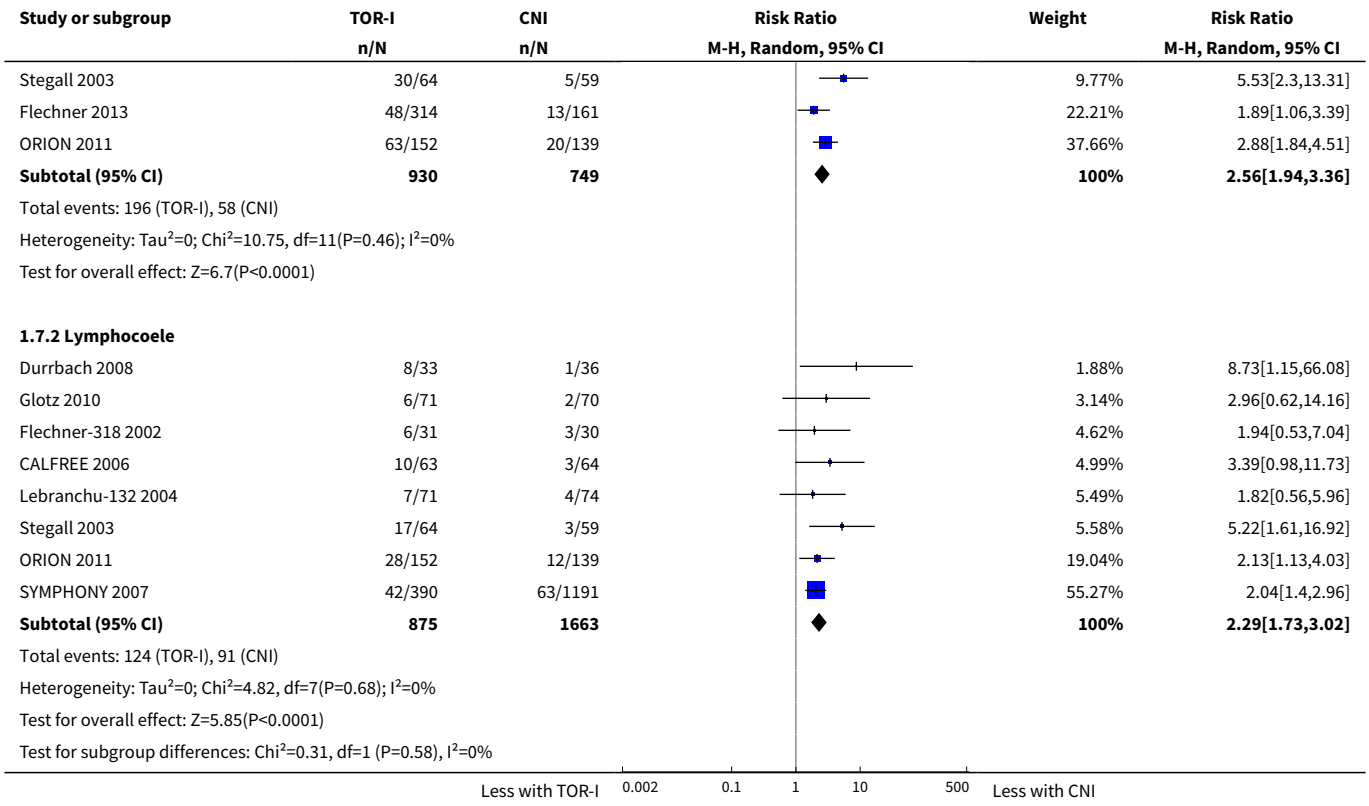
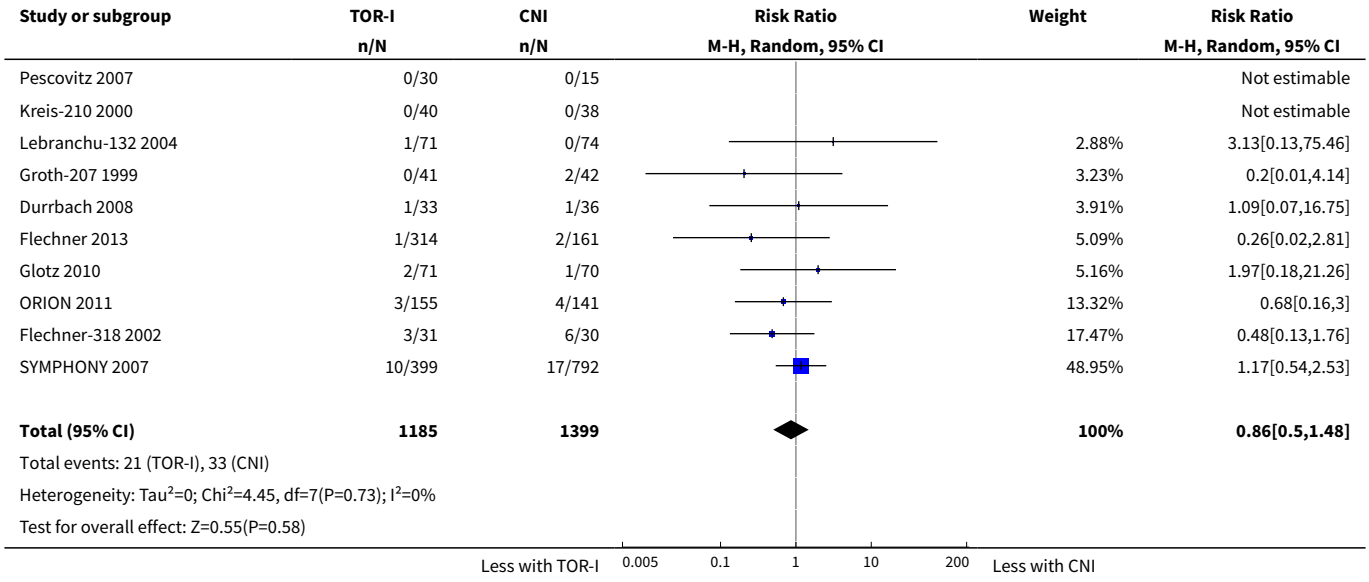


Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Stegall 2003	30/64	5/59		9.77%	5.53[2.3,13.31]
Flechner 2013	48/314	13/161		22.21%	1.89[1.06,3.39]
ORION 2011	63/152	20/139		37.66%	2.88[1.84,4.51]
Subtotal (95% CI)	**930**	**749**		**100%**	**2.56[1.94,3.36]**
Total events: 196 (TOR-I), 58 (CNI)					
Heterogeneity: Tau²=0; Chi²=10.75, df=11(P=0.46); I²=0%					
Test for overall effect: Z=6.7(P<0.0001)					
1.7.2 Lymphocoele					
Durrbach 2008	8/33	1/36		1.88%	8.73[1.15,66.08]
Glotz 2010	6/71	2/70		3.14%	2.96[0.62,14.16]
Flechner-318 2002	6/31	3/30		4.62%	1.94[0.53,7.04]
CALFREE 2006	10/63	3/64		4.99%	3.39[0.98,11.73]
Lebranchu-132 2004	7/71	4/74		5.49%	1.82[0.56,5.96]
Stegall 2003	17/64	3/59		5.58%	5.22[1.61,16.92]
ORION 2011	28/152	12/139		19.04%	2.13[1.13,4.03]
SYMPHONY 2007	42/390	63/1191		55.27%	2.04[1.4,2.96]
Subtotal (95% CI)	**875**	**1663**		**100%**	**2.29[1.73,3.02]**
Total events: 124 (TOR-I), 91 (CNI)					
Heterogeneity: Tau²=0; Chi²=4.82, df=7(P=0.68); I²=0%					
Test for overall effect: Z=5.85(P<0.0001)					
Test for subgroup differences: Chi²=0.31, df=1 (P=0.58), I²=0%					

Analysis 1.8. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 8 All malignancies.



Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pescovitz 2007	0/30	0/15			Not estimable
Kreis-210 2000	0/40	0/38			Not estimable
Lebranchu-132 2004	1/71	0/74		2.88%	3.13[0.13,75.46]
Groth-207 1999	0/41	2/42		3.23%	0.2[0.01,4.14]
Durrbach 2008	1/33	1/36		3.91%	1.09[0.07,16.75]
Flechner 2013	1/314	2/161		5.09%	0.26[0.02,2.81]
Glotz 2010	2/71	1/70		5.16%	1.97[0.18,21.26]
ORION 2011	3/155	4/141		13.32%	0.68[0.16,3]
Flechner-318 2002	3/31	6/30		17.47%	0.48[0.13,1.76]
SYMPHONY 2007	10/399	17/792		48.95%	1.17[0.54,2.53]
Total (95% CI)	**1185**	**1399**		**100%**	**0.86[0.5,1.48]**
Total events: 21 (TOR-I), 33 (CNI)					
Heterogeneity: Tau²=0; Chi²=4.45, df=7(P=0.73); I²=0%					
Test for overall effect: Z=0.55(P=0.58)					

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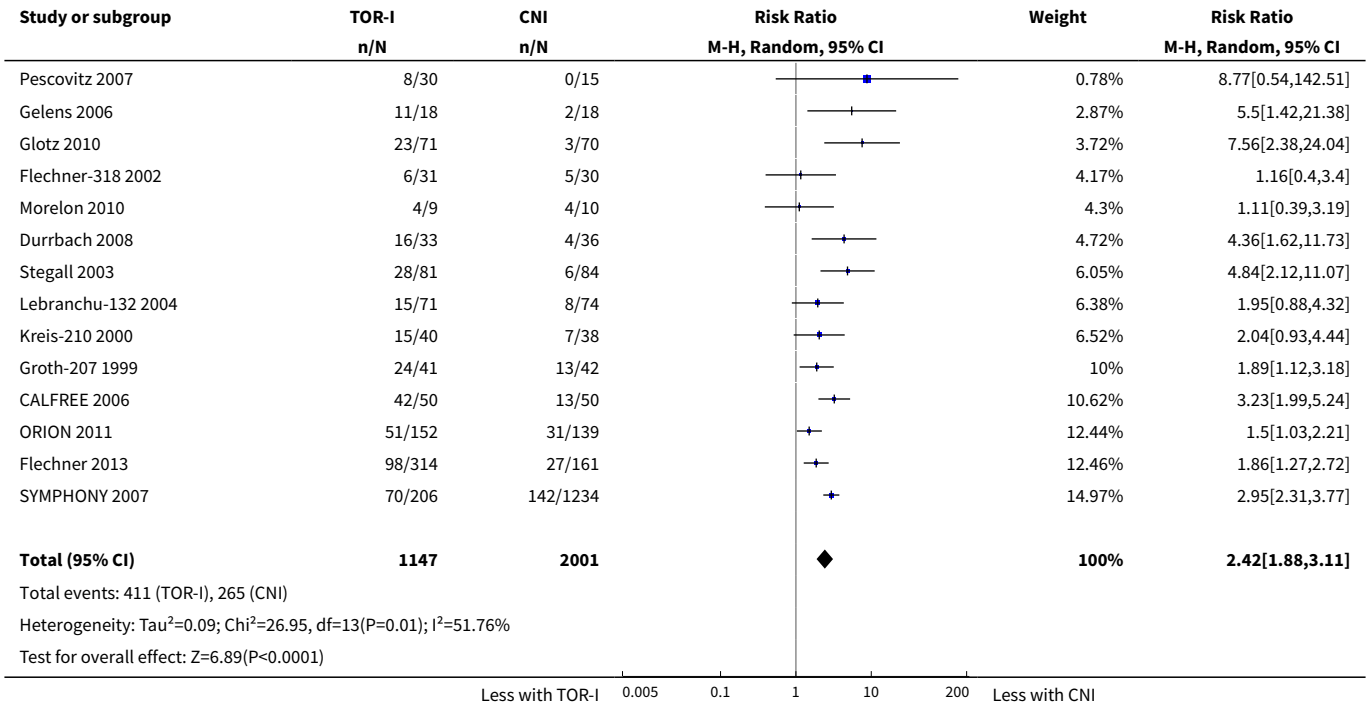
Analysis 1.9. Comparison 1 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): primary outcomes, Outcome 9 Number needing to change treatment.



Comparison 2. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New-onset diabetes mellitus	13	2791	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.69, 1.26]
1.1 Tacrolimus	6	1274	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.16]
1.2 Cyclosporin	8	1517	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.74, 1.99]
2 Lymphoma/PTLD	8	2537	Risk Ratio (M-H, Random, 95% CI)	2.47 [0.78, 7.86]
3 Number with BK virus infection	3	386	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.16, 1.29]
4 Adverse cosmetic outcomes	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Tremor	6	799	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.15, 0.41]
4.2 Gingival hyperplasia - cyclosporin	3	222	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.02, 0.57]
4.3 Hirsutism - cyclosporin	1	78	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.03, 2.03]
4.4 Acne/rash	4	622	Risk Ratio (M-H, Random, 95% CI)	3.51 [1.75, 7.02]
5 Glomerular filtration rate	15	2983	Mean Difference (IV, Random, 95% CI)	2.20 [-1.29, 5.68]

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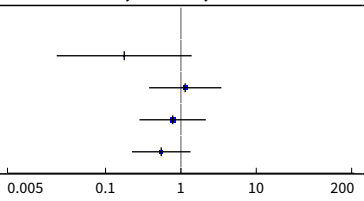
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Serum creatinine	10	672	Mean Difference (IV, Random, 95% CI)	-10.64 [-19.19, -2.10]
7 Number with elevated lipid levels	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Hypercholesterolaemia	4	1877	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.17, 2.59]
7.2 Hypertriglyceridaemia	5	1922	Risk Ratio (M-H, Random, 95% CI)	1.72 [1.20, 2.46]
8 Lipid outcomes	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Cholesterol	7	579	Mean Difference (IV, Random, 95% CI)	0.77 [0.45, 1.09]
8.2 Triglycerides	8	843	Mean Difference (IV, Random, 95% CI)	0.57 [0.28, 0.86]
9 Number with abnormal haematological values	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Anaemia	6	2216	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.28, 1.70]
9.2 Leucopenia	5	1922	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.95, 2.44]
9.3 Thrombocytopenia	4	593	Risk Ratio (M-H, Random, 95% CI)	5.26 [2.87, 9.63]
10 Haematological outcomes	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Haemoglobin [g/dL]	5	481	Mean Difference (IV, Random, 95% CI)	-0.64 [-1.17, -0.11]
10.2 White cell count [per mm^3]	5	433	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.21, -0.41]
10.3 Platelet count [per mm^2]	3	247	Mean Difference (IV, Random, 95% CI)	0.03 [-1.79, 1.85]

Analysis 2.1. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 1 New-onset diabetes mellitus.

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Tacrolimus					
Fernandes-Charpiot 2014	1/33	6/35		2.11%	0.18[0.02,1.39]
Schaefer 2006	6/41	5/39		7.4%	1.14[0.38,3.44]
Stegall 2003	6/81	8/84		8.76%	0.78[0.28,2.14]
ORION 2011	7/117	12/110		11.23%	0.55[0.22,1.34]



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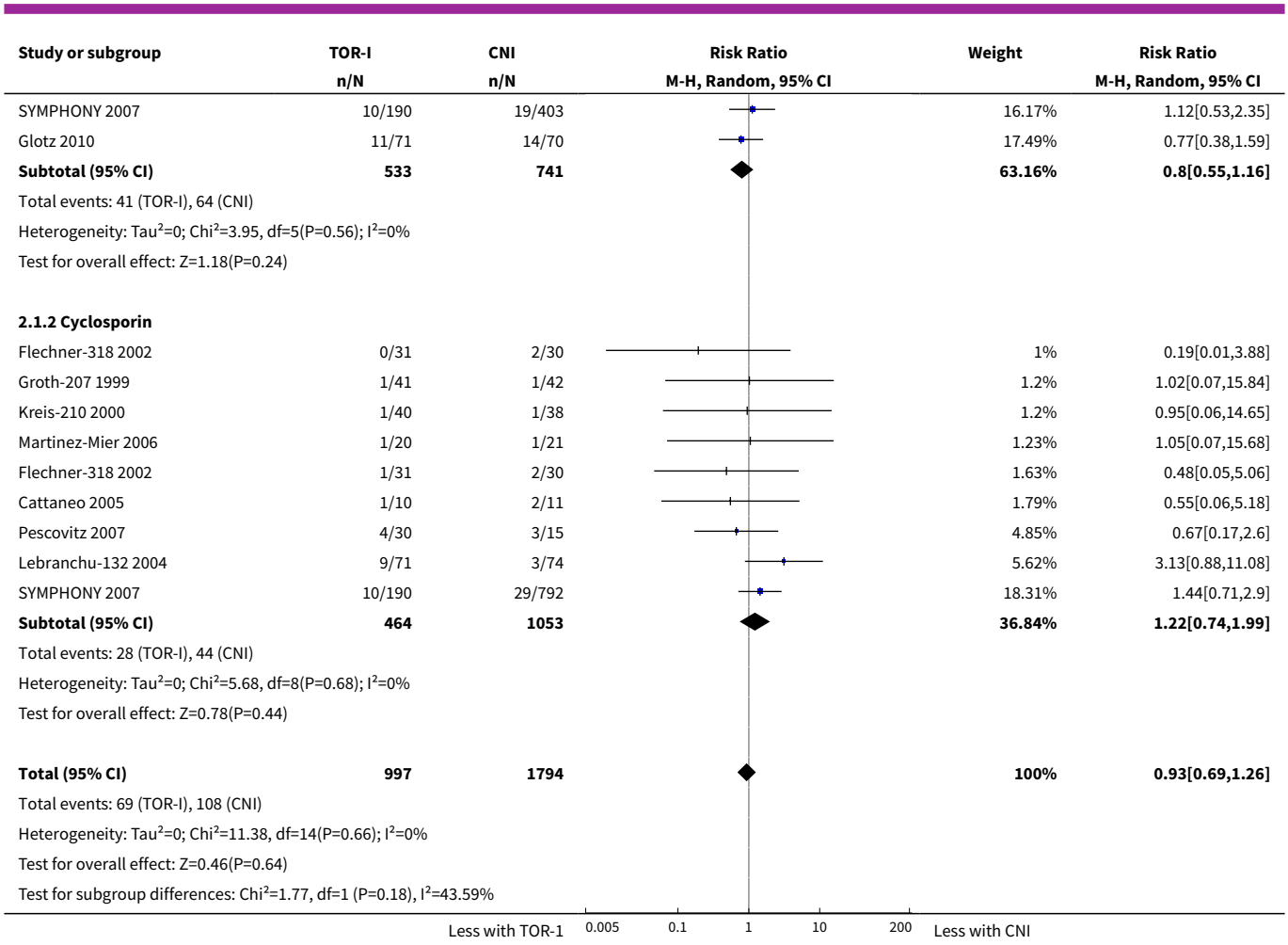
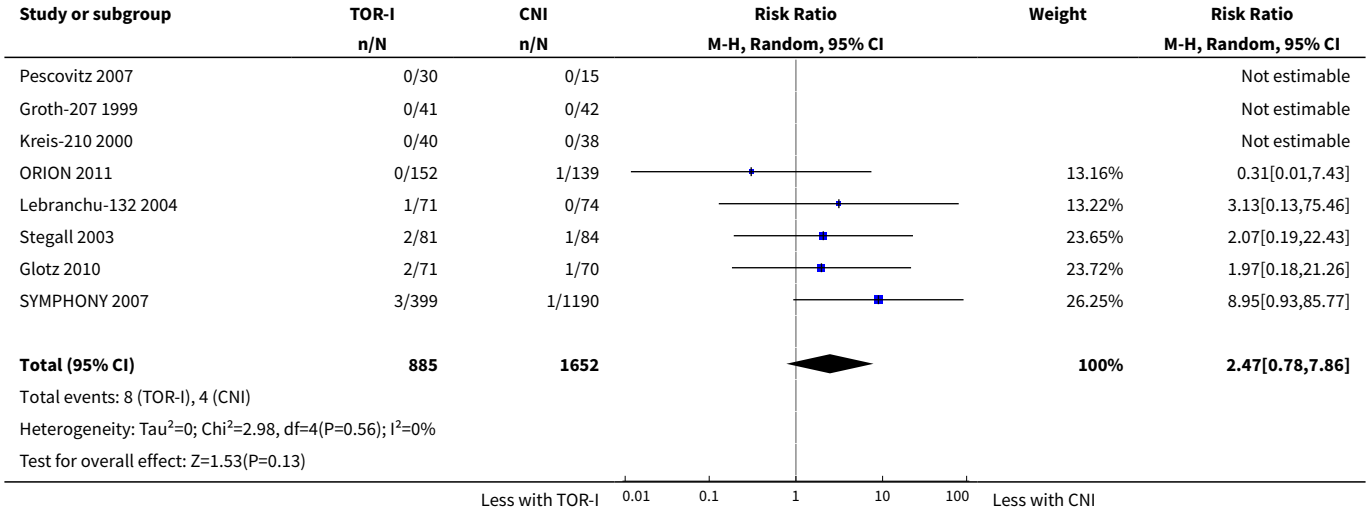


Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SYMPHONY 2007	10/190	19/403		16.17%	1.12[0.53,2.35]
Glotz 2010	11/71	14/70		17.49%	0.77[0.38,1.59]
Subtotal (95% CI)	**533**	**741**		**63.16%**	**0.8[0.55,1.16]**
Total events: 41 (TOR-I), 64 (CNI)					
Heterogeneity: Tau²=0; Chi²=3.95, df=5(P=0.56); I²=0%					
Test for overall effect: Z=1.18(P=0.24)					
2.1.2 Cyclosporin					
Flechner-318 2002	0/31	2/30		1%	0.19[0.01,3.88]
Groth-207 1999	1/41	1/42		1.2%	1.02[0.07,15.84]
Kreis-210 2000	1/40	1/38		1.2%	0.95[0.06,14.65]
Martinez-Mier 2006	1/20	1/21		1.23%	1.05[0.07,15.68]
Flechner-318 2002	1/31	2/30		1.63%	0.48[0.05,5.06]
Cattaneo 2005	1/10	2/11		1.79%	0.55[0.06,5.18]
Pescovitz 2007	4/30	3/15		4.85%	0.67[0.17,2.6]
Lebranchu-132 2004	9/71	3/74		5.62%	3.13[0.88,11.08]
SYMPHONY 2007	10/190	29/792		18.31%	1.44[0.71,2.9]
Subtotal (95% CI)	**464**	**1053**		**36.84%**	**1.22[0.74,1.99]**
Total events: 28 (TOR-I), 44 (CNI)					
Heterogeneity: Tau²=0; Chi²=5.68, df=8(P=0.68); I²=0%					
Test for overall effect: Z=0.78(P=0.44)					
Total (95% CI)	**997**	**1794**		**100%**	**0.93[0.69,1.26]**
Total events: 69 (TOR-I), 108 (CNI)					
Heterogeneity: Tau²=0; Chi²=11.38, df=14(P=0.66); I²=0%					
Test for overall effect: Z=0.46(P=0.64)					
Test for subgroup differences: Chi²=1.77, df=1 (P=0.18), I²=43.59%					

Analysis 2.2. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 2 Lymphoma/PTLD.



Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pescovitz 2007	0/30	0/15			Not estimable
Groth-207 1999	0/41	0/42			Not estimable
Kreis-210 2000	0/40	0/38			Not estimable
ORION 2011	0/152	1/139		13.16%	0.31[0.01,7.43]
Lebranchu-132 2004	1/71	0/74		13.22%	3.13[0.13,75.46]
Stegall 2003	2/81	1/84		23.65%	2.07[0.19,22.43]
Glotz 2010	2/71	1/70		23.72%	1.97[0.18,21.26]
SYMPHONY 2007	3/399	1/1190		26.25%	8.95[0.93,85.77]
Total (95% CI)	**885**	**1652**		**100%**	**2.47[0.78,7.86]**
Total events: 8 (TOR-I), 4 (CNI)					
Heterogeneity: Tau²=0; Chi²=2.98, df=4(P=0.56); I²=0%					
Test for overall effect: Z=1.53(P=0.13)					

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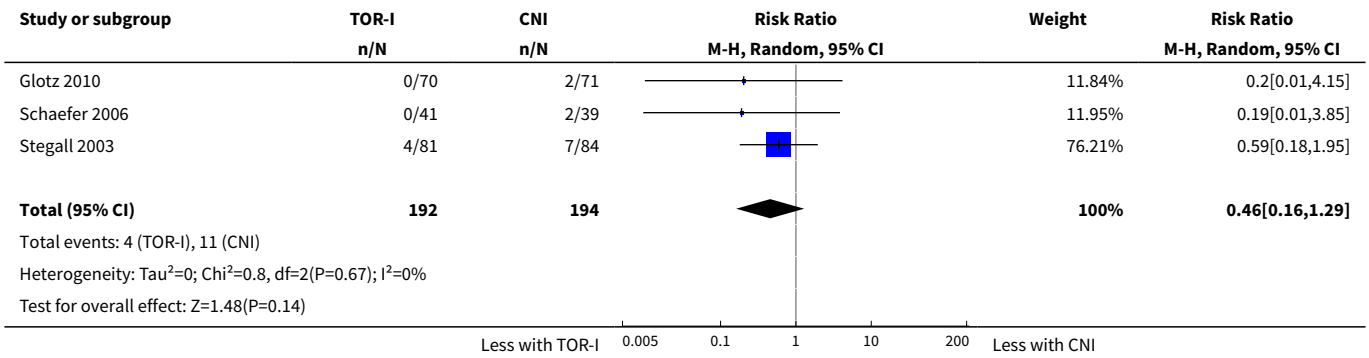
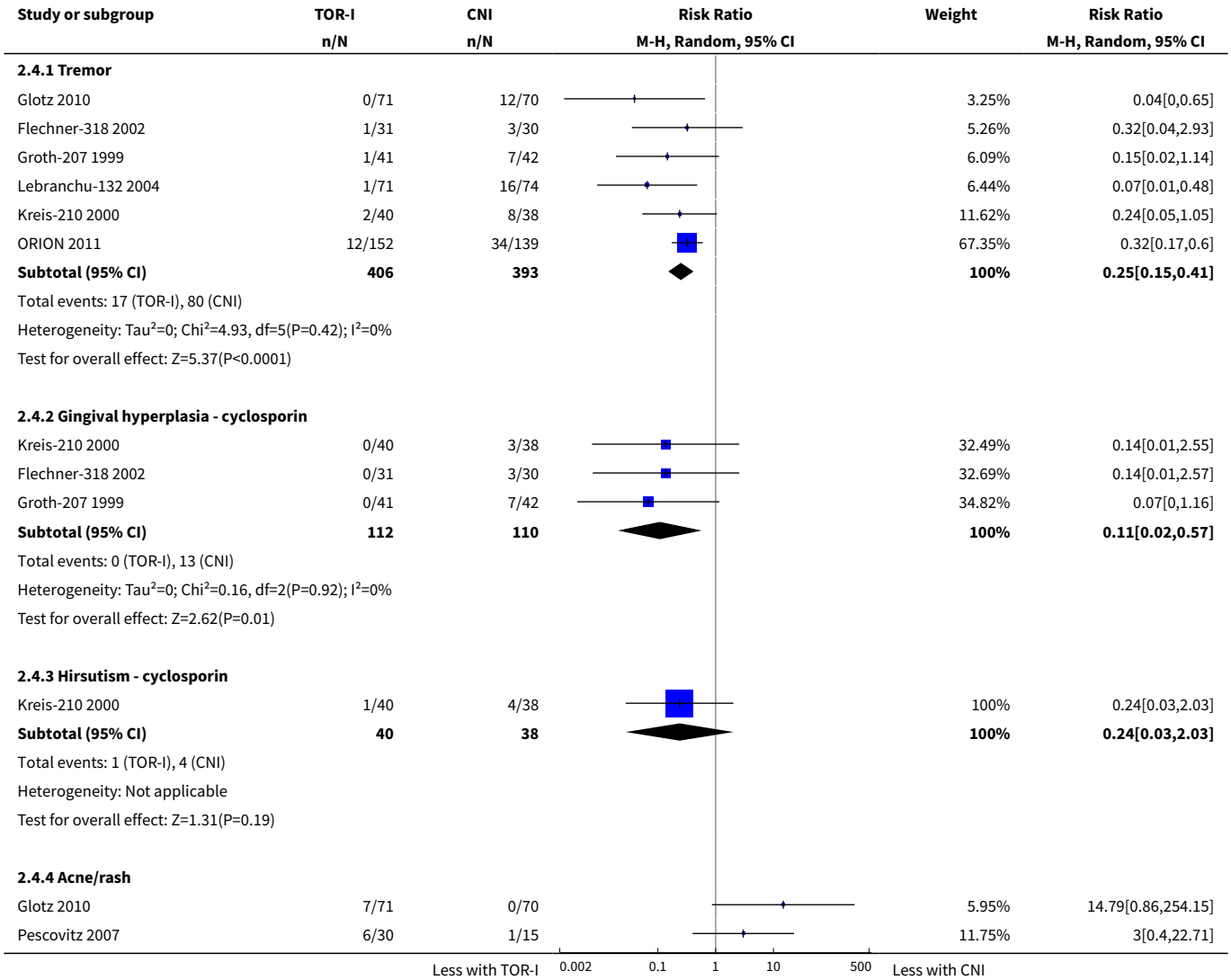
Analysis 2.3. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 3 Number with BK virus infection.



Analysis 2.4. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 4 Adverse cosmetic outcomes.



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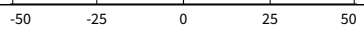
Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ORION 2011	14/152	3/139		32.05%	4.27[1.25,14.54]
Lebranchu-132 2004	13/71	5/74		50.26%	2.71[1.02,7.21]
Subtotal (95% CI)	**324**	**298**		**100%**	**3.51[1.75,7.02]**
Total events: 40 (TOR-I), 9 (CNI)					
Heterogeneity: Tau^2=0; Chi^2=1.44, df=3(P=0.7); I^2=0%					
Test for overall effect: Z=3.55(P=0)					
Test for subgroup differences: Chi^2=40.98, df=1 (P<0.0001), I^2=92.68%					

Less with TOR-I — Less with CNI

Analysis 2.5. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 5 Glomerular filtration rate.

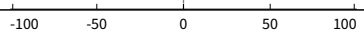
Study or subgroup	TOR-I N	TOR-I Mean(SD)	CNI N	CNI Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cattaneo 2005	11	52 (20)	10	50 (16)		3.41%	2[-13.43,17.43]
Martinez-Mier 2006	18	73 (19)	19	68 (19)		4.53%	5[-7.25,17.25]
Pescovitz 2007	30	83 (24)	15	78 (15)		4.87%	5[-6.46,16.46]
Groth-207 1999	18	70 (17)	23	59 (17)		5.32%	11[0.51,21.49]
FIBRASIC 2009	24	49 (13)	21	53 (21)		5.38%	-4[-14.38,6.38]
Flechner-318 2002	29	81 (24)	29	61 (15)		5.42%	20[9.7,30.3]
Lebranchu-132 2004	71	60 (27)	74	57 (21)		6.73%	3[-4.9,10.9]
Durrbach 2008	33	45 (17)	36	42 (15)		6.9%	3[-4.59,10.59]
Riad 2007	41	60 (15)	39	61 (17)		7.24%	-1[-8.04,6.04]
CALFREE 2006	63	45 (20)	64	42 (15)		7.78%	3[-3.16,9.16]
Glotz 2010	71	68 (20)	70	62 (16)		7.89%	6[0.03,11.97]
ORION 2011	80	66 (20)	88	68 (19)		7.92%	-2[-7.91,3.91]
Stegall 2003	64	56 (16)	65	55 (17)		8.06%	1[-4.7,6.7]
Flechner 2013	185	67 (19)	103	67 (15)		9.05%	0[-3.99,3.99]
SYMPHONY 2007	399	115 (27)	1190	123 (26)		9.52%	-8[-11.03,-4.97]
Total ***	**1137**		**1846**			**100%**	**2.2[-1.29,5.68]**
Heterogeneity: Tau^2=30.89; Chi^2=53.45, df=14(P<0.0001); I^2=73.81%							
Test for overall effect: Z=1.23(P=0.22)							



Higher with CNI — Higher with TOR-I

Analysis 2.6. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 6 Serum creatinine.

Study or subgroup	TOR-I N	TOR-I Mean(SD)	CNI N	CNI Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cattaneo 2005	11	159 (97)	10	141 (35)		1.83%	18[-43.29,79.29]
Durrbach 2008	29	171 (53)	35	171 (65)		6.79%	0[-28.91,28.91]
Flechner-318 2002	29	117 (29)	29	157 (67)		7.73%	-40[-66.57,-13.43]
Kreis-210 2000	26	128 (45)	30	143 (44)		9.29%	-15[-38.39,8.39]
Groth-207 1999	18	116 (38)	24	133 (38)		9.39%	-17[-40.22,6.22]
Martinez-Mier 2006	18	118 (31)	19	115 (28)		12.13%	3[-16.07,22.07]
ORION 2011	86	140 (54)	88	137 (73)		12.14%	3[-16.05,22.05]



Lower with TOR-I — Lower with CNI

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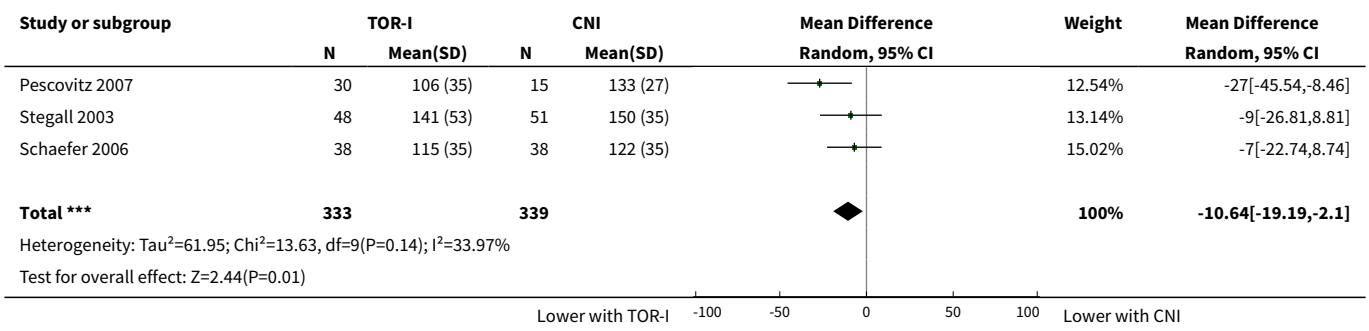
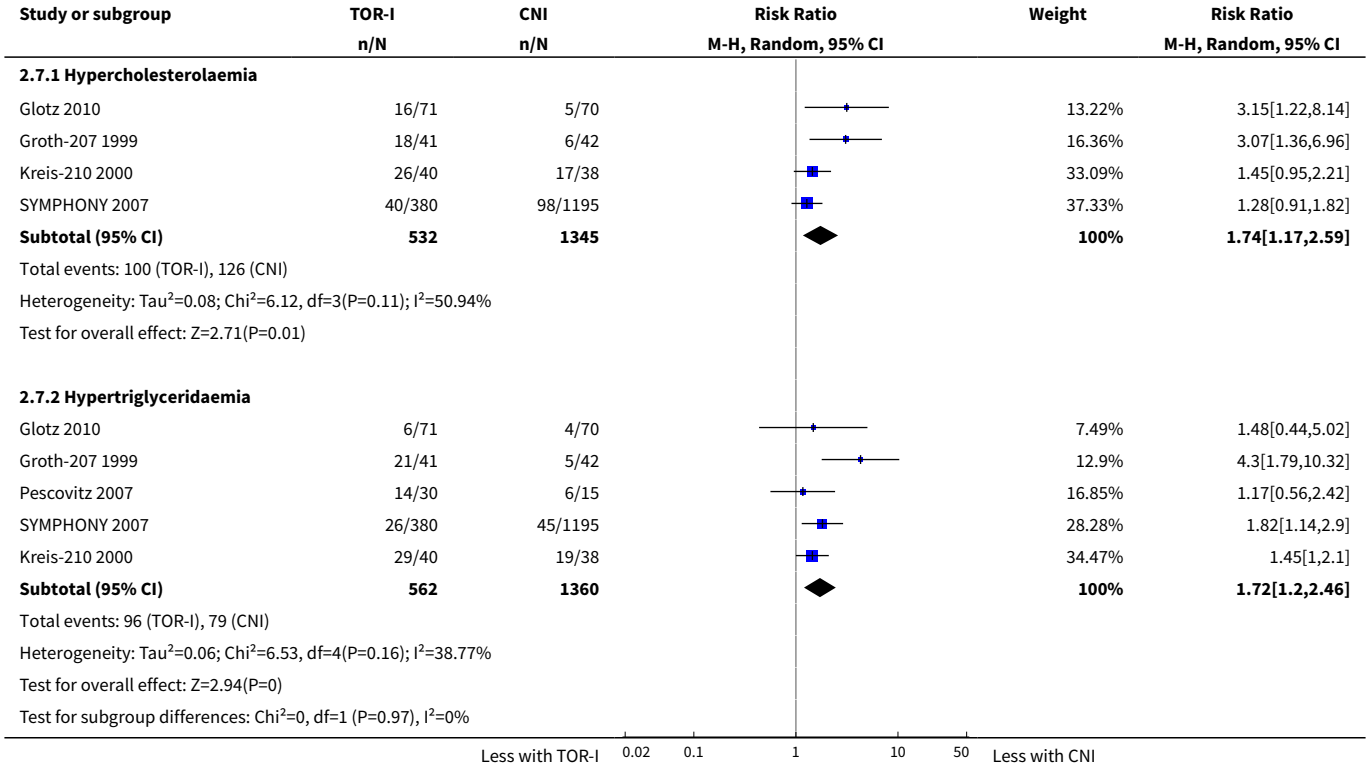
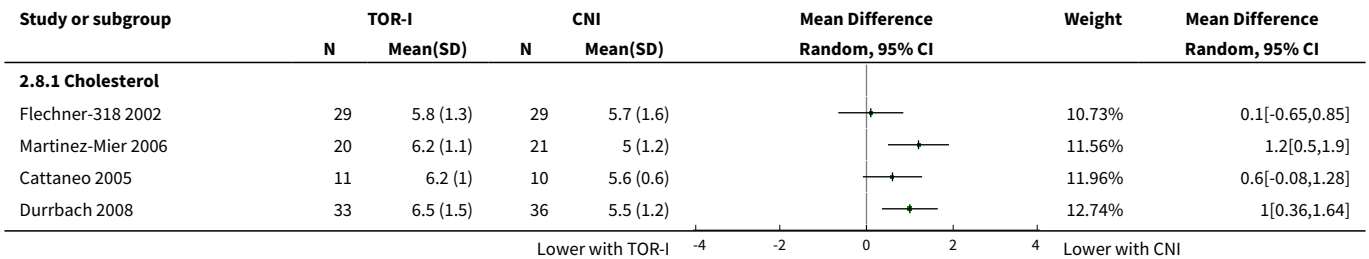


Analysis 2.7. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 7 Number with elevated lipid levels.



Analysis 2.8. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 8 Lipid outcomes.



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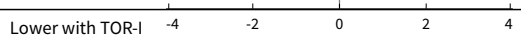
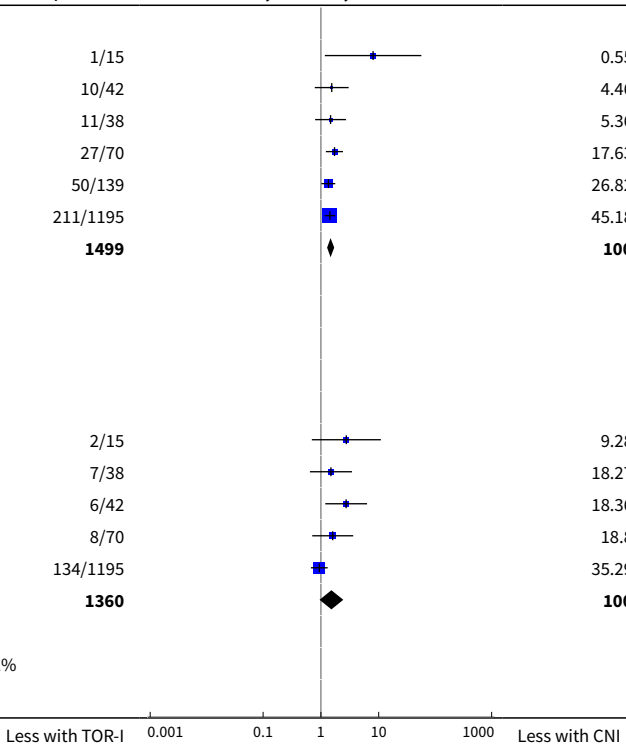
Study or subgroup	TOR-I N	TOR-I Mean(SD)	CNI N	CNI Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Schaefer 2006	41	6.6 (1.6)	39	5.1 (1.1)		13.73%	1.5[0.9,2.1]
Lebranchu-132 2004	71	5.7 (1.1)	74	5.1 (1.3)		19.12%	0.6[0.21,0.99]
Stegall 2003	81	5.7 (1.4)	84	5.2 (0.9)		20.16%	0.5[0.15,0.85]
Subtotal * **	**286**		**293**			**100%**	**0.77[0.45,1.09]**
Heterogeneity: Tau²=0.1; Chi²=13.6, df=6(P=0.03); I²=55.87%							
Test for overall effect: Z=4.77(P<0.0001)							
2.8.2 Triglycerides							
Martinez-Mier 2006	20	2.8 (1.7)	21	1.4 (0.6)		8.43%	1.4[0.61,2.19]
Durrbach 2008	33	2.4 (1.2)	36	2.3 (1.6)		10.13%	0.08[-0.6,0.76]
Flechner-318 2002	29	2.6 (1.5)	29	2.3 (1.1)		10.17%	0.27[-0.41,0.95]
Cattaneo 2005	11	1.6 (0.6)	10	1.9 (0.9)		10.64%	-0.3[-0.95,0.35]
Lebranchu-132 2004	63	2.2 (2.1)	68	1.7 (1.2)		11.64%	0.5[-0.09,1.09]
Schaefer 2006	41	3.1 (1.3)	39	2.3 (1)		13.47%	0.8[0.3,1.3]
Stegall 2003	76	2.8 (1.5)	76	2 (1.2)		15%	0.8[0.37,1.23]
ORION 2011	152	2.5 (0.6)	139	1.7 (1)		20.52%	0.8[0.61,0.99]
Subtotal * **	**425**		**418**			**100%**	**0.57[0.28,0.86]**
Heterogeneity: Tau²=0.1; Chi²=18.85, df=7(P=0.01); I²=62.87%							
Test for overall effect: Z=3.84(P=0)							
Test for subgroup differences: Chi²=0.81, df=1 (P=0.37), I²=0%							



Analysis 2.9. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 9 Number with abnormal haematological values.

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Anaemia					
Pescovitz 2007	16/30	1/15		0.55%	8[1.17,54.72]
Groth-207 1999	15/41	10/42		4.46%	1.54[0.78,3.02]
Kreis-210 2000	17/40	11/38		5.36%	1.47[0.79,2.72]
Glotz 2010	47/71	27/70		17.63%	1.72[1.22,2.41]
ORION 2011	75/155	50/139		26.82%	1.35[1.02,1.77]
SYMPHONY 2007	96/380	211/1195		45.18%	1.43[1.16,1.77]
Subtotal (95% CI)	**717**	**1499**		**100%**	**1.47[1.28,1.7]**
Total events: 266 (TOR-I), 310 (CNI)					
Heterogeneity: Tau²=0; Chi²=4.31, df=5(P=0.51); I²=0%					
Test for overall effect: Z=5.34(P<0.0001)					
2.9.2 Leucopenia					
Pescovitz 2007	11/30	2/15		9.28%	2.75[0.7,10.86]
Kreis-210 2000	11/40	7/38		18.27%	1.49[0.65,3.45]
Groth-207 1999	16/41	6/42		18.36%	2.73[1.19,6.29]
Glotz 2010	13/71	8/70		18.8%	1.6[0.71,3.62]
SYMPHONY 2007	40/380	134/1195		35.29%	0.94[0.67,1.31]
Subtotal (95% CI)	**562**	**1360**		**100%**	**1.52[0.95,2.44]**
Total events: 91 (TOR-I), 157 (CNI)					
Heterogeneity: Tau²=0.14; Chi²=7.96, df=4(P=0.09); I²=49.72%					
Test for overall effect: Z=1.73(P=0.08)					



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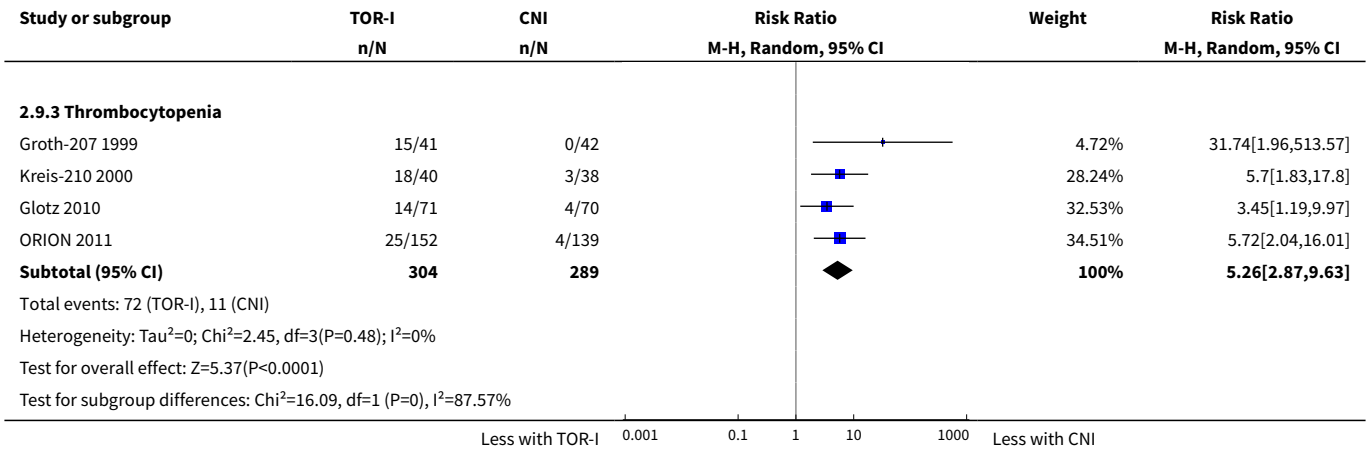
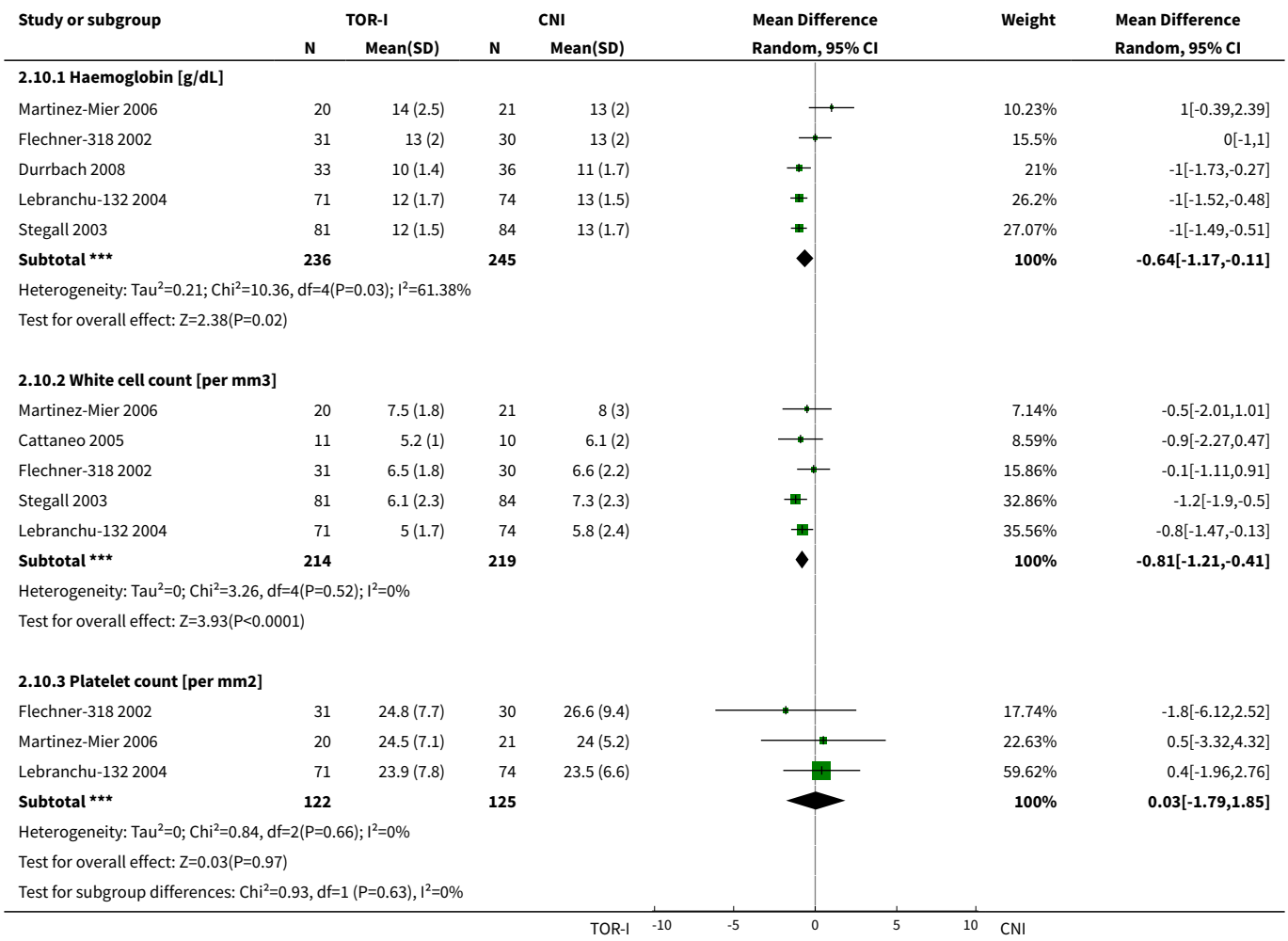


Analysis 2.10. Comparison 2 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): secondary outcomes, Outcome 10 Haematological outcomes.



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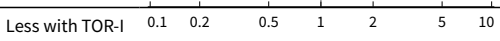
Comparison 3. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): outcomes at 5 to 8 years post transplant

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death	2	206	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.60, 3.08]
2 Total graft loss	2	206	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.44, 1.68]
3 Graft loss censored for death	2	206	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.25, 1.81]
4 Malignancies	2	206	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.20, 1.13]
5 Glomerular filtration rate	2	163	Mean Difference (IV, Random, 95% CI)	13.51 [6.94, 20.08]

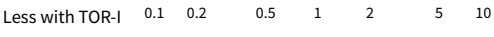
Analysis 3.1. Comparison 3 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): outcomes at 5 to 8 years post transplant, Outcome 1 Death.

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Flechner-318 2002	4/31	3/30		33.78%	1.29[0.31,5.29]
Lebranchu-132 2004	8/71	6/74		66.22%	1.39[0.51,3.8]
Total (95% CI)	**102**	**104**		**100%**	**1.36[0.6,3.08]**
Total events: 12 (TOR-I), 9 (CNI)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=0.73(P=0.47)					



Analysis 3.2. Comparison 3 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): outcomes at 5 to 8 years post transplant, Outcome 2 Total graft loss.

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Flechner-318 2002	5/31	9/30		34.68%	0.54[0.2,1.42]
Lebranchu-132 2004	18/71	17/74		65.32%	1.1[0.62,1.97]
Total (95% CI)	**102**	**104**		**100%**	**0.86[0.44,1.68]**
Total events: 23 (TOR-I), 26 (CNI)					
Heterogeneity: Tau^2=0.09; Chi^2=1.56, df=1(P=0.21); I^2=35.85%					
Test for overall effect: Z=0.44(P=0.66)					



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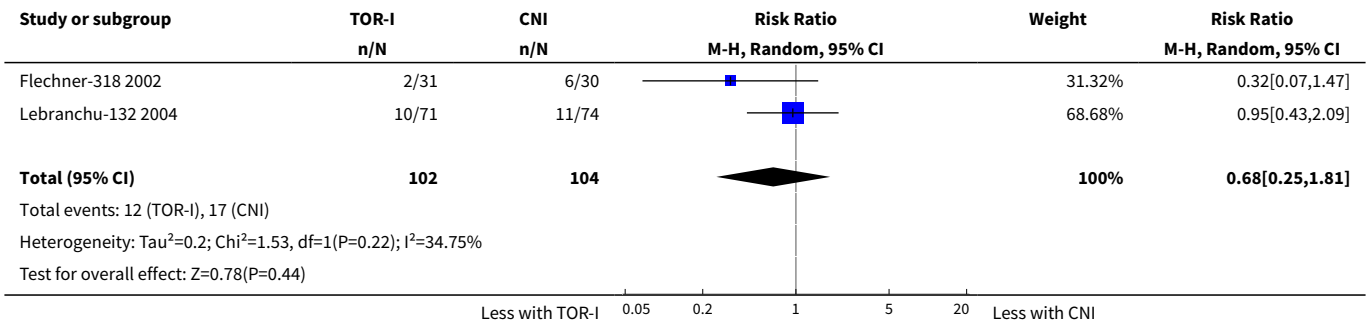
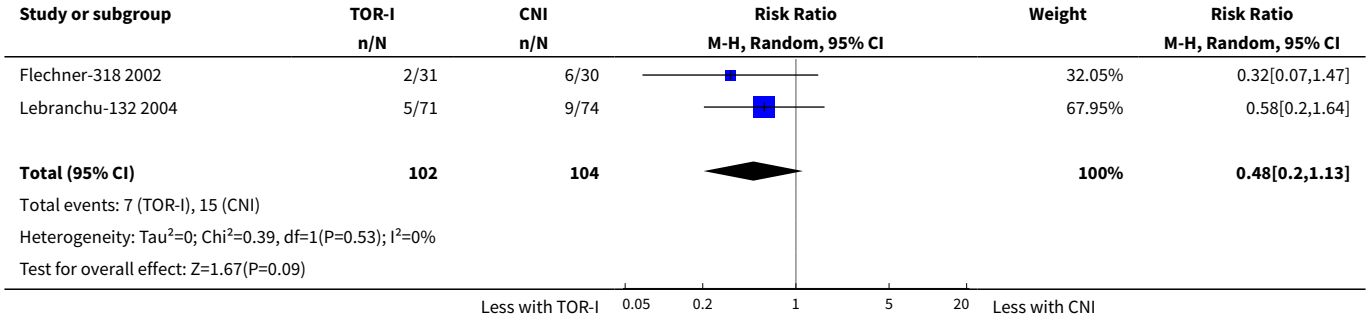
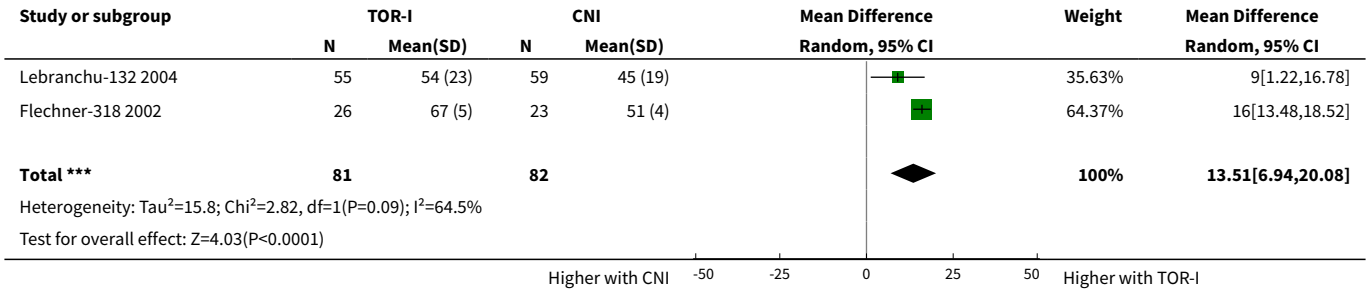
Analysis 3.3. Comparison 3 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): outcomes at 5 to 8 years post transplant, Outcome 3 Graft loss censored for death.



Analysis 3.4. Comparison 3 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): outcomes at 5 to 8 years post transplant, Outcome 4 Malignancies.



Analysis 3.5. Comparison 3 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): outcomes at 5 to 8 years post transplant, Outcome 5 Glomerular filtration rate.



Comparison 4. Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	31	10482	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.84, 1.33]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Total graft loss	27	7626	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.93, 1.40]
3 Graft loss censored for death	26	8966	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.82, 1.45]
4 All acute rejection	31	10075	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.02]
5 Biopsy-proven acute rejection	24	10101	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.81, 1.12]
5.1 TOR-I/reduced CNI versus AM/standard CNI	7	4170	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.87, 1.40]
5.2 TOR-I/standard CNI versus AM/standard CNI	17	5931	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.74, 1.09]
6 CMV infection	25	10049	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.34, 0.58]
7 Adverse wound outcomes	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 All complications	17	6913	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.28, 1.91]
7.2 Lymphocoele	16	8415	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.32, 1.81]
8 All malignancies	17	8799	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.64, 1.07]
9 Number needing to change treatment	25	9747	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.28, 1.90]

Analysis 4.1. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 1 Death.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Stallone 2004	0/21	0/24			Not estimable
Shetty 2015	0/19	0/20			Not estimable
Ciancio 2016	0/15	0/15			Not estimable
Takahashi 2013a	0/61	0/61			Not estimable
Paoletti 2012	0/10	0/20			Not estimable
RECORD 2017	1/76	0/75		0.51%	2.96[0.12,71.55]
Gallon 2006	1/37	0/45		0.52%	3.63[0.15,86.6]
Favi 2009	0/30	1/30		0.52%	0.33[0.01,7.87]
Favi 2012	1/21	0/21		0.53%	3[0.13,69.7]
Gelens 2006	1/18	0/18		0.53%	3[0.13,69.09]
Souza 2017	2/12	0/15		0.6%	6.15[0.32,117.21]
Machado 2001	2/35	1/35		0.94%	2[0.19,21.06]
van Gurp 2010	1/318	3/316		1.02%	0.33[0.03,3.17]
Sampaio 2008	3/50	1/50		1.05%	3[0.32,27.87]
Durlik 2008	2/22	2/40		1.46%	1.82[0.27,12.03]
Anil Kumar 2005	2/75	4/75		1.88%	0.5[0.09,2.65]
Bertoni 2011	3/56	3/50		2.16%	0.89[0.19,4.22]

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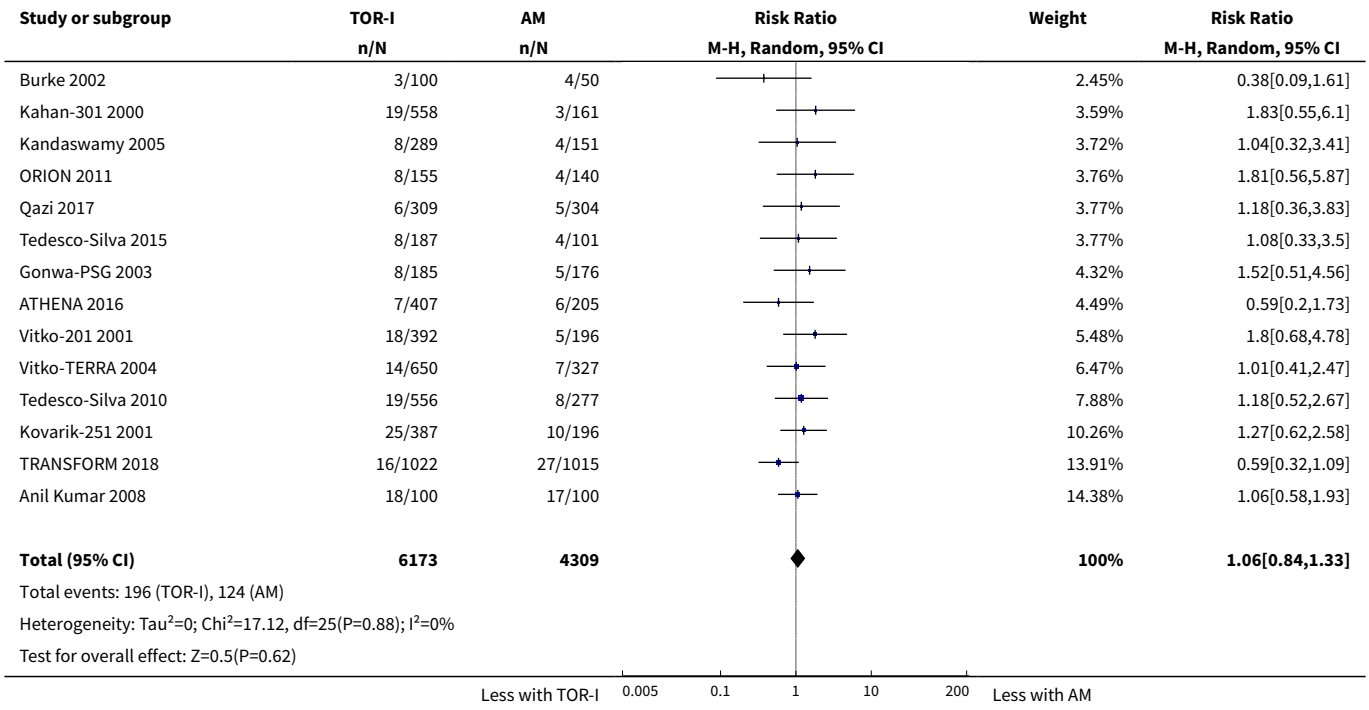
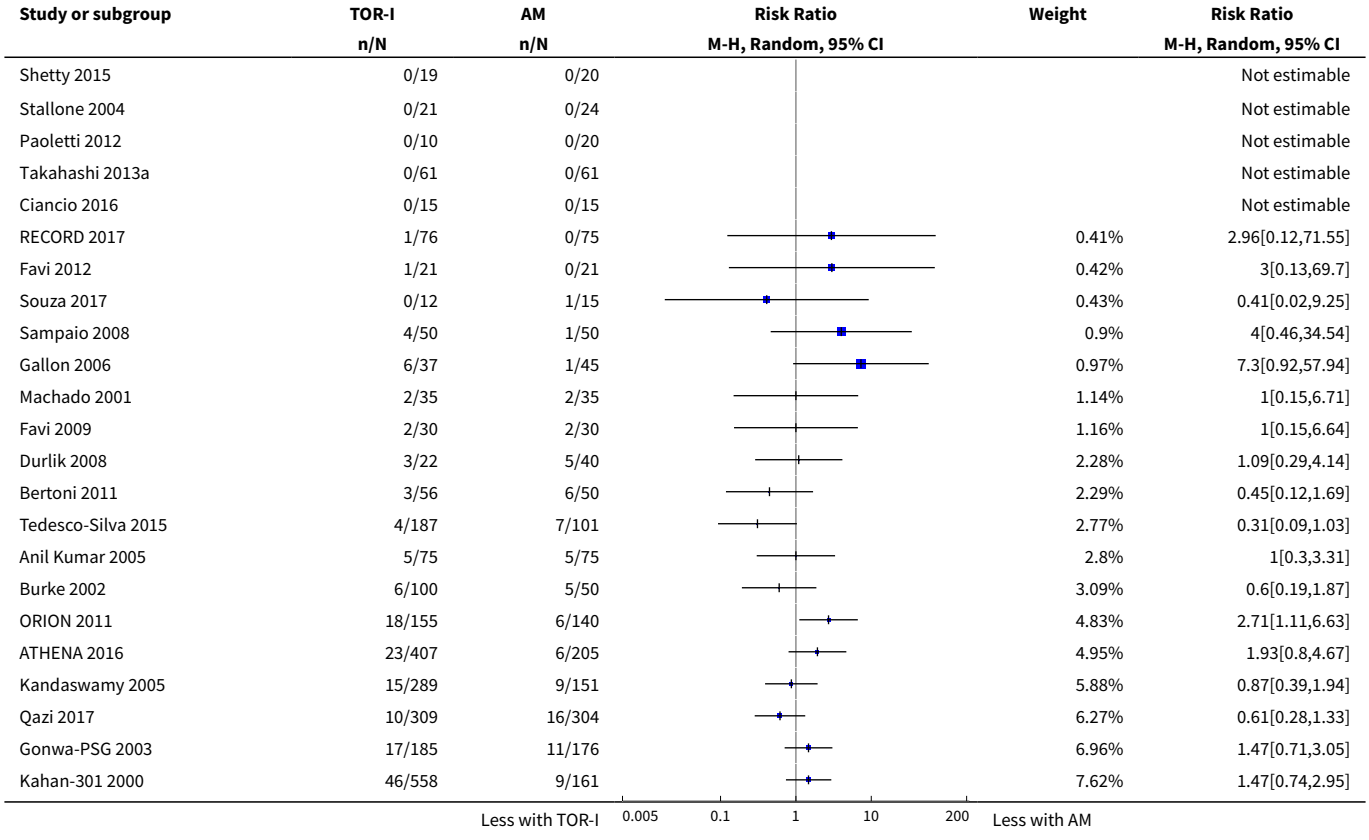


Analysis 4.2. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 2 Total graft loss.



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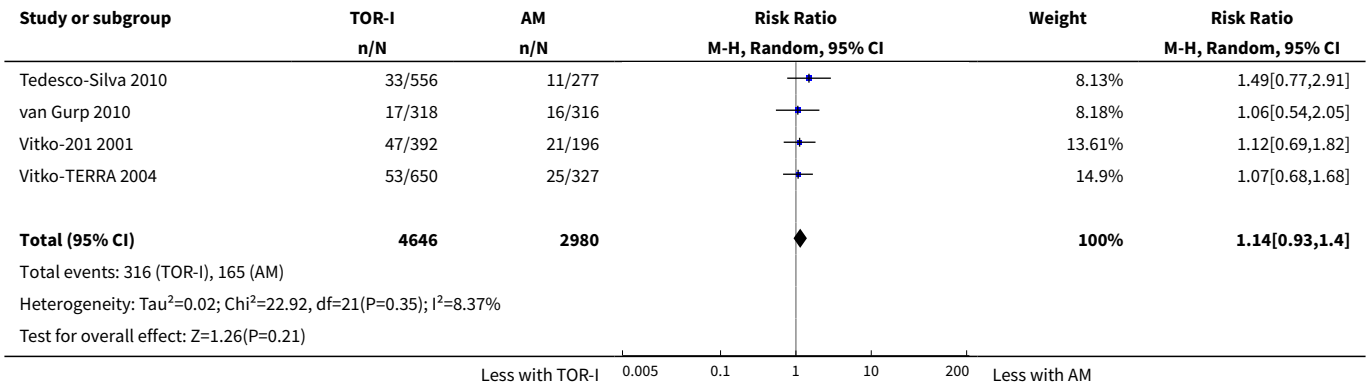
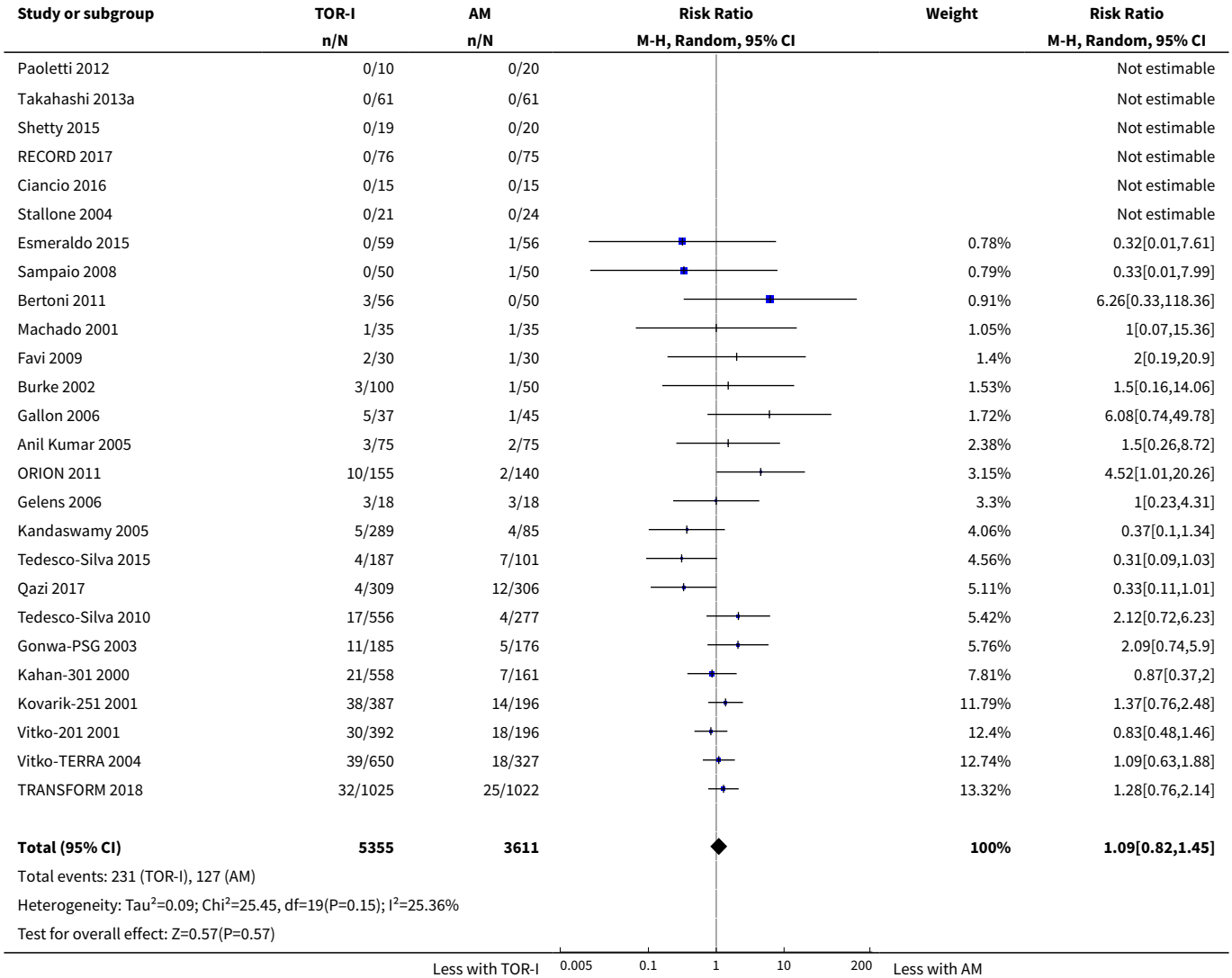


Analysis 4.3. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 3 Graft loss censored for death.



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Analysis 4.4. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 4 All acute rejection.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Favi 2012	0/21	1/21		0.17%	0.33[0.01,7.74]
Shetty 2015	0/19	3/20		0.2%	0.15[0.01,2.72]
Paoletti 2012	1/10	2/20		0.32%	1[0.1,9.75]
Ciancio 2016	1/15	3/15		0.36%	0.33[0.04,2.85]
Esmeraldo 2015	2/59	2/56		0.44%	0.95[0.14,6.51]
Stallone 2004	2/21	2/24		0.47%	1.14[0.18,7.42]
Burke 2002	9/100	2/50		0.72%	2.25[0.51,10.02]
Takahashi 2013a	3/61	5/61		0.82%	0.6[0.15,2.4]
Souza 2017	2/12	7/15		0.84%	0.36[0.09,1.41]
Gelens 2006	3/18	5/18		0.97%	0.6[0.17,2.14]
RECORD 2017	4/76	10/75		1.23%	0.39[0.13,1.2]
Favi 2009	7/30	5/30		1.42%	1.4[0.5,3.92]
Anil Kumar 2005	6/75	9/75		1.54%	0.67[0.25,1.78]
Machado 2001	8/35	7/35		1.8%	1.14[0.46,2.81]
Anil Kumar 2008	6/100	16/100		1.81%	0.38[0.15,0.92]
Bertoni 2011	10/56	9/50		2.12%	0.99[0.44,2.24]
Sampaio 2008	10/50	10/50		2.26%	1[0.46,2.19]
Gallon 2006	11/37	9/45		2.35%	1.49[0.69,3.2]
ORION 2011	20/289	13/140		2.91%	0.75[0.38,1.45]
Durlik 2008	10/22	13/40		3.12%	1.4[0.74,2.65]
Tedesco-Silva 2015	26/187	16/101		3.65%	0.88[0.49,1.56]
Gonwa-PSG 2003	24/185	20/176		3.81%	1.14[0.65,1.99]
Kandaswamy 2005	30/289	28/151		4.68%	0.56[0.35,0.9]
Qazi 2017	59/309	34/305		5.87%	1.71[1.16,2.53]
Vitko-201 2001	84/392	47/196		7.25%	0.89[0.65,1.22]
Tedesco-Silva 2010	97/556	53/277		7.47%	0.91[0.67,1.23]
Kahan-301 2000	102/558	50/161		7.73%	0.59[0.44,0.79]
Kovarik-251 2001	99/387	52/151		7.96%	0.74[0.56,0.98]
van Gurp 2010	82/318	77/316		8.14%	1.06[0.81,1.39]
Vitko-TERRA 2004	133/650	73/327		8.5%	0.92[0.71,1.18]
TRANSFORM 2018	136/1022	127/1015		9.08%	1.06[0.85,1.33]
Total (95% CI)	**5959**	**4116**		**100%**	**0.9[0.79,1.02]**
Total events: 987 (TOR-I), 710 (AM)					
Heterogeneity: Tau^2=0.04; Chi^2=46.21, df=30(P=0.03); I^2=35.07%					
Test for overall effect: Z=1.66(P=0.1)					

Analysis 4.5. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 5 Biopsy-proven acute rejection.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 TOR-I/reduced CNI versus AM/standard CNI					
Paoletti 2012	1/10	2/20		0.48%	1[0.1,9.75]
Takahashi 2013a	3/61	5/61		1.21%	0.6[0.15,2.4]

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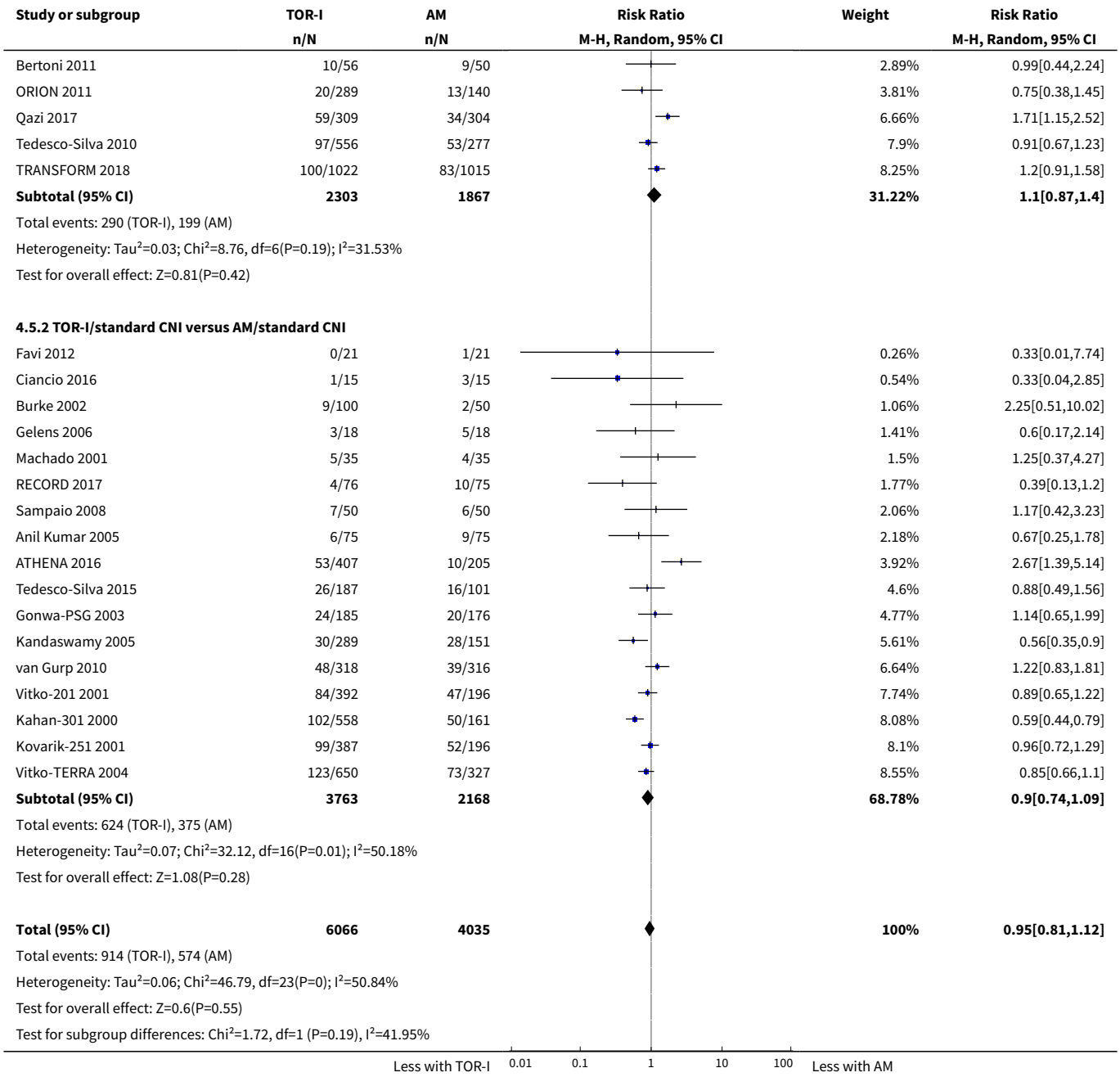
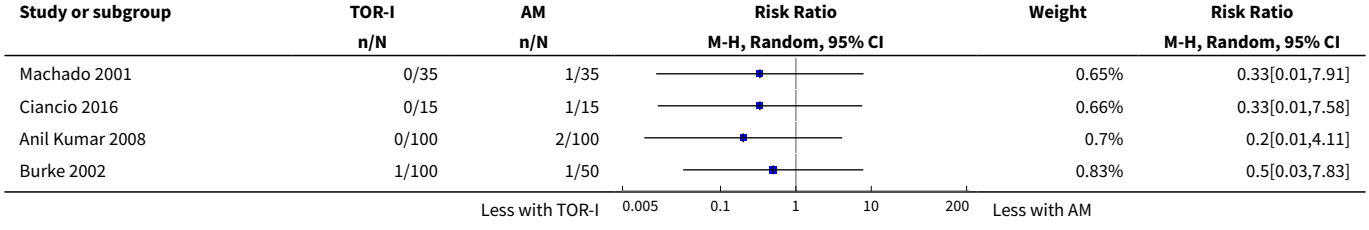


Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bertoni 2011	10/56	9/50		2.89%	0.99[0.44,2.24]
ORION 2011	20/289	13/140		3.81%	0.75[0.38,1.45]
Qazi 2017	59/309	34/304		6.66%	1.71[1.15,2.52]
Tedesco-Silva 2010	97/556	53/277		7.9%	0.91[0.67,1.23]
TRANSFORM 2018	100/1022	83/1015		8.25%	1.2[0.91,1.58]
Subtotal (95% CI)	**2303**	**1867**		**31.22%**	**1.1[0.87,1.4]**
Total events: 290 (TOR-I), 199 (AM)					
Heterogeneity: Tau²=0.03; Chi²=8.76, df=6(P=0.19); I²=31.53%					
Test for overall effect: Z=0.81(P=0.42)					
4.5.2 TOR-I/standard CNI versus AM/standard CNI					
Favi 2012	0/21	1/21		0.26%	0.33[0.01,7.74]
Ciancio 2016	1/15	3/15		0.54%	0.33[0.04,2.85]
Burke 2002	9/100	2/50		1.06%	2.25[0.51,10.02]
Gelens 2006	3/18	5/18		1.41%	0.6[0.17,2.14]
Machado 2001	5/35	4/35		1.5%	1.25[0.37,4.27]
RECORD 2017	4/76	10/75		1.77%	0.39[0.13,1.2]
Sampaio 2008	7/50	6/50		2.06%	1.17[0.42,3.23]
Anil Kumar 2005	6/75	9/75		2.18%	0.67[0.25,1.78]
ATHENA 2016	53/407	10/205		3.92%	2.67[1.39,5.14]
Tedesco-Silva 2015	26/187	16/101		4.6%	0.88[0.49,1.56]
Gonwa-PSG 2003	24/185	20/176		4.77%	1.14[0.65,1.99]
Kandaswamy 2005	30/289	28/151		5.61%	0.56[0.35,0.9]
van Gurp 2010	48/318	39/316		6.64%	1.22[0.83,1.81]
Vitko-201 2001	84/392	47/196		7.74%	0.89[0.65,1.22]
Kahan-301 2000	102/558	50/161		8.08%	0.59[0.44,0.79]
Kovarik-251 2001	99/387	52/196		8.1%	0.96[0.72,1.29]
Vitko-TERRA 2004	123/650	73/327		8.55%	0.85[0.66,1.1]
Subtotal (95% CI)	**3763**	**2168**		**68.78%**	**0.9[0.74,1.09]**
Total events: 624 (TOR-I), 375 (AM)					
Heterogeneity: Tau²=0.07; Chi²=32.12, df=16(P=0.01); I²=50.18%					
Test for overall effect: Z=1.08(P=0.28)					
Total (95% CI)	**6066**	**4035**		**100%**	**0.95[0.81,1.12]**
Total events: 914 (TOR-I), 574 (AM)					
Heterogeneity: Tau²=0.06; Chi²=46.79, df=23(P=0); I²=50.84%					
Test for overall effect: Z=0.6(P=0.55)					
Test for subgroup differences: Chi²=1.72, df=1 (P=0.19), I²=41.95%					

Analysis 4.6. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 6 CMV infection.



Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Machado 2001	0/35	1/35		0.65%	0.33[0.01,7.91]
Ciancio 2016	0/15	1/15		0.66%	0.33[0.01,7.58]
Anil Kumar 2008	0/100	2/100		0.7%	0.2[0.01,4.11]
Burke 2002	1/100	1/50		0.83%	0.5[0.03,7.83]

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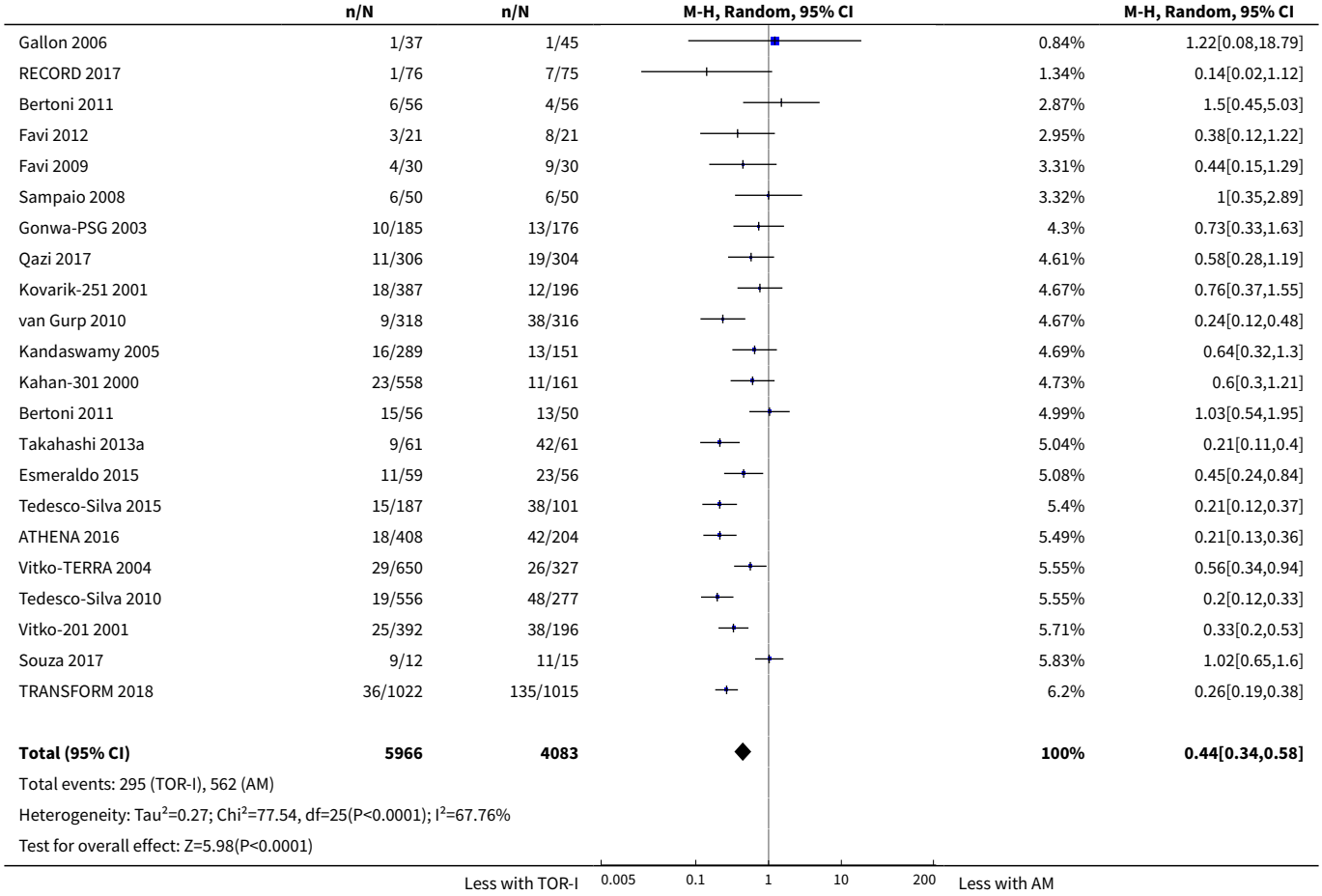
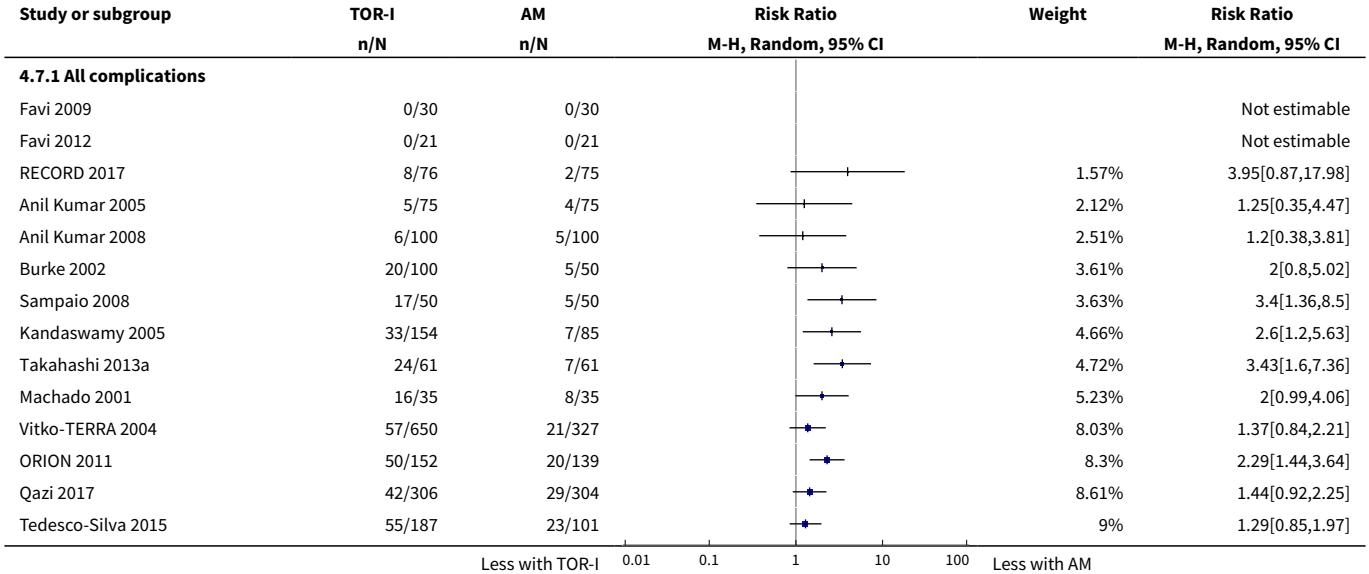


Analysis 4.7. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 7 Adverse wound outcomes.



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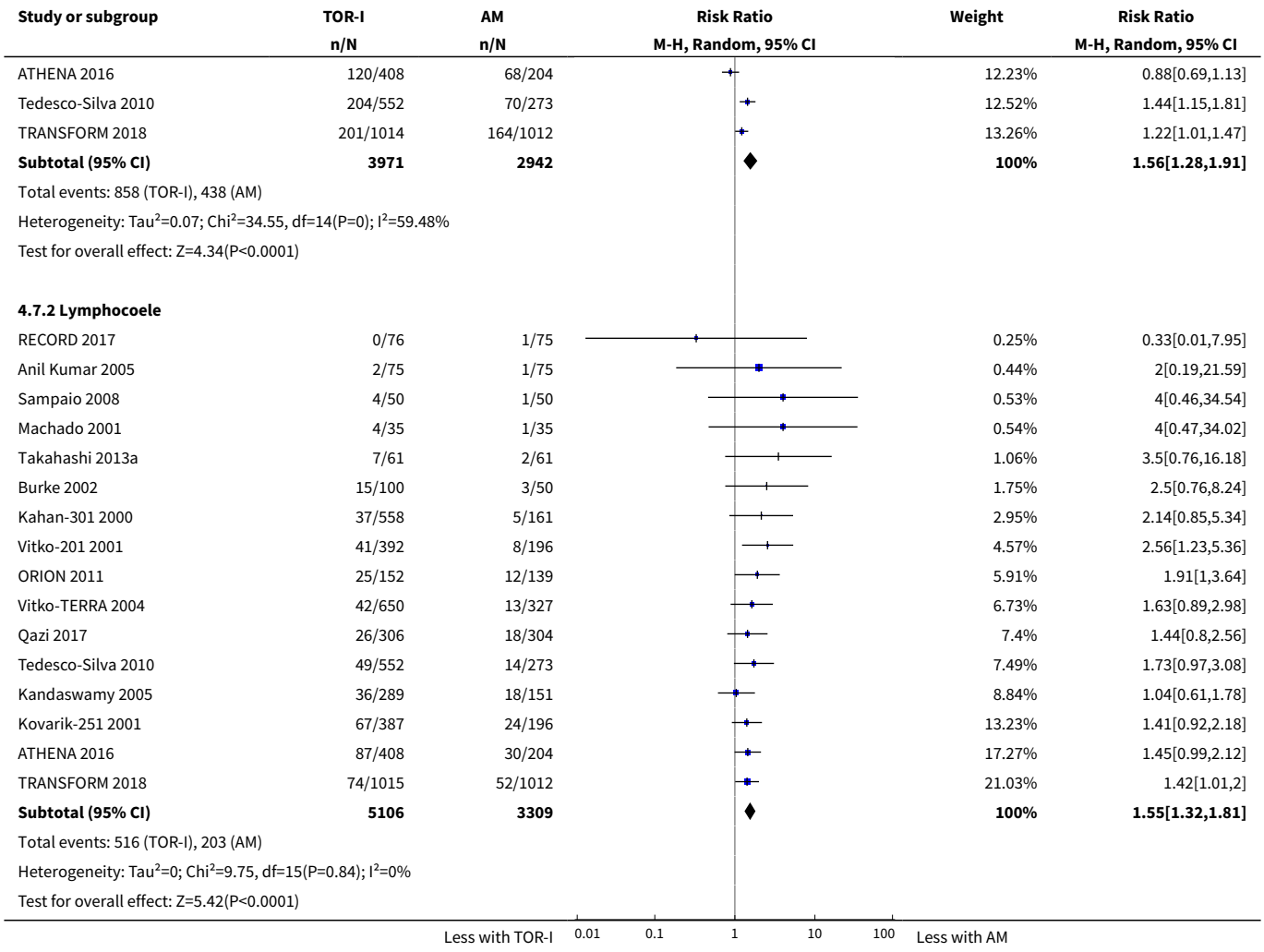
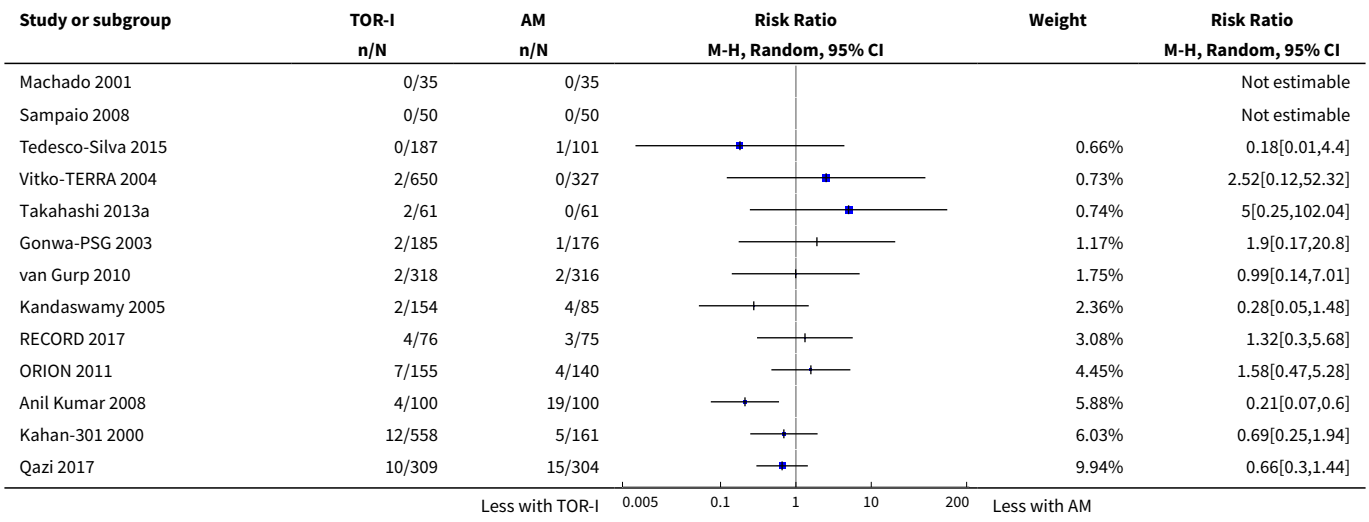


Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ATHENA 2016	120/408	68/204		12.23%	0.88[0.69,1.13]
Tedesco-Silva 2010	204/552	70/273		12.52%	1.44[1.15,1.81]
TRANSFORM 2018	201/1014	164/1012		13.26%	1.22[1.01,1.47]
Subtotal (95% CI)	**3971**	**2942**		**100%**	**1.56[1.28,1.91]**
Total events: 858 (TOR-I), 438 (AM)					
Heterogeneity: Tau²=0.07; Chi²=34.55, df=14(P=0); I²=59.48%					
Test for overall effect: Z=4.34(P<0.0001)					
4.7.2 Lymphocoele					
RECORD 2017	0/76	1/75		0.25%	0.33[0.01,7.95]
Anil Kumar 2005	2/75	1/75		0.44%	2[0.19,21.59]
Sampaio 2008	4/50	1/50		0.53%	4[0.46,34.54]
Machado 2001	4/35	1/35		0.54%	4[0.47,34.02]
Takahashi 2013a	7/61	2/61		1.06%	3.5[0.76,16.18]
Burke 2002	15/100	3/50		1.75%	2.5[0.76,8.24]
Kahan-301 2000	37/558	5/161		2.95%	2.14[0.85,5.34]
Vitko-201 2001	41/392	8/196		4.57%	2.56[1.23,5.36]
ORION 2011	25/152	12/139		5.91%	1.91[1,3.64]
Vitko-TERRA 2004	42/650	13/327		6.73%	1.63[0.89,2.98]
Qazi 2017	26/306	18/304		7.4%	1.44[0.8,2.56]
Tedesco-Silva 2010	49/552	14/273		7.49%	1.73[0.97,3.08]
Kandaswamy 2005	36/289	18/151		8.84%	1.04[0.61,1.78]
Kovarik-251 2001	67/387	24/196		13.23%	1.41[0.92,2.18]
ATHENA 2016	87/408	30/204		17.27%	1.45[0.99,2.12]
TRANSFORM 2018	74/1015	52/1012		21.03%	1.42[1.01,2]
Subtotal (95% CI)	**5106**	**3309**		**100%**	**1.55[1.32,1.81]**
Total events: 516 (TOR-I), 203 (AM)					
Heterogeneity: Tau²=0; Chi²=9.75, df=15(P=0.84); I²=0%					
Test for overall effect: Z=5.42(P<0.0001)					

Analysis 4.8. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 8 All malignancies.



Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Machado 2001	0/35	0/35			Not estimable
Sampaio 2008	0/50	0/50			Not estimable
Tedesco-Silva 2015	0/187	1/101		0.66%	0.18[0.01,4.4]
Vitko-TERRA 2004	2/650	0/327		0.73%	2.52[0.12,52.32]
Takahashi 2013a	2/61	0/61		0.74%	5[0.25,102.04]
Gonwa-PSG 2003	2/185	1/176		1.17%	1.9[0.17,20.8]
van Gurp 2010	2/318	2/316		1.75%	0.99[0.14,7.01]
Kandaswamy 2005	2/154	4/85		2.36%	0.28[0.05,1.48]
RECORD 2017	4/76	3/75		3.08%	1.32[0.3,5.68]
ORION 2011	7/155	4/140		4.45%	1.58[0.47,5.28]
Anil Kumar 2008	4/100	19/100		5.88%	0.21[0.07,0.6]
Kahan-301 2000	12/558	5/161		6.03%	0.69[0.25,1.94]
Qazi 2017	10/309	15/304		9.94%	0.66[0.3,1.44]

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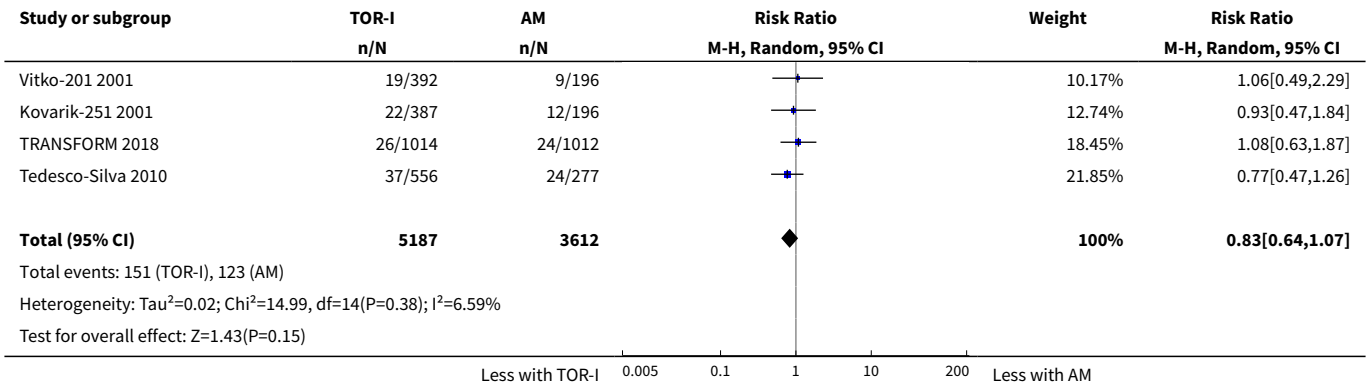
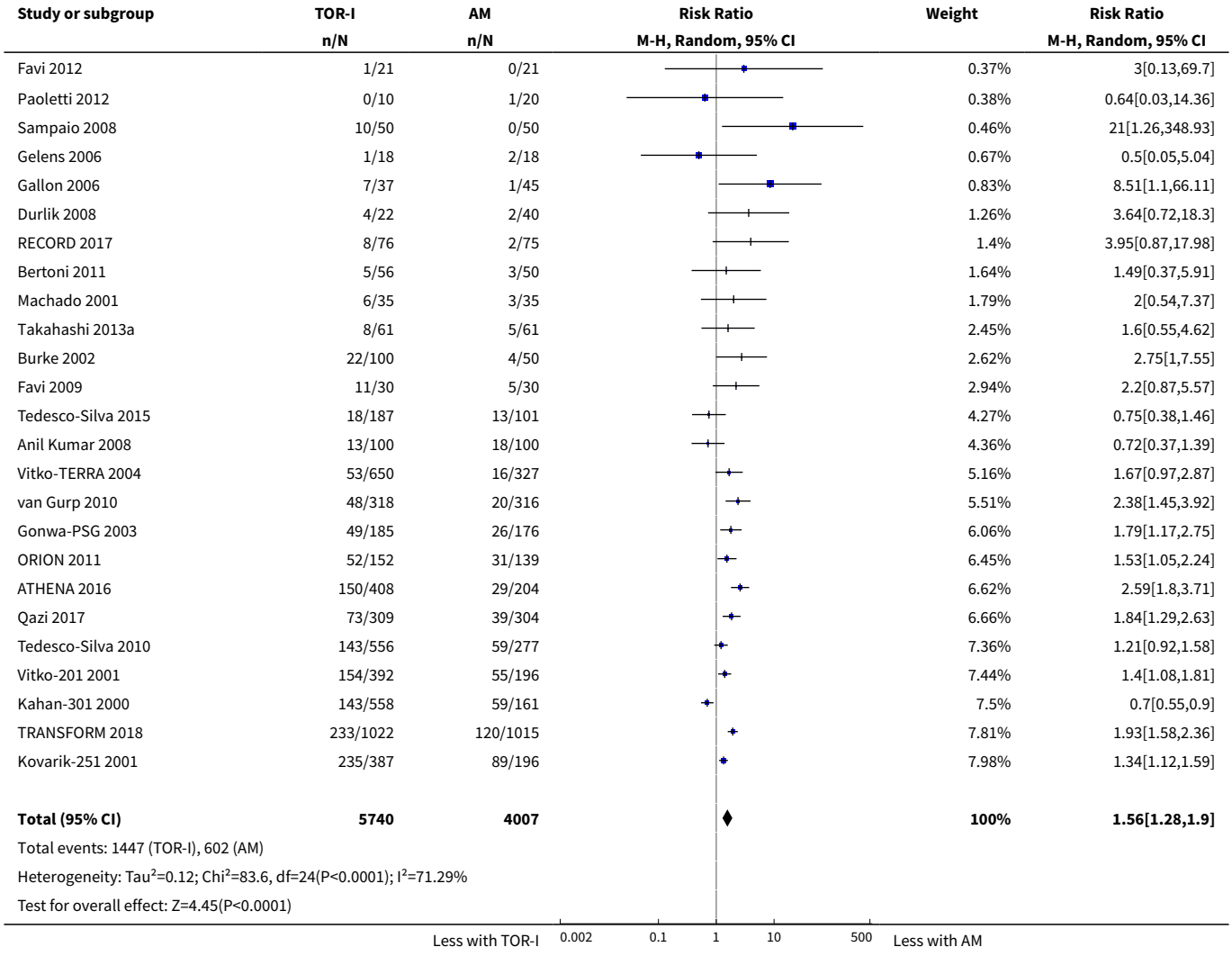


Analysis 4.9. Comparison 4 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): primary outcomes, Outcome 9 Number needing to change treatment.



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Comparison 5. Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New-onset diabetes mellitus	23	8728	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.07, 1.54]
2 Lymphoma/PTLD	14	5415	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.62, 3.72]
3 BK virus infection	12	5152	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.50, 0.76]
4 Tremor and adverse cosmetic outcomes	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Tremor	5	3803	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.66, 1.15]
4.2 Gingival hyperplasia	2	903	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.15, 0.60]
4.3 Hirsutism	2	1542	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.30, 5.28]
4.4 Acne/Rash	5	2022	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.08, 2.81]
5 Glomerular filtration rate	25	8099	Mean Difference (IV, Random, 95% CI)	-2.89 [-4.91, -0.88]
5.1 TOR-I/reduced CNI versus AM/standard CNI	8	3954	Mean Difference (IV, Random, 95% CI)	1.58 [-1.12, 4.28]
5.2 TOR-I/standard CNI versus AM/standard CNI	17	4145	Mean Difference (IV, Random, 95% CI)	-5.45 [-7.55, -3.35]
6 Serum creatinine	16	4453	Mean Difference (IV, Random, 95% CI)	10.22 [1.72, 18.72]
7 Elevated lipid levels	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Hypercholesterolaemia	12	5725	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.48, 2.25]
7.2 Hypertriglyceridaemia	9	4698	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.26, 1.74]
8 Lipid outcomes	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Cholesterol	14	5176	Mean Difference (IV, Random, 95% CI)	0.57 [0.43, 0.71]
8.2 Triglycerides	13	5099	Mean Difference (IV, Random, 95% CI)	0.40 [0.29, 0.51]
9 Abnormal haematological values	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Anaemia	15	8595	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.92, 1.23]
9.2 Leucopenia	15	8396	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.56]
9.3 Thrombocytopenia	8	5028	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.38, 2.79]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
10 Haematological outcomes	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 Haemoglobin [g/dL]	6	1035	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.63, -0.12]
10.2 White cell count [per mm^3]	7	3635	Mean Difference (IV, Random, 95% CI)	0.47 [-0.03, 0.96]
10.3 Platelet count [per mm^2]	6	3569	Mean Difference (IV, Random, 95% CI)	-0.01 [-1.43, 1.41]

Analysis 5.1. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 1 New-onset diabetes mellitus.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Favi 2009	2/30	0/30		0.37%	5[0.25,99.95]
Ciancio 2016	2/15	0/15		0.38%	5[0.26,96.13]
Gallon 2006	2/37	1/45		0.59%	2.43[0.23,25.78]
Favi 2012	2/21	1/21		0.61%	2[0.2,20.41]
Kandaswamy 2005	13/289	1/151		0.79%	6.79[0.9,51.43]
Anil Kumar 2005	2/75	2/75		0.87%	1[0.14,6.91]
Machado 2001	2/35	2/35		0.89%	1[0.15,6.71]
Paoletti 2012	2/10	2/20		0.99%	2[0.33,12.18]
Anil Kumar 2008	4/100	3/100		1.46%	1.33[0.31,5.81]
Takahashi 2013a	7/61	3/61		1.82%	2.33[0.63,8.61]
RECORD 2017	6/76	9/75		3.04%	0.66[0.25,1.76]
van Gurp 2010	5/287	20/278		3.14%	0.24[0.09,0.64]
Sampaio 2008	12/50	6/50		3.55%	2[0.81,4.91]
Burke 2002	22/86	5/37		3.6%	1.89[0.78,4.62]
Tedesco-Silva 2015	24/187	6/101		3.82%	2.16[0.91,5.11]
Gonwa-PSG 2003	15/185	14/176		5.36%	1.02[0.51,2.05]
ORION 2011	27/120	12/110		6.29%	2.06[1.1,3.87]
Kahan-301 2000	49/558	13/161		6.97%	1.09[0.61,1.95]
Qazi 2017	25/309	22/304		7.6%	1.12[0.64,1.94]
Tedesco-Silva 2010	68/556	20/277		9.16%	1.69[1.05,2.73]
ATHENA 2016	65/408	26/204		10.58%	1.25[0.82,1.91]
Vitko-TERRA 2004	64/586	28/295		10.61%	1.15[0.75,1.75]
TRANSFORM 2018	134/1014	122/1012		17.52%	1.1[0.87,1.38]
Total (95% CI)	**5095**	**3633**		**100%**	**1.28[1.07,1.54]**
Total events: 554 (TOR-I), 318 (AM)					
Heterogeneity: Tau^2=0.04; Chi^2=28.3, df=22(P=0.17); I^2=22.26%					
Test for overall effect: Z=2.64(P=0.01)					

Less with TOR-I | Less with AM

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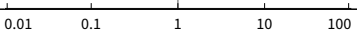
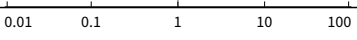
Analysis 5.2. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 2 Lymphoma/PTLD.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Tedesco-Silva 2015	0/187	0/101			Not estimable
Machado 2001	0/35	0/35			Not estimable
Favi 2012	0/21	0/21			Not estimable
Sampaio 2008	0/50	0/50			Not estimable
van Gurp 2010	1/318	0/316		7.89%	2.98[0.12,72.9]
Gonwa-PSG 2003	1/185	0/176		7.9%	2.85[0.12,69.62]
ORION 2011	0/152	1/139		7.91%	0.31[0.01,7.43]
Takahashi 2013a	1/61	0/61		7.97%	3[0.12,72.23]
Vitko-TERRA 2004	2/650	0/327		8.76%	2.52[0.12,52.32]
Kandaswamy 2005	2/289	0/151		8.78%	2.62[0.13,54.24]
Vitko-201 2001	4/392	0/196		9.48%	4.51[0.24,83.37]
Kovarik-251 2001	4/387	0/196		9.48%	4.57[0.25,84.45]
Kahan-301 2000	3/558	1/161		15.84%	0.87[0.09,8.26]
Anil Kumar 2008	1/100	3/100		15.98%	0.33[0.04,3.15]
Total (95% CI)	**3385**	**2030**		**100%**	**1.52[0.62,3.72]**
Total events: 19 (TOR-I), 5 (AM)					
Heterogeneity: Tau^2=0; Chi^2=4.79, df=9(P=0.85); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					



Analysis 5.3. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 3 BK virus infection.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Favi 2012	0/21	0/21			Not estimable
Sampaio 2008	0/50	0/50			Not estimable
Shetty 2015	0/19	1/20		0.43%	0.35[0.02,8.1]
Burke 2002	3/100	0/50		0.49%	3.53[0.19,67.13]
Kandaswamy 2005	1/289	1/151		0.56%	0.52[0.03,8.3]
Ciancio 2016	2/15	1/15		0.81%	2[0.2,19.78]
Takahashi 2013a	2/61	2/61		1.15%	1[0.15,6.87]
RECORD 2017	4/76	9/75		3.31%	0.44[0.14,1.36]
Tedesco-Silva 2010	5/552	9/273		3.62%	0.27[0.09,0.81]
Qazi 2017	34/309	38/306		22.5%	0.89[0.57,1.37]
TRANSFORM 2018	44/1014	81/1012		33.47%	0.54[0.38,0.77]
ATHENA 2016	54/408	46/204		33.66%	0.59[0.41,0.84]
Total (95% CI)	**2914**	**2238**		**100%**	**0.62[0.5,0.76]**
Total events: 149 (TOR-I), 188 (AM)					
Heterogeneity: Tau^2=0; Chi^2=8.47, df=9(P=0.49); I^2=0%					
Test for overall effect: Z=4.58(P<0.0001)					



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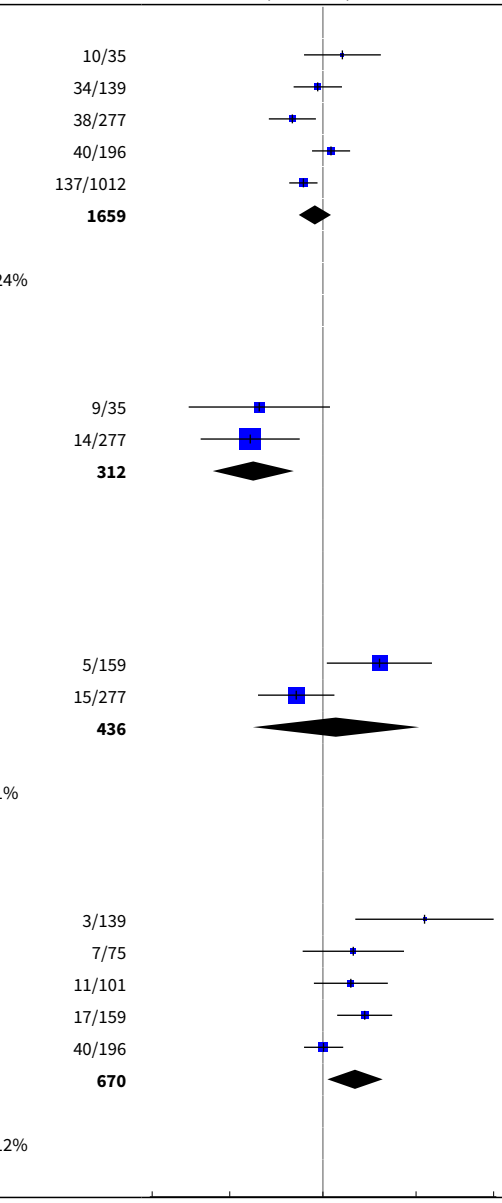
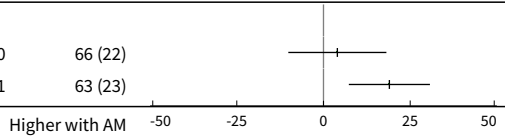
Analysis 5.4. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 4 Tremor and adverse cosmetic outcomes.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.4.1 Tremor					
Machado 2001	14/35	10/35		11.54%	1.4[0.72,2.72]
ORION 2011	34/152	34/139		19.21%	0.91[0.6,1.39]
Tedesco-Silva 2010	45/556	38/277		19.57%	0.59[0.39,0.89]
Kovarik-251 2001	91/387	40/196		22.89%	1.15[0.83,1.6]
TRANSFORM 2018	98/1014	137/1012		26.81%	0.71[0.56,0.91]
Subtotal (95% CI)	**2144**	**1659**		**100%**	**0.87[0.66,1.15]**
Total events: 282 (TOR-I), 259 (AM)					
Heterogeneity: Tau²=0.06; Chi²=10.59, df=4(P=0.03); I²=62.24%					
Test for overall effect: Z=0.99(P=0.32)					
5.4.2 Gingival hyperplasia					
Machado 2001	3/35	9/35		33.03%	0.33[0.1,1.13]
Tedesco-Silva 2010	8/556	14/277		66.97%	0.28[0.12,0.67]
Subtotal (95% CI)	**591**	**312**		**100%**	**0.3[0.15,0.6]**
Total events: 11 (TOR-I), 23 (AM)					
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%					
Test for overall effect: Z=3.37(P=0)					
5.4.3 Hirsutism					
Kahan-301 2000	46/550	5/159		47.69%	2.66[1.07,6.58]
Tedesco-Silva 2010	19/556	15/277		52.31%	0.63[0.33,1.22]
Subtotal (95% CI)	**1106**	**436**		**100%**	**1.25[0.3,5.28]**
Total events: 65 (TOR-I), 20 (AM)					
Heterogeneity: Tau²=0.91; Chi²=6.58, df=1(P=0.01); I²=84.81%					
Test for overall effect: Z=0.31(P=0.76)					
5.4.4 Acne/Rash					
ORION 2011	19/152	3/139		10.76%	5.79[1.75,19.15]
RECORD 2017	12/76	7/75		15.62%	1.69[0.7,4.06]
Tedesco-Silva 2015	33/187	11/101		20.71%	1.62[0.86,3.07]
Kahan-301 2000	121/550	17/159		24.75%	2.06[1.28,3.31]
Kovarik-251 2001	80/387	40/196		28.16%	1.01[0.72,1.42]
Subtotal (95% CI)	**1352**	**670**		**100%**	**1.74[1.08,2.81]**
Total events: 265 (TOR-I), 78 (AM)					
Heterogeneity: Tau²=0.18; Chi²=12.17, df=4(P=0.02); I²=67.12%					
Test for overall effect: Z=2.27(P=0.02)					



Analysis 5.5. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 5 Glomerular filtration rate.

Study or subgroup	TOR-I N	TOR-I Mean(SD)	AM N	AM Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.5.1 TOR-I/reduced CNI versus AM/standard CNI							
Shetty 2015	19	70 (23)	20	66 (22)		1.58%	4[-10.14,18.14]
Bertoni 2011	48	82 (33)	41	63 (23)		2.09%	19[7.31,30.69]



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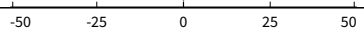
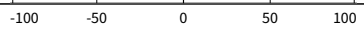
Study or subgroup	TOR-I N	TOR-I Mean(SD)	AM N	AM Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Takahashi 2013a	56	62 (19)	58	56 (15)		4.17%	6[-0.3,12.3]
Stallone 2004	21	62 (11)	24	60 (9)		4.37%	2[-3.92,7.92]
ORION 2011	152	59 (24)	139	62 (24)		4.6%	-3[-8.52,2.52]
Tedesco-Silva 2010	489	56 (20)	248	54 (26)		5.69%	2[-1.69,5.69]
Qazi 2017	309	63 (22)	304	63 (20)		5.9%	0[-3.33,3.33]
TRANSFORM 2018	1014	53 (22)	1012	54 (22)		6.61%	-1[-2.92,0.92]
Subtotal * **	**2108**		**1846**			**34.98%**	**1.58[-1.12,4.28]**
Heterogeneity: Tau²=7.49; Chi²=17.54, df=7(P=0.01); I²=60.08%							
Test for overall effect: Z=1.15(P=0.25)							
5.5.2 TOR-I/standard CNI versus AM/standard CNI							
Burke 2002	93	72 (26)	43	84 (39)		1.83%	-12[-24.8,0.8]
Favi 2009	30	56 (26)	30	58 (24)		1.86%	-2[-14.66,10.66]
Favi 2012	21	52 (21)	21	51 (17)		2.12%	1[-10.56,12.56]
Anil Kumar 2005	48	71 (21)	48	74 (35)		2.12%	-3[-14.55,8.55]
Machado 2001	33	60 (20)	33	68 (25)		2.29%	-8[-18.92,2.92]
Durlik 2008	22	50 (20)	40	62 (21)		2.39%	-12[-22.59,-1.41]
Esmeraldo 2015	59	72 (23)	58	77 (23)		3.19%	-5[-13.34,3.34]
Gallon 2006	34	50 (16)	45	65 (18)		3.55%	-15[-22.52,-7.48]
Sampaio 2008	50	63 (17)	50	68 (16)		4.07%	-5[-11.47,1.47]
Kandaswamy 2005	289	63 (33)	151	65 (28)		4.4%	-2[-7.87,3.87]
Gonwa-PSG 2003	185	71 (27)	176	77 (28)		4.51%	-6[-11.68,-0.32]
Tedesco-Silva 2015	187	63 (21)	101	70 (22)		4.76%	-7[-12.24,-1.76]
RECORD 2017	76	52 (15)	75	53 (15)		5.03%	-1[-5.79,3.79]
Kahan-301 2000	558	59 (25)	161	68 (23)		5.43%	-9[-13.11,-4.89]
van Gurp 2010	289	65 (22)	289	64 (22)		5.75%	1[-2.59,4.59]
Vitko-201 2001	236	51 (19)	133	57 (15)		5.79%	-6[-9.52,-2.48]
ATHENA 2016	310	61 (17)	171	68 (18)		5.91%	-7[-10.3,-3.7]
Subtotal * **	**2520**		**1625**			**65.02%**	**-5.45[-7.55,-3.35]**
Heterogeneity: Tau²=8.25; Chi²=31.67, df=16(P=0.01); I²=49.47%							
Test for overall effect: Z=5.08(P<0.0001)							
Total * **	**4628**		**3471**			**100%**	**-2.89[-4.91,-0.88]**
Heterogeneity: Tau²=15.04; Chi²=80.26, df=24(P<0.0001); I²=70.1%							
Test for overall effect: Z=2.81(P=0)							
Test for subgroup differences: Chi²=16.21, df=1 (P<0.0001), I²=93.83%							



Analysis 5.6. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 6 Serum creatinine.

Study or subgroup	TOR-I N	TOR-I Mean(SD)	AM N	AM Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Burke 2002	93	128 (124)	45	106 (133)		2.48%	22[-24.32,68.32]
Anil Kumar 2005	69	177 (141)	84	168 (71)		3.42%	9[-27.57,45.57]
Stallone 2004	21	141 (44)	24	150 (62)		4.15%	-9[-40.14,22.14]
ORION 2011	119	161 (144)	112	137 (73)		4.45%	24[-5.19,53.19]
Machado 2001	33	159 (53)	33	141 (53)		5.06%	18[-7.57,43.57]
Favi 2009	30	124 (53)	30	141 (44)		5.23%	-17[-41.65,7.65]



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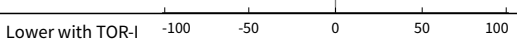
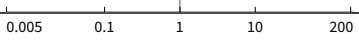
Study or subgroup	TOR-I N	TOR-I Mean(SD)	AM N	AM Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Gonwa-PSG 2003	185	156 (126)	176	127 (40)		6.35%	29[9.91,48.09]
Paoletti 2012	20	-4 (34)	20	-7 (26)		6.42%	3[-15.76,21.76]
Sampaio 2008	50	141 (44)	50	124 (27)		7.39%	17[2.69,31.31]
Shetty 2015	19	70 (23)	20	66 (22)		7.43%	4[-10.14,18.14]
van Gurp 2010	289	138 (58)	289	145 (94)		7.73%	-7[-19.73,5.73]
Kahan-301 2000	558	167 (86)	161	133 (65)		7.82%	34[21.68,46.32]
Tedesco-Silva 2010	489	142 (89)	248	142 (75)		7.84%	0[-12.22,12.22]
Kandaswamy 2005	289	133 (42)	151	141 (65)		8%	-8[-19.44,3.44]
Tedesco-Silva 2015	187	129 (51)	101	115 (44)		8.03%	14[2.73,25.27]
Vitko-201 2001	312	179 (77)	146	149 (36)		8.21%	30[19.65,40.35]
Total * **	**2763**		**1690**			**100%**	**10.22[1.72,18.72]**
Heterogeneity: Tau²=201.12; Chi²=61.54, df=15(P<0.0001); I²=75.63%							
Test for overall effect: Z=2.36(P=0.02)							



Analysis 5.7. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 7 Elevated lipid levels.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.7.1 Hypercholesterolaemia					
Machado 2001	2/35	0/35		0.47%	5[0.25,100.53]
Burke 2002	21/98	1/45		1.06%	9.64[1.34,69.48]
Qazi 2017	25/309	4/304		3.37%	6.15[2.17,17.46]
Takahashi 2013a	7/61	6/61		3.44%	1.17[0.42,3.27]
van Gurp 2010	35/318	18/316		8.69%	1.93[1.12,3.34]
Vitko-TERRA 2004	62/650	18/327		9.47%	1.73[1.04,2.88]
Tedesco-Silva 2010	89/556	17/277		9.66%	2.61[1.58,4.29]
Gallon 2006	20/37	16/45		9.78%	1.52[0.93,2.49]
Gonwa-PSG 2003	54/185	21/176		10.53%	2.45[1.54,3.87]
Vitko-201 2001	119/392	35/196		13.83%	1.7[1.22,2.38]
Kovarik-251 2001	112/387	44/196		14.8%	1.29[0.95,1.75]
Kahan-301 2000	193/558	38/161		14.89%	1.47[1.09,1.98]
Subtotal (95% CI)	**3586**	**2139**		**100%**	**1.83[1.48,2.25]**
Total events: 739 (TOR-I), 218 (AM)					
Heterogeneity: Tau²=0.05; Chi²=20.19, df=11(P=0.04); I²=45.53%					
Test for overall effect: Z=5.67(P<0.0001)					
5.7.2 Hypertriglyceridaemia					
Machado 2001	1/35	0/35		0.26%	3[0.13,71.22]
Shetty 2015	3/19	1/20		0.56%	3.16[0.36,27.78]
Qazi 2017	11/309	3/304		1.61%	3.61[1.02,12.8]
Tedesco-Silva 2010	29/556	7/277		3.73%	2.06[0.92,4.65]
Vitko-TERRA 2004	43/650	11/327		5.62%	1.97[1.03,3.76]
Vitko-201 2001	44/392	13/196		6.56%	1.69[0.93,3.07]
Kahan-301 2000	209/558	38/161		18.9%	1.59[1.18,2.14]
Gonwa-PSG 2003	103/185	67/176		25.56%	1.46[1.16,1.84]
Kovarik-251 2001	252/338	97/160		37.2%	1.23[1.07,1.41]



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Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**3042**	**1656**	♦	**100%**	**1.48[1.26,1.74]**
Total events: 695 (TOR-I), 237 (AM)					
Heterogeneity: Tau^2=0.01; Chi^2=10.82, df=8(P=0.21); I^2=26.09%					
Test for overall effect: Z=4.7(P<0.0001)					
Test for subgroup differences: Chi^2=2.47, df=1 (P=0.12), I^2=59.5%					

Less with TOR-I 0.005 0.1 1 10 200 Less with AM

Analysis 5.8. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 8 Lipid outcomes.

Study or subgroup	TOR-I N	TOR-I Mean(SD)	AM N	AM Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.8.1 Cholesterol							
Machado 2001	16	5.9 (1.4)	18	5.3 (1.2)		2.32%	0.63[-0.23,1.49]
Sampaio 2008	50	5.6 (1.8)	38	4.9 (1.3)		3.71%	0.7[0.06,1.34]
Paoletti 2012	10	0.9 (0.6)	20	-0.4 (0.9)		4.71%	1.24[0.7,1.78]
Favi 2009	30	6.1 (1.1)	30	5.3 (1.1)		4.74%	0.76[0.22,1.3]
Kahan-301 2000	558	6.5 (2.8)	161	5.8 (2.9)		5.09%	0.66[0.15,1.17]
Burke 2002	91	5.2 (1)	38	5 (1.3)		5.57%	0.18[-0.29,0.65]
Bertoni 2011	48	5.7 (1.2)	41	5.4 (1)		5.72%	0.31[-0.15,0.77]
Favi 2012	21	5.5 (1)	21	5.4 (0.1)		6.16%	0.1[-0.34,0.54]
Tedesco-Silva 2015	187	5.6 (1.2)	101	4.8 (1.3)		8.78%	0.85[0.55,1.15]
Kandaswamy 2005	154	4.9 (1.1)	85	4.3 (1.1)		9.22%	0.57[0.29,0.85]
Gonwa-PSG 2003	185	5.6 (1.6)	176	5 (1)		9.54%	0.67[0.4,0.94]
Tedesco-Silva 2010	321	5.6 (1.4)	174	4.9 (1.5)		9.76%	0.74[0.48,1]
van Gurp 2010	285	5.2 (1.4)	291	5 (1.1)		11.19%	0.2[-0.01,0.41]
TRANSFORM 2018	1014	5.5 (1.4)	1012	4.9 (1.1)		13.49%	0.59[0.48,0.7]
Subtotal ***	**2970**		**2206**		◆	**100%**	**0.57[0.43,0.71]**
Heterogeneity: Tau^2=0.04; Chi^2=32.87, df=13(P=0); I^2=60.45%							
Test for overall effect: Z=7.83(P<0.0001)							
5.8.2 Triglycerides							
Sampaio 2008	50	2.9 (2.3)	50	2.6 (2.2)		1.55%	0.35[-0.52,1.22]
Kahan-301 2000	558	3.4 (4.8)	161	2.6 (5)		1.58%	0.8[-0.06,1.66]
Favi 2009	30	2.2 (1)	30	2 (1.9)		1.94%	0.23[-0.54,1]
Favi 2012	21	2 (1.3)	21	1.8 (1.2)		2.03%	0.2[-0.55,0.95]
Paoletti 2012	10	0.6 (0.7)	20	0.1 (0.6)		3.9%	0.53[0.01,1.05]
Machado 2001	16	2.6 (0.6)	18	2.1 (0.9)		4.19%	0.56[0.06,1.06]
Kandaswamy 2005	154	2.5 (2)	85	2.3 (1.4)		5.3%	0.21[-0.22,0.64]
Gonwa-PSG 2003	185	2.8 (1.9)	176	2.2 (1.5)		7.04%	0.58[0.22,0.94]
Tedesco-Silva 2015	187	2.6 (1.9)	101	1.9 (1.1)		7.28%	0.65[0.3,1]
Tedesco-Silva 2010	321	2.5 (1.7)	174	2 (1.3)		10.19%	0.52[0.25,0.79]
van Gurp 2010	285	2.3 (1.6)	291	2.1 (1.5)		10.92%	0.2[-0.05,0.45]
TRANSFORM 2018	1014	2.3 (1.7)	1012	1.8 (1)		19.33%	0.47[0.35,0.59]
Burke 2002	91	2 (0)	38	1.7 (0)		24.75%	0.27[0.26,0.28]
Subtotal ***	**2922**		**2177**		◆	**100%**	**0.4[0.29,0.51]**
Heterogeneity: Tau^2=0.01; Chi^2=25.57, df=12(P=0.01); I^2=53.07%							
Test for overall effect: Z=7.05(P<0.0001)							
Test for subgroup differences: Chi^2=3.21, df=1 (P=0.07), I^2=68.8%							

Lower with TOR-I -2 -1 0 1 2 Lower with AM

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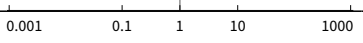
Analysis 5.9. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 9 Abnormal haematological values.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.9.1 Anaemia					
Gonwa-PSG 2003	8/185	1/176		0.48%	7.61[0.96,60.23]
Gallon 2006	6/37	8/45		1.91%	0.91[0.35,2.39]
Machado 2001	7/35	10/35		2.38%	0.7[0.3,1.63]
Anil Kumar 2008	15/100	39/100		4.64%	0.38[0.23,0.65]
Tedesco-Silva 2015	44/187	18/101		5.03%	1.32[0.81,2.16]
van Gurp 2010	52/318	68/316		7.42%	0.76[0.55,1.05]
ATHENA 2016	114/408	44/204		7.78%	1.3[0.96,1.76]
Kovarik-251 2001	138/387	42/196		7.87%	1.66[1.23,2.25]
ORION 2011	62/152	50/139		7.98%	1.13[0.85,1.52]
Qazi 2017	85/306	69/304		8.3%	1.22[0.93,1.61]
Vitko-201 2001	107/392	63/196		8.57%	0.85[0.65,1.1]
Vitko-TERRA 2004	148/650	73/327		8.81%	1.02[0.8,1.31]
Tedesco-Silva 2010	166/556	68/277		8.88%	1.22[0.95,1.55]
Kandaswamy 2005	162/289	67/151		9.54%	1.26[1.03,1.55]
TRANSFORM 2018	245/1014	249/1012		10.42%	0.98[0.84,1.14]
Subtotal (95% CI)	**5016**	**3579**		**100%**	**1.06[0.92,1.23]**
Total events: 1359 (TOR-I), 869 (AM)					
Heterogeneity: Tau^2=0.05; Chi^2=42.8, df=14(P<0.0001); I^2=67.29%					
Test for overall effect: Z=0.82(P=0.41)					
5.9.2 Leucopenia					
Shetty 2015	0/19	1/20		0.72%	0.35[0.02,8.1]
Takahashi 2013a	0/61	2/61		0.78%	0.2[0.01,4.08]
Machado 2001	0/35	5/35		0.86%	0.09[0.01,1.58]
Kandaswamy 2005	35/289	0/151		0.9%	37.21[2.3,602.47]
Gallon 2006	2/37	6/45		2.65%	0.41[0.09,1.89]
Qazi 2017	5/306	8/304		4.51%	0.62[0.21,1.88]
Tedesco-Silva 2015	5/187	10/101		4.9%	0.27[0.09,0.77]
van Gurp 2010	5/318	27/316		5.68%	0.18[0.07,0.47]
Kovarik-251 2001	8/387	14/196		6.49%	0.29[0.12,0.68]
Tedesco-Silva 2010	15/556	33/277		9.65%	0.23[0.13,0.41]
Kahan-301 2000	49/558	19/161		11.14%	0.74[0.45,1.23]
Vitko-TERRA 2004	33/650	32/327		11.69%	0.52[0.32,0.83]
Gonwa-PSG 2003	25/185	43/176		12.04%	0.55[0.35,0.87]
ATHENA 2016	31/408	39/204		12.16%	0.4[0.26,0.62]
TRANSFORM 2018	94/1014	192/1012		15.83%	0.49[0.39,0.62]
Subtotal (95% CI)	**5010**	**3386**		**100%**	**0.43[0.33,0.56]**
Total events: 307 (TOR-I), 431 (AM)					
Heterogeneity: Tau^2=0.11; Chi^2=28.66, df=14(P=0.01); I^2=51.14%					
Test for overall effect: Z=6.09(P<0.0001)					
5.9.3 Thrombocytopenia					
Tedesco-Silva 2015	0/187	1/101		1.2%	0.18[0.01,4.4]
Machado 2001	1/35	0/35		1.22%	3[0.13,71.22]
Gonwa-PSG 2003	9/185	2/176		5.03%	4.28[0.94,19.54]
Kandaswamy 2005	7/289	4/151		7.59%	0.91[0.27,3.07]



Less with TOR-I Less with AM

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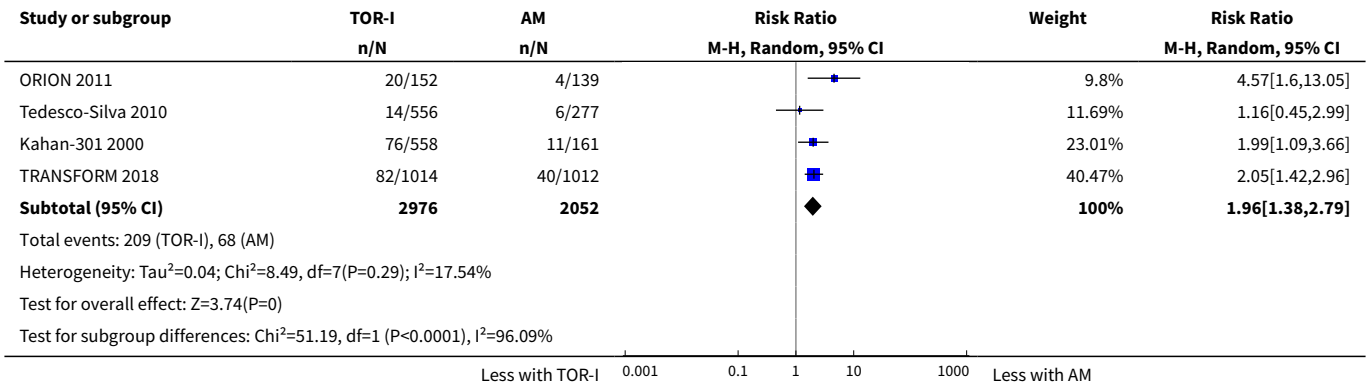
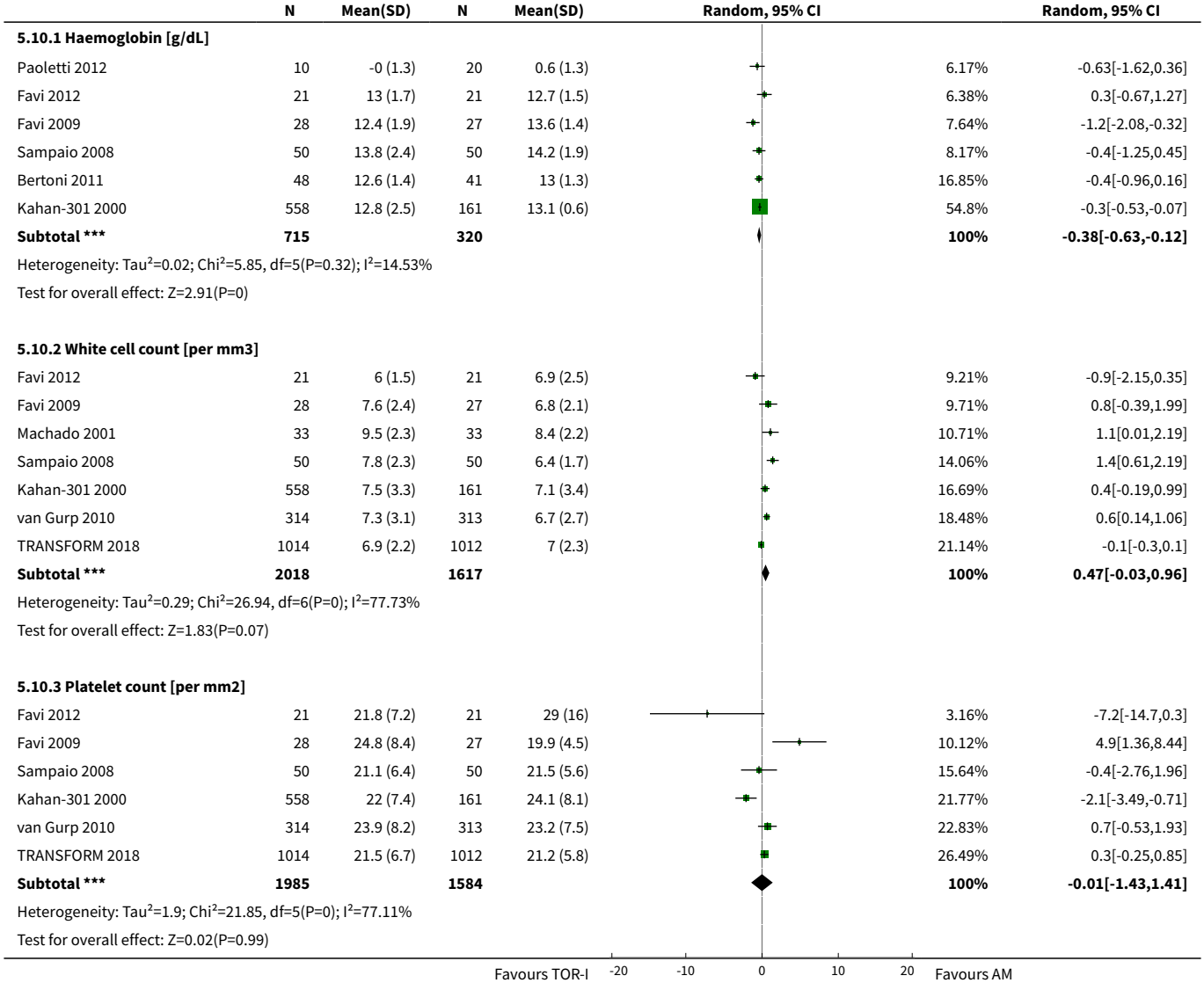


Analysis 5.10. Comparison 5 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): secondary outcomes, Outcome 10 Haematological outcomes.



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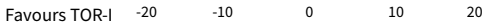
Study or subgroup	TOR-I N	TOR-I Mean(SD)	AM N	AM Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=8.8, df=1 (P=0.01), I²=77.27%							

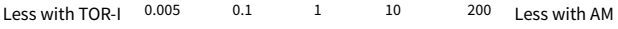


Comparison 6. Target of rapamycin inhibitors (TOR-I) versus antimetabolite (AM): outcomes at 5 to 8 years post-transplant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	5	791	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.72, 1.39]
2 Total graft loss	5	791	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.73, 1.60]
3 Graft loss censored for death	5	791	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.51, 2.00]
4 Malignancies	3	617	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.47, 1.05]
5 GFR	5	534	Mean Difference (IV, Random, 95% CI)	-7.21 [-19.50, 5.08]

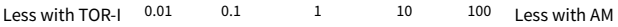
Analysis 6.1. Comparison 6 Target of rapamycin inhibitors (TOR-I) versus antimetabolite (AM): outcomes at 5 to 8 years post-transplant, Outcome 1 Death.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Takahashi 2013a	0/13	1/11		1.1%	0.29[0.01,6.38]
Gallon 2006	3/37	0/45		1.24%	8.47[0.45,158.99]
Tedesco-Silva 2010	9/66	5/29		10.59%	0.79[0.29,2.15]
Burke 2002	20/100	7/50		17%	1.43[0.65,3.15]
Kandaswamy 2005	60/300	30/140		70.07%	0.93[0.63,1.38]
Total (95% CI)	**516**	**275**		**100%**	**1[0.72,1.39]**
Total events: 92 (TOR-I), 43 (AM)					
Heterogeneity: Tau²=0; Chi²=3.82, df=4(P=0.43); I²=0%					
Test for overall effect: Z=0(P=1)					



Analysis 6.2. Comparison 6 Target of rapamycin inhibitors (TOR-I) versus antimetabolite (AM): outcomes at 5 to 8 years post-transplant, Outcome 2 Total graft loss.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Takahashi 2013a	0/13	1/11		1.53%	0.29[0.01,6.38]
Gallon 2006	11/37	4/45		10.77%	3.34[1.16,9.64]



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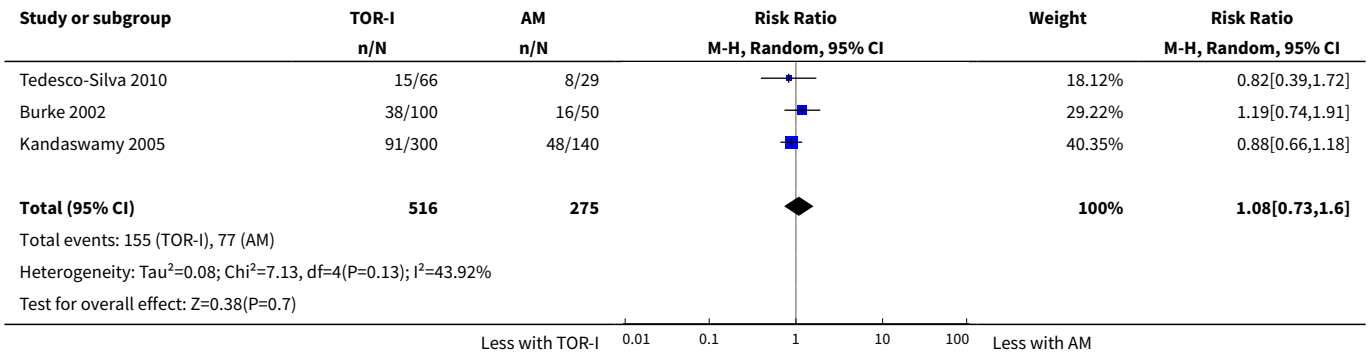
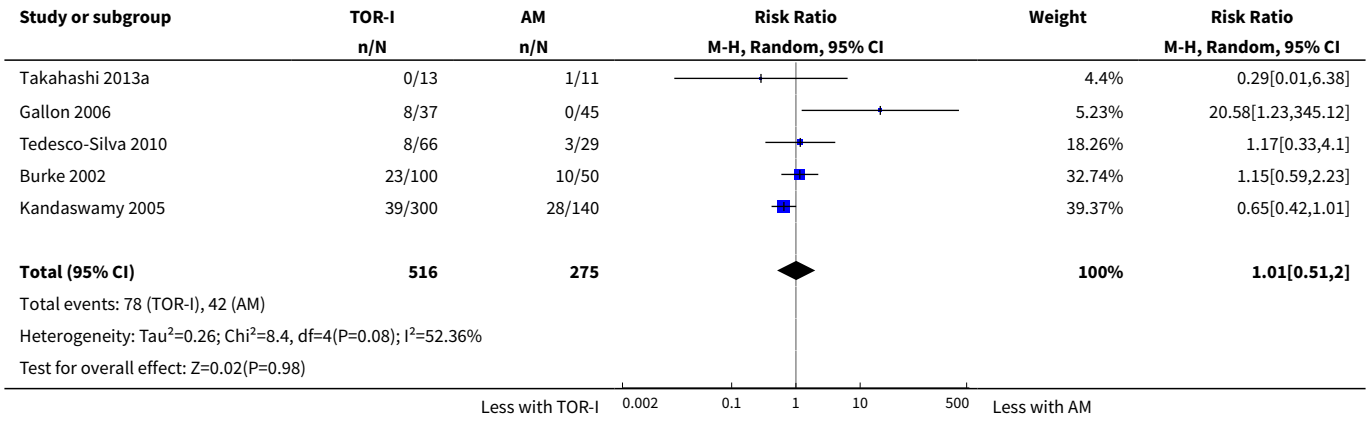
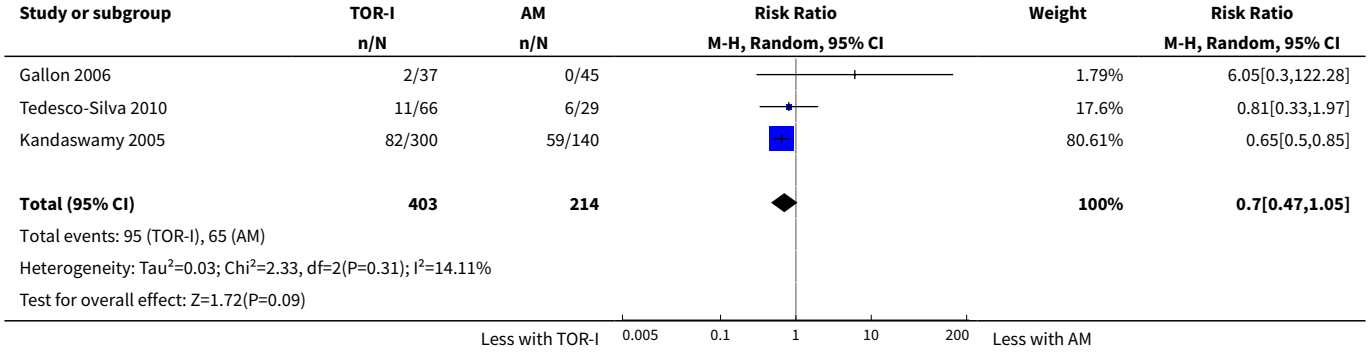


Analysis 6.3. Comparison 6 Target of rapamycin inhibitors (TOR-I) versus antimetabolite (AM): outcomes at 5 to 8 years post-transplant, Outcome 3 Graft loss censored for death.



Analysis 6.4. Comparison 6 Target of rapamycin inhibitors (TOR-I) versus antimetabolite (AM): outcomes at 5 to 8 years post-transplant, Outcome 4 Malignancies.



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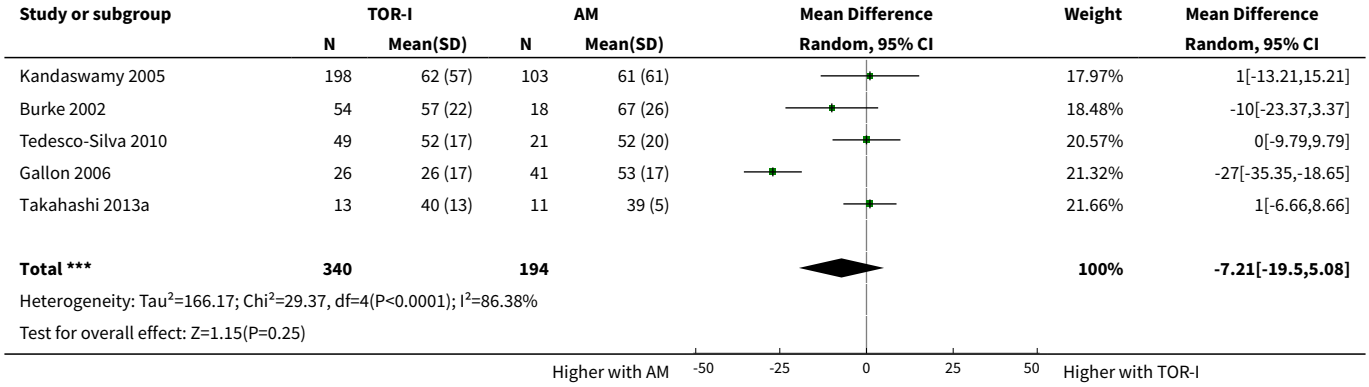
Analysis 6.5. Comparison 6 Target of rapamycin inhibitors (TOR-I) versus antimetabolite (AM): outcomes at 5 to 8 years post-transplant, Outcome 5 GFR.



Comparison 7. Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	9	1501	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.64, 1.78]
2 Total graft loss	8	1385	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.68, 1.75]
3 Graft loss censored for death	8	1385	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.54, 2.20]
4 All acute rejection	9	1509	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.67, 1.07]
5 Biopsy-proven acute rejection	8	1381	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.13]
6 CMV infection	5	865	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.78, 2.60]
7 Adverse wound outcomes	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 All complications	3	291	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.53, 1.71]
7.2 Lymphocoele	3	702	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.45, 1.63]
8 All malignancies	7	1163	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.36, 3.04]
9 Number needing to change treatment	5	734	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.58, 2.42]

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Analysis 7.1. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 1 Death (all causes).

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Lo 2004	1/16	0/23		2.63%	4.24[0.18,97.82]
Russ 2003	2/33	0/31		2.88%	4.71[0.23,94.31]
EVEREST 2009	2/143	2/142		6.84%	0.99[0.14,6.95]
Grinyo 2004	2/43	2/44		7.06%	1.02[0.15,6.94]
Bechstein-193 2013	2/65	5/63		10.08%	0.39[0.08,1.93]
Velosa-212 2001	3/97	4/100		11.97%	0.77[0.18,3.37]
Kandaswamy 2005	3/141	5/140		12.98%	0.6[0.15,2.45]
Cohen 2002	6/142	6/154		21.08%	1.08[0.36,3.29]
Kahan-203 1999	7/47	6/77		24.48%	1.91[0.68,5.34]
Total (95% CI)	**727**	**774**		**100%**	**1.07[0.64,1.78]**
Total events: 28 (Low TOR-I), 30 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=5.3, df=8(P=0.73); I^2=0%					
Test for overall effect: Z=0.25(P=0.8)					

Analysis 7.2. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 2 Total graft loss.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Russ 2003	3/33	1/31		4.29%	2.82[0.31,25.68]
Lo 2004	1/16	4/23		4.73%	0.36[0.04,2.92]
Bechstein-193 2013	3/65	5/63		9.79%	0.58[0.15,2.33]
Velosa-212 2001	7/97	5/100		13.98%	1.44[0.47,4.39]
Grinyo 2004	5/43	6/44		14.05%	0.85[0.28,2.59]
Kandaswamy 2005	6/149	9/140		16.26%	0.63[0.23,1.71]
EVEREST 2009	16/143	5/142		16.98%	3.18[1.2,8.44]
Cohen 2002	9/142	10/154		19.92%	0.98[0.41,2.33]
Total (95% CI)	**688**	**697**		**100%**	**1.09[0.68,1.75]**
Total events: 50 (Low TOR-I), 45 (High TOR-I)					
Heterogeneity: Tau^2=0.1; Chi^2=8.86, df=7(P=0.26); I^2=20.97%					
Test for overall effect: Z=0.36(P=0.72)					

Analysis 7.3. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 3 Graft loss censored for death.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Lo 2004	0/16	4/23		5.45%	0.16[0.01,2.73]
Russ 2003	1/33	1/31		5.91%	0.94[0.06,14.38]
Bechstein-193 2013	1/65	2/63		7.52%	0.48[0.05,5.21]

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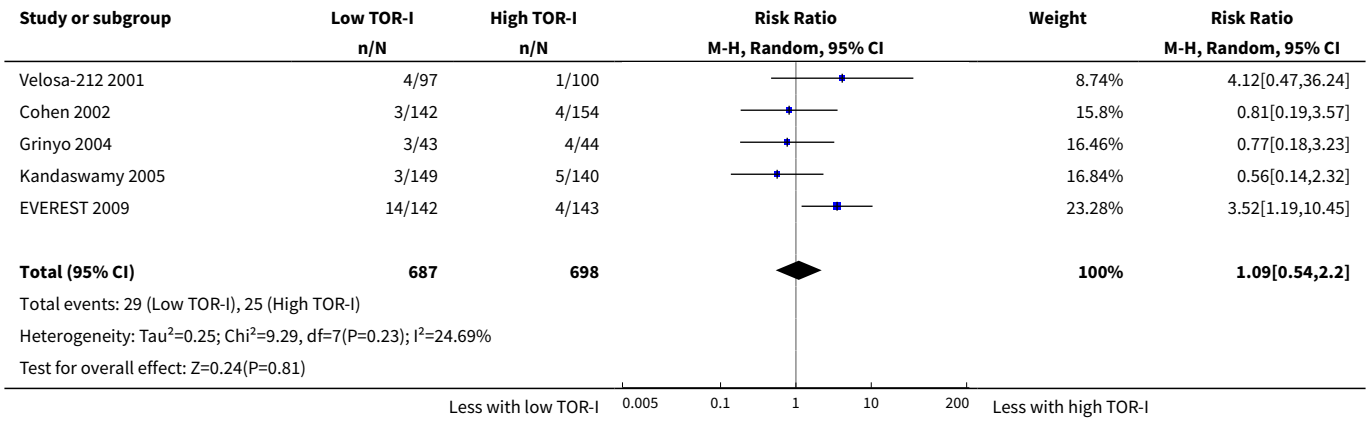
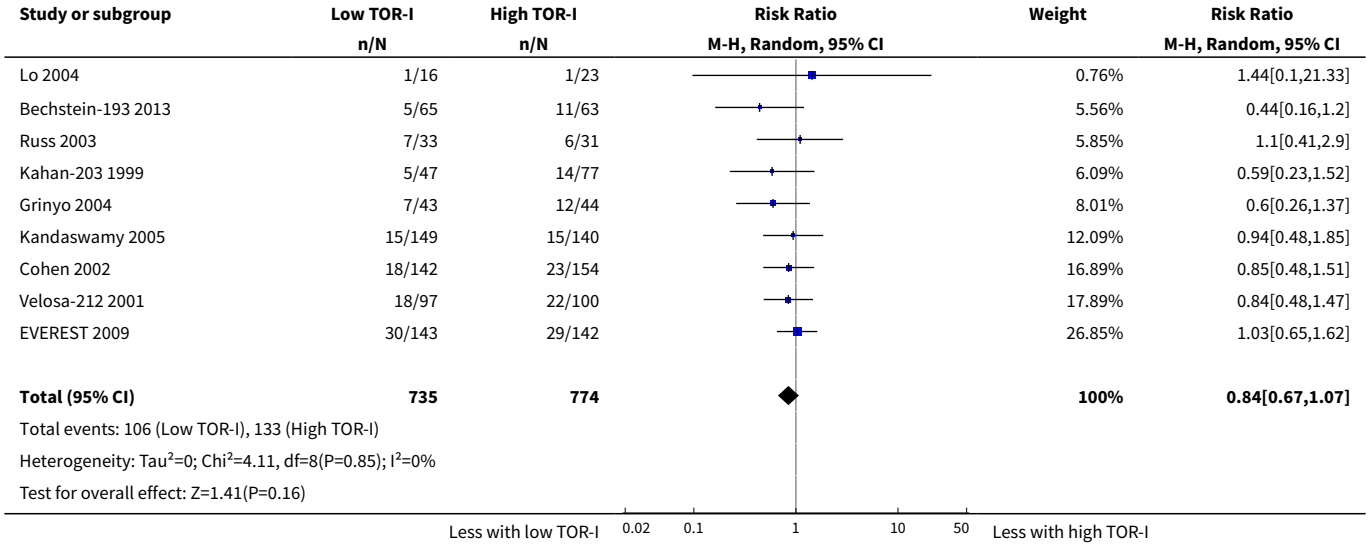
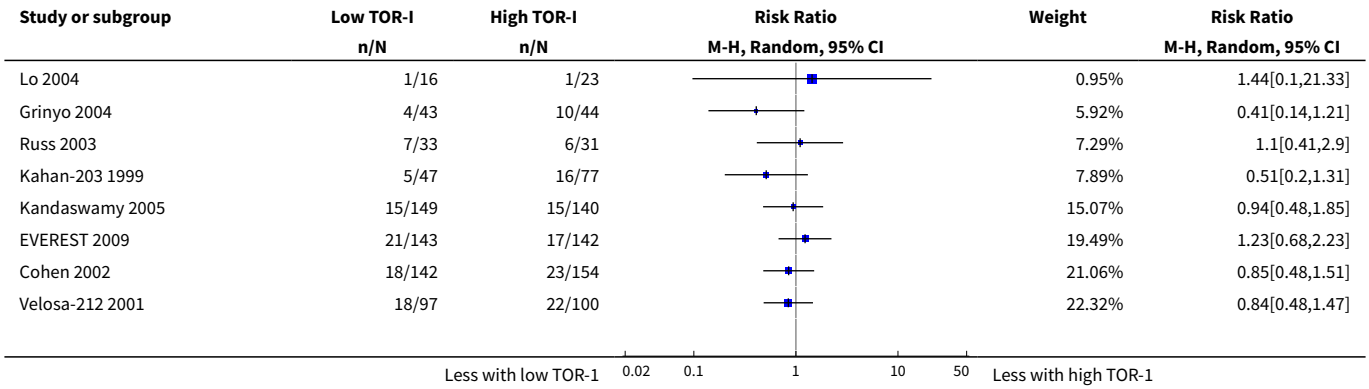


Analysis 7.4. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 4 All acute rejection.



Analysis 7.5. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 5 Biopsy-proven acute rejection.



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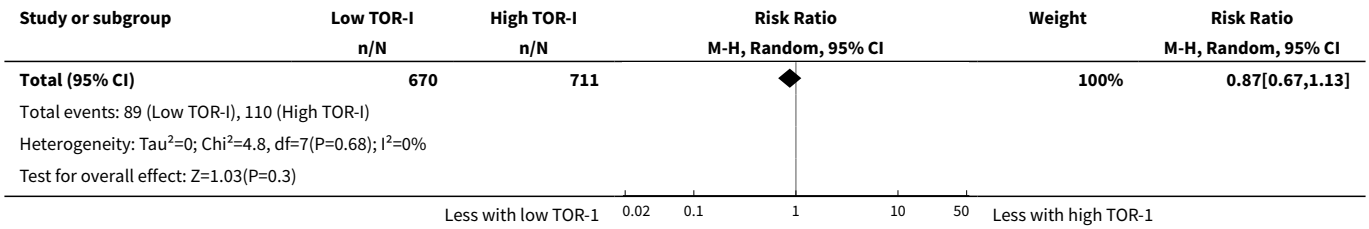
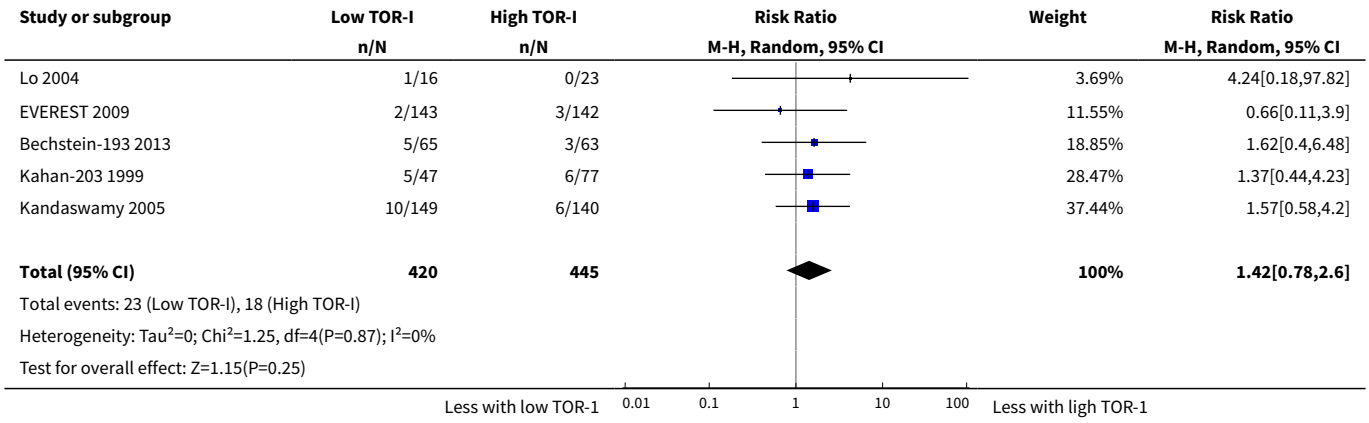
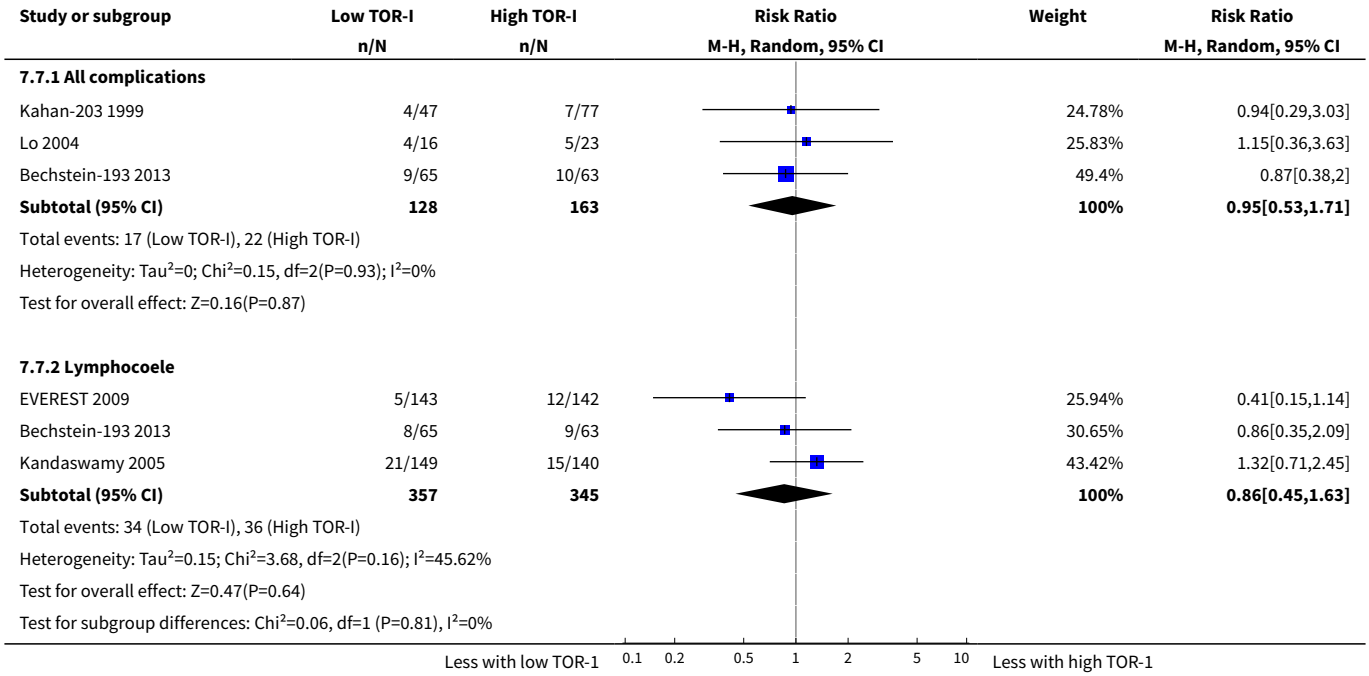


Analysis 7.6. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 6 CMV infection.



Analysis 7.7. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 7 Adverse wound outcomes.



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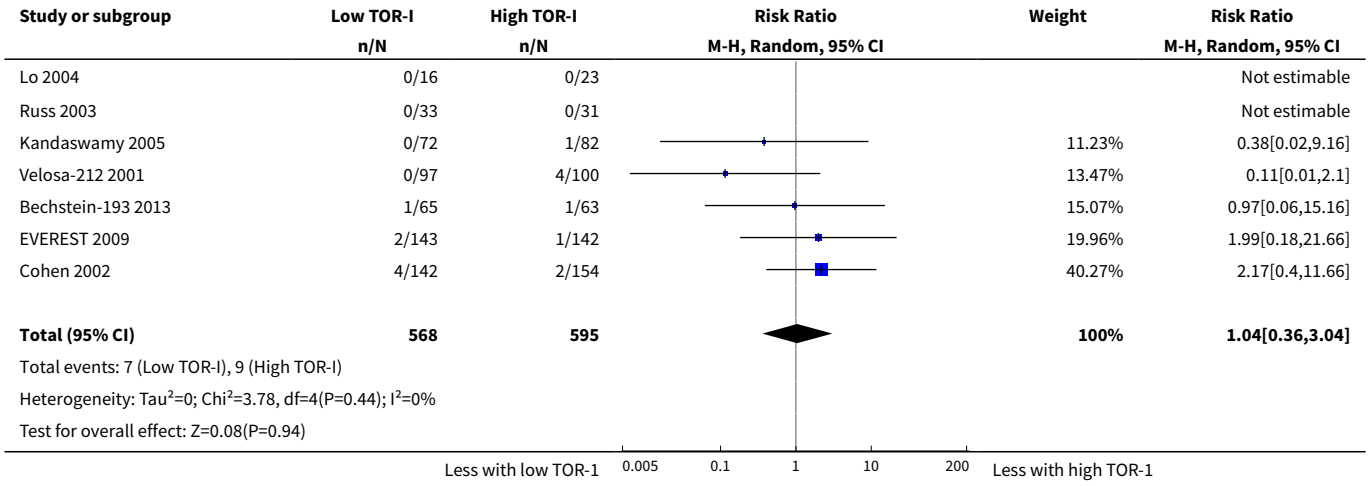
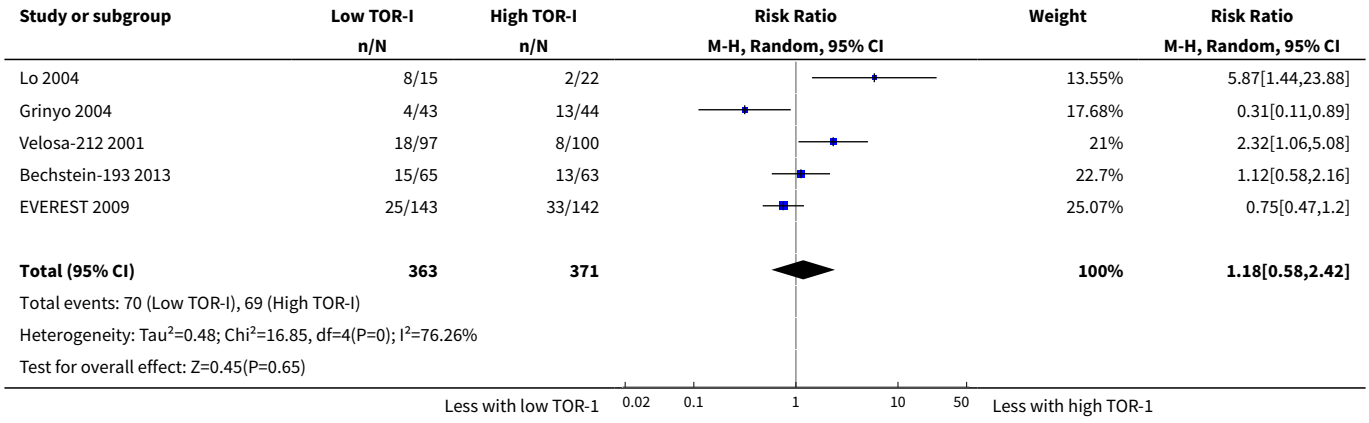
Analysis 7.8. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 8 All malignancies.



Analysis 7.9. Comparison 7 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): primary outcomes, Outcome 9 Number needing to change treatment.



Comparison 8. Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New-onset diabetes mellitus	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Tacrolimus	5	580	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.99, 3.23]
1.2 Cyclosporin	3	606	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.27, 1.20]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Lymphoma/PTLD	7	1298	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.15, 3.07]
3 Adverse cosmetic outcomes	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Tremor	3	537	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.34, 2.45]
3.2 Gingival hyperplasia - cyclosporin	1	285	Risk Ratio (M-H, Random, 95% CI)	2.98 [0.12, 72.52]
3.3 Hirsutism - cyclosporin	1	186	Risk Ratio (M-H, Random, 95% CI)	20.56 [1.22, 345.79]
4 Glomerular filtration rate	7	1305	Mean Difference (IV, Random, 95% CI)	-5.96 [-9.54, -2.38]
5 Serum creatinine	9	1368	Mean Difference (IV, Random, 95% CI)	1.53 [-8.82, 11.89]
6 Elevated lipid levels	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Hypercholesterolaemia	4	734	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.22]
6.2 Hypertriglyceridaemia	4	734	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.73, 1.01]
7 Lipid outcomes	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Total cholesterol	4	709	Mean Difference (IV, Random, 95% CI)	0.24 [-0.98, 1.45]
7.2 Total triglycerides	3	413	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.55, 0.29]
8 Abnormal haematologic values	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Anaemia	6	1074	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.08]
8.2 Leucopenia	5	1012	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.70, 1.40]
8.3 Thrombocytopenia	5	888	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.07]
9 Haematological outcomes	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 White cell count [per mm^3]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Haemoglobin [g/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Platelet count [per mm^2]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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Analysis 8.1. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 1 New-onset diabetes mellitus.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Tacrolimus					
Grinyo 2004	3/36	1/26		7.14%	2.17[0.24,19.68]
Bechstein-193 2013	8/65	3/63		21.18%	2.58[0.72,9.3]
Kandaswamy 2005	10/149	3/140		21.56%	3.13[0.88,11.15]
Russ 2003	5/33	4/31		23.35%	1.17[0.35,3.98]
Lo 2004	4/15	5/22		26.77%	1.17[0.38,3.67]
Subtotal (95% CI)	**298**	**282**		**100%**	**1.79[0.99,3.23]**
Total events: 30 (Low TOR-I), 16 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=2.13, df=4(P=0.71); I^2=0%					
Test for overall effect: Z=1.94(P=0.05)					
8.1.2 Cyclosporin					
Kahan-203 1999	2/47	5/77		21.62%	0.66[0.13,3.24]
EVEREST 2009	3/143	7/142		31.14%	0.43[0.11,1.61]
Velosa-212 2001	5/97	8/100		47.24%	0.64[0.22,1.9]
Subtotal (95% CI)	**287**	**319**		**100%**	**0.57[0.27,1.2]**
Total events: 10 (Low TOR-I), 20 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=2(P=0.88); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					
Test for subgroup differences: Chi^2=5.62, df=1 (P=0.02), I^2=82.21%					

Less with low TOR-1 — Less with high TOR-1

Analysis 8.2. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 2 Lymphoma/PTLD.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
EVEREST 2009	0/143	0/142			Not estimable
Russ 2003	0/33	0/31			Not estimable
Lo 2004	0/16	0/23			Not estimable
Velosa-212 2001	0/97	1/100		22.49%	0.34[0.01,8.33]
Bechstein-193 2013	1/65	0/63		22.59%	2.91[0.12,70.1]
Kandaswamy 2005	0/149	2/140		24.95%	0.19[0.01,3.88]
Cohen 2002	1/142	1/154		29.97%	1.08[0.07,17.18]
Total (95% CI)	**645**	**653**		**100%**	**0.68[0.15,3.07]**
Total events: 2 (Low TOR-I), 4 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=1.79, df=3(P=0.62); I^2=0%					
Test for overall effect: Z=0.51(P=0.61)					

Less with low TOR-1 — Less with high TOR-1

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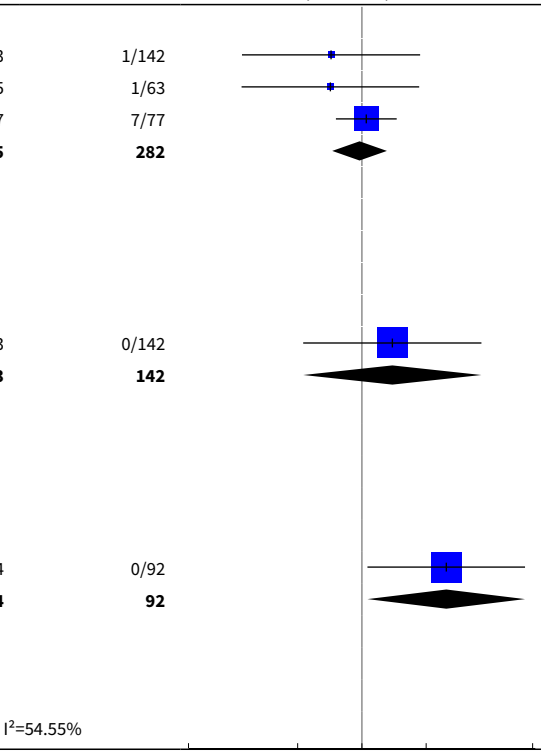
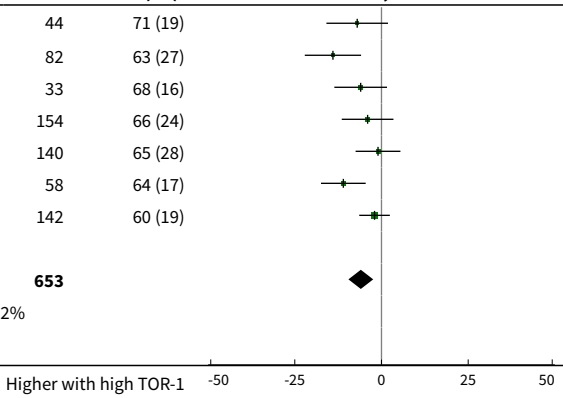
Analysis 8.3. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 3 Adverse cosmetic outcomes.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.3.1 Tremor					
EVEREST 2009	0/143	1/142		9.43%	0.33[0.01,8.06]
Bechstein-193 2013	0/65	1/63		9.49%	0.32[0.01,7.79]
Kahan-203 1999	5/47	7/77		81.08%	1.17[0.39,3.48]
Subtotal (95% CI)	**255**	**282**		**100%**	**0.92[0.34,2.45]**
Total events: 5 (Low TOR-I), 9 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=1.01, df=2(P=0.6); I^2=0%					
Test for overall effect: Z=0.17(P=0.87)					
8.3.2 Gingival hyperplasia - cyclosporin					
EVEREST 2009	1/143	0/142		100%	2.98[0.12,72.52]
Subtotal (95% CI)	**143**	**142**		**100%**	**2.98[0.12,72.52]**
Total events: 1 (Low TOR-I), 0 (High TOR-I)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
8.3.3 Hirsutism - cyclosporin					
Velosa-212 2001	10/94	0/92		100%	20.56[1.22,345.79]
Subtotal (95% CI)	**94**	**92**		**100%**	**20.56[1.22,345.79]**
Total events: 10 (Low TOR-I), 0 (High TOR-I)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.1(P=0.04)					
Test for subgroup differences: Chi^2=4.4, df=1 (P=0.11), I^2=54.55%					



Analysis 8.4. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 4 Glomerular filtration rate.

Study or subgroup	Low TOR-I N	Low TOR-I Mean(SD)	High TOR-I N	High TOR-I Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Grinyo 2004	43	64 (23)	44	71 (19)		10.6%	-7[-15.88,1.88]
Velosa-212 2001	82	49 (26)	82	63 (27)		11.88%	-14[-22.11,-5.89]
Russ 2003	31	62 (15)	33	68 (16)		12.85%	-6[-13.59,1.59]
Cohen 2002	142	62 (39)	154	66 (24)		13.14%	-4[-11.45,3.45]
Kandaswamy 2005	149	64 (28)	140	65 (28)		15.31%	-1[-7.46,5.46]
Bechstein-193 2013	62	53 (19)	58	64 (17)		15.35%	-11[-17.44,-4.56]
EVEREST 2009	143	58 (19)	142	60 (19)		20.87%	-2[-6.41,2.41]
Total ***	**652**		**653**			**100%**	**-5.96[-9.54,-2.38]**
Heterogeneity: Tau^2=10.88; Chi^2=11.57, df=6(P=0.07); I^2=48.12%							
Test for overall effect: Z=3.27(P=0)							



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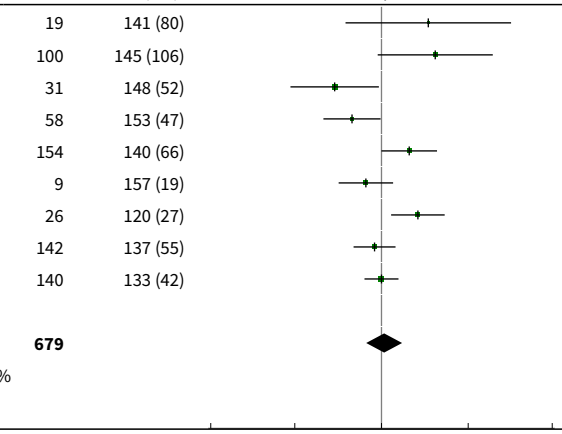
Analysis 8.5. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 5 Serum creatinine.

Study or subgroup	Low TOR-I N	Low TOR-I Mean(SD)	High TOR-I N	High TOR-I Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lo 2004	15	168 (62)	19	141 (80)		3.74%	27[-20.73,74.73]
Velosa-212 2001	97	176 (130)	100	145 (106)		6.35%	31[-2.18,64.18]
Russ 2003	33	121 (52)	31	148 (52)		8.66%	-27[-52.49,-1.51]
Bechstein-193 2013	62	136 (45)	58	153 (47)		12.47%	-17[-33.49,-0.51]
Cohen 2002	142	156 (74)	154	140 (66)		12.69%	16[-0.02,32.02]
Kahan-203 1999	12	148 (17)	9	157 (19)		12.85%	-9[-24.7,6.7]
Grinyo 2004	36	141 (35)	26	120 (27)		12.97%	21[5.56,36.44]
EVEREST 2009	143	133 (49)	142	137 (55)		14.6%	-4[-16.1,8.1]
Kandaswamy 2005	149	133 (43)	140	133 (42)		15.67%	0[-9.8,9.8]
Total ***	**689**		**679**			**100%**	**1.53[-8.82,11.89]**
Heterogeneity: Tau²=153.22; Chi²=25.54, df=8(P=0); I²=68.68%							
Test for overall effect: Z=0.29(P=0.77)							



Analysis 8.6. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 6 Elevated lipid levels.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.6.1 Hypercholesterolaemia					
Bechstein-193 2013	9/65	8/63		7.7%	1.09[0.45,2.65]
EVEREST 2009	21/143	22/142		19.96%	0.95[0.55,1.64]
Kahan-203 1999	14/47	25/77		20.44%	0.92[0.53,1.58]
Velosa-212 2001	38/97	41/100		51.9%	0.96[0.68,1.34]
Subtotal (95% CI)	**352**	**382**		**100%**	**0.96[0.75,1.22]**
Total events: 82 (Low TOR-I), 96 (High TOR-I)					
Heterogeneity: Tau²=0; Chi²=0.11, df=3(P=0.99); I²=0%					
Test for overall effect: Z=0.36(P=0.72)					
8.6.2 Hypertriglyceridaemia					
Bechstein-193 2013	15/65	17/63		7.05%	0.86[0.47,1.56]
Kahan-203 1999	21/47	30/77		13.56%	1.15[0.75,1.75]
EVEREST 2009	64/143	86/142		38.76%	0.74[0.59,0.93]
Velosa-212 2001	57/97	66/100		40.63%	0.89[0.72,1.11]
Subtotal (95% CI)	**352**	**382**		**100%**	**0.85[0.73,1.01]**
Total events: 157 (Low TOR-I), 199 (High TOR-I)					
Heterogeneity: Tau²=0; Chi²=3.58, df=3(P=0.31); I²=16.13%					
Test for overall effect: Z=1.88(P=0.06)					

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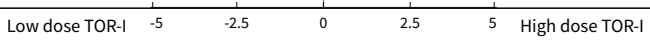
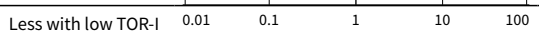
Analysis 8.7. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 7 Lipid outcomes.

Study or subgroup	Low TOR-I N	Low TOR-I Mean(SD)	High TOR-I N	High TOR-I Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.7.1 Total cholesterol							
Velosa-212 2001	97	6.2 (1.9)	100	6.8 (2.1)		24.63%	-0.58[-1.14,-0.02]
Cohen 2002	142	7.8 (2.4)	154	5.7 (1.9)		24.91%	2.11[1.62,2.6]
Grinyo 2004	36	5.4 (0.9)	26	6.3 (0.9)		25.04%	-0.86[-1.32,-0.4]
Kandaswamy 2005	72	5 (1.1)	82	4.8 (1.1)		25.42%	0.27[-0.08,0.62]
Subtotal ***	**347**		**362**			**100%**	**0.24[-0.98,1.45]**
Heterogeneity: Tau^2=1.48; Chi^2=86.13, df=3(P<0.0001); I^2=96.52%							
Test for overall effect: Z=0.38(P=0.7)							
8.7.2 Total triglycerides							
Velosa-212 2001	97	2.6 (2.4)	100	3.1 (2.6)		26.45%	-0.47[-1.16,0.22]
Kandaswamy 2005	72	2.6 (2.2)	82	2.3 (1.8)		29.7%	0.33[-0.31,0.97]
Grinyo 2004	36	1.9 (1)	26	2.1 (0.9)		43.86%	-0.23[-0.69,0.23]
Subtotal ***	**205**		**208**			**100%**	**-0.13[-0.55,0.29]**
Heterogeneity: Tau^2=0.05; Chi^2=3.12, df=2(P=0.21); I^2=35.85%							
Test for overall effect: Z=0.59(P=0.55)							
Test for subgroup differences: Chi^2=0.31, df=1 (P=0.58), I^2=0%							



Analysis 8.8. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 8 Abnormal haematologic values.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.8.1 Anaemia					
EVEREST 2009	1/143	1/142		0.29%	0.99[0.06,15.72]
Bechstein-193 2013	17/65	18/63		7.04%	0.92[0.52,1.61]
Kahan-203 1999	15/47	29/77		8.75%	0.85[0.51,1.41]
Grinyo 2004	22/36	14/26		11.56%	1.13[0.73,1.76]
Velosa-212 2001	37/94	38/92		18.39%	0.95[0.67,1.35]
Kandaswamy 2005	79/149	83/140		53.95%	0.89[0.73,1.1]
Subtotal (95% CI)	**534**	**540**		**100%**	**0.93[0.8,1.08]**
Total events: 171 (Low TOR-I), 183 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=1.08, df=5(P=0.96); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					
8.8.2 Leucopenia					
EVEREST 2009	3/143	2/142		3.86%	1.49[0.25,8.78]
Kahan-203 1999	6/47	5/77		9.51%	1.97[0.64,6.09]
Bechstein-193 2013	9/65	10/63		17.57%	0.87[0.38,2]
Velosa-212 2001	11/94	14/92		22.44%	0.77[0.37,1.6]
Kandaswamy 2005	25/149	24/140		46.61%	0.98[0.59,1.63]
Subtotal (95% CI)	**498**	**514**		**100%**	**0.99[0.7,1.4]**
Total events: 54 (Low TOR-I), 55 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=2.16, df=4(P=0.71); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					



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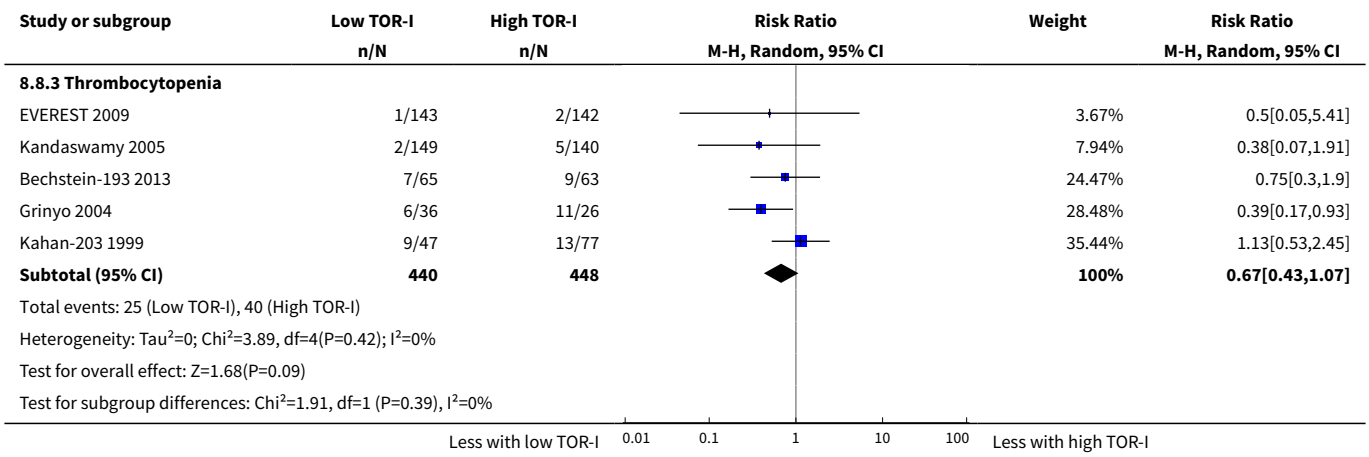
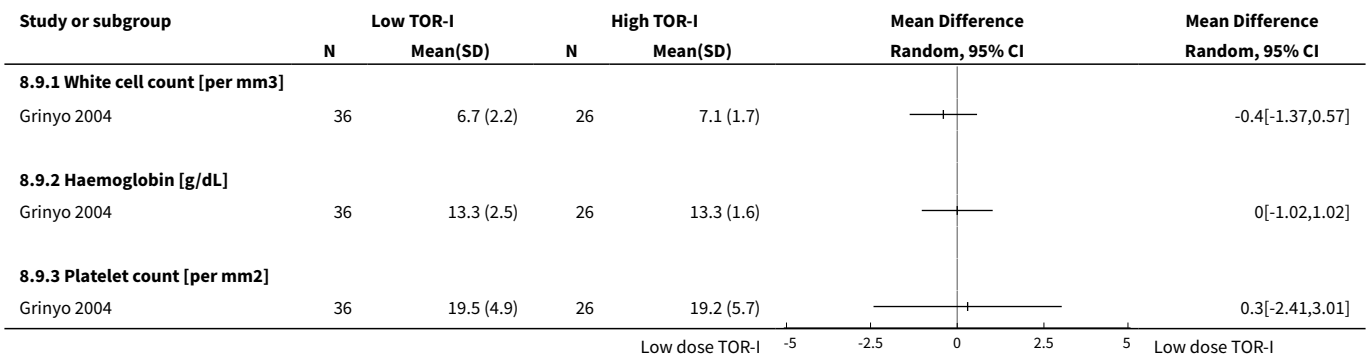


Analysis 8.9. Comparison 8 Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): secondary outcomes, Outcome 9 Haematological outcomes.



Comparison 9. Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	13	3894	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.63, 1.25]
2 Total graft loss	11	3476	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.67, 1.06]
3 Graft loss censored for death	12	3863	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.19]
4 All acute rejection	13	3898	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.10, 1.42]
5 Biopsy-proven acute rejection	11	3731	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.10, 1.43]
6 CMV infection	9	3099	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.21]
7 All malignancy	10	3175	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.32]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Adverse wound outcomes	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 All wound complications	7	2792	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.29]
8.2 Lymphocoele	10	3302	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.04]
9 Number needing to change treatment	10	3652	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.05]

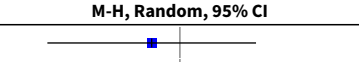
Analysis 9.1. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 1 Death.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Tedesco-Silva 2003	0/34	0/36			Not estimable
Pascual 2010	0/15	0/20			Not estimable
van Hooff 2003	1/50	0/26		1.2%	1.59[0.07,37.68]
Kramer-2307 2003	0/117	2/139		1.31%	0.24[0.01,4.89]
Hamdy 2005	2/65	0/67		1.32%	5.15[0.25,105.29]
Kahan-157 2001	3/68	0/35		1.39%	3.65[0.19,68.78]
Kovarik-2306 2004	1/112	6/125		2.72%	0.19[0.02,1.52]
Vitko-TERRA 2004	7/325	7/325		11.19%	1[0.35,2.82]
Vitko-201 2001	10/194	8/198		14.56%	1.28[0.51,3.16]
Kahan-301 2000	8/284	11/274		14.98%	0.7[0.29,1.72]
MacDonald-302 2001	8/227	11/219		15.11%	0.7[0.29,1.71]
Tedesco-Silva 2010	9/274	10/278		15.34%	0.91[0.38,2.21]
Kovarik-251 2001	12/193	13/194		20.86%	0.93[0.43,1.98]
Total (95% CI)	**1958**	**1936**		**100%**	**0.89[0.63,1.25]**
Total events: 61 (Low TOR-I), 68 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=6.4, df=10(P=0.78); I^2=0%					
Test for overall effect: Z=0.68(P=0.5)					

Less with low TOR-I — Less with high TOR-I

Analysis 9.2. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 2 Total graft loss.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Tedesco-Silva 2003	1/34	2/36		0.97%	0.53[0.05,5.57]
Kahan-157 2001	5/68	1/35		1.21%	2.57[0.31,21.18]
Kramer-2307 2003	2/117	7/139		2.23%	0.34[0.07,1.6]
Hamdy 2005	6/65	3/67		2.97%	2.06[0.54,7.9]
van Hooff 2003	8/50	4/26		4.41%	1.04[0.35,3.13]
Kovarik-2306 2004	6/112	10/125		5.59%	0.67[0.25,1.78]



Less with low TOR-I — Less with high TOR-I

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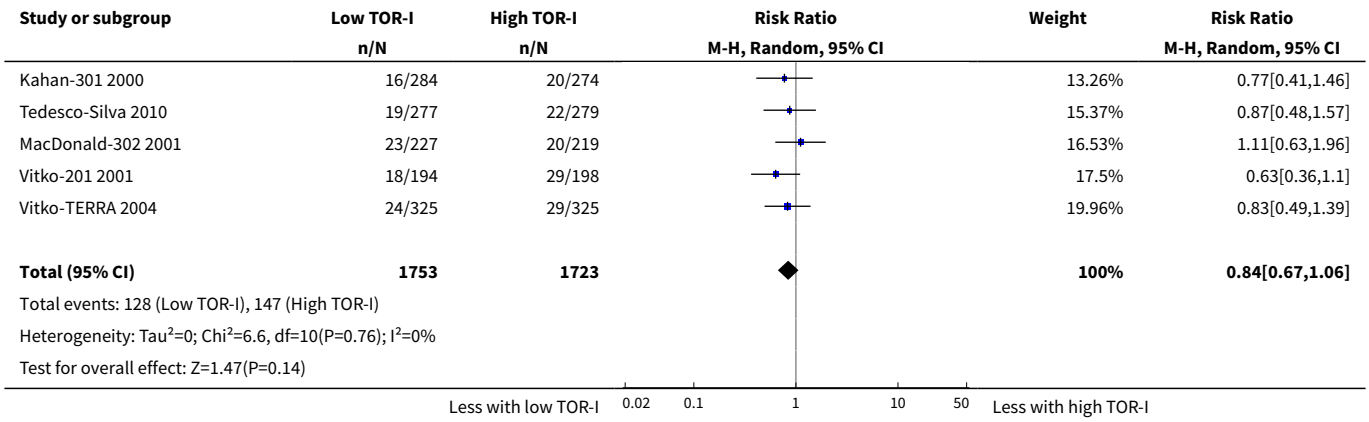
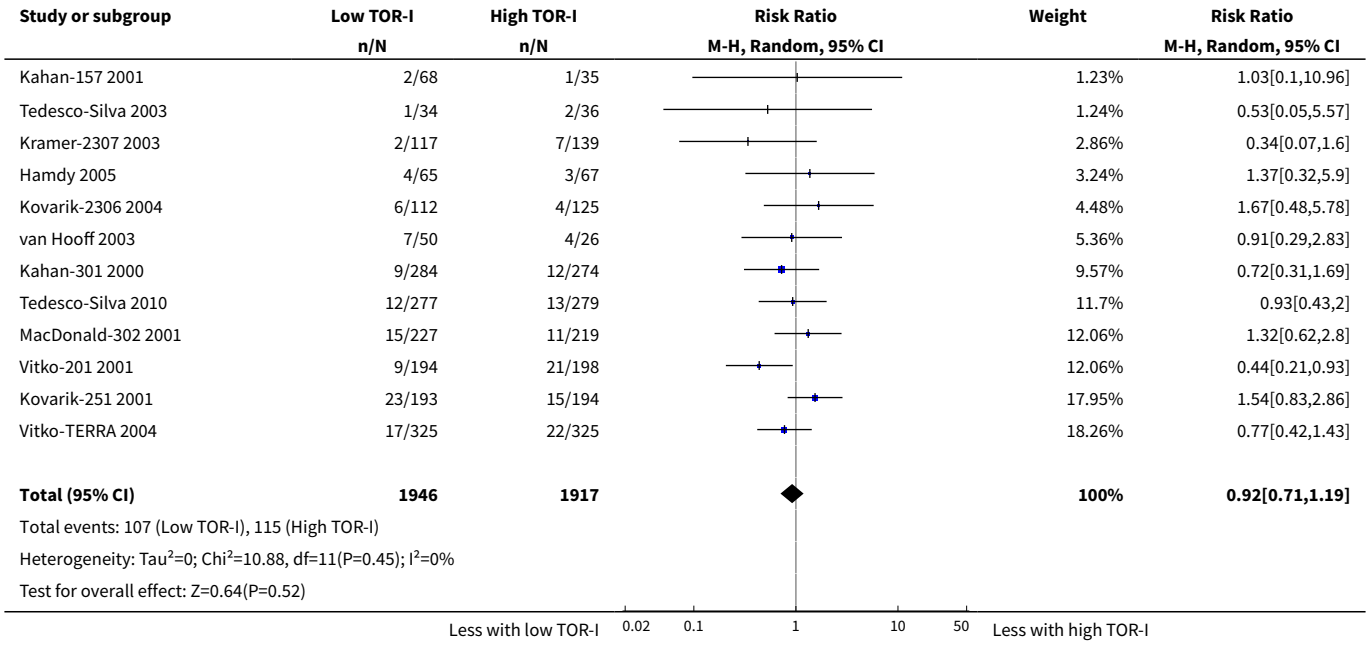
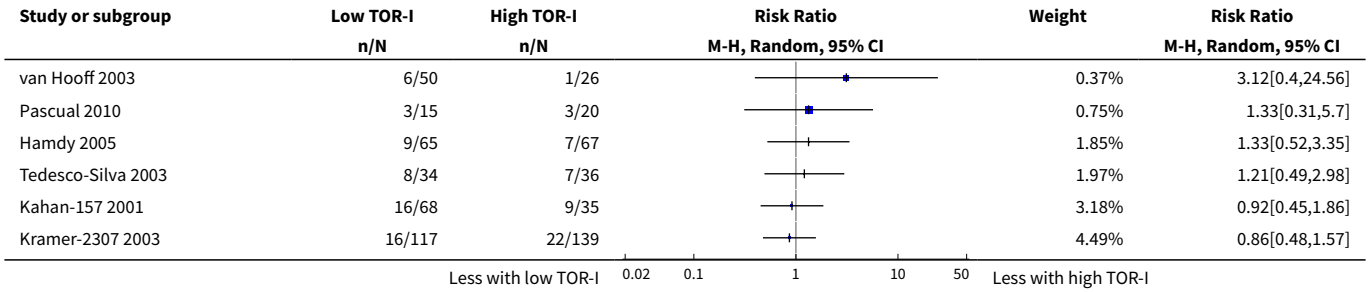


Analysis 9.3. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 3 Graft loss censored for death.



Analysis 9.4. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 4 All acute rejection.



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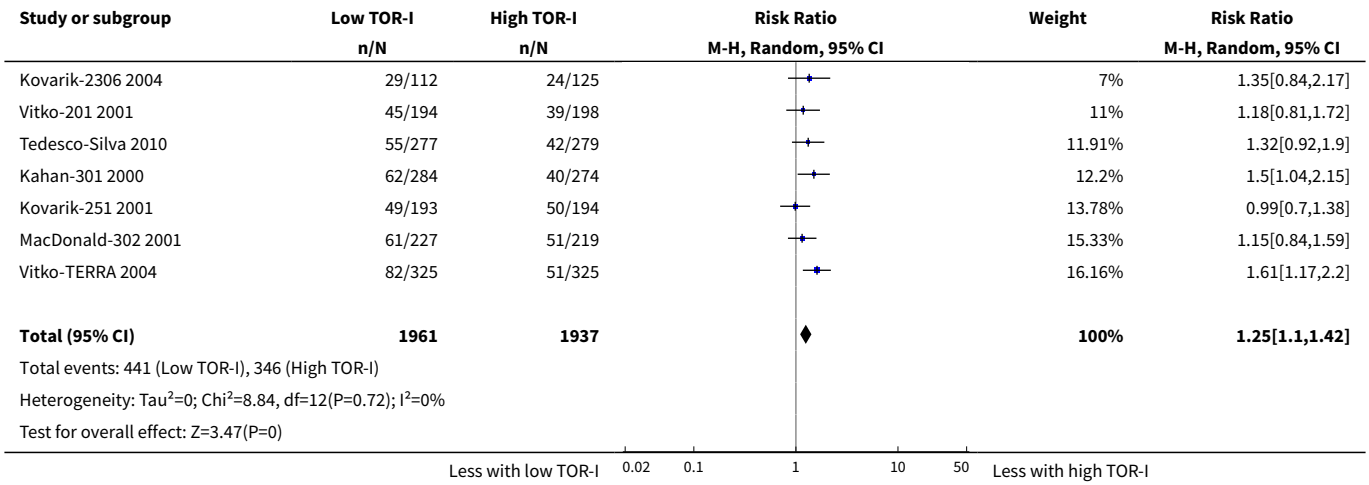
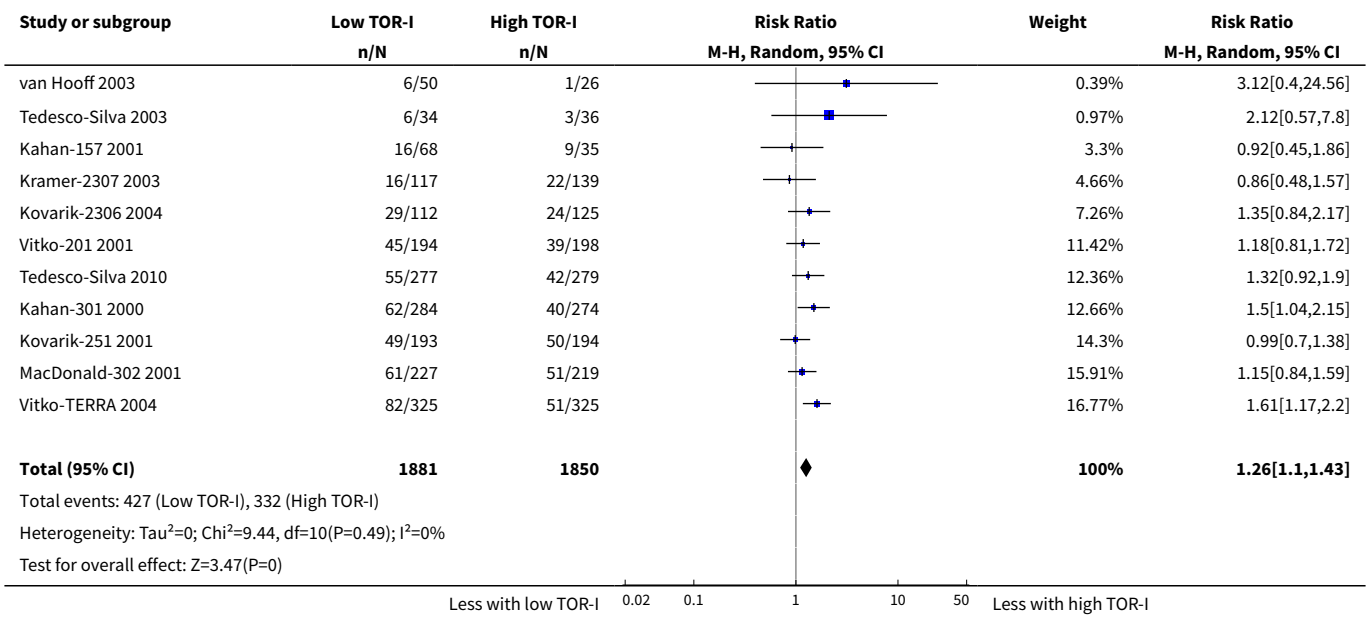
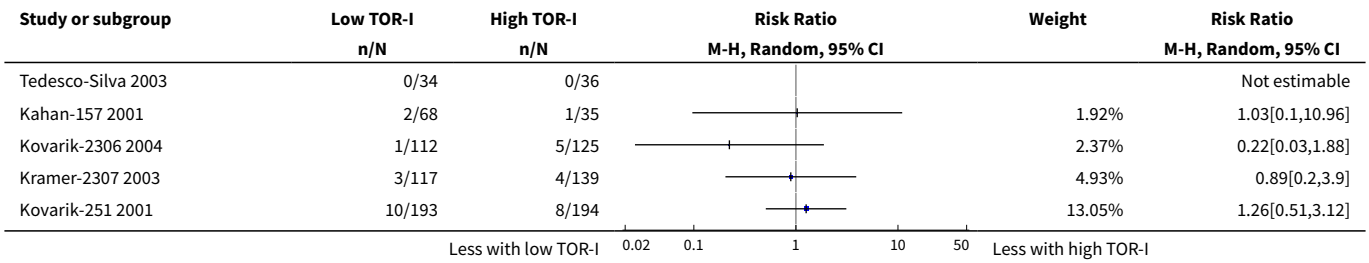


Analysis 9.5. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 5 Biopsy-proven acute rejection.



Analysis 9.6. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 6 CMV infection.



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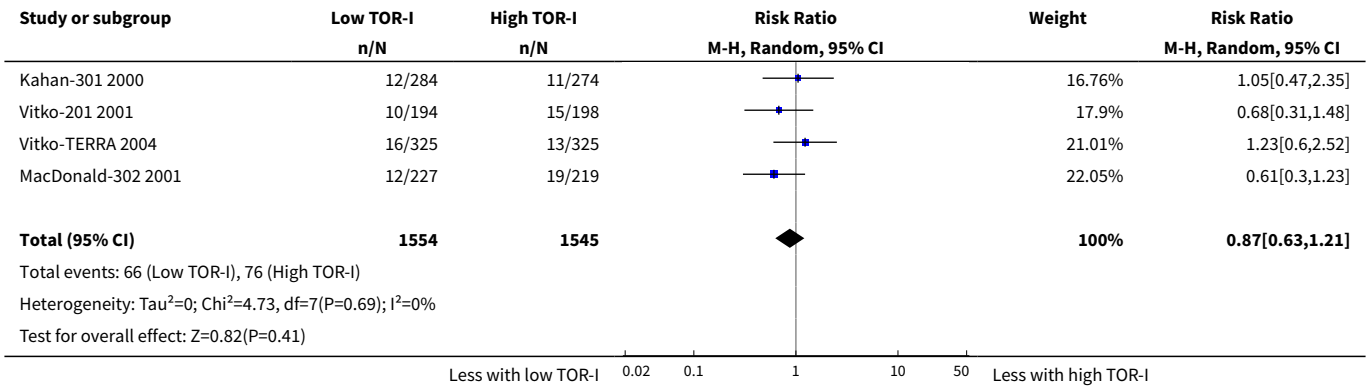
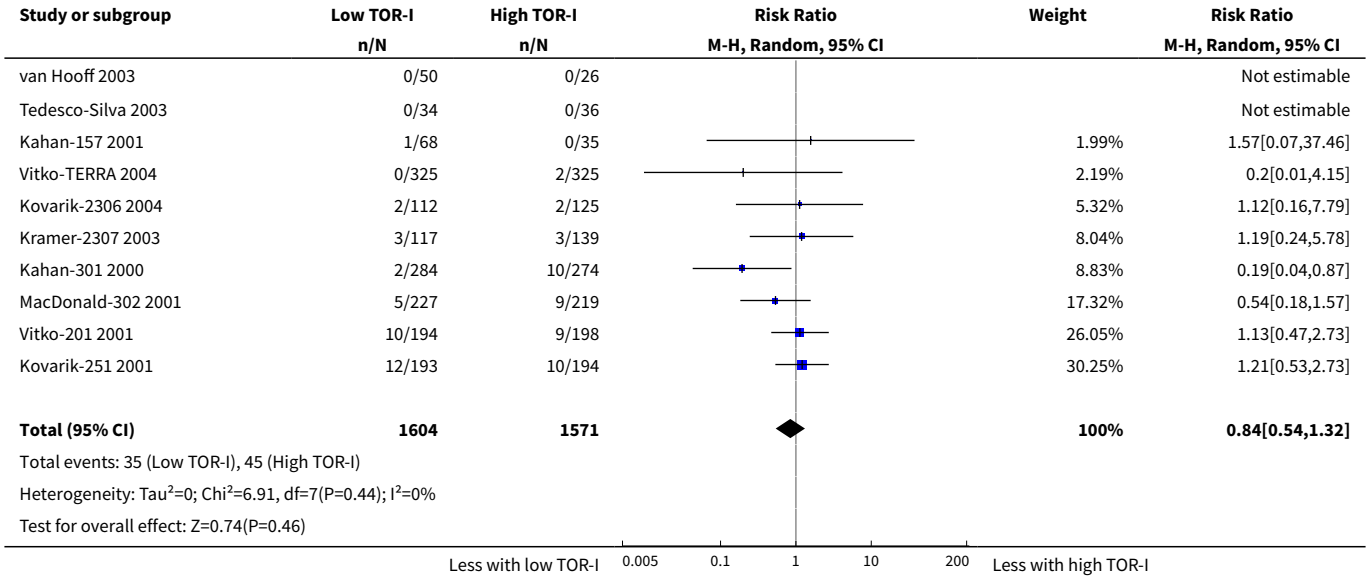
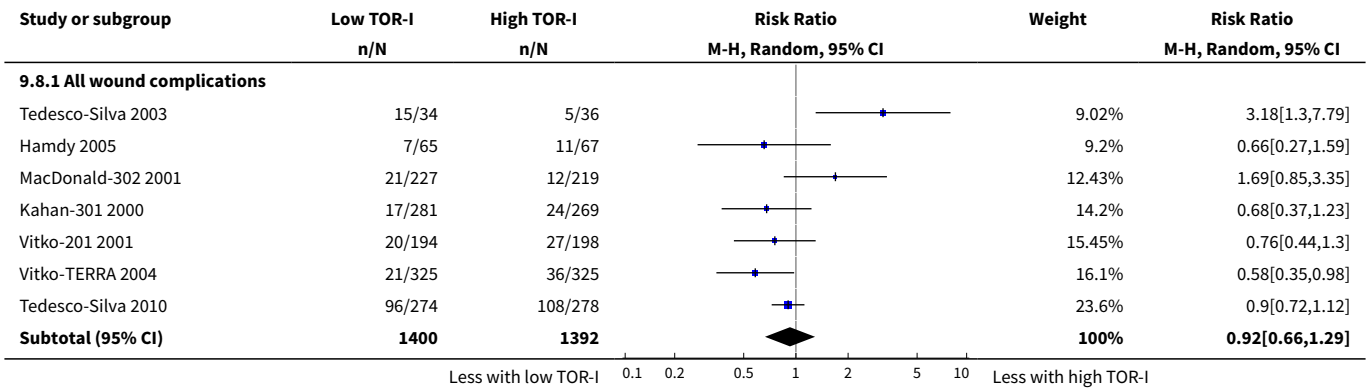


Analysis 9.7. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 7 All malignancy.



Analysis 9.8. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 8 Adverse wound outcomes.



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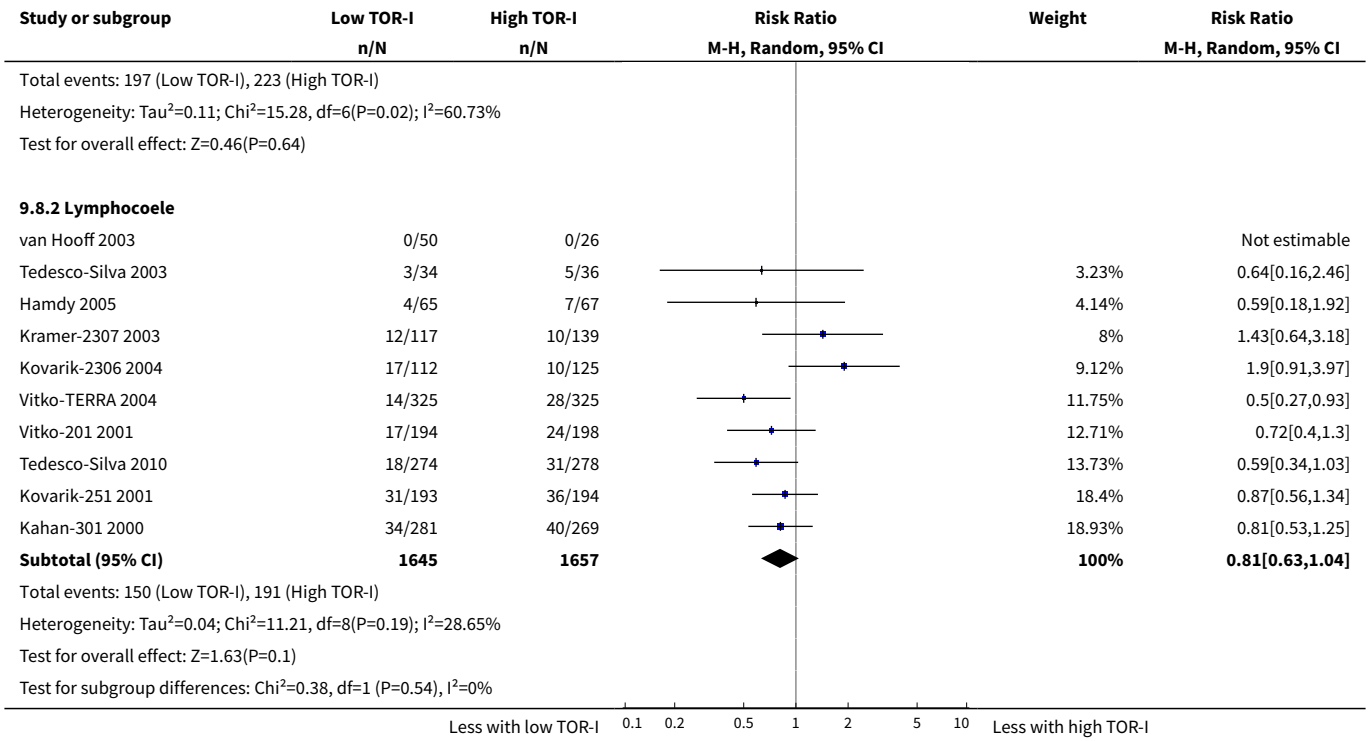
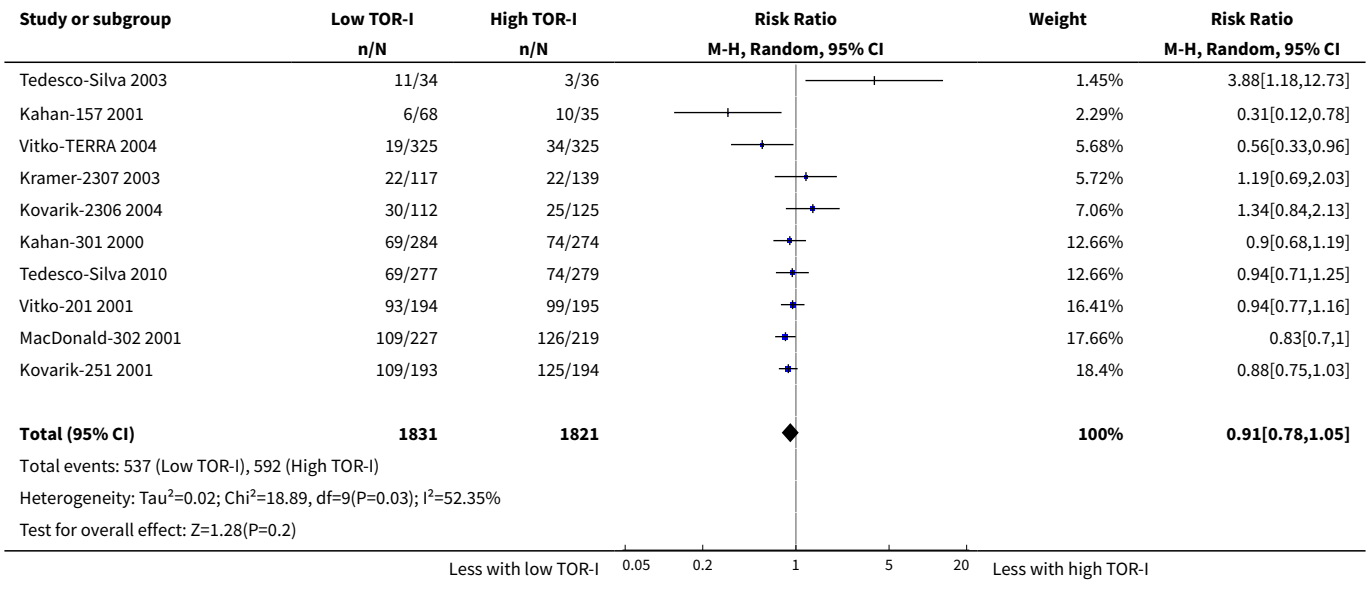


Analysis 9.9. Comparison 9 Low versus higher dose target of rapamycin inhibitors (TOR-I): primary outcomes, Outcome 9 Number needing to change treatment.



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Comparison 10. Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 New-onset diabetes mellitus	6	2125	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
2 Lymphoma/PTLD	7	2792	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.25, 1.73]
3 Adverse cosmetic outcomes	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Tremor	1	387	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.63, 1.29]
3.2 Gingival hyperplasia	2	622	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.48, 4.42]
3.3 Hirsutism	2	1102	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.30, 0.85]
3.4 Acne/rash	6	2408	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.62, 1.21]
4 Glomerular filtration rate	7	1863	Mean Difference (IV, Random, 95% CI)	2.88 [-0.71, 6.48]
5 Serum creatinine	7	1951	Mean Difference (IV, Random, 95% CI)	-2.21 [-13.68, 9.26]
6 Elevated lipid levels	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Hypercholesterolaemia	9	3250	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.78, 0.98]
6.2 Hypertriglyceridaemia	5	1064	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.47, 1.07]
7 Lipid outcomes	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Cholesterol	5	1041	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.35, 0.08]
7.2 Triglycerides	4	1041	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.72, -0.03]
8 Abnormal haematological values	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Anaemia	10	3179	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.72, 0.91]
8.2 Leucopenia	12	3831	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.57, 0.92]
8.3 Thrombocytopenia	9	2242	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.44, 0.75]
9 Haematological outcomes	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 Haemoglobin [g/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 White cell count [per mm^3]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Platelet count [per mm^2]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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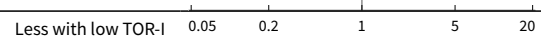
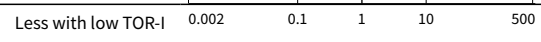
Analysis 10.1. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 1 New-onset diabetes mellitus.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Tedesco-Silva 2003	4/34	2/36		3.19%	2.12[0.41,10.82]
Kovarik-2306 2004	8/112	10/125		9.92%	0.89[0.37,2.18]
Kramer-2307 2003	15/117	19/139		18.16%	0.94[0.5,1.76]
MacDonald-302 2001	17/218	23/208		19.84%	0.71[0.39,1.28]
Kahan-301 2000	20/281	29/269		22.97%	0.66[0.38,1.14]
Vitko-TERRA 2004	20/296	44/290		25.92%	0.45[0.27,0.74]
Total (95% CI)	**1058**	**1067**		**100%**	**0.69[0.51,0.93]**
Total events: 84 (Low TOR-I), 127 (High TOR-I)					
Heterogeneity: Tau^2=0.02; Chi^2=5.96, df=5(P=0.31); I^2=16.14%					
Test for overall effect: Z=2.47(P=0.01)					



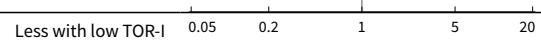
Analysis 10.2. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 2 Lymphoma/PTLD.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kramer-2307 2003	0/117	1/139		9.09%	0.4[0.02,9.62]
Kahan-157 2001	1/68	0/35		9.19%	1.57[0.07,37.46]
Vitko-TERRA 2004	0/325	2/325		10.07%	0.2[0.01,4.15]
Vitko-201 2001	4/194	0/198		10.9%	9.18[0.5,169.46]
Kahan-301 2000	1/284	2/274		16.15%	0.48[0.04,5.29]
MacDonald-302 2001	1/227	5/219		20.24%	0.19[0.02,1.64]
Kovarik-251 2001	2/193	2/194		24.36%	1.01[0.14,7.06]
Total (95% CI)	**1408**	**1384**		**100%**	**0.66[0.25,1.73]**
Total events: 9 (Low TOR-I), 12 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=5.69, df=6(P=0.46); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					



Analysis 10.3. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 3 Adverse cosmetic outcomes.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.3.1 Tremor					
Kovarik-251 2001	43/193	48/194		100%	0.9[0.63,1.29]
Subtotal (95% CI)	**193**	**194**		**100%**	**0.9[0.63,1.29]**
Total events: 43 (Low TOR-I), 48 (High TOR-I)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					



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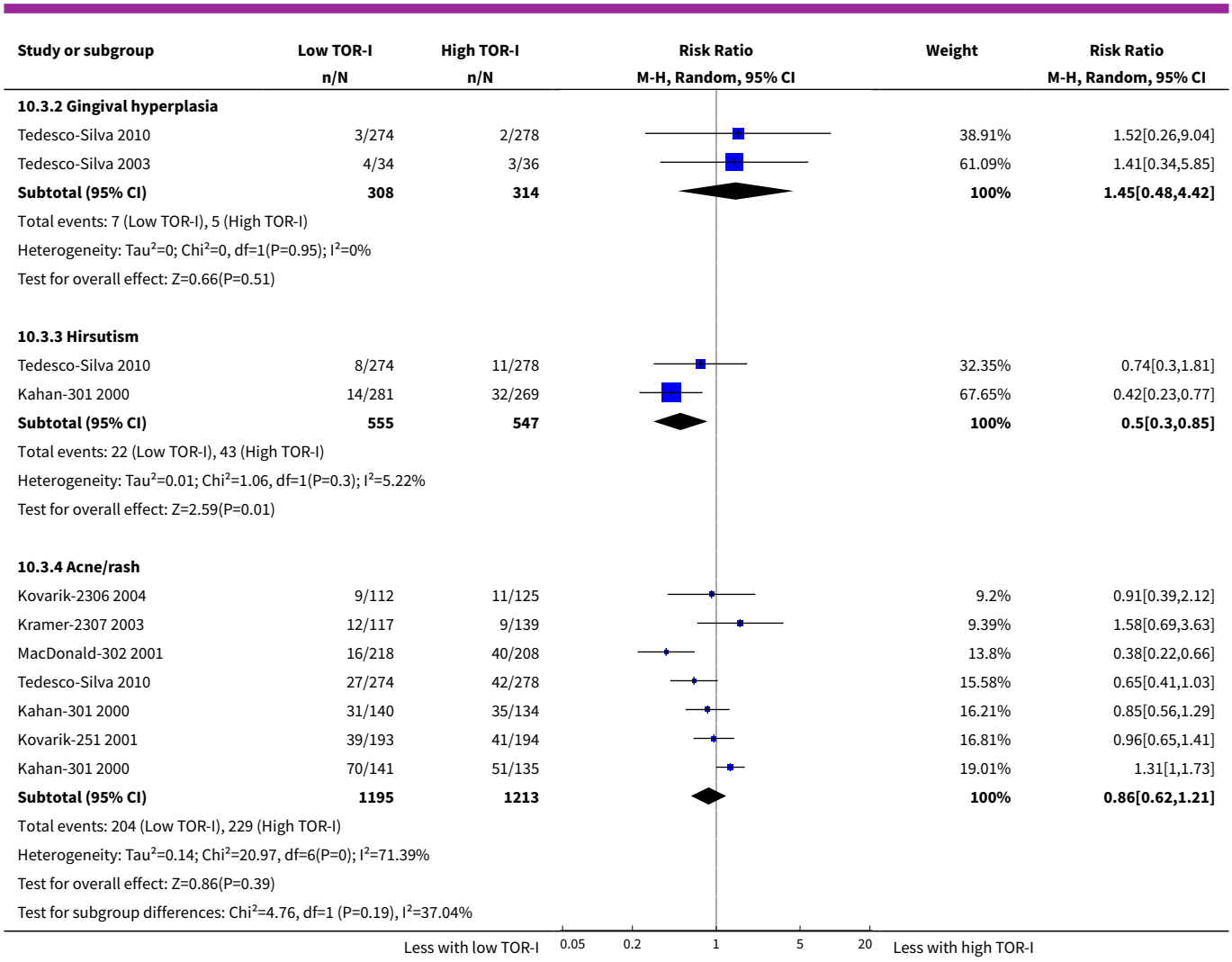
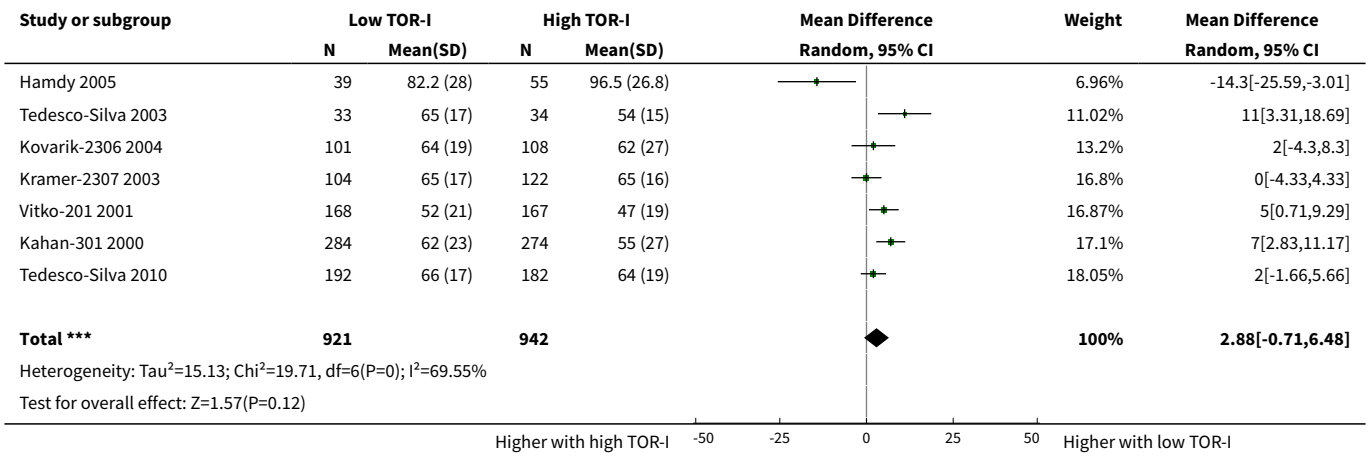


Analysis 10.4. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 4 Glomerular filtration rate.



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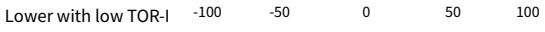
Analysis 10.5. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 5 Serum creatinine.

Study or subgroup	Low TOR-I N	Low TOR-I Mean(SD)	High TOR-I N	High TOR-I Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hamdy 2005	39	125 (39)	55	107 (30)		17.41%	18[3.42,32.58]
Kahan-301 2000	284	160 (81)	274	172 (73)		18.62%	-12[-24.79,0.79]
Kovarik-2306 2004	105	147 (104)	112	140 (53)		12.71%	7[-15.18,29.18]
Kramer-2307 2003	110	140 (75)	124	136 (45)		16.4%	4[-12.1,20.1]
MacDonald-302 2001	227	156 (66)	219	162 (64)		19.11%	-6[-18.06,6.06]
Tedesco-Silva 2003	33	141 (44)	34	141 (97)		7.18%	0[-35.89,35.89]
Vitko-201 2001	168	175 (82)	167	216 (191)		8.57%	-41[-72.51,-9.49]
Total * **	**966**		**985**			**100%**	**-2.21[-13.68,9.26]**

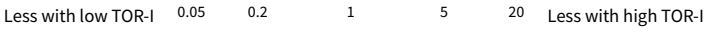
Heterogeneity: Tau²=141.37; Chi²=17.05, df=6(P=0.01); I²=64.8%

Test for overall effect: Z=0.38(P=0.71)



Analysis 10.6. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 6 Elevated lipid levels.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.6.1 Hypercholesterolaemia					
Kahan-157 2001	12/68	7/35		1.89%	0.88[0.38,2.04]
Vitko-TERRA 2004	19/325	43/325		4.97%	0.44[0.26,0.74]
van Hooff 2003	21/50	13/26		5.25%	0.84[0.51,1.39]
Kramer-2307 2003	24/117	31/139		5.96%	0.92[0.57,1.48]
Kovarik-2306 2004	25/112	33/125		6.49%	0.85[0.54,1.33]
Tedesco-Silva 2010	49/274	50/278		10.45%	0.99[0.7,1.42]
Vitko-201 2001	58/194	61/198		14.79%	0.97[0.72,1.31]
MacDonald-302 2001	81/218	91/208		24.86%	0.85[0.67,1.07]
Kahan-301 2000	93/284	99/274		25.33%	0.91[0.72,1.14]
Subtotal (95% CI)	**1642**	**1608**		**100%**	**0.87[0.78,0.98]**
Total events: 382 (Low TOR-I), 428 (High TOR-I)					
Heterogeneity: Tau²=0; Chi²=7.92, df=8(P=0.44); I²=0%					
Test for overall effect: Z=2.35(P=0.02)					
10.6.2 Hypertriglyceridaemia					
Kahan-157 2001	2/68	3/35		5.55%	0.34[0.06,1.96]
van Hooff 2003	4/50	2/26		6.34%	1.04[0.2,5.31]
Kovarik-2306 2004	4/112	11/125		13.52%	0.41[0.13,1.24]
Kramer-2307 2003	7/117	12/139		20.82%	0.69[0.28,1.7]
Vitko-201 2001	20/194	24/198		53.78%	0.85[0.49,1.49]
Subtotal (95% CI)	**541**	**523**		**100%**	**0.71[0.47,1.07]**
Total events: 37 (Low TOR-I), 52 (High TOR-I)					
Heterogeneity: Tau²=0; Chi²=2.25, df=4(P=0.69); I²=0%					
Test for overall effect: Z=1.63(P=0.1)					
Test for subgroup differences: Chi²=0.88, df=1 (P=0.35), I²=0%					



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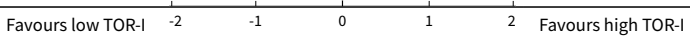
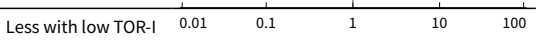
Analysis 10.7. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 7 Lipid outcomes.

Study or subgroup	Low TOR-I N	Low TOR-I Mean(SD)	High TOR-I N	High TOR-I Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
10.7.1 Cholesterol							
Tedesco-Silva 2003	33	6.5 (1.6)	34	6.5 (1.7)		7.6%	0[-0.77,0.77]
Kahan-157 2001	34	6.4 (1.1)	35	6 (1.7)		10.12%	0.41[-0.26,1.08]
Kahan-301 2000	284	6.4 (2.9)	276	6.5 (2.8)		20.5%	-0.14[-0.61,0.33]
MacDonald-302 2001	109	6.1 (1.4)	69	6.4 (1.4)		25.7%	-0.29[-0.71,0.13]
Vitko-201 2001	87	5.8 (1)	80	6 (1.3)		36.07%	-0.2[-0.55,0.15]
Subtotal ***	**547**		**494**			**100%**	**-0.13[-0.35,0.08]**
Heterogeneity: Tau²=0; Chi²=3.33, df=4(P=0.5); I²=0%							
Test for overall effect: Z=1.23(P=0.22)							
10.7.2 Triglycerides							
Tedesco-Silva 2003	33	3.2 (1.8)	34	3 (2)		12.81%	0.11[-0.8,1.02]
Kahan-301 2000	284	3.3 (4.7)	274	3.5 (4.8)		16.33%	-0.25[-1.04,0.54]
Vitko-201 2001	87	2.6 (1.7)	80	2.8 (1.8)		30.46%	-0.2[-0.73,0.33]
MacDonald-302 2001	137	3.1 (0.8)	112	3.8 (2.2)		40.41%	-0.71[-1.14,-0.28]
Subtotal ***	**541**		**500**			**100%**	**-0.37[-0.72,-0.03]**
Heterogeneity: Tau²=0.03; Chi²=3.87, df=3(P=0.28); I²=22.5%							
Test for overall effect: Z=2.12(P=0.03)							
Test for subgroup differences: Chi²=1.35, df=1 (P=0.25), I²=25.72%							



Analysis 10.8. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 8 Abnormal haematological values.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.8.1 Anaemia					
Tedesco-Silva 2003	1/34	9/36		0.33%	0.12[0.02,0.88]
Hamdy 2005	4/65	5/67		0.83%	0.82[0.23,2.94]
van Hooff 2003	21/50	12/26		4.81%	0.91[0.54,1.54]
Kovarik-2306 2004	25/112	39/125		7.16%	0.72[0.46,1.1]
Kramer-2307 2003	28/117	41/139		7.86%	0.81[0.54,1.23]
MacDonald-302 2001	36/219	56/208		9.61%	0.61[0.42,0.89]
Vitko-201 2001	54/194	71/198		15.56%	0.78[0.58,1.04]
Vitko-TERRA 2004	72/325	76/325		16.68%	0.95[0.71,1.26]
Kovarik-251 2001	62/193	75/194		18.22%	0.83[0.63,1.09]
Tedesco-Silva 2010	72/274	85/278		18.94%	0.86[0.66,1.12]
Subtotal (95% CI)	**1583**	**1596**		**100%**	**0.81[0.72,0.91]**
Total events: 375 (Low TOR-I), 469 (High TOR-I)					
Heterogeneity: Tau²=0; Chi²=7.77, df=9(P=0.56); I²=0%					
Test for overall effect: Z=3.59(P=0)					
10.8.2 Leucopenia					
van Hooff 2003	2/50	1/26		1.02%	1.04[0.1,10.94]
Tedesco-Silva 2003	2/34	3/36		1.9%	0.71[0.13,3.97]
Kahan-157 2001	3/68	4/35		2.73%	0.39[0.09,1.63]



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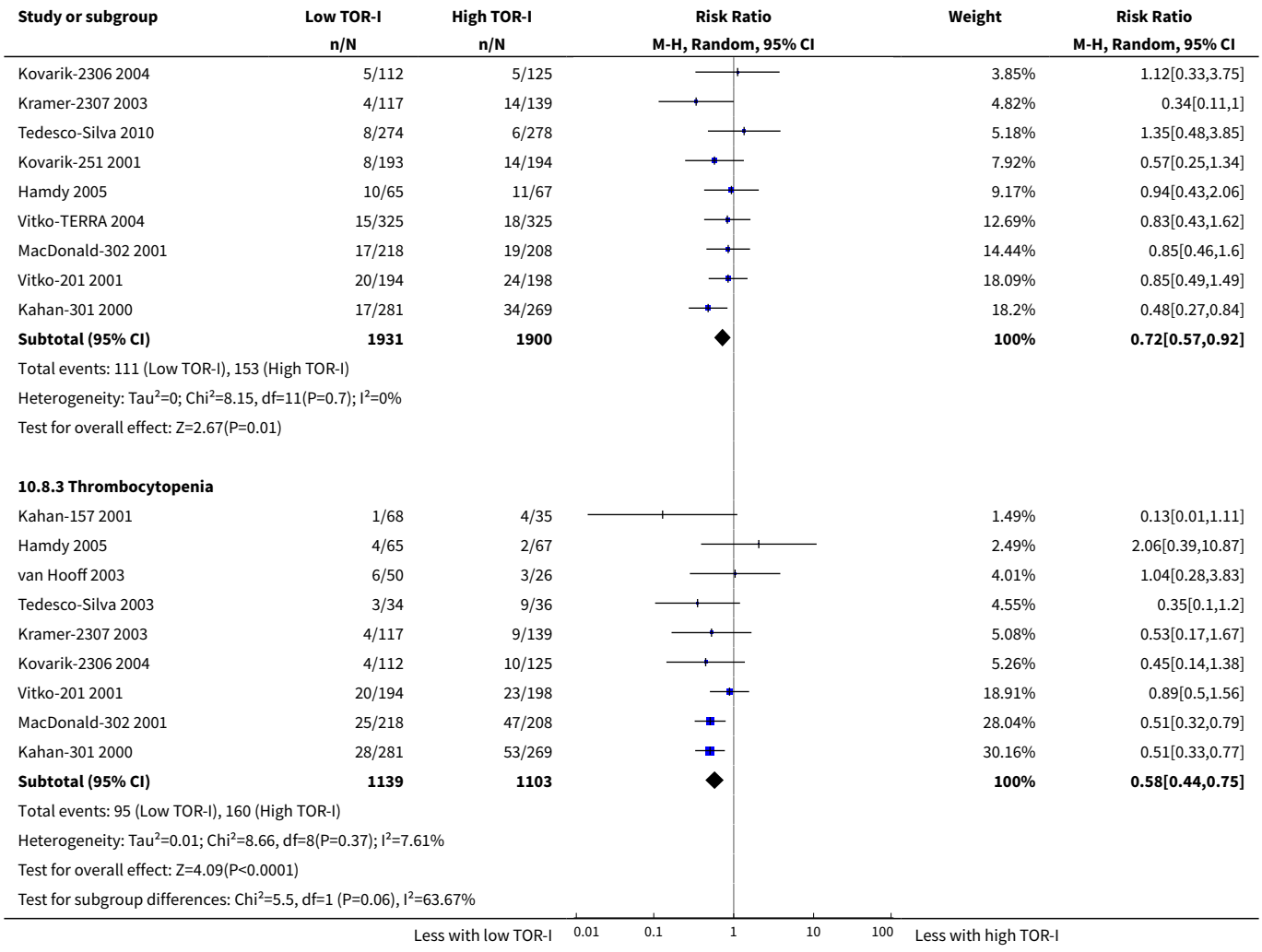
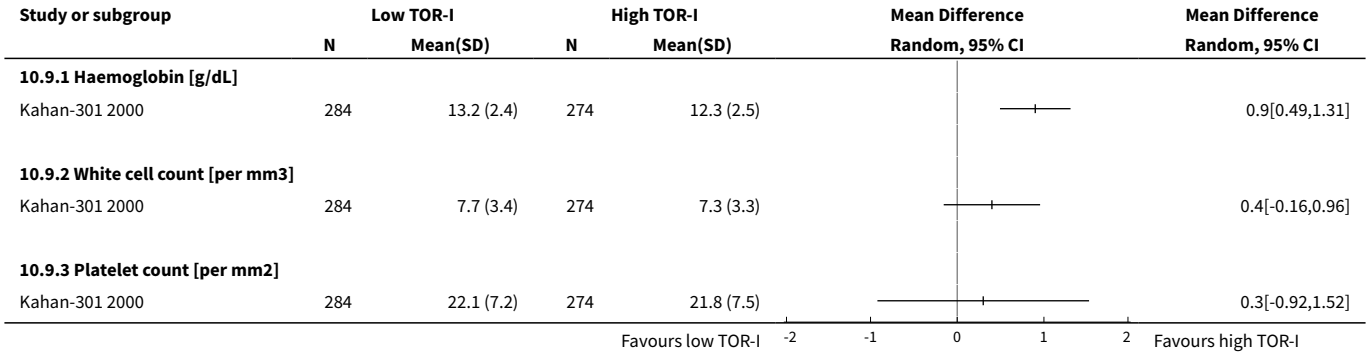


Analysis 10.9. Comparison 10 Low versus higher dose target of rapamycin inhibitors (TOR- I): secondary outcomes, Outcome 9 Haematological outcomes.



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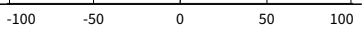
Comparison 11. Sirolimus versus everolimus: outcomes at 3 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Estimated glomerular filtration rate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Lipid outcomes	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Cholesterol	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Triglycerides	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

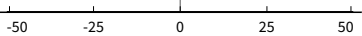
Analysis 11.1. Comparison 11 Sirolimus versus everolimus: outcomes at 3 months, Outcome 1 Serum creatinine.

Study or subgroup	Sirolimus N	Sirolimus Mean(SD)	Everolimus N	Everolimus Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Rostaing 2001	16	135 (52)	12	102 (31.2)		33[2,64]



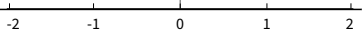
Analysis 11.2. Comparison 11 Sirolimus versus everolimus: outcomes at 3 months, Outcome 2 Estimated glomerular filtration rate.

Study or subgroup	Sirolimus N	Sirolimus Mean(SD)	Everolimus N	Everolimus Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Rostaing 2001	16	47 (16)	12	64 (16)		-17[-28.98,-5.02]



Analysis 11.3. Comparison 11 Sirolimus versus everolimus: outcomes at 3 months, Outcome 3 Lipid outcomes.

Study or subgroup	Sirolimus N	Sirolimus Mean(SD)	Everolimus N	Everolimus Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
11.3.1 Cholesterol						
Rostaing 2001	16	6.1 (0.3)	12	7.1 (0.2)		-1[-1.18,-0.82]
11.3.2 Triglycerides						
Rostaing 2001	16	2.5 (0.2)	12	2.8 (0.2)		-0.3[-0.44,-0.16]



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Comparison 12. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All acute rejection (publication type)	19	3016	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.31, 1.92]
1.1 Abstract	3	228	Risk Ratio (M-H, Random, 95% CI)	2.03 [1.13, 3.65]
1.2 Journal	16	2788	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.26, 1.92]
2 All acute rejection (risk of bias for sequence generation and allocation concealment)	19	3016	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.31, 1.92]
2.1 Low risk of bias	7	1841	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.98, 2.15]
2.2 High or unclear risk of bias	12	1175	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.35, 2.14]
3 All acute rejection (CNI comparator)	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Tacrolimus	7	1384	Risk Ratio (M-H, Random, 95% CI)	2.19 [1.71, 2.81]
3.2 Cyclosporin	13	2233	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.20, 1.83]
4 All acute rejection (antibody induction)	17	2795	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.29, 1.99]
4.1 No induction	4	307	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.91, 1.68]
4.2 Antibody induction	13	2488	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.35, 2.50]
5 Graft loss censored for death (CNI comparator)	14	3277	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.96, 1.81]
5.1 Tacrolimus	5	1238	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.17, 3.25]
5.2 Cyclosporin	10	2039	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.68, 1.54]
6 Acute rejection (antimetabolite co-intervention)	6	670	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.81, 1.48]
6.1 Azathioprine	1	83	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.64, 1.85]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.2 Mycophenolate	5	587	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.75, 1.59]

Analysis 12.1. Comparison 12 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): subgroup analyses, Outcome 1 All acute rejection (publication type).

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.1.1 Abstract					
Schaefer 2006	5/41	1/39		0.8%	4.76[0.58,38.91]
Fernandes-Charpiot 2014	7/33	4/35		2.6%	1.86[0.6,5.76]
Riad 2007	16/41	8/39		5.65%	1.9[0.92,3.93]
Subtotal (95% CI)	**115**	**113**		**9.05%**	**2.03[1.13,3.65]**
Total events: 28 (TOR-I), 13 (CNI)					
Heterogeneity: Tau^2=0; Chi^2=0.7, df=2(P=0.7); I^2=0%					
Test for overall effect: Z=2.36(P=0.02)					
12.1.2 Journal					
Morelon 2010	1/9	1/10		0.52%	1.11[0.08,15.28]
Cattaneo 2005	2/11	1/10		0.71%	1.82[0.19,17.12]
Martinez-Mier 2006	3/20	1/21		0.75%	3.15[0.36,27.83]
Durrbach 2008	4/33	3/36		1.7%	1.45[0.35,6.02]
Pescovitz 2007	12/30	2/15		1.84%	3[0.77,11.72]
Flechner-318 2002	4/31	7/30		2.65%	0.55[0.18,1.7]
Lebranchu-132 2004	9/71	6/74		3.38%	1.56[0.59,4.17]
Gelens 2006	9/18	5/18		4.11%	1.8[0.75,4.32]
Kreis-210 2000	11/40	7/38		4.45%	1.49[0.65,3.45]
Glotz 2010	12/71	9/70		4.83%	1.31[0.59,2.92]
Flechner 2013	60/314	8/161		5.84%	3.85[1.89,7.84]
Stegall 2003	15/80	12/82		6.1%	1.28[0.64,2.56]
ORION 2011	43/156	13/140		8.13%	2.97[1.67,5.29]
Groth-207 1999	17/41	16/42		9.2%	1.09[0.64,1.85]
CALFREE 2006	29/63	23/64		12.43%	1.28[0.84,1.95]
SYMPHONY 2007	87/200	246/789		24.33%	1.4[1.15,1.69]
Subtotal (95% CI)	**1188**	**1600**		**90.95%**	**1.56[1.26,1.92]**
Total events: 318 (TOR-I), 360 (CNI)					
Heterogeneity: Tau^2=0.04; Chi^2=20.59, df=15(P=0.15); I^2=27.16%					
Test for overall effect: Z=4.08(P<0.0001)					
Total (95% CI)	**1303**	**1713**		**100%**	**1.59[1.31,1.92]**
Total events: 346 (TOR-I), 373 (CNI)					
Heterogeneity: Tau^2=0.03; Chi^2=22.44, df=18(P=0.21); I^2=19.8%					
Test for overall effect: Z=4.75(P<0.0001)					
Test for subgroup differences: Chi^2=0.7, df=1 (P=0.4), I^2=0%					

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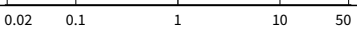
Analysis 12.2. Comparison 12 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): subgroup analyses, Outcome 2 All acute rejection (risk of bias for sequence generation and allocation concealment).

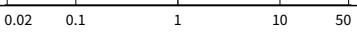
Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.2.1 Low risk of bias					
Morelon 2010	1/9	1/10		0.52%	1.11[0.08,15.28]
Durrbach 2008	4/33	3/36		1.7%	1.45[0.35,6.02]
Flechner-318 2002	4/31	7/30		2.65%	0.55[0.18,1.7]
Lebranchu-132 2004	9/71	6/74		3.38%	1.56[0.59,4.17]
Flechner 2013	60/314	8/161		5.84%	3.85[1.89,7.84]
Groth-207 1999	17/41	16/42		9.2%	1.09[0.64,1.85]
SYMPHONY 2007	87/200	246/789		24.33%	1.4[1.15,1.69]
Subtotal (95% CI)	**699**	**1142**		**47.6%**	**1.45[0.98,2.15]**
Total events: 182 (TOR-I), 287 (CNI)					
Heterogeneity: Tau^2=0.11; Chi^2=11.85, df=6(P=0.07); I^2=49.38%					
Test for overall effect: Z=1.86(P=0.06)					
12.2.2 High or unclear risk of bias					
Cattaneo 2005	2/11	1/10		0.71%	1.82[0.19,17.12]
Martinez-Mier 2006	3/20	1/21		0.75%	3.15[0.36,27.83]
Schaefer 2006	5/41	1/39		0.8%	4.76[0.58,38.91]
Pescovitz 2007	12/30	2/15		1.84%	3[0.77,11.72]
Fernandes-Charpiot 2014	7/33	4/35		2.6%	1.86[0.6,5.76]
Gelens 2006	9/18	5/18		4.11%	1.8[0.75,4.32]
Kreis-210 2000	11/40	7/38		4.45%	1.49[0.65,3.45]
Glotz 2010	12/71	9/70		4.83%	1.31[0.59,2.92]
Riad 2007	16/41	8/39		5.65%	1.9[0.92,3.93]
Stegall 2003	15/80	12/82		6.1%	1.28[0.64,2.56]
ORION 2011	43/156	13/140		8.13%	2.97[1.67,5.29]
CALFREE 2006	29/63	23/64		12.43%	1.28[0.84,1.95]
Subtotal (95% CI)	**604**	**571**		**52.4%**	**1.7[1.35,2.14]**
Total events: 164 (TOR-I), 86 (CNI)					
Heterogeneity: Tau^2=0; Chi^2=8.73, df=11(P=0.65); I^2=0%					
Test for overall effect: Z=4.49(P<0.0001)					
Total (95% CI)	**1303**	**1713**		**100%**	**1.59[1.31,1.92]**
Total events: 346 (TOR-I), 373 (CNI)					
Heterogeneity: Tau^2=0.03; Chi^2=22.44, df=18(P=0.21); I^2=19.8%					
Test for overall effect: Z=4.75(P<0.0001)					
Test for subgroup differences: Chi^2=0.45, df=1 (P=0.5), I^2=0%					



Less with TOR-I — Less with CNI

Analysis 12.3. Comparison 12 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): subgroup analyses, Outcome 3 All acute rejection (CNI comparator).

Study or subgroup	TOR-I n/N	CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.3.1 Tacrolimus					
Schaefer 2006	5/41	1/39		1.39%	4.76[0.58,38.91]
Fernandes-Charpiot 2014	7/33	4/35		4.64%	1.86[0.6,5.76]
Gelens 2006	9/18	5/18		7.55%	1.8[0.75,4.32]



Less with TOR-I — Less with CNI

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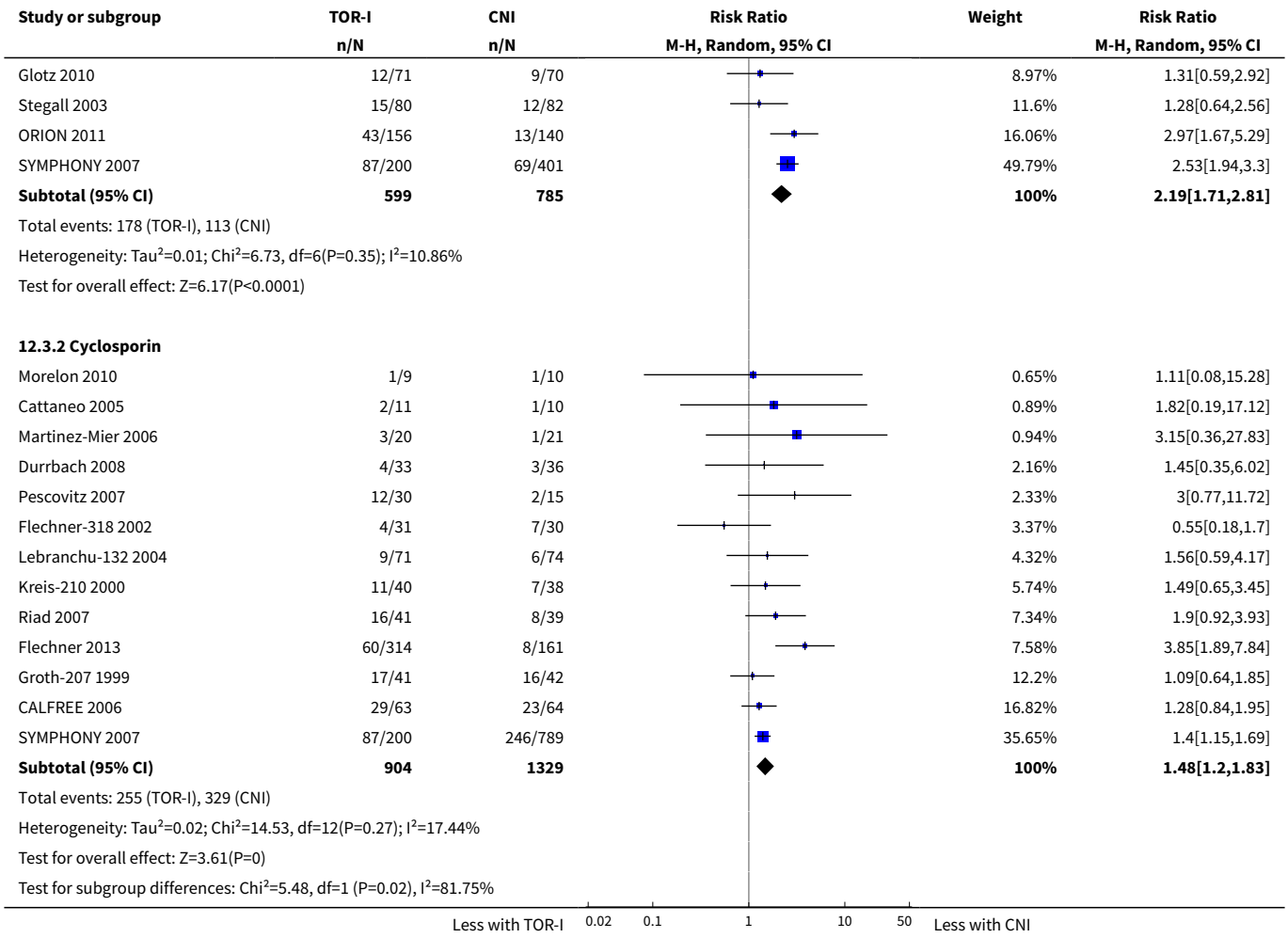
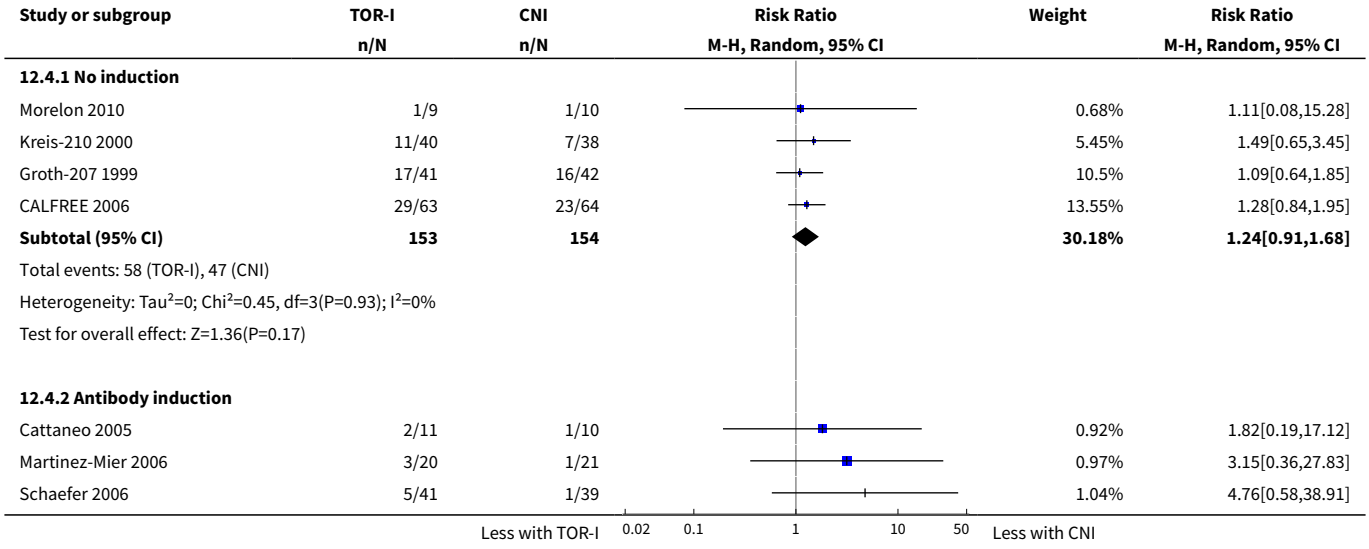


Analysis 12.4. Comparison 12 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): subgroup analyses, Outcome 4 All acute rejection (antibody induction).



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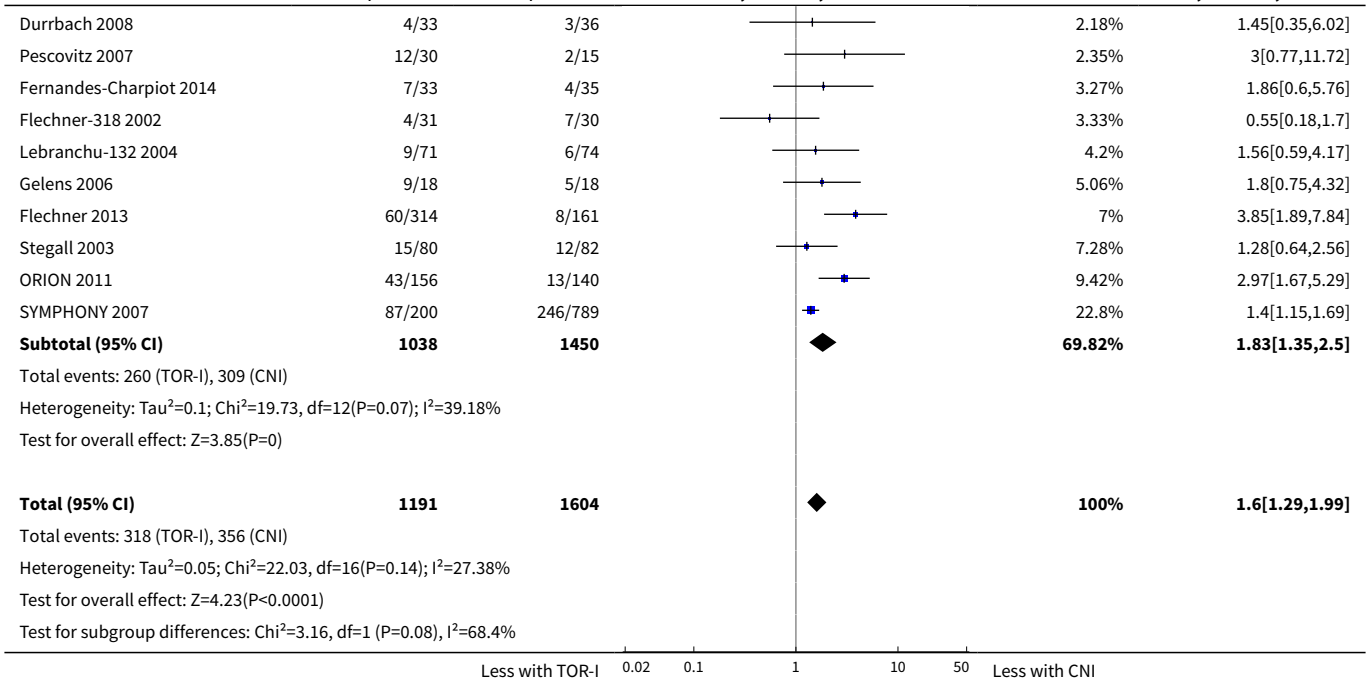
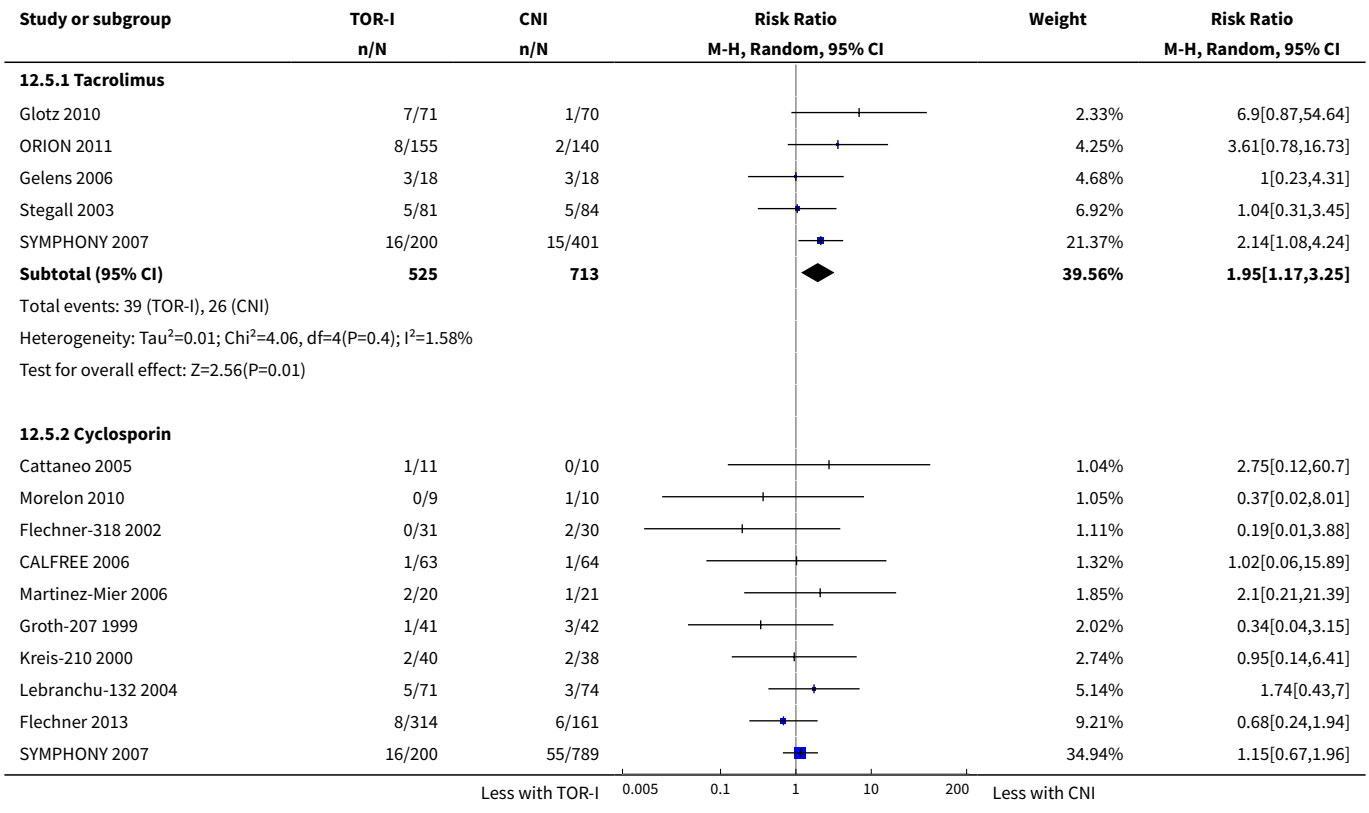


Analysis 12.5. Comparison 12 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): subgroup analyses, Outcome 5 Graft loss censored for death (CNI comparator).



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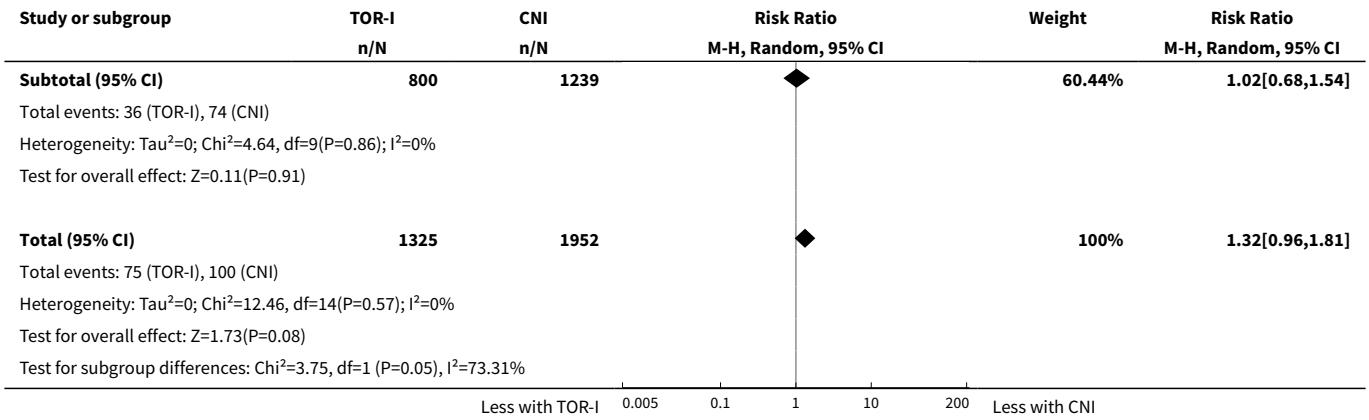
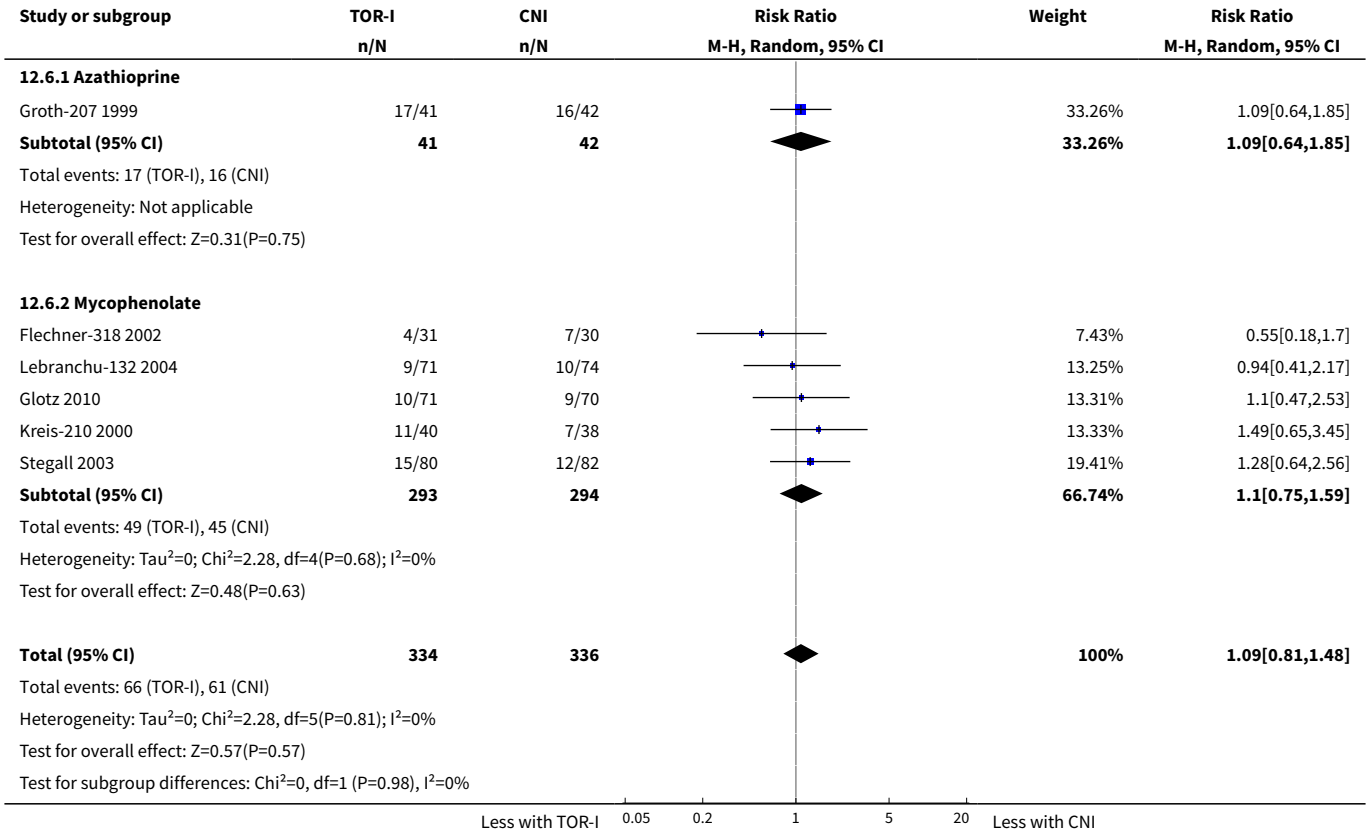


Analysis 12.6. Comparison 12 Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): subgroup analyses, Outcome 6 Acute rejection (antimetabolite co-intervention).



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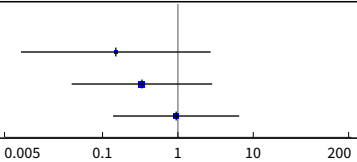
Comparison 13. Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection (publication type)	32	10687	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.07]
1.1 Abstract	5	273	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.29, 1.61]
1.2 Journal	27	10414	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.80, 1.08]
2 Acute rejection (risk of bias for sequence generation and allocation concealment	32	10535	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.09]
2.1 Low risk of bias	12	7313	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.73, 1.06]
2.2 High risk or unclear risk of bias	20	3222	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.26]
3 Acute rejection (CNI co-intervention)	27	7437	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.02]
3.1 Tacrolimus	18	4341	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.14]
3.2 Cyclosporin	9	3096	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.93]
4 Acute rejection (TOR-I)	32	10538	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.08]
4.1 Everolimus	16	6126	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.85, 1.26]
4.2 Sirolimus	16	4412	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.04]
5 Acute rejection (antibody induction)	31	10476	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.07]
5.1 No induction	10	5293	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.12]
5.2 Antibody induction	21	5183	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.70, 1.16]
6 Acute rejection (antimetabolite comparator)	32	10538	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.08]
6.1 Azathioprine	2	789	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.39, 1.28]
6.2 Mycophenolate	30	9749	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]

Analysis 13.1. Comparison 13 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): subgroup analyses, Outcome 1 Acute rejection (publication type).

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.1.1 Abstract					
Shetty 2015	0/19	3/20		0.24%	0.15[0.01,2.72]
Ciancio 2016	1/15	3/15		0.42%	0.33[0.04,2.85]
Esmeraldo 2015	2/59	2/56		0.52%	0.95[0.14,6.51]



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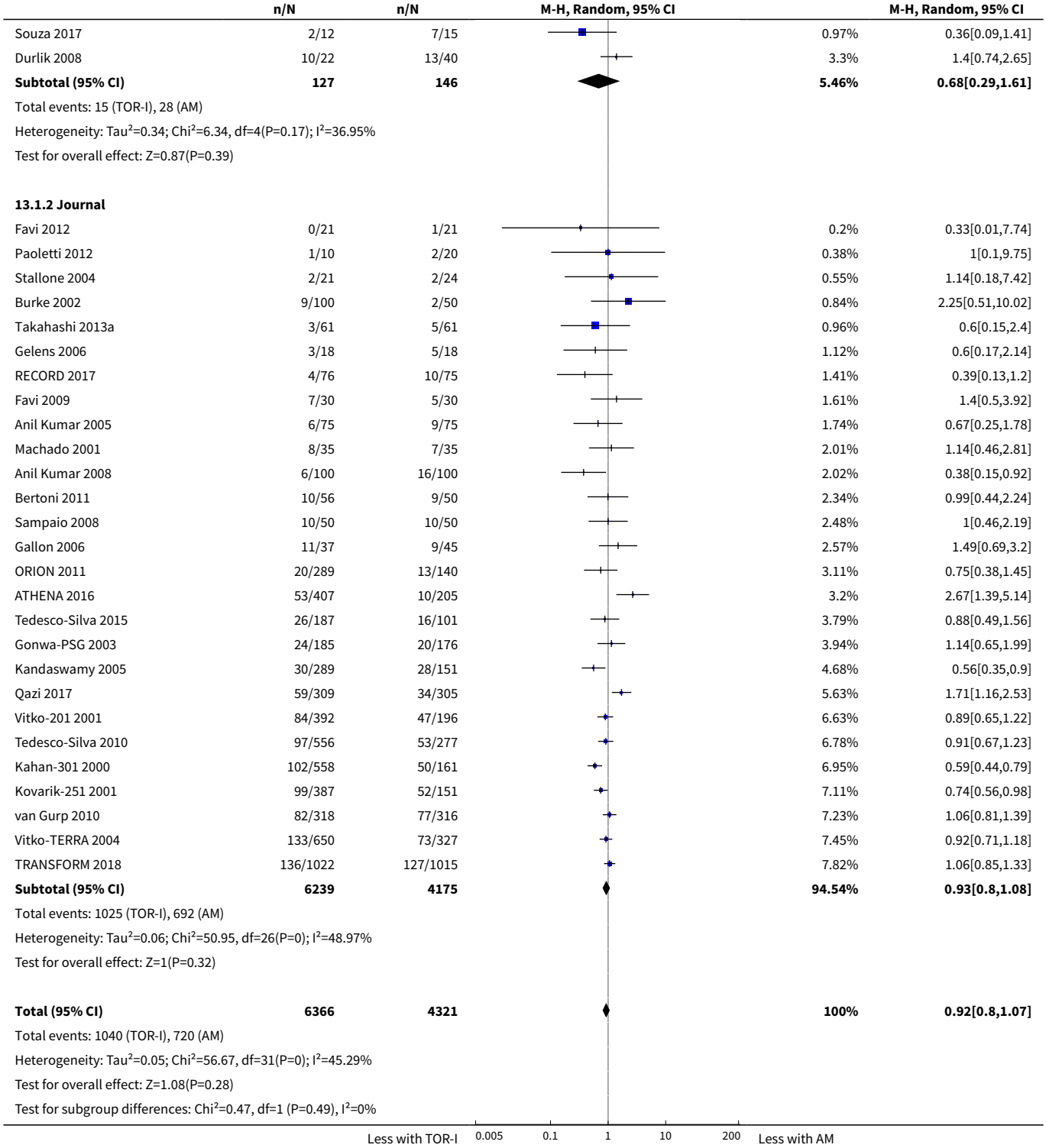

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Souza 2017	2/12	7/15		0.97%	0.36[0.09,1.41]
Durlik 2008	10/22	13/40		3.3%	1.4[0.74,2.65]
Subtotal (95% CI)	**127**	**146**		**5.46%**	**0.68[0.29,1.61]**
Total events: 15 (TOR-I), 28 (AM)					
Heterogeneity: Tau²=0.34; Chi²=6.34, df=4(P=0.17); I²=36.95%					
Test for overall effect: Z=0.87(P=0.39)					
13.1.2 Journal					
Favi 2012	0/21	1/21		0.2%	0.33[0.01,7.74]
Paoletti 2012	1/10	2/20		0.38%	1[0.1,9.75]
Stallone 2004	2/21	2/24		0.55%	1.14[0.18,7.42]
Burke 2002	9/100	2/50		0.84%	2.25[0.51,10.02]
Takahashi 2013a	3/61	5/61		0.96%	0.6[0.15,2.4]
Gelens 2006	3/18	5/18		1.12%	0.6[0.17,2.14]
RECORD 2017	4/76	10/75		1.41%	0.39[0.13,1.2]
Favi 2009	7/30	5/30		1.61%	1.4[0.5,3.92]
Anil Kumar 2005	6/75	9/75		1.74%	0.67[0.25,1.78]
Machado 2001	8/35	7/35		2.01%	1.14[0.46,2.81]
Anil Kumar 2008	6/100	16/100		2.02%	0.38[0.15,0.92]
Bertoni 2011	10/56	9/50		2.34%	0.99[0.44,2.24]
Sampaio 2008	10/50	10/50		2.48%	1[0.46,2.19]
Gallon 2006	11/37	9/45		2.57%	1.49[0.69,3.2]
ORION 2011	20/289	13/140		3.11%	0.75[0.38,1.45]
ATHENA 2016	53/407	10/205		3.2%	2.67[1.39,5.14]
Tedesco-Silva 2015	26/187	16/101		3.79%	0.88[0.49,1.56]
Gonwa-PSG 2003	24/185	20/176		3.94%	1.14[0.65,1.99]
Kandaswamy 2005	30/289	28/151		4.68%	0.56[0.35,0.9]
Qazi 2017	59/309	34/305		5.63%	1.71[1.16,2.53]
Vitko-201 2001	84/392	47/196		6.63%	0.89[0.65,1.22]
Tedesco-Silva 2010	97/556	53/277		6.78%	0.91[0.67,1.23]
Kahan-301 2000	102/558	50/161		6.95%	0.59[0.44,0.79]
Kovarik-251 2001	99/387	52/151		7.11%	0.74[0.56,0.98]
van Gurp 2010	82/318	77/316		7.23%	1.06[0.81,1.39]
Vitko-TERRA 2004	133/650	73/327		7.45%	0.92[0.71,1.18]
TRANSFORM 2018	136/1022	127/1015		7.82%	1.06[0.85,1.33]
Subtotal (95% CI)	**6239**	**4175**		**94.54%**	**0.93[0.8,1.08]**
Total events: 1025 (TOR-I), 692 (AM)					
Heterogeneity: Tau²=0.06; Chi²=50.95, df=26(P=0); I²=48.97%					
Test for overall effect: Z=1(P=0.32)					
Total (95% CI)	**6366**	**4321**		**100%**	**0.92[0.8,1.07]**
Total events: 1040 (TOR-I), 720 (AM)					
Heterogeneity: Tau²=0.05; Chi²=56.67, df=31(P=0); I²=45.29%					
Test for overall effect: Z=1.08(P=0.28)					
Test for subgroup differences: Chi²=0.47, df=1 (P=0.49), I²=0%					

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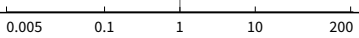
Analysis 13.2. Comparison 13 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): subgroup analyses, Outcome 2 Acute rejection (risk of bias for sequence generation and allocation concealment.

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.2.1 Low risk of bias					
Takahashi 2013a	3/61	5/61		0.9%	0.6[0.15,2.4]
RECORD 2017	4/76	10/75		1.33%	0.39[0.13,1.2]
Anil Kumar 2005	6/75	9/75		1.66%	0.67[0.25,1.78]
Anil Kumar 2008	6/100	16/100		1.94%	0.38[0.15,0.92]
Tedesco-Silva 2015	26/187	16/101		3.8%	0.88[0.49,1.56]
Qazi 2017	59/309	34/305		5.91%	1.71[1.16,2.53]
Vitko-201 2001	84/392	47/196		7.15%	0.89[0.65,1.22]
Tedesco-Silva 2010	97/556	53/277		7.34%	0.91[0.67,1.23]
Kahan-301 2000	102/558	50/161		7.56%	0.59[0.44,0.79]
van Gurp 2010	82/318	77/316		7.92%	1.06[0.81,1.39]
Vitko-TERRA 2004	123/650	73/327		8.14%	0.85[0.66,1.1]
TRANSFORM 2018	136/1022	127/1015		8.72%	1.06[0.85,1.33]
Subtotal (95% CI)	**4304**	**3009**		**62.36%**	**0.88[0.73,1.06]**
Total events: 728 (TOR-I), 517 (AM)					
Heterogeneity: Tau^2=0.06; Chi^2=28.79, df=11(P=0); I^2=61.79%					
Test for overall effect: Z=1.31(P=0.19)					
13.2.2 High risk or unclear risk of bias					
Favi 2012	0/21	1/21		0.19%	0.33[0.01,7.74]
Shetty 2015	0/19	3/20		0.22%	0.15[0.01,2.72]
Paoletti 2012	1/10	2/20		0.35%	1[0.1,9.75]
Ciancio 2016	1/15	3/15		0.39%	0.33[0.04,2.85]
Esmeraldo 2015	2/59	2/56		0.48%	0.95[0.14,6.51]
Stallone 2004	2/21	2/24		0.51%	1.14[0.18,7.42]
Burke 2002	9/100	2/50		0.78%	2.25[0.51,10.02]
Souza 2017	2/12	7/15		0.91%	0.36[0.09,1.41]
Gelens 2006	3/18	5/18		1.05%	0.6[0.17,2.14]
Favi 2009	7/30	5/30		1.53%	1.4[0.5,3.92]
Kandaswamy 2005	9/154	6/85		1.61%	0.83[0.31,2.25]
Machado 2001	8/35	7/35		1.93%	1.14[0.46,2.81]
Bertoni 2011	10/56	9/50		2.26%	0.99[0.44,2.24]
Sampaio 2008	10/50	10/50		2.41%	1[0.46,2.19]
Gallon 2006	11/41	9/45		2.46%	1.34[0.62,2.9]
ORION 2011	20/289	13/140		3.07%	0.75[0.38,1.45]
ATHENA 2016	53/407	10/205		3.16%	2.67[1.39,5.14]
Durlik 2008	10/22	13/40		3.27%	1.4[0.74,2.65]
Gonwa-PSG 2003	24/185	20/176		3.96%	1.14[0.65,1.99]
Kovarik-251 2001	80/387	47/196		7.09%	0.86[0.63,1.18]
Subtotal (95% CI)	**1931**	**1291**		**37.64%**	**1.04[0.87,1.26]**
Total events: 262 (TOR-I), 176 (AM)					
Heterogeneity: Tau^2=0.01; Chi^2=19.64, df=19(P=0.42); I^2=3.23%					
Test for overall effect: Z=0.46(P=0.65)					
Total (95% CI)	**6235**	**4300**		**100%**	**0.95[0.83,1.09]**
Total events: 990 (TOR-I), 693 (AM)					
Heterogeneity: Tau^2=0.04; Chi^2=49.87, df=31(P=0.02); I^2=37.84%					
Test for overall effect: Z=0.76(P=0.44)					
Test for subgroup differences: Chi^2=1.56, df=1 (P=0.21), I^2=36.1%					



Less with TOR-I — Less with AM

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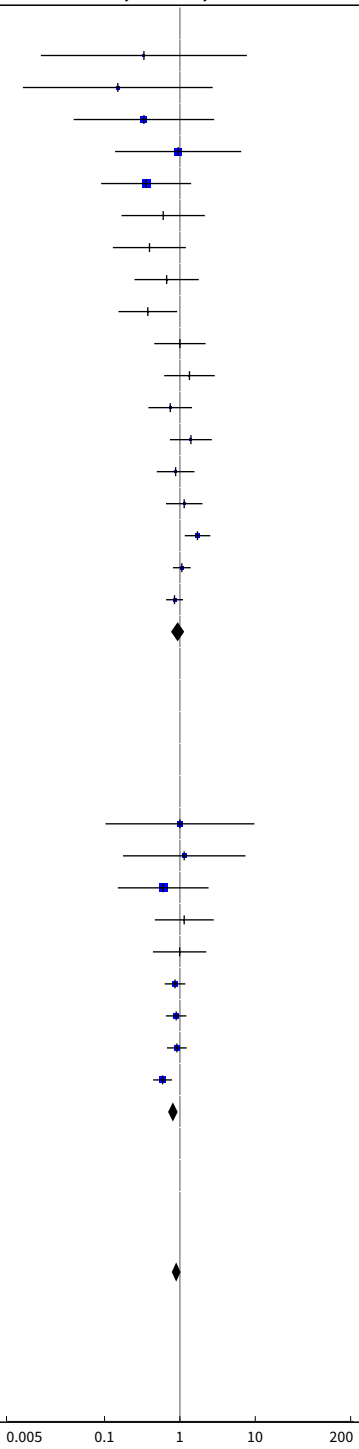
Analysis 13.3. Comparison 13 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): subgroup analyses, Outcome 3 Acute rejection (CNI co-intervention).

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.3.1 Tacrolimus					
Favi 2012	0/21	1/21		0.18%	0.33[0.01,7.74]
Shetty 2015	0/19	3/20		0.22%	0.15[0.01,2.72]
Ciancio 2016	1/15	3/15		0.39%	0.33[0.04,2.85]
Esmeraldo 2015	2/59	2/56		0.48%	0.95[0.14,6.51]
Souza 2017	2/12	7/15		0.92%	0.36[0.09,1.41]
Gelens 2006	3/18	5/18		1.07%	0.6[0.17,2.14]
RECORD 2017	4/76	10/75		1.37%	0.39[0.13,1.2]
Anil Kumar 2005	6/75	9/75		1.72%	0.67[0.25,1.78]
Anil Kumar 2008	6/100	16/100		2.03%	0.38[0.15,0.92]
Sampaio 2008	10/50	10/50		2.56%	1[0.46,2.19]
Gallon 2006	11/41	9/45		2.62%	1.34[0.62,2.9]
ORION 2011	20/289	13/140		3.33%	0.75[0.38,1.45]
Durlik 2008	10/22	13/40		3.57%	1.4[0.74,2.65]
Tedesco-Silva 2015	26/187	16/101		4.23%	0.88[0.49,1.56]
Gonwa-PSG 2003	24/185	20/176		4.43%	1.14[0.65,1.99]
Qazi 2017	59/309	34/305		7.08%	1.71[1.16,2.53]
van Gurp 2010	82/318	77/316		10.24%	1.06[0.81,1.39]
Vitko-TERRA 2004	123/650	73/327		10.61%	0.85[0.66,1.1]
Subtotal (95% CI)	**2446**	**1895**		**57.06%**	**0.93[0.76,1.14]**
Total events: 389 (TOR-I), 321 (AM)					
Heterogeneity: Tau^2=0.05; Chi^2=25.55, df=17(P=0.08); I^2=33.45%					
Test for overall effect: Z=0.67(P=0.5)					
13.3.2 Cyclosporin					
Paoletti 2012	1/10	2/20		0.35%	1[0.1,9.75]
Stallone 2004	2/21	2/24		0.51%	1.14[0.18,7.42]
Takahashi 2013a	3/61	5/61		0.91%	0.6[0.15,2.4]
Machado 2001	8/35	7/35		2.01%	1.14[0.46,2.81]
Bertoni 2011	10/56	9/50		2.39%	0.99[0.44,2.24]
Kovarik-251 2001	80/387	47/196		8.88%	0.86[0.63,1.18]
Vitko-201 2001	84/392	47/196		8.97%	0.89[0.65,1.22]
Tedesco-Silva 2010	97/556	53/277		9.28%	0.91[0.67,1.23]
Kahan-301 2000	102/558	50/161		9.64%	0.59[0.44,0.79]
Subtotal (95% CI)	**2076**	**1020**		**42.94%**	**0.81[0.7,0.93]**
Total events: 387 (TOR-I), 222 (AM)					
Heterogeneity: Tau^2=0; Chi^2=6.97, df=8(P=0.54); I^2=0%					
Test for overall effect: Z=2.88(P=0)					
Total (95% CI)	**4522**	**2915**		**100%**	**0.89[0.78,1.02]**
Total events: 776 (TOR-I), 543 (AM)					
Heterogeneity: Tau^2=0.03; Chi^2=35.9, df=26(P=0.09); I^2=27.58%					
Test for overall effect: Z=1.63(P=0.1)					
Test for subgroup differences: Chi^2=1.31, df=1 (P=0.25), I^2=23.87%					



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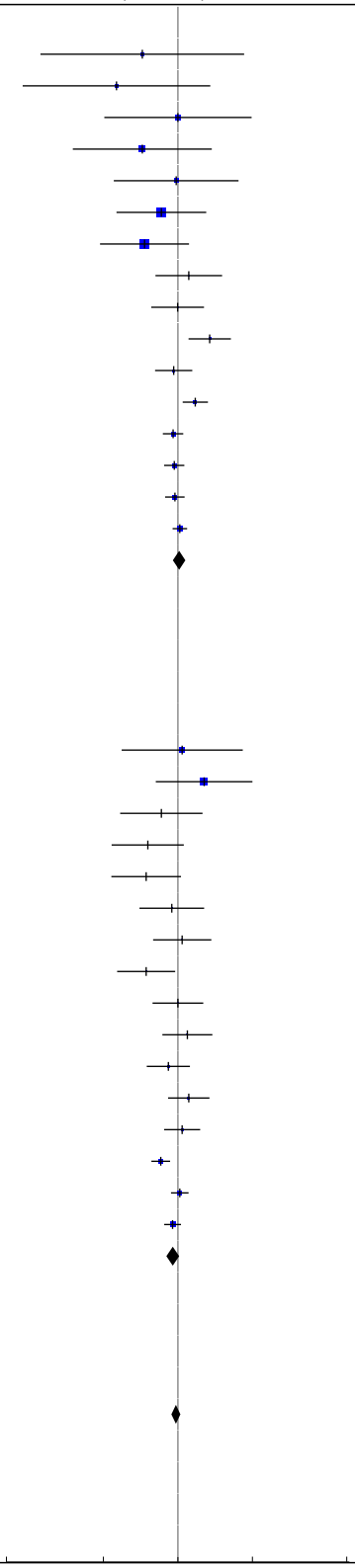
Analysis 13.4. Comparison 13 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): subgroup analyses, Outcome 4 Acute rejection (TOR-I).

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.4.1 Everolimus					
Favi 2012	0/21	1/21		0.2%	0.33[0.01,7.74]
Shetty 2015	0/19	3/20		0.23%	0.15[0.01,2.72]
Paoletti 2012	1/10	2/20		0.37%	1[0.1,9.75]
Ciancio 2016	1/15	3/15		0.42%	0.33[0.04,2.85]
Esmeraldo 2015	2/59	2/56		0.51%	0.95[0.14,6.51]
Takahashi 2013a	3/61	5/61		0.94%	0.6[0.15,2.4]
Souza 2017	2/12	7/15		0.96%	0.36[0.09,1.41]
Favi 2009	7/30	5/30		1.6%	1.4[0.5,3.92]
Bertoni 2011	10/56	9/50		2.34%	0.99[0.44,2.24]
ATHENA 2016	53/407	10/205		3.25%	2.67[1.39,5.14]
Tedesco-Silva 2015	26/187	16/101		3.87%	0.88[0.49,1.56]
Qazi 2017	59/309	34/305		5.9%	1.71[1.16,2.53]
Kovarik-251 2001	80/387	47/196		6.99%	0.86[0.63,1.18]
Vitko-201 2001	84/392	47/196		7.04%	0.89[0.65,1.22]
Tedesco-Silva 2010	97/556	53/277		7.21%	0.91[0.67,1.23]
TRANSFORM 2018	136/1022	127/1015		8.45%	1.06[0.85,1.33]
Subtotal (95% CI)	**3543**	**2583**		**50.28%**	**1.04[0.85,1.26]**
Total events: 561 (TOR-I), 371 (AM)					
Heterogeneity: Tau^2=0.04; Chi^2=24.19, df=15(P=0.06); I^2=37.98%					
Test for overall effect: Z=0.37(P=0.71)					
13.4.2 Sirolimus					
Stallone 2004	2/21	2/24		0.54%	1.14[0.18,7.42]
Burke 2002	9/100	2/50		0.82%	2.25[0.51,10.02]
Gelens 2006	3/18	5/18		1.1%	0.6[0.17,2.14]
RECORD 2017	4/76	10/75		1.39%	0.39[0.13,1.2]
Anil Kumar 2005	4/69	13/84		1.49%	0.37[0.13,1.1]
Kandaswamy 2005	9/154	6/85		1.68%	0.83[0.31,2.25]
Machado 2001	8/35	7/35		2%	1.14[0.46,2.81]
Anil Kumar 2008	6/100	16/100		2.01%	0.38[0.15,0.92]
Sampaio 2008	10/50	10/50		2.49%	1[0.46,2.19]
Gallon 2006	11/41	9/45		2.55%	1.34[0.62,2.9]
ORION 2011	20/289	13/140		3.15%	0.75[0.38,1.45]
Durlik 2008	10/22	13/40		3.35%	1.4[0.74,2.65]
Gonwa-PSG 2003	24/185	20/176		4.03%	1.14[0.65,1.99]
Kahan-301 2000	102/558	50/161		7.42%	0.59[0.44,0.79]
van Gurp 2010	82/318	77/316		7.74%	1.06[0.81,1.39]
Vitko-TERRA 2004	123/650	73/327		7.94%	0.85[0.66,1.1]
Subtotal (95% CI)	**2686**	**1726**		**49.72%**	**0.85[0.7,1.04]**
Total events: 427 (TOR-I), 326 (AM)					
Heterogeneity: Tau^2=0.05; Chi^2=23.49, df=15(P=0.07); I^2=36.14%					
Test for overall effect: Z=1.58(P=0.11)					
Total (95% CI)	**6229**	**4309**		**100%**	**0.94[0.82,1.08]**
Total events: 988 (TOR-I), 697 (AM)					
Heterogeneity: Tau^2=0.05; Chi^2=52.19, df=31(P=0.01); I^2=40.6%					
Test for overall effect: Z=0.85(P=0.39)					
Test for subgroup differences: Chi^2=1.92, df=1 (P=0.17), I^2=47.97%					



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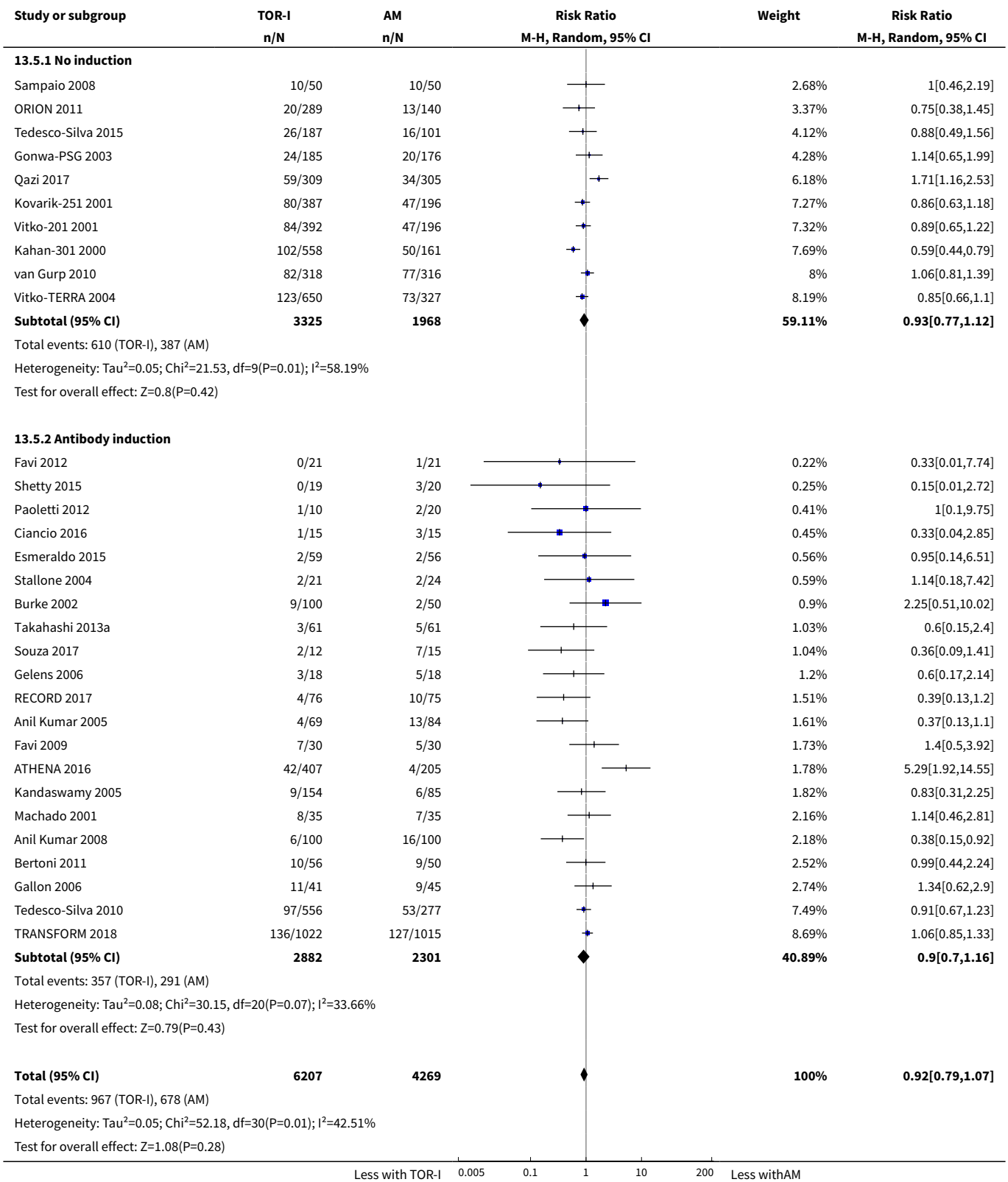
Analysis 13.5. Comparison 13 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): subgroup analyses, Outcome 5 Acute rejection (antibody induction).



Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.5.1 No induction					
Sampaio 2008	10/50	10/50		2.68%	1[0.46,2.19]
ORION 2011	20/289	13/140		3.37%	0.75[0.38,1.45]
Tedesco-Silva 2015	26/187	16/101		4.12%	0.88[0.49,1.56]
Gonwa-PSG 2003	24/185	20/176		4.28%	1.14[0.65,1.99]
Qazi 2017	59/309	34/305		6.18%	1.71[1.16,2.53]
Kovarik-251 2001	80/387	47/196		7.27%	0.86[0.63,1.18]
Vitko-201 2001	84/392	47/196		7.32%	0.89[0.65,1.22]
Kahan-301 2000	102/558	50/161		7.69%	0.59[0.44,0.79]
van Gurp 2010	82/318	77/316		8%	1.06[0.81,1.39]
Vitko-TERRA 2004	123/650	73/327		8.19%	0.85[0.66,1.1]
Subtotal (95% CI)	**3325**	**1968**		**59.11%**	**0.93[0.77,1.12]**
Total events: 610 (TOR-I), 387 (AM)					
Heterogeneity: Tau^2=0.05; Chi^2=21.53, df=9(P=0.01); I^2=58.19%					
Test for overall effect: Z=0.8(P=0.42)					
13.5.2 Antibody induction					
Favi 2012	0/21	1/21		0.22%	0.33[0.01,7.74]
Shetty 2015	0/19	3/20		0.25%	0.15[0.01,2.72]
Paoletti 2012	1/10	2/20		0.41%	1[0.1,9.75]
Ciancio 2016	1/15	3/15		0.45%	0.33[0.04,2.85]
Esmeraldo 2015	2/59	2/56		0.56%	0.95[0.14,6.51]
Stallone 2004	2/21	2/24		0.59%	1.14[0.18,7.42]
Burke 2002	9/100	2/50		0.9%	2.25[0.51,10.02]
Takahashi 2013a	3/61	5/61		1.03%	0.6[0.15,2.4]
Souza 2017	2/12	7/15		1.04%	0.36[0.09,1.41]
Gelens 2006	3/18	5/18		1.2%	0.6[0.17,2.14]
RECORD 2017	4/76	10/75		1.51%	0.39[0.13,1.2]
Anil Kumar 2005	4/69	13/84		1.61%	0.37[0.13,1.1]
Favi 2009	7/30	5/30		1.73%	1.4[0.5,3.92]
ATHENA 2016	42/407	4/205		1.78%	5.29[1.92,14.55]
Kandaswamy 2005	9/154	6/85		1.82%	0.83[0.31,2.25]
Machado 2001	8/35	7/35		2.16%	1.14[0.46,2.81]
Anil Kumar 2008	6/100	16/100		2.18%	0.38[0.15,0.92]
Bertoni 2011	10/56	9/50		2.52%	0.99[0.44,2.24]
Gallon 2006	11/41	9/45		2.74%	1.34[0.62,2.9]
Tedesco-Silva 2010	97/556	53/277		7.49%	0.91[0.67,1.23]
TRANSFORM 2018	136/1022	127/1015		8.69%	1.06[0.85,1.33]
Subtotal (95% CI)	**2882**	**2301**		**40.89%**	**0.9[0.7,1.16]**
Total events: 357 (TOR-I), 291 (AM)					
Heterogeneity: Tau^2=0.08; Chi^2=30.15, df=20(P=0.07); I^2=33.66%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**6207**	**4269**		**100%**	**0.92[0.79,1.07]**
Total events: 967 (TOR-I), 678 (AM)					
Heterogeneity: Tau^2=0.05; Chi^2=52.18, df=30(P=0.01); I^2=42.51%					
Test for overall effect: Z=1.08(P=0.28)					

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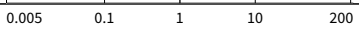
Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.02, df=1 (P=0.88), I²=0%					

Analysis 13.6. Comparison 13 Target of rapamycin inhibitors (TOR-I) versus antimetabolites (AM): subgroup analyses, Outcome 6 Acute rejection (antimetabolite comparator).

Study or subgroup	TOR-I n/N	AM n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.6.1 Azathioprine					
Machado 2001	8/35	7/35		2%	1.14[0.46,2.81]
Kahan-301 2000	102/558	50/161		7.42%	0.59[0.44,0.79]
Subtotal (95% CI)	**593**	**196**		**9.42%**	**0.71[0.39,1.28]**
Total events: 110 (TOR-I), 57 (AM)					
Heterogeneity: Tau²=0.1; Chi²=1.9, df=1(P=0.17); I²=47.42%					
Test for overall effect: Z=1.13(P=0.26)					
13.6.2 Mycophenolate					
Favi 2012	0/21	1/21		0.2%	0.33[0.01,7.74]
Shetty 2015	0/19	3/20		0.23%	0.15[0.01,2.72]
Paoletti 2012	1/10	2/20		0.37%	1[0.1,9.75]
Ciancio 2016	1/15	3/15		0.42%	0.33[0.04,2.85]
Esmeraldo 2015	2/59	2/56		0.51%	0.95[0.14,6.51]
Stallone 2004	2/21	2/24		0.54%	1.14[0.18,7.42]
Burke 2002	9/100	2/50		0.82%	2.25[0.51,10.02]
Takahashi 2013a	3/61	5/61		0.94%	0.6[0.15,2.4]
Souza 2017	2/12	7/15		0.96%	0.36[0.09,1.41]
Gelens 2006	3/18	5/18		1.1%	0.6[0.17,2.14]
RECORD 2017	4/76	10/75		1.39%	0.39[0.13,1.2]
Anil Kumar 2005	4/69	13/84		1.49%	0.37[0.13,1.1]
Favi 2009	7/30	5/30		1.6%	1.4[0.5,3.92]
Kandaswamy 2005	9/154	6/85		1.68%	0.83[0.31,2.25]
Anil Kumar 2008	6/100	16/100		2.01%	0.38[0.15,0.92]
Bertoni 2011	10/56	9/50		2.34%	0.99[0.44,2.24]
Sampaio 2008	10/50	10/50		2.49%	1[0.46,2.19]
Gallon 2006	11/41	9/45		2.55%	1.34[0.62,2.9]
ORION 2011	20/289	13/140		3.15%	0.75[0.38,1.45]
ATHENA 2016	53/407	10/205		3.25%	2.67[1.39,5.14]
Durlik 2008	10/22	13/40		3.35%	1.4[0.74,2.65]
Tedesco-Silva 2015	26/187	16/101		3.87%	0.88[0.49,1.56]
Gonwa-PSG 2003	24/185	20/176		4.03%	1.14[0.65,1.99]
Qazi 2017	59/309	34/305		5.9%	1.71[1.16,2.53]
Kovarik-251 2001	80/387	47/196		6.99%	0.86[0.63,1.18]
Vitko-201 2001	84/392	47/196		7.04%	0.89[0.65,1.22]
Tedesco-Silva 2010	97/556	53/277		7.21%	0.91[0.67,1.23]
van Gurp 2010	82/318	77/316		7.74%	1.06[0.81,1.39]
Vitko-TERRA 2004	123/650	73/327		7.94%	0.85[0.66,1.1]
TRANSFORM 2018	136/1022	127/1015		8.45%	1.06[0.85,1.33]
Subtotal (95% CI)	**5636**	**4113**		**90.58%**	**0.98[0.86,1.12]**
Total events: 878 (TOR-I), 640 (AM)					



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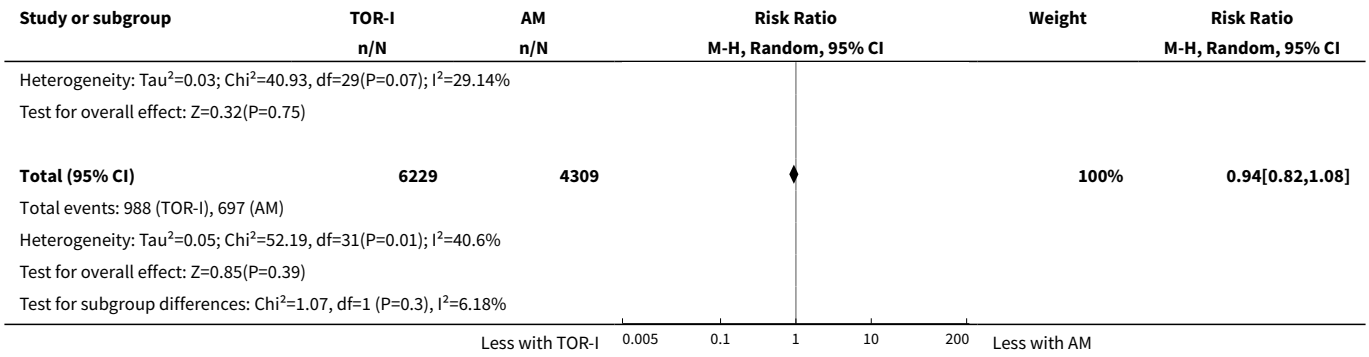

Comparison 14. Variable dose target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection (publication type)	9	1517	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.04]
1.1 Abstract	2	370	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.53, 1.42]
1.2 Journal	7	1147	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.62, 1.06]
2 Acute rejection (risk of bias for sequence generation and allocation concealment	9	1517	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.04]
2.1 Low risk of bias	2	370	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.50, 1.46]
2.2 High or unclear risk of bias	7	1147	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.59, 1.06]
3 Acute rejection (CNI co-intervention)	9	1517	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.04]
3.1 Tacrolimus	5	603	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.51, 1.16]
3.2 Cyclosporin	4	914	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.14]
4 Acute rejection (TOR-I)	9	1517	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.04]
4.1 Everolimus	2	593	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.32]
4.2 Sirolimus	7	924	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.03]
5 Acute rejection (antibody induction)	9	1517	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.04]
5.1 No induction	6	904	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.53, 0.98]
5.2 Antibody induction	3	613	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.69, 1.46]

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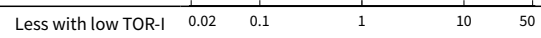
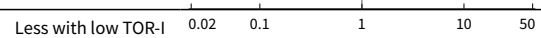
Analysis 14.1. Comparison 14 Variable dose target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): subgroup analyses, Outcome 1 Acute rejection (publication type).

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
14.1.1 Abstract					
Russ 2003	7/31	6/31		5.88%	1.17[0.44,3.08]
Cohen 2002	18/154	23/154		16.75%	0.78[0.44,1.39]
Subtotal (95% CI)	**185**	**185**		**22.63%**	**0.87[0.53,1.42]**
Total events: 25 (Low TOR-I), 29 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=0.56(P=0.58)					
14.1.2 Journal					
Lo 2004	1/16	1/23		0.76%	1.44[0.1,21.33]
Bechstein-193 2013	5/65	11/63		5.55%	0.44[0.16,1.2]
Kahan-203 1999	5/47	16/77		6.31%	0.51[0.2,1.31]
Grinyo 2004	7/43	12/42		8.04%	0.57[0.25,1.31]
Kandaswamy 2005	15/149	15/140		12.06%	0.94[0.48,1.85]
Velosa-212 2001	18/97	22/100		17.85%	0.84[0.48,1.47]
EVEREST 2009	30/143	29/142		26.79%	1.03[0.65,1.62]
Subtotal (95% CI)	**560**	**587**		**77.37%**	**0.81[0.62,1.06]**
Total events: 81 (Low TOR-I), 106 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=4.48, df=6(P=0.61); I^2=0%					
Test for overall effect: Z=1.52(P=0.13)					
Total (95% CI)	**745**	**772**		**100%**	**0.82[0.65,1.04]**
Total events: 106 (Low TOR-I), 135 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=5.02, df=8(P=0.76); I^2=0%					
Test for overall effect: Z=1.61(P=0.11)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%					



Analysis 14.2. Comparison 14 Variable dose target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): subgroup analyses, Outcome 2 Acute rejection (risk of bias for sequence generation and allocation concealment.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
14.2.1 Low risk of bias					
Grinyo 2004	7/43	12/42		8.04%	0.57[0.25,1.31]
EVEREST 2009	30/143	29/142		26.79%	1.03[0.65,1.62]
Subtotal (95% CI)	**186**	**184**		**34.84%**	**0.85[0.5,1.46]**
Total events: 37 (Low TOR-I), 41 (High TOR-I)					
Heterogeneity: Tau^2=0.06; Chi^2=1.49, df=1(P=0.22); I^2=32.98%					
Test for overall effect: Z=0.59(P=0.56)					
14.2.2 High or unclear risk of bias					
Lo 2004	1/16	1/23		0.76%	1.44[0.1,21.33]
Bechstein-193 2013	5/65	11/63		5.55%	0.44[0.16,1.2]
Russ 2003	7/31	6/31		5.88%	1.17[0.44,3.08]
Kahan-203 1999	5/47	16/77		6.31%	0.51[0.2,1.31]
Kandaswamy 2005	15/149	15/140		12.06%	0.94[0.48,1.85]



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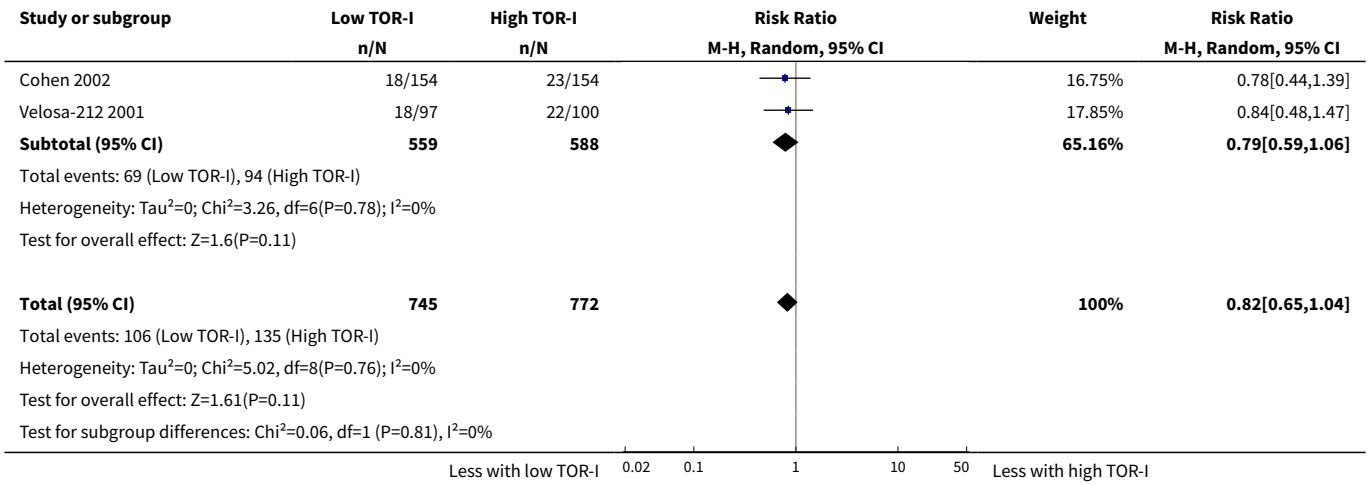
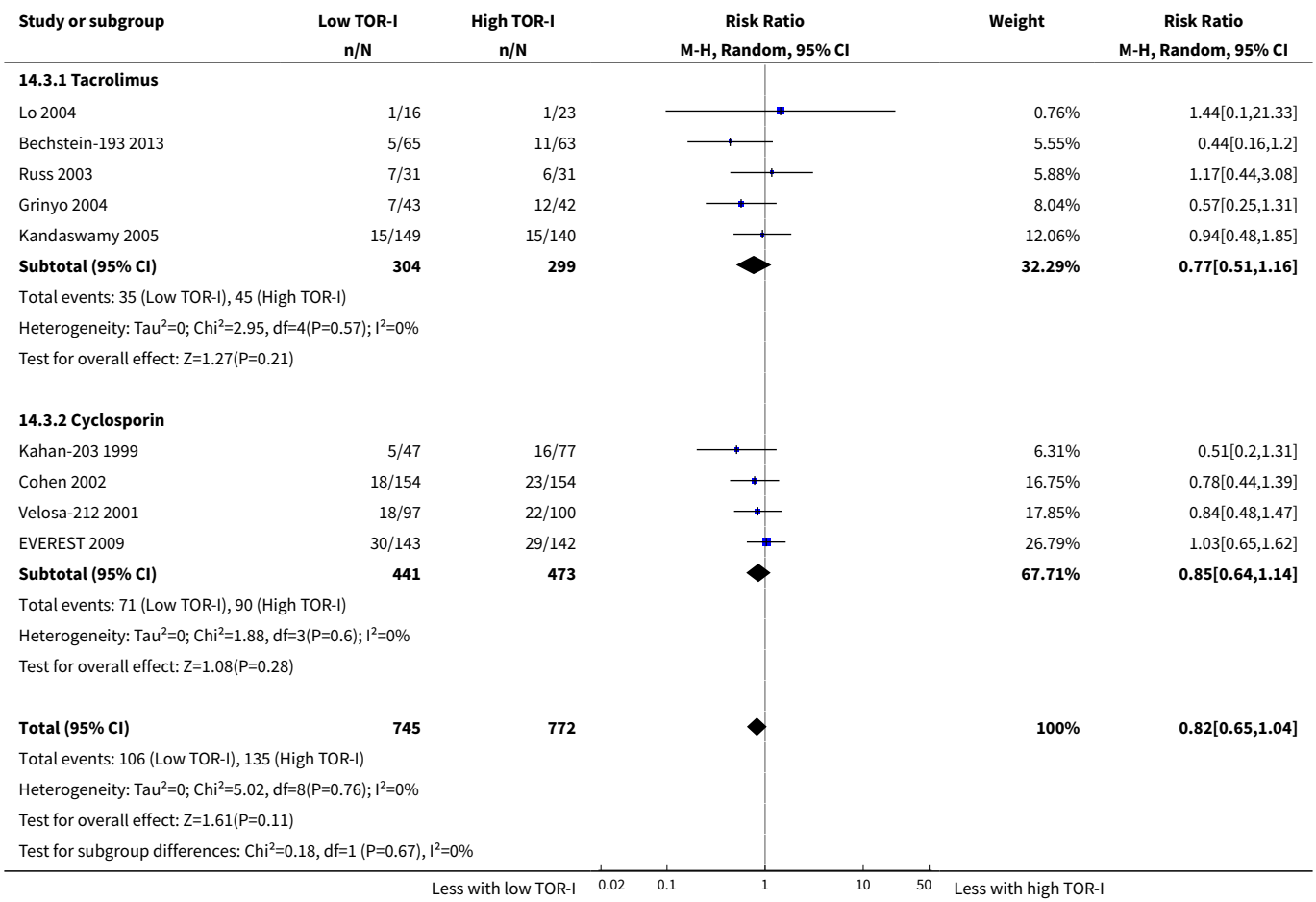


Analysis 14.3. Comparison 14 Variable dose target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): subgroup analyses, Outcome 3 Acute rejection (CNI co-intervention).



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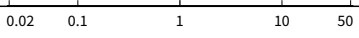
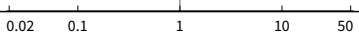
Analysis 14.4. Comparison 14 Variable dose target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): subgroup analyses, Outcome 4 Acute rejection (TOR-I).

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
14.4.1 Everolimus					
Cohen 2002	18/154	23/154		16.75%	0.78[0.44,1.39]
EVEREST 2009	30/143	29/142		26.79%	1.03[0.65,1.62]
Subtotal (95% CI)	**297**	**296**		**43.54%**	**0.93[0.65,1.32]**
Total events: 48 (Low TOR-I), 52 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=0.43(P=0.67)					
14.4.2 Sirolimus					
Lo 2004	1/16	1/23		0.76%	1.44[0.1,21.33]
Bechstein-193 2013	5/65	11/63		5.55%	0.44[0.16,1.2]
Russ 2003	7/31	6/31		5.88%	1.17[0.44,3.08]
Kahan-203 1999	5/47	16/77		6.31%	0.51[0.2,1.31]
Grinyo 2004	7/43	12/42		8.04%	0.57[0.25,1.31]
Kandaswamy 2005	15/149	15/140		12.06%	0.94[0.48,1.85]
Velosa-212 2001	18/97	22/100		17.85%	0.84[0.48,1.47]
Subtotal (95% CI)	**448**	**476**		**56.46%**	**0.75[0.55,1.03]**
Total events: 58 (Low TOR-I), 83 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=3.77, df=6(P=0.71); I^2=0%					
Test for overall effect: Z=1.76(P=0.08)					
Total (95% CI)	**745**	**772**		**100%**	**0.82[0.65,1.04]**
Total events: 106 (Low TOR-I), 135 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=5.02, df=8(P=0.76); I^2=0%					
Test for overall effect: Z=1.61(P=0.11)					
Test for subgroup differences: Chi^2=0.71, df=1 (P=0.4), I^2=0%					



Analysis 14.5. Comparison 14 Variable dose target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): subgroup analyses, Outcome 5 Acute rejection (antibody induction).

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
14.5.1 No induction					
Bechstein-193 2013	5/65	11/63		5.55%	0.44[0.16,1.2]
Russ 2003	7/31	6/31		5.88%	1.17[0.44,3.08]
Kahan-203 1999	5/47	16/77		6.31%	0.51[0.2,1.31]
Grinyo 2004	7/43	12/42		8.04%	0.57[0.25,1.31]
Cohen 2002	18/154	23/154		16.75%	0.78[0.44,1.39]
Velosa-212 2001	18/97	22/100		17.85%	0.84[0.48,1.47]
Subtotal (95% CI)	**437**	**467**		**60.39%**	**0.72[0.53,0.98]**
Total events: 60 (Low TOR-I), 90 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=3.1, df=5(P=0.69); I^2=0%					
Test for overall effect: Z=2.09(P=0.04)					
14.5.2 Antibody induction					
Lo 2004	1/16	1/23		0.76%	1.44[0.1,21.33]



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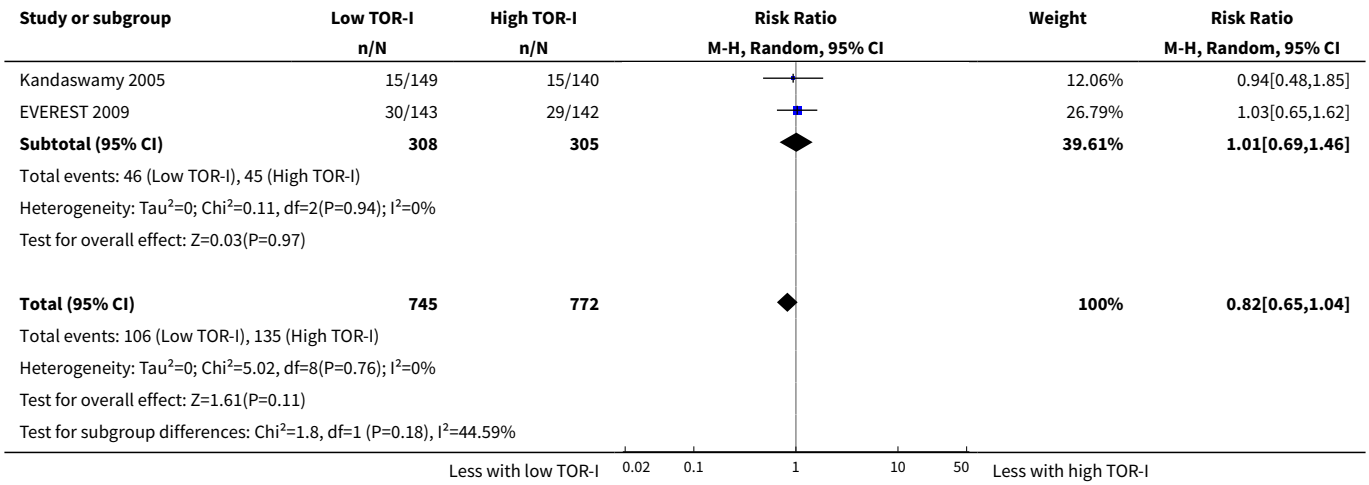

Comparison 15. Low versus higher dose target of rapamycin inhibitors (TOR-I): subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection (publication type)	13	3898	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.10, 1.41]
1.1 Abstract	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Journal	13	3898	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.10, 1.41]
2 Acute rejection (risk of bias for sequence generation and allocation concealment	13	3898	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.10, 1.41]
2.1 Low risk of bias	5	2602	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.15, 1.55]
2.2 High or unclear risk of bias	8	1296	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.84, 1.33]
3 Acute rejection (CNI co-intervention)	12	3766	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.09, 1.41]
3.1 Tacrolimus	3	761	Risk Ratio (M-H, Random, 95% CI)	1.62 [1.19, 2.19]
3.2 Cyclosporin	9	3005	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.02, 1.35]
4 Acute rejection (antibody induction)	13	3898	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.10, 1.41]
4.1 No induction	10	2954	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.09, 1.45]
4.2 Antibody induction	3	944	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.90, 1.62]
5 Acute rejection (TOR-I)	13	3898	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.10, 1.41]
5.1 Everolimus	7	1966	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.93, 1.33]
5.2 Sirolimus	6	1932	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.16, 1.66]

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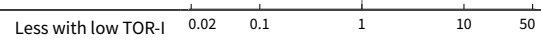
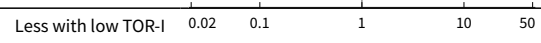
Analysis 15.1. Comparison 15 Low versus higher dose target of rapamycin inhibitors (TOR-I): subgroup analyses, Outcome 1 Acute rejection (publication type).

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
15.1.1 Abstract					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Low TOR-I), 0 (High TOR-I)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
15.1.2 Journal					
van Hooff 2003	6/50	1/26		0.38%	3.12[0.4,24.56]
Pascual 2010	3/15	3/20		0.77%	1.33[0.31,5.7]
Tedesco-Silva 2003	6/34	4/36		1.18%	1.59[0.49,5.14]
Hamdy 2005	9/65	7/67		1.89%	1.33[0.52,3.35]
Kahan-157 2001	16/68	9/35		3.24%	0.92[0.45,1.86]
Kramer-2307 2003	16/117	21/139		4.48%	0.91[0.5,1.65]
Kovarik-2306 2004	29/112	24/125		7.14%	1.35[0.84,2.17]
Kovarik-251 2001	37/193	43/194		10.59%	0.86[0.58,1.28]
Vitko-201 2001	45/194	39/198		11.23%	1.18[0.81,1.72]
Tedesco-Silva 2010	55/277	42/279		12.15%	1.32[0.92,1.9]
Kahan-301 2000	62/284	40/274		12.45%	1.5[1.04,2.15]
Vitko-TERRA 2004	82/325	51/325		16.49%	1.61[1.17,2.2]
MacDonald-302 2001	67/227	57/219		18%	1.13[0.84,1.53]
Subtotal (95% CI)	**1961**	**1937**		**100%**	**1.24[1.1,1.41]**
Total events: 433 (Low TOR-I), 341 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=10.29, df=12(P=0.59); I^2=0%					
Test for overall effect: Z=3.37(P=0)					
Total (95% CI)	**1961**	**1937**		**100%**	**1.24[1.1,1.41]**
Total events: 433 (Low TOR-I), 341 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=10.29, df=12(P=0.59); I^2=0%					
Test for overall effect: Z=3.37(P=0)					
Test for subgroup differences: Not applicable					



Analysis 15.2. Comparison 15 Low versus higher dose target of rapamycin inhibitors (TOR-I): subgroup analyses, Outcome 2 Acute rejection (risk of bias for sequence generation and allocation concealment.

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
15.2.1 Low risk of bias					
Vitko-201 2001	45/194	39/198		11.23%	1.18[0.81,1.72]
Tedesco-Silva 2010	55/277	42/279		12.15%	1.32[0.92,1.9]
Kahan-301 2000	62/284	40/274		12.45%	1.5[1.04,2.15]
Vitko-TERRA 2004	82/325	51/325		16.49%	1.61[1.17,2.2]
MacDonald-302 2001	67/227	57/219		18%	1.13[0.84,1.53]
Subtotal (95% CI)	**1307**	**1295**		**70.33%**	**1.33[1.15,1.55]**
Total events: 311 (Low TOR-I), 229 (High TOR-I)					



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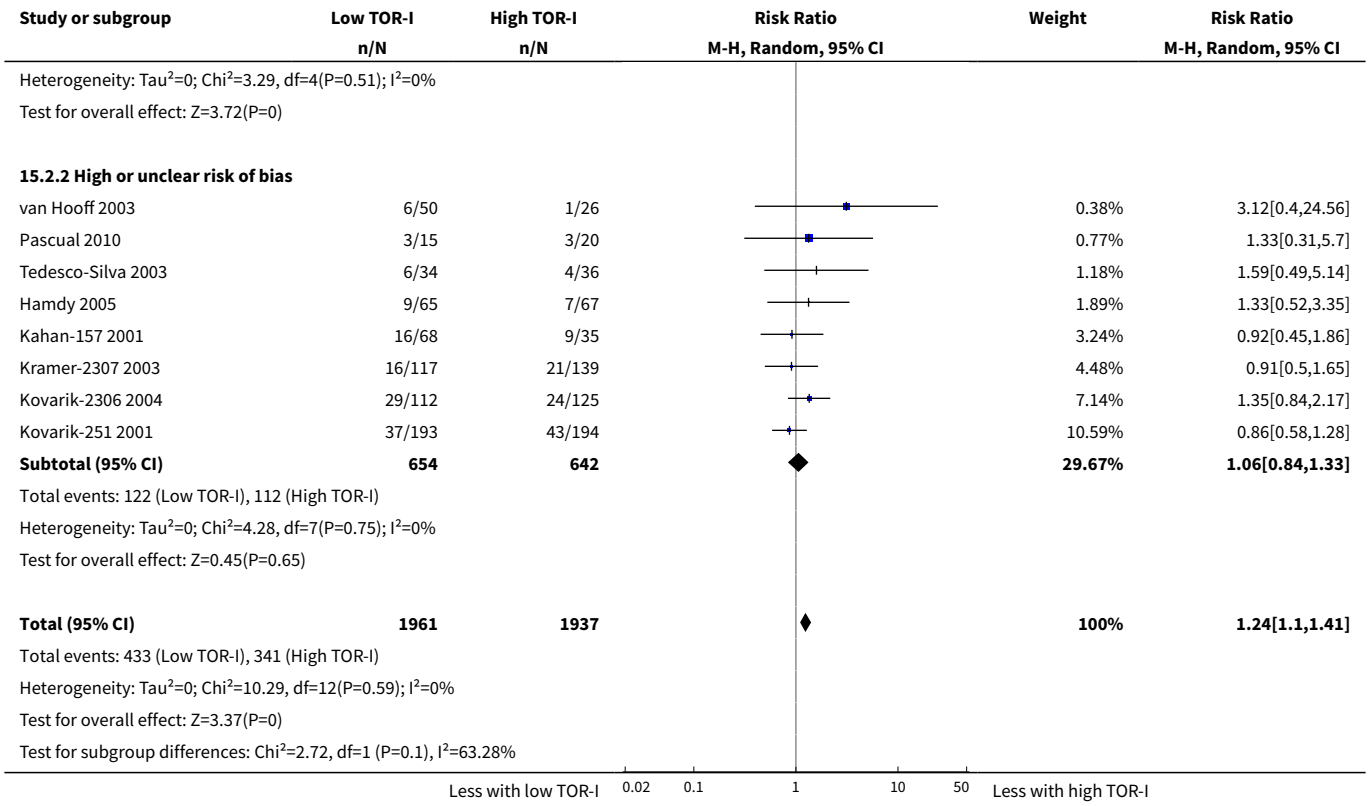
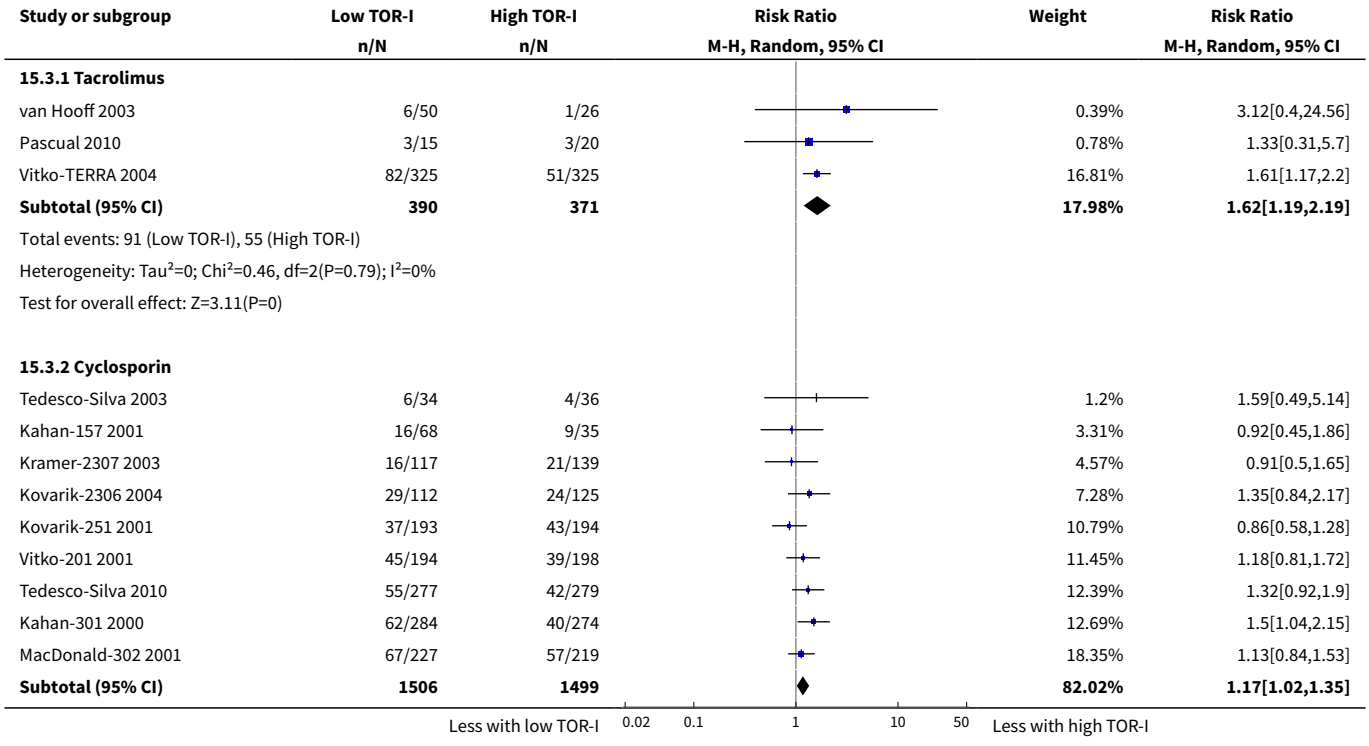


Analysis 15.3. Comparison 15 Low versus higher dose target of rapamycin inhibitors (TOR-I): subgroup analyses, Outcome 3 Acute rejection (CNI co-intervention).



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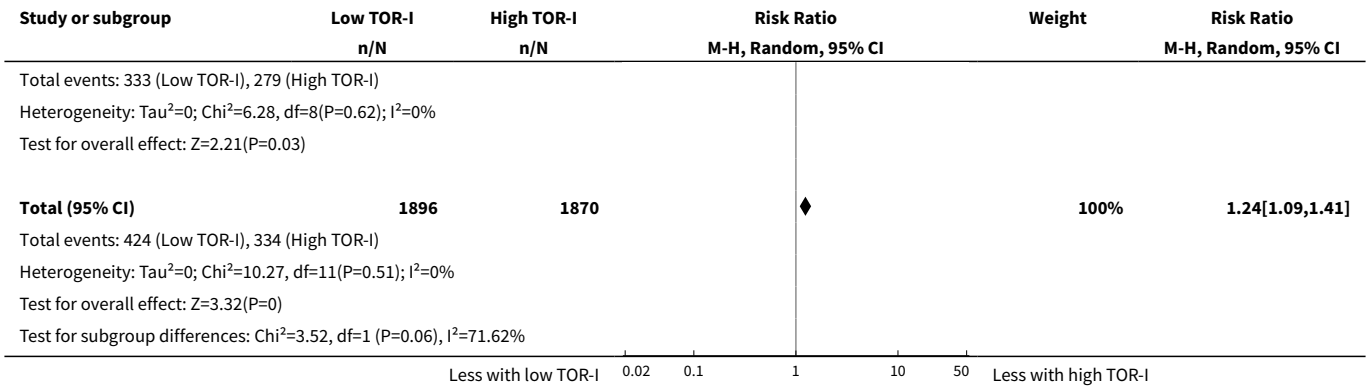
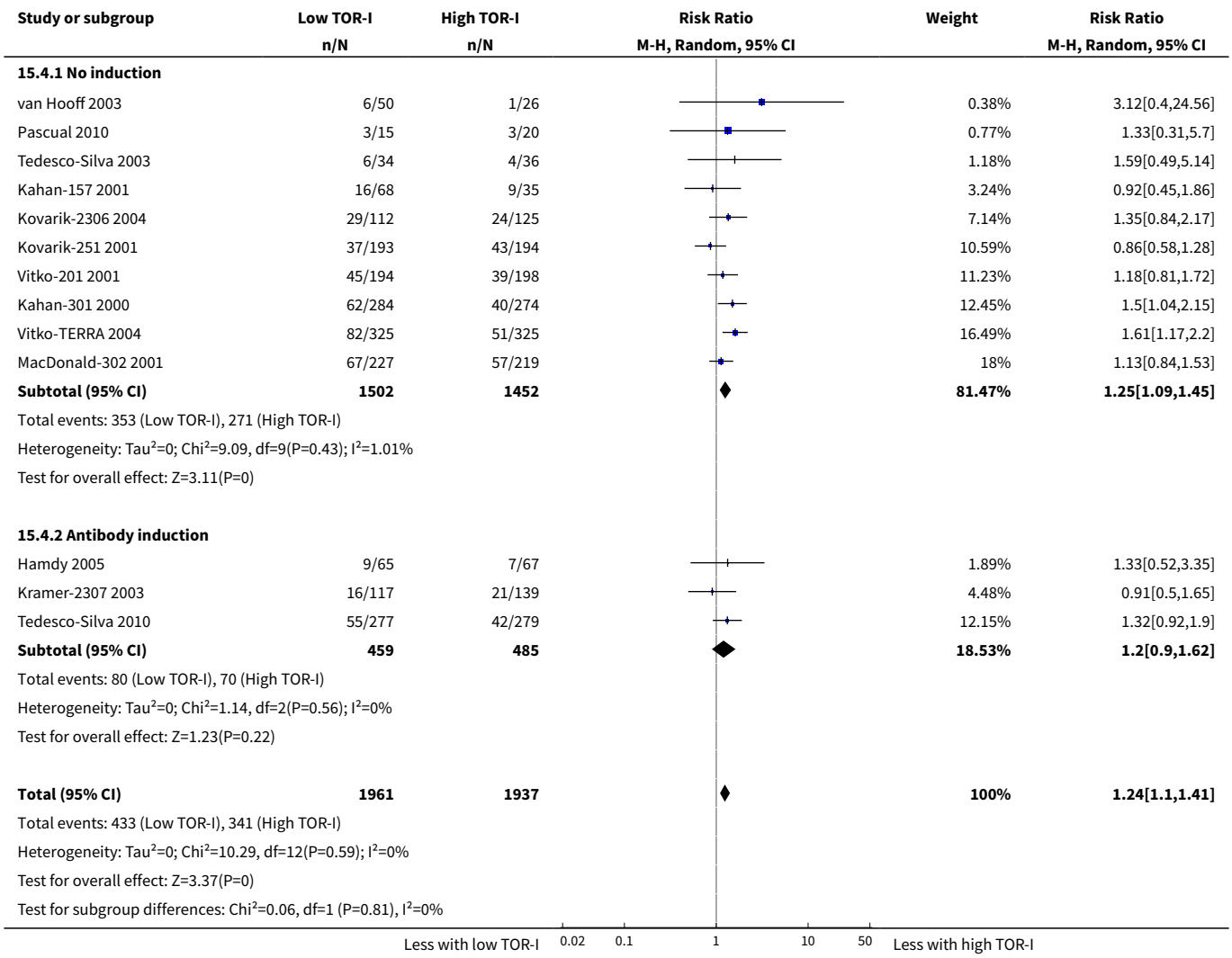


Analysis 15.4. Comparison 15 Low versus higher dose target of rapamycin inhibitors (TOR-I): subgroup analyses, Outcome 4 Acute rejection (antibody induction).



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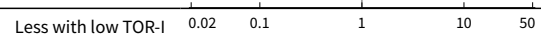
Analysis 15.5. Comparison 15 Low versus higher dose target of rapamycin inhibitors (TOR-I): subgroup analyses, Outcome 5 Acute rejection (TOR-I).

Study or subgroup	Low TOR-I n/N	High TOR-I n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
15.5.1 Everolimus					
Pascual 2010	3/15	3/20		0.77%	1.33[0.31,5.7]
Kahan-157 2001	16/68	9/35		3.24%	0.92[0.45,1.86]
Kramer-2307 2003	16/117	21/139		4.48%	0.91[0.5,1.65]
Kovarik-2306 2004	29/112	24/125		7.14%	1.35[0.84,2.17]
Kovarik-251 2001	37/193	43/194		10.59%	0.86[0.58,1.28]
Vitko-201 2001	45/194	39/198		11.23%	1.18[0.81,1.72]
Tedesco-Silva 2010	55/277	42/279		12.15%	1.32[0.92,1.9]
Subtotal (95% CI)	**976**	**990**		**49.61%**	**1.11[0.93,1.33]**
Total events: 201 (Low TOR-I), 181 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=3.93, df=6(P=0.69); I^2=0%					
Test for overall effect: Z=1.15(P=0.25)					
15.5.2 Sirolimus					
van Hooff 2003	6/50	1/26		0.38%	3.12[0.4,24.56]
Tedesco-Silva 2003	6/34	4/36		1.18%	1.59[0.49,5.14]
Hamdy 2005	9/65	7/67		1.89%	1.33[0.52,3.35]
Kahan-301 2000	62/284	40/274		12.45%	1.5[1.04,2.15]
Vitko-TERRA 2004	82/325	51/325		16.49%	1.61[1.17,2.2]
MacDonald-302 2001	67/227	57/219		18%	1.13[0.84,1.53]
Subtotal (95% CI)	**985**	**947**		**50.39%**	**1.39[1.16,1.66]**
Total events: 232 (Low TOR-I), 160 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=3.42, df=5(P=0.64); I^2=0%					
Test for overall effect: Z=3.6(P=0)					
Total (95% CI)	**1961**	**1937**		**100%**	**1.24[1.1,1.41]**
Total events: 433 (Low TOR-I), 341 (High TOR-I)					
Heterogeneity: Tau^2=0; Chi^2=10.29, df=12(P=0.59); I^2=0%					
Test for overall effect: Z=3.37(P=0)					
Test for subgroup differences: Chi^2=2.94, df=1 (P=0.09), I^2=66.03%					



ADDITIONAL TABLES

Table 1. Target of rapamycin inhibitor (TOR-I) versus calcineurin inhibitor (CNI) or antimetabolite: subgroup analyses of study methodology and design features for all acute rejection

Variable	TOR-I versus CNI^			TOR-I versus antimetabolite*		
	Studies	RR (95% CI)	P-value for sub-group differences	Studies	RR (95% CI)	P-value for sub-group differences
Publication type						

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Table 1. Target of rapamycin inhibitor (TOR-I) versus calcineurin inhibitor (CNI) or antimetabolite: subgroup analyses of study methodology and design features for all acute rejection *(Continued)*

Abstract	3	RR 2.03 (95% CI 1.13 to 3.65)	0.35	5	RR 0.68 (95% CI 0.29 to 1.61)	0.49
Journal	16	RR 1.53 (95% CI 1.23 to 1.90)		27	RR 0.93 (95% CI 0.80 to 1.08)	
Risk of bias						
Low risk	7	RR 1.64 (95% CI 1.31 to 2.06)	0.65	12	RR 0.85 (95% CI 0.50 - 1.46)	0.21
High or unclear risk	12	RR 1.61 (95% CI 1.28 to 2.03)		21	RR 1.04 (95% CI 0.87 to 1.26)	
CNI co-intervention						
Tacrolimus	7^^	RR 2.09 (95% CI 1.56 to 2.78)	0.06	18**	RR 0.93 (95% CI 0.76 to 1.14)	0.25
Cyclosporin	13	RR 1.48 (95% CI 1.20 to 1.83)		9	RR 0.85 (95% CI 0.64 - 1.14)	
TOR-I						
Everolimus	1	Not analysed^^^	--	16	RR 1.04 (95% CI 0.85 to 1.28)	0.17
Sirolimus	18	Not analysed^^^		16	RR 0.85 (95% CI 0.70 - 1.04)	
Antimetabolite comparator						
Azathioprine	1	Not analysed^^^	--	2	RR 0.71 (95% CI 0.39 - 1.28)	0.30
Mycophenolate	18	Not analysed^^^		30	RR 0.98 (95% CI 0.86 to 1.12)	
Antibody induction						
No induction	4	RR 1.24 (95% CI 0.91 to 1.68)	0.13	10***	RR 0.93 (95% CI 0.77 - 1.12)	0.88
Antibody induction	13^^^^	RR 1.81 (95% CI 1.29 to 2.53)		21	RR 0.90 (95% CI 0.70 to 1.16)	

* Includes 32 studies, which compared TOR-I with an antimetabolite and reported the outcome of all acute rejection
**CNI co-intervention: 5 studies excluded as they used both tacrolimus and cyclosporin
*** One study excluded as it did not report whether antibody induction was administered
^ Includes 19 studies, which compared TOR-I with a CNI and reported the outcome of all acute rejection
^^ Includes 20 studies as one study (SYMPHONY 2007) had separate groups receiving cyclosporin and tacrolimus
^^^ Analyses not carried out as only one study used the TOR-I, everolimus, and only one study used the antimetabolite, azathioprine
^^^^ Two studies only used induction in TOR-I arm

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Table 2. Variable doses of target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI) and lower versus higher doses of TOR-I: subgroup analysis of study methodology and design features for all acute rejection

Variable	Variable doses of TOR-I and CNI*			Lower versus higher doses of TOR-I**		
	Studies	RR (95% CI)	P-value for subgroup differences	Studies	RR (95% CI)	P-value for subgroup differences
Publication type						
Abstract	2	RR 0.85 (95% CI 0.50 - 1.46)	0.7	0	No studies	Not applicable
Journal	7	RR 0.83 (95% CI 0.63 - 1.08)		13	(RR 1.24, 95% CI 1.10 to 1.41)	
Risk of bias						
Low risk	2	RR 0.85 (95% CI 0.50 - 1.46)	0.81	5	(RR 1.33, 95% CI 1.15 to 1.55)	0.10
High or unclear risk	7	RR 0.79 (95% CI 0.59 - 1.06)		8	(RR 1.06, 95% CI 0.84 to 1.33)	
CNI co-intervention						
Tacrolimus	5	RR 0.77 (95% CI 0.51 - 1.16)	0.67	3	(RR 1.62, 95% CI 1.19 to 2.19)	0.06
Cyclosporin	4	RR 0.85 (95% CI 0.64 - 1.14)		9	(RR 1.17, 95% CI 1.02 to 1.35)	
Antibody induction						
No induction	6	RR 0.72 (95% CI 0.53 - 0.98)	0.97	10	(RR 1.25, 95% CI 1.09 to 1.45)	0.81
Antibody induction	3	RR 1.01 (95% CI 0.69 - 1.46)		3	(RR 1.20, 95% CI 0.90 to 1.62)	
TOR-I						
Everolimus	2	(RR 0.93, 95% CI 0.65 to 1.32)	0.4	7	(RR 1.11, 95% CI 0.93 to 1.33)	0.09
Sirolimus	7	(RR 0.75, 95% CI 0.55 to 1.03)		6	(RR 1.39, 95% CI 1.16 to 1.66)	

* Includes 9 studies, which reported the outcome of all acute rejection
** Includes 13 studies, which reported the outcome of all acute rejection

Table 3. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): comparison in outcomes between 2006 review and 2019 update

Outcomes	2006 review (8 studies)	2019 update (22 studies)
Death	No difference	No difference
All graft loss	No difference	No difference
Graft loss censored for death	No difference	No difference
All acute rejection	**No difference**	**Increased with TOR-I**

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Table 3. Target of rapamycin inhibitors (TOR-I) versus calcineurin inhibitors (CNI): comparison in outcomes between 2006 review and 2019 update *(Continued)*

Biopsy-proven acute rejection	**No difference**	**Increased with TOR-I**
CMV infection	**No difference**	**Reduced with TOR-I**
Wound complications	Increased with TOR-I	Increased with TOR-I
Malignancies	No difference	No difference
Need to change treatment	Increased with TOR-I	Increased with TOR-I
New-onset diabetes mellitus	No difference	No difference
Lymphoma/PTLD	No difference	No difference
BK virus infection	No difference (1 study)	No difference
Tremor	Reduced with TOR-I	Reduced with TOR-I
Acne/rash	Increased with TOR-I	Increased with TOR-I
GFR	**Increased with TOR-I**	**No difference**
SCr	Reduced with TOR-I	Reduced with TOR-I
Hypercholesterolaemia	**No difference**	**Increased with TOR-I**
Hypertriglyceridaemia	**No difference**	**Increased with TOR-I**
Bone marrow suppression	Increased with TOR-I	Increased with TOR-I

Change in results have been **highlighted**
CMV - cytomegalovirus; GFR - glomerular filtration rate; PTLD - post-transplant lymphoproliferative disease; SCr - serum creatinine

Table 4. Target of rapamycin inhibitors (TOR-I) versus antimetabolite: comparison in outcomes between 2006 review and 2019 update

Outcomes	2006 review (11 studies)	2019 update (33 studies)
Death	No difference	No difference
All graft loss	No difference	No difference
Graft loss censored for death	No difference	No difference
All acute rejection	**Reduced with TOR-I**	**No difference**
Biopsy-proven acute rejection	**Reduced with TOR-I**	**No difference**
CMV infection	Reduced with TOR-I	Reduced with TOR-I
Wound complications	Increased with TOR-I	Increased with TOR-I
Malignancies	No difference	No difference

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Table 4. Target of rapamycin inhibitors (TOR-I) versus antimetabolite: comparison in outcomes between 2006 review and 2019 update *(Continued)*

Need to change treatment	**No difference**	**Increased with TOR-I**
New-onset diabetes mellitus	**No difference**	**Increased with TOR-I**
Lymphoma/PTLD	No difference	No difference
BK virus infection	**Not reported**	**Lower with TOR-I**
Tremor	No difference (1 study)	No difference
Acne/rash	Increased with TOR-I (1 study)	Increased with TOR-I
GFR	Reduced with TOR-I	Reduced with TOR-I
SCr	Increased with TOR-I	Increased with TOR-I
Hypercholesterolaemia	Increased with TOR-I	Increased with TOR-I
Hypertriglyceridaemia	Increased with TOR-I	Increased with TOR-I
Leucopenia	Reduced with TOR-I	Reduced with TOR-I
Thrombocytopenia	Increased with TOR-I	Increased with TOR-I

Change in results have been **highlighted**
CMV - cytomegalovirus; GFR - glomerular filtration rate; PTLD - post-transplant lymphoproliferative disease; SCr - serum creatinine

Table 5. Variable target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): comparison in outcomes between 2006 review and 2019 update

Outcome	2006 review (8 studies)	2019 update (9 studies)
Death	No difference	No difference
All graft loss	No difference	No difference
Graft loss censored for death	No difference	No difference
All acute rejection	**Reduced in low TOR-I**	**No difference**
Biopsy-proven acute rejection	**Reduced in low TOR-I**	**No difference**
CMV infection	No difference	No difference
Wound complications	No difference	No difference
Malignancies	No difference	No difference
Need to change treatment	No difference	No difference
New-onset diabetes mellitus	No difference	No difference
Lymphoma/PTLD	No difference	No difference

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Table 5. Variable target of rapamycin inhibitors (TOR-I) and calcineurin inhibitors (CNI): comparison in outcomes between 2006 review and 2019 update *(Continued)*

BK virus infection	**Not reported**	**No difference**
Tremor	No difference (1 study)	No difference
Acne/rash	**Not reported**	**No difference**
GFR	Increased in low TOR-I	Increased in low TOR-I
SCr	No difference	No difference
Hypercholesterolaemia	No difference	No difference
Hypertriglyceridaemia	No difference	No difference
Leucopenia	No difference	No difference
Thrombocytopenia	No difference	No difference

Change in results have been **highlighted**
CMV - cytomegalovirus; GFR - glomerular filtration rate; PTLD - post-transplant lymphoproliferative disease; SCr - serum creatinine

Table 6. Low versus high target of rapamycin inhibitors (TOR-I): comparison in outcomes between 2006 review and 2019 update

Outcome	**2006 review (8 studies)**	**2019 update (13 studies)**
Death	No difference	No difference
All graft loss	No difference	No difference
Graft loss censored for death	No difference	No difference
All acute rejection	Reduced in high TOR-I	Reduced in high TOR-I
Biopsy-proven acute rejection	Reduced in high TOR-I	Reduced in high TOR-I
CMV infection	No difference	No difference
Wound complications	No difference	No difference
Malignancies	No difference	No difference
Need to change treatment	No difference	No difference
New-onset diabetes mellitus	Increased in high TOR-I	Increased in high TOR-I
Lymphoma/PTLD	No difference	No difference
BK virus infection	Not reported	Not reported
Tremor	Not reported	No difference
Acne/rash	No difference	No difference

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Table 6. Low versus high target of rapamycin inhibitors (TOR-I): comparison in outcomes between 2006 review and 2019 update *(Continued)*

GFR	Reduced in high TOR-I	Reduced in high TOR-I
SCr	No difference	No difference
Hypercholesterolaemia	**No difference**	**Increased in high TOR-I**
Hypertriglyceridaemia	No difference	No difference
Leucopenia	Increased in high TOR-I	Increased in high TOR-I
Thrombocytopenia	Increased in high TOR-I	Increased in high TOR-I

Change in results have been **highlighted**
CMV - cytomegalovirus; GFR - glomerular filtration rate; PTLD - post-transplant lymphoproliferative disease; SCr - serum creatinine

APPENDICES

Appendix 1. Electronic search strategies

Electronic databases	Search terms
CENTRAL	1. MeSH descriptor: [Kidney Transplantation] this term only 2. MeSH descriptor: [Sirolimus] explode all trees 3. sirolimus:ti,ab,kw in Trials 4. rapamycin*:ti,ab,kw in Trials 5. rapamune:ti,ab,kw in Trials 6. everolimus:ti,ab,kw in Trials 7. "SDZ RAD":ti,ab,kw in Trials 8. (RAD or RAD100):ti,ab,kw in Trials 9. certican:ti,ab,kw in Trials 10."TOR-I":ti,ab,kw in Trials 11.deforolimus:ti,ab,kw in Trials 12.temsirolimus:ti,ab,kw in Trials 13.mtor and inhibitor*:ti,ab,kw in Trials 14.{OR #2-#23} in Trials 15.{AND #1, #14 in Trials
MEDLINE	1. kidney transplantation/ 2. exp Sirolimus/ 3. sirolimus.tw. 4. rapamycin.tw. 5. rapamune.tw. 6. ay 22-989.tw. 7. everolimus.tw. 8. SDZ RAD.tw. 9. (RAD or RAD100).tw. 10.certican.tw. 11."TOR-1".tw. 12.or/2-11

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(Continued)

	13.and/1,12
EMBASE	1. exp "mammalian target of rapamycin inhibitor"/ 2. sirolimus.tw. 3. rapamycin.tw. 4. rapamune.tw. 5. everolimus.tw. 6. ay 22989.tw. 7. SDZ RAD.tw. 8. (RAD or RAD100).tw. 9. certican.tw. 10.deforolimus.tw. 11.temsirolimus.tw. 12.(mtor and inhibitor$).tw. 13.or/1-12

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; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

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(Continued)

	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised 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. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

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WHAT'S NEW

Date	Event	Description
11 November 2019	New citation required and conclusions have changed	New studies added - some changes to direction of results
11 November 2019	New search has been performed	37 new studies added

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 2, 2006

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

CONTRIBUTIONS OF AUTHORS

Writing of protocol and review - AW, VSWL, JRC, JCC
Screening of titles and abstracts - AW, VSWL, DH, EH, LH
Assessment for inclusion - AW, VSWL, DH, EH, LH
Quality assessment - AW, VSWL, DH, EH, LH
Data extraction - AW, VSWL,DH, EH, LH
Data entry into RevMan - AW, VSWL, DH, EH, LH
Data analysis - AW, VSWL, DH, EH
Disagreement resolution - AW, JRC, JCC, DH, EH
Writing of the update review - LH, DH, EH, AW, VSWL
Review procedures for update - LH, DH, EH, AW

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update, risk of bias assessment and GRADE have been used

INDEX TERMS

Medical Subject Headings (MeSH)

*Immunosuppression; *Kidney Transplantation; Everolimus; Immunosuppressive Agents [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Sirolimus [adverse effects] [*analogs & derivatives] [antagonists & inhibitors] [*therapeutic use]

MeSH check words

Humans

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